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Is gross total resection reasonable in adults with craniopharyngiomas with hypothalamic involvement ?

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Abstract: 250 max

Objective: The treatment of hypothalamus-invading craniopharyngiomas, based on pediatric experience, is subtotal resection (STR) with radiotherapy. This strategy sometimes leads to uncontrollable tumor progression. In adults, with the use of endoscopic endonasal surgery (EES), does removing the hypothalamic part of the tumor – whenever possible – compromise the outcome of the patients?

Methods: We included adults with craniopharyngioma treated by a first EES in 2008-2016 by E.J. Endocrine, ophthalmological and hypothalamic data were retrospectively collected, including BMI, cognitive and social status, with a systematic follow-up interview. MRI were graded according to Puget: 0 – no hypothalamic involvement, 1 – hypothalamic displacement, 2 – hypothalamic involvement. Grade 2 tumors were separated into gross total resection (GTR) or STR.

Results: We included 22 patients, aged 18 to 79. Presenting symptoms were visual (14, 64%), endocrine dysfunction (10, 45%), BMI>30 (8, 36%), cognitive/psychiatric impairment (9, 41%). Fourteen (64%) were grade 2 craniopharyngiomas. GTR was performed in 14 (64%). Postoperatively, 12/14 (86%) cases improved visually, and 20 (91%) needed hormone replacement therapy. There was no difference in BMI evolution in the GTR versus STR group, cognitive status was stable or improved in all patients except one; 4/8 patients with STR experienced progression needing adjuvant treatment, versus no patient with GTR.

Conclusions: EES GTR of grade 2 craniopharyngiomas does not cause major hypothalamic worsening, in contrast with children operated by cranial approaches. The surgeon's experience is key in deciding when to stop the dissection. Offering GTR whenever possible aims at avoiding tumor progression and radiotherapy.

Introduction:

Craniopharyngiomas are rare suprasellar tumors which may present with hypothalamic involvement, causing dramatic symptoms such as morbid obesity, cognitive decline, feeding and sleep disturbances, in addition to endocrine and ophthalmological deficits. Besides endocrine substitution, craniopharyngiomas can be treated by surgery, radiation therapy, or “in situ” pharmacological injections such as interferon when cystic. The current strategy derives from paediatric series with subtotal resection (STR) and radiotherapy when hypothalamus is involved¹. This may expose to therapeutic failure if tumor volume kept in place is not responsive to radiotherapy. Several reasons made that paradigm controversial in adult, who are not tall children. First, to the best of our knowledge, there is no homogeneous adult series, except a limited one focusing on intraventricular lesions², and most results rely on mixed paediatric and adult cases. Second, childhood-onset and adult tumors are different regarding histology and anatomy. Adamantinomatous type, which harbours *CTNNB1* mutations, arises primarily in children, whereas papillary tumors, characterized by *BRAF V600E* mutation, are found almost exclusively in adult patients³. Tumors are also different regarding their locations with more suprasellar and retrochiasmatic extensions in adults. Thirdly, consequences of hypothalamic involvement are certainly quite different in young and adults. Finally, this paradigm was promoted under the microscopic era. With the development of extended endonasal endoscopic surgery, the conditions and possibilities have changed with a better hypothalamic exposure, through a different surgical canal.

As a skull base centre with extensive surgical experience in sellar and suprasellar surgery (140 cases per year since more than 10 years), we retrospectively analysed a local series, and report the first cases of purely adult-onset craniopharyngiomas. Our therapeutical management relies on a maximal endonasal endoscopic removal of the tumor, even in patients with hypothalamic involvement. We evaluated the consequences of hypothalamic invasion in the preoperative and postoperative courses of the disease to answer the question: did removing the hypothalamic part of the tumor – whenever possible – compromise the quality of life and outcome of the patients?

Material & methods:

We retrospectively analysed our local series of adult patients who underwent a first procedure of endonasal endoscopic surgery of adult-onset craniopharyngioma between 2008 and 2016 in the Skull Base Unit of the neurosurgical department, Pierre Wertheimer Hospital of Neurology and Neurosurgery, Lyon, France. We excluded redo surgery, cranial surgery, cases lacking sufficient imaging or consistent histological findings, recent cases without follow-up and adult patients with proved childhood-onset tumors. The patients consent for retrospective analysis was obtained.

The surgical technique used was done by the senior author (EJ) consisting in an extended trans tubercular transsellar bi-nostril approach under neuronavigation. The closure technique has evolved over time consisting for the first period (2008-2012) in a multilayer technique using glue inside the suprasellar space to restore a “pseudo-arachnoid”, an extradural dura mater substitute bio-absorbable (SEAMDURA®, Codman) with an artificial bone substitute (MEDPOR®, Stryker) covered by a vascularized naso-septal flap made on one side after a middle turbinectomy. The sphenoid sinus was therefore plugged by fat and a nasal plugging was done by a simple mesh removed at day 3. During the second period, a Gasket-seal technique derived from Schwartz⁴ was used to close the osteo-dural defect with a piece of fascia lata and the MEDPORE still covered by the naso-septal flap. These surgical techniques have been described before^{4,5}.

Preoperative and postoperative clinical data (visual, endocrine, neurological, cognitive and social statuses, height and weight) and cranial MRI were collected in the medical record, including hypothalamic function (appetite dysregulation with weight gain or anorexia, body temperature dysregulation, cognitive impairment, in particular behavioural alteration and memory issues, psychosis, sleep-wake cycle, diabetes insipidus⁶) and the last follow-up was completed in a telephone interview (C.A.). Pituitary MRI included T1- and T2-weighted, FLAIR and gadolinium-enhanced T1 sequences. Preoperative and postoperative MRI grading for hypothalamic involvement was assessed according to Puget¹ by two authors (E.J. and C.A.): preoperatively, grade 0, no hypothalamic involvement; grade 1, the tumor abutting or displacing the hypothalamus; grade 2, hypothalamic involvement; postoperatively, our purpose was to compare the benefit or risk of hypothalamic surgery. We used the Puget classification as follows: grade 0, no hypothalamic damage; grade 1, negligible hypothalamic damage (small hole) or residual tumor displacing the hypothalamus; grade 2, significant hypothalamic damage (hole in the floor of the third ventricle, visible on MRI). In theory, postoperative grade 1 could

define either STR with residual tumor in the third ventricle, or GTR without hypothalamic damage, but in practice grade 1 defined STR in previously grade 2 whereas postoperative grade 2 was defined as a hole in the third ventricle allowing GTR. The appearance of the tumor, of the contrast enhancement and presence of a hypothalamic oedema has been collected as well. Subjective quality of life and hypothalamic outcome (weight, cognitive functions, daily and professional activities) were studied more particularly. Statistics were performed using SPSS statistics 20.0.0 (IBM, USA).

Results:

We analysed 22 consecutive cases among 53 adults treated for craniopharyngiomas during the same period at our center. There were 7 male (30%) and 15 female (70%) patients and the mean age was 58 years, ranging from 18 to 79. All were operated on using the extended endoscopic endonasal route. Presentation, surgical complications and long-term outcome are summarized in table 1.

Preoperatively, 14 patients (70%) presented with visual impairment, including visual field abnormalities or decreased visual acuity. Visual deficit was the main reason for consultation in 13 patients (65%). Endocrine status was normal in 12 patients (55%) whereas 6 (27%) presented panhypopituitarism, 2 (9%) isolated hypogonadism, 2 (9%) hyperprolactinemia, Diabetes insipidus was present in 4 (18%).

Few patients complained of neurological symptoms: 1 patient had vertigo, 2 - headaches, and 2 others - signs of elevated intracranial pressure. In contrast, 5 patients (23%) showed cognitive impairment with pseudo-dementia (decreased Mini Mental Score, amnesia and attentional troubles), with episodes of acute confusion. In 4 more patients (18%), cognitive slow-down mimicked depressive symptoms. Psychiatric expert diagnosis was not established in all cases. The social burden of the disease was noticed in 3 of the 14 working patients (21%), who stopped, whereas 11 (79%) were still working despite their symptoms. Eight (36%) patients were retired, with varied impact on their daily activities. Concerning weight, 6 (27%) patients had a BMI<25; 8 (36%) were overweight (BMI 25- 30), whereas 5 (23%) were obese (BMI 30-35) and 3 (14%) had a BMI>35.

On preoperative MRI, 1 patients (4%) was grade 0, 7 (32%) grade 1, and 14 (64%) grade 2. Ten tumors (45%) of all grades were purely solid and 12 (55%) included both a solid and a cystic component. Fifteen (68%) were homogeneously contrast-enhanced, whereas 6 (27%) had an irregular appearance. Fifteen (68%) were associated with hypothalamic oedema. Sixteen (73%) involved the pituitary stalk. Five (23%) were associated with hydrocephalus on MRI and 8 (37%) were partly calcified.

In our series, preoperative symptoms (BMI, ophthalmological, endocrinologic or neuropsychological impairment) were not significantly correlated with the MRI grade. However, five out of the six patients who presented with the higher BMI (BMI>31.5) had grade 2 tumors. Hypothalamic oedema was not significantly correlated to the clinic either.

Postoperative data is described in table 1, and results according to the preoperative grade in figure 1. The visual function was improved in 12/14 preoperatively impaired patients (86%), was stable in preoperatively normal patients and worsened in one case (5%). On the endocrine point of view, none of the patients improved their pituitary function, with 12 new panhypopituitarism (total 18, 90%) and 9 new diabetes insipidus (total 13, 65%), still needing medication on long-term follow-up. Two patients were free of any hormonal substitution. Preserving the pituitary stalk was not correlated with the absence of diabetes insipidus. Concerning the hypothalamic outcome, cognitive and social statuses improved noticeably in 2 out of 5 patients (40%) and 1 patient worsened, developing psychiatric symptoms. Patients with a normal preoperative weight did not develop obesity, including two grade 2 tumors. Among 6 overweighted patients, 2 developed obesity, and among obese patients, 2 developed morbid obesity (cf figure 2). Four patients had a BMI increase by more than 2 points. Two of them had grade 1 tumors and 2 had grade 2 tumors. Two of them underwent GTR that led to a defect in the third ventricle floor, while the two others had a STR respecting the part of the tumor invading the third ventricle. Overweight issue was not correlated with the extent of resection. Other hypothalamic symptoms were not systematically tested, but several patients did report sleep disturbances before and after surgery.

On postoperative MRI, 8 patients (36%) were grade 0, 4 (18%) grade 1, and 10 (46%) grade 2. GTR could be performed in 14 cases (64%), comprising all grades 0-1 and half of grade 2 tumors. Histological analysis showed that 16 craniopharyngiomas were adamantinous (76%), 5 were papillary (24%), and 1 could not be specified because of artifact. No patient with GTR developed tumor recurrence or received any adjuvant treatment. Among the 8 patients with STR, 4 developed tumor progression. Six patients received stereotactic radiotherapy (3 at recurrence and 3 upfront for postoperative residual tumor, one of which recurred), and two also received local interferon therapy for cystic recurrence. The median follow-up period is 5.3 years (from 2.1 to 9.9 years) for STR and 3.7 years (from 1.7 to 9.9) for GTR.

The grading and extent of resection were not correlated with postoperative complications. Rhinorrhoea needed surgical revisions in 4 patients (18%), but the CSF leakage rate dropped after the modification of the surgical protocol as described in the methods. Two patients with severe comorbidities died in the three months following the surgery, one from rectal abscess with multi-organ failure, the other from pneumonia (cf. figure 3).

Discussion:

Craniopharyngiomas are rare tumors in adults and, to the best of our knowledge, all series tackle the issue of childhood-onset craniopharyngiomas. Puget et al. have contributed to give a precise description of postoperative course in children operated for craniopharyngiomas transcranially under microscope leading to an algorithm of treatment^{1,7}. As a consequence, the strategy of STR and radiotherapy was commonly adopted for grade 2 tumors, in adults as well as in children, in order to avoid postoperative disabling hypothalamic sequelae. However, in several patients with STR, we experimented rapid tumor growth with local invasion and severe symptoms with radiotherapy failure. It led us to question this approach and to modify our strategy in order to aim to remove the tumor totally even in case of hypothalamic involvement, whenever possible. This strategy has also been discussed in a recent study in a mixed pediatric-adult population, that shows that combined trans-ventricular and endonasal approach might help remove cystic craniopharyngiomas radically without causing disastrous hypothalamic lesions⁸. Our retrospective study focuses only on adults without previous significant surgery or radiotherapy, in order to analyze a homogeneous population, with a native tumor-hypothalamus interface.

The initial symptoms in our series are similar to those reported in the literature⁹, with visual impairment in more than two third of the population and endocrine dysfunction in more than half the population. The most important difference between our adult-onset series and mixed or childhood-onset ones^{1,9,10} is the higher rate of acute hydrocephalus in children (68%, with 38% needing emergency treatment, versus chronic hydrocephalus in 10% in adults). Preoperative pituitary deficits were found in 80% of children, versus 48% in adults and visual deficits in 44% versus 70%. The global picture shows that adult craniopharyngiomas reveal more slowly, often with visual deficiencies, which actually are the most frequent reason for emergency procedures. An explanation could be the suprasellar retrochiasmatic / intrasellar location of the craniopharyngiomas in our series, without anterior and lateral extensions, a bias due to their frequency in adults and compatibility with the endonasal approach. As described in the methods, our study relies on experimented surgical techniques already described by other authors^{4,5,9,11}. Concerning the hypothalamic access in this context, the surgical field is narrow, and it cannot be seen before most of the tumor has been removed ; some authors have proposed that a relevant preoperative CT landmark is the angle between the tuberculum sellae and the optic apparatus, with a sharp angle ($< 118^\circ$) predictive of difficult visualization of the

suprasellar space¹². When the access is possible, dissection is critical and differentiation between hypothalamus tissue and gliosis may be difficult, making long surgical practice mandatory. In our experience, when the tumor could be mobilized with smooth dissection, we decided to remove it ; on the opposite, when sharp dissection was needed, we decided to leave these tumor pieces. When we could not distinguish between a cyst wall in the third ventricle and the hypothalamus, we left the cyst remnant in place and it was considered as STR.

The postoperative outcome in our series is beneficial on the visual point of view for 95% of patients. On the opposite, the pituitary function is clearly made worse, necessitating life-long hormonal replacement therapy. Although it has been suggested that preservation of the pituitary stalk may be associated with endocrine preservation^{9,13}, it does not seem compatible with GTR, as craniopharyngiomas often arise from it. Therefore, it has not been a priority in our surgical strategy. We noticed that panhypopituitarism and diabetes insipidus still developed in two patients, despite preservation of the pituitary stalk. Moreover, in series with preservation of the stalk, the recurrence rate is higher, and preservation does not guarantee preservation of the endocrinological function¹³.

Hypothalamic dysfunction includes a panel of symptoms that, unfortunately, were not systematically tested in our patients, but were explored clinically. When isolated, most signs are not specific, for instance weight gain, which may be related to hypothalamus dysfunction when it occurs a few months or years before diagnosis without neither any reasons nor endocrine dysfunction. Concerning postoperative hypothalamic results, all preoperatively valid patients but one recovered their daily life or social activities without any limitations after surgery. Two patients with pseudodementia symptoms experienced a major improvement, and only one patient deteriorated. A closer discussion with his family showed that he actually presented cognitive decline for a few months that had not been mentioned preoperatively. This underlines the fact that preoperative neuropsychologic testing is necessary preoperatively when the clinical context allows it. In our small series, the extent of surgery (GTR or STR) was not correlated to the postoperative cognitive status. In terms of BMI, the only quantitative assessment of hypothalamic dysfunction we have access to, there are strikingly different populations in the different series: in our population, 8 patients (38%) initially presented with obesity (BMI > 30), versus only 2 (11%) in Yano et al. We notice that, out of the 7 more obese patients (BMI >31), 5 presented with preoperative grade 2 tumors, and 2 with grade 1. Hypothalamic edema, which was present in 6 patients in our series (30%), was not correlated

with obesity, although this has been described as a marker of hypothalamic involvement⁹. Patients who developed obesity or morbid obesity were all overweighted preoperatively. It is worth mentioning that several obese patients did not improve despite professional dietary counselling. The extent of surgery was not correlated to the BMI progression. This suggests that the hypothalamic troubles may have been caused by the tumor itself rather than the surgery. Some grade 2 tumors could be entirely removed without causing major deterioration, even when the floor of the third ventricle was invaded. In theory, the precise radiological knowledge of the hypothalamic extent of the tumor could help predict the surgical risk but the anatomical boundaries of the hypothalamus may not be detectable on MRI, and anatomy isn't strictly correlated to the function due to plasticity. This may explain the difficulty to grade the tumors reproducibly and the clinical heterogeneity among tumors with the same apparent grade, as exemplified in the two cases we present in figure 3. Moreover, STR did not guarantee that the hypothalamic symptoms would remain stable: a 64-year-old female patient had a preoperative grade 2 tumor and postoperative grade 1 tumor, with no surgical damage to the hypothalamus but a remnant which could not be totally removed. Her psychiatric symptoms improved postoperatively, but she underwent preventive radiotherapy on the remaining part, and her BMI then increased from 31.2 to 45.2, without tumor progression on MRI. When the tumor has invaded the hypothalamus preoperatively, it seems that it can be removed without causing additional damage when it doesn't stick too much to the hypothalamic wall. This points out the importance of the surgeon's experience, who must decide how far he can go during the surgery.

It is worth noticing that, in our series, invasive grade 2 craniopharyngiomas were mostly of adamantinomatous type (13/14, 93%), that are reported to arise more often in children, whereas non-invasive grade 0-1 tumors were papillary tumors (5/8, 63%) (cf. figure 1). Concerning the oncological outcome, no patient with GTR experienced tumor recurrence or needed any adjuvant treatment after a median period of 3.7 years. On the opposite, out of 8 patients with STR, 4 showed tumor growth needing radiotherapy and, in two cases, local interferon, after a period of 5.3 years. Tumor regrowth happened in the first two years after surgery. One patient severely deteriorated after radiotherapy. One more patient underwent preventive radiotherapy on the tumor residual. In all cases, STR was a matter of technical issue rather than a preoperative strategy, and surgery was stopped because the lesion could not be visualized or accessed safely.

Puget's classification based on a grade 0-1-2 description of the tumor¹ is simple to use and we chose it to analyse our series because the standard of care for treatment relies on these criteria.

This classification can be confusing since the postoperative grading is not comparable with the preoperative one, especially for postoperative grade 1 tumors that can refer to both GTR and STR without major hypothalamic damage, possibly mixing damages due to the tumor itself and to the surgical resection. More recent studies offer supplementary criteria for stratifying the risk of postoperative hypothalamic damage based on MRI findings: the position of the hypothalamus in relation to the tumor, the type of pituitary stalk distortion and the tumor shape¹⁴; the authors have also proposed a model of predictive adherence of the tumor to the hypothalamus based on pre- and peroperative characteristics: the intracranial structures attached to the tumor, the morphology of the adhesion and the adhesion strength¹⁵. These studies are helpful to anticipate the surgical difficulty of hypothalamic dissection, however we find they are not easily reproducible, they do not always provide practical information and, more importantly, that we cannot make a therapeutic decision based on these classifications. Deciding not to offer GTR to a patient because of pejorative factors in any of these classifications could lead to a loss of complete treatment opportunity. The final decision remains up to the surgeon's peroperative experience. Indeed, our experience in this series shows that performing GTR whenever possible, even in a hypothalamus invading tumor, prevents tumor progression and additional damage due to radiotherapy, and does not worsen the quality of life of the patients, with the majority of patients coming back to life standards comparable to their preoperative status. GTR is not associated to significant clinical worsening compared to STR in patients with grade 2 tumors. The key element, in addition to the MRI findings, before planning the surgery, is the general clinical status of the patient and palliative treatment should sometimes be considered. In our series, the two patients who died in the postoperative period were in very poor general condition, with severe comorbidities and hypothalamic dysfunction (grade 2 tumors with cognitive deterioration, BMI 36 and 37.7) and, retrospectively, it would have been reasonable to offer them palliative care only. There is no evidence that age is a limiting factor, with craniopharyngiomas affecting patients older than 60 in 20% of cases (43% in our purely adult series), and even older than 80 in 2.7%¹⁶, and we think that surgery is an option if the clinical state of the patient allows it.

Conclusions:

In our experience, endonasal endoscopic GTR of craniopharyngiomas does not cause major worsening of preoperative hypothalamic syndrome, even if the lesion invades the third ventricle, suggesting that hypothalamic damage may be caused by the tumor itself. Severe pre-existing hypothalamic syndrome, in particular morbid obesity in patients with major comorbidity, seems to be a contraindication for surgery because of the high risk of neurological and general complications. There is a need for a systematic thorough hypothalamic evaluation preoperatively and postoperatively in order to determine the optimal strategy in these patients, since it seems that favouring STR in patients with aggressive preoperative MRI findings is not appropriate in all cases.

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References:

1. Puget S, Garnett M, Wray A, et al. Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. *J Neurosurg.* 2007;106(1 Suppl):3-12. doi:10.3171/ped.2007.106.1.3
2. Forbes JA, Ordóñez-Rubiano EG, Tomasiewicz HC, et al. Endonasal endoscopic transsphenoidal resection of intrinsic third ventricular craniopharyngioma: surgical results. *Journal of Neurosurgery.* 2018;1(aop):1-11. doi:10.3171/2018.5.JNS18198
3. Hölsken A, Sill M, Merkle J, et al. Adamantinomatous and papillary craniopharyngiomas are characterized by distinct epigenomic as well as mutational and transcriptomic profiles. *Acta Neuropathol Commun.* 2016;4. doi:10.1186/s40478-016-0287-6
4. Garcia-Navarro V, Anand VK, Schwartz TH. Gasket seal closure for extended endonasal endoscopic skull base surgery: efficacy in a large case series. *World Neurosurg.* 2013;80(5):563-568. doi:10.1016/j.wneu.2011.08.034
5. Zenonos GA, Snyderman CH, Gardner PA. Endoscopic Endonasal Approach for a Suprasellar Craniopharyngioma. *J Neurol Surg B Skull Base.* 2018;79(Suppl 3):S241-S242. doi:10.1055/s-0038-1623522
6. Asa SL. Hypothalamic Disease. In: Martini L, ed. *Encyclopedia of Endocrine Diseases.* New York: Elsevier; 2004:678-687. doi:10.1016/B0-12-475570-4/00714-9
7. Puget S. Treatment Strategies in Childhood Craniopharyngioma. *Front Endocrinol (Lausanne).* 2012;3. doi:10.3389/fendo.2012.00064
8. Deopujari CE, Karmarkar VS, Shah N, et al. Combined endoscopic approach in the management of suprasellar craniopharyngioma. *Childs Nerv Syst.* 2018;34(5):871-876. doi:10.1007/s00381-018-3735-8
9. Yano S, Hide T, Shinojima N. Surgical Outcomes of Endoscopic Endonasal Skull Base Surgery of Craniopharyngiomas Evaluated According to the Degree of Hypothalamic Extension. *World Neurosurg.* 2017;100:288-296. doi:10.1016/j.wneu.2017.01.005
10. Mou J, Wang X, Huo G, et al. Endoscopic Endonasal Surgery for Craniopharyngiomas: A Series of 60 Patients. *World Neurosurg.* January 2019. doi:10.1016/j.wneu.2018.12.110
11. de Divitiis E, Cappabianca P, Cavallo LM, Esposito F, de Divitiis O, Messina A. Extended endoscopic transsphenoidal approach for extrasellar craniopharyngiomas. *Neurosurgery.* 2007;61(5 Suppl 2):219-227; discussion 228. doi:10.1227/01.neu.0000303220.55393.73
12. de Notaris M, Solari D, Cavallo LM, et al. The “suprasellar notch,” or the tuberculum sellae as seen from below: definition, features, and clinical implications from an endoscopic endonasal perspective. *J Neurosurg.* 2012;116(3):622-629. doi:10.3171/2011.11.JNS111162
13. Ordóñez-Rubiano EG, Forbes JA, Morgenstern PF, et al. Preserve or sacrifice the stalk? Endocrinological outcomes, extent of resection, and recurrence rates following endoscopic endonasal resection of craniopharyngiomas. *J Neurosurg.* November 2018:1-9. doi:10.3171/2018.6.JNS18901
14. Prieto R, Pascual JM, Rosdolsky M, Barrios L. Preoperative Assessment of

Craniopharyngioma Adherence: Magnetic Resonance Imaging Findings Correlated with the Severity of Tumor Attachment to the Hypothalamus. *World Neurosurg.* 2018;110:e404-e426. doi:10.1016/j.wneu.2017.11.012

15. Prieto R, Pascual JM, Rosdolsky M, et al. Craniopharyngioma adherence: a comprehensive topographical categorization and outcome-related risk stratification model based on the methodical examination of 500 tumors. *Neurosurgical Focus.* 2016;41(6):E13. doi:10.3171/2016.9.FOCUS16304

16. Zacharia BE, Bruce SS, Goldstein H, Malone HR, Neugut AI, Bruce JN. Incidence, treatment and survival of patients with craniopharyngioma in the surveillance, epidemiology and end results program. *Neuro-oncology.* 2012;14(8):1070-1078. doi:10.1093/neuonc/nos142

Table 1: Preoperative and postoperative characteristics of the patients operated for endoscopic endonasal surgery of craniopharyngioma (n=22)

Figure 1: Comparison of the preoperative and postoperative characteristics of the patients according to the craniopharyngioma hypothalamic involvement (Puget's grading). Preoperative grades 0-1 craniopharyngiomas are distant from the hypothalamus or displace it without invading the floor of the third ventricle (left column). Grade 2 tumors involve the hypothalamus, which is not clearly identifiable (right column). In the postoperative period, grade 1 tumors refer to subtotal resection without hypothalamic damage whereas grade 2 to hypothalamic damage as created by the tumor in order to achieve gross total resection. There is major hypothalamic worsening in the patients with grade 2 tumors, after STR or GTR. STR : subtotal resection, GTR : gross total resection, BMI : body mass index.

Figure 2: Individual evolution of preoperative (first point) and postoperative (second point) BMI A) for all patients, B) for patients with postoperative grade 0-1 tumors, C) for patients with postoperative grade 2 tumors, i.e. with a defect in the floor of the third ventricle. There is no increase of BMI worsening in patients with GTR involving the hypothalamic part of the tumor. GTR: gross total resection, BMI: body mass index.

Figure 3: pre- and postoperative MRI, coronal, gadolinium-enhanced T1 sequence, for illustrative cases with preoperative grade 2 craniopharyngiomas, and postoperative grade 2 with GTR.

A-B) Case 1 was an active 30-year-old woman, preoperative BMI 32.9, who presented with hyperprolactinemia. On preoperative MRI, she had a grade 2 solid flocculent craniopharyngioma arising from the pituitary stalk. After GTR, she developed panhypopituitarism, and her BMI was 36.9 but decreased to preoperative level after dietetic measures. She remained normal on a cognitive point of view and kept working as previously.

C-D) Case 2 was an active 63-year-old male who also presented with a grade 2 solid flocculent tumor. He had visual field abnormalities, mild cognitive impairment with psychiatric symptoms, and a BMI of 29.6. After GTR, he developed obesity (BMI 34.5), and his cognitive and psychiatric functions worsened, impeding his quality of life. He is the only patient in the series who deteriorated on a cognitive point of view.

E-F) Case 3 was a 58-year-old retired woman, preoperative BMI 22.7, who presented with right visual deterioration and headache. On preoperative MRI, she had a grade 2 solid

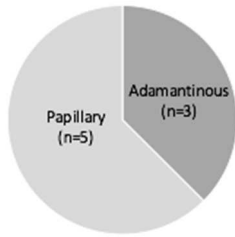
craniopharyngioma invading the third ventricle. After GTR, she developed panhypopituitarism with diabetes insipidus, but her visual function improved, her BMI was stable and she was able to resume all her daily activities. MRI follow-up is normal after 3 years.

G-H) Case 4 was a 68-year-old retired man with preoperative morbid obesity (BMI 37.7), bilateral visual abnormalities, erectile dysfunction and cognitive decline with depression. On preoperative MRI, he had a grade 2 solid and cystic craniopharyngioma. After GTR, he developed panhypopituitarism without diabetes insipidus, and hydrocephalus. He died from infectious pulmonary disease in the intensive care department three months after the surgery, after having developed postoperative ventriculitis.

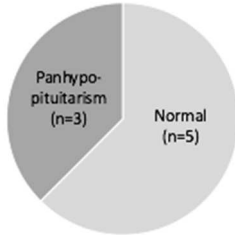
These cases illustrate that MRI is not predictive of hypothalamus damage and that clinical and surgical evaluation remain central in making therapeutical decisions. GTR: gross total resection, BMI: body mass index.

Preoperative grades 0-1

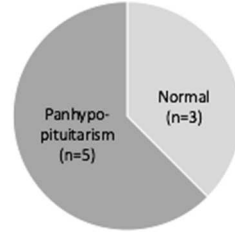
Pathology



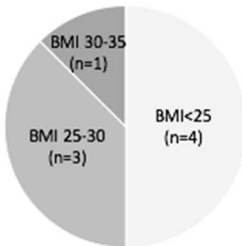
Preoperative endocrine status



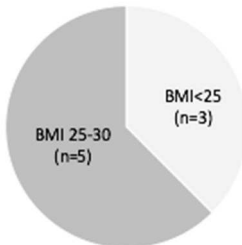
Postoperative endocrine status



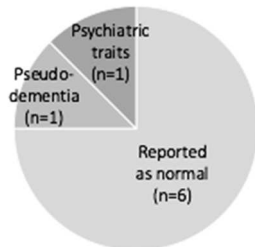
Preoperative BMI



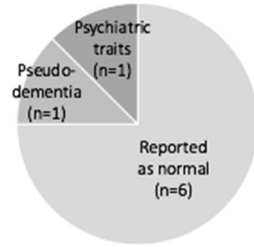
Postoperative BMI



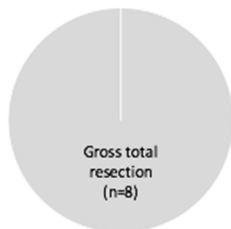
Preoperative cognitive status



Postoperative cognitive status

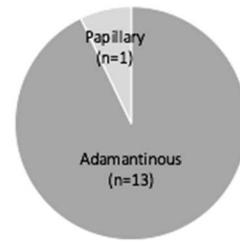


Resection

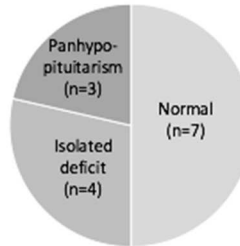


Preoperative grade 2

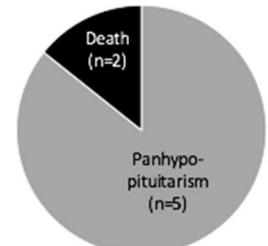
Pathology



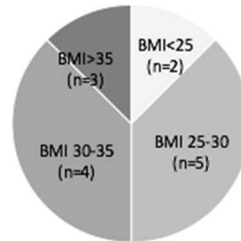
Preoperative endocrine status



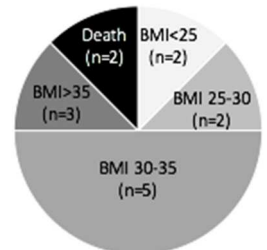
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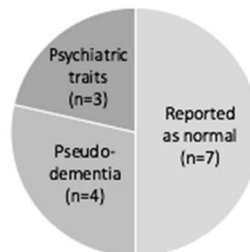
Preoperative BMI



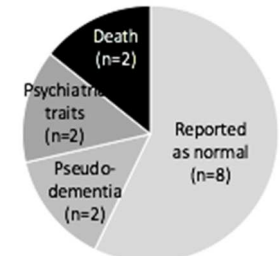
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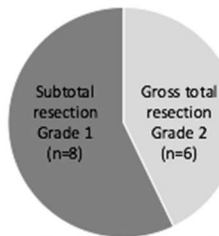
Preoperative cognitive status



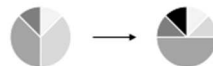
Postoperative cognitive status



Resection



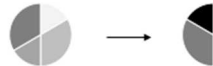
Preoperative BMI



Postoperative BMI



Preoperative BMI



Postoperative BMI

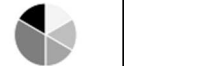


Figure 1: Comparison of the preoperative and postoperative characteristics of the patients according to the craniopharyngioma hypothalamic involvement (Puget's grading). Preoperative grades 0-1 craniopharyngiomas are distant from the hypothalamus or displace it without invading the floor of the third ventricle (left column). Grade 2 tumours involve the hypothalamus, which is not clearly identifiable (right column). In the postoperative period, grade 1 tumours refer to subtotal resection without hypothalamic damage whereas grade 2 to hypothalamic damage as created by the tumour in order to achieve gross total resection. There is major hypothalamic worsening in the patients with grade 2 tumours, after STR or GTR. STR : subtotal resection, GTR : gross total resection, BMI : body mass index.

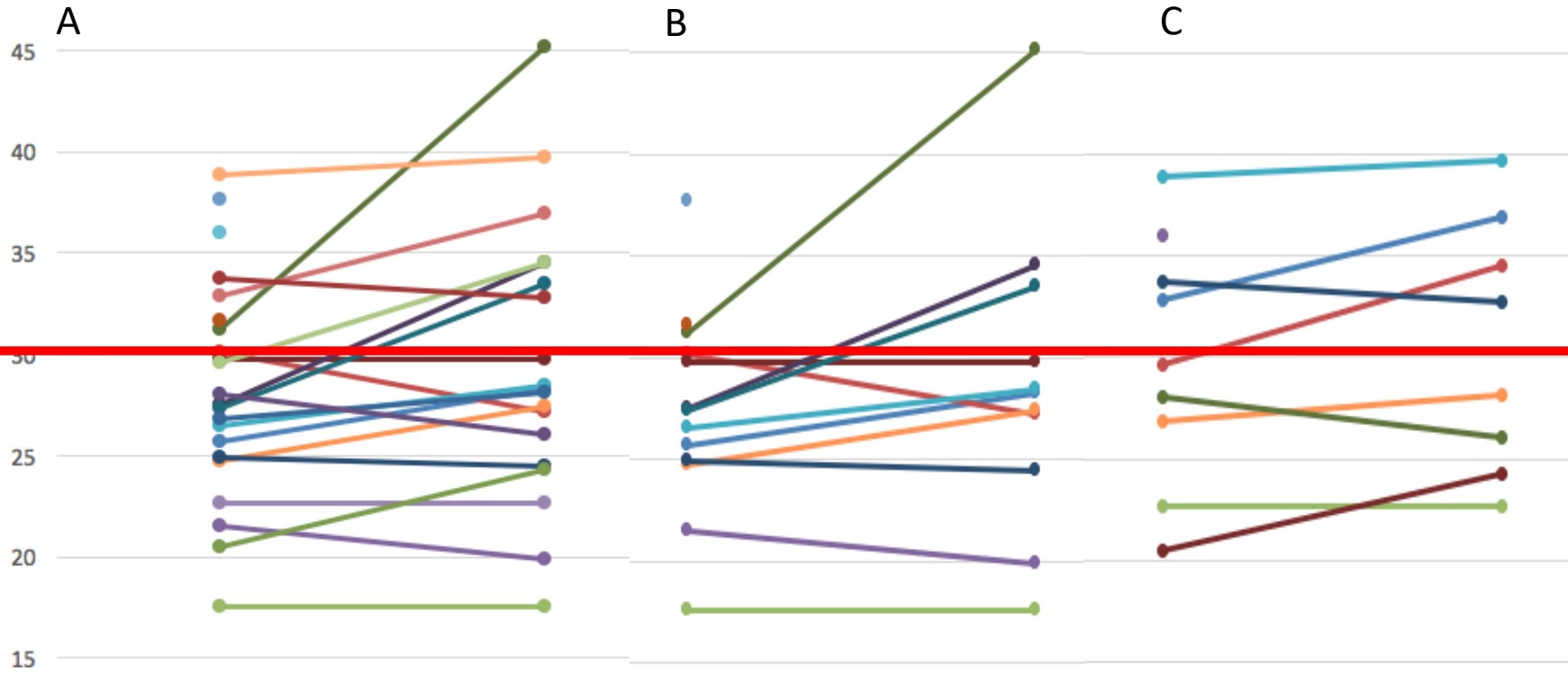


Figure 2: individual evolution of preoperative (first point) and postoperative (second point) BMI A) for all patients, B) for patients with postoperative grade 0-1 tumors, C) for patients with postoperative grade 2 tumors, i.e. with a defect in the floor of the third ventricle. There is no increase of BMI worsening in patients with GTR involving the hypothalamic part of the tumor.

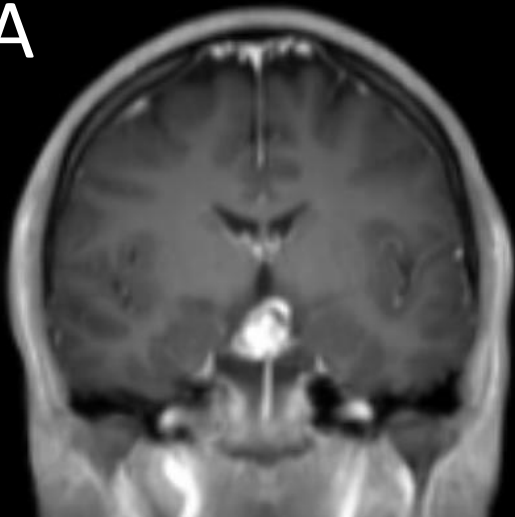
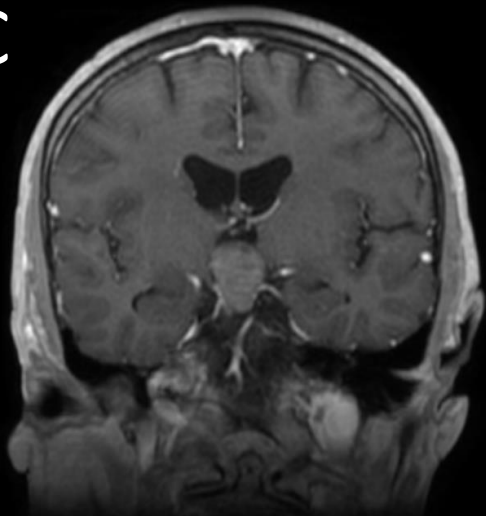
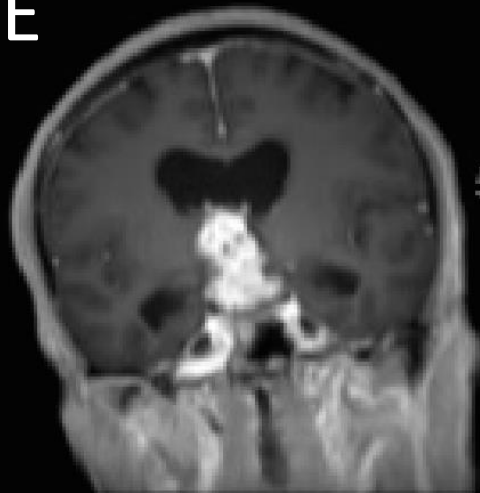
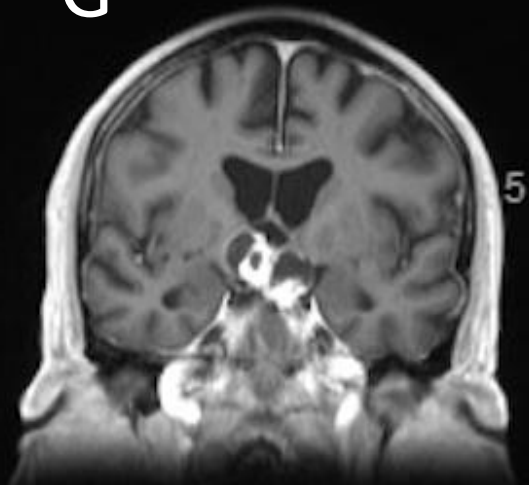
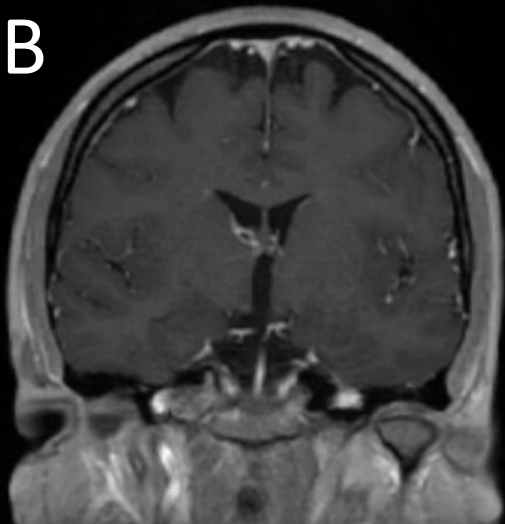
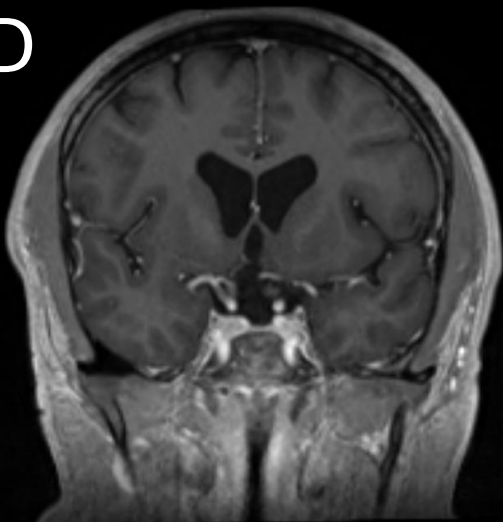
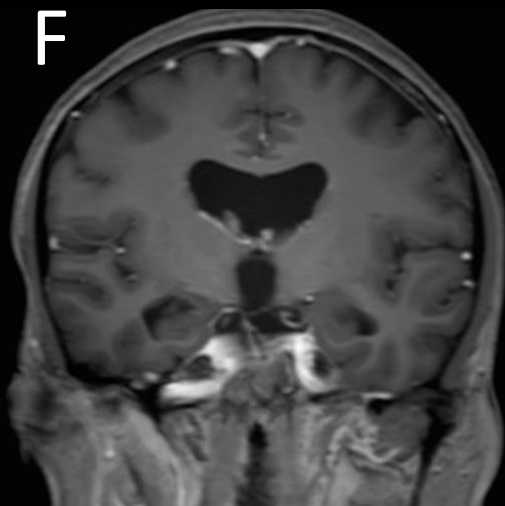
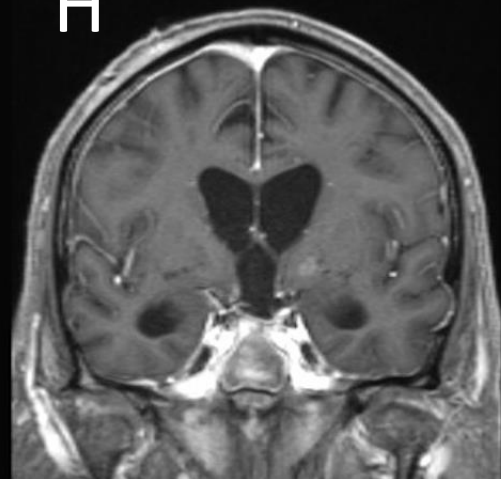
A**C****E****G****B****D****F****H**

Figure 3: pre- and post-operative MRI, coronal, gadolinium-enhanced T1 sequence, for illustrative cases with preoperative grade 2 craniopharyngiomas, and postoperative grade 2 with GTR.

A-B) Case 1 was an active 30-year-old woman, preoperative BMI 32.9, who presented with hyperprolactinemia. On preoperative MRI, she had a grade 2 solid flocculent craniopharyngioma arising from the pituitary stalk. After GTR, she developed panhypopituitarism, and her BMI was 36.9 but decreased to preoperative level after dietetic measures. She remained normal on a cognitive point of view and kept working as previously.

C-D) Case 2 was an active 63-year-old male who also presented with a grade 2 solid flocculent tumor. He had visual field abnormalities, mild cognitive impairment with psychiatric symptoms, and a BMI of 29.6. After GTR, he developed obesity (BMI 34.5), and his cognitive and psychiatric functions worsened, impeding his quality of life. He is the only patient in the series who deteriorated on a cognitive point of view.

E-F) Case 3 was a 58-year-old retired woman, preoperative BMI 22.7, who presented with right visual deterioration and headache. On preoperative MRI, she had a grade 2 solid craniopharyngioma invading the 3rd ventricle. After GTR, she developed panhypopituitarism with diabetes insipidus, but her visual function improved, her BMI was stable and she was able to resume all her daily activities. MRI follow-up is normal after 3 years.

G-H) Case 4 was a 68-year-old retired man with preoperative morbid obesity (BMI 37.7), bilateral visual abnormalities, erectile dysfunction and cognitive decline with depression. On preoperative MRI, he had a grade 2 solid and cystic craniopharyngioma. After GTR, he developed panhypopituitarism without diabetes insipidus, and hydrocephalus. He died from infectious pulmonary disease in the intensive care department three months after the surgery, after having developed postoperative ventriculitis.

These cases illustrate that MRI is not predictive of hypothalamus damage and that clinical and surgical evaluation remain central in making therapeutical decisions. GTR: gross total resection, BMI: body mass index.

Table 1. Preoperative and postoperative characteristics of the patients operated for endoscopic endonasal resection of craniopharyngioma (n=22)

Parameter	Our series (n=22)		
	n	%	
Population			
Sex	Male	7	30
	Female	15	70
Age (years), median	58 (18-79)		
Preoperative characteristics			
Visual status (n=20)	Normal	6	30
	Visual field abnormalities	11	55
	Unilateral decreased visual acuity	7	35
	Bilateral decreased visual acuity	5	23
	Visual impairment as main complaint	13	65
Endocrine status	Normal	12	55
	Panhypopituitarism	6	27
	Isolated hypogonadism	2	9
	Isolated hyperprolactinemy	2	9
	Diabetes insipidus	4	18
Neurological status	Vertigo	1	5
	Signs of elevated intracranial pressure	2	9
	Headaches	2	9
Cognitive status	Cognitive impairment	5	23
	Slow-down or signs of depression	4	18
Social status	Working	11	50
	Retired	8	36
	Work stoppage	3	14
Weight	BMI < 25	6	27
	BMI]25 ; 30]	8	36
	BMI]30 ; 35]	5	23
	BMI > 35	3	14
Height	Female	161+/-3	
	Male	176+/-5	
MRI grading	Grade 0	1	4
	Grade 1	7	32
	Grade 2	14	64
Postoperative course (n=22)			
Complete resection	14	64	
Mortality (after 3months)	2	9	
Complications	Death	2	9
	Meningitis	5	23
	Surgical closure for rhinorrhea	4	18
	Severe hyponatremia	1	5
Need for internal ventricular drainage	4	18	
MRI grading (n=22)	Grade 0	8	36
	Grade 1	4	18
	Grade 2	10	46

Long-term follow-up (n=20)			
Visual status (n=19)	Amelioration	12	63
	Deterioration	1	5
	Stability	6	32
Endocrine status	Normal	2	10
	Panhypopituitarism	18	90
	Diabetes insipidus	13	65
Cognitive/social status (n=18)	Major improvement	2	11
	Stability	15	83
	Worsening	1	6
Weight (n=19)	BMI < 25	5	26
	BMI]25 ; 30]	7	37
	BMI]30 ; 35]	4	21
	BMI > 35	3	16
Tumor progression (n=20)		4	20
Postoperative treatment (n=20)	Radiation therapy	5	25
	Medical treatment (interferon)	2	10