Exoscopic vs. microscopic transsphenoidal surgery for Cushing’s disease: a retrospective single-center study on 388 patients

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Abstract
Microscopic and endoscopic transsphenoidal surgeries represent the standard treatment for Cushing’s disease (CD). At our institution a new exoscopic approach was implemented. After proof of the general use for transsphenoidal pituitary surgery, the aim of this study was to compare the exoscopic 4K3D video microscope with the microscopic transsphenoidal surgery for patients with CD. We conducted a retrospective analysis on 388 patients with CD treated in our medical center via microscopic transsphenoidal surgery (MTS) between January 2008 and July 2019 or via exoscopic transsphenoidal surgery (ExTS) between May 2019 and May 2021. Parameters investigated included histology, pre- and postoperative MRI with tumor size, pre- and postoperative ACTH and cortisol levels, duration of surgery, perioperative and postoperative complications as well as clinical outcome. Patients who underwent ExTS in CD experienced a lower incidence of SIADH/diabetes insipidus \( (p = 0.0164) \), a higher rate of remission \( (p = 0.0422) \), and a shorter duration of surgery \( (p < 0.0001) \), compared to MTS. However, there was no significant difference regarding new postoperative pituitary insufficiency and intraoperative CSF space opening. We found that ExTS had multiple benefits compared to MTS for tumor resection in case of CD. These results are in line with our previous publication on the general applicability of an exoscope in pituitary surgery. To our knowledge, this is the first clinical study proving the superiority of ExTS in CD. These results are promising, nevertheless further studies comparing exoscopic with the endoscopic approach are necessary to finally evaluate the utility of the new technique.

Keywords Cushing’s disease · Microscopic transsphenoidal surgery · Exoscopic transsphenoidal surgery · ACTH · Cortisol

Introduction
Endonasal transsphenoidal surgery remains the standard treatment for Cushing’s disease (CD). The two main operative techniques consist of microscopic (MTS) and endoscopic transsphenoidal surgery (ETS). MTS has been the most popular surgical procedure for pituitary adenomas to date. However, in recent years the endoscopic approach was applied increasingly, as it offers better image resolution with higher magnification and the opportunity for additional surgical exposure if necessary [1]. Moreover, the endoscopic technique was associated with shorter mean duration of surgery [2], similar rate of postoperative pituitary insufficiency [3, 4] and other postoperative complications such as diabetes insipidus [3], a higher incidence of cerebrospinal fluid (CSF) leaks [3] as well as higher remission rates compared to MTS [1, 2] with predominance seen by macroadenomas [2, 3]. However, the data regarding incidence of cerebrospinal fluid (CSF) leaks [1,
An exoscope is a new high-definition digital imaging system which has recently been successfully implemented in different fields of neurosurgery such as neurovascular, tumor or peripheral nerve surgery and offers better maneuverability, ergonomics, and stereoscopic visualization, in comparison to the standard microscope [7–11]. First experiences with the exoscopic 4 K 3D video microscope (Orbeye, Olympus) for transsphenoidal surgery from our center have already been reported [12] and have shown that, among all pituitary surgeries, the exoscopic technique seems to create an advantage in image quality, depth perception, surgical ergonomics, and learning curve, compared to MTS. In the current study, we aim to compare MTS to exoscopic transsphenoidal surgery (ExTS), especially regarding duration of surgery as well as complication and remission rates for the isolated cohort of patients with Cushing’s disease. In theory, ExTS would be an ideal approach for this selected collective comprising relatively small tumors.

**Methods**

**Patient selection**

A total number of 388 patients after 418 transsphenoidal surgical procedures in the treatment of CD were retrospectively analyzed. Surgeries were performed either via MTS between January 2008 and July 2019 or via ExTS between May 2019 and May 2021. CD was defined according to the endocrine society guidelines [13]. In unclear cases, central venous sampling like inferior petrosal sinus sampling (IPSS) or cavernous sinus sampling (CSS) was required.

**Laboratory studies**

Serum cortisol, adreno-corticotropic hormone (ACTH), prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone or estrogen, growth hormone (GH), insulin-like growth factor-1 (IGF-1), thyroid-stimulating hormone (TSH), and thyroid hormones (fT3 and fT4) were examined preoperatively 1 day prior to surgery and were drawn on postoperative days 1 and 3 as well as on varying postoperative days before discharge.

**Radiological evaluation**

Focused-sellar MRI exams were performed either in an outpatient setting or inpatient prior to surgery. Tumor size was measured in the preoperative MRI and then classified as micro- (<1 cm), macroadenoma (≥ 1 cm and < 4 cm) or giant tumor (≥ 4 cm). Furthermore, suprasellar, cavernous sinus, sphenoid sinus, and clival invasion were evaluated. Preoperative intratumoral hemorrhage was also assessed.

**Histological examination**

Intraoperative specimens were fixed in 4% paraformaldehyde, dehydrated, embedded in paraffin, and then sectioned in 4-µm slices according to standard lab protocols and underwent H & E staining as well as periodic acid–Schiff reaction staining. Immunohistochemistry for pituitary hormones (adreno-corticotropic hormone, somatotropic hormone, prolactin, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone); S100 protein; pancytokeratin (KL1 or Ca m 5.2); Tpit expression; mitotic marker phosphohistone-3 (PH3); proliferation marker Ki-67 (MIB-1); and accumulation of tumor suppressor protein p53 were performed using an automated staining protocol (Ventana BenchMark TX, Roche Diagnostics, Mannheim, Germany).

Tissue specimens were examined by senior physicians of the Department of Neuropathology at the University Medical Center Hamburg-Eppendorf.

**Surgical procedure**

Surgeries were performed by a team of experienced neurosurgeons either via microscopic or exoscopic transsphenoidal surgery. In the microscopic and exoscopic surgery, the patient’s positioning does not differ. The patient is positioned in a semi-sitting position with fixed rotation of the head towards the surgeon sitting at the right patient’s side. In the microscopic technique, the oculars of the microscope are placed in front of the nostrils, with the surgeon’s head following the oculars when changing the direction of view.

In the exoscopic technique, the smaller camera is positioned in front of the nostrils while the surgeon is watching the picture on a 4 K screen behind the patient’s head with 3D glasses. When changing the camera’s direction of view, the surgeon’s head and posture can maintain its position. Both operative techniques have previously been described [12, 14, 15]. Duration of surgery was defined as incision-suture time.

**Statistical analyses**

Clinical data was acquired from the patients’ electronic files via systematic data search. Data is reported as means with standard deviations (SD) for continuous variables, and as frequencies for categorical variables. The Kolmogorov–Smirnov test was performed to determine normal distribution. Means were compared using the unpaired t-test when data distribution was normal, or by the Wilcoxon rank-sum test when variables were not normally distributed. For categorical analyses, a chi-square test and
Fisher’s exact test were used. A \( p \) value < 0.05 was considered statistically significant. The statistical tests and data visualization were performed in GraphPad Prism (Version 8.4.3).

**Results**

**Demographic and clinical data**

Twenty-seven out of 388 patients had to undergo two or three surgeries (2 surgeries in 24/27 cases and three surgeries in 3/27 cases). There were 237 females (75.5%) in the MTS group and 58 females (78.4%) in the ExTS cohort. Mean age was 43.4 years (range: 6.3–80 years) and 41.5 years (range: 4.3–72 years), respectively. The MTS group comprised 193 microadenomas, 93 macroadenomas, and two giant tumors. Thirty-three patients showed no visible tumor on MRI, and tumor size in preoperative imaging was not available in 21 cases. Preoperative intratumoral hemorrhage occurred in four patients (1.2%). Primary surgeries amounted to 258; 82 patients had undergone prior surgery. Suprasellar invasion was found in 40, cavernous sinus invasion in 83, clival invasion in 5, and sphenoid sinus invasion in 13 cases, respectively.

The ExTS cohort encompassed 43 microadenomas, 20 macroadenomas, 12 patients without detectable tumor, and 3 specimens in which tumor size was not available. Preoperative intratumoral hemorrhage was radiologically identified in one patient (1.3%). Sixty patients underwent primary surgery and 18 recurrence surgery. Tumor invasion was present in 23 cases with suprasellar invasion in 10, cavernous sinus invasion in 17, clival invasion in 2, and sphenoid sinus invasion in 3 cases, respectively.

All results are summarized in Table 1.

**Histological analyses**

Histological examination after the 340 MTS procedures revealed 213 densely granulated corticotrophic adenomas, 81 sparsely granulated corticotrophic adenomas, and 4 Crooke’s cell adenomas. In 9 cases, the granularity pattern could not be specified. In 33 specimens, no tumor could be detected in the histological examination.

Among the 78 patients operated via ExTS we diagnosed, 45 densely granulated corticotrophic adenomas, 12 sparsely granulated corticotrophic adenomas, and 6 Crooke’s cell adenomas, according to WHO 2017 classification. In 3 cases of adenoma, the granulation pattern could not be evaluated. Twelve patients only presented with Crooke’s cells as a sign of hypercortisolemia without tumor.

**Follow-up**

All patients were scheduled for regular postoperative follow-up exams, which comprised clinical, laboratory, and MRI evaluation. Remission rate was defined taking into account all available parameters like abnormal circadian rhythm by late night salivary cortisol or midnight serum cortisol; impaired cortisol feedback by dexamethasone suppression test and increased 24-h cortisol by urinary free cortisol and additionally the available MRI scans. The mean follow-up period was 32.5 months (range: 0–137 months) for the MTS cohort and 8.8 months (range: 0–26) for the ExTS group. Ninety-two patients did not attend the recommended postoperative examination at our clinic. On follow-up, radiological and laboratory remission was achieved in 217/388 surgeries. Overall a higher remission rate was achieved after tumor resection via ExTS, compared to MTS (81% vs. 66.3%, \( p = 0.0422 \)). Differences were observed after primary surgeries of both microadenoma (95.5% vs. 83.7%, \( p = 0.2986 \)) and macroadenoma (84.6% vs. 62.7%, \( p = 0.1912 \)) as well as for repeated surgery of macroadenoma (25% vs. 15.4%, \( p = 0.5384 \)) and transsphenoidal surgery without histologically proven tumor (54.5% vs. 42.9%, \( p = 0.7120 \)); however, these differences were not statistically significant. No difference regarding remission rates was observed for repeated surgery of microadenoma (50% vs. 51.6%, \( p = 0.9999 \)). Overall, higher remission rates were attained after resection of microadenoma, compared to macroadenoma within both the ExTS and MTS groups. The complete comparison is presented in Table 2. For 3 patients, no clinical data was available.

**Surgical aspects, complications, and distinctive features**

Mean duration of surgery was significantly shorter in ExTS, compared to MTS (72.5 (± 21.8) minutes vs. 90.7 (± 36.2), \( p < 0.0001 \)). Subgroup analyses were performed with respect to tumor size, the presence or absence of tumor (in MRI and in histology), and a history of prior surgeries. Significantly shorter duration of surgery could be observed in all tumor resections (71.9 (± 19.8) min vs. 87.5 (± 34.1) min, \( p < 0.0001 \)), but especially with a predominance in primary surgeries of microadenomas (67.2 (± 15.9) min vs. 83.9 (± 34) min, \( p = 0.0027 \)) and macroadenomas (67.8 (± 13.6) min vs. 84.5 (± 24.9) min, \( p = 0.0191 \)). In CD with absence of histological tumor detection, no significant difference in surgical duration could be found between both surgical procedures (75 (± 30.4) min vs. 110.4 (± 45.5) min, \( p = 0.0977 \)). Intraoperative CSF space opening (9% vs. 11.9%, \( p = 0.5558 \)) and new postoperative pituitary insufficiency (6.4% vs. 11%, \( p = 0.2986 \)) were comparable between ExTS and MTS.
The incidence of electrolyte imbalances in the ExTS collective was lower compared to MTS. Other less common postoperative complications after both MTS and ExTS are summarized in Table 3.

### Discussion

#### Surgical procedures, complications and remission

Here, we present the first study comparing the mean duration of surgery as well as complication and remission rates between MTS and ExTS in CD. The idea was that the new exoscopic technique combining some benefits of the microscopic and endoscopic techniques could be useful especially in CD with frequently more circumscribed lesions of the sella, when the use of an endoscope is not necessary.

Our results show a statistically significant higher remission rate after ExTS compared to MTS (81% vs. 66.3%, \( p = 0.0422 \)) and shorter mean duration of surgery in ExTS compared to MTS (72.5 (± 21.8) min vs. 90.7 (± 36.2), \( p < 0.0001 \)), which could be explained by higher image resolution, enhanced depth perception, and a steeper learning curve in ExTS as already described in the literature [12]. In our opinion, the exoscope offers a better maneuverability compared to the more unwieldy microscopes due to the more flexible and lighter camera.

Since the posture does not need to be changed when changing the viewing angle, the ergonomics is more pleasant especially for long surgeries and while operating on obese patients or patients with a rigid cervical spine (particularly

| Characteristic                                      | MTS          | ExTS          |
|-----------------------------------------------------|--------------|---------------|
| Total number of patients                            | 314          | 74            |
| Female                                              | 237 (75.5%)  | 58 (78.4%)    |
| Male                                                | 77 (24.5%)   | 16 (21.6%)    |
| Number of surgeries                                 | 340          | 78            |
| Age in yrs (range)                                  | 43.4 (6.3–80)| 41.5 (4.3–72) |
| Duration of follow-up in months (range)             | 32.5 (0–137) | 8.8 (0–26)    |
| Tumor size                                          |              |               |
| Microadenoma                                        | 193 (56.8%)  | 43 (55.1%)    |
| Mean tumor size in cm cor/sag/ax                    | 0.47/0.45/0.42| 0.59/0.56/0.45|
| Macroadenoma                                        | 91 (26.8%)   | 20 (25.6%)    |
| Mean tumor size in cm cor/sag/ax                    | 1.57/1.55/1.44| 1.42/1.25/1.19|
| Giant tumor                                         | 2 (0.6%)     | 0 (0%)        |
| Mean tumor size in cm cor/sag/ax                    |              |               |
| No tumor                                            | 33 (9.7%)    | 12 (15.4%)    |
| Mean tumor size available                           | 21 (6.2%)    | 3 (3.9%)      |
| Overall mean tumor size in cm cor/sag/ax*           | 0.74/0.66/0.64| 0.69/0.63/0.56|
| Preoperative intratumoral hemorrhage                | 4 (1.2%)     | 1 (1.3%)      |
| Associated hyperprolactinemia with prolactin levels < 100 ng/ml | 6 (1.8%) | 1 (1.3%) |
| Histopathological subgroups according to WHO 2017 Classification | | |
| Densely granulated corticotrophic adenoma           | 213 (62.7%)  | 45 (57.7%)    |
| Sparsely granulated corticotrophic adenoma          | 81 (23.8%)   | 12 (15.4%)    |
| Crooke’s cell adenoma                               | 4 (1.8%)     | 6 (7.7%)      |
| No tumor, Crooke cells                              | 33 (9.7%)    | 12 (15.4%)    |
| Adenoma — granulation histologically not specified | 9 (2.6%)     | 3 (3.8%)      |
| Invasiveness                                        | 110 (32.4%)  | 23 (29.5%)    |
| Suprasellar invasion                                | 40 (11.8%)   | 10 (12.8%)    |
| Cavernous sinus invasion                            | 83 (24.4%)   | 17 (21.8%)    |
| Sphenoid sinus invasion                             | 13 (3.8%)    | 3 (3.8%)      |
| Clival invasion                                     | 5 (1.5%)     | 2 (2.6%)      |
| Primary surgery                                     | 258 (75.9%)  | 60 (76.9%)    |
| Repeated surgery                                    | 82 (24.1%)   | 18 (23.1%)    |

*MTS microscopic transsphenoidal surgery, ExTS exoscopic transsphenoidal surgery, ax axial, cm centimeter, cor coronal; sag sagittal, yrs years*
in those cases in the microscopic technique, the surgeon sometimes has to bend his torso over the patient in order to approach the patient’s left nostril, which could lead to early fatigue and back pain).

Differences in incision-suture time are especially remarkable in primary surgeries of microadenomas and macroadenomas. On the other hand, we did not observe a significant difference between both techniques for tumor recurrence surgeries, which could be explained by the small number of patients in these groups and the manifold variables associated with prior surgeries such as previous operative technique, primary surgeon, extent

### Table 2 Results

| Characteristic                  | MTS  | ExTS  | p-value |
|--------------------------------|------|-------|---------|
| **Microadenoma — first surgery** |      |       |         |
| Mean (± SD) duration of surgery in minutes | 83.9 (± 34) | 67.2 (± 15.9) | 0.0027 |
| Intraoperative CSF space opening | 11 (7%) | 1 (3%) | 0.6955 |
| Remission                      | 103/123 (83.7%) | 21/22 (95.5%) | 0.2000 |
| Diabetes insipidus/SIADH        | 15 (9.7%) | 1 (3%) | 0.3131 |
| New pituitary insufficiency     | 16 (10.3%) | 2 (6%) | 0.7442 |

| **Microadenoma — repeated surgery** |      |       |         |
| Mean (± SD) duration of surgery in minutes | 97.7 (± 35) | 86.5 (± 26.9) | 0.0625 |
| Intraoperative CSF space opening | 7 (18.4%) | 3 (3%) | 0.4143 |
| Remission                      | 16/31 (51.6%) | 3/6 (50%) | >0.9999 |
| Diabetes insipidus/SIADH        | 5 (13.2%) | 0 (0%) | 0.5689 |
| New pituitary insufficiency     | 2 (5.3%) | 1 (1%) | 0.5123 |

| **Macroadenoma — first surgery** |      |       |         |
| Mean (± SD) duration of surgery in minutes | 84.5 (± 24.9) | 67.8 (± 13.6) | 0.0191 |
| Intraoperative CSF space opening | 7 (11.1%) | 2 (12.5%) | <0.9999 |
| Remission                      | 32/51 (62.7%) | 11/13 (84.6%) | 0.1912 |
| Diabetes insipidus/SIADH        | 8 (12.7%) | 0 (0%) | 0.1973 |
| New pituitary insufficiency     | 11 (17.5%) | 1 (6.25%) | 0.4417 |

| **Macroadenoma — repeated surgery** |      |       |         |
| Mean (± SD) duration of surgery in minutes | 105.7 (± 41.3) | 100.3 (± 15.5) | >0.9999 |
| Intraoperative CSF space opening | 8 (28.6%) | 0 (0%) | 0.5947 |
| Remission                      | 4/26 (15.4%) | 1/4 (25%) | 0.5384 |
| Diabetes insipidus/SIADH        | 4 (14.3%) | 0 (0%) | <0.9999 |
| New pituitary insufficiency     | 5 (17.9%) | 1 (25%) | <0.9999 |

| **All tumors**                  |      |       |         |
| Mean (± SD) duration of surgery in minutes | 87.5 (± 34.1) | 71.9 (± 19.8) | <0.0001 |
| Intraoperative CSF-leakage       | 38/304 (12.5%) | 6/91 (9.1%) | 0.5331 |
| Remission                      | 163/246 (66.3%) | 39/48 (81%) | 0.0422 |
| Diabetes insipidus/SIADH        | 33/304 (10.9%) | 1 (1.5%) | 0.0164 |
| New pituitary insufficiency     | 35/304 (11.5%) | 5 (7.6%) | 0.5109 |

| **No tumor**                    |      |       |         |
| Mean (± SD) duration of surgery in minutes | 110.4 (± 45.5) | 75 (± 30.4) | 0.0977 |
| Intraoperative CSF-leakage       | 2 (6.1%) | 1 (8.3%) | >0.9999 |
| Remission                      | 9/21 (42.9%) | 6/11 (54.5%) | 0.7120 |
| Diabetes insipidus/SIADH        | 2 (6.1%) | 1 (8.3%) | >0.9999 |
| New pituitary insufficiency     | 2 (6.1%) | 0 (0%) | >0.9999 |

| **All operations**             |      |       |         |
| Mean (± SD) duration of surgery in minutes | 90.7 (± 36.2) | 72.5 (± 21.8) | <0.0001 |
| Intraoperative CSF space opening | 40/337 (11.9%) | 7 (9%) | 0.5558 |
| Remission                      | 172/267 (64.4%) | 45/59 (76.3%) | 0.0939 |
| Diabetes insipidus/SIADH        | 35/337 (10.4%) | 2 (2.6%) | 0.0269 |
| New pituitary insufficiency     | 37/337 (11%) | 5 (6.4%) | 0.2986 |

n number of patients, SIADH—syndrome of inappropriate antidiuretic hormone secretion
of resection and complications, which could not be completely accounted for in our analysis.

Interestingly, we could observe a high inconsistency regarding the incidence of complications and remission rate after MTS in the literature [1–3, 6, 16], which can result from batch effects.

Studies with a percentage frequency distribution of micro- and macroadenomas similar to our cohort revealed similar remission rates [1, 17]. Higher remission rates presented in other studies may be associated with a higher percentage of microadenomas within these cohorts [2, 3, 6]. Analyses considering microadenomas and macroadenomas separately revealed remission rates comparable with our results [3, 5, 6]. Another feasible cause for varying remission rates may be a different cut-off value for remission in the biochemical results, especially as every laboratory has individual normal ranges for the same biochemical parameters. Moreover, many studies did not present their criteria for remission rates. Studies revealed similar incidences of new postoperative pituitary insufficiency after ETS and MTS [3, 4], ranging between 6 and 11.5% for ETS and 6 and 9.4% for MTS, and comparable with results from our study.

Incidence of diabetes insipidus reported in the literature after ETS were lower than after MTS3, but much higher compared to our study.

Endoscopic transsphenoidal pituitary surgery (ETS) is a well-established technique in the treatment of CD, especially for invasive adenomas, as it may provide better visualization for suprasellar extension or lateral invasion of the tumor, and it is associated with a lower incidence of new postoperative pituitary insufficiency [2, 3, 6]. Data regarding remission and gross total resection (GTR) rates remain incoherent [2, 3, 6].

ExTS offered postoperative high remission rates comparable with that after ETS, but with a lower rate of postoperative complications such as new hypopituitarism or SIADH/diabetes insipidus and a shorter mean duration of surgery, when comparing ExTS to ETS described in the literature [1–3, 6, 18, 19]. Based on these results, ExTS may present a further development in the treatment for Cushing’s disease by evolution of the optical possibilities and thus improving the postoperative results.

**Study limitations**

Our study is limited partly by the retrospective character of the analysis. Moreover, not all patients were available for follow-up analyses. For three patients, clinical data were not available. A certain bias could be possible due to the slight changing of the operating surgeons.

**Conclusions**

Our study presents the largest available cohort of patients after exoscopic transsphenoidal surgery and confirms the utility of this operative technique in the management of Cushing’s disease, as it shows lower postoperative SIADH/diabetes insipidus rates, a higher remission rate, and a shorter duration of surgery, compared to microscopic transsphenoidal surgery. Additionally, no significant differences between both techniques were observed with respect to postoperative new pituitary insufficiency. These results are in line with our previous publication on the general applicability of an exoscope in pituitary surgery. For Cushing’s disease, it might be even more meaningful, due to the relatively small adenomas, which lack

| Table 3 Other complications after microscopic and exoscopic transsphenoidal surgery |
|---------------------------------|---------------------------------|---|
| Complication          | Comment                                              | %  |
| MTS                   | 1 CN palsy w/diplopia CN III                      | 0.3 |
| 6 CSF-leakage         | 1 with meningitis, 1 with ventriculitis, 2 w/reoperation, and 1 with vp-shunt | 1.8 |
| 1 abscess             | Intracerebral                                   | 0.3 |
| 3 postoperative hemorrhage | 1 subdural hematoma, 1 subarachnoid hemorrhage with vasospasm, bleeding after inferior petrosal sinus sampling | 0.6 |
| 4 epistaxis           |                                                   | 1.2 |
| 10 required intensive care | Mostly due to electrolyte imbalance                   | 2.9 |
| Endocrinological      | 11 adrenal crisis                                  | 1.3 |
| Other                 | 2 sinusitis, 1 stroke of middle cerebral artery, 2 venous thromboembolism | 1.5 |
| ExTS                  | 2 epistaxis                                       | 2.6 |
| 1 required intensive care | Due to respiratory insufficiency                  | 1.3 |
| 1 CSF-leakage         |                                                   | 1.3 |
| Endocrinological      | 1 adrenal crisis                                   | 1.3 |

*CN cranial nerves, op operation, reop reoperation, vp-shunt ventriculoperitoneal shunt*
the necessity of an endoscopic approach. These first results are very promising; however, further studies comparing with the endoscopic approach are necessary to fully evaluate the utility of the operative technique.

Author contribution Conception and design: Rotermund, Sumislawski. Acquisition of data: Sumislawski, Rotermund, Ryba, Piffko, Burkhardt, Saeger. Analysis and interpretation of data: Sumislawski, Rotermund. Drafting the article: Sumislawski, Rotermund. Critically revising the article: Rotermund, Aberle, Flitsch, Huckhagel, Burkhardt. Reviewed submitted version of manuscript: all the authors. Approved the final version of the manuscript on behalf of all the authors: Rotermund. Administrative/technical/material support: Saeger. Study supervision: Rotermund.

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Data Availability Underlying data can be provided upon reasonable request.

Declarations

Ethical approval and consent to participate Approval of the study was obtained from the local ethics committee (Ethikkommission der Ärztekammer Hamburg). Informed consent was obtained from all patients (above 16 years old) and their legal guardian(s) (below 16 years of age). The study was performed in accordance with the Declaration of Helsinki.

Data availability All data generated or analysed during the study are included in this published article.

Human and animal ethics Not applicable.

Consent for publication The authors affirm that informed consent for publication was given by all the participants.

Competing interests Jörg Flitsch has been a lecturer for Olympus.

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