



Outcome of Surgery for Acromegaly Performed by Different Surgeons: Importance of Surgical Experience

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Abstract. Aim: The aim of this study was to evaluate transsphenoidal surgery results in acromegalic patients which were performed not by a single surgeon but by different surgeons. Methods: The study included 30 (M/F: 13/17) patients whose follow-up data were available. Basal or nadir postglucose growth hormone levels of less than 2 ng/ml were accepted as cure criteria. Six of them underwent a further operation due to previous surgical failure. Results: Cure was achieved in 33% of patients while hypopituitarism was observed in 10% (3/30) of patients after the first operation. The cure rates were 63% and 15% in patients with microadenomas ($n = 11$) and macroadenomas ($n = 19$) respectively ($p = 0.042$). Only one of the patients (16%) who underwent a second operation achieved remission, while hypopituitarism was observed in five of them (83%). There was no significant difference in the cure rates between the first and second operation, but the risk of hypopituitarism was significantly higher in patients who underwent further surgery ($p = 0.008$). Conclusion: The cure rate following surgery is significantly lower in acromegalic patients with macroadenomas than in patients with microadenomas. Cure probability decreases with a further operation, while complication risk increases significantly. Octreotide therapy, which could be used as an alternative therapy to the surgery, revealed high success rates in both microadenomas and macroadenomas. The low cure rates found in this study compared with published series could be attributed to the fact that operations were performed by inexperienced surgeons.

Key Words. acromegaly, transsphenoidal surgery, octreotide, hypopituitarism

Introduction

The aim of acromegaly treatment is to eliminate local and secretory effects of the tumor. Different cure criteria have been used in the treatment of acromegaly and although there is no clear consensus, in recent years it is generally accepted that cure of acromegaly is to achieve serum growth hormone (GH) levels less than 1 ng/mL and normal levels of plasma IGF-1. Before this recent consensus, there were many reports in which suppression of GH levels to below 2 ng/ml was accepted as cure criteria [1,2].

Neurosurgery is currently considered as the treatment of choice but cure rates vary with both patient

characteristics and with the surgeon's experience. Published surgical success rates are between 42% and 76%, these rates being modified by tumor size, infiltration of cavernous sinus, preoperative levels of GH and IGF-1 and experience of the surgeon [3,4]. If surgery is unsuccessful, adjuvant pituitary irradiation and/or medical GH suppressive treatment with depot preparations of long acting somatostatin analogs can be used. The major effects of radiotherapy are seen during the first 2–5 years after treatment and the possibility of radiation induced hypopituitarism is very high. Long acting somatostatin analogs are currently used after surgery or radiotherapy and they are effective in controlling GH hypersecretion in 69–72% of patients with acromegaly [5,6].

In this retrospective study, the medical records of acromegalic patients treated in our center during the previous ten years were analyzed with the aim of clarifying which parameters are important in prediction of surgical success rate prior to transsphenoidal operation. The success rates of initial and follow-up surgery, radiotherapy and octreotide therapy were compared with the results of other published reports and discrepancies were evaluated.

Material and Methods

A retrospective chart review was performed on 30 acromegalic patients with an average postoperative follow-up period of 42 ± 38 months (Table 1). Patients with clinical symptoms, with subsequent basal GH levels above 25 ng/ml and who had intrasellar adenomas in their magnetic resonance (MR) images were diagnosed as acromegaly. Eight patients whose basal GH hormone levels were between 2–25 ng/ml but in whom GH levels could not be suppressed below 2 ng/ml during oral glucose tolerance test (OGTT) were also diagnosed as acromegaly. Because IGF-1 levels could not be measured regularly in our center, IGF-1 measurements were not used in the statistical analysis. Pituitary

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Table 1. Patient features

No. of patients	30
Age (year)	43 ± 10
Age at diagnosis of acromegaly (year)	39 ± 9
Microadenoma/macroadenoma	11/19
Diabetes mellitus (%)	9/30 (30)
Hypertension (%)	7/30 (23)

adenoma was found in all patients and had been resected transsphenoidally by 7 different surgeons 1–12 months after the diagnosis. It was noted that the maximum number of operations performed by any one surgeon was nine and maximum mean cases per year for a surgeon was 0.9.

All patients were evaluated for pituitary dysfunction following surgery. Basal or glucose suppressed GH level of 2 ng/ml or less was used as the cure criteria of acromegaly. Hypopituitarism was defined as clinical and biochemical evidence of pituitary dysfunction or requirement for hormone replacement. Cranial MR images were obtained three to six months after operations. Six patients with remnant resectable tumors underwent further surgery. Conventional radiotherapy ($n = 8$) or gamma-knife therapy ($n = 3$) was administered to 11 patients with unsuccessful surgical resection. Thirteen patients who were not cured with surgery were treated with octreotide-LAR. Octreotide-LAR treatment which was administered at a dose of 10 mg every 28 days and titrated to a maximum dose of 30 mg until GH levels below 2 ng/ml were achieved. In spite of inadequate suppression of GH secretion, there were two patients in whom octreotide-LAR dose could not be increased above 10 mg and who finally discontinued therapy due to economic factors.

Serum GH levels were measured by chemiluminescence (Nichols Institute Diagnostics, San Juan Capistrano, LA). Data were reported as mean ± standard deviation. Chi square test, Pearson correlation analysis and Student's t-test were used for statistical analysis.

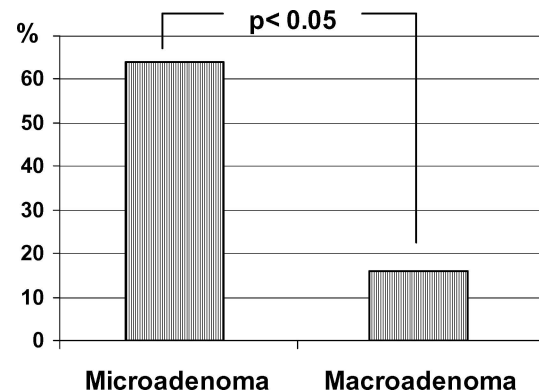
Results

After the first operation mean GH level decreased from 47 ± 75 ng/mL to 26 ± 56 ng/mL (Table 2). Basal GH levels were below 2 ng/ml in 10 patients and above 25 ng/ml in six patients postoperatively. Oral glucose tolerance test was performed on five patients. GH levels were between 2–25 ng/ml but none of these patients' GH levels could be suppressed below 2 ng/ml after glucose load. It was agreed that after the first operation, cure was achieved in only 10 patients (33%).

Postoperatively, there was no tumor residue in the MR images of 15 patients while there were microadenomas in seven and macroadenomas in eight patients. Cure confirmed in nine of 15 patients whose pituitary adenomas did not exist in their subsequent MR images. A 0.2 cm pituitary adenoma was observed in postopera-

Table 2. Some parameters of patients before and after first transsphenoidal surgery

	Preoperative	Postoperative
Growth hormone (ng/ml)	47 ± 75	26 ± 56
GH levels during OGTT (ng/ml)	13.3 ± 7.5	6.8 ± 1.8
Growth hormone <2 ng/ml	0/30	10/30
No. of macroadenomas	19/30	8/30

**Fig. 1.** Surgical cure rates of patients with microadenoma and macroadenoma

tive MR images of one patient cured by first operation. Cure could not be obtained in the remaining 20 patients following surgery and the remnant adenoma size was larger than 1 cm in eight of them.

Cure rates were also determined with respect to tumor size. As shown in Figure 1(a), biochemical cure in the presence of a macroadenoma was achieved in a significantly lower proportion of patients (19 vs. 3, 15%) compared with those with microadenomas (11 vs. 7, 63%). The difference between cure rates of macroadenoma and microadenoma was statistically significant (Fig. 1). After further surgery on six patients, the cure rate was only 17% (1/6) and hypopituitarism developed in five (83%) of them (Table 3). There was no significant difference in the cure rates between the first and second operations, but the risk of hypopituitarism was significantly higher in patients who had undergone further surgery ($p = 0.008$).

Following surgery eight patients were treated with conventional and three patients with gamma-knife radiotherapy. Cure was obtained in three of the patients who underwent conventional radiotherapy at 34th, 32nd and 23rd months and in one of gamma knife radio-

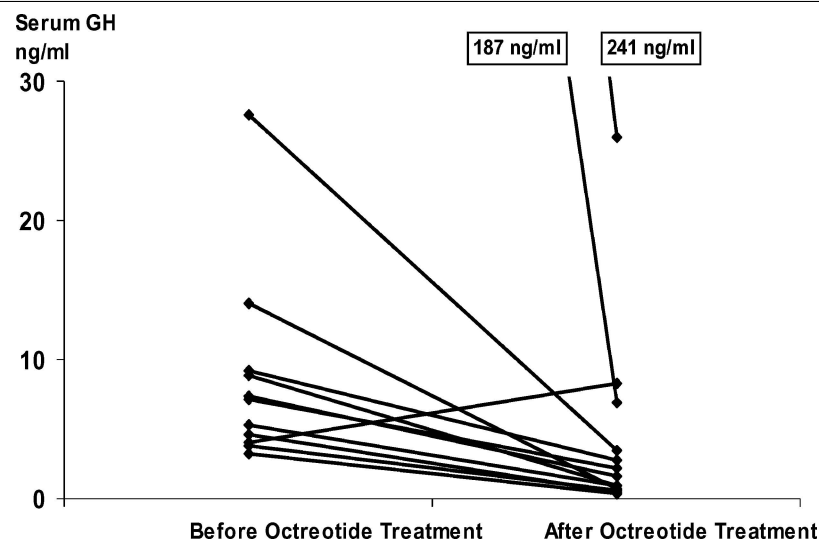
Table 3. Complication rates after first and second surgery

	First operation	Second operation
Hypopituitarism (%)	3/30 (10)	5/6 (83)
Diabetes insipidus (%)	2/30 (6.7)	3/6 (50)
Rhinorrhea (%)	2/30 (6.7)	0/6 (0)

Table 4. Summary of published results of surgical outcome for acromegaly

	Definition of cure (ng/ml)	No. of (micro/macroadenomas)	Cure rate in micros (%)	Cure rate in macros (%)	Total cure rate (%)
Davis et al. [21]	Basal GH<2 Nadir GH<2 during OGTT	175 (90/85)	–	–	52
Lissett et al. [10]	Mean during OGTT GH<2	73 (18/51)	39	12	18
Fahlbusch et al. [9]	Basal GH< 5	396 (105/291)	83	70	73
Sheaves et al. [3]	Mean GH<2	100 (53/47)	61	23	42
Swearingen et al. [12]	Nadir GH<2 during OGTT IGF-1 normalization	162 (33/129)	91	48	57
Abosch et al. [4]	Mean GH<5	254 (??)	–	–	76*
Ahmed et al. [18]	Mean GH<2	139 (79/60)	91	46	67
Gittoes et al. [8]	Basal GH<2 Nadir GH<0,8 during OGTT	66 (22/44)	86	52	64
Biermasz et al. [25]	Basal GH<2 Nadir GH<2 during OGTT IGF-1 normalization	59 (??)	67	60	61
Shimon et al. [7]	MeanGH<2 Nadir GH<2 during OGTT IGF-1 normalization	98 (46/52)	84	64	74
Erturk et al.	Basal GH<2 Nadir GH<2 during OGTT	30 (11/19)	63	15	33

*Based on short-term surgical results.

**Fig. 2.** Effects of octreotide-LAR treatment on serum GH levels

therapy patient at month 13. Maximum follow up periods for conventional therapy was 122 months and for gamma knife radiotherapy, 26 months. Hypopituitarism developed in two patients cured by radiotherapy.

Thirteen patients were treated with octreotide-LAR and GH levels were suppressed below 2 ng/ml in eight of them (Fig. 2). The dose of octreotide-LAR was 20 mg in three cases and 10 mg in five patients. Growth hormone suppression was not confirmed in five patients in whom the dose of octreotide-LAR could not be increased. This was due to economic problems in two pa-

tients and failure to attend follow-up a previous dose increase in two patients and failure of GH suppression even with a 30 mg dose in one patient.

Discussion

Transsphenoidal microsurgery is generally considered to be the first line therapy in the treatment of acromegalic patients with microadenomas and macroadenomas at present. With surgery it is possible to completely remove the tumor and obviate its local and secretory

effects, although the success rates of surgery are not excellent at all centers. Comparing previously reported results of surgery in acromegalic patients is not easy due to the use of different cure criteria. Success rates of surgery are very different in published series (Table 3). A number of studies have demonstrated that the possibility of surgical cure in the presence of a microadenoma is significantly better than in macroadenomas and also that surgical remission rates are better when operations have been performed by a single experienced surgeon [4,7,8].

In the present study, the proportion of patients in whom GH levels decreased to a safe margin was considerably low compared with published series. Moreover, the difference in cure rates remained low when tumors were analyzed specifically as micro and macroadenomas. While some studies achieved success rates reaching 70% of patients with macroadenomas [9], remission rate was achieved in 63% of our patients with microadenomas and only 15% of patients with macroadenomas. A recent report from Lisset et al. [10] revealed poor cure rates, especially in macroadenomas, similar to our results. In study, the authors suggested that the poor results were due to the dilution of experience when a large number of surgeons performed the surgical procedure, as in our study. These results reveal that surgical experience is an important factor, especially in macroadenomas. In six patients who underwent further surgery, cure was established in only one of them (16%). Previous studies also report that success rates of following surgery are lower than the first operation in acromegalic patients, with rates between 8–31% in several studies [7,9,11].

Development of isolated or total hypopituitarism is an important complication that is associated with transsphenoidal operations. After initial surgery, hypopituitarism rates are reported as 2–5% in the literature but this rate may rise to 50% in the second operation [4,12,13]. In our study the isolated or mixed hypopituitarism rate was 10% (3/30) after the initial surgery but 83% (5/6) after the second operation. It should therefore be emphasized that the second operation carries a significantly higher risk of hypopituitarism than the first one. Our elevated levels of hypopituitarism rates may also be attributed to the involvement of several surgeons at each operation.

In two published series with long term follow-up, cure rates by pituitary irradiation were 35–75%, 53–76% and 66–87% at 5, 10 and 15 years respectively [14,15]. Although our follow up period was short; GH levels could be suppressed to safe levels in 4 of 11 patients (36%) after radiotherapy. In two of them (18%) hypopituitarism developed. Medical therapy with or without radiotherapy was initiated in patients in whom cure was not achieved after surgery. Long-acting somatostatin analogues are widely used for acromegaly treatment in recent years. Octreotide-LAR, when administered as either primary therapy or as an adjunctive therapy after surgery, is effective in controlling GH hypersecretion

in most patients. Tumor shrinkage is also observed in de novo patients during octreotide-LAR treatment, suggesting that it can be used as a primary therapy in patients who are less likely to be cured after surgery [5,6,16]. Colao et al. [5] published results of 24 months octreotide-LAR treatment in 36 patients (15 de novo; 21 with post-operative residue tumor). GH hypersecretion was controlled in 69.4% of patients whereas normal IGF-1 levels were achieved in 61.1% of patient and tumor shrinkage was detected in 12 of 15 de novo patients in this study. Similar results were reported in the study of Cozzie et al. [6]. In our study octreotide-LAR was administered to 13 patients who could not be cured by surgery and GH levels were suppressed to below 2 ng/ml in eight (61%) of them. Two patients discontinued therapy due to economic factors, two patients whose dose was increased did not attend further follow-up and in one patient (7%) using 30mg octreotide-LAR monthly, GH level could not be suppressed to desired levels. Gall-bladder stones occurred in 25% of patients but no other severe side effects were observed during therapy. Gastrointestinal side-effects such as transient abdominal flatulence and nausea (8%) and gall-bladder disease (18–26%) can be observed with the use of long-acting somatostatin analogues and these are usually self-limiting [6,17]. Octreotide-LAR treatment appears to be a very effective and safe therapy according to the side effect profile, compared with radiotherapy and surgery.

In conclusion, our data highlighted the importance of surgical experience in the treatment of acromegaly. It was observed that our surgical success rates were very poor, especially in macroadenomas. This was probably due to inexperience, occurring as a result of a large number of surgeons performing these procedures in our center. The present study shows that probability of remission with follow-up surgery was very low, resembling rates in recent reports and that a second operation should only be considered if there is an immediate need for providing relief from the symptoms of a sellar mass. If surgery is unsuccessful in normalizing GH hypersecretion, the economic cost of adjunctive therapies will be very high. Transsphenoidal surgery should therefore be undertaken by an experienced surgeon; to prevent the potential increased costs of adjunctive treatments. The incidence of acromegaly is 3–4 per million per year; it is thus a rare disease and there is limited opportunity for improving surgical expertise. Since acromegaly is a rare disease it is rather being logical that to refer these patients especially macroadenomas to specialized centers on pituitary surgery. Otherwise, in these circumstances, medical therapy with its costly expenses will be another appropriate therapeutic option.

References

1. Melmed S, Jackson I, Kleinberg D, Klibanski A. Current treatment guidelines for acromegaly. *J Clin Endocrinol Metab* 1998;83:2646–2652.

2. Holdaway IM, Rajasoorya CR, Gamble GD, Stewart AW. Long-term treatment outcome in acromegaly. *Growth Horm IGF Res* 2003;13:185–192.
3. Sheaves R, Jenkins P, Blackburn P, Huneidi AH, Afshar F, Medbak S, Grossman AB, Besser GM, Wass JA. Outcome of transsphenoidal surgery for acromegaly using strict criteria for surgical cure. *Clin Endocrinol (Oxf)* 1996;45:407–413.
4. Abosch A, Tyrrell JB, Lamborn KR, Hannegan LT, Applebury CB, Wilson CB. Transsphenoidal microsurgery for growth hormone-secreting pituitary adenomas: initial outcome and long-term results. *J Clin Endocrinol Metab* 1998;83:3409–3410.
5. Colao A, Ferone D, Marzullo P, Cappabianca P, Cirillo S, Boerlin V, Lancranjan I, Lombardi G. Long-term effects of depot long-acting somatostatin analog octreotide on hormone levels and tumor mass in acromegaly. *J Clin Endocrinol Metab* 2001;86:2779–2786.
6. Cozzi R, Attanasio R, Montini M, Pagani G, Lasio G, Lodrini S, Barausse M, Albizzi M, Dallabonzana D, Pedroncelli AM. Four-year treatment with octreotide-long-acting repeatable in 110 acromegalic patients: Predictive value of short-term results? *J Clin Endocrinol Metab* 2003;88:3090–3098.
7. Shimon I, Cohen ZR, Ram Z, Hadani M. Transsphenoidal surgery for acromegaly: endocrinological follow-up of 98 patients. *Neurosurgery* 2001;48:1239–1243.
8. Gittoes NJ, Sheppard MC, Johnson AP, Stewart PM. Outcome of surgery for acromegaly—the experience of a dedicated pituitary surgeon. *QJM* 1999;92:741–745.
9. Fahlbusch R, Honegger J, Buchfelder M. Evidence supporting surgery as treatment of choice for acromegaly. *J Endocrinol* 1997;155(Suppl 1):S53–S55.
10. Lissett CA, Peacey SR, Laing I, Tetlow L, Davis JR, Shalet SM. The outcome of surgery for acromegaly: the need for a specialist pituitary surgeon for all types of growth hormone (GH) secreting adenoma. *Clin Endocrinol (Oxf)* 1998;49:653–657.
11. Long H, Beauregard H, Somma M, Comtois R, Serri O, Hardy J. Surgical outcome after repeated transsphenoidal surgery in acromegaly. *J Neurosurg* 1996;85:239–247.
12. Swearingen B, Barker FG II, Katznelson L, Biller BM, Grinspoon S, Klibanski A, Moayeri N, Black PM, Zervas NT. Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. *J Clin Endocrinol Metab* 1998;83:3409–3410.
13. Abe T, Ludecke DK. Recent results of secondary transnasal surgery for residual or recurring acromegaly. *Neurosurgery* 1998;42:1013–1021.
14. Barrande G, Pittino-Lungo M, Coste J, Ponvert D, Bertagna X, Luton JP, Bertherat J. Hormonal and metabolic effects of radiotherapy in acromegaly: Long-term results in 128 patients followed in a single center. *J Clin Endocrinol Metab* 2000;85:3779–3785.
15. Biermasz NR, Dulken HV, Roelfsema F. Postoperative radiotherapy in acromegaly is effective in reducing GH concentration to safe levels. *Clin Endocrinol (Oxf)* 2000;53:321–327.
16. Newman CB, Melmed S, George A, Torigian D, Duhaney M, Snyder P, Young W, Klibanski A, Molitch ME, Gagel R, Sheeler L, Cook D, Malarkey W, Jackson I, Vance ML, Barkan A, Frohman L, Kleinberg DL. Octreotide as primary therapy for acromegaly. *J Clin Endocrinol Metab* 1998;83:3031–3033.
17. Bevan JS, Atkin SL, Atkinson AB, Bouloux PM, Hanna F, Harris PE, James RA, McConnell M, Roberts GA, Scanlon MF, Stewart PM, Teasdale E, Turner HE, Wass JA, Wardlaw JM. Primary medical therapy for acromegaly: An open, prospective, multicenter study of the effects of subcutaneous and intramuscular slow-release octreotide on growth hormone, insulin-like growth factor-I, and tumor size. *J Clin Endocrinol Metab* 2002;87:4554–4563.
18. Ahmed S, Elsheikh M, Stratton IM, Page RC, Adams CB, Wass JA. Outcome of transphenoidal surgery for acromegaly and its relationship to surgical experience. *Clin Endocrinol (Oxf)* 1999;50:561–567.
19. Clayton RN. How many surgeons to operate on acromegalic patients? *Clin Endocrinol (Oxf)* 1999;50:557–559.
20. Attanasio R, Epaminonda P, Motti E, Giugni E, Ventrella L, Cozzi R, Farabola M, Loli P, Beck-Peccoz P, Arosio M. Gamma-knife radiosurgery in acromegaly: A 4-year follow-up study. *J Clin Endocrinol Metab* 2003;88:3105–3112.
21. Davis DH, Laws ER Jr, Ilstrup DM, Speed JK, Caruso M, Shaw EG, Abboud CF, Scheithauer BW, Root LM, Schleck C. Results of surgical treatment for growth hormone-secreting pituitary adenomas. *J Neurosurg* 1993;79:70–75.
22. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: A retrospective cohort study. United Kingdom Acromegaly Study Group. *J Clin Endocrinol Metab* 1998;83:2730–2734.
23. Bates AS, Van't Hoff W, Jones JM, Clayton RN. An audit of outcome of treatment in acromegaly. *Q J Med* 1993;86:293–299.
24. Holdaway IM, Rajasoorya C. Epidemiology of acromegaly. *Pituitary* 1999;2(1):29–41.
25. Biermasz NR, van Dulken H, Roelfsema F. Ten-year follow-up results of transsphenoidal microsurgery in acromegaly. *J Clin Endocrinol Metab* 2000;85:4596–4602.