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ORIGINAL ARTICLE

Acromegaly surgery in Manchester revisited – The impact of reducing surgeon numbers and the 2010 consensus guidelines for disease remission

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Summary

Introduction Surgical remission rates for acromegaly vary and are dependent on the tumour morphology, biochemical definition of disease remission and surgical expertise. A previous report from the Manchester region in 1998 reported an overall surgical remission rate of 27% using accepted criteria for biochemical remission at the time. The establishment of the 2010 Consensus guidelines further tightens biochemical criteria for remission. This report aims to assess the impact of establishing a specialist pituitary surgery service in Manchester in 2005, with reduced surgeon numbers on the remission rates for acromegaly surgery.

Methods Patients with acromegaly undergoing first time endoscopic transsphenoidal surgery between 2005 and 2010 were studied. Surgery was performed by a single surgeon. Review of a prospectively collected acromegaly surgery database was performed with documentation of pre- and postoperative biochemical tests [oral glucose tolerance test (oGTT) and IGF-1], as well as clinical, pathological and radiological data. Definition of disease remission was according to the 2010 Consensus criteria (GH nadir <0·4 μg/l following an oGTT and normalized population matched IGF-1).

Results There were 43 consecutive patients with acromegaly, with 13 (30%) microadenomas and 12 (28%) invasive adenomas. Overall, surgical remission was achieved in 29 (67%) patients. The remission rates were similar between micro (77%), macro (63%) and giant (67%) adenomas. There were nonsignificant trends towards higher remission rates for noninvasive tumours compared with invasive tumours (74% *vs* 50%) and for patients with a preoperative GH nadir <10 μg/l (73% *vs* 54%) and IGF-1 standard deviation score <15 (72% *vs* 54%).

Conclusions Remission rates for acromegaly surgery have improved following establishment of a specialist surgical service, with a reduction in surgeon numbers. Endoscopic trans-sphenoidal surgery remains an effective first-line treatment for achieving biochemical remission in acromegaly, despite the introduction of the more stringent 2010 consensus guidelines.

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Introduction

Untreated acromegaly is associated with an increased risk of morbidity from cardiovascular, respiratory and oncological conditions related to long-term exposure to an excess of growth hormone (GH) and/or insulin growth factor (IGF-1).[1] Mortality rates are also increased, with an average reduction in life expectancy of approximately 5–6 years compared with age-matched population; rates are reported to return to normal with a return of mean circulating GH levels to below 5 mU/l (approximately 1·7 μg/l) and normalization of serum IGF-1 levels.[1–4]

In acromegaly, surgical and medical therapies aim to reduce GH levels, although there is ongoing discussion as to the optimum GH levels and what constitutes normal levels.[1,3,4] Over recent decades, the criteria defining disease remission have become more stringent.[1,3–9] Before the availability of sensitive GH assays, some of the early studies considered disease remission at a mean GH level of <5 μg/l or even higher.[6] The consensus guidelines in 2000 redefined remission as GH levels suppressed to <1·0 μg/l (approximately 3 mU/l) during an oral glucose tolerance test (oGTT), together with a normal age- and sex-matched IGF-1 and resolution of the clinical symptoms.[3] This was very recently updated in 2010 to reflect the increasing sensitivity of GH assays, with 'controlled disease' now defined as a GH nadir of <0·4 μg/l on oGTT, in conjunction with a normal age- and sex-matched IGF-1.[4] Indeed it has been suggested that even these more stringent criteria may be still inadequate, as the majority of the normal population would suppress to even lower GH levels following an oGTT.[4,10] In this context, there is also an ongoing debate as to the relative importance of

IGF-1 and GH levels and whether the latter should be measured in terms of a mean GH on a day curve and/or GH nadir on an oGTT.[4]

The published rates of biochemical remission following trans-sphenoidal surgery for growth hormone-producing pituitary adenomas vary enormously from 24% to 85%.[5–9,11–23] Such a wide variation in remission rates is attributable to a number of factors, including tumour size and tumour invasiveness, preoperative growth hormone levels, criteria used to define biochemical remission and the expertise of the operating surgeon.[7,24] With respect to the latter, a previous study looking at endocrine outcome following acromegaly surgery in Manchester reported an overall remission rate of 24%.[5] The authors also noted that during the study period (1974–1997), surgery was undertaken by nine neurosurgeons, and this was suggested as the main contributor to the poor endocrine outcome.

Since 2005, surgery for functioning pituitary tumours in the Greater Manchester region with a population of around 3·5 million has been performed by a single neurosurgeon employing the endoscopic trans-sphenoidal approach. In this report, we examine the impact of the reduction in surgeon numbers and the introduction of endoscopic pituitary surgery and apply the more stringent 2010 consensus guidelines to assess disease remission in acromegaly.[4]

Patients and methods

All patients undergoing endoscopic trans-sphenoidal surgery for the first time for a GH producing adenoma between 2005 and 2010 were included in this study. Patients were referred from the Greater Manchester Neuro-endocrine multi-disciplinary team covering a population of about 3·5 million. The patient demographics, clinical details, pre- and postoperative biochemical assessments were obtained from a prospectively collated pituitary surgery database.

GH and IGF-1 assays

The GH axis was primarily tested using an oGTT. Some patients had additional 5-point GH day curves. For measurement of the GH nadir during an oGTT, 75 mg of glucose was administered orally following an overnight fast with GH measurements performed on serum specimens collected at 0, 30, 60, 90 and 120 min after ingestion of the glucose. Concomitant glucose measurements were performed at all time-points.

For the duration of the study period, GH was assayed by chemiluminescent immunoassay utilizing the Siemens Immulite 2000 GH Assay (lower detection threshold, 0·05 μg/l; analytical sensitivity, 0·01 μg/l), with standardization using the current World Health Organisation (WHO) international standard (WHO IS 98/574). GH units were expressed in international units (mU/l) prior to June 2008, and in mass units (μg/l) after this time. In this study, all GH measurements are expressed in μg/l with a conversion factor of 3:1, when results were obtained prior to 2008.[4]

Plasma IGF-1 levels were determined by chemi-luminescent immunoassay (Siemens Immulite 2000 IGF-1, Deerfield, IL, USA.) with standardization using the WHO 1st IRR 87/518 expressed in nmols per litre. For plasma IGF-1 concentrations, results are expressed in standard deviation (SD) scores as recommended by the consensus guidelines of 2010.[4] A SD score of <2·0 was considered normal in this study.

Endocrine testing

Acromegaly was diagnosed in the context of appropriate clinical symptoms and signs, and biochemical confirmation by the elevation of plasma IGF-1 in conjunction with a failure to suppress on oGTT (GH nadir >1·0 μg/l), and/or an elevated basal GH level (>1·7 μg/l).[3]

Postoperatively, all patients underwent testing of the GH axis (GH nadir on oGTT and IGF-1) at regular intervals (i.e. 1–2 weeks and then at varying intervals, at least yearly). When early testing suggested residual tumour, as also supported by findings on a repeat MR scan, further re-exploratory surgery at 2–4 weeks postoperatively was undertaken in some patients. All GH and IGF-1 values presented in this study are values taken before the commencement of any medical therapy for the acromegaly. Those patients already on medical therapy at least a 3-month drug washout period was allowed before undertaking the surgery and the endocrine assessments. In this article, the postoperative endocrine results presented are from the latest follow-up.

Prior to 2010, definition of disease remission used was normalization of age- and sex-adjusted IGF-1 and a GH nadir of <1·0 μg/l on oGTT as per the 2000 consensus guidelines for disease remission in acromegaly.[3] The updated consensus guidelines of 2010 defines disease remission in acromegaly with a GH nadir of <0·4 μg/l on oGTT, in the presence of a normal age- and sex-adjusted IGF-1.[24] These criteria were used to retrospectively assess remission rates, and surgical remission was considered to be achieved when the above biochemical criteria were met, without the need for additional medical or radiotherapy.[4]

Patients also underwent postoperative testing of the remainder of the pituitary axis with a glucagon or insulin stress test. Postoperative hypopituitarism and the need for hormone replacement were noted.

Radiological assessment

All patients underwent magnetic resonance imaging of the sellar region using a specific pituitary protocol, preoperatively and at 6 months postoperatively. Scans were performed on the Siemens 1·5 Tesla machine, acquiring sagittal (T1-weighted) and coronal (T1- and T2-weighted) 2-mm slices. Gadolinium contrast was not routinely given unless dynamic scans were performed looking for microadenomas not clearly apparent on standard scan sequences.

Each tumour was subcategorized by size into micro- (<10 mm), macro- (10–25 mm) and giant (>25 mm) adenomas on maximal vertical and transverse dimensions. Degree of tumour spread outside the pituitary fossa was assessed using the Hardy grading system. In this classification, tumour grades III/IV and D/E indicate tumour invasiveness and spread outside the sellar.[25]

Trans-sphenoidal surgery

All trans-sphenoidal surgeries were performed by a single surgeon employing an endoscopic trans-sphenoidal approach as previously

described in detail.[26] Surgical data were obtained from the electronic operative reports, and this included information on the surgeon's intra-operative observations regarding tumour invasion, degree of tumour resection and intra-operative complications (e.g. CSF leak).

Primary surgical debulking was attempted in patients when the preoperative MR scan revealed the presence of circumferential tumour extension around the carotid arteries. In all other cases, gross total resection of the adenoma was attempted, irrespective of tumour size. Those patients already on medical therapy and in whom a gross total resection of the adenoma was attempted, at least a 3-month drug wash-out period, were allowed before undertaking the surgery and the endocrine assessments.

Statistical analysis

Data were processed using commercially available statistical software (SPSS Inc., Chicago, IL, USA). Nonparametric data (e.g. remission rate, etc.) were tested using the Pearson Chi-square and Mann–Whitney *U* tests. Normally distributed parametric data were compared using Student's *t*-test or ANOVA and *post hoc* Bonferroni tests.

Results

Demographics

Forty-three patients underwent first time endoscopic trans-sphenoidal surgery for acromegaly during the study period. Mean ± SD age of the patients was 49 ± 14 (range 26–52), with a slight female preponderance (F:M = 1·4:1). Mean duration of follow-up was 34 ± 19 months (range 6–64). In two patients, complete follow-up data were not available, with one patient lost to follow-up at 36 months, and one patient died of unrelated causes at 12 months postoperatively.

There were 13 (30%) micro, 27 (63%) macro and 3 (7%) giant adenomas. Twelve (28%) patients had invasive tumours (i.e. Hardy grades D–E and/or III–IV). Preoperative medical treatment was given to 13 (30%) patients (somatostatin receptor analogue in 11 and dopamine agonists in 2). A primary debulking surgery was planned in three patients with extensive tumour invasion and circumferential extension around the carotid artery evident on the preoperative MR scan.

Endocrinological outcome

Postoperative remission rates by differing remission criteria are tabulated in Table 1. At last follow-up and using the 2010 consensus guidelines, surgical remission was achieved in 29 (67%) patients. This was unchanged when using the 2000 consensus guidelines. The surgical remission rate was higher (88%) when using the criteria described in the previous study from Manchester (GH nadir <1·7 μg/l; Lissett *et al.*[5]). On an 'intention to cure' basis, and after excluding the three patients in whom primary debulking surgery was planned, remission rate was achieved in 29 (73%) patients (Table 1). In total, six patients underwent early re-exploration for residual tumour at 2–4 weeks following the first operation and at final follow-up disease remission was achieved in three of these patients.

Table 1. Surgical remission rates for the present study group (2005–2010), according to different biochemical criteria and consensus guidelines

	Remission criteria	*n*	Patients in remission (%)
Lissett *et al.*[36]	GH nadir <1·7 μg/l	43	38 (88)
2000 Consensus guidelines[23]	GH nadir <1·0 μg/l and normal IGF-1	43	29 (67)
2010 Consensus guidelines[24]	GH nadir <0·4 μg/l and normal IGF-1	43	29 (67)
'Intention to Cure' by 2010 Consensus guidelines[24]	Patients for planned debulking surgery ($n = 3$) excluded	40	29 (73)

Figure 1 demonstrates the changes in surgeon numbers and remission rates for acromegaly between 1974 and 2010 in Manchester.

There was no significant difference in remission rates between micro (77%), macro (63%) and giant adenomas (67%; $P = 0{\cdot}7$; χ^2 test; Table 2). Invasive tumours demonstrated lower remission rates compared with noninvasive tumours, but this was not significant (50% *vs* 74%; $P = 0{\cdot}12$, χ^2 test; Table 2). There were trends towards higher remission rates in those patients with a preoperative GH nadir <10 μg/l (73% *vs* 54%) and preoperative IGF-1 <15 SD scores (72% *vs* 54%; Table 2), but these were not significant.

The differences in the mean pre- and postoperative GH nadir and IGF-1 values are tabulated in Table 3. Overall, there was a decrease in both the mean GH nadir and IGF-1 levels following transsphenoidal surgery ($P < 0{\cdot}01$; Repeated measures ANOVA; Table 3). All patients demonstrated a reduction in GH and IGF-1 levels postsurgery. In this respect, there was no significant difference between micro, macro and giant adenomas, which all

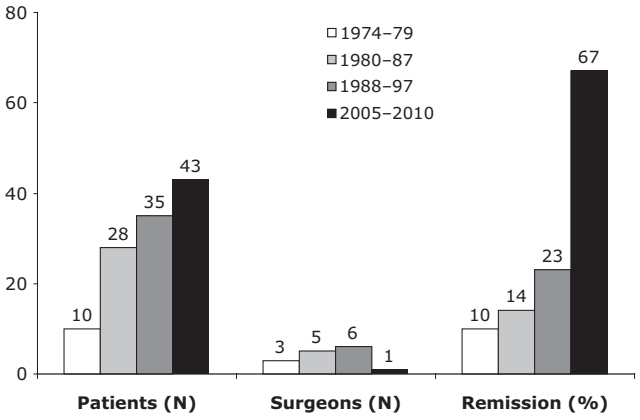

Fig. 1 Changes in remission rate for acromegaly in Manchester between 1974 and 2010. Results from current study (2005–2010; Remission according to 2010 consensus guidelines[24]) are compared with the previous study carried out in Manchester[36](Study period 1974–1997; Criteria for remission, GH nadir <1·7 μg/l).

Table 2. Surgical remission rates categorized by tumour size, invasiveness and preoperative GH nadir on oral glucose tolerance test and IGF-1 levels (χ^2 test)

	n	Remission by 2010 criteria (%)	*P*-value
Overall	43	29 (67)	
Tumour size			
Micro (<10 mm)	13	10 (77)	0·68
Macro (10–25 mm)	27	17 (63)	
Giant (>25 mm)	3	2 (67)	
Invasiveness			
Noninvasive (Hardy I–II, A–C)	31	23 (74)	0·12
Invasive (Hardy III–IV, D–E)	12	6 (50)	
Preoperative GH nadir (μg/l)			
<10·0	30	22 (73)	0·20
>10·0	13	7 (54)	
Preoperative IGF-1 (SD score)			
<15	29	21 (72)	0·24
>15	13	7 (54)	

SD, standard deviation.

demonstrated similar decreases in the overall mean GH nadir and IGF-1, pre- *vs* postoperatively (Table 2). Patients with invasive adenomas and those with persistent disease at final follow-up had higher mean IGF-1 ($P < 0{\cdot}05$; Repeated measures ANOVA; Table 3).

The differences between those patients receiving preoperative medical therapy prior to surgery ($n = 13$) and those not receiving any ($n = 30$) are tabulated in Table 4. There was a trend towards lower remission rates in those on preoperative medical therapy, but this was not significant (54% *vs* 73%; $P = 0{\cdot}2$, χ^2 test; Table 4). The two groups were similar with respect to the other parameters, with the exception of a larger number of patients undergoing planned debulking surgery in those on preoperative medical therapy (Table 4).

Patients not in remission

Persistent disease was seen in 14 (33%) patients as defined by the 2010 consensus criteria.[4] Of these, planned debulking surgery was performed in three patients because of extensive extra-sellar invasion, with circumferential extension around the carotid artery seen on preoperative imaging. In a further three patients in whom complete resection was planned, obvious tumour spread into the cavernous sinus and/or bony clivus was apparent intra-operatively. One of the patients with a noninvasive microadenoma but with persistent disease after surgery was later discovered to have familial acromegaly. Discordant biochemical results were seen in 4 (9%) patients with persistent disease. All four demonstrated an elevation of IGF-1 levels (SD scores ranged from 2·9 to 8), but with a GH nadir <0·4 μg/l, at last follow-up.

Adjuvant medical therapy was commenced for 12 of these patients with active disease (four medical and radiotherapy; eight medical therapy alone). In two clinically asymptomatic patients, serum levels of IGF-1 remained just above the normal ranges, and conservative treatment with serial GH and IGF-1 level checks was advocated by the treating endocrinologist.

Postoperative Complications

Five (11%) patients with an intact hypothalamic-pituitary axis prior to surgery demonstrated new onset hypopituitarism requiring replacement therapy, following surgery. Transient diabetes insipidus (DI) was experienced by 14 (32%) patients in the immediate postoperative period, and only 2 (5%) patients went on to develop permanent DI, requiring long-term desmopressin therapy.

Cerebrospinal fluid rhinorrhoea and subsequent meningitis developed in one patient following trans-sphenoidal surgery for

Table 3. Pre- and postoperative (at latest follow-up) levels of GH nadir on oral glucose tolerance test and IGF-1 as categorized by tumour size, invasiveness and persistence of disease postsurgery. Mean ± SD values are shown (Repeated measures ANOVA and *post hoc* Bonferroni test)

		GH nadir (μg/l)		IGF-1 (SD score)	
	n	Preoperative	Postoperative	Preoperative	Postoperative
Overall	43	8·6 ± 8	0·8 ± 2*	15·2 ± 6	2·5 ± 6*
Size					
Micro (<10 mm)	13	6·0 ± 5	0·4 ± 0·3*	12·2 ± 4	1·2 ± 3*
Macro (10–25 mm)	27	9·3 ± 8	0·9 ± 1·9*	16·6 ± 6	3·4 ± 7*
Giant (>25 mm)	3	14·4 ± 16	0·6 ± 0·9*	16·7 ± 5	1·0 ± 4*
Invasiveness					
Noninvasive (Hardy I–II, A–C)	31	7·8 ± 7	0·4 ± 0·5*	15·1 ± 6	1·2 ± 3*
Invasive (Hardy III–IV, D–E)	12	10·9 ± 11	1·8 ± 3*	15·8 ± 6	6·0 ± 9*[a]
Disease status					
Remission	29	7·7 ± 7	0·2 ± 0·1*	15·2 ± 7	0·2 ± 2*
Persistent	14	10·6 ± 11	1·8 ± 3*	15·5 ± 5	8·1 ± 7*[b]

SD, standard deviation.
*$P < 0{\cdot}01$ *vs* corresponding pre operative value; [a]$P<0{\cdot}05$ *vs* 'noninvasive' group; [b]$P<0{\cdot}05$ *vs* 'remission' group.

Table 4. Patient demographics and surgical outcome in patients stratified by preoperative medication use.

	Preoperative medications	
	No	Yes
n	30	13
Tumour size >1 cm	21 (70%)	9 (69%)
Invasive (Hardy III–IV, D–E)	9 (30%)	3 (23%)
Preoperative GH nadir (μg/l)	9·9 ± 9	5·8 ± 7
Preoperative IGF-1 (SD score)	16·0 ± 6	13·7 ± 5
Planned debulk	1 (3%)	2 (15%)
Remission (by 2010 guidelines)		
All ($n = 43$)	22 of 30 (73%)	7 of 13 (54%)*
Tumour size <1 cm ($n = 13$)	8 of 9 (89%)	2 of 4 (50%)
Tumour size >1 cm ($n = 30$)	14 of 21 (67%)	5 of 9 (56%)

SD, standard deviation.
*$P = 0{\cdot}2$; χ^2 test.

acromegaly. This was successfully treated with lumbar drainage and a course of intra-venous antibiotics. No neurological or vascular injury was noted in our patients. There was no perioperative mortality in our series.

Table 5 summarises the remission rates for some of the previously published studies and the criteria used to define disease remission in each study.

Discussion

The primary goal in treatment of acromegaly is restoration of the body's GH physiology to normal levels, with the long-term aim of avoiding the increased morbidity and mortality associated with uncontrolled serum GH levels. Surgical resection has been the first-line therapy in achieving these goals; however, in more recent times, medical therapy has been increasingly used as adjunctive or indeed primary therapy.[27]

In this study, spanning the 2005–2010 period, we attained an overall surgical remission rate of 67%. This is an improvement from our institution's previously published rate of 24%, over the period 1974–1997[5] (Fig. 1). This was despite the increasing stringency of the biochemical criteria defining disease remission for acromegaly, over the same period. Based on the criteria used in our previous study,[5] the remission rate would be higher still at 88%. Our current remission rate also compares favourably to the other large published series, employing both microscopic and endoscopic transsphenoidal approaches (Table 5). Such a transformation in surgical outcome cannot be entirely attributed to the introduction of endoscopic pituitary surgery in our unit. A number of other factors, not least the establishment of a specialist pituitary surgical practice, with a reduction in the number of surgeons performing pituitary surgery, advances in neuro-imaging, surgical and anaesthetic techniques are likely to have been important. The number of surgical acromegaly cases per year has also increased when compared with the previous study by our group.[26] This is in part because of an increase in the catchment area for our unit. The increased volume of cases and the expected increase in surgical experience may have also had a positive influence on the biochemical outcome.

Others have also reported a similar improvement in the remission rates for acromegaly surgery with a reduction in surgeon numbers.[23] Thus, another UK centre observed a near doubling of the remission rate from 33% to 64% with a concomitant reduction in surgeon numbers from 8 to 1.[28] Likewise, in a Japanese centre, the remission rate went up from 37% to 81% when all acromegaly surgeries were undertaken by a single surgeon instead of many.[29] Such subspecialization and consequent increase in surgical experience may have a positive influence on surgical outcome for acromegaly over time.[7] This is further supported by data from the UK acromegaly database that demonstrated an improvement in UK surgical results coinciding with a trend to concentrate pituitary surgery in the hands of a smaller number of specialists.[30] 'Operative learning curves' are also recognized for a variety of procedures in a number of surgical disciplines. We and others have also previously highlighted the existence of such an 'operative learning curve' for other outcome parameters in pituitary surgery such as visual recovery, operation time and complication rates.[26,31] This study further highlights the benefits of subspecialization and limiting surgeon numbers in pituitary surgery, especially for functioning pituitary tumours.

Surgical outcome in acromegaly is also reported to depend on a number of other factors, including tumour size.[7,24] Interestingly, we failed to observe a major difference in remission rates between micro, macro or giant adenomas (77–63%). This was surprising and contrary to other large published microscopic transsphenoidal surgical series that generally report improved outcomes for microadenomas (Table 5). Whilst this may in part reflect the relatively small numbers of patients in our study, our findings in this respect are consistent with a recent review of endocrine outcome in functioning tumours operated by endoscopic *vs* microscopic approaches.[32] Allowing for methodological discrepancies between studies, the author suggested better overall remission rates with the endoscopic than microscopic approach for macro-adenomas (67% *vs* 52%), but similar remission rates for microadenomas (85% *vs* 80%).[32] Similar observations were made for GH-, ACTH- and prolactin secreting tumours.[32] The improved optics of the modern endoscopes and the availability of 30–70° angled scope are said to provide superior visualization especially of the lateral and suprasellar recesses that are difficult to access directly with the microscopic approach.[32,33] Such improved visualization may help with greater tumour removal, especially for macroadenomas that are likely to extend outside the confines of the pituitary fossa and thus not directly visualized with the microscopic approach.[32,33] However, for microadenomas that are invariably located within the pituitary fossa, the endoscope may not carry a similar advantage with respect to visualization over the microscope.

In this study, we also observed trends towards reduced remission rates with adenomas that were radiologically graded to be invasive (i.e. Hardy grades III/IV,D/E) and those with a preoperative GH nadir more than 10 μg/l or an IGF-1 SD score more than 15. Others have also reported similar observations, although these are not universal findings.[19,34] Variability in these factors may also account for some of the differences apparent in the remission rates between

Table 5. Table summarizing the remission rates for selected studies on surgical outcome in patients with acromegaly, using varying remission criteria: 2000 consensus guidelines (GH nadir <1·0 μg/l and normalization of age-/sex-matched IGF-1); 2010 consensus guidelines (GH nadir <0·4 μg/l, plus normalization of age-/sex-matched IGF-1

Study	No of cases	Remission rate (%); (micro/macro)	Operative approach	Criteria for cure	Number of surgeons	Comments
Fahlbusch *et al.*[8]	396	58 (68/54)	Microscopic	oGTT GH nadir <2·0 μg/l	3	Octreotide pretreatment in large/ invasive tumours
Lissett *et al.*[5]	73	24 (59/14)	Microscopic	oGTT GH nadir <1·7 μg/l	9	Preoperative GH level >10 μg/l negatively predictive of outcome
Abosch *et al.*[6]	254	76	Microscopic	GH approximately 5 μg/l	1	
Ahmed *et al.*[7]	139	67 (91/60)	Microscopic	GH <1·7 μg/l	1	Improved outcomes with increased surgical experience
Freda *et al.*[12]	99	61 (88/53)	Microscopic	oGTT GH nadir <2·0 μg/l; and/or normal IGF-1	Not stated	26% invasive
Shimon *et al.*[20]	91	74 (84/64)	Microscopic	oGTT GH nadir <2·0 μg/l; and/or normal IGF-1	1	Improved outcome with random preoperative GH <50 ng/ml. Giant adenoma(>20 mm) remission rate was 20%
Kabil *et al.*[14]	48	85	Endoscopic	Normal postoperative IGF-1	1	
De *et al.*[23]	90	63 (79/56)	Microscopic	2000 consensus	3	Improved remission rates with dedicated pituitary neurosurgeon
Beauregard *et al.*[11]	99	63 (82/60)	Microscopic	2000 consensus	1	Long-term remission rate (>10 years) 52%
Kreutzer *et al.*[21]	57	70	Microscopic	2000 consensus	1	Extra-sellar growth, dural invasion, co-secreting adenomas (GH/PRL) had poorer outcomes
Trepp *et al.*[17]	69	42 (80/39)	Microscopic	2000 consensus	1	
Nomikos *et al.*[9]	506	57 (75/50)	Microscopic	2000 consensus	Not stated	Transcranial (5%) and redo (21%) surgeries had lower remission rate. Recurrence rate over 10 years = 0·4%
Kim *et al.*[18]	42	64 (67/60)	Microscopic	2000 consensus	Not stated	Invasive tumours had 30% remission rate
Bourdelot *et al.*[22]	189	49	Microscopic	2000 consensus	Multiple	Preoperative IGF-1 level negatively predictive of outcome
Gondim *et al.*[15]	67	75 (86/72)	Endoscopic	2000 consensus	1	Adenomas with large cavernous sinus invasion excluded
Campbell *et al.*[16]	26	58 (75/55)	Endoscopic	2000 consensus	2	Tumour volume and invasiveness predictive of outcome
Hofstetter *et al.*[19]	24	46 (75/42)	Endoscopic	2010 consensus	Not stated	Smaller tumour volume positively predictive of outcome
Present study	43	67 (77/63)	Endoscopic	2010 consensus	1	Excluded patients previously operated on

oGTT, oral glucose tolerance test.

previous studies (Table 5). Cavernous sinus invasion occurs in around 6–10% of all pituitary adenomas.[16] Whilst endoscopic techniques continue to evolve, enabling better visualization and resective strategies within the cavernous sinus, it remains a difficult area to access. Even with aggressive surgical approaches, remission rates for GH-secreting adenomas are modest with a significant risk of major blood loss and carotid artery injury.[35] In these circumstances, consideration should be given to the use of adjuvant medical therapy and focused radiotherapy following surgical debulking.

A significant proportion of our study cohort (30%) was treated with primary medical therapy prior to referral for surgery. There was a lower remission rate in these patients, although this was not significant (54% *vs* 73%). Although the numbers of patients involved are relatively small, both groups were reasonable well matched in terms of tumour size, invasiveness and preoperative biochemical results. In our cohort of medically treated patients with acromegaly, referral for surgical intervention was also usually made following failure of primary medical therapy,

suggesting that this subgroup may represent a more aggressive and invasive subtype of GH-secreting adenomas. These factors may partly account for the inferior surgical outcome noted in the medically treated sub-group. Previous studies have reported conflicting results with regards the benefits of preoperative medical therapy on surgical outcome in acromegaly.[36,37] In a small randomized study, improvement in surgical remission rates following 6 months pretreatment with octreotide was noted for acromegaly patients with macroadenomas.[36] However, in this study, the overall remission rates from surgical intervention were low (30%), and curiously the remission rate in patients with micro-adenoma was lower after octreotide pretreatment.[36] Shrinkage of adenomas is also reported in 30–50% of cases treated with primary medical therapy.[37] It has also been suggested that the process of tumour shrinkage and subsequent fibrosis may render surgery more difficult. However, this view is not universally held and is likely to be difficult to demonstrate in a comparative study.[3]

It is also important to consider surgical morbidity in pursuing biochemical remission in acromegaly. In this study, we observed that 11% of patients developed new onset hypopituitarism and one patient suffered postoperative CSF rhinorrhoea and meningitis. These rates are largely comparable to published literature, although the risk of permanent DI (5%) was marginally higher.[32] A more aggressive surgical resection strategy may improve the likelihood of achieving disease remission, but at the expense of increased risk of disturbing normal pituitary function and other surgical complications. Whilst these endocrine deficiencies are medically manageable, care must be taken to consider the risk-benefit profile of aggressive surgical resection strategies.

Conclusions

We observed improved surgical outcomes for acromegaly following the establishment of a specialist pituitary surgical service with reduction in surgeon numbers. Endoscopic trans-sphenoidal surgery is an effective first-line treatment for achieving biochemical remission in acromegaly patients. As the criteria for biochemical remission continues to evolve, the remission rates following surgery may reduce further. Thus careful patient selection with considered use of adjuvant medical and radiotherapy, particularly in cases where the chance of surgical success may be low, should be the appropriate way forward.

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Disclosure

The authors report no conflict of interest concerning the materials used in this study or the findings specified in this article.

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