Craniopharyngioma and the Third Ventricle: This Inescapable Topographical Relationship

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INTRODUCTION

The Third-Ventricle Craniopharyngioma Surgical Challenge, a Hot Topic in Frontiers in Oncology

Craniopharyngiomas (CPs) are widely categorized as a group of benign epithelial tumors developed around the region of the sella turcica (1). However, from a surgical viewpoint, CPs have consistently been considered a particularly challenging intracranial tumor, owing to their close relationship to the hypothalamus and their biological infiltrating behavior (2, 3). The exceedingly heterogeneous CP topography and their usual extension into the third ventricle (3V) remain significant impediments to standardize a common management (4). Consequently, a wide array of surgical approaches, resection philosophies and adjuvant treatment guidelines have been employed and advocated, with no clear consensus being reached among authors (5, 6).

In the last decade, the experience gained from using the endonasal endoscopically assisted approach (EEA) has made this technique the gold standard for treating most sellar and suprasellar CPs (7, 8). Nevertheless, a high rate of CPs develop primarily at the infundibulo-tuberal region of the third ventricle floor (3VF) and expand within the 3V, above an intact pituitary gland and stalk (9, 10). The pervasive problem of identifying a “safe” cleavage plane through the tenacious adherence between the CP and the adjacent hypothalamus has remained the major obstacle for radical excision of infundibulo-tuberal CPs employing the EEA (11, 12). This difficulty becomes particularly delicate when dealing with papillary CPs (PCPs) having a strict or intrinsic 3V location, for which the EEA was originally regarded unsuitable and too risky, as it forced breaking through the seemingly functional 3VF, a maneuver that could potentially cause irreversible hypothalamic sequelae (13, 14). Therefore, transcranial-transventricular methods of approach have been employed to remove these intraventricular CPs, usually through the corpus callosum or by opening the lamina terminalis, a choice based on an accurate preoperative MRI diagnosis of the strict 3V topography (15–17).

Frontiers in Oncology’s research topic, “Advances in craniopharyngiomas: from physiology to clinical management” gathers a series of papers specifically focused on the clinical assessment and surgical treatment of the subgroup of intrinsic or strictly 3V CPs (18–21). The studies by Deopujary

Abbreviations: ACP, adamantinomatous craniopharyngioma; CP, craniopharyngioma; MRI, Magnetic Resonance Imaging; PCP, Squamous-papillary craniopharyngioma; 3VF, third ventricle floor; 3V, Third ventricle.
et al. and Zhao et al. direct their attention on the physiological and neuropsychological disturbances derived from the hypothalamic injury caused by resecting intra-3V CPs (18, 19). The feasibility of combining the extended endonasal endoscopically assisted approach (EEEA) with a trans-lamina terminalis (TLT) access to successfully remove strictly 3V CPs is the major objective of Cao et al. and Zhou et al. papers (20, 21). Potentially, a paradigm shift in the surgical method of choice to remove 3V CPs might occur from these studies, from the dominant use of transcranial-transventricular routes to a new band of non-functional gliotic tissue (10). Infundibulo-tuberal CPs constitute approximately 40% of lesions in the adult CP population. The majority belong to the adamantinomatous type (ACPs) and show the strongest and riskiest attachments to the hypothalamus (28). The scarcer subgroup of strictly 3V CPs only comprises about 5% of cases, also involves predominantly adults (92%) and largely includes lesions of the papillary type (82%). Strictly 3V PCPs characteristically present weaker, lower-risk attachments to the 3VF than not strictly intraventricular ACPs (12, 23). Interestingly, despite their more benign attachment, these PCPs with an intrinsic or strict intra-3V development very often cause a wide range of psychiatric disturbances (in up to 60% of patients), owing to the severe tumoral compression upon the hypothalamus (10, 29). These emotional, behavioral and cognitive alterations, poorly addressed in most surgical CP series, represent a true organic model of psychiatric disease of great potential relevance for elucidating the neurobiological basis of psychiatric disorders (29).

More recently, we were able to compile and analyze comprehensively the cohort of CPs with a verified strictly 3V topography (n=245), as well as the historical cohort of well-described papillary CPs published in the medical literature (n=350) (30, 31). Although the strictly 3V topography has remained controversial throughout history, some authors considering it an exceptional, ectopic location (32), while others even argue over its validity (33), the surgical series by Depoujarny (18), Cao (20), and Zhou (21) contribute to verify this particularly challenging location, confirming the anatomical integrity of the 3VF found in numerous strictly 3V CPs in prior studies (see Table 1) (34–49). The optimal surgical view of the brain undersurface obtained through the EEA unequivocally show the ballooned and stretched infundibulum wrapping around the lower pole of these lesions, which stay hidden within the 3VF chamber (13, 14, 40, 46). In 5 out of 6 strict CP cases in the series by Cao (83%) and 6 out of 9 in Zhou’s paper (66%), the lesions corresponded to the papillary type, percentages that fit well with the 82% rate of papillary lesions found in our systematic review (20, 21, 30). Depoujarny observed preoperatively symptoms related to hypothalamic dysfunction in 60% of their 3V CP patients overall, the most prominent being memory loss (25%), increased sleepiness (20%) and abnormal uninhibited behaviors, including hyperphagia (36%) (18). These figures also match with the rate of mental alterations in strictly 3V CPs (59%) and papillary CPs (50%) identified in our reviews (30, 31). Visual and endocrine symptoms, typical of ACPs with a suprasellar location below the 3V, were, however, rather low, in the range between 40-55% in both Depoujarny and Zhou studies (18, 21).

The Combined EEA-Translamina Terminalis Approach for Strictly 3V CPs: A Promising Surgical Strategy

The controversy about what should be the optimal surgical strategy for strictly 3V CPs has remained unresolved ever since. The complex problem of dealing with the CP-hypothalamus
plane of adherence within the 3V under a good direct view has stimulated the use of multiple transcranial routes, mainly the frontal-transventricular, the transcallosal and the translaminar-stimulated the use of multiple transcranial routes, mainly the plane of adherence within the 3V under a good direct view has

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expertise gained with the use of the EEEA allowed pituitary surgery to incorporate the translaminar terminalis corridor to the technique to successfully remove strictly 3V CPs without mortality, as shown in the series by Cao (87.5% gross total removal, GTR) and Zhou (89% GTR) (20, 21). Accordingly, should this combination of EEEA plus TLT technique be considered the definitive method capable of overcoming the impediment of CP adherence and/or infiltration into the hypothalamus intrinsic to intra-3V development? (26, 28, 33, 50).

In our 2004 comparative analysis of the surgical approaches employed to remove intraventricular CPs up to that date, all performed through open craniotomies, we found that the TLT approach was superior to the others (transcallosal and frontal-transventricular) in terms of null postoperative mortality (23). Notably, partial degrees of tumor removal yielded poorer postoperative outcomes than total excisions, an apparently paradoxical result highlighting the damaging effect that unsuccessful attempts to dissect tight CP-hypothalamic adhesions had on the ultimate clinical outcome. The results of this research may be cautiously extrapolated to define the current indications for total removal of strictly 3V CPs employing the
### TABLE 1 | Epidemiological, clinico-pathological and surgical characterization of third ventricle craniopharyngiomas (3V CPs) included in modern CP surgical series.

| CP series/Year [ref] | No. 3V CPs/Adults Rate | Rate 3V CPs/Total No. CPs | Histology Types | Hypothalamic/Psychic symptoms | Main Approach/GTR rate | Mortality/Postop H.I. † | Recurrence/Follow-up |
|----------------------|-------------------------|---------------------------|----------------|-------------------------------|------------------------|-------------------------|----------------------|
| Yasargil et al. (34) | 7/100% A | 4% | NA | NA | TC: 100% | NA | NA |
| Davies et al. (35)   | 6/100% A | NA | 3 pCP/3 aCP | 16.5%/16.5% | TLT: 100% | 0% | 50% |
| Maira et al. (36)    | 8/100% A | 11% | 2 pCP/6 aCP | 25%/25% | TLT: 100% | 12.5% (1y) | 14% |
| Behari et al. (37)   | 6/66% A | 8% | NA | 33% | TC: 50% | 16.6% | 0% |
| Pascual et al. (23)  | 105/85% A | 29 pCP/29 aCP | 55% | FTv/TC: 68% | NA | 29% | NA |
| Sohma et al. (38)    | 5/NA | 3 pCP | 40% | TLT: 100% | 0% | 20% |
| Shi et al. (39)      | 23/8% | NA | NA | NA | TLT: 56% | NA | NA |
| Pan et al. (15)      | 17/15 A | 8.7%/195 | 6 pCP | 47% | TLT: 100% | 12% | 17.5% |
| Jung et al. (16)     | 4/100% A | NA | 4 aCP | 0% | TC: 100% | 0% | 50% |
| Cavallo et al. (40)  | 12/92% A | 29%/41 | NA | 16.6% | EEA: 100% | 8.3% | 9% |
| Yu et al. (41)       | 24/830 > 15y | 3%/14 aCP | 33.3%/33.3% | TLT: 100% | 12.5% | 25% |
| Morisako et al. (42) | 12/72 | 16.5%/10 aCP | 33% | TLT: 100% | 0% | 0% |
| Zoli et al. (43)     | 10/100% A | NA | 5 pCP | 100% | EEA: 100% | 0% | 10% |
| Nishioka et al. (44) | 3/2 A | NA | 2 pCP | 0% | EEA: 100% | 0% | 0% |
| Mortini (45)         | 6/100% A | NA | NA | 66.6% | TLT: 100% | 0% | 0% |
| Forbes et al. (46)   | 10/100% A | 12.5%/80 | 3 pCP | 40% | EEA: 100% | 0% | 20% |
| Seo et al. (47)      | 26/76% A | 34%/76 | 11 pCP | 23% | EEA: 100% | 0% | 3.8% |
| Fan et al. (48)      | 26/92% A | 11.5%/223 | 5 pCP | 34.5% | EEA: 100% | 0% | 4% |
| Hung et al. (49)     | 5/100% A | NA | 5 pCP | NA | FTV: 4; TLT: 1 | NA | NA |
| Deopujari et al. (18) | 25/NA | 4.3% | NA | 60% | FTV: 56% | 8% | 20% |
| Zhao et al. (19)     | 17/NA | 10% | NA | NA | EEA: 44% | 40% | 30% |
| Cao et al. (20)      | 8/100% A | 5.3%/149 SS | 6 pCP | 37.5% | EEA-TLT: 100% | 0% | 12.5% |
| Zhou et al. (21)     | 9/100% A | NA | 6 pCP | 33% | EEA-TLT: 100% | 0% | 12.5% |
| Prieto et al. (30)   | 245/93% A | 5.6%/3,821 | 182 pCP | 65% | FTV/TLC: 41% | 3.3% | 14.5% |

A, adults; aCP, adamantinomatous type; CP, craniopharyngioma; EEA, endonasal endoscopic approach; FTV, frontal transventricular approach; GTR, gross total removal; H.I., hypothalamic injury; †, NA, not available; No., number; pCP, papillary type; postop, postoperative; TC, transcallosal; TLT, trans lamina terminalis; y, years; 3V, third ventricle.

*Suprasellar tumors; **Mortality rate for the tumors operated on in the most recent period between 2006-2021 (n=61).

† Postoperative hypothalamic injury rates include any of the following worsening of and/or sequelae: severe obesity (> 30% of BMI) with hyperphagia, severe hydroelectrolytic or autonomic disturbances, hyperthermia/poikilothermic dysfunction, gait ataxia, sphincters incontinence, psychiatric disturbances, Korsakoff-like memory defects and/or cognitive decline, all preventing autonomous life.
trans-infundibular and translamina-terminalis corridors through the EEEA. Undoubtedly, in expert hands this procedure offers the great advantage over transcranial methods of allowing an easier sharp dissection of the CP-hypothalamic plane of adherence from the initial stages of surgery (13, 20, 40). It also ensures the preservation of the hypothalamus and chiasm, blood supply through basal perforating vessels, which usually remain hidden from view when employing transcranial approaches. Avoiding mechanical and ischemic injuries to the hypothalamus caused by forceful blind pulling maneuvers on the intra-3V tumor bulk is essential for the postoperative improvement of psychiatric and neuropsychological disturbances, as is shown in the study by Zhao (19, 51). Nevertheless, the type of CP-hypothalamic attachment is the crucial factor determining the possibility of eventually accomplishing a successful total removal (4, 26).

CONCLUDING REMARKS

The infiltrative nature of CPs developed at the infundibulotuberal region, with finger-like tumor extensions protruding into the adjacent hypothalamus has been repeatedly confirmed on histological studies of CP boundaries (15, 26, 28, 33, 52). As rightly noted by Depujarny, poorer clinical outcomes have been reported for CP patients showing a breached 3VF after radical removal of 3V CPs tightly attached to the 3VF (18, 36, 53, 54). Psychiatric disturbances due to hypothalamic injury can be truly devastating for the personal autonomy and social integration of CP patients (10, 55). Consequently, not all strict 3V CPs should undergo radical removal (6, 10). Regarding this, it is worth mentioning the lack of reliable information about the actual prevalence of long-term neuropsychiatric disturbances in large surgical series employing the EEA. The neuropsychiatry inventory-questionary (NPI-Q) used in the study by Zhao, taking into account the six fundamental categories of psychological disorders related to hypothalamic injury by CPs (emotional control loss, abnormal moods, odd behavioral changes, memory defects, dementia-like cognitive impairment; and/or psychotic symptoms), could well be incorporated into the standard battery of clinical tests to assess the postoperative long-term outcome of CP patients (19, 29). The concept of “maximum safe resection”, which prioritizes the preservation of hypothalamic functions and psychological autonomy over the completeness of resection should guide surgical actions when dealing with such a complex lesion as a 3V CP, regardless of how sophisticated or technologically well-equipped the surgical procedure might be (10, 18).

AUTHOR CONTRIBUTIONS

Conception and design: JP. Acquisition of data: JP, RP. Analysis of data: JP, RP. Drafting the article: JP. Critically revising the article: RP. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Burger PC, Scheithauer BW, Vogel FS. Region of the Sella Turcica. Craniopharyngiomas. In: Surgical Pathology of the Nervous System and Its Coverings, 4. New York: Churchill Livingstone (2002). p. 475–83.
2. Pascual JM, Prieto R. Harvey Cushing’s Craniopharyngioma Treatment. Part 1. Identification and Clinicopathological Characterization of This Challenging Pituitary Tumor. J Neurosurg (2018) 131:949–63. doi: 10.3171/2018.5.JNS18153
3. Prieto R, Pascual JM. Harvey Cushing’s Craniopharyngioma Treatment. Part 2. Surgical Strategies and Results of His Pioneering Series. J Neurosurg (2018) 131:964–78. doi: 10.3171/2018.5.JNS18154
4. Prieto R, Rosdolsky M, Hofecker V, Barrios L, Pascual JM. Craniopharyngioma Treatment: An Updated Summary of Important Clinicopathological Concepts. Expert Rev Endocr Metab (2020) 15:261–82. doi: 10.1080/17446651.2020.1770081
5. Pascual JM, Prieto R, Castro-Dufourny I, Carrasco R, Strauss S, Barrios L. Development of Intracranial Approaches for Craniopharyngiomas: An Analysis of the First 160 Historical Procedures. Neurosurg Focus (2014) 36: E13. doi: 10.3171/2014.2.FOCUS13567
6. Müller HL, Merchant TE, Warmuth-Metz M, Martinez-Barbera JP, Puget S. Craniopharyngioma. Nat Rev Dis Primers (2019) 5:75. doi: 10.1038/s41572-019-0125-9
7. Moussazadeh N, Prabhu V, Bander ED, Cusic RC, Tsioris AJ, Anand VK, et al. Endoscopic Endonasal Versus Open Transcranial Resection of Craniopharyngiomas: A Case-Matched Single-Institution Analysis. Neurosurg Focus (2016) 41:E7. doi: 10.3171/2016.9.FOCUS16299
8. Henderson F Jr, Schwartz TH. Update on Management of Craniopharyngiomas. J Neurooncol (2022) 156:97–108. doi: 10.1007/s11060-021-03906-4
9. Pascual JM, Carrasco R, Prieto R, Gonzalez-Llanos F, Alvarez F, Roda JM. Craniopharyngioma Classification. J Neurosurg (2008) 109:1180–2. doi: 10.3171/JNS.2008.109.12.1180
10. Pascual JM, Prieto R, Rosdolsky M. Craniopharyngiomas Primarily Affecting the Hypothalamus. Handb Clin Neurol (2021) 181:75–115. doi: 10.1016/B978-0-12-820683-6.00007-5
11. Pascual JM, Prieto R, Carrasco R, Castro-Dufourny I, Barrios L. Letters to the Editor: Craniopharyngioma Adherence to the Hypothalamus. Neurosurg Focus (2014) 37:1–7. doi: 10.3171/2014.3.FOCUS1464
12. Prieto R, Pascual JM, Rosdolsky M, Castro-Dufourny I, Carrasco R, Strauss S, et al. Craniopharyngioma Adherence: A Comprehensive Topographical
50. Kawamata T, Kubo O, Hori T. Histological Findings at the Boundary of Craniopharyngiomas. *Brain Tumor Pathol* (2005) 22:75–8. doi: 10.1007/s10014-005-0191-4

51. Giese H, Haenig B, Haenig A, Unterberg A, Zweckberger K. Neurological and Neuropsychological Outcome After Resection of Craniopharyngiomas. *J Neurosurg* (2019) 132:1425–34. doi: 10.3171/2018.10.JNS181557

52. Yang L, Xie S, Tang B, Wu X, Tong Z, Fang C, et al. Hypothalamic Injury Patterns After Resection of Craniopharyngiomas and Correlation to Tumor Origin: A Study Based on Endoscopic Observation. *Cancer Med* (2020) 9:8950–61. doi: 10.1002/cam4.3589

53. De Vile CJ, Grant DB, Hayward RD, Kendall BE, Neville BG, Stanhope R. Obesity in Childhood Craniopharyngioma: Relation to Post-Operative Hypothalamic Damage Shown by Magnetic Resonance Imaging. *J Clin Endocrinol Metab* (1996) 81:2734–27. doi: 10.1210/jcem.81.7.8675604

54. Puget S, Garnett M, Wray A, Grill J, Habrand JL, Boadert N, 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

55. Castro-Dufourny I, Carrasco R, Prieto R, Barrios L, Pascual JM. The Infundibulo-Tuberal Syndrome Caused by Craniopharyngiomas: Clinicopathological Evidence From an Historical French Cohort (1705-1973). *Pituitary* (2015) 18:642–57. doi: 10.1007/s11102-014-0623-4

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