# Surgical complications after transsphenoidal microscopic and endoscopic surgery for pituitary adenoma: a consecutive series of 506 procedures

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# Forord

Oppgaven er basert på data hentet fra en prospektiv database over alle utførte tumoroperasjoner og gjennomgang av pasientjournaler ved Oslo Universitetssykehus. Arbeidet strekker seg over en 2-årsperiode fra våren 2011 og våren 2013.

Tusen takk til veileder og professor i nevrokirurgi Eirik Helseth og nevrokirurg Jon Ramm-Pettersen for uvurderlig hjelp og veiledning. Videre skal nevrokirurg Pål Rønning ha stor takk for sin innsats når det gjelder statistiske beregninger. Sist men ikke minst vil jeg takke professor i nevrokirurgi Jon Berg-Johnsen og endokrinolog Kari Lima for bidrag til datainnsamling.

Helene Halvorsen, 8. Mars 2013.

# Surgical complications after transsphenoidal microscopic and endoscopic surgery for pituitary adenoma: a consecutive series of 506 procedures

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# Abstract

**Background:** The aim of this study was to establish the rates of postoperative complications after transsphenoidal microscopic and endoscopic surgery.

**Method:** All transsphenoidal procedures for histologically verified pituitary adenomas performed between September 2002 and February 2011 were included in this retrospective study. The data were retrieved from a prospectively collected database of all tumor surgeries performed and from medical record review. No patients were lost to follow-up, with a median follow-up time of 28 months (range 3 – 103 months).

**Results:** There were 506 transsphenoidal procedures performed on 446 patients in the defined period. Median age at time of surgery was 57 years (range 9 – 85 years), and 58% were males. There were 268 microscopic and 238 endoscopic procedures. There were 352 non-functioning adenomas and 154 hormone secreting. A total of 73% of the procedures were primary surgeries and 27% were repeat surgery for tumor recurrence. The overall complication rate was 9.1%. The three most frequent complications were CSF leakage (4.7%), meningitis (2%) and visual deterioration (2%). Multivariate analyses showed an increased overall risk for complications with increasing age, surgery for recurrent tumor and surgery performed by low volume surgeons. There was no significant difference in the overall complication rate between microsurgical and endoscopic technique. The surgical mortality was 0.6%, and overall survival at 1 and 5 years was 95% and 90%, respectively.

**Conclusions:** We did not find any significant difference between the two techniques, though one must keep in mind that the introductory period of the endoscopic technique is included in the study. Surgical mortality was low. Overall survival at 1 and 5 years was, however, significantly lower for patients undergoing transsphenoidal surgery compared to the control population, most likely due to the pituitary disease per se.

# Introduction

Pituitary adenomas constitute approximately 10% of all primary intracranial tumors[1]. They are classified according to hormonal activity (non-secreting, prolactinoma, adenocorticotropic hormone (ACTH)-, growth hormone (GH)- or thyroid stimulating hormone (TSH)-producing)[2]. Surgery is the treatment of choice for most patients, although prolactinomas are usually initially treated with dopamine agonists.

The preferred surgical approach is transsphenoidal, either microscopic or endoscopic. At our institution the endoscopic transsphenoidal technique for pituitary adenoma surgery was introduced in 2005/2006 and has since then gradually replaced transsphenoidal microsurgery. The purpose of adopting a new surgical technique is to accomplish less invasive, more radical surgery with fewer complications. Hence, it is essential for all surgeons and departments to review their complication- and success rates when a new operative technique is implemented.

It is generally recognized that radical surgery is not obtained in the majority of patients with pituitary adenomas, and that approximately 15-20% need repeat surgery due to tumor recurrence[3,4]. The fact that many patients harbor remnant tumors is also demonstrated by the relatively low cure rates for hormone secreting adenomas, ranging from 15 to 50% for GH-producing macroadenomas to 34% for ACTH producing macroadenomas[5,6,7]. Despite having tumor remnants or going through repeat surgery, quality of life for many patients can be quite good[8,9]. Thus, striving for radicality must be carefully balanced against the risk and ramifications of surgical morbidity.

The aim of this study was to establish the rates of postoperative complications after transsphenoidal microscopic and endoscopic surgery. Most previous studies comparing the two techniques include patients operated by a single surgeon or team[10,11,12,13]. Norway is well suited for population-bases epidemiological studies because of its stable population and public health care system. This single institution consecutive series of transsphenoidal procedures includes all patients in a defined population of 2.6 million inhabitants operated during a time period.

# Methods and materials

## Study design

A total of 506 consecutive transsphenoidal procedures in 446 patients performed between September 2002 and February 2011 were included in this retrospective study. All procedures were carried out at the Oslo University Hospital (OUH)-affiliated hospitals, Rikshospitalet and Ullevål. The data were retrieved from a prospectively collected database of all tumor surgeries performed at our institution and from medical record review. Only histologically verified pituitary adenomas were included. Vital status (alive or deceased) and time of death were obtained from the Norwegian Population Registry (Folkeregisteret) on November 5, 2011.

## Variables recorded

The following patient characteristics were registered: age (at surgery), gender, type of adenoma (non-secreting, GH-, ACTH-, TSH- or prolactin producing), tumor size (microadenoma (<10 mm) or macroadenoma (≥10 mm)), preoperative visual deficit, preoperative hormone substitution (glucocorticoid, thyroxin, growth hormone, gonadotropins, antidiuretic hormone (ADH)), number of previous surgeries for pituitary adenoma, primary surgery or reoperation, vital status and time of death.
The following postoperative complications were recorded; visual deterioration, neurological deterioration other than visual, cerebrospinal fluid (CSF) leakage requiring lumbar drainage or surgical repair, reoperation for hematoma, meningitis (requiring antibiotics for ≥7 days), carotid artery injury and deep vein thrombosis (DVT)/pulmonary embolism (PE).

Furthermore, hospital (Rikshospitalet or Ullevål), surgical technique (microsurgery or endoscopic) and number of surgical procedures per surgeon were recorded. The surgeons were divided into two units for comparison. One consisting of the most experienced pituitary surgeon at our institution, referred to as high-volume surgeon, and the other containing the remaining surgeons referred to as low-volume surgeons.

**Surgical technique**

All patients were operated under general anesthesia. In the majority of the cases total intravenous anesthesia (TIVA) was used. Before 2005/2006 the standard microsurgical endonasal transseptal approach was used. The right nostril was entered, making an incision in the anterior part of the septum, and performed a dissection of the mucosa from the septal cartilage and bone. The anterior wall of the sphenoid sinus was opened bilaterally and any septum in the sphenoid removed as necessary. The floor of the sella was opened with a high-speed drill, and tumor was removed with standard instruments like curettes, suction and micro forceps. After tumor removal, the floor of the sella was reconstructed in most cases. Materials and techniques used for floor reconstruction depended on intraoperative findings and the individual surgeons preference. In pediatric patients with very small nostrils a sublabial approach was used. All patients had nasal packing that was removed the first postoperative day.

From 2005/2006 the endoscopic endonasal transsphenoidal approach was performed. One or both nostrils were entered dependent on the space available and the need for exposure during surgery. Standard Storz endoscopes (180/4 mm) with 0, 30 and 45 degrees angulations coupled to cameras were used, in the later period of the study coupled to HD cameras. According to the individual surgeons preferences some used a fixed endoscope support while others did not. The middle turbinate was lateralized to improve access to the sphenoethmoid recess and the sphenoid ostium identified and enlarged to allow passage of endoscope and surgical instruments. Septums in the sphenoid sinus were removed as necessary. Tumor resection was performed with standard surgical instruments like curettes, suction and micro forceps dependent on the tumor size and firmness. In tumors with parasellar extension an ultrasonic Doppler probe was used for localization of the internal carotid artery. As a result of the broader view possible with the endoscope, the opening of the sella was extended, making the closure of the sella floor more challenging. Floor of sella reconstruction was most often performed in a multilayer fashion with different autologous and artificial material. A vascularized nasal septal flap was also used when needed.

As infection prophylaxis, all patients were given 2 grams of cephalotin at the beginning of surgery. In patients with suspected hypersensitivity to cephalotin, 600 mg of clindamycin was used. All patients, except those with Cushing's disease, were given an intraoperative i.v. infusion with 12mg/h of hydrocortisone (Solu-Cortef®), continuing until 8 a.m. the first

postoperative day. Thereafter, cortisone was given orally, starting with 50 mg x 4, tapering down over a period of 7 days to a maintenance dose of 12.5 mg x 2. The patients were kept on this dose until scheduled follow-up three months postoperative in the department of endocrinology. Patients with Cushing's disease were not given any postoperative steroids unless they showed clinical symptoms of hypocortisolism or serum cortisol values below 100 μmol/L. Patients were mobilized and given low molecular weight heparin subcutaneously from the first postoperative day.

**Follow-up**

All patients had a scheduled follow-up, including an MRI-scan and an ophthalmologic evaluation, at the referring department of endocrinology after three months. Thereafter, most patients had follow-ups every 6 months. When needed, patients were discussed in a multidisciplinary pituitary meeting, or seen in a neuroendocrine outpatient ward consulted by both an endocrinologist and a neurosurgeon in the same session.

**Statistical analysis**

Standardized statistical analyses with Student's t-test for identifying differences between groups were performed. We used uni- and multivariate Cox and logistic regression analyses after ascertaining that assumptions of these models were fulfilled (Table 3 and 4).
Survival curves were generated using the Kaplan meier estimator. The logrank test was used to compare different survival curves. Survival curves for the general population was created using life tables from statistics Norway (www.statbank.ssb.no) matched on age, cohort and sex. A p-value less than 0.05 was considered significant. R v 2.15 was used for the statistical analyses.

**Ethics**

The Data Protection Official at Oslo University Hospital approved this study.

# Results

This single institution consecutive series consists of 506 transsphenoidal procedures performed on 446 patients between September 2002 and February 2011. The patient characteristics are shown in Table 1. Median age at time of surgery was 57 years (range 9 – 85 years). There were 79 GH-secreting, 51 ACTH-secreting, 20 prolactin-secreting, 4 TSH-secreting and 352 non-secreting adenomas. 88,9% were macroadenomas. The technique was microscopic in 268 (53%) and endoscopic in 238 (47%) of the procedures. Endoscopy-assisted microsurgery was included in the microscopy group. A total of 73% of the surgeries were primary and 27% were repeat surgery for tumor recurrence. Of the patients undergoing repeat surgery 103 had their second operation, 22 their third, 9 their fourth, 2 their fifth, 1 his sixth and seventh. No patients were lost to follow-up with a median follow-up of 28 months (range 3 – 103 months).

**Surgeon experience**

A total of 15 different surgeons performed one or more of the 506 procedures as main surgeon. One surgeon performed 238 procedures, four between 26-102 and 10 surgeons had < 5 procedures each. The surgeon who performed 238 procedures, referred to as high-volume surgeon, is compared to the remaining surgeons, referred to as low-volume surgeons, collectively as a group.

**Overall complication rate**

The total number of complications recorded was 61, occurring in 46/506 (9.1%) of the procedures (Table 2). The number of complications per procedure was 0 in 460, 1 in 35, 2 in 8, 3 in 2 and 4 in 1. Univariate and multivariate analyses of potential risk factors for complications are presented in table 3 (Table 3). The multivariate analyses revealed an increased overall risk for complications with increasing age, surgery for recurrent tumor and surgery performed by low volume surgeons. There was no significant difference in the overall complication rate between microsurgical and endoscopic technique, although there was a tendency towards a higher complication rate in the endoscopy group (Table 4).

**CSF leakage**

Postoperative CSF leakage occurred after 24 (4.7%) procedures and was the most frequent complication. The treatment was either lumbar drainage or surgical exploration and repair, or

both. CSF leakage was significantly more frequent after surgery for recurrent tumor than after primary surgery (p=0.036), and after surgery performed by low-volume surgeons (p=0.023). There was no significant difference in CSF leakage rate between endoscopic and microscopic transsphenoidal surgery (p=0.305).

**Meningitis**

Meningitis was the second most frequent complication. There were ten cases (2%), each successfully treated with antibiotics. In half of these cases there was a concurrent CSF leakage. Meningitis was significantly more frequent following endoscopic surgery than microsurgery (p=0.042), and there was also a significantly higher rate of meningitis following surgery performed by a low volume surgeon (p=0.013). There was a slight difference in the occurrence of meningitis between primary and recurrent surgery (p=0.076) that did not reach statistical significance.

**Neurological deterioration**

46% of the procedures were performed on patients with visual deficits prior to surgery. Nine procedures (2%) caused visual deterioration, either due to intraoperative manipulation of the optic chiasm or nerve (n=6) or to a postoperative hematoma compressing the optic pathways (n=3). Five procedures (1%) demonstrated new neurological postop deficits other than visual deterioration. One patient acquired a hemiparesis secondary to carotid artery injury, one displayed diffuse neurological impairment due to cerebral infarction, two showed signs of ophtalmoplegia and one became anosmic.

**Vascular complications**

Six patients required reoperation for hematomas. Two patients sustained injury to the internal carotid artery during surgery and four suffered from postoperative DVT/PE. All twelve patients with vascular complications had macroadenomas.

**Surgical mortality**

Surgical mortality defined as death within 30 days of surgery was 0.6 % (3 patients). Two patients with large macroadenomas died from massive PE 15 and 25 days after surgery, respectively. The third patient was moribund prior to surgery due to pituitary apoplexy and died 12 days post operatively from generalized cerebral edema.

**Survival**

Overall survival at 1 and 5 years was 95% and 90%, respectively, which is significantly lower than in the age, sex and cohort adjusted control population (Figure 1). Univariate- and multivariate analyses of potential factors predicting less favourable survival are presented in table 5. Increasing age was associated with reduced survival (HR 1.11 (95% CI 1.071-1.152)). Overall survival was not significantly associated with surgical method ($p = 0.216$) nor with primary versus recurrent surgery ($p = 0.709$).

# Discussion

This study was carried out to establish the rates and types of postoperative complications after transsphenoidal microscopic and endoscopic surgery. The overall surgical complication rate was 9.1%, of which CSF leakage (4.7%), meningitis (2%) and visual deterioration (2%) were the most frequent complications. There was no significant difference in the overall complication rate between microsurgical technique and endoscopic technique.

### Overall complication rate

An overall complication rate at 9.1% and this corresponds well to other published rates[14,15,16,17]. Multivariate analyses showed an increased overall risk for complications with increasing age, surgery for recurrent tumor and surgery performed by low volume surgeons. The overall complication rate has previously been shown to be dependent on several different factors like anatomical localization, firmness and size of the tumor, extent of removal, prior surgery and radiotherapy[18,19]. In microsurgical series, it has been reported to be in the range 8.2 to 47%[20,21,22], and with the endoscopic technique 10 to 26.3%[11,12,23,24]. Obviously, these rates are contingent on the authors' definition of complication. For instance, in this study we have not included endocrinological and nasal complications.

### Postoperative CSF leakage

The most frequent complication associated with transsphenoidal surgery in our series was CSF leakage with a rate of 4.7%. Significant risk factors for CSF leakage were surgery for recurrent tumor and surgery performed by a low-volume surgeon. There was no significant difference in CSF leakage rate between endoscopic and microscopic surgery. Others report leakage rates between 0.5 - 6.0%[12,15,25,26]. The lowest rates are from studies where the procedures are performed by just a single surgeon. The risk of CSF leakage is reported to be higher in macroadenomas than in microadenomas[26,27]. Our series contains a high proportion of macroadenomas (89%), which may contribute to the relative high incidence of CSF leakage. A recent publication showed that elevated body mass index is an independent predictor of postoperative CSF leakage after endoscopic transsphenoidal surgery[28].

### Meningitis

The second most frequent complication was meningitis, seen in ten cases (2%). Published data show an incidence of meningitis between 0.4 and 2.19%, and seems to be closely

correlated to the incidence of CSF-leakage[11,12,23,24,29,30,31]. Half of our patients with meningitis had concurrent CSF-leakage. Risk factors for meningitis were endoscopic surgery and surgery performed by a low volume surgeon. Thus, meticulous closure and reconstruction of the skull base appears to be the most important measure to prevent postoperative meningitis.

**Neurological deterioration**

Nine procedures were followed by visual deterioration (1.8%). Mechanical injury to the optic nerves and chiasm is a well-known complication, and can be caused by trauma, hemorrhage or ischemia[32]. A large proportion of our patients had preoperative visual field deficits due to large tumors with supra sellar extension, making them vulnerable to additional optic nerve dysfunction. Other surgery related neurological injuries are rare, totalling 5 procedures (1%) in this study. These can be caused by pressure on cranial nerves, vascular occlusion or affection of the hypothalamus or brainstem.

**Complications related to surgical method**

During the study period, a new surgical method was applied with the introduction of the endoscopic endonasal technique for transsphenoidal surgery. There was no significant difference in the overall complication rates between the new endoscopic approach and the traditional microscopic method. Three meta-analyses comparing the two surgical methods have recently been published, showing lower complication rates with endoscopic than microscopic surgery[13,33,34]. By including all patients operated with the new endoscopic technique the problems connected to the learning curve were simultaneously incorporated. Thus, as more experience is gained, one can anticipate a further decrease in the number of complications. The objective of implementing this new surgical technique was, as mentioned above, to accomplish more radical, less invasive surgery with fewer complications, but only time will tell if these goals can be achieved.

**Complications related to surgeons' experience**

Multivariate analyses show an increased overall risk of complications with surgery performed by low volume surgeons, which has also been demonstrated previously[35]. Other studies on the endoscopic technique have revealed a decrease in complications with increased surgeon experience[11,23,36,37]. It is similarly shown that experience increases the cure rate in hormone secreting tumors[38,39]. Clayton and co-workers have stated that a pituitary center should serve a population of 5 million people as a minimum, managed by only 2 surgeons to ensure proper

quality of treatment. This aim for centralization, however, must be balanced against the ability to offer a 24 hour service throughout a wide and sparsely populated country as Norway with its 5 million inhabitants.

**Complications related to primary or recurrent surgery**

Surgery for recurrent tumor was an independent risk factor for surgery related complications, in corroboration with other series reporting the rate of surgical complications after repeat surgery as high as 50%[40,41]. The reason may be that the delicate anatomical layers that can be used as dissection planes in primary surgery are destroyed and invaded with fibrous tissue[42], and in our experience the tumor may become more fibrous and firm at repeat surgery.

**Complications related to tumor size**

Unexpectedly, no difference in the rate of surgical complications between macro- and microadenomas was found. Tumor volume is a strong predictor of complication risk and outcome for large and giant Pituitary adenomas[18,43]. However, giant tumors that are soft in consistency, located in the midline and non-invasive may be easily removed, whereas small, fibrous and laterally located tumors with invasive growth may serve as a great challenge[44].

**Surgical mortality**

Surgical mortality in our series was 0.6% (3 patients). There are few systematic reviews on the surgical mortality for transsphenoidal surgery for pituitary adenomas. Most data available is from relatively small, uncontrolled case series, from a single center and performed by one surgeon. However, a systematic meta-analysis of publications regarding transsphenoidal surgery for non-functioning pituitary adenomas including 1232 patients, found a surgical mortality of 1%[14]. In the largest series published to date on pituitary surgery, Laws et al found a surgical mortality of 1.05%[15]. In a recent published series of 301 adenomas operated with endoscopic endonasal technique, the surgical mortality was 1%[16]. Comparing surgical mortality for transsphenoidal surgery with transcranial surgery there is a significant difference in favor of transsphenoidal surgery (1% vs. 7%)[14].

**Long-term survival**

Overall survival at 1 and 5 years was 95% and 90%, respectively. This is significantly lower than in the control population adjusted for age, cohort and gender. Age was the only identified parameter with significantly increased hazard ratio for shorter survival after surgery. Patients

with hormone-secreting adenomas have an increased long-term mortality rate, and for both somatotroph and corticotroph adenomas, the standardized mortality rate has been shown to be as high as 3.2 times the general population[45]. For non-functioning adenomas the data on long-term survival has been more conflicting, although most studies reported an increased mortality rate, particularly from cerebrovascular and cardiovascular disease. A prospective study has shown that hypopituitarism is an independent risk factor for increased mortality, predominately from vascular and respiratory disease[46]. Our study includes both non-functioning and hormone secreting adenomas, and the reduced long-term survival in this population is probably related to the pituitary disease per se rather than transsphenoidal surgery.

**Limitations and strengths**

The study is retrospective, but the data were retrieved from a prospectively collected database of all tumor surgeries performed at our institution and from thorough medical record review. The follow-up scheme is very rigid, where all patients are controlled at the endocrinology department either at our institution or at their local hospital. Thus, we have follow-up data on all patients with pituitary adenomas treated in this time period.

The data were limited to a single health center (Oslo University Hospital), and all procedures were carried out at the Oslo University Hospital (OUH)-affiliated hospitals Rikshospitalet and Ullevål, thereby reducing the possible confounding effect of variations in access to health care.

# Conclusion

The complication rate appears to be lower with the endoscopic technique, shown in several newly published meta-analyses. We did not find any significant difference between the two techniques, though one must keep in mind that the introductory period of the endoscopic technique is included in the study.

The mortality of transsphenoidal surgery for pituitary adenoma in this study is low, with no deaths directly related to the procedure. However, overall survival at 1 and 5 years was significantly lower for patients undergoing transsphenoidal surgery than for the control population, most likely due to the pituitary disease per se.

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**Table 1:** Characteristics in 446 patients undergoing 506 transsphenoidal procedures.

| | | N (%) |
|---|---|---|
| Hospital | Ullevål | 165 |
| | Rikshospitalet | 341 |
| Sex | Female | 215 (42.5) |
| | Male | 291 (57.5) |
| Age group | 0-14 years | 5 |
| | 15-29 | 24 |
| | 30-44 | 104 |
| | 45-59 | 163 |
| | 60-74 | 158 |
| | 75-89 | 52 |
| Hormone secretion | Non-secreting | 352 (69.6) |
| | GH | 79 (15.6) |
| | ACTH | 51 (10.1) |
| | Prolactin | 20 (4.0) |
| | TSH | 4 (0.8) |
| Visual deficit | Yes | 233 (46.0) |
| | No | 273 (54.0) |
| Tumor size | Micro | 56 (11.1) |
| | Macro | 450 (88.9) |
| Hormone substitution | Glucocorticoid | 132 (26.1) |
| | Thyroxin | 128 (25.3) |
| | Growth Hormone | 22 (4.3) |
| | Gonadotropins | 57 (11.3) |
| | ADH | 3 (0.6) |
| Primary or repeat surgery | Primary | 368 (72.7) |
| | Recurrent | 138 (27.3) |
| Surgical technique | Microsurgery | 268 (53.0) |
| | Endoscopic surgery | 238 (47.0) |

**Table 2:** Surgical complications in 506 transsphenoidal procedures.

| Type of complication | N (%) |
|---|---|
| CSF leakage | 24 (4.7) |
| Meningitis | 10 (2.0) |
| Increased visual deficit | 9 (1.8) |
| Reoperation for hematoma | 6 (1.2) |
| New neurological deficits | 5 (1.0) |
| Surgical mortality | 3 (0.6) |
| Carotid injury | 2 (0.4) |
| DVT/PE | 2 (0.4) |
| Total | 61 |

**Table 3:** Univariate and multivariate analysis of surgical complications

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| **Variable** | **Odds ratio** | **95% conf.int** | **Odds ratio** | **95% conf.int** |
| Sex | | | | |
| Female | Ref | | | |
| Male | 1.289 | (0.689, 2.412) | 1.199 | (0.617, 2.327) |
| Age | 1.033 | (1.010, 1.055)** | 1.027 | (1.003, 1.051)* |
| Surgery | | | | |
| Primary | Ref | | | |
| Recurrent | 2.016 | (1.082, 3.759)* | 1.909 | (1.004, 3.629)* |
| Surgeon experience | | | | |
| High volume | Ref | | | |
| Low volume | 2.430 | (1.247, 4.737)** | 2.191 | (1.102, 4.357)* |
| Method | | | | |
| Microscopic | Ref | | | |
| Endoscopic | 1.852 | (0.996, 3.442) | 1.627 | (0.861, 3.077) |
| Hormone secretion | | | | |
| Functioning adenoma | Ref | | | |
| Non functioning adenoma | 2.209 | (1.005, 4.853)* | 1.801 | (0.614, 5.280) |
| Tumor size | | | | |
| Microadenoma | Ref | | | |
| Macroadenoma | 1.338 | (0.461, 3.884) | 0.422 | (0.101, 1.768) |

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

**Table 4:** Complications related to surgical technique

| | Microscopic | Endoscopic |
|---|---|---|
| **No** | **268** | **238** |
| CSF-leakage | 12 | 12 |
| Meningitis | 2 | 8 |
| Increased visual deficit | 4 | 5 |
| Reoperation for hematoma | 3 | 3 |
| New neurological deficits | 0 | 5 |
| Surgical mortality | 0 | 3 |
| Carotid injury | 1 | 1 |
| DVT/PE | 0 | 2 |
| **Total no. of complications** | **22 (8,2%)** | **39 (16,4%)** |

Table 5. Univariate and multivariate analysis of overall survival

| | Univariate | | Multariate | |
|---|---|---|---|---|
| **Variable** | **Hazard ratio** | **95% conf.int** | **Hazard ratio** | **95% conf.int** |
| Sex | | | | |
| Female | Ref | | | |
| Male | 1.007 | (0.525, 1.930) | 0.936 | (0.480, 1.826) |
| Age | 1.114 | (1.078, 1.151)*** | 1.111 | (1.071, 1.152)*** |
| Surgery | | | | |
| Primary | Ref | | | |
| Recurrent | 0.904 | (0.427, 1.917) | 0.729 | (0.338, 1.573) |
| Surgeon experience | | | | |
| High volume | Ref | | | |
| Low volume | 2.316 | (1.156, 4.636)* | 1.380 | (0.680, 2.801) |
| Method | | | | |
| Microscopic | Ref | | | |
| Endoscopic | 1.677 | (0.813, 3.458) | 1.741 | (0.827, 3.663) |
| Hormone secretion | | | | |
| Functioning adenoma | Ref | | | |
| Non functioning adenoma | 3.211 | (1.250, 8.251)* | 0.733 | (0.260, 2.066) |

- $p<0.05$, ** $p<0.01$, *** $p<0.001$

**Figure 1:** Overall survival for patients treated with transsphenoidal surgery for pituitary adenoma compared to the general population adjusted for age, cohort and gender.