Prospective integrated individualized clinical decision-making and outcome evaluation for surgery in patients with acromegaly: a new paradigm?

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ORIGINAL ARTICLE

Prospective Integrated Individualized Clinical Decision-making and Outcome Evaluation for Surgery in Patients with Acromegaly: A New Paradigm?

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Background. Growth-hormone-producing pituitary adenomas have variable likelihood for biochemical remission (BR). During preoperative counseling, individual estimated surgical likelihoods/risks should be balanced against alternative (medical) treatments, which is necessary for accurate outcome presentation. Preoperative estimation of BR or total resection (TR) likelihoods have not been reported, resulting in extrapolation of individual outcomes.

Aims. To share an innovative outcome reporting paradigm by integrating surgical decision-making, and expected/realized results, resulting from the Value-Based Health Care (VBHC) care path with periodical performance evaluation and care innovation cycle.

Methods. Prospective cohort study of consecutive patients with acromegaly undergoing surgery (January 2016–December 2020; postoperative follow-up ≥6 months) reporting on both classic, and novel innovative outcome evaluations.

Results. Fifty eight patients (66 procedures) were included. Intended TR was achieved in 34/50 procedures, whereas intended debulking was achieved in 15/16 procedures. 38/66 procedures resulted in BR, and 4 procedures resulted in permanent complications. Achieving intended surgical goal was estimated preoperatively as *likely* in 33 (goal achieved (GA) in 28/33), *potentially* in 27 (GA in 19/27), and *unlikely* in 6 procedures (GA in 2/6). Integrated Outcome Square 1 (IOQ1) –intended effect achieved without complications– was achieved in 46/66 patients.

Conclusion. Implementation of the developed quality process positively affects preoperative individual shared decision-making, resulting in improved (individual) outcomes, particularly in complex patients for whom preoperative chances are not fully reflected by tumor size and KNOSP grade, e.g., reoperations, or other challenging circumstances identified during preoperative counseling. Through repeated evaluations, our *own* team's knowledge increased, allowing for improved individualized treatment strategies.

Key Words: Pituitary adenoma, Transsphenoidal surgery, Outcomes, Acromegaly.

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Introduction

Acromegaly is a clinical syndrome caused by a growth hormone (GH)-secreting pituitary adenoma in the vast majority of cases. The combination of debilitating symptoms resulting in increased mortality and impaired quality of life necessitates effective treatment, which should be aimed at normalizing GH excess and controlling tumor volume. Treatment modalities include surgery, (a combination of) medical treatment (e.g., first- or second-generation somatostatin receptor ligands (SRL), GH receptor antagonists, or dopamine agonists), radiotherapy, or a combination of these modalities.

Endoscopic transsphenoidal surgery (ETSS) is the first-line treatment, although many patients require multimodality treatment with multiple interventions (including repeat surgery) to control GH hypersecretion and tumor volume, particularly in those with larger and invasive tumors. With effective treatment, mortality risk is reduced substantially and is considered near-normal. Rates and severity of comorbidities also improve, although consequences of the pre-diagnosis GH excess might persist (1–3).

Total tumor resection with preservation of physiological pituitary gland function is hypothesized to yield the best outcome, especially when compared to lifelong individualized medical treatment (with side effects), or radiotherapy (with high risk of pituitary deficits). Therefore, ETSS is the sole strategy that may result in a drug-free future. Unfortunately, as many patients with acromegaly present with macroadenomas, typically with (inferolateral) cavernous sinus invasion, surgical cure with normal gland preservation is a challenge.

In our pituitary reference center, ETSS has been the cornerstone of treatment for acromegaly for 40 years. From the first procedure, the performance of our surgical team was critically evaluated by publishing consecutive retrospective series (4,5). Thereafter, long-acting SRL, endoscopic TSS, GH receptor antagonists, and new techniques in radiotherapy were sequentially introduced as new treatment options, which changed the treatment landscape. Temporary preoperative SRL and primary medical treatment were used at the discretion of the multidisciplinary team (MDT). As a consequence, selection of surgical cases is inevitable, and needs to be taken into account in more recent surgical outcome reports.

From 2014 onwards, the Value-Based Health Care (VBHC) principle was implemented in our center, which resulted in the prospective recording of case-mix and baseline variables of patients with acromegaly, care was delivered in a semi-standardized care path, and outcome measures were systematically collected, periodically evaluated, and discussed in the MDT (6). Quality evaluations were introduced at different levels of clinical care with different purposes according to the plan-do-check-act (PDCA) cycle: *at the individual patient level*: expected and realized outcomes per case, *at patient group level,* periodical performance reports for trends in short term outcome guiding adjustments in the care path, and *at long-term overarching level*: 1–2 year evaluation of the care path results, focusing on remission and complication rates and effects of interventions in the care path guiding changes in the decision-making process.

As a result of these PDCA cycles, functional imaging with ^{11}C-methionine-PET-CT co-registered with MRI (Met-PET/MRI^{CR}) was introduced for complex cases to improve visualization of small functional tumor remnants, and the use of PROMS measurements in outcome evaluations was implemented to report on the patient perspective of results (6–9). Moreover, the PDCA-cycles guided us to develop local protocols for preoperative surgical planning and counseling, which expanded beyond known predictive factors for resectability, e.g., tumor size and KNOSP classification, and intraoperative surgical decision-making (10). The awareness of real-time outcomes by MDT members started a continuous learning process, aided the decision-making process in new patients, and improved the care pathway for all patients.

Ultimately, a novel, innovative manner for reporting on surgical outcomes was developed in our Pituitary Tumor Centre of Excellence (PTCOE) as a result of the ongoing cycle of care innovation via the individual, group and overarching PDCA-cycle-based evaluations, structured prospective outcome measurements, and MDT discussions of both surgical successes and failures. Therefore, we report on the surgical outcomes of the cohort of patients with acromegaly operated between 2016–2020 using the classical method of outcome reporting, and the newly developed innovative outcome analysis, which includes data on the surgical decision-making process and preoperative expected results and risk assessment, combined with the postoperative realized results and complications.

Methods

Design and Ethics

A prospective cohort of consecutive patients undergoing surgery for acromegaly between January 2016 and December 2020 were included, for whom outcomes were evaluated in a systematic way (6,11). The need for informed consent was waived by the Ethical Committee (G19.011).

Patients

Active acromegaly was confirmed with elevated insulin-like growth factor-I (IGF-1, $>+2$ standard deviation) adjusted for age and sex, insufficient GH suppression during an OGTT (GH nadir >0.4 ug/L or >1.2 mU/L), accompanied by clinical symptoms of acromegaly, and a pituitary mass suspect for adenoma with confirmative positive immunohistochemical staining for GH.

Setting

This study was performed at a both nationally and internationally endorsed (e.g., Endo-ERN) tertiary referral center for pituitary and (complex) endoscopic skull base surgery, performing an increasing total number of endoscopic surgeries annually (50 in 2015 vs. 150 in 2020), with the current volume of patients operated for acromegaly being 10–15 years.

All patients are cared for in a predefined VBHC pituitary care pathway, as described previously (6), in which patients are counseled during combined outpatient clinic visits, visits during which an endocrinologist and neurosurgeon see the patient simultaneously, and cared for by the team orchestrated by a multidisciplinary case-manager overseeing the endocrine and neurosurgical part of care.

The flow diagram for clinical preoperative surgical decision-making for pituitary adenomas (including acromegaly), as published in 2020, was shaped gradually from 2014–2020, and was used in this manuscript (Figure 1) (10). Briefly, if a patient is considered fit for surgery, and complete adenoma resection is *likely* with low risk of complications, surgery is proposed (e.g., first surgical procedure in a clear microadenoma/small macroadenoma without clear cavernous sinus invasion). Correspondingly, when the likelihood of complete resection is considered as *potentially* (i.e., due to suspected cavernous sinus invasion, stalk proximity, or previous unsuccessful surgical attempt(s)), surgery is proposed only in cases of (high) need for resection (e.g., drug intolerance or resistance, suboptimal biochemistry/clinical situation, or neurovascular compression), and when anticipated risks are low (e.g., by adapting the intraoperative-surgical strategy when faced with a unfavorable surgical conditions). When complete adenoma resection is estimated as *unlikely*, the planning of a (partial) resection is based on careful evaluation of anticipated risks and benefits and the added value of debulking surgery weighed against alternative (drug) treatments. The preference of the patient and the clinical situation is integrated in this approach during counseling. All aspects of the surgical decision-making, including treatment goals, preoperative estimation of surgical cure, and risk assessment, are explicitly recorded in the electronic patient files.

All patients underwent preoperative MRI and CT (neuro-navigation)-imaging. All surgical procedures, standard is ETSS, are performed by two dedicated and experienced pituitary neurosurgeons (from a team of three), who in complex extended approaches are assisted by an experienced endoscopic skull base ENT-surgeon.

During the postoperative combined outpatient clinic, individual outcomes are discussed, and additional diagnostics and treatments are proposed if necessary. Patients are seen in combination as long as surgical (re-)intervention is considered a feasible possibility enabling careful weighing of options, thereafter patients are followed at the endocrinology department.

Study Parameters and Outcome Measures

Clinical Characteristics

Data on patient characteristics (e.g., age, sex), disease characteristics (e.g., GH and IGF-1 levels, duration of disease), and tumor characteristics (e.g., size and invasion) were recorded, which included clinical symptoms, pituitary function assessment, previous treatments, ophthalmological clinical history, and relation of the tumor to the optic pathways.

Classic Outcome Evaluation of Biochemical Efficacy Outcomes and Complications

Collected classic outcome parameters were postoperative endocrine remission and tumor status, as well as data on ophthalmological outcomes. Post-operative remission at 6 months was defined as normal IGF-1 levels and a normal OGTT, or by expert opinion consensus in case of discrepancies between the tests. Discrepant biochemical and clinical results were resolved by repeat measurements of disease activity, and MDT discussions. Recurrence was defined as a period of initial remission followed by progression of clinical symptoms, increased levels of GH/IGF-1, regardless of tumor regrowth on follow-up MRI scans.

Complications were collected according to the Clavien-Dindo classification (12) and included: transient complications (DI, (subclinical) hyponatremia due to SIADH necessitating readmission, epistaxis necessitating an intervention, cranial nerve dysfunction, CSF leakage), and permanent (persisting for >6 months postoperatively) complications (new onset permanent pituitary dysfunction, or persisting decreased visual fields and/or visual acuity). Subgroups were based on preoperative tumor characteristics.

Innovative Outcome Analysis of Expected and Realized Results Including Surgical Decision-making and Risk Assessment

Preoperative Assessment. Data on the intended effect of surgery – achieving biochemical remission (BR), total resection (TR), or decrease in disease activity by tumor volume reduction (debulking), including individual treatment goals – were collected. For the intended effect(s) of surgery and achievement of BR/TR, the preoperative estimation of the likelihood of achieving the intended effect of surgery was recorded as either *likely, potentially*, or *unlikely* as evaluated by the experienced surgeons and the MDT. Surgical success depends on the pre-operative defined surgical goal; if a complete resection is impossi-

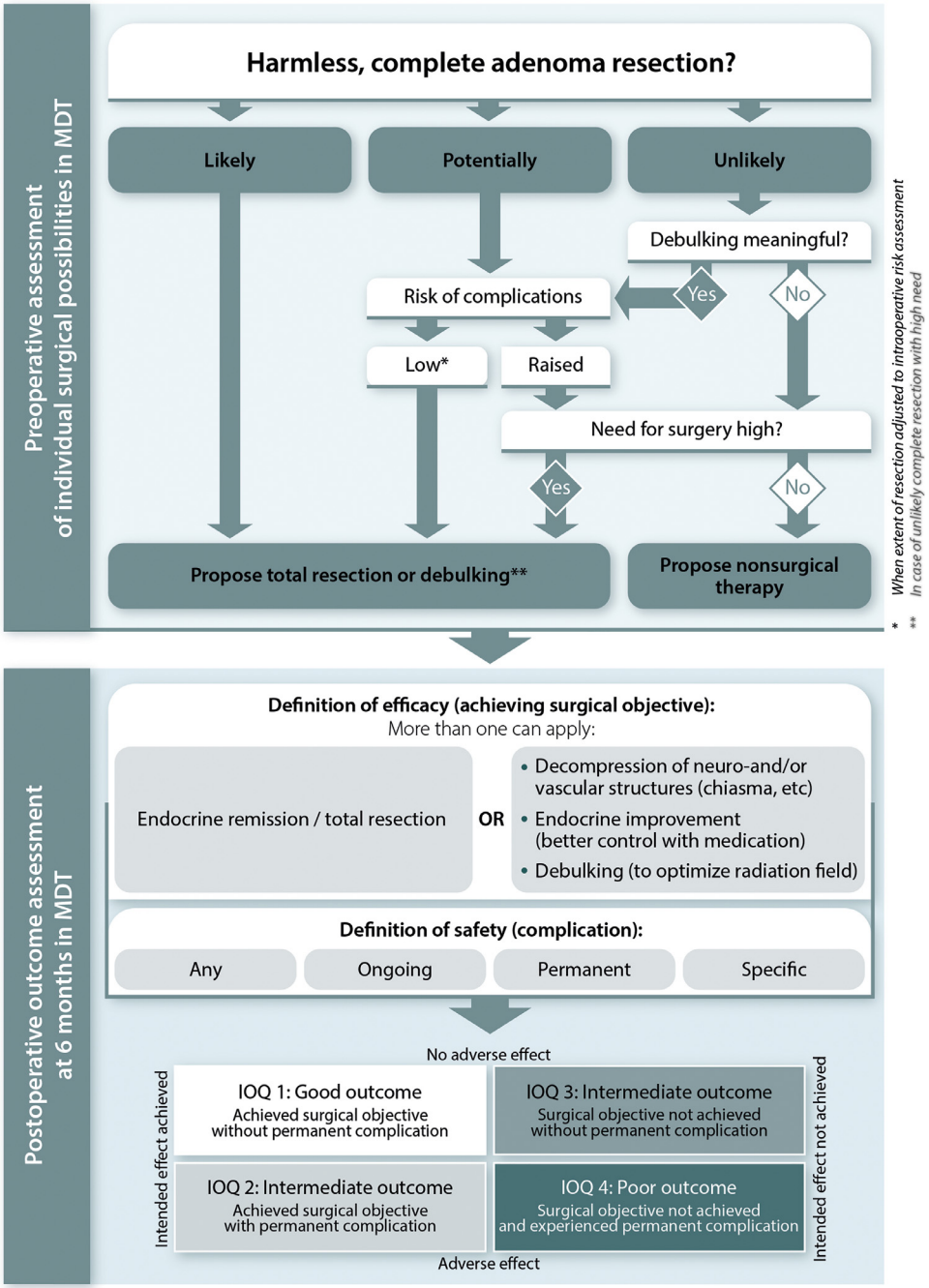

Figure 1. Innovative pre- and postoperative outcome assessment. Modification and integration of both pre-operative assessment of individual surgical possibilities and post-operative outcome (10,11).

ble or unlikely, tumor debulking can be meaningful, i.e., in case of chiasm compression, or suboptimal effect of maximized medication. The likelihood of surgical remission depends among others on tumor size, adenoma invasiveness in the cavernous sinus, the adenoma's relation to neuro-and vascular structures and on surgical experience. Additionally, the estimated individualized risks of complications were recorded. The estimation of surgical risk was mainly based on tumor volume, KNOSP grade, pre -operative pituitary function, visibility of the normal gland on MRI, and our experience combined with the surgical intended effect. The surgical risk for complications was estimated as qualitative, but reflecting low<2%, raised 2–5%, high>5%. We estimated the preoperative or primary complexity based on tumor visibility, extension, KNOSP-grade (13), previous surgery, intended effect of the surgery, pre-operative pituitary function and team experience.

Postoperative Assessment. Postoperatively, all the outcome scores in the preoperative phase were systematically assessed and (re)evaluated. The preoperative and postoperative pituitary function tests and MRI scans were simultaneously analyzed addressing and assessing various parameters necessary for accurate outcome evaluation: the surgical goal/intended effect, (probability of) reaching this surgical goal, (estimated) chance of biochemical remission, the pre-operative surgical risk, the quality of imaging, evaluation of the complexity. The postoperative or secondary complexity included the same items as the preoperative complexity score with the extension of intraoperative findings, postoperative imaging and the intra-and postoperative course taken into account.

Integrated outcome squares (IOQ), as reported by our group recently (11), were used for the evaluation of surgical outcome. These outcome squares represent an overarching Hippocratian approach to outcomes by integrating efficacy and safety (focusing on permanent complication/adverse effects) of the surgery, while evaluating whether the intended effect was reached/surgical goal was achieved. IOQs are divided into four categories: IOQ1, good outcome, patients in whom the main preoperative surgical goal was accomplished without adverse effect; IOQ2, intermediate outcome, patients in whom the main preoperative surgical goal was accomplished with permanent complication/adverse effect; IOQ3, intermediate outcome, patients in whom the main preoperative goal was not accomplished without permanent adverse effect; or IOQ4, poor outcome, patients in whom the main preoperative goal was not accomplished with permanent complication/adverse effect).

Statistical Analysis

Descriptive statistical analyses were performed using SPSS for Windows version 26.0 (IBM, USA). Depending on normality testing, numerical data are presented as mean ± standard deviation, or median (range). Categorical data are presented as numbers (percentages). The following data were presented per intervention (i.e., first or re-operation), unless otherwise specified: preoperative clinical characteristics, postoperative outcome analysis (e.g., efficacy and safety outcomes), preoperative estimation of surgical possibilities (e.g., chances and expectations of planned surgery), comparison of preoperatively expected and postoperatively realized efficacy and safety outcomes, and integrated outcome analysis using outcome squares for the combination of efficacy and safety measures.

Results

Patient Characteristics

Sixty-six surgical procedures were performed in 58 consecutive patients with acromegaly (Table 1). Twenty-four micro-adenomas (10 first procedures), 35 macroadenomas (29 first procedures) and 7 giant adenomas (4 first procedures) were operated on. Eleven procedures (9%) were performed in patients with KNOSP-grade 4. In 26 surgeries, patients were treated with SRL preoperatively. In 23 of the procedures, patients were operated prior (18 patients were operated once, 4 patients were operated twice, and 1 patient was operated five times prior to the present procedure). Of the 23 reoperations, the vast majority was for persistent disease (n = 22), as only one patient had disease recurrence after 11 years of remission. Median follow-up duration was 29 months (range 6–64).

Classical Outcome Evaluation of Biochemical Efficacy Outcomes and Complications

Biochemical Outcomes of Total Group and Per First or Re-operation and Per Tumor Size

Serum IGF-1 concentration decreased in 61/66 procedures (92%), of which 36/66 (55%) resulted in complete normalization of IGF-1 levels. Outcomes for both postoperative IGF-1 levels, as well as dynamic testing using OGTT were available for 40 procedures, since OGTT was not routinely performed in case of non-remission. Based on the application of both parameters and clinical evaluation by the team at 6 months postoperative, 38/66 patients (58%) were considered in remission after the procedure, whereas 28/66 (42%) were not in remission, and required additional therapy (Table 2).

With respect to primary surgery or reoperation, remission was reached in 28/43 (65%) primary procedures, and in 10/23 (43%) of reoperations. Regarding the size of the adenoma, biochemical remission was achieved in 67% of all microadenoma procedures (15/24; (8/10 first surgery, 7/14 reoperation), 66% of all macroadenoma procedures (23/35) (20/29 first surgery, 3/6 reoperation), and none in giant adenomas.

Complications

Four procedures (6%) resulted in long-term complications: 3 cases had permanent diabetes insipidus, one of which also had new onset hypopituitarism. One patient had moderate cognitive impairment at presentation that mildly deteriorated postoperatively (giant adenoma including hydrocephalus). Transient complications occurred in 47% of all procedures. Postoperative CSF leakage occurred in 4 procedures, requiring surgical closure in 1 case and lumbar drainage in 3 cases. In 3 cases postoperative epistaxis occurred, which was treated with nasal packing. The most common transient complication was DI (n = 10/66), with a heterogenous course from 1–23 d (median 5 d).

Table 1. Patient characteristics of 66 consecutive surgical procedures for acromegaly.

Clinical characteristics		**All procedures $n = 66$**
Age (in years)		47.2 ± 12.6
Sex (female)		38 (58%)
Clinical symptoms	Severe	52 (79%)
	Mild	4 (6%)
Previous operation		23 (35%)
Tumor size	Microadenoma	24 (36%)
	Macroadenoma	35 (53%)
	Giant adenoma	7 (11%)
KNOSP-classification	0-2	48 (66%)
	3a-3b	11 (17%)
	4	11 (17%)
Follow-up duration (in months)		29 (6-64)

Values are reported as N (%), mean ± SD, or median (range); *N*, number of procedures; SD, standard deviation.

Table 2. Classical report of surgical outcomes in patients with acromegaly.

Patient cohort	***N***	**Efficacy**	**Complications**	
		Biochemical remission	**Transient**	**Permanent**
Unselected				
All procedures	66	38/66 (58%)	31/66 (47%)	4/66 (6%)
Selection based on tumor size				
Micro	24	15/24 (63%)	8/24 (33%)	1/24 (4%)
Macro	35	23/35 (66%)	18/35 (51%)	3/35 (9%)
Giant	7	0/7 (0%)	5/7 (63%)	0/7 (0%)
Selection based on previous surgery				
First surgery	43	28/43 (65%)	25/43 (58%)	3/43 (6%)
First surgery on micro adenoma	10	8/10 (80%)	6/10 (60%)	0/8 (0%)
First surgery on macro adenoma	29	20/29 (69%)	16/29 (55%)	3/29 (10%)
Re-operation	23	10/23 (43%)	6/23 (26%)	1/23 (4%)
Re-operation on micro adenoma	14	7/14 (50%)	12/14 (86%)	1/14 (7%)
Re-operation on macro adenoma	6	3/6 (50%)	2/6 (33%)	0/6 (0%)
Selection based on KNOSP grade				
0-2	44	30/44 (68%)	18/44 (41%)	2/44 (4%)
3a-3b	11	8/11 (73%)	8/11 (73%)	1/11 (9%)
4	11	0/11 (0%)	5/11 (45%)	1/11 (9%)

Values are reported as *N* (%); *N*, number of procedures.

Innovative Outcome Analysis of Expected and Realized Results Including Surgical Decision-making and Risk Assessment

The number of (re)operations, and the preoperative estimations of the likelihood of achieving the goal are summarized in Table 3, and whether the surgical goals were achieved are summarized in Table 4, and the innovative outcome analysis is presented in Table 5 for all procedures. All outcomes are discussed per intent of surgery, namely, total resection (TR) for biochemical remission, or debulking for volume reduction, and are divided into groups based on the preoperative estimation of the likelihood of reaching the intended effect, or reaching biochemical remission (i.e., *likely, potentially, unlikely*).

Intended Gross total Resection

Likely. Twenty-four preoperative cases were considered to *likely* achieve remission or TR. Seven of these were microadenomas (4 reoperations), and 17 were macroadenomas (1 reoperation). Remission was realized in 19/24 (79%) procedures. Four of the non-remissions were first procedures in macroadenomas, the 5th case was a second procedure. After a thorough work-up a second operation was performed in 3/5 cases, with remission being achieved in all patients. Case four and five are planned for additional surgery, and opted to continue medication, respectively.

Potentially. Twenty-six cases were considered to *potentially* achieve remission or TR. Reasons for more caution were either an uncertain or high KNOSP classification

Table 3. Innovative re-operative estimation/prediction of likelihood of outcomes and risks in patients with acromegaly.

Patient cohort	Number of operations			Surgical goal		Preoperative estimations of likelihood of achieving remissiona			Preoperative estimations of likelihood of achieving surgical goal[b]			Elevated risk[c]
	All procedures	1st surgery	Re-operation	D	R	Likely	Potentially	Unlikely	Likely	Potentially	Unlikely	
All procedures	66	43	23	16	50	23	23	4	33	27	6	32
Stratification based on tumor size												
Micro adenoma	24	10	14	1	23	7	14	2	7	15	2	9
Macro adenoma	35	29	6	8	27	16	9	2	22	11	2	16
Giant adenoma	7	4	3	7	0	0	0	0	4	1	2	7
Stratification based on cavernous sinus invasion												
KNOSP 0-2	44	27	17	3	41	18	21	2	21	21	2	12
KNOSP 3a-3b	11	11	0	3	8	5	2	1	7	3	1	9
KNOSP 4	11	5	6	10	1	0	0	1	5	3	3	11

Values are reported as *N*. [a]Pre-operative estimated likelihood of achieving remission for the 50 intended biochemical remission/TR procedures as defined during MDT meeting. [b]Pre-operative estimated likelihood of reaching the surgical goal (biochemical remission/TR, or debulking) for all 66 procedures as defined during MDT meeting. [c]Pre-operative estimated risks of the surgical goal for all 66 procedures as defined during MDT meeting. D, surgical goal was debulking; MDT, multidisciplinary team; N, number of procedures; R, surgical goal was remission; TR, total resection.

Table 4. Pre-operatively defined surgical goals and achievements in patients with acromegaly.

	Surgical goal						Surgical goal achieved[c]					
	All procedures $N = 66$		1st surgery[a] $N = 43$		Re-operation[b] $N = 23$		All procedures $N = 66$		1st surgery $N = 43$		Re-operation[b] $N = 23$	
	R	*D*	*R*	*D*	*R*	*D*	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*
All procedures	50	16	33	10	17	6	49	17	35	8	14	9
Stratification by tumor size												
Micro	23	1	10	0	13	1	16	8	8	2	8	6
Macro	27	8	23	6	4	2	26	9	23	6	3	3
Giant	0	7	0	4	0	3	7	0	4	0	3	0
Stratification by cavernous sinus invasion												
KNOSP 0-2	41	3	25	2	16	1	30	14	20	7	10	7
KNOSP 3a-3b	8	3	8	3	0	0	10	1	10	1	0	0
KNOSP 4	1	10	0	5	1	5	9	2	5	0	4	2

Values are reported as N.
[a]First surgical procedure for this patient
[b]Second or >2nd surgical procedure for this patient. [c]Surgical goal achieved: remission (TR) or debulking.D, surgical goal was debulking; *N*, number of procedures; R, surgical goal was remission (TR). TR, total resection

Table 5. Innovative report of surgical outcomes concerning efficacy and complications in patients with acromegaly.

Patient cohort	***N***	**Efficacy**			**Complications**		**IOQ for achieving surgical goal**	
		Goal achieved	**Remission achieved**	**Debulking achieved**	**Transient**	**Permanent**	**IOQ 1** **IOQ 2**	**IOQ 3** **IOQ 4**
All procedures	66	49/66 (74%)	38/66 (58%)	NA	31 (47%)	4 (6%)	70% 5%	24% 2%
Surgical goal: Remission	50	34/50 (68%)	34/50 (68%)	NA	21 (42%)	3 (6%)	64% 4%	30% 2%
Surgical goal: Debulking	16	15/16 (94%)	4/16 (25%)	15/16 (94%)	10 (63%)	1 (6%)	88% 6%	6% 0%
	N	All procedures	Goal remission	Goal debulking	Transient	Permanent	IOQ for achieving remission	
							All procedures	Goal remission
Likely	24	19/24 (79%)	18/23 (78%)	1/1 (100%)	15/24 63%)	2/24 (8%)	71% 8%	21% 0%	70% 9%	22% 0%
Potentially	26	19/26 (73%)	16/23 (70%)	3/3 (100%)	9/26 (35%)	1/26 (4%)	73% 0%	23% 4%	70% 0%	26% 4%
Unlikely*	16	0/16 (0%)	0/4 (0%)	0/12 (0%)	7/16 (44%)	1/16 (6%)	0% 0%	94% 6%	0% 0%	100% 0%

Values are reported as N (%).

*In the unlikely to achieve remission group, as predicted, none of the patients achieved biochemical remission (BR). By contrast, of the 16 patients in this group, 11/12 (92%) with the goal of debulking achieved the surgical goal, and 0/4 (0%) procedures with the goal of remission achieved the goal.BR, biochemical remission; GA, goal achieved; IOQ, integrated outcome square; N, number of procedures; NA, not applicable.

(KNOSP >2), previous unsuccessful surgery, poor visibility on MRI, or a combination of these factors. Nevertheless, remission was achieved in 19/26 (73%) procedures.

Unlikely. Remission or TR was considered *unlikely* for 16 procedures, and indeed was not achieved for any of these procedures. Procedures were classified as unlikely due to tumor volume (giant adenoma ($n = 7$), (remnant) tumor extension with KNOSP grade 3b/4 ($n = 12$)), or no visible tumor (remnant) ($n = 3$). When applied, functional imaging did not alter the initial estimation. Although we assessed the remission chance as unlikely, the need for surgery was high due to drug intolerance/resistance, with a high disease burden and complementary unsatisfactory clinical status, resulting in partial tumor volume reduction as the primary goal in 12 procedures, and the secondary goal in 4 procedures.

Intended Debulking

Tumor debulking was the main intended effect of surgery in 16 procedures (6 reoperations). This was mainly for decompression of the optico-chiasmatic system in the majority ($n = 11$), and otherwise for possible dose reduction of medication ($n = 3$), reduction of the radiotherapeutic field ($n = 1$), and closure of a cerebral spinal fluid leakage ($n = 1$). Adequate tumor reduction was achieved in 15/16 procedures (94%). Remarkably, in 4 procedures (25%), biochemical remission was achieved.

Risk Analysis

In total, 32 procedures were considered to have an elevated risk for complication (medium-risk $n = 21$, and high-risk $n = 11$). Dividing procedures into low-risk and high-risk, remission rates were better in low-risk (23/34 (68%)) than in high-risk procedures (4/11 (36%)). In relation to complications, transient complications occurred in respectively 18/34 (53%) low-risk, in 8/21 (38%) medium-risk, and in 5/11 (45%) high-risk procedures. Long-term, permanent complications occurred in 3/34 (8%) low-risk, 0/21 (0%) medium-risk, and 1/11 (9%) high-risk procedures.

Complexity Analysis

Since weighing the complexity of each procedure in relation to the surgical goal (including alternatives) is essential for shared decision-making, the complexity of all procedures was estimated both pre- and postoperatively. In some cases, the preoperative estimation of complexity did not match the actual intraoperative/postoperative complexity, of which we provide some examples.

Three procedures (3/23) were considered as low complexity pre- and intraoperatively, but were postoperatively reclassified as raised complexity in 1 case and high complexity in 2 cases. The first case was considered a straightforward procedure on a patient with a macroadenoma, in whom resection of the adenoma, with histopathological confirmation, unexpectedly did not result in remission with persistent normal-to-high IGF-1 levels postoperatively. In the other two procedures, improvement of GH-levels without normalization in one procedure, and unchanged GH levels in the other procedure were observed. Upon reevaluation of preoperative MRI scans, ambiguous, unclear cavernous sinus invasion was observed, which was not recognized preoperatively.

Furthermore, in a different procedure (that did not result in biochemical remission), the insufficient quality of preoperative imaging limited the interpretation, resulting in changing the complexity score from raised-complexity preoperatively to high-complexity postoperatively.

A postoperative de-escalation of complexity score from raised-complexity to low-complexity also occurred. In retrospect, this case was estimated as raised-complexity being a reoperation on a patient with a recurrence, although the lesion was clear and noninvasive on preoperative imaging, resulting in a low-complexity case.

Multiple Operations

In total, 23 procedures were performed as a 2nd or multiple procedure. Second surgery was performed in 18 procedures (5 *likely*, 7 *potentially* and 6 *unlikely* for remission). In 4/5 *likely* and 5/7 *potentially* estimated procedures remission was accomplished (9/12 (82%)). In macroadenomas, 3/6 reinterventions (50%) resulted in remission.

Overall, 18/23 re-operations (78%) resulted in an improved clinical or biochemical status. In 6/8 cases with $\geq$2 procedures and *unlikely* remission, biochemical disease activity was improved in patients with drug intolerance/resistance, resulting in the reduction of drug dose (i.e., surgical goal). Multiple operations were mainly performed in lower KNOSP-graded tumors (17/23 in KNOSP grade$\leq$2), although the last operation was graded to the last procedure, meaning that along the clinical process it turned out that the KNOSP-grade was underestimated as reason for failure or that tumor growth resulted in increased invasion of the cavernous sinus. Reoperations did not lead to more long-term complications than first surgical procedures.

In 12 procedures, preoperative functional imaging with 10 Met-PET/MRI^{CR} and/or 2 FET-PET/MRI^{CR} was acquired. Biochemical remission was achieved in 8/12 (67%) procedures.

Integrated Outcomes of Efficacy and Adverse Effects (IOQ)

All procedures. The surgical goal (remission or debulking) was achieved in 49 out of 66 procedures (74.2%) (Table 5), resulting in an IOQ1 of 69.7% and IOQ2 of

4.5% (all first surgical procedures and macroadenomas). In 17 procedures, the surgical goal was not achieved, of which 16 procedures had an uneventful course (IOQ3 of 24.2%), whereas in 1 procedure, the intended surgical goal was not achieved with a permanent complication (IOQ4 of 1.5%). Moreover, remission was achieved in 38 of 66 (58%) procedures regardless of the surgical goal. Of the 50 procedures with biochemical remission as the intended effect, remission was achieved in 34 (68%) procedures (IOQ1+2), with remission being achieved in 25/33 (76%) first operations, and 9 /17 multiple operations (53%; 3 macro- and 6 microadenomas). Of the 16 procedures with debulking as the intended effect, adequate debulking was achieved in 15/16 procedures (94%, IOQ1+2), with 1 procedure resulting in permanent complications (IOQ2, 1/16). For the one procedure not resulting in adequate debulking, safe debulking was considered not possible intraoperatively.

Accuracy of Estimation of Achieving Biochemical Remission

In the group with a *likely* estimated chance for remission, regardless of the surgical goal, 19 of 24 (79%) procedures achieved an IOQ1+2 (IOQ1 71%, IOQ2 8%). Two patients had a permanent complication resulting in IOQ2. No procedure resulted in complications without achieving the intended effect (IOQ4 0%). Assessing the patients with surgical goal remission and the estimation of achieving biochemical remission as *likely*, 18/23 procedures (78%) resulted in remission (IOQ1+2), with 2/23 (9%) having permanent complications (IOQ2).

In the *potentially* estimated procedures for remission, IOQ1 was 73% (19/26), with no patients reaching the intended effect with complication (IOQ2 0%). By contrast, 1 procedure did not reach the intended effect but did suffer a permanent complication, resulting in an IOQ4 of 4%. Of the 23 procedures with intended remission estimated as *potentially*, 16 procedures (70%) resulted in remission (IOQ1+2), with no procedures having permanent complications.

In the *unlikely* estimated for remission, none of the 16 procedures resulted in remission, and therefore both IOQ1 and IOQ2 were 0%. 1 permanent complication occurred, resulting in an IOQ3 of 94 and IOQ4 of 6%. Of the patients with intended remission, none of the procedures resulted in permanent complications, resulting in an IOQ3 of 100 and IOQ4 of 0%.

Integrated Outcomes Depending on Tumor Size and Risk

Of the 24 procedures on microadenomas, 16/24 procedures were classified as IOQ1 (66.7%), 0/24 (0%) procedures as IOQ2, 7/24 (29.2%) as IOQ3, and 1/24 (4.2%) as IOQ4. Of the 35 procedures on macroadenomas, 23/35 procedures were classified as IOQ1 (65.7%), 3/35 (8.6%) procedures as IOQ2, 9/35 (25.7%) as IOQ3, and 0/35 (0%) as IOQ4. Of the 7 giant adenomas, IOQ1 was 100%.

In the estimated low-risk group, 22/34 (64.7%) procedures resulted in an IOQ1, 2/34 (5.9%) in IOQ2, 9/34 (26.5%) in an IOQ3, and 1/34 (2.9%) in an IOQ4. This last patient was estimated for a *potentially* remission, but did not achieve remission and was suffering from a permanent DI. In the *likely* estimated group for remission there was no IOQ4 patient. In case of a preoperative high-risk, still an IOQ1 of 72% was achieved.

Discussion

For over 40 years, TSS has been the cornerstone of treatment for acromegaly in our pituitary reference center. Our surgical performance was evaluated using a consecutive prospective cohort, as published previously (4–6). In recent years, a VBHC approach with a defined care path, systematic outcome measures, and an innovation cycle was developed. Thus, the MDT is aware of real-time outcomes and quality evaluation of the surgical performance. Being a PTCOE, and an endorsed Endo-ERN reference center, periodical evaluations of our results have become integrated in our care path. We encountered that the registration of preoperative judgment of likelihood of achieving either remission or the intended effect, as well as risks, is important to enable evaluation of meaningful outcomes for future shared decision-making in clinical practice. Local protocols for preoperative surgical decision-making included the prospective recording of treatment indication, the intended effect of treatment, expected and realized risks and outcomes and complexity of surgery.

The use of the adapted version of the previously published surgical decision-making flow chart (Figure 1) (10) aids the preoperative decision-making by classifying patients based on the preoperative MDT evaluation of the likelihood to be cured, rather than predominantly based on e.g., tumor size. When looking at procedures performed with an intent to achieve remission, Babu et al. (14) reported a postoperative remission rate of 43/55 (78%). In our total cohort, remission was reached in in 34/50 procedures (68%) with remission as the intended effect, which is a somewhat lower percentage, which might be explained by differences in case mix (multiple surgeries, larger (giant) adenomas and differences in KNOSP grades).

More important than expressing the intent of surgery may be to estimate and express the likelihood of reaching this surgical goal in the individual case, e.g., *likely, potentially, unlikely*. For our cohort, remission was achieved in 79% of *likely* procedures, 73% of *potentially* procedures, and 0% of *unlikely* procedures, highlighting the additional value of making explicit estimation during the preoperative decision-making process. Nevertheless, of the 24 preoperative likely-to-achieve-remission assessments, 5 procedures (21%) did not result in remission. Critical re-analysis of

these non-remission procedures showed a suboptimal surgical approach in two cases leading to a suboptimal exposure of the surgical field, mainly to avoid CSF-leakage, or to be cautious in case of a narrow inter-carotid space. Both cases achieved remission following a second surgical attempt. One patient only had mild persisting disease, with a satisfactory clinical result from a patient's point of view. In this case, cavernous sinus invasion (KNOSP grade 3b) was observed in retrospect, which was initially assessed as a KNOSP grade 1. On postoperative imaging, a dubious very small remnant was observed, which is monitored closely. In 2 cases, no clear explanation regarding why the surgical procedure was not completely successful could be found other than unsatisfactory exposure of the surgical field, resulting in postoperative remnants. One of these patients is awaiting a 2nd surgery, with a small but clear remnant anteriorly. The last patient has IGF-1 levels below the upper limit of normal (SD+1.09), resulting in close monitoring for the need for adjuvant therapy. Based on these 5 cases, we conclude that total resection of a GH adenoma can be more difficult than apparent on the preoperative imaging, and that sufficient exposure of the surgical field was the only identifiable factor that could be improved. In those situations, careful reevaluation may result in a reoperation and a surgical cure.

When comparing remission as the intended effect, a small difference between *likely* and *potentially* procedures of 78 vs. 70%, respectively, might suggest that we were too cautious in estimating the remission chances, that the anticipation of higher complexity positively influenced the outcome, or factors associated with favorable outcome were unknown. On the other hand, of the 5 procedures with a *likely* estimation and no initial remission, second surgery in 3 patients resulted in 100% remission (3/3), indicating that a *likely* estimation indeed related significantly to high chances for potential remission albeit after repeat surgery. Moreover, of procedures aiming for debulking, 25% of procedures resulted in disease remission, indicating that positive outcomes were possible in more difficult procedures.

The added value of individual preoperative quantification of risks and success likelihoods per patient is that it allows for evaluation of local knowledge, and assumptions these assessments are based on. Through repeated evaluations, the knowledge of surgical performance of our *own* team increases, which allows for better individualized treatment strategies for future patients. For instance, potential success was often ascribed to adenoma localization in the cavernous sinus. With focused surgical strategy, adenoma removal from the medial compartment of the cavernous sinus by us was proven safe and effective. While other PTCOE had previously published this (15), we know now that we can safely offer this approach to our patients. Integrated outcome evaluation, using our IOQ model with only 4 outcome categories according to the two axes of the Hippocratic oath, i.e., safety and efficacy, greatly facilitated this process. To make such a clear distinction between success and failure, the team needs to agree on all used definitions and operationalization of outcomes. Again, this allowed us to expand our knowledge in an organized, multidisciplinary way. Increased knowledge reduces assumptions in individual shared decision-making. The awareness of outcome and risks, and confirmation of pre-operative estimated chances adds value in the individual surgical decision process. A flow-chart (Figure 1) can be helpful in complex cases with multiple treatment options.

The overall results of a second attempt in our series encourage performing repeat surgery if there is a reasonable surgical target, which was previously reported by Wilson et al. (16). In our series of 18 second operations, 9 procedures resulted in biochemical remission (50%). Of these 18 reoperations, 4 were estimated as *unlikely*, mainly because of previous unsuccessful surgical attempts. Of the 18 second operations, 12 were considered to *likely* or *potentially* achieve their goal, and remission was achieved in 9/12 (75%) procedures, indicating the value of repeat surgery in our current treatment philosophy. Importantly, patients without long-term complications can ultimately achieve remission without adverse effects (e.g., IOQ1 after repeat surgery in patients with an IOQ3 procedure in the past). Moreover, even if biochemical remission is unlikely, improvement of biochemical parameters could lead to improved clinical performance. Moreover, of procedures aiming for debulking, 25% of procedures resulted in disease remission. Therefore, we believe in multiple surgical attempts, taking risks and surgical intentions into account, although the exact relation between improved biochemistry and clinical performance, as well as the relation between tumor mass and biochemical activity, is difficult to predict.

The probability of remission prediction was highly dependent on tumor size. However, looking at tumor sizes separately, the group of microadenomas, including small remnants, had a remission rate of 65%, which is relatively low, and is probably explained by the number of multiple procedures ($n = 14$). Regarding only first procedures in microadenomas, the remission rate was 80%, matching the remission rates in literature (17). For multiple surgical procedures in microadenomas, the remission rate was 57% at second attempt, and dropped to 20% for the third attempt, although 2 of 3 patients with a remnant and a 3rd surgical procedure showed clinically significant reduction of symptoms and biochemistry. Therefore, it might be concluded that only in highly selected cases clinical remission is still possible in 3rd (or more) surgical attempts, and physicians should be reluctant in estimating a high probability of remission. On the other hand, a clinically successful 2nd or 3rd surgery can be of added value to the patient. Although the preoperative estimation of remission chances is not implemented in other centers, our results show that preoperative estimations resemble the clinical

outcome of the patient, and aided in performing 2nd or even 3rd surgical intervention.

Cavernous sinus invasion is the most significant independent predictor of unfavorable outcome (13–15,17–20), also supported with the presented data. Therefore, KNOSP-grade is a cornerstone in the preoperative estimation of resectability of these tumors, with an experienced MDT being able to provide nuanced preoperative surgical estimations of TR. In addition to KNOSP, non- or poorly visible adenomas, poorly delineated adenomas, prior medical treatment, and suprasellar extension are factors that determine the pre-operative estimation of resectability.

Remarkably, we did not find a significant relation between the estimated risk and long-term complications, which might be explained by 2 reasons. The occurrence of complications was underpowered for statistical evaluation, and a relation between estimated risks and actual complications is therefore difficult to demonstrate. Additionally, there were a few cases of unpredicted permanent diabetes insipidus in microadenoma. Importantly, intensive preparation for prevention was applied as soon as increased risks were identified. Furthermore, in the selection of suitable patients for surgery, as patients with an a-priori very high risk of complications were not operated. Moreover, remarkably low complication rates for interventions concerning the cavernous sinus were observed.

Several limitations need to be addressed. One limitation is the lack of statistical analysis as the numbers are small. However, we intended primarily to share our concept of looking at the process of development and implementation in daily practice of integrated outcome, since we sincerely believe this aided in improving our understanding of our outcomes. Moreover, some of the prospectively collected data points needed reevaluation by members of the MDT, resulting in some variables being altered retrospectively.

Conclusions

In conclusion, the process of shared decision-making showed acceptable preoperative estimations concerning the intended effect of surgery, biochemical remission, and risks. Besides the classical report of outcome, the innovative use of outcome squares represents a more clinically relevant, and patient-centered display of outcomes in surgical procedures for patients with acromegaly. In selected cases, 2nd or even third-look procedures may also be successful after careful consideration of the pros and cons in shared decision-making with the team and the patient.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.arcmed.2023.102918.

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