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ORIGINAL ARTICLE - PITUITARIES

The Zurich Pituitary Score predicts utility of intraoperative high-field magnetic resonance imaging in transsphenoidal pituitary adenoma surgery

Victor E. Staartjes[1] · Carlo Serra[1] · Nicolai Maldaner[1] · Giovanni Muscas[2] · Oliver Tschopp[3] · Michael B. Soyka[4] · David Holzmann[4] · Luca Regli[1]

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Abstract

Background It is currently unclear if there are subsets of patients undergoing transsphenoidal surgery (TSS) in which intraoperative high-field magnetic resonance imaging (3T-iMRI) is particularly advantageous. We aimed to investigate whether a radiological grading scale predicts the utility of 3T-iMRI in pituitary adenoma (PA) TSS.

Methods From a prospective registry, patients who underwent endoscopic TSS for PA using 3T-iMRI were identified. Adenomas were graded using the Zurich Pituitary Score (ZPS). We assessed improvement after 3T-iMRI in terms of gross total resection (GTR), residual volume (RV), and extent of resection (EOR).

Results Among 95 patients, rates of conversion to GTR after 3T-iMRI decreased steadily from 33% for grade I to 0% for grade IV adenomas, with a statistically significant conversion rate only for grade I ($p = 0.008$) and grade II ($p < 0.001$). All grade I adenomas were completely resected after 3T-iMRI. Median RV change was statistically significant for grades I to III, but not for grade IV ($p = 0.625$). EOR improvement ranged from a median change of 0.0% (IQR 0.0–4.5%) for grade I to 4.4% (IQR 0.0–9.0%) for grade IV, with a significant improvement only for grades I to III ($p < 0.05$).

Conclusions Interestingly, this study shows that clinical utility of 3T-iMRI is highest in the more "simple" adenomas (ZPS grades I–II) than for the more "complex" ones (ZPS grade III–IV). Grade I adenomas are amenable to GTR if 3T-iMRI is implemented. In grade III adenomas, EOR and RV can be improved to clinically relevant levels. Conversely, in grade IV adenomas, 3T-iMRI may be of limited use.

Keywords Intraoperative imaging · Magnetic resonance imaging · Zurich Pituitary Score · Gross total resection · Extent of resection · Outcome prediction

Victor E. Staartjes and Carlo Serra contributed equally to this work.

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✉ Carlo Serra
c.serra@hotmail.it

[1] Department of Neurosurgery, Clinical Neuroscience Center, University Hospital Zurich, University of Zurich, Frauenklinikstrasse 10, 8091 Zurich, Switzerland

[2] Department of Neurosurgery, Tuscany School of Neurosurgery, University of Firenze, Florence, Italy

[3] Department of Endocrinology, Diabetes, and Clinical Nutrition, University Hospital Zurich, University of Zurich, Zurich, Switzerland

[4] Department of Otolaryngology, Head and Neck Surgery, University Hospital Zurich, University of Zurich, Zurich, Switzerland

Introduction

In recent decades, endonasal transsphenoidal surgery (TSS) has established itself as the gold standard technique for surgical treatment of pituitary adenomas (PA)[1–5] With both endoscopic and microscopic techniques, high rates of gross total resection (GTR) can be achieved in a relatively safe procedure with minimal morbidity and mortality [1, 6–9].

Several factors are known to influence the likelihood of GTR, including adenoma and sellar morphology [3, 9–13], diameter, and volume [13, 14], as well as invasion into the cavernous sinus space (CSS) [8, 9, 11] and sellar dura [15]. Some of these factors have been compounded into classification schemes, such as the Knosp classification [9, 11] and the Zurich Pituitary Score (ZPS) [13]. Both demonstrate a strong correlation with the likelihood of GTR [9, 13]. There is some evidence that the Knosp classification may be more suitable for prediction of residual tumor in the CSS [8, 9, 13], while the ZPS relates more strongly to volumetric extent of resection (EOR) and residual tumor volume (RV) and has excellent interrater agreement [9, 13, 16].

In patients harboring hormone-secreting adenomas, especially, but not exclusively, GTR is the primary surgical goal [17], since residual tumor volume is associated with postoperative morbidity and mortality [17–20]. Preservation and if possible restoration of endocrinological and neurological function and nasal quality of life [2, 21–24] are further treatment goals. Intraoperative high-field magnetic resonance imaging (3T-iMRI) is an assistive technique which has been reported to improve GTR, RV, and EOR by several authors [25–37].

The utility of intraoperative MRI for pituitary surgery is highly debated in the neurosurgical community. Several authors keep that the reported improvement in GTR, RV, and EOR rate would be the result of the more conservative attitude of those surgeons who, knowing they will perform 3T-iMRI, tend to be less aggressive in the surgical phase prior to imaging [38]. Other authors recommend not to use intraoperative imaging due to its alleged high incidence of false positives [39]. Indeed, despite its clear benefits, 3T-iMRI is costly, prolongs operative time, and is not always available. Understanding better whether 3T-iMRI is going to be of value in a particular patient has the potential to improve patient counseling, surgical decision-making, cost-effectiveness, and outcome prediction.

The purpose of this study was to investigate whether simple pre-operative imaging grading systems can predict the utility of 3T-iMRI in patients undergoing endoscopic TSS for PA. Specific interest was set to test the common assumption that intraoperative imaging leads to measurable benefits particularly in higher-grade PAs.

Materials and methods

Patients

A consecutive series of patients that underwent 3T-iMRI-assisted endoscopic TSS for PA performed by two senior neurosurgeons (L.R. and C.S.) at the Department of Neurosurgery of our institution was evaluated. From October 2012 onwards, all patients undergoing TSS for a PA were treated according to the same protocol with clinical and radiological data collected in a prospective registry [34]. A mononostril approach was used in all patients in this series. Inclusion criteria were the availability of pre-, intra-, and 3-month postoperative imaging. Patients undergoing transcranial or combined procedures, as well as those in which the initial surgical goal was decompression only, were excluded. 3T-iMRI was carried out routinely, unless medically contraindicated [40]. This manuscript was compiled according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [41]. The registry was approved by our institutional committee (KEK St-V-Nr 2015-0142), and data were treated according to the Declaration of Helsinki.

Outcome measures

Primary endpoint was the rate of conversion to GTR after 3T-iMRI, defined as the percentage of patients who underwent further resection because of 3T-iMRI, eventually reaching GTR.

All patients underwent pre-, intra-, and 3-month postoperative volumetric contrast-enhanced MRI (Siemens 3-T Skyra VD13) at a field strength of 3 T. Extent of resection (EOR) was measured on the 3-month postoperative MRI and was calculated as the percentagewise reduction of RV to baseline tumor volume on preoperative MRI. GTR was defined as an EOR of 100%. Adenoma morphology was graded according to the ZPS [13] as well as the modified Knosp classification [9]. Each adenoma was manually contoured on source volumetric sequences to allow subsequent 3D rendering and volumetric measurement (iPlan Cranial, BrainLab). The utility of 3T-iMRI was assessed as the difference in outcome measures between the endoscopic result (3T-iMRI) and the final result (3-month MRI).

Statistical analysis

Continuous data are given as mean ± standard deviation (SD), medians (interquartile ranges (IQR)), and ranges, whereas categorical data are presented as numbers (percentages). Since no missing data was observed for the analyzed variables and the included patients, there was no need for imputation. Comparisons of paired continuous data were made using the exact version of Wilcoxon's

signed-rank test [42], while McNemar's test was used on dichotomous data. Trends over ZPS grades were statistically tested for. The Cochrane-Armitage test was applied for dichotomous variables, and the exact version of the Jonckheere-Terpstra test, based on 10,000 permutations, was applied for continuous variables. A $p \leq 0.05$ was considered statistically significant. All analyses were carried out in R version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria) [43]. The statistical code is provided as Supplementary Methods 1.

Results

Patient population

A total of 95 patients underwent TSS using 3T-iMRI and fit criteria for inclusion (Table 1). There was no missing data. Most patients (68%) harbored non-functioning adenomas (NFPA). Adenoma morphology corresponded most commonly to ZPS grade II (49%), Hardy grade II (33%), and Knosp grade 2 (29%).

Gross total resection

Overall, GTR conversion rates increased from an endoscopic 44% to a final 72% (Table 2). When stratified by ZPS grade, endoscopic GTR rates were 67%, 43%, 25%, and 0% for ZPS I to IV, respectively (Fig. 1). On 3-month follow-up imaging, we observed GTR in 100%, 74%, 38%, and 0% of patients, respectively ($p < 0.001$). Rates of conversion to GTR after 3T-iMRI were significantly higher in low-ZPS-grade patients (Fig. 2), decreasing steadily from 33% for grade I to 0% for grade IV adenomas. Statistically significant conversion rates were seen only for grade I ($p = 0.008$) and grade II ($p < 0.001$).

Residual tumor volume

The median preoperative tumor volume was 3.1 (IQR 1.17 to 5.93) cm^3, which decreased to a median intraoperative RV of 0.08 (IQR 0.0 to 0.4) cm^3 and a median overall final RV of 0.0 (0.0 to 0.08, $p < 0.001$) cm^3 (Table 3). Median reduction of RV per ZPS grade was statistically significant for grade I (− 0.0, IQR − 0.06 to 0.0, $p = 0.004$) and grade II (0.0, IQR − 0.32 to 0.0, $p < 0.001$), as well as grade III (− 0.15, IQR − 0.42 to 0.0, $p = 0.001$), but not for grade IV (− 0.35, IQR − 0.55 to 0.0, $p = 0.625$) adenomas (Fig. 3). The decreasing trend in RV change reached statistical significance ($p = 0.008$).

Extent of resection

Overall, EOR increased from an endoscopic median of 97.8% (IQR 90.2 to 100%) to a final 100% (IQR 99.0 to 100%) at 3 months postoperatively (Table 4). When stratified by ZPS grade, median endoscopic GTR rates were 100%, 97.1%, 95.9%, and 80.5% for ZPS I to IV, respectively (Supplementary Figure 1). On 3-month follow-up imaging, we observed median EORs of 100%, 100%, 99.0%, and 89.5% respectively. Rates of improvement in EOR after 3T-iMRI were significant only for grades I to III (all $p < 0.05$) although the trend in EOR change failed to reach statistical significance ($p = 0.085$).

Table 1 Baseline characteristics of the included patients.

Parameter	Value ($n = 95$)
Male gender, *n* (%)	53 (56)
Age (years)	
Mean ± SD	53.8 ± 15.9
Median (IQR)	53.6 (42.5 to 67.4)
Range	20 to 82
Tumor type, *n* (%)	
Non-functioning	65 (68)
GH-secreting	19 (20)
Prolactin-secreting	9 (9)
ACTH-secreting	2 (2)
Revision TSS, *n* (%)	9 (9)
Preoperative tumor volume (cm^3)	
Mean ± SD	4.85 ± 5.41
Median (IQR)	3.1 (1.17 to 5.93)
Range	0.07 to 33.67
ZPS ratio	
Mean ± SD	1.0 ± 0.4
Median (IQR)	1.0 (0.7 to 1.2)
Range	0.3 to 2.3
ZPS, *n* (%)	
Grade I	27 (28)
Grade II	47 (49)
Grade III	16 (17)
Grade IV	5 (5)
Knosp classification, *n* (%)	
Grade 0	22 (23)
Grade 1	20 (21)
Grade 2	28 (29)
Grade 3A	15 (16)
Grade 3B	5 (5)
Grade 4	5 (5)
Hardy classification (sellar), *n* (%)	
Grade 0	2 (2)
Grade I	12 (13)
Grade II	31 (33)
Grade III	15 (16)
Grade IV	35 (37)

SD, standard deviation; *IQR*, interquartile range; *TSS*, transsphenoidal surgery; *ZPS*, Zurich Pituitary Score

Table 2 Surgical results in terms of gross total resection (GTR) rates, given as overall values and stratified by the Zurich Pituitary Score. The change from endoscopic to final GTR for each ZPS grade is statistically evaluated using McNemar's test. The trend in terms of EOR change among the four grades was assessed using the Cochran-Armitage test

Parameter	Overall	Zurich Pituitary Score			
	($n = 95$)	Grade I ($n = 27$)	Grade II ($n = 47$)	Grade III ($n = 16$)	Grade IV ($n = 5$)
Endoscopic GTR					
n (%)	42 (44)	18 (67)	20 (43)	4 (25)	0 (0)
Final GTR (3 months)					
n (%)	68 (72)	27 (100)	35 (74)	6 (38)	0 (0)
Conversion to GTR					
n (%)	27 (28)	9 (33)	15 (32)	3[a] (19)	0 (0)
P (endoscopic to final)	< 0.001*	0.008*	< 0.001*	0.617	–
P (trend)	0.055				

GTR, gross total resection

*$p \leq 0.05$

[a] Three grade III patients converted from subtotal resection intraoperatively to GTR at 3 months. Furthermore, complete extirpation was observed intraoperatively in a patient in whom recurring tumor was observed in the cavernous sinus space at 3 months

Discussion

In a prospective registry of patients operated for PA, we investigated whether subsets of patients exist in which 3T-iMRI is most valuable as an intraoperative assistive technique and conversely such in which it is of little added value. Our approach was to identify these subsets of patients by grading adenoma morphology and invasion into adjacent structures according to the ZPS which had shown to be effective in predicting GTR, EOR, and RV [13]. Our data demonstrate that there are differences in the utility of intraoperative imaging when patients are stratified by this radiological classification. In particular, GTR can virtually always be achieved in ZPS grade I adenomas when 3T-iMRI is utilized. Conversely, the benefit in grade IV adenomas is inconsequential, since it is likely that no improvement in GTR rate can be achieved, while the change in EOR and RV is not clinically relevant. For medium-grade adenomas, intraoperative imaging may be useful, as both EOR and RV can be improved to satisfactory levels, although no statistically significant benefit in GTR was proven in our series.

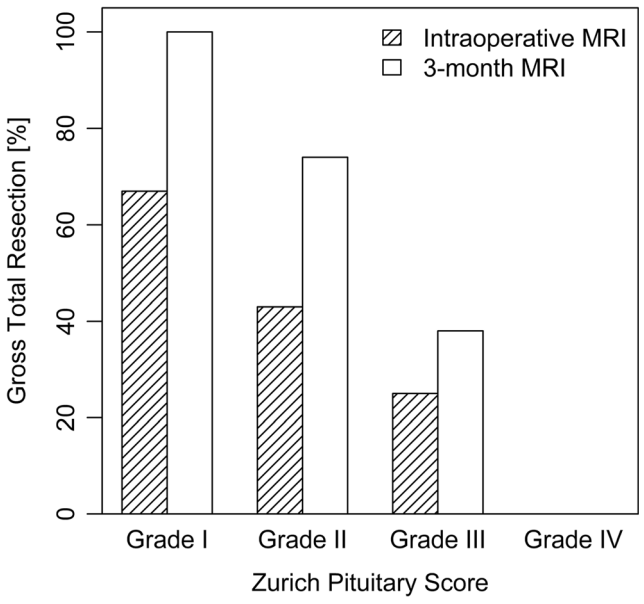

Fig. 1 Rates of gross total resection (GTR) on intraoperative and on 3-month postoperative magnetic resonance imaging, stratified by the Zurich Pituitary Score. In none of the grade IV cases was GTR observed. MRI, magnetic resonance imaging

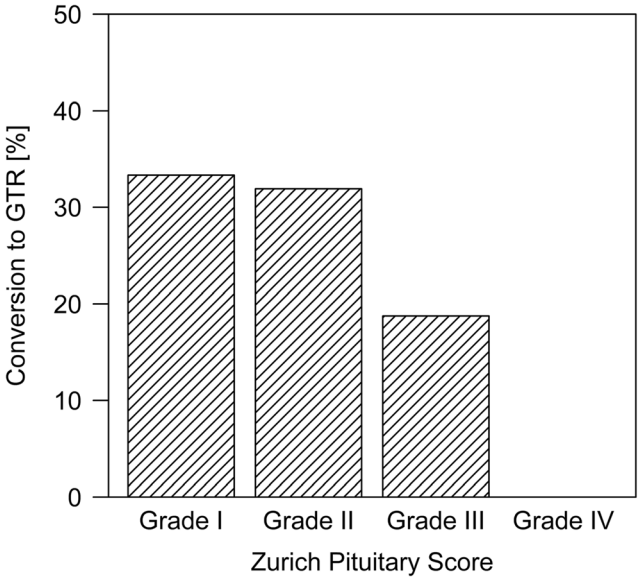

Fig. 2 Rates of conversion to gross total resection (GTR) from the intraoperative high-field magnetic resonance imaging (MRI) to the 3-month follow-up MRI. Conversion rates are stratified by the Zurich Pituitary Score. No conversions to GTR were observed for grade IV adenomas. GTR, gross total resection;

Table 3 Surgical results in terms of residual volume (RV), given as overall values in cm^3 and stratified by the Zurich Pituitary Score. The change from endoscopic to final RV for each ZPS grade is statistically evaluated using paired Wilcoxon's signed-rank tests. The trend in terms of RV change among the four grades was assessed using the Jonckheere-Terpstra test

Parameter	Overall	Zurich Pituitary Score			
	($n = 95$)	Grade I ($n = 27$)	Grade II ($n = 47$)	Grade III ($n = 16$)	Grade IV ($n = 5$)
Endoscopic RV (cm^3)					
Mean ± SD	0.47 ± 1.57	0.06 ± 0.16	0.33 ± 0.52	1.34 ± 3.6	1.25 ± 1.15
Median (IQR)	0.08 (0.0 to 0.4)	0.0 (0.0 to 0.06)	0.15 (0.0 to 0.45)	0.32 (0.06 to 0.59)	0.76 (0.37 to 2.45)
Range	0.0 to 14.55	0.00 to 0.78	0.0 to 2.32	0.0 to 14.55	0.14 to 2.51
Final RV (3 months) (cm^3)					
Mean ± SD	0.13 ± 0.34	0.0 ± 0.0	0.11 ± 0.33	0.19 ± 0.30	0.88 ± 0.62
Median (IQR)	0.0 (0.0 to 0.08)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.01)	0.09 (0.0 to 0.16)	0.76 (0.41 to 0.94)
Range	0.00 to 1.95	0.0 to 0.0	0.0 to 1.95	0.0 to 1.00	0.37 to 1.90
Change in RV (cm^3)					
Mean ± SD	− 0.34 ± 1.46	− 0.06 ± 0.16	− 0.22 ± 0.55	− 1.14 ± 3.36	− 0.37 ± 0.81
Median (IQR)	0.0 (− 0.26 to 0.0)	0.0 (− 0.06 to 0.0)	0.0 (− 0.32 to 0.0)	− 0.15 (− 0.42 to 0.0)	− 0.35 (− 0.55 to 0.0)
Range	− 13.55 to 1.52	− 0.78 to 0.0	− 2.32 to 1.52	− 13.55 to 0.02	− 1.57 to 0.62
P (endoscopic to final)	< 0.001*	0.004*	< 0.001*	0.001*	0.625
P (trend)	0.008*				

RV, residual volume; *SD*, standard deviation; *IQR*, interquartile range

*$p \leq 0.05$

In the modern era, maximization of tumor resection is possible with minimal morbidity and mortality [2, 23, 26, 37]. In the quest for maximal resection, several adjuvant techniques have been introduced, among them endoscopy and intraoperative imaging [39]. Although class I evidence is lacking, such tools are reported by several centers to be beneficial for reaching higher GTR rates and are thus seeing increased use [27].

Currently, only few centers have implemented high-field intraoperative MRI in their routine clinical practice. This may be partially explained by the inherent costs and prolonged operative time [27, 28]. Furthermore, 3T-iMRI is not always feasible, either for logistic or for medical reasons. Little is known on the specific utility of 3T-iMRI in certain morphological subsets of pituitary adenomas. Pal'a et al. found that in 28 patients who underwent endoscopic TSS, GTR

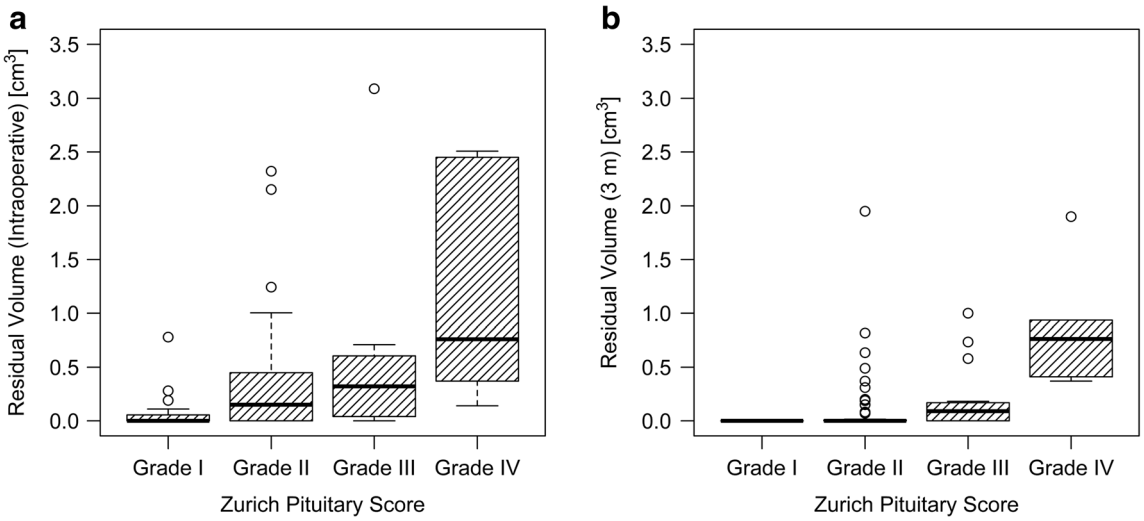

Fig. 3 Residual tumor volumes (RV) as measured **a** on intraoperative magnetic resonance imaging (MRI) and **b** on the 3-month follow-up MRI, stratified by the Zurich Pituitary Score. Values are provided in cubic centimeters. An extreme outlier (grade III) presenting with an intraoperative RV of 14.55 cm^3 is not depicted in order to preserve scale

Table 4 Surgical results in terms of extent of resection (EOR), given as overall values and stratified by the Zurich Pituitary Score. The change from endoscopic to final EOR for each ZPS grade is statistically evaluated using paired Wilcoxon's signed-rank tests. The trend in terms of EOR change among the four grades was assessed using the Jonckheere-Terpstra test

Parameter	Overall	Zurich Pituitary Score			
	($n = 95$)	Grade I ($n = 27$)	Grade II ($n = 47$)	Grade III ($n = 16$)	Grade IV ($n = 5$)
Endoscopic EOR (%)					
Mean ± SD	92.1 ± 13.3	95.7 ± 8.4	91.4 ± 15.6	91.1 ± 12.0	83.3 ± 14.0
Median (IQR)	97.8 (90.2 to 100)	100 (95.5 to 100)	97.1 (90.5 to 100)	95.9 (86.9 to 99.6)	80.5 (80.2 to 93.8)
Range	19.6 to 100	69.7 to 100	19.6 to 100	56.8 to 100	63.0 to 99.0
Final EOR (3 month) (%)					
Mean ± SD	98.2 ± 3.8	100 ± 0.0	98.3 ± 3.6	97.6 ± 4.2	89.7 ± 4.4
Median (IQR)	100 (99.0 to 100)	100 (100 to 100)	100 (99.8 to 100)	99.0 (97.1 to 100)	89.5 (86.2 to 93.8)
Range	83.1 to 100	100 to 100	86.7 to 100	83.1 to 100	84.6 to 94.6
Change in EOR (%)					
Mean ± SD	6.1 ± 13.0	4.3 ± 8.4	7.0 ± 15.9	6.5 ± 10.5	6.4 ± 10.6
Median (IQR)	0.0 (0.0 to 6.4)	0.0 (0.0 to 4.5)	0.0 (0.0 to 6.0)	3.4 (0.0 to 6.8)	4.4 (0.0 to 9.0)
Range	− 10.4 to 80.4	0.0 to 30.3	− 10.4 to 80.4	− 0.4 to 40.2	− 4.4 to 23.2
P (endoscopic to final)	< 0.001*	0.004*	< 0.001*	0.001*	0.250
P (trend)	0.085				

EOR, extent of resection; *SD*, standard deviation; *IQR*, interquartile range

*$p \leq 0.05$

increased by 6.6% for Knosp grade 0–2 adenomas and by 15.4% for Knosp grade 3–4 adenomas after 1.5T-iMRI [32]. They conclude that the added value of intraoperative imaging increases with the complexity of the treated tumor. Apart from this data, the analysis of our prospective registry is the only currently available report dedicated to this research question.

Our analysis indicates that the added value of 3T-iMRI may be greatest in low-grade adenomas. Although this may seem paradoxical at first, it reflects our clinical experience in using routine 3T-iMRI for PA in TSS. Intrasellar remnants are technically always removable. However, even in experienced hands, they may be missed by endoscopic inspection, particularly if they are very small (see Table 3). The use of high-field intraoperative (io)-MRI guarantees that such tiny rests do not go overlooked. Intracavernous remnants on the contrary will not be resectable even detected on io-MRI. Because ZPS grade I and II adenomas are unlikely to infiltrate laterally into the CSS and because in these cases, the surgical corridor allows full access to the entire extent of the tumor [10, 13], these adenomas should in theory always be amenable to GTR. In other words, a missed intrasellar residual, particularly in ZPS grade I, should be considered as a gross surgical failure. In our series, the benefit of 3T-iMRI in ZPS grade I and II adenomas was evident, increasing the rate of GTR from 51% intraoperatively to 84% at 3 months and leading to GTR in 100% of grade I adenomas. To a lesser extent, GTR in grade III tumors increased from 25 to 38%, without statistical significance. Still, in grade III adenomas, we demonstrated a statistically significant improvement in both EOR and RV, both reaching excellent levels (see Table 3). High EOR and low RV have been repeatedly proven to be associated with improved outcome, particularly for functioning adenomas [44–46]. Thus, one could say that particularly in grade I and II adenomas, the use of high-field intraoperative imaging shows the highest benefit, since GTR should always be the desired outcome (Fig. 4).

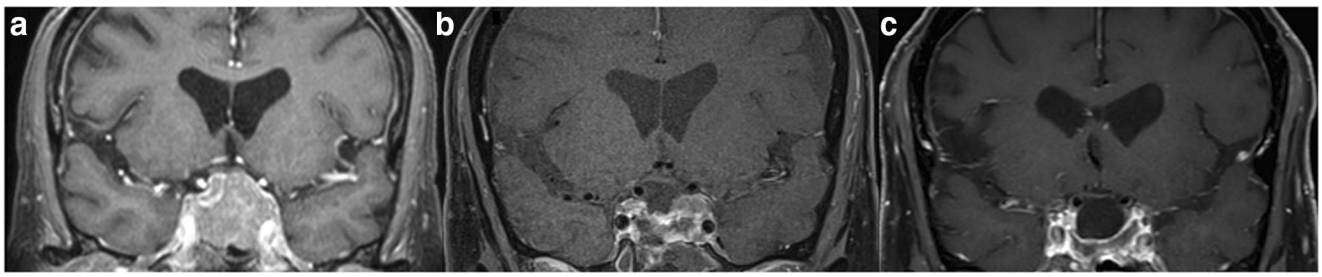

Fig. 4 Illustrative case. Preoperatively, a large macroadenoma with a Zurich Pituitary Score of III was seen (**a**). On intraoperative magnetic resonance imaging (**b**), residual tumor tissue was detected intrasellarly and invading into the left cavernous sinus space, which was fully resected after intraoperative imaging (**c**)

Pituitary adenomas encasing the internal carotid artery (grade IV) did not appear to benefit in the same way. Intuitively, one might be inclined to think that especially in very complex and invasive tumors, the utility of intraoperative imaging may be the highest [32]. In our series, 3T-iMRI did not lead to conversion to GTR in any of the grade IV cases, and only marginal improvements in RV and EOR were observed. While this improvement probably did not reach statistical significance due to low statistical power, clinical significance is not given because 3T-iMRI failed to elevate both EOR and RV to clinically relevant levels, i.e., to a negligibly low final RV. This is illustrated in Figs. 3 and 4. In addition, this finding is corroborated by case series both with and without high-field intraoperative MRI, which all report an extremely low rate of GTR in adenomas encasing the internal carotid artery [8, 9, 13, 35].

However, other reasons for which intraoperative imaging may be useful in more complex PA must be taken into account but are not the purpose of this report. For example, in adenomas extending into the suprasellar space, the surgeon may opt for 3T-iMRI to monitor the position of the diaphragma sellae to reduce the risk of intraoperative CSF leaks and postoperative fistulas or to image a specific part of the tumor compressing the optic chiasm, such as reported by Zaidi et al. [37].

Limitations

Even though data were obtained from a prospective registry, this was a retrospective analysis. Thus, selection bias is possible, albeit inclusion criteria were clearly defined and the majority of patients in the registry were eligible for inclusion. All data used in this analysis stem from the same center, possibly limiting the generalizability of our findings. However, the baseline characteristics of the included patients, as well as the surgical results, are in line with the available literature. As expected, the number of grade IV adenomas was low, limiting the pairwise statistical analysis in power.

Conclusions

Using data from a prospective registry of TSS for PA, we demonstrate that there are subsets of patients in which the use of 3T-iMRI is particularly advantageous. These subsets can be described by the ZPS. The clinical utility of 3T-iMRI is probably most noticeable in ZPS grade I–III adenomas. In particular, grade I adenomas were always amenable to GTR if 3T-iMRI is implemented. Conversely, in grade IV adenomas, 3T-iMRI may be of limited use, because it does not appear that its use leads to clinically relevant improvements in surgical outcome. Our findings warrant validation in external populations.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Cantonal Ethics Committee Zürich, KEK St-V-Nr 2015-0142) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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