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Impact of transsphenoidal surgery for pituitary adenomas on overall health-related quality of life: A longitudinal cohort study

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Abbreviation list:

CCI Charlson comorbidity index

CI confidence interval

HRQoL health-related quality of life

ICU intensive care unit

MCID minimal clinically important difference

MRI magnetic resonance imaging

OR odds ratio

PROMs patient-reported outcome measures

QoL quality of life

SD standard deviation

VAS visual analogue scale

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Abstract

Background: Previous studies show a moderate improvement in health-related quality of life (HRQoL) following transsphenoidal surgery for pituitary adenomas, but no consistent predictors of HRQoL outcome have been identified. We aimed to evaluate overall HRQoL changes following such surgery, and assess potential patient or tumour characteristics that predict HRQoL outcome.

Materials and methods: Sixty adult patients undergoing transsphenoidal resection of pituitary adenomas were prospectively enrolled. They completed the EQ-5D 3L, a generic HRQoL questionnaire, preoperatively, and at one (n=57) and six months (n=56) postoperatively. HRQoL was assessed as both postoperative change in median EQ-5D 3L score, and as change greater than the minimal clinically important difference (MCID) in EQ-5D 3L score. Multivariable logistic regression analyses were performed to assess potential predictors of clinically significant HRQoL changes (>MCID) at six months postoperatively.

Results: There was a slight, but statistically significant, improvement in median EQ-5D 3L scores at six months postoperatively compared to preoperatively. Sixteen patients (29%) reported a clinically significant improvement in HRQoL at six months postoperatively, and larger preoperative tumour volume was a statistically significant predictor of such improvement. Eight patients (14%) reported a clinically significant deterioration in HRQoL at six months, but none of the assessed variables predicted such deterioration.

Conclusions: Patient-reported overall HRQoL improved slightly after transsphenoidal surgery for pituitary adenomas at group level. Patients with larger tumours might have more HRQoL benefits from surgery, but the mechanisms behind the predictive nature of tumour volume remain unknown.

Key words: patient-reported outcome measures; pituitary adenoma; quality of life; pituitary surgery.

Introduction

An important aim of treatment is to improve or preserve health-related quality of life (HRQoL). Patient-reported outcome measures (PROMs) have gained acceptance and are more often assessed following neurosurgical interventions (1). Prior to treatment, patients with pituitary adenomas report reduced HRQoL compared to the general population, with different degrees of impairment depending on tumour type (2). Previous studies have reported temporary reductions in predominantly site-specific (sinonasal) quality of life (QoL) two to three weeks after transsphenoidal surgery, followed by slight, but sustained improvement up to one year postoperatively (3-5). In the few previous studies assessing predictors of postoperative changes in HRQoL, younger age and male gender predicted improvement in generic (general) HRQoL (6), while subtotal resection predicted deterioration in site-specific QoL (5). In many cases the indication for pituitary surgery may be relative and avoiding loss of overall HRQoL is crucial. Although there is some understanding of the impact of surgery on site-specific QoL, a better understanding of the postoperative dynamics of overall generic HRQoL can help elucidate the impact of both pituitary disease and surgical treatment. This may facilitate realistic expectations for both surgeons and patients.

The aim of the present study was to describe the postoperative dynamics of generic HRQoL up to six months following transsphenoidal surgery for pituitary adenomas. We further sought to assess potential patient or tumour characteristics that could predict clinically significant postoperative changes in generic HRQoL.

Materials and methods

Study population

We prospectively collected data from patients aged above 18 years undergoing transsphenoidal resection of pituitary adenomas at St. Olav´s University Hospital from October 2011 through November 2015. Surgery was performed using direct microscopy with endoscope assistance in selected cases. Data collection was approved by The Regional Committee for Medical and Health Research Ethics in Central Norway. All patients provided written informed consent before inclusion. A flow chart of the inclusion process is shown in Fig. 1.

Figure 1 near here

Outcome assessment

HRQoL can be described as an individual´s or group´s perceived physical and mental health over time (7). Generic HRQoL instruments assess general aspects of HRQoL, and allow for comparisons across different diseases and patient populations, as opposed to disease- or site-specific instruments (8). The EQ-5D 3L questionnaire is a generic HRQoL instrument developed by the EuroQol Group that is validated in the Norwegian population (9, 10). Five single-item dimensions are assessed: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension has three levels: "No problem", "Slight problem", and "Major problem". The responses can be converted into a single index value (score) by using an empirically derived set of valuations. In the present study, the index value calculations were based on a British survey with scores ranging from -0.594 to one (11), where one corresponds to perfect health, zero to death, and negative values are considered to be worse than death. The questionnaire also consists of EQ VAS (visual analogue scale),

which is a quantitative measure of the patients´ perceptions of their health state ranging from worst imaginable health state (0) to best imaginable (100).

Data collection

Included patients completed the EQ-5D 3L questionnaire at admission one to three days preoperatively, and at one and six months postoperatively with structured telephone interviews by a study nurse. Clinical data were collected from medical records at our institution. Adenomas were classified based on clinical and biochemical assessment. Preoperative tumour volume was assessed with preoperative MRI and determined using the ellipsoid formula ($(4\pi r_1 \bullet r_2 \bullet r_3)/3$, with r_x defined as diameter/2 from the largest perpendicular diameters in the coronar and sagittal view). Gross total resection was determined based on data from routine postoperative follow-up visits at three months with MRI and endocrinological evaluation. Gross total resection in functional adenomas was defined as endocrinological normalization, and in non-functional adenomas as lack of residual tumour on MRI. Hypopituitarism was defined as the need for replacement therapy in at least one axis. Visual disturbances were defined as impaired vision or having a visual field defect documented by an ophthalmologist. Preoperative headache was defined as any report of headache in referral letters or hospital medical records. Complications within 30 days after surgery were classified using the Landriel classification system (12). Charlson Comorbidity Index (CCI) was used to classify comorbidities (13).

Statistical analysis

All analyses were performed using SPSS statistics, version 24.0 (IBM Corporation, Armonk, New York). Statistical level of significance was set to $p < 0.05$ (two-sided). No correction for multiple significance testing was performed. We performed complete data analyses (i.e. no

imputations), assuming that data was missing at random. Normal distribution of data was assessed with Q-Q-plots. Mean with 95% CI (Confidence Interval) are presented for normally distributed data, while median and range are presented for skewed data. Comparisons between continuous and normally distributed data before and after surgery were performed using related samples Student's t-test, while related samples Wilcoxon signed-rank test was used for skewed data. Pearson's Chi square test or Fisher's exact test was used for categorical variables in contingency tables, and McNemars test was used for paired samples.

We categorized postoperative EQ-5D 3L index values into improved, unchanged, and deteriorated in relation to their preoperative values, as defined by a change greater than the minimal clinically important difference (MCID). MCID is a change in patient-reported score following an intervention that is of importance to the patient (14). MCID can be useful for clinicians when deciding whether or not changes detected by QoL instruments are clinically significant for the patient, either beneficial or harmful. MCID values depend on type of disorder and has not been established for EQ-5D 3L in patients with pituitary adenomas. However, MCID for EQ-5D 3L was calculated to be 0.14 among patients with intradural extramedullary tumours (mainly schwannomas and meningiomas) (15), and 0.13 to 0.15 for intracranial gliomas (16). Based on these studies we estimated that an MCID value of 0.14 would be a reasonable cut-off in our analyses.

The presence of a ceiling effect for EQ-5D 3L index values was evaluated by reporting the proportion of patients with the highest achievable index value. The ceiling effect was considered small if ≤ 15% of patients achieved the highest index value and moderate if > 15% (17). A series of univariable analyses were performed to determine if preoperative EQ-5D 3L

index values differed between subgroups of patients. Skewed continuous data was assessed using Mann-Whitney U test.

The following variables were screened for potential inclusion in multivariable logistic regression analyses described below: gender, age, functional adenomas (y/n), preoperative visual disturbances (y/n), preoperative tumour volume (ml), primary surgery (y/n), preoperative headache (y/n), preoperative hypopituitarism (y/n), hypopituitarism three months postoperatively (y/n), gross total resection (y/n). Variables associated with trends ($p < 0.1$) in univariable analyses were entered in multivariable logistic regression analyses to identify factors independently associated with clinically significant (> MCID) improvement or deterioration in EQ-5D 3L index value at six months postoperatively compared to preoperatively.

For sample size calculation, values for standard deviation (0.25) and MCID (0.14) were obtained from published literature on glioma patients (16), since EQ-5D 3L has not previously been used on patients with pituitary adenomas. A sample size calculation for paired samples were performed using SamplePower, 27 patients were required to provide power of 0.8 with alpha level of 0.05. Due to the skewed distribution of EQ-5D 3L index values, 15% was added resulting in a total of 31 patients.

Results

The final study sample consisted of 60 patients with pituitary adenomas (Figure 1). Median (range) follow-up was at four (3-6) weeks and six (5-7) months postoperatively. Patient and

treatment characteristics are presented in Table 1. As seen, the majority of patients had non-functional adenomas and mean age at surgery was 54 years.

Table 1 near here

EQ-5D 3L index values and EQ VAS preoperatively and at one and six months postoperatively are presented in Table 2. For the 57 patients assessed at one month, there was no statistically significant improvement in median EQ-5D 3L index value compared to the preoperative value (0.81 vs. 0.80), $p = 0.06$. Twelve patients (21%) reported a clinically significant improvement (>MCID), while seven (12%) reported a clinically significant deterioration, and 41 (68%) remained unchanged. Among the seven patients that reported a clinically significant deterioration, three reported the highest achievable EQ-5D 3L index value (1.0) preoperatively. For the 56 patients assessed at six months, there was a statistically significant improvement in median index value compared to the preoperative value (0.85 vs. 0.80), $p = 0.03$. Sixteen patients (29%) reported a clinically significant improvement, while eight (14%) reported a clinically significant deterioration, and 32 (57%) remained unchanged. Among the eight patients that reported a clinically significant deterioration, five reported the highest achievable EQ-5D 3L index value preoperatively. There was no statistically significant difference between median EQ-5D 3L index value at one and six months postoperatively. No statistically significant differences in EQ VAS were found among the 53 patients who completed EQ VAS at all three test points.

Table 2 near here

In the series of univariable analyses, the median EQ-5D 3L index value preoperatively was statistically significantly lower among women, patients with functional adenomas and patients with headache (Table 3).

Table 3 near here

Predictors of clinically significant (>MCID) postoperative improvement in EQ-5D 3L index value at six months in univariable analyses were younger age, larger preoperative tumour volume and having non-functional adenomas. Table 4 shows the outcome of the multivariable logistic regression analysis predicting the likelihood of clinically significant postoperative improvement in EQ-5D 3L index value at six months postoperatively. The model was statistically significant ($\chi 2 = 16.3$, $p = 0.001$), explained 36% (Nagelkerke R^2) of the variance, and correctly classified 79% of cases. In the multivariable logistic regression analysis predicting likelihood of clinically significant postoperative improvement in EQ-5D 3L index value, larger preoperative tumour volume was an independent predictor at six months postoperatively (Table 4). We failed to identify predictors of clinically significant postoperative deterioration in EQ-5D 3L index value.

Table 4 near here

The percentages of patients reporting any problem (slight or major) for each of the five EQ-5D 3L dimensions before and after surgery are presented in Figure 2.

Figure 2 near here

Discussion

We found that overall generic HRQoL was generally good in patients both before and after transsphenoidal surgery for pituitary adenomas. There was a slight, but statistically significant improvement in HRQoL at six months postoperatively compared to preoperatively. Approximately one third of patients reported a clinically significant improvement in HRQoL six months postoperatively. Larger preoperative tumour volume was associated with higher odds of such improvement. Preoperative headache and having a functional adenoma were associated with worse preoperative HRQoL, but these were not significant predictors of postoperative improvement. Although we did not identify predictors of clinically significant postoperative deterioration in HRQoL, 14% of patients reported such deterioration.

Although there was a statistically significant improvement in HRQoL at 6 months postoperatively, there was no such improvement at one month postoperatively. This may be explained by transitory postoperative discomfort and is in concordance with previous reports of reduced sinonasal QoL in the first postoperative month (3-5). Preoperative tumour volume has not been assessed in previous studies seeking to identify predictors of postoperative improvement in HRQoL after transsphenoidal surgery for pituitary adenomas (5, 6). We observed an association between larger preoperative tumour volume and higher odds of clinically significant postoperative improvement in HRQoL. This might reflect that patients with larger tumours suffer from symptoms that respond well to surgery, such as visual disturbances, thereby improving HRQoL. Due to limited power, our analysis does not exclude other potential predictors, such as hormone secretion and headache. Additionally, the generic HRQoL questionnaire used is associated with a significant ceiling effect, as demonstrated by one third of patients reporting the highest achievable score before surgery. Thus, our methods are not sensitive enough to detect less pronounced symptoms that might or might not have

improved after surgery. Given the good preoperative HRQoL, the potential for postoperative improvement is low and the potential benefit is easily lost if adverse effects occur, especially in the short-term.

In our study, younger age was not predictive of postoperative improvement in overall generic HRQoL. In comparison, a previous study found that younger age was predictive of improvement in psychological distress three months postoperatively, but it was not predictive of improvement detected by the other three QoL instruments used (6). This leads us to question the predictive importance of age on postoperative improvement in HRQoL. In our study, male gender was associated with higher HRQoL preoperatively compared to females, but it was not predictive of postoperative HRQoL improvement. This is opposed to the findings by Milian et al. who reported that male gender favoured postoperative improvement in HRQoL, although the conclusions from that study may be less certain due to the multiple analyses performed (6). The gender-difference detected preoperatively in our sample, may reflect those of the general population rather than disease-related gender-differences (18). Furthermore, having a functional adenoma was associated with lower HRQoL preoperatively compared to non-functional adenomas in our study. This is in concordance with previous findings of markedly impaired HRQoL especially among patients with Cushing´s disease (2).

In guidelines for the treatment of pituitary incidentalomas, unremitting headache is an indication for considering surgery (19). Approximately one in four patients in our study reported headache preoperatively, although headache type was not further classified. Patients with headache reported significantly reduced HRQoL preoperatively compared to those without, but preoperative headache was not predictive of postoperative improvement in overall HRQoL. There was a reduction in the number of patients reporting pain/discomfort

postoperatively compared to preoperatively, but as no information on headache at follow-up was available, it is not possible to either confirm or refute that this was because of reduced headache. Previous studies have generally not found larger pituitary tumour volume to be associated with headache frequency (20-22). Thus, headache alone may still be a controversial indication for treating pituitary adenomas (20, 22-24).

The EQ-5D 3L dimensions that patients reported markedly less problems with postoperatively compared to preoperatively, were Pain/Discomfort, Usual Activities and Anxiety/Depression, thereby explaining the improved HRQoL reported by some patients. The observed reduction in the number of patients reporting problems with Anxiety/Depression could perhaps be interpreted as postoperative relief of surgery-related anxiety, rather than disease- and treatment-associated changes. Anxiety and depression are also prevalent conditions in the general population (25), and the observed high prevalence both before and after surgery might partly be caused by comorbid conditions.

Even though we failed to identify predictors of clinically significant postoperative deterioration in overall HRQoL, approximately one in six patients reported such deterioration. Such patients may have few symptoms preoperatively, but undergo surgery to prevent later problems, such as progressive visual disturbances. Consequently, they have little short-term gain from surgery, and at least a temporary deterioration in HRQoL may then be expected. The reason why some patients deteriorated may be multifactorial, possibly reflecting random fluctuations in the condition, other conditions affecting HRQoL, or unrelated life events. Nonetheless, combined with the relatively benign nature of some pituitary adenomas and the risk of adverse events following surgical interventions, this highlights the importance of careful and well-founded selection of patients for surgery.

Strengths of this study include a prospective, longitudinal design, and the use of MCID defining clinically significant postoperative changes in HRQoL. The EQ-5D 3L was chosen due to its multidimensional structure and simplicity. Generic HRQoL instruments help establish the relative merit of different interventions, and can be useful for allocating resources (8). However, a disease-specific questionnaire such as the Leiden Bother and Needs Questionnaire presumably would have been more sensitive to problems commonly encountered by pituitary adenoma patients, but this was not developed at the time of patient inclusion (26). A major limitation is the relatively small sample size resulting in vulnerability to bias and reduced statistical power. Assessment of gross total resection and hypopituitarism were based on medical records from routine appointments, hence the endocrinological assessment may differ among included patients. The exploratory nature of our study combined with the lack of correction for multiple significance testing, raises the risk of false positive findings. It is possible that a follow-up time of six months is neither sufficient for long-term correction of hormonal imbalances nor for the negative effects of a functional adenoma to be fully reversed. This could explain QoL impairments beyond six months detected in some other studies (27-30). Furthermore, we observed a large ceiling effect in EQ-5D 3L index values resulting in reduced responsiveness. This may partly explain why it proved difficult to identify predictors of postoperative improvement, since a considerable proportion of patients reported so high HRQoL preoperatively that it was impossible to achieve a clinically significant improvement postoperatively.

Conclusions

In this series of functional and non-functional adenomas resected through the transsphenoidal route, overall generic HRQoL was generally good in the majority of patients both before and after surgery. Patients with preoperative headache or functional adenomas reported worse preoperative HRQoL. At group level, HRQoL improved slightly at six months postoperatively compared to preoperatively. Patients with larger tumours were more likely to experience clinically significant postoperative improvement in HRQoL.

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References:

1. Ghimire P, Hasegawa H, Kalyal N, Hurwitz V, Ashkan K. Patient-Reported Outcome Measures in Neurosurgery: A Review of the Current Literature. Neurosurgery. 2017.
2. Johnson MD, Woodburn CJ, Vance ML. Quality of life in patients with a pituitary adenoma. Pituitary. 2003;6(2):81-7.
3. Little AS, Kelly DF, Milligan J, Griffiths C, Prevedello DM, Carrau RL, et al. Comparison of sinonasal quality of life and health status in patients undergoing microscopic and endoscopic transsphenoidal surgery for pituitary lesions: a prospective cohort study. J Neurosurg. 2015;123(3):799-807.
4. McCoul ED, Anand VK, Schwartz TH. Improvements in site-specific quality of life 6 months after endoscopic anterior skull base surgery: a prospective study. J Neurosurg. 2012;117(3):498-506.
5. McCoul ED, Bedrosian JC, Akselrod O, Anand VK, Schwartz TH. Preservation of multidimensional quality of life after endoscopic pituitary adenoma resection. J Neurosurg. 2015;123(3):813-20.
6. Milian M, Honegger J, Gerlach C, Psaras T. Health-related quality of life and psychiatric symptoms improve effectively within a short time in patients surgically treated for pituitary tumors--a longitudinal study of 106 patients. Acta Neurochir (Wien). 2013;155(9):1637-45; discussion 45.
7. Centers for Disease Control and Prevention. Measuring Healthy Days. Atlanta, Georgia: CDC; 2000.
8. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. Med Care. 1989;27(3 Suppl):S217-32.
9. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.
10. Nord E. EuroQol: health-related quality of life measurement. Valuations of health states by the general public in Norway. Health Policy. 1991;18(1):25-36.
11. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35(11):1095-108.
12. Landriel Ibanez FA, Hem S, Ajler P, Vecchi E, Ciraolo C, Baccanelli M, et al. A new classification of complications in neurosurgery. World Neurosurg. 2011;75(5-6):709-15; discussion 604-11.
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
14. Cook CE. Clinimetrics Corner: The Minimal Clinically Important Change Score (MCID): A Necessary Pretense. J Man Manip Ther. 2008;16(4):E82-3.
15. Zuckerman SL, Chotai S, Devin CJ, Parker SL, Stonko DP, Wick JB, et al. Surgical Resection of Intradural Extramedullary Spinal Tumors: Patient Reported Outcomes and Minimum Clinically Important Difference. Spine (Phila Pa 1976). 2016;41(24):1925-32.
16. Sagberg LM, Jakola AS, Solheim O. Quality of life assessed with EQ-5D in patients undergoing glioma surgery: what is the responsiveness and minimal clinically important difference? Qual Life Res. 2014;23(5):1427-34.
17. McHorney CA, Tarlov AR. Individual-patient monitoring in clinical practice: are available health status surveys adequate? Qual Life Res. 1995;4(4):293-307.

18. Loge JH, Kaasa S. Short form 36 (SF-36) health survey: normative data from the general Norwegian population. Scand J Soc Med. 1998;26(4):250-8.
19. Freda PU, Beckers AM, Katznelson L, Molitch ME, Montori VM, Post KD, et al. Pituitary incidentaloma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(4):894-904.
20. Levy MJ, Jager HR, Powell M, Matharu MS, Meeran K, Goadsby PJ. Pituitary volume and headache: size is not everything. Arch Neurol. 2004;61(5):721-5.
21. Wolf A, Goncalves S, Salehi F, Bird J, Cooper P, Van Uum S, et al. Quantitative evaluation of headache severity before and after endoscopic transsphenoidal surgery for pituitary adenoma. J Neurosurg. 2016;124(6):1627-33.
22. Gravdahl GB, Tronvik EA, Fougner SL, Solheim O. Pituitary Adenoma and Non-acute Headache: Is There an Association, and Does Treatment Help? World Neurosurg. 2016;92:284-91.
23. Levy MJ, Matharu MS, Meeran K, Powell M, Goadsby PJ. The clinical characteristics of headache in patients with pituitary tumours. Brain. 2005;128(Pt 8):1921-30.
24. Schankin CJ, Reifferscheid AK, Krumbholz M, Linn J, Rachinger W, Langer S, et al. Headache in patients with pituitary adenoma: clinical and paraclinical findings. Cephalalgia. 2012;32(16):1198-207.
25. Norwegian Institute of Public Health. Mental health among adults 2014 [Available from: https://www.fhi.no/nettpub/hin/helse-og-sykdom/psykisk-helse-hos-voksne---folkehel/.
26. Andela CD, Scharloo M, Ramondt S, Tiemensma J, Husson O, Llahana S, et al. The development and validation of the Leiden Bother and Needs Questionnaire for patients with pituitary disease: the LBNQ-Pituitary. Pituitary. 2016;19(3):293-302.
27. Biermasz NR, Pereira AM, Smit JW, Romijn JA, Roelfsema F. Morbidity after long-term remission for acromegaly: persisting joint-related complaints cause reduced quality of life. J Clin Endocrinol Metab. 2005;90(5):2731-9.
28. Dekkers OM, van der Klaauw AA, Pereira AM, Biermasz NR, Honkoop PJ, Roelfsema F, et al. Quality of life is decreased after treatment for nonfunctioning pituitary macroadenoma. J Clin Endocrinol Metab. 2006;91(9):3364-9.
29. Lindsay JR, Nansel T, Baid S, Gumowski J, Nieman LK. Long-term impaired quality of life in Cushing's syndrome despite initial improvement after surgical remission. J Clin Endocrinol Metab. 2006;91(2):447-53.
30. van der Klaauw AA, Kars M, Biermasz NR, Roelfsema F, Dekkers OM, Corssmit EP, et al. Disease-specific impairments in quality of life during long-term follow-up of patients with different pituitary adenomas. Clin Endocrinol (Oxf). 2008;69(5):775-84.

Table 1 Patient and treatment characteristics

Age in years, mean (SD)	53.7 (15.0)
Female, n (%)	32 (53)
Preoperative CCI > 1, n (%)	5 (8)
Preoperative symptoms, n (%)	
Headache	17 (28)
Visual disturbances	23 (38)
Primary surgery, n (%)	51 (85)
Adenoma type, n (%)	
Non-functional	36 (60)
Adrenocorticotropic-secreting	7 (12)
Growth hormone-secreting	16 (27)
Prolactinoma	1 (2)
Preoperative tumour volume in ml, median (range)	3.3 (0.013-23.2)
Gross total resection[a], n (%)	27 (47)
Hypopituitarism[b], n (%)	
Preoperative	21 (35)
Postoperative	33 (55)
Landriel classification grading, n (%)	
No complications	35 (58)
Grade 1 (non-life-threatening)	21 (35)
Grade 2 (requiring invasive treatment)	2 (3)
Grade 3 (life-threatening, ICU management)	0 (0)
Grade 4 (death)	1 (2)
Complications, n (%)	
Transient DI	9 (15)
Persistent DI	4 (7)
UTI	6 (10)
Sinusitis	4 (7)
CSF leak	3 (5)
Other infections	3 (5)
Epistaxis	3 (5)
Pneumonia	3 (5)
Symptomatic cavity hematoma	3 (5)
Cerebral infarction	2 (3)
SIADH	1 (2)
Cerebral edema	1 (2)

SD Standard deviation, *CCI* Charlson comorbidity index, *ICU* Intensive care unit, *DI* Diabetes insipidus, *UTI* Urinary tract infection, *CSF* Cerebrospinal fluid, *SIADH* Syndrome of inappropriate antidiuretic hormone. [a]Defined as endocrinological normalization in functional adenomas, and as lack of residual tumour on MRI in non-functional. [b]Defined as the need for replacement therapy in at least one axis.

Table 2 EQ-5D 3L index values and EQ VAS before and after transsphenoidal surgery for pituitary adenomas. Follow-up data compared to preoperative data

	Preoperatively, n = 60	**One month postoperatively, n = 57**	**Six months postoperatively, n = 56**
EQ-5D 3L index value, median (range)	0.80 (0.10-1.0)	0.81 (-0.07-1.0)	0.85 (0.09-1.0)
MCID group, n (%)			
Improved		12 (21)	16 (29)
Unchanged		41 (68)	32 (57)
Deteriorated		7 (12)	8 (14)
No. of patients (%) with maximum index value (1.0)	18 (30)	22 (39)	23 (41)
EQ VAS, median (range)	75 (38-100)	75 (25-100)	80 (20-100)

MCID Minimal clinically important difference; defined as minimum 0.14 difference in EQ-5D 3L index value, Sagberg et al. (16), *VAS* visual analogue scale.

Table 3 Univariable analyses of median EQ-5D 3L index values for various patient and tumour characteristics before transsphenoidal surgery for pituitary adenomas

Characteristic	**Median EQ-5D 3L index value**		***P***
	Yes	**No**	
Female gender	0.71	0.82	0.01
Age ≤ 60 years	0.78	0.80	0.34
Primary surgery	0.80	0.88	0.48
Functional adenoma	0.75	0.80	0.04
Adrenocorticotropic-secreting	0.56	0.80	0.13
Growth hormone-secreting	0.78	0.80	0.47
Preoperative headache	0.69	0.81	0.001
Preoperative visual disturbances	0.80	0.80	0.69
Preoperative hypopituitarism[a]	0.80	0.80	0.73

[a]Defined as the need for replacement therapy in at least one axis.

Table 4 Multivariable logistic regression analysis (enter) predicting likelihood of clinically significant (>MCID) postoperative improvement in EQ-5D 3L index value after transsphenoidal surgery for pituitary adenomas

Predictor	**Six months postoperatively**		
	OR	95% CI OR	*P*
Age	0.95	0.89-1.00	0.06
Preoperative tumour volume	1.27	1.08-1.48	0.003
Functional adenomas[a]	0.26	0.05-1.39	0.12

OR Odds Ratio, *CI* Confidence Interval. [a]Functional adenomas (=1), non-functional (=0).