Pituitary (2017) 20:76–83
DOI 10.1007/s11102-016-0765-7

The surgical treatment of acromegaly

Michael Buchfelder[1] · Sven-Martin Schlaffer[1]

Published online: 21 October 2016

Abstract

Purpose Surgical extraction of as much tumour mass as possible is considered the first step of treatment in acromegaly in many centers. In this article the potential benefits, disadvantages and limitations of operative acromegaly treatment are reviewed.

Methods Pertinent literature was selected to provide a review covering current indications, techniques and results of operations for acromegaly.

Results The rapid reduction of tumour volume is an asset of surgery. To date, in almost all patients, minimally invasive, transsphenoidal microscopic or endoscopic approaches are employed. Whether a curative approach is feasible or a debulking procedure is planned, can be anticipated on the basis of preoperative magnetic resonance imaging. The radicality of adenoma resection essentially depends on localization, size and invasive character of the tumour. The normalization rates of growth hormone and IGF-1 secretion, respectively, depend on tumour-related factors such as size, extension, the presence or absence of invasion and the magnitude of IGF-1 and growth hormone oversecretion. However, also surgeon-related factors such as experience and patient load of the centers have been shown to strongly affect surgical results and the rate of complications. As compared to most medical treatments, surgery is relatively cheap since the costs occur only once and not repeatedly. There are several new technical gadgets which aid in the surgical procedure: navigation and variants of intraoperative imaging.

Conclusions For the mentioned reasons, current algorithms of acromegaly management suggest an initial operation, unless the patients are unfit for surgery, refuse an operation or only an unsatisfactory resection is anticipated. A few suggestions are made when a re-operation could be considered.

Keywords Transsphenoidal surgery · Operation · Pituitary tumour · Acromegaly · Debulking · Complications

Introduction

The operative treatment of pituitary adenomas causing acromegaly is a widely accepted first line standard therapy [1–3]. The pertinent algorithms developed in consensus conferences or by scientific societies suggest surgery as a first procedure for most patients. After all, the mechanical extraction of growth hormone-secreting tumour tissue acts rapidly and leads to normal biochemical parameters in the majority of the patients who undergo initial surgery. Standard treatment implies the attempt to most aggressively resect the tumoural tissue selectively, by identifying and preserving the normal pituitary gland in an attempt of reaching remission of acromegaly without sacrificing pituitary function [4–6]. This is most easily achieved during transsphenoidal operations, which allow direct visualization of normal and pathological tissues.

To date, more than 95 % of patients operated upon for acromegaly undergo transsphenoidal surgery [4, 7, 8]. The biochemical parameters used to define remission changed over time [9, 10] and became more stringent. Nevertheless, with development of surgical techniques, improved imaging and visualization techniques, accumulated experience and interdisciplinary co-operations one gets the impression

✉ Michael Buchfelder
michael.buchfelder@uk-erlangen.de

[1] Department of Neurosurgery, University Hospital Erlangen, Schwabachanlage 6, 91054 Erlangen, Germany

that the amount of tumour tissue resected during the operations and the rate of “normal” growth hormone and IGF-1 levels achieved, increased considerably.

Surgical techniques

As already mentioned, the vast majority of pituitary tumour operations in patients with acromegaly are to date performed by the transsphenoidal approach [4]. There are many variations possible, which start with the positioning of the patient. While some surgeons, like us, prefer to operate on a patient in supine position with the head slightly extended, others favor a semi-sitting position, thus facing the patient [6, 7, 11]. Some surgeons still use an image intensifier for navigation purposes; others prefer the routine use of neuronavigation. This operation can be performed with and without dissection of the nasal septal mucosa. Dissection of a submucosal tunnel is mostly performed following a medial nasal incision. A nasal speculum keeps the mucosal tunnel open. At this stage, the operating microscope is usually brought into place. The vomer is used as a midline orientation. A sphenoidotomy is performed. Septations of the sphenoid sinus are resected so one has an unobstructed visualization of the sellar floor through the sphenoid sinus (transsphenoidal). In patients with incomplete pneumatisation of the sphenoid sinus, extensive drilling is required to expose the posterior basal surface of the tumour. Thereafter, the basal dura of the sella is incised. Frequently soft tumours produce spontaneously through the dural opening. Variously shaped curettes and microforceps are available for tumour extraction. The normal pituitary, which is often deformed and compressed against the cavernous sinus or into the posterior portion of the fossa is identified and every possible attempt is made to preserve it.

The extent of tumour resection is estimated by inspection and palpation of the tumour cavity. Frequently the arachnoid that covers the superior surface of the tumour decends into the intrasellar space. It has a smooth surface and can thus be easily recognized. However, whenever it descends in several folds, each of them has to be probed separately since tumour may be hidden within the pouches. Generally speaking, the wider the connection between intra- and extra-sellar tumour portions, the easier is the resection of a large adenoma [11, 12].

Invasive nature of a tumour restricts its resectability. Localized invasion, may be dealt with by resection of the invaded mucosa of the sphenoid sinus and drilling invaded bone of the skull base. Parasellar tumour is usually traced along the perforations that have been created by the tumour. Tumour, that is located lateral from the carotid artery can usually not be resected. The term “enlarged adenomectomy” refers to a small layer of normal gland (“periadenoma”), that is resected around the adenoma. The most perfect overview of an adenoma cavity after selective adenomectomy is usually achieved in microadenomas and moderately sized macroadenomas.

Even with utmost experience and optimal technical equipment there are still pituitary adenomas that cannot be resected completely. Mirrors and particularly endoscopes allow improved visualization of tumour portions, particularly those localized outside of the midline. There are several methods to reconstruct the sellar floor by implants. Many neurosurgeons apply a regimen of external lumbar CSF drainage for a few days in case of intraoperative CSF leaks. Often a nasal tamponade is required [4, 7].

As an increasingly frequently practiced variant, a direct peri-nasal approach to the sphenoid sinus can be chosen. In this case the speculum is guided by radiofluoroscopic control or navigation techniques to the rostrum. Mucosal incision and sphenoidotomy are then performed just in front of the vomer. The operation is then continued as just described [11]. Endoscopic transsphenoidal surgeons use this direct peri-nasal approach and do not need a nasal speculum [5]. There are technical advantages and disadvantages of endoscopic versus microsurgical techniques [5, 13, 14] Still, many data, particularly on the long-term follow-up results largely derive from microsurgery series, in some of which the endoscopy was additionally utilized when the surgeon felt that it could be useful [8]

Extrasellar tumour extension of the adenoma is no more a contraindication for transsphenoidal surgery. With the extended transsphenoidal approaches, which imply opening to the tuberculum sellae or drilling through the clivus, tumour location and extensions, which in the past presented contraindications for transsphenoidal surgery, can to date also be treated via the nasal route. Unfortunately, one of the disadvanteges of the extended transsphenoidal approach is a high frequency of postoperative CSF leaks [5].

In certainly less than 10 % of patients who harbour tumours with extreme asymmetrical intracranial extension which have a poor communication with intrasellar portions, still transcranial approaches are needed to reduce the tumour mass [7, 8, 15, 16]. Mostly, frontal or fronto-temporal, basal craniotomies are used. The tumour tissue is dissected under direct vision from the arachnoid layers of the basal cisterns, blood vessels, cranial nerves and the infundibulum. It is not only much more difficult to preserve pituitary tissue and function but also to resect a tumour completely during transcranial surgery [15].

Surgical results

Expert neurosurgical centers with a high degree of focus on pituitary diseases reach normalization rates between 75 and 90 % in growth hormone-secreting pituitary microadenomas

Table 1 Results of transsphenoidal surgery for GH-secreting pituitary adenomas using current criteria for remission [2, 9, 10]

Author	Year	Endcrinological remission in (%)					
		n	Overall	Micro	Macro	Remission criteria	Technique
Kaltsas et al. [51]	2001	67	34	59	26	Normal IGF-I, OGTT < 1 ng/ml	Microscope
Shimon et al. [52]	2001	88	74	84	64	Normal IGF-I, OGTT < 1 ng/ml	Microscope
Kreutzer et al. [53]	2001	57	70			Normal IGF-I, OGTT < 1 ng/ml	Microscope
Cappabianca et al.	2002	36	64	83	60	Normal IGF-I, OGTT < 1 ng/ml	Endoscope
De et al. [54]	2003	90	63	79	56	Normal IGF-I, OGTT < 1 ng/ml	Microscope
Beauregard et al. [55]	2003	103	52	82	47	Normal IGF-I, OGTT < 1 ng/ml	Microscope
Esposito et al. [56]	2004	67	57	77	52	Normal IGF-I, OGTT < 1 ng/ml	Microscope
Trepp et al. [57]	2005	69	42	80	39	Normal IGF-I, OGTT < 1 ng/ml	Microscope
Nomikos et al. [8]	2005	506	57	75	50	Normal IGF-I, OGTT < 1 ng/ml	Microscope
Kabil et al. [58]	2005	48	85	100	80		Endoscope
Rudnik et al. [58]	2005	12	73				Endoscope
Ludecke and Abe [59]	2006	147	72	95	68	Normal IGF-I, OGTT < 1 ng/ml	Microscope
Frank et al. [60]	2006	83	70	83	65		Endoscope
Dehdashti et al. [61]	2008	34	71	83	65	Normal IGF-I, OGTT < 1 ng/ml	Endoscope
Kim et al. [62]	2009	42	64	67	60	Normal IGF-I, OGTT < 1 ng/ml	Microscope
Tabaee et al. [63]	2009	6	73			Normal IGF-I, OGTT < 1 ng/ml	Endoscope
Yano et al. [64]	2009	31	71			Normal IGF-I, OGTT < 1 ng/ml	Endoscope
Hofstetter et al. [65]	2010	24	38			Normal IGF-I, OGTT < 0.4 or random GH < 1 ng/ml	Endoscope
Gondim et al. [66]	2010	67	75	86	72	Normal IGF-I, OGTT < 1 ng/ml	Endoscope
Campbell et al. [67]	2010	26	58	75	55	Normal IGF-I, OGTT < 1 ng/ml	Endoscope
Jane et al. [17]	2011	60	70	100	61	Normal IGF-I, OGTT < 0.4 or random GH < 1 ng/ml	Endoscope
Wang et al. [68]	2012	43	67	77	63	Normal IGF-I, OGTT < 0.4 or random GH < 1 ng/ml	Endoscope
Starke et al. [22]	2013	43	70	82	66	Normal IGF-I, OGTT < 0.4 or random GH < 1 ng/ml	Microscope
Starke et al. [22]	2013	72	71	88	66	Normal IGF-I, OGTT < 0.4 or random GH < 1 ng/ml	Endoscope
Shin et al. [69]	2013	53	49	83	46	Normal IGF-I, OGTT < 0.4 or random GH < 1 ng/ml	Endoscope
Hazer et al. [70]	2013	214	63	63	63	Normal IGF-I, OGTT < 0.4 or random GH < 1 ng/ml	Endoscope
Yildirim et all [71]	2014	56	66	80	67	Normal IGF-I, OGTT < 0.4 or random GH < 1 ng/ml	Endoscope
Fathalla et al. [23]	2015	41	45			Normal IGF-I, OGTT < 0.4 or random GH < 1 ng/ml	Endoscope
Fathalla et al. [23]	2015	23	34			Normal IGF-I, OGTT < 0.4 or random GH < 1 ng/ml	Microscope
Netuka et al. [50]	2016	105	61	75	58	Normal IGF-I, OGTT < 0.4 or random GH < 1 ng/mlv	Endoscope
Overall		2313	62	81	59		

A tabular survey of selected literature

and some 45–70 % in pituitary macroadenomas. In most papers there is no distinction between patients with acromegaly and gigantism. Table 1 provides an overview on a selection of surgical series published between 2000 and 2016. The individual results between the centers are difficult to compare, since the selection of which patient is going to be operated and which one will be exposed to primary medical therapy is not homogenously performed.

There are unequivocal prognostic factors such as the size of the tumour, the magnitude of preoperative GH and, respectively, IGF-1 oversecretion. One extremely important factor is whether the tumour harbors an invasive growth pattern, particularly as the cavernous sinus is concerned [17–19]. The degree of parasellar extension can be assessed by preoperative magnetic resonance imaging (Fig. 1).

However, the frequently employed Knosp classification correlates imaging findings with the percent likelihood of invasion [20, 21]. Generally speaking, once there is massive invasion, the long-term surgical normalization rate approaches zero. A normal postoperative MRI is usually considered a prerequisite for surgical normalization (Fig. 2), but in a few cases persistent tumour has been documented by imaging, with biochemical normalization according to strict criteria. These are, according to the Endocrine Society Practice Guidelines, proposed such as a random GH below 1 ng/ml, suppression to below 0.4 ng/ml, also associated with a normal IGF-1 [2]. Microscopic and endoscopic transsphenoidal operations produced similar results [22, 23]. In one center, a direct comparison between an experienced microsurgeon and an experienced

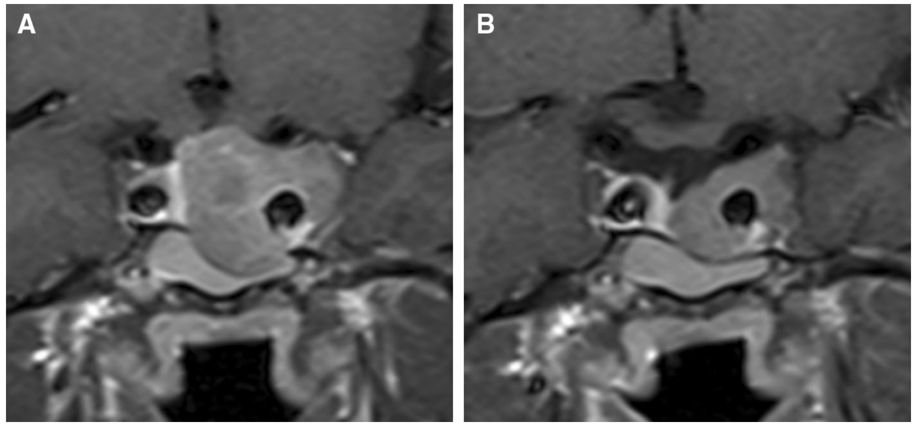

Fig. 1 Invasive pituitary macroadenoma of the left cavernous sinus and encasement of the carotid artery (Knosp Grade IV) in a 41-year-old male patient in coronal T1-weightes MRI sections. The large tumoru (**a**) is decreased in size (**b**) but invasive portions remained. Preoperative GH dropped from 12.9 to 3.3 ng/ml 3 months postoperatively and IGF-levels were decreased from 781 to 535 ng/ml

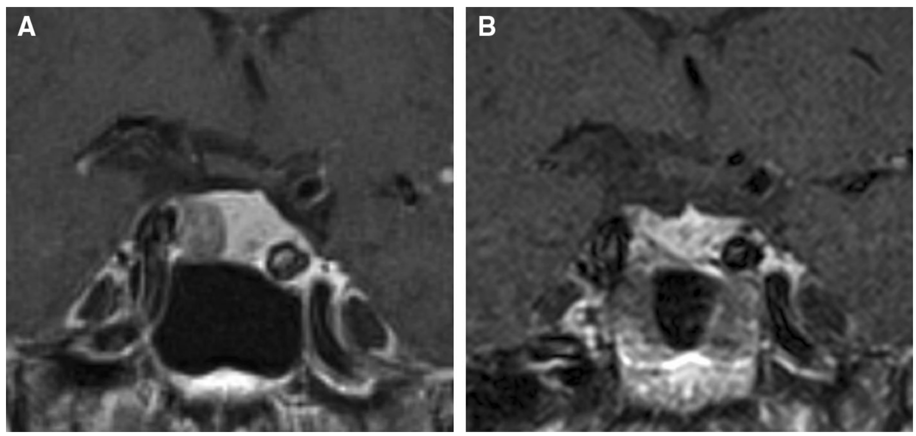

Fig. 2 68-year-old female patient presenting with a non-invasive 9 mm large microadenoma adjacent to the right cavernous sinus depicted in coronal T1-weighted MRI (**a**). Postoperatively there is no more tumour visible (**b**). GH-(0.33 ng/m) and IGF-1-levels (127 ng/ml) respectively were normalized

endoscopic surgeon revealed no differences in remission and complication rates, respectively [22]. The assay variabilities between different GH and IGF-1 determinations raise some concern in this connection [24]. Moreover, the excellent results published from a few expert centers are not to be expected in each and any place across a country. An analysis of the British Acromegaly Registry revealed enormous differences in the remission rate reached in 26 different neurosurgical departments [25]. Patient numbers varies from 3 to 79. The rate of normal IGF-1 postoperatively, as determined at least 3 months after the operation ranged from 0 % in one center to 68 % in another one and averaged 39 %. Likewise the complications rates seem to strongly correlate with the experience of the surgeon and the patient load of the neurosurgical center [16, 26, 27]

Socio-economic considerations

Surgery is an ablative procedure and thus, treatment costs usually occur only once, whereas medical treatments are associated with continuous expenses over the lifetime of the patient. The costs for treatment are thus relatively low and the remission rate is high, particularly in experienced, specialized reference centers. Germany, to date (in 2016), the reimbursement for either transsphenoidal or transcranial surgery, unless this is associated with complications, is 7895 € [28], whereas an annual treatment with octreotide LAR (30 mg/every 4 weeks) costs 33.099 €, lanreotide LAR (120 mg/every 4 weeks). pasireotide LAR (60 mg/4 weeks) 62.745 € and pegvisomant (30 mg daily) 109.950 € [29].

Financially considered, the health system of a country saves a lot of money, particularly of the remission rate of the surgical centers is high, the complication rate is low and if young patients are treated surgically, of whom most do need long-term expensive medical treatments. Resources are needed for these who require combined treatments. In one hypothetical calculation performed in the United States, the savings for one 40 year-old patient with a pituitary microadenoma and a life expectancy of 78 years, amount to 2.5 million US$ [30].

Debulking

Debulking denotes surgery in a patient in whom a biochemical remission of acromegaly is not expected for that the tumour harbors features that would prevent total excision. Parasellar encasement of the carotid artery, giant size and excessively increased growth hormone levels are all unfavorable prognostic parameters. Since normalization is not expected after the operation, postoperative therapies are required. The rationale of debulking is, that one can expect a better out-come in response to subsequent medical treatments after an operation that has been successful at lowering GH levels, even if not to normal levels, by removing some or most of the pituitary tumour mass [31].

The studies which are available in the medical literature which have compared the efficacies of preoperative and postoperative medical treatment with somatostatin analogs have convincingly shown the value of debulking. After surgery, in all four studies, the rate of patients achieving remission of the disease by (*in some studies identical*) drug treatments were significantly improved [32–35]. The finding that percent reduction of growth hormone levels correlates closely with percent resected tumour volume in acromegaly also supports the value of debulking surgery [36].

Reoperations

In contrast to the initial management of an acromegalic patient, reoperations do not have a fixed place in the treatment algorithms [2]. There are several scenarios (Fig. 3), in which reoperations can be considered, such as an unsatisfactory amount of tumour resection when a much more complete excision was to be expected on the basis of preoperative imaging. Tumour progression or the failure to achieve a remission under medical treatments are other indication for redo procedures. Furthermore, one could imagine that it makes sense to reduce a tumour's volume to make it suitable for treatments in which size restrictions exist, e.g. radiosurgery.

Scarring resulting from the previous operation, tissue defects which cause a distortion of the anatomy, partial cisternal herniation and other postoperative sequelae make a reoperation technically more difficult and challenging. The results are generally less favourable than in primary operations and the rate of some complications is definitely increased in pituitary tumour reoperations [37–39].

Preoperative medical therapy

The issue of preoperative medical therapy before surgery is still a matter of controversy, at least if a potential improvement of the surgical results is considered. Most neurosurgeons would agree that primary medical therapy as a pretreatment can improve the clinical condition of an acromegalic patient who is severely affected by the potential comorbidity. Whether the normalization rates by surgery are affected by pretreatment with somatostatin analogs is another issue. Whereas some authors [40, 41] find no positive effect on such pretreatments, others claim an improvement of surgical normalization rates [4, 42–44].

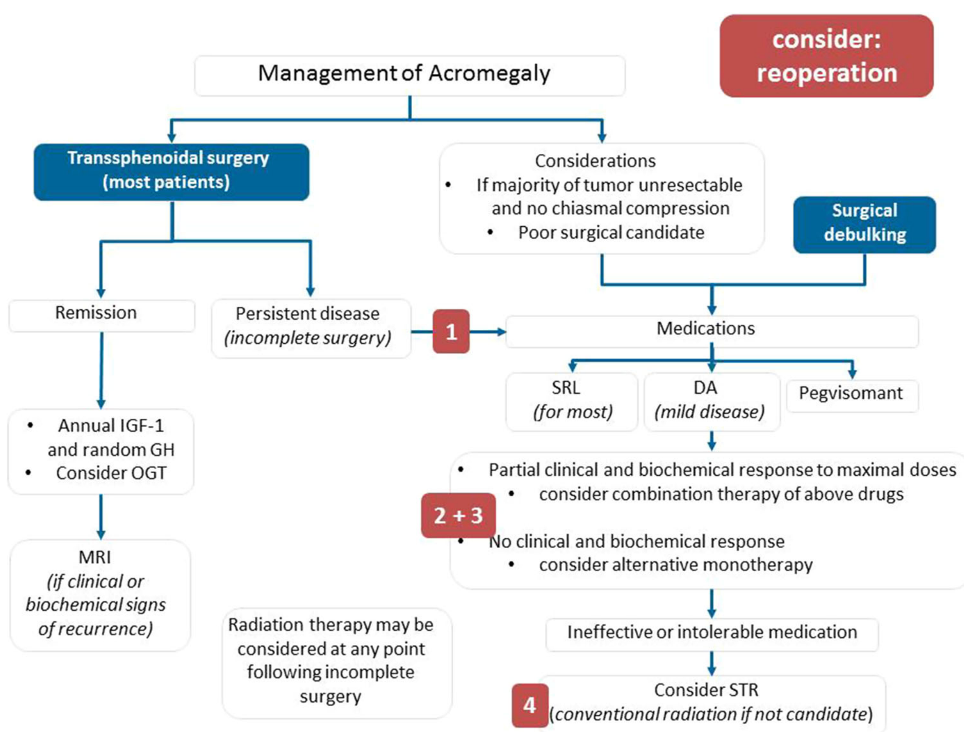

Fig. 3 Modified algorithm of the Endocrine Society's Clinical Practiceguidelines according to Katznelson et al. [2] with the author's suggestions in which a re-operation may be considered: *1* if a non-invasive remnant is visible on post-op MRI-scan, *2* to enhance the effect of medical therapy by further debulking, *3* debulking procedure when residual adenoma is increasing in size during medial therapy, *4* ability to apply radiosurgery instead of conventional radiotherapy by further debulking of residual adenoma

It is conspicuous that the groups who found a difference had surprisingly low remission rates in their cohorts of non-pretreated patients which ranged from 18 to 24 % and thus achieved much worse results that the average recorded from 26 centers in Great Britain in a study which has been already quotes above [25].

We know from morphological studies that the visible effects of somatostatin analog treatment on adenoma tissue in acromegaly are minor [45]. Moreover, at least in one study, the finding of improved results was only found 3 months after the operation and no more maintained after 1 year [44]. Thus, in summary, a definitive conclusion as to the usefulness of preoperative treatment with somatostatin analogs is lacking, let alone an appreciation of the effects of dopamine agonist or pegvisomant treatment where as yet there are no data.

Intraoperative imaging

The imaging method of choice for pituitary lesions is magnetic resonance scanning, since it has the best soft tissue contrast. For some time intraoperative MRI became available which allowed to objectively assess the radicality of tumour extraction. Studies in non-functioning pituitary adenomas showed in increased rate of total tumour resections and also a convincing increase in the amount of tumour tissue extracted [46]. When residual tumour was depicted the surgeon could trace and try to remove it, since the patient remained in the operating theatre.

Only a few series with application of intraoperative MR imaging in acromegaly are reported. Fahlbusch et al. [47] improved the amount of adenoma resection in 5 out of an unfavourable cohort of 23 patients using a 1.5T high field system. However, in only two of these radical resection was accomplished. Bellut et al. [48] performed 39 operations in 39 acromegalic patients, using a low field 0.15T system. Intraoperative MRI revealed residual tumour in eight patients, but only two of these achieved a biochemical remission. Tanei et al. [49] treated seven patients with acromegaly and achieved a remission in six of these. In three of these six patients, residual adenoma tissue was identified in the basis of intraoperative MRI and resected in the second step of the operation. In the most recent study, Netuka et al. [50] operated a total of 105 patients with acromegaly with a total remission rate of 60.9 % in their 3T intraoperative MRI suite. There were 16 microadenomas and 89 macroadenomas. Re-resection on the basis of intraoperative MRI were performed in 22 patients, of whom 9 had normal GH and IGF-1 levels postoperatively. Thus, in all of these investigations in patients with acromegaly, an improvement in the surgical results was achieved. The benefit was pronounced in some and only slight in other series.

Moreover there are many other technical supports and gadgets available which help the surgeon in individual situations which details discussion was performed elsewhere [41].

Conclusion

After a long evolution of finding indications, development of appropriate surgical techniques and perioperative managements, particularly the transsphenoidal operation in acromegaly is to date a safe, relatively inexpensive and efficient treatment option. There is a huge bunch of medical literature supporting its place and value. Thus, it is not surprising that its use is frequently recommended as the first step of treatment by expert conferences and management recommendations. It is, however, important to realize that the excellent results and safety data published by expert centers cannot be expected in each and any place across any country.

References

1. Katznelson L, Atkinson JL, Cook DM, Ezzat SZ, Hamrahian AH, Miller KK (2011) American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly–2011 update: executive summary. Endocrine Pract 17(4):636–646
2. Katznelson L, Laws ER Jr, Melmed S, Molitch ME, Murad MH, Utz A, Wass JA (2014) Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 99(11):3933–3951
3. Melmed S, Casanueva FF, Cavagnini F, Chanson P, Frohman L, Grossman A, Ho K, Kleinberg D, Lamberts S, Laws E, Lombardi G, Vance ML, Werder KV, Wass J, Giustina A (2002) Guidelines for acromegaly management. J Clin Endocrinol Metab 87(9):4054–4058
4. Buchfelder M, Schlaffer S (2009) Surgical treatment of pituitary tumours. Best practice & research. Clin Endocrinol Metab 23(5):677–692
5. Cappabianca P, Cavallo LM, de Divitiis E (2004) Endoscopic endonasal transsphenoidal surgery. Neurosurgery 55(4):933–940 **discussion 940-931**
6. Hardy J (1969) Transphenoidal microsurgery of the normal and pathological pituitary. Clin Neurosurg 16:185–217
7. Couldwell WT (2004) Transsphenoidal and transcranial surgery for pituitary adenomas. J Neurooncol 69(1–3):237–256
8. Nomikos P, Buchfelder M, Fahlbusch R (2005) The outcome of surgery in 668 patients with acromegaly using current criteria of biochemical 'cure'. Eur J Endocrinol 152(3):379–387
9. Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, Von Werder K, Melmed S (2000) Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab 85(2):526–529

10. Giustina A, Chanson P, Bronstein MD, Klibanski A, Lamberts S, Casanueva FF, Trainer P, Ghigo E, Ho K, Melmed S (2010) A consensus on criteria for cure of acromegaly. J Clin Endocrinol Metab 95(7):3141–3148
11. Buchfelder M, Fahlbusch R (2002) The "classic" transsphenoidal approach for resection of pituitary tumors. Oper Techn Neurosurg 5(4):210–217
12. Buchfelder M (2005) Treatment of pituitary tumors: surgery. Endocrine 28(1):67–75
13. Rudnik A, Kos-Kudla B, Larysz D, Zawadzki T, Bazowski P (2007) Endoscopic transsphenoidal treatment of hormonally active pituitary adenomas. Neuro Endocrinol Lett 28(4):438–444
14. Mortini P (2014) Cons: endoscopic endonasal transsphenoidal pituitary surgery is not superior to microscopic transsphenoidal surgery for pituitary adenomas. Endocrine 47(2):415–420
15. Fahlbusch R, Honegger J, Buchfelder M (1992) Surgical management of acromegaly. Endocrinol Metab Clin N Am 21(3):669–692
16. Mortini P, Losa M, Barzaghi R, Boari N, Giovanelli M (2005) Results of transsphenoidal surgery in a large series of patients with pituitary adenoma. Neurosurgery 56(6):1222–1233 **discussion 1233**
17. Jane JA Jr, Starke RM, Elzoghby MA, Reames DL, Payne SC, Thorner MO, Marshall JC, Laws ER Jr, Vance ML (2011) Endoscopic transsphenoidal surgery for acromegaly: remission using modern criteria, complications, and predictors of outcome. J Clin Endocrinol Metab 96(9):2732–2740
18. Rajasoorya C, Holdaway IM, Wrightson P, Scott DJ, Ibbertson HK (1994) Determinants of clinical outcome and survival in acromegaly. Clin Endocrinol 41(1):95–102
19. Swearingen B, Barker FG 2nd, Katznelson L, Biller BM, Grinspoon S, Klibanski A, Moayeri N, Black PM, Zervas NT (1998) Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. J Clin Endocrinol Metab 83(10):3419–3426
20. Knosp E, Steiner E, Kitz K, Matula C (1993) Pituitary adenomas with invasion of the cavernous sinus space: a magnetic resonance imaging classification compared with surgical findings. Neurosurgery 33(4):610–617 **discussion 617–618**
21. Micko AS, Wohrer A, Wolfsberger S, Knosp E (2015) Invasion of the cavernous sinus space in pituitary adenomas: endoscopic verification and its correlation with an MRI-based classification. J Neurosurg 122(4):803–811
22. Starke RM, Raper DM, Payne SC, Vance ML, Oldfield EH, Jane JA Jr (2013) Endoscopic vs microsurgical transsphenoidal surgery for acromegaly: outcomes in a concurrent series of patients using modern criteria for remission. J Clin Endocrinol Metab 98(8):3190–3198
23. Fathalla H, Cusimano MD, Di Ieva A, Lee J, Alsharif O, Goguen J, Zhang S, Smyth H (2015) Endoscopic versus microscopic approach for surgical treatment of acromegaly. Neurosurg Rev 38(3):541–548 **discussion 548–549**
24. Junnila RK, Strasburger CJ, Bidlingmaier M (2015) Pitfalls of insulin-like growth factor-i and growth hormone assays. Endocrinol Metab Clin N Am 44(1):27–34
25. Bates PR, Carson MN, Trainer PJ, Wass JA, Group, U.K.N.A.R.S. (2008) Wide variation in surgical outcomes for acromegaly in the UK. Clin Endocrinol 68(1):136–142
26. Barker FG 2nd, Klibanski A, Swearingen B (2003) Transsphenoidal surgery for pituitary tumors in the United States, 1996–2000: mortality, morbidity, and the effects of hospital and surgeon volume. J Clin Endocrinol Metab 88(10):4709–4719
27. Clayton RN, Stewart PM, Shalet SM, Wass JA (1999) Pituitary surgery for acromegaly. Should be done by specialists. BMJ 319(7210):588–589
28. Institut für das Entgeltsystem im Krankenhaus (2016) G-DRG-Fallpauschalen-Katalog
29. Rote Liste Service GmbH (2016) ROTE LISTE 2016. Rote Liste Service GmbH, Frankfurt (Main)
30. Marko NF, LaSota E, Hamrahian AH, Weil RJ (2012) Comparative effectiveness review of treatment options for pituitary microadenomas in acromegaly. J Neurosurg 117(3):522–538
31. Wass J (2005) Debulking of pituitary adenomas improves hormonal control of acromegaly by somatostatin analogues. Eur J Endocrinol 152(5):693–694
32. Colao A, Attanasio R, Pivonello R, Cappabianca P, Cavallo LM, Lasio G, Lodrini A, Lombardi G, Cozzi R (2006) Partial surgical removal of growth hormone-secreting pituitary tumors enhances the response to somatostatin analogs in acromegaly. J Clin Endocrinol Metab 91(1):85–92
33. Jallad RS, Musolino NR, Kodaira S, Cescato VA, Bronstein MD (2007) Does partial surgical tumour removal influence the response to octreotide-LAR in acromegalic patients previously resistant to the somatostatin analogue? Clin Endocrinol 67(2):310–315
34. Karavitaki N, Turner HE, Adams CB, Cudlip S, Byrne JV, Fazal-Sanderson V, Rowlers S, Trainer PJ, Wass JA (2008) Surgical debulking of pituitary macroadenomas causing acromegaly improves control by lanreotide. Clin Endocrinol 68(6):970–975
35. Petrossians P, Borges-Martins L, Espinoza C, Daly A, Betea D, Valdes-Socin H, Stevenaert A, Chanson P, Beckers A (2005) Gross total resection or debulking of pituitary adenomas improves hormonal control of acromegaly by somatostatin analogs. Eur J Endocrinol 152(1):61–66
36. Schwyzer L, Starke RM, Jane JA Jr, Oldfield EH (2015) Percent reduction of growth hormone levels correlates closely with percent resected tumor volume in acromegaly. J Neurosurg 122(4):798–802
37. Wilson TJ, McKean EL, Barkan AL, Chandler WF, Sullivan SE (2013) Repeat endoscopic transsphenoidal surgery for acromegaly: remission and complications. Pituitary 16(4):459–464
38. Yamada S, Fukuhara N, Oyama K, Takeshita A, Takeuchi Y (2010) Repeat transsphenoidal surgery for the treatment of remaining or recurring pituitary tumors in acromegaly. Neurosurgery 67(4):949–956
39. Jahangiri A, Wagner J, Han SW, Zygourakis CC, Han SJ, Tran MT, Miller LM, Tom MW, Kunwar S, Blevins LS Jr, Aghi MK (2014) Morbidity of repeat transsphenoidal surgery assessed in more than 1000 operations. J Neurosurg 121(1):67–74
40. Biermasz NR, van Dulken H, Roelfsema F (1999) Direct postoperative and follow-up results of transsphenoidal surgery in 19 acromegalic patients pretreated with octreotide compared to those in untreated matched controls. J Clin Endocrinol Metab 84(10):3551–3555
41. Buchfelder M, Schlaffer SM (2016) Novel techniques in the surgical treatment of acromegaly: applications and efficacy. Neuroendocrinology 103(1):32–41
42. Colao A, Ferone D, Cappabianca P, del Basso De Caro ML, Marzullo P, Monticelli A, Alfieri A, Merola B, Cali A, de Divitiis E, Lombardi G (1997) Effect of octreotide pretreatment on surgical outcome in acromegaly. J Clin Endocrinol Metab 82(10):3308–3314
43. Mao ZG, Zhu YH, Tang HL, Wang DY, Zhou J, He DS, Lan H, Luo BN, Wang HJ (2010) Preoperative lanreotide treatment in acromegalic patients with macroadenomas increases short-term postoperative cure rates: a prospective, randomised trial. Eur J Endocrinol 162(4):661–666
44. Shen M, Shou X, Wang Y, Zhang Z, Wu J, Mao Y, Li S, Zhao Y (2010) Effect of presurgical long-acting octreotide treatment in acromegaly patients with invasive pituitary macroadenomas: a prospective randomized study. Endocr J 57(12):1035–1044

45. Ezzat S, Horvath E, Harris AG, Kovacs K (1994) Morphological effects of octreotide on growth hormone-producing pituitary adenomas. J Clin Endocrinol Metab 79(1):113–118
46. Buchfelder M, Schlaffer SM (2012) Intraoperative magnetic resonance imaging during surgery for pituitary adenomas: pros and cons. Endocrine 42(3):483–495
47. Fahlbusch R, Keller B, Ganslandt O, Kreutzer J, Nimsky C (2005) Transsphenoidal surgery in acromegaly investigated by intraoperative high-field magnetic resonance imaging. Eur J Endocrinol 153(2):239–248
48. Bellut D, Hlavica M, Schmid C, Bernays RL (2010) Intraoperative magnetic resonance imaging-assisted transsphenoidal pituitary surgery in patients with acromegaly. Neurosurg Focus 29(4):E9
49. Tanei T, Nagatani T, Nakahara N, Watanabe T, Nishihata T, Nielsen ML, Takebayashi S, Hirano M, Wakabayashi T (2013) Use of high-field intraoperative magnetic resonance imaging during endoscopic transsphenoidal surgery for functioning pituitary microadenomas and small adenomas located in the intrasellar region. Neurol Med Chir 53(7):501–510
50. Netuka D, Majovsky M, Masopust V, Belsan T, Marek J, Krsek M, Hana V, Jezkova J, Hana V Jr, Benes V (2016) Intraoperative magnetic resonance imaging during endoscopic transsphenoidal surgery of growth hormone-secreting pituitary adenomas. World Neurosurg 91:490–496
51. Kaltsas GA, Isidori AM, Florakis D, Trainer PJ, Camacho-Hubner C, Afshar F, Sabin I, Jenkins JP, Chew SL, Monson JP, Besser GM, Grossman AB (2001) Predictors of the outcome of surgical treatment in acromegaly and the value of the mean growth hormone day curve in assessing postoperative disease activity. J Clin Endocrinol Metab 86(4):1645–1652
52. Shimon I, Cohen ZR, Ram Z, Hadani M (2001) Transsphenoidal surgery for acromegaly: endocrinological follow-up of 98 patients. Neurosurgery 48(6):1239–1243 **discussion 1244–1235**
53. Kreutzer J, Vance ML, Lopes MB, Laws ER Jr (2001) Surgical management of GH-secreting pituitary adenomas: an outcome study using modern remission criteria. J Clin Endocrinol Metab 86(9):4072–4077
54. De P, Rees DA, Davies N, John R, Neal J, Mills RG, Vafidis J, Davies JS, Scanlon MF (2003) Transsphenoidal surgery for acromegaly in wales: results based on stringent criteria of remission. J Clin Endocrinol Metab 88(8):3567–3572
55. Beauregard C, Truong U, Hardy J, Serri O (2003) Long-term outcome and mortality after transsphenoidal adenomectomy for acromegaly. Clin Endocrinol 58(1):86–91
56. Esposito V, Santoro A, Minniti G, Salvati M, Innocenzi G, Lanzetta G, Cantore G (2004) Transsphenoidal adenomectomy for GH-, PRL- and ACTH-secreting pituitary tumours: outcome analysis in a series of 125 patients. Neurol Sci 25(5):251–256
57. Trepp R, Stettler C, Zwahlen M, Seiler R, Diem P, Christ ER (2005) Treatment outcomes and mortality of 94 patients with acromegaly. Acta Neurochir 147(3):243–251 **discussion 250–241**
58. Kabil MS, Eby JB, Shahinian HK (2005) Fully endoscopic endonasal vs. transseptal transsphenoidal pituitary surgery. Minim Invasive Neurosurg 48(6):348–354
59. Ludecke DK, Abe T (2006) Transsphenoidal microsurgery for newly diagnosed acromegaly: a personal view after more than 1000 operations. Neuroendocrinology 83(3–4):230–239
60. Frank G, Pasquini E (2006) Endoscopic endonasal cavernous sinus surgery, with special reference to pituitary adenomas. Front Horm Res 34:64–82
61. Dehdashti AR, Ganna A, Karabatsou K, Gentili F (2008) Pure endoscopic endonasal approach for pituitary adenomas: early surgical results in 200 patients and comparison with previous microsurgical series. Neurosurgery 62(5):1006–1015 **discussion 1015–1007**
62. Kim MS, Jang HD, Kim OL (2009) Surgical results of growth hormone-secreting pituitary adenoma. J Korean Neurosurg Soc 45(5):271–274
63. Tabaee A, Anand VK, Barron Y, Hiltzik DH, Brown SM, Kacker A, Mazumdar M, Schwartz TH (2009) Endoscopic pituitary surgery: a systematic review and meta-analysis. J Neurosurg 111(3):545–554
64. Yano S, Kawano T, Kudo M, Makino K, Nakamura H, Kai Y, Morioka M, Kuratsu J (2009) Endoscopic endonasal transsphenoidal approach through the bilateral nostrils for pituitary adenomas. Neurol Med Chir 49(1):1–7
65. Hofstetter CP, Mannaa RH, Mubita L, Anand VK, Kennedy JW, Dehdashti AR, Schwartz TH (2010) Endoscopic endonasal transsphenoidal surgery for growth hormone-secreting pituitary adenomas. Neurosurg Focus 29(4):E6
66. Gondim JA, Almeida JP, de Albuquerque LA, Gomes E, Schops M, Ferraz T (2010) Pure endoscopic transsphenoidal surgery for treatment of acromegaly: results of 67 cases treated in a pituitary center. Neurosurg Focus 29(4):E7
67. Campbell PG, Kenning E, Andrews DW, Yadla S, Rosen M, Evans JJ (2010) Outcomes after a purely endoscopic transsphenoidal resection of growth hormone-secreting pituitary adenomas. Neurosurg Focus 29(4):E5
68. Wang M, Mou C, Jiang M, Han L, Fan S, Huan C, Qu X, Han T, Qu Y, Xu G (2012) The characteristics of acromegalic patients with hyperprolactinemia and the differences in patients with merely GH-secreting adenomas: clinical analysis of 279 cases. Eur J Endocrinol 166(5):797–802
69. Shin SS, Tormenti MJ, Paluzzi A, Rothfus WE, Chang YF, Zainah H, Fernandez-Miranda JC, Snyderman CH, Challinor SM, Gardner PA (2013) Endoscopic endonasal approach for growth hormone secreting pituitary adenomas: outcomes in 53 patients using 2010 consensus criteria for remission. Pituitary 16(4):435–444
70. Hazer DB, Isik S, Berker D, Guler S, Gurlek A, Yucel T, Berker M (2013) Treatment of acromegaly by endoscopic transsphenoidal surgery: surgical experience in 214 cases and cure rates according to current consensus criteria. J Neurosurg 119(6):1467–1477
71. Yildirim AE, Sahinoglu M, Divanlioglu D, Alagoz F, Gurcay AG, Daglioglu E, Okay HO, Belen AD (2014) Endoscopic endonasal transsphenoidal treatment for acromegaly: 2010 consensus criteria for remission and predictors of outcomes. Turk Neurosurg 24(6):906–912