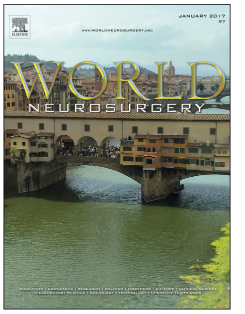
Management of Obstructive Hydrocephalus Associated with Pineal Region Cysts and Tumors and Its Implication in Long-Term Outcome

Choque-Velasquez, J

2021-05

Choque-Velasquez , J , Resendiz-Nieves , J , Colasanti , R & Hernesniemi , J 2021 , ' Management of Obstructive Hydrocephalus Associated with Pineal Region Cysts and Tumors and Its Implication in Long-Term Outcome ' , World Neurosurgery , vol. 149 , pp. E913-E923 . https://doi.org/10.1016/j.wneu.2021.01.078

http://hdl.handle.net/10138/343051
https://doi.org/10.1016/j.wneu.2021.01.078



Management of obstructive hydrocephalus associated with pineal region cysts and tumors and its implication in long-term outcome

Joham Choque-Velasquez, MD, Julio Resendiz-Nieves, MD, PhD, Roberto Colasanti, MD, Juha Hernesniemi, MD, PhD

PII: S1878-8750(21)00109-1

DOI: https://doi.org/10.1016/j.wneu.2021.01.078

Reference: WNEU 16706

To appear in: *World Neurosurgery*

Received Date: 27 October 2020

Revised Date: 17 January 2021

Accepted Date: 18 January 2021

Please cite this article as: Choque-Velasquez J, Resendiz-Nieves J, Colasanti R, Hernesniemi J, Management of obstructive hydrocephalus associated with pineal region cysts and tumors and its implication in long-term outcome, *World Neurosurgery* (2021), doi: https://doi.org/10.1016/j.wneu.2021.01.078.

Credit author statement

Title

Management of obstructive hydrocephalus associated with pineal region cysts and tumors and its implication in long-term outcome

Author names and affiliations:

Joham Choque-Velasquez. Manuscript redaction and statistical analysis

Julio Resendiz-Nieves. Methods and data collection

Roberto Colasanti. Text revision and discussion redaction

Juha Hernesniemi. Supervision

Title page

Title

Management of obstructive hydrocephalus associated with pineal region cysts and tumors and its implication in long-term outcome

Author names and affiliations:

Joham Choque-Velasquez, MD,[1] Julio Resendiz-Nieves, MD, PhD,[1] Roberto Colasanti, MD,[2,3] Juha Hernesniemi, MD, PhD [6]

[1]Department of Neurosurgery, Helsinki University Hospital, University of Helsinki, Helsinki, Finland

[2]Department of Neurosurgery, Umberto I General Hospital, Università Politecnica delle Marche, Ancona, Italy

[3]Department of Neurosurgery, Ospedali Riuniti Marche Nord, Pesaro, Italy

[6]"Juha Hernesniemi" International Center for Neurosurgery, Henan Provincial People´s Hospital, Zhengzhou, China

E-mail: *Joham Choque-Velasquez, johchove@hotmail.com; Julio C. Resendiz-Nieves, julio.resendiz-nieves@hus.fi; Roberto Colasanti, roberto.colasanti@gmail.com; Juha Hernesniemi, juha.hernesniemi@icloud.com

Corresponding author:

Joham Choque-Velasquez, MD

Department of Neurosurgery, Helsinki University Hospital,

Topeliuksenkatu 5, 00260 Helsinki, Finland

Email: johchove@hotmail.com

Title

Management of obstructive hydrocephalus associated with pineal region cysts and tumors and its implication in long-term outcome

Abstract

Background. Different treatment options have been proposed for obstructive hydrocephalus associated with pineal lesions. We discuss the obstructive hydrocephalus management associated with pineal region tumors and cysts in Helsinki Neurosurgery.

Methods. This paper evaluates the hydrocephalus treatment by tumor-cyst removal (40), shunt surgery (25), and endoscopic ventriculostomies (3) in 68 obstructive hydrocephalus among 136 pineal region tumor and cyst patients. Multivariate statistical analysis was followed by univariate and multivariate regression models of last functional status, last tumor-free imaging, and disease-specific mortality of the study population.

Results. Preoperative hydrocephalus linked to higher WHO-tumor grades, poor functional status, higher mortality, and incomplete resection of pineal region cysts and tumors. Preoperative hydrocephalus remained a predictor of poor last functional status after multivariate regression. Pineal lesion removal with the posterior third ventricle opening as primary hydrocephalus treatment resulted in better last functional status, fewer postoperative shunts, fewer hydrocephalus-related procedures, and less postoperative infections than the shunt-treatment group. Multivariate regression analysis linked higher WHO-tumor grade, poor immediate functional status, postoperative complications, and incomplete surgical resection as independent predictors of disease mortality in hydrocephalus patients. Same variables -except immediate mRS- and higher number of shunt surgeries became independent predictors of poor last functional status at multivariate analysis. Incomplete resection was the only independent predictor of tumor-free MRI at the last evaluation.

Conclusion. Direct removal of pineal lesions with the opening of the posterior third ventricle could represent effective and reliable management of the associated obstructive hydrocephalus. Further research is required to generalize our inferences.

Keywords

Pineal cysts, pineal tumors, hydrocephalus, shunt surgery, long-term outcome

Title

Management of obstructive hydrocephalus associated with pineal region cysts and tumors and its implication in long-term outcome

Introduction

The pineal region may harbor a wide variety of lesions from the pineal gland and the surrounding structures. We have recently published about the long-term outcomes of all surgically treated pineal region cysts and tumors in Helsinki University Hospital (HUH) between 1997 and 2015. Obstructive hydrocephalus was present in 70% of the pineal region tumors and 25% of the pineal cysts. Shunt surgeries were frequently used during the first period of the study. Nonetheless, in the last ten years of the study, the direct removal of the tumors and cysts became the standard procedure for treating hydrocephalus caused by a pineal lesion. On the other hand, endoscopic procedures were rarely used in HUH during the study period.[1,2]

In the last decades, different treatment options have been proposed for obstructive hydrocephalus associated with pineal lesions. Direct removal of the lesions, endoscopic third ventriculostomy (ETV) plus biopsy, and shunt procedures are the most frequently carried out. However, standard protocols are still not well-established.[3–10] Here, we present and discuss obstructive hydrocephalus management associated with pineal region tumors and cysts in HUH.

Methods

Study population and design

This is a single-center retrospective study of 136 consecutive pineal region cysts and tumors treated in the Department of Neurosurgery of HUH between 1997 and 2015. This study was approved by the Ethics Committee of HUH. Patient information was retrieved from our database. Obstructive hydrocephalus, defined as the ventricular enlargement due to abnormal accumulation of cerebrospinal liquid in the cerebral ventricles, was confirmed by the CT or MRI studies. Hydrocephalus resolution was confirmed in each case by a comparison between the pre- and postoperative imaging. Pediatric patients were considered up to 21 years old, as established by the American Academy of Pediatrics [11,12].

Analysis of the data

We have used IBM® SPSS® Statistics for Macintosh Version 25.0 (IBM Corp., Armonk, NY, USA) for the statistical analysis. The population study was classified in patients with and without obstructive hydrocephalus for the baseline analysis. Moreover, we classified the study population according to the treatment modality of the obstructive hydrocephalus: patients who underwent direct removal of the pineal lesion with the opening of the posterior third ventricle, patients who underwent shunt surgery, and patients who underwent ETV. Due to the limited amount of endoscopic procedures, we preferred not to consider them for the statistical analysis. Thus, we compared the patients who underwent shunt surgery to those who received a direct removal of the pineal lesions. The Chi-square (Pearson/likelihood) test, the Student t-test, Pearson correlation, and the Log-rank test were appropriately tested. Bivariate correlation of the variables was followed by simple and multiple regression analysis of the last mRS, the persistence of tumor/cyst at the last MRI, overall survival, and disease-specific (DS) survival in the group of patients with hydrocephalus. The single and multiple (stepwise) analysis of the last modified Rankin scale (mRS) underwent linear regression models. The analysis of tumor/cyst evidence at the last MRI underwent binomial logistic regression. Single and multiple (Cox-regression models) overall and DS survival analyses were also performed. The raw p-value limit for significance was established at 0.05. The Benjamini-Hochberg procedure was used for the p-value adjustment with a significance level at $\alpha=0.1$.

Pineal region cysts and tumors management in HUH

Gross total resection (GTR) of pineal region lesions with opening of the posterior third ventricle was introduced in Helsinki after the senior author (JH) became the chairman of the Department of Neurosurgery in 1997. In this regard, subtotal resection usually represents a tiny and firmly adhesive residual tumor attached to the venous walls or infiltrating critical structures.

General studies for a patient carrying a pineal region neoplasm include the evaluation of tumor markers in blood and cerebrospinal fluid (CSF), endocrine assessment, basal pituitary hormone tests, CSF sampling for cytology, CT studies, MRI in different T1WI, T2WI, T1 with gadolinium-enhanced/fat suppression, FLAIR, and diffusion-weighted sequences. Moreover, spectroscopy, tractography, CSF flow studies, proton density, and MR angiography/venography were performed as required. During the study period, acute hydrocephalus associated with a pineal lesion underwent initial treatment with the decision of the neurosurgeon in charge. However, chronic or slow progressive hydrocephalus generally underwent direct removal of the lesion with opening of the posterior third ventricle, particularly in the last ten years of study. Moreover, the senior author was available for emergency surgery in patients harboring pineal region lesions associated with hydrocephalus. Thus, even emergency patients underwent eventually direct surgery with the opening of the posterior third ventricle. The therapeutic protocol of the patients after initial evaluation followed the recommendation of a neurooncological team composed of a neurologist, a neuropathologist, a neurosurgeon, a pathologist, and a radiologist.

Results

Characteristics of the population

Tables 1 and 2 describe the surgically treated pineal cyst and tumor patients classified as 68 hydrocephalus and 65 non-hydrocephalus cases. Patients with preoperative hydrocephalus were associated with larger pineal lesions, a higher number of hydrocephalus-related procedures, a reduced extent of surgical resection, and reduced preoperative, immediate postoperative, and long-term mRS scores compared to the patients without preoperative hydrocephalus.

Significant differences also existed in terms of the pathological diagnosis with most of the gliomas, germ cell tumors (GCT), pineoblastomas, and pineal parenchymal tumors of intermediate differentiation (PPTID) in the "hydrocephalus group". Pineal cysts and pineocytomas were more frequent in the "non-hydrocephalus population". The preoperative hydrocephalus together with the patient´s age and sex, the tumor WHO grade, preoperative mRS, tumor size, postoperative complications, and GTR underwent multivariate regression for the overall and disease specific survival, tumor at the last imaging, and functional status at the last evaluation of the 136 pineal lesions. Preoperative hydrocephalus resulted only an independent predictor of worse functional status at the last evaluation (Log HR: -0.9, p: 0.006).

In simple regression models, after the exclusion of the pineal cyst cases from the analysis, preoperative hydrocephalus was significantly associated with higher WHO tumor grades (Log HR: 0.13; $p < 0.011$), DS mortality (Log HR: 1.3, p: 0.001), and the presence of tumor/cyst at the last MRI (Log HR: -0.232, p: 0.001) of the 76 pineal tumor patients. However, the predictive value of preoperative hydrocephalus was not confirmed in the multiple linear regression analysis.

Obstructive hydrocephalus treatment

Of the 68 patients with preoperative hydrocephalus, 40 underwent direct surgery with opening of the posterior third ventricle, 25 ventriculoperitoneal/ventriculoatrial shunt surgery, and three patients underwent preoperative endoscopic procedures for the management of the hydrocephalus. As mentioned, most of the shunt surgeries were performed during the first ten years of the study period. Thus, the direct removal of the lesions represented an improvement of the experience and expertise of HUH neurosurgeons. Of the three endoscopic procedures, two (67%) were sufficient for hydrocephalus management. However, one PPTID patient who underwent biopsy and brachytherapy required an additional shunt procedure to manage persistent hydrocephalus. Table 3 details the characteristics of the hydrocephalus patients according to the different treatments (shunt *versus* direct removal of the lesion) they received. The remission rate of preoperative obstructive hydrocephalus was superior in the "direct removal group" compared to the "preoperative shunt group". Thus, the preoperative shunt group $(M = 0.9, SD = 2)$ underwent higher number of postoperative shunts compared to the direct removal group $(M = 0.1, SD = 0.3)$, $t(63) = 2.4, p = 0.02$. The number of hydrocephalus-related procedures was higher in the shunt group $(M = 2.4, SD = 2.2)$ compared to the direct removal group $(M = 0.3, SD = 0.5)$, $t(63) = 5.8, p < 0.001$. The number of shunt removals and external ventriculostomies was indeed higher in the preoperative shunt group. The rate of postoperative infections was higher in the shunt group than the direct removal of the pineal lesions, $X^2 (1, N = 65) = 5.6, p = 0.018$. Moreover, the final mRS score was also significantly better in the direct tumor removal group. No differences were observed in terms of DS mortality and the last tumor-free MRI.

Pediatric population

Table 4 details information of the pediatric patients who presented hydrocephalus associated with pineal cysts and tumors. 23/42 (11 females) pediatric patients had hydrocephalus. The preoperative functional status of pediatric patients was significantly better compared to adult patients. Significant differences also existed in terms of the pathological diagnosis, with higher proportions of PPTIDs and meningiomas in the adults and more non-germinomatous germ cell tumors in the pediatric population. Only an 18-year-old patient harbored a radiosensitive germinoma associated with hydrocephalus in this series. No differences were observed in terms of DS mortality and the last tumor-free MRI.

Long-term clinical and radiological evaluation

The paired evaluation of the pre- and postoperative functional status of the hydrocephalus patients revealed a significant improvement of the immediate postoperative mRS ($p < 0.001$), as well as of the last mRS score ($p = 0.003$), compared to the preoperative mRS.

In the single regression analysis, the predictors for unfavorable last mRS scores of pineal region lesions associated with hydrocephalus included: high WHO tumor grade, male sex, poor preoperative mRS, large tumor volume, presence of pre- and postoperative shunt, repeated shunt procedures, a large number of hydrocephalus-related procedures, presence of major postoperative complications, reduced extent of tumor removal, and reduced GTR at FU. However, only the WHO tumor grade, the extent of the surgical resection at FU, the presence of major complications, and the number of shunt surgeries remained independent predictors of the functional status at the last evaluation in the multivariate analysis (Table 5). Moreover, after regression analysis, only the presence of GTR at FU remained an independent predictor of tumor-free MRI at the last evaluation.

Mortality

The overall and DS mortality of the surgically treated pineal cysts and tumors of HUH are well detailed in previous publications (Table 2).[1,2,13–15] The overall and DS survival of the subgroup of patients with preoperative hydrocephalus was 70% and 83%, respectively, at an average FU of 175 ± 131 months. In the single Cox regression analysis, the predictors for the overall mortality of the pineal region lesions associated with hydrocephalus included: higher WHO tumor grade, older age, poorer preoperative and immediate postoperative mRS, presence of postoperative complications, reduced GTR at FU, and tumor evidence at the last MRI. All of them, except the preoperative mRS and the GTR at FU, were confirmed as independent predictors for the multivariate analysis (Table 6). The predictors for the DS mortality of the same group of patients with pineal lesions determining preoperative hydrocephalus both in the univariate and in the multivariate analysis comprised: higher WHO tumor grade, worse immediate mRS, presence of major postoperative complications, reduced GTR at FU, and tumor evidence at the last MRI (Table 6).

Discussion

Here, we analyze the management of preoperative obstructive hydrocephalus in one of the largest and more complete long-term series of surgically treated pineal region cysts and tumors reported in the literature.[2–4,16–18] Our main findings may be summarized as:

1. The onset of obstructive hydrocephalus may more frequently represent the presence of a high WHO grade pineal region tumor, since preoperative hydrocephalus is associated with reduced long-term functional status, disease survival, and presence of tumor/cyst at the last MRI.

2. In regards to the treatment modality of obstructive hydrocephalus due to pineal region cysts and tumors, the direct removal of the pineal lesions was associated with better long-term functional status and reduced postoperative infections compared to the shunt procedures.

3. The large number of shunt-surgeries, together with the higher WHO tumor grade, major postoperative complications, and reduced extent of surgical resection, represented independent predictors for reduced functionality of the patients at the last evaluation.

4. The hydrocephalus treatment modalities did not represent independent predictors for overall, nor DS mortality in pineal region lesions associated with hydrocephalus.

5. Independent predictors of DS mortality in hydrocephalus associated with pineal cysts and tumors included higher WHO tumor grade, worse immediate postoperative mRS, major postoperative complications, reduced GTR at FU, and evidence of the neoplasm at the last MRI study.

Some remarkable factors might explain the lower use of the endoscopic procedures and biopsies in HUH along the study period, such as the low incidence of radiosensitive germinomas in the study population. In fact, the most common pineal region tumors in HUH were the pineal parenchymal tumors followed by gliomas. Germinomas only represented 9% of all pineal region tumors and 5% of all cysts and tumors. Thus, the probability for a patient harboring a pineal lesion to receive radiotherapy as the unique treatment modality was very limited in our series. Besides, even though only three preliminary endoscopic procedures were performed, one of these patients required an additional shunt procedure for hydrocephalus management. Finally, as mentioned above, the direct removal of the pineal lesions in patients with or without preoperative hydrocephalus in HUH along the second decade of the study period represented an improvement of the surgical experience and expertise of the senior author (JH).

In our series, even if the direct removal of the lesions represented an improvement of the experience and expertise of HUH neurosurgeons to elaborate most effective and efficient procedures, there was not a statistically significant difference in terms of gross total resection rate between patients with obstructive hydrocephalus who underwent direct lesion removal and those who received preoperative shunt surgery (p=0.11). However, the patients who underwent direct lesion removal had better long-term functional status (p=0.03) and reduced postoperative infections (p=0.017) than those undergoing preoperative shunt placement. Moreover, the preoperative hydrocephalus remission rate was superior in the "direct removal group" compared to the "preoperative shunt group".

Various techniques have been used for the treatment of obstructive hydrocephalus associated with pineal region lesions.[6,19–21] Several authors have advocated adopting external ventricular drainage to relieve the intracranial pressure pre-operatively.[6,19–21] The placement of a priori ventriculoperitoneal shunt has lost popularity because of the potential risk of a peritoneal seeding of malignant cells and shunt dysfunctions. Moreover, many patients may no longer require a CSF diversion after lesion removal.[6,19–24] The ETV represents a well-validated minimally invasive technique widely used for obstructive hydrocephalus associated with pineal region lesions.[21–24] Moreover, the tumor biopsy associated with the ETV, particularly for the diagnosis of germ cell tumors, could avoid a surgical resection due to their high radiosensitivity.[21–24] Besides, the diagnostic accuracy for endoscopic biopsies is about 50-78.6%.[21–24]

The extent of surgical resection has been recognized to play a significant role in determining the long-term outcome of non-germ cell tumors, except probably for pineal region gliomas.[1,2,13–15,19,20,25–27] The primary and radical removal of the lesion, with the opening of the posterior third ventricle, allows satisfactory and immediate restoration of the CSF pathways by relieving the compression of the third ventricle outflow tract and aqueduct, thus avoiding other hydrocephalus procedures.[19,22–24,28,29]

According to some authors, endoscopic-assisted surgery could permit higher gross total resection rates than microsurgery.[20] Moreover, endoscopic-assisted surgery could allow a safer incision of the posterior wall of the third ventricle, as well as to check the complete removal of tumors, potential blood clots, and the opening of the cerebral aqueduct.[20]

As above mentioned, in order to draw a conclusion about the proper management of preoperative hydrocephalus associated with pineal region lesions, one of the most important aspects to be considered is represented by the incidence and the prevalence of the different types of pineal tumors in the target population. This aspect appears to be relevant since Asian and North-American populations have high rates of germinomas, especially in pediatric populations, thus making ETV *plus* biopsy *plus* subsequent radiotherapy a potential option.[16,17] However, some other countries showed a higher incidence of pineal parenchymal tumors in their statistics.[3,4] In our series, the PPTIDs represented the most common pineal region tumors followed by the non-diffuse gliomas, and meningiomas, thus increasing the importance of the extent of the surgical resection and limiting the use of radiotherapy as the unique treatment modality.[2,15] In Figure 1, we present a simplified algorithm for the management of the pineal region tumors with associated pre-operative hydrocephalus.

Limitations

Since ETV currently represents almost the gold standard treatment for obstructive hydrocephalus, the lack of ETV plus biopsy cases is a critical limitation of this series analysis. However, as mentioned above, the incidence and the prevalence of the different types of pineal tumors in the target population are essential for proper pineal region tumor management. The retrospective single-center nature of the study, with most lesions operated by the senior author (JH), represents another limitation to generalize our results. However, we believe that our findings add to the current literature on this topic since large series of surgically treated pineal lesions with long-term FU are lacking.

Conclusion

In the setting of the high microsurgical treatment of pineal region cysts and tumors, our data confirmed that the direct removal of the lesions with the posterior third ventricle opening could represent effective and reliable management of the associated obstructive hydrocephalus. Further research is required to generalize our inferences.

References

1. Choque-Velasquez J, Resendiz-Nieves JC, Rezai Jahromi B, et al. The microsurgical management of benign pineal cysts: Helsinki experience in 60 cases. *Surg Neurol Int*. 2019;10:103. doi:10.25259/SNI-180-2019

2. Choque-Velasquez J, Resendiz-Nieves J, Jahromi BR, et al. Extent of resection and long-term survival of pineal region tumors in Helsinki Neurosurgery. *World neurosurgery*. Published online July 29, 2019. doi:S1878-8750(19)32085-6 [pii]

3. Konovalov AN, Pitskhelauri DI. Principles of treatment of the pineal region tumors. *Surgical neurology*. 2003;59(4):250-268. doi:10.1016/s0090-3019(03)00080-6

4. Mottolese C, Beuriat PA, Szathmari A. Pineal tumours: Experience of the French National Register and the Lyon School, results and considerations. *Neuro-Chirurgie*. 2015;61(2-3):223-235. doi:10.1016/j.neuchi.2014.02.006 [doi]

5. Starke RM, Cappuzzo JM, Erickson NJ, Sherman JH. Pineal cysts and other pineal region malignancies: determining factors predictive of hydrocephalus and malignancy. *Journal of neurosurgery*. 2017;127(2):249-254. doi:10.3171/2016.8.JNS16220 [doi]

6. Zhang Z, Wang H, Cheng H, et al. Management of hydrocephalus secondary to pineal region tumors. *Clin Neurol Neurosurg*. 2013;115(9):1809-1813. doi:10.1016/j.clineuro.2013.05.009

7. Song Z, Chen X, Tang Y, Zhou L, Yu X, Zhou D. [Endoscopic treatment strategy of obstructive hydrocephalus induced by pineal region tumors]. *Zhonghua Yi Xue Za Zhi*. 2015;95(11):845-848.

8. Mottolese C, Szathamari A, Beuriat PA, Grassiot B, Simon E. Neuroendoscopy and pineal tumors: A review of the literature and our considerations regarding its utility. *Neurochirurgie*. 2015;61(2-3):155-159. doi:10.1016/j.neuchi.2013.12.008

9. Quick-Weller J, Lescher S, Baumgarten P, et al. Stereotactic Biopsy of Pineal Lesions. *World Neurosurg*. 2016;96:124-128. doi:10.1016/j.wneu.2016.04.130

10. Májovský M, Netuka D, Beneš V. [Surgical approaches to pineal region - review article]. *Rozhl Chir*. 2016;95(8):305-311.

11. Hardin AP, Hackell JM. Age Limit of Pediatrics. *Pediatrics*. 2017;140(3). doi:10.1542/peds.2017-2151

12. American Academy of Pediatrics Council on Child and Adolescent Health: Age limits of pediatrics. *Pediatrics*. 1988;81(5):736.

13. Choque-Velasquez J, Resendiz-Nieves JC, Jahromi BR, et al. Pineoblastomas: A long-term follow up study of three cases in Helsinki Neurosurgery. *Interdisciplinary Neurosurgery*. 2019;18:100477. doi:https://doi.org/10.1016/j.inat.2019.100477

14. Choque-Velasquez J, Resendiz-Nieves JC, Jahromi BR, et al. Pineocytomas: a long-term follow up study of four cases in Helsinki Neurosurgery. *Journal of Case Reports in Medicine*. 2019;8(1):5-5.

15. Choque-Velasquez J, Resendiz-Nieves JC, Jahromi BR, et al. Pineal Parenchymal Tumors of Intermediate Differentiation: A long-Term Follow-Up Study in Helsinki Neurosurgery. *World neurosurgery*. Published online November 1, 2018. doi:S1878-8750(18)32426-4 [pii]

16. Shibui S, Nomura K. Statistical analysis of pineal tumors based on the data of Brain Tumor Registry of Japan. *Progress in neurological surgery*. 2009;23:1-11. doi:10.1159/000210049 [doi]

17. Al-Hussaini M, Sultan I, Abuirmileh N, Jaradat I, Qaddoumi I. Pineal gland tumors: experience from the SEER database. *Journal of neuro-oncology*. 2009;94(3):351-358. doi:10.1007/s11060-009-9881-9 [doi]

18. Oliveira J, Cerejo A, Silva PS, Polonia P, Pereira J, Vaz R. The infratentorial supracerebellar approach in surgery of lesions of the pineal region. *Surgical neurology international*. 2013;4:154-7806.122504. eCollection 2013. doi:10.4103/2152-7806.122504 [doi]

19. Hernesniemi J, Romani R, Albayrak BS, et al. Microsurgical management of pineal region lesions: personal experience with 119 patients. *Surg Neurol*. 2008;70(6):576-583. doi:10.1016/j.surneu.2008.07.019

20. Xin C, Xiong Z, Yan X, et al. Endoscopic-assisted surgery versus microsurgery for pineal region tumors: a single-center retrospective study. *Neurosurg Rev*. Published online March 20, 2020. doi:10.1007/s10143-020-01283-6

21. Schulz M, Afshar-Bakshloo M, Koch A, et al. Management of pineal region tumors in a pediatric case series. *Neurosurg Rev*. Published online June 6, 2020. doi:10.1007/s10143-020-01323-1

22. Sonabend AM, Bowden S, Bruce JN. Microsurgical resection of pineal region tumors. *J Neurooncol*. 2016;130(2):351-366. doi:10.1007/s11060-016-2138-5

23. Westphal M, Emami P. Pineal Lesions: A Multidisciplinary Challenge. In: *Advances and Technical Standards in Neurosurgery*. Advances and Technical Standards in Neurosurgery. Springer, Cham; 2015:79-102. doi:10.1007/978-3-319-09066-5_5

24. Zaazoue MA, Goumnerova LC. Pineal region tumors: a simplified management scheme. *Childs Nerv Syst*. 2016;32(11):2041-2045. doi:10.1007/s00381-016-3157-4

25. Choque-Velasquez J, Resendiz-Nieves J, Colasanti R, Collan J, Hernesniemi J. Microsurgical management of vascular malformations of the pineal region. *World Neurosurg*. Published online June 23, 2018. doi:10.1016/j.wneu.2018.06.110

26. Choque-Velasquez J, Colasanti R, Resendiz-Nieves J, et al. Papillary Tumor of the Pineal Region in Children: Presentation of a Case and Comprehensive Literature Review. *World Neurosurg*. 2018;117:144-152. doi:10.1016/j.wneu.2018.06.020

27. Choque-Velasquez J, Resendiz-Nieves J, Jahromi BR, et al. Long-term survival outcomes of pineal region gliomas. *J Neurooncol*. 2020;148(3):651-658. doi:10.1007/s11060-020-03571-z

28. Choque-Velasquez J, Colasanti R, Resendiz-Nieves JC, et al. Supracerebellar Infratentorial Paramedian Approach in Helsinki Neurosurgery: Cornerstones of a Safe and Effective Route to the Pineal Region. *World Neurosurg*. 2017;105:534-542. doi:10.1016/j.wneu.2017.06.007

29. Choque-Velasquez J, Resendiz-Nieves J, Jahromi BR, et al. Midline and Paramedian Supracerebellar Infratentorial Approach to The Pineal Region: A Comparative Clinical Study in 112 Patients. *World Neurosurg*. 2020;137:e194-e207. doi:10.1016/j.wneu.2020.01.137

Figure 1. Simplified algorithm for the management of the pineal region tumors. The pineal tumor incidence-prevalence and the tumor size support the therapeutic-decision process (Modified from the Doctoral dissertation Microneurosurgery of pineal region cysts and tumors: Techniques, indications, and long-term outcomes by Choque-Velasquez J. Page 108)

Table 1.
General comparison between patients harboring pineal lesions with (n = 68) and without (n = 65) associated pre-operative hydrocephalus. For numeric variables, mean ± standard deviation [min-max]

	All *N:133*	**Hydrocephalus** *N:68*	**Non-hydrocephalus** *N:65*	**P value**	**Adjusted p-value**	**N**
Age in years	34±21 (0-82)	37±23 (0-79)	32±18 (1-82)	0.22	0.22	133
Sex: females	81 (61%)	36 (53%)	45 (69%)	0.054	0.07	133
Preoperative mRS (patients)	0 (7), 1 (9), 2 (38), 3 (33), 4 (31), 5 (14)	0 (0), 1 (0), 2 (11), 3 (18), 4 (25), 5 (14)	0 (7), 1 (9), 2 (27), 3 (15), 4 (6), 5 (0)	**<0.001**	**<0.1**	132
Tumor size:						
AP	24±12 (10-90)	29±13 (11-90)	20±8 (10-54)	**<0.001**	**<0.1**	124
CC	20±11 (6-73)	24±12 (8-73)	15±9 (6-58)	**<0.001**	**<0.1**	122
AW	21±11 (7-58)	26±11 (9-589	17±8 (7-48)	**<0.001**	**<0.1**	123
Bone flap						
CC diameter	41±7 (25-68)	42±8 (25-68)	40±5 (29-53)	0.14	0.2	105
AW	35±6 (21-51)	37±7 (21-51)	34±5 (23-44)	0.13	0.2	110
Pre-shunt	25 (19%)	25 (37%)	0	**<0.001**	**<0.1**	133
Number of Post shunts	0.2±0.9 (0-8)	0.4±1.3 (0-8)	0.02±0.1 (0-1)	**0.013**	**0.02**	133
EV and shunt removals	0.1±0.3 (0-2)	02±0.4 (0-2)	0	**0.001**	**<0.1**	133
Hydrocephalus-related procedures	0.6±1.4 (0-11)	1.1±1.8 (0-11)	0.05±0.2 (0-1)	**<0.001**	**<0.1**	133
Diagnosis				**<0.001**	**<0.1**	133
Diffuse glioma	6 (5%)	5 (7%)	1 (2%)			
Germinoma	7 (5%)	5 (7%)	2 (3%)			
Meningioma	10 (8%)	5 (7%)	5 (8%)			
NGGCT	5 (4%)	5 (7%)	0			
non-diffuse glioma	12 (9%)	10 (15%)	2 (3%)			
Other tumors	10 (8%)	6 (9%)	4 (6%)			
Pineal cyst	59 (44%)	15 (22%)	44 (68%)			
Pineoblastoma	3 (2%)	3 (4%)	0			
Pineocytoma	4 (3%)	1 (1%)	3 (5%)			
PPTID II-III	15 (11%)	11 (16%)	4 (6%)			
Undefined	2 (2%)	2 (3%)	0			

Values with statistical significance in bold.
AP, anterior-posterior; AW, axial width; CC, cranio-caudal; EV, external ventriculostomy; NGGCT, non germinomatous germ cell tumor; PPTID, pineal parenchymal tumor of intermediate differentiation.

Table 2. Intraoperative and follow-up variables of obstructive hydrocephalus in pineal region cysts and tumors surgery.
For numeric variables, mean ± standard deviation [min-max]

	All *N:133*	**Hydrocephalus** *N:68*	**Non-hydrocephalus** *N:65*	**P value**	**Adj. p-value**	**N**
Surgical approach				0.33	0.5	133
Paramedian SCIT	60 (45%)	27 (40%)	33 (51%)			
Midline SCIT	57 (43%)	30 (44%)	27 (42%)			
OIH	8 (6%)	4 (6%)	4 (6%)			
Combined	4 (3%)	3 (4%)	1 (2%)			
PTC	1 (1%)	1 (1%)	0			
Puncture	3 (2%)	3 (4%)	0			
Extent of resection at FU				**0.006**	**0.03**	133
GTR	110 (83%)	49 (72%)	61 (94%)			
STR	15 (11%)	11 (16%)	4 (6%)			
PR	5 (4%)	5 (7%)	0			
Biopsy	3 (2%)	3 (4%)	0			
Immediate mRS (patients)	0 (35), 1 (41), 2 (35), 3 (11), 4 (6) 5 (4)	0 (14), 1 (15), 2 (23), 3 (7), 4 (4), 5 (4)	0 (21) 1 (26), 2 (12), 3 (4), 4 (2)	**0.002**	**0.02**	132
Post complications	39 (29%)	19 (28%)	20 (31%)	0.72	0.8	133
Post infections	16 (12%)	6 (9%)	10 (15%)	0.25	0.5	133
Post meningitis	11 (8%)	4 (6%)	7 (11%)	0.31	0.5	133
Wound infection	7 (5%)	3 (4%)	4 (6%)	0.65	0.8	133
Other complications	27 (20%)	14 (21%)	13 (20%)	0.93	0.9	133
CSF leak	4 (3%)	0	4 (6%)	**0.038**	**0.09**	
Minor complication	18 (14%)	10 (15%)	8 (12%)	0.69	0.8	133
Major complication	6 (5%)	4 (6%)	2 (3%)	0.44	0.6	
Final mRS (patients)	0 (68), 1 (25), 2 (14), 3 (7), 4 (3), 5 (2), 6 (14)	0 (25), 1 (14), 2 (11), 3 (3), 4 (2), 5 (2), 6 (11)	0 (43), 1 (11), 2 (3), 3 (4), 4 (1), 6 (3)	**0.001**	**0.02**	133
Clinical FU	45±62 (0-324)	58±73 (0-324)	30±43 (1-180)	**0.01**	**0.04**	128
Last MRI				**0.005**	**0.03**	133
No tumor	107 (80%)	47 (69%)	60 (92%)			
Pineal recurrence	17 (13%)	14 (21%)	3 (5%)			
Other location Rec.	4 (3%)	4 (6%)	0			
Pineal and other location recurrence	5 (4%)	3 (4%)	2 (3%)			
Radiological FU	60±65 (0-233)	69±67 (0-233)	49±61 (0-227)	0.10	0.2	120
Overall survival	79%	70%	89%	**0.01**	**0.04**	133
Disease survival	89%	83%	95%	**0.036**	**0.09**	133
Survival FU	136±89 (0-588)	131±102 (0-588)	145±72 (5-376)	0.37	0.5	133

Values with statistical significance in bold.
CSF, cerebrospinal fluid; FU, follow-up; GTR, gross total resection; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; OIH, occipital interhemispheric approach; PR, partial resection; PTC, parietal transcortical approach; SCIT supracerebellar infratentorial approach; STR, subtotal resection.

Table 3. Management of the obstructive pre-operative hydrocephalus due to pineal region lesions. For numeric variables, mean ± standard deviation [min-max].

	Total *N:65*	**Shunt surgery** *N:25*	**Direct lesion removal** *N:40*	**P-value**	**Adj. p-value**	**N**
Age in years	37±23 (0-79)	31±22 (2-79)	40±23 (0-79)	0.13	0.2	65
Sex: females	35 (54%)	10 (40%)	25 (63%)	0.08	0.2	65
Preoperative mRS (patients)	2 (11), 3 (16), 4 (25), 5 (13)	2 (4), 3 (5), 4 (11), 5 (5)	2 (7), 3 (11), 4 (14), 5 (8)	0.68	0.8	64
Tumor volume(mm^3)	15063±22195	19127±21562	12467±22502	0.26	0.4	59
Bone flap (mm^2)	1209±377	1290±369	1163±379	0.25	0.4	53
Post temporary EV	5 (8%)	1 (4%)	4 (10%)	0.36	0.5	65
Number of post shunt	0.4±1.3 (0-8)	0.9±2 (0-8)	0.1±0.3 (0-1)	**0.02**	**0.06**	65
EV and shunt removals	0.2±0.4 (0-2)	0.5±0.6 (0-2)	0	**<0.001**	**<0.1**	65
Post endoscopy	3 (5%)	1 (4%)	2 (5%)	0.85	1	65
Total shunt surgeries	1±1.8 (0-11)	2.4±2.2 (1-11)	0.3±0.5 (0-2)	**<0.001**	**<0.1**	65
Total hydrocephalus procedures	1±1.8 (0-11)	2.4±2.2 (1-11)	0.3±0.6 (0-2)	**<0.001**	**<0.1**	65
Diagnosis: GCT, glioma, meningioma, PC, PPT, other	10, 14, 5, 14, 14, 8	4, 8, 0, 1, 8, 4	6, 6, 5, 13, 6, 4	**0.005**	**0.02**	65
Approach: midline SCIT, paramedian SCIT, OIH, Other	30, 26, 4, 5	17, 5, 0, 3	13, 21, 4, 2	**0.006**	**0.02**	65
Extent of resection at FU: GTR, STR, PR, Biopsy	48, 11, 5, 1	16, 7, 1, 0	32, 7, 1, 0	0.11	0.2	65
Immediate mRS (patients)	0 (13), 1 (14), 2 (23), 3 (6), 4 (4), 5 (4)	0 (4), 1 (6), 2 (9), 3 (3), 4 (3), 5 (2)	0 (9), 1 (8), 2 (14), 3 (3), 4 (3), 5 (2)	0.93	1	65
Post infections	6 (9%)	5 (20%)	1 (3%)	**0.017**	**0.05**	65
Post meningitis	4 (6%)	3 (12%)	1 (3%)	0.13	0.2	65
Wound infection	3 (5%)	2 (8%)	1 (3%)	0.31	0.4	
Other complications	13 (20%)	5 (20%)	8 (20%)	1	1	65
Final mRS (patients)	0 (23), 1 (14), 2 (11), 3 (3), 4 (2), 5 (2), 6 (10)	0 (7), 1 (3), 2 (4), 3 (3), 4 (1), 5 (1), 6 (6)	0 (16), 1 (11), 2 (7), 3 (0), 4 (1), 5 (1), 6 (4)	**0.034**	**0.08**	65
Clinical FU	57±73 (0-324)	90±94 (1-324)	36±48 (0-215)	**0.004**	**0.03**	63
Last MRI: no tumor, pineal recurrence, other location recurrence, pineal and other recurrence	12, 46, 4, 3	6, 16, 2, 1	6, 30, 2, 2	0.76	0.9	65
Radiological FU	68±68 (0-233)	92±80 (0-233)	54±55 (0-209)	**0.031**	**0.08**	62
Disease survival	84%	74%	90%	0.52	0.7	65
Survival FU	129±104 (0-588)	175±131 (0-588)	101±71 (1-247)	**0.004**	**0.02**	65

Values with statistical significance in bold.
EV, external ventriculostomy; FU, follow-up; GCT, germ cell tumor; GTR, gross total resection; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; OIH, occipital interhemispheric approach; PC, pineal cyst; PPT, pineal parenchymal tumor; PR, partial resection; SCIT, supracerebellar infratentorial approach; STR, subtotal resection.

Table 4.
Comparison between pediatric (n = 23) and adult (n = 45) patients with obstructive preoperative hydrocephalus due to pineal lesions.
For numeric variables, mean ± standard deviation [min-max]

	Hydrocephalus ***N:68***	**Pediatric** ***N:23***	**Adults** ***N:45***	**P value**	**Adj p-value**	**N**
Age in years	37±23 (0-79)	13±7 (0-21)	49±17 (22-79)	-	-	68
Sex: females	36 (53%)	11 (48%)	25 (56%)	0.6	0.87	68
Preoperative mRS (patients)	2 (11), 3 (18), 4 (25), 5 (14)	2 (8), 3 (5), 4 (8), 5 (2)	2 (3), 3 (13), 4 (17), 5 (12)	**0.007**	**0.05**	68
Tumor volume (mm^3)	14497±21794	22085±32850	10883±12850	0.058	0.25	62
Total shunt surgeries	1±1.8 (0-11)	1.4±2.5 (0-11)	0.8±1.2 (0-6)	0.22	0.48	68
Diagnosis: Diffuse glioma, germinoma, NGGCT, non-diffuse glioma, PC, PBT, PCT, PPTID, other, undefined	5, 5, 5, 5, 10, 15, 3, 1, 11, 6, 2	1, 1, 0, 5, 4, 7, 2, 0, 0, 2, 1	4, 4, 5, 0, 6, 8, 1, 1, 11, 4, 1	**0.001**	**0.01**	68
Approach: paramedian SCIT, midline SCIT, OIH, other	27, 30, 4, 3, 1, 3	8, 12, 1, 0, 1, 1	19, 18, 3, 3, 0, 2	0.36	0.67	68
Extent of resection at FU: GTR, STR, PR, Biopsy	49, 11, 5, 3	16, 5, 1, 1	33, 6, 4, 2	0.8	0.87	68
Immediate mRS (patients)	0 (14), 1 (15), 2 (23), 3 (7), 4 (4), 5 (4)	0 (6), 1 (7), 2 (6), 3 (2), 4 (1), 5 (0)	0 (8), 1 (8), 2 (17), 3 (5), 4 (3), 5 (4)	0.07	0.23	67
Post complications	19 (28%)	7 (30%)	12 (27%)	0.7	0.91	68
Final mRS (patients)	0 (25), 1 (14), 2 (11), 3 (3), 4 (2), 5 (2), 6 (11)	0 (12), 1 (3), 2 (1), 3 (1), 4 (1), 5 (0), 6 (5)	0 (13), 1 (11), 2 (10), 3 (2), 4 (1), 5 (2), 6 (6)	0.9	0.9	68
Last MRI: No tumor, pineal recurrence, other location recurrence, pineal and other recurrence	47, 14, 4, 3	16, 3, 2, 2	31, 11, 2, 1	0.4	0.65	68
Disease survival	83%	78%	86%	0.7	0.83	66
Survival FU	131±102 (0-588)	151±133 (1-588)	120±82 (0-247)	0.2	0.52	68

Values with statistical significance in bold.
FU, follow-up; NGGCT, non-germinomatous germ cell tumor; GTR, gross total resection; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; OIH, occipital interhemispheric approach; PBT, pineoblastoma; PC, pineal cyst; PCT, pineocytoma; PPT, pineal parenchymal tumor; PPTID, pineal parenchymal tumor of intermediate differentiation; PR, partial resection; SCIT, supracerebellar infratentorial approach; STR, subtotal resection.

Table 5. Predictors for last functional status (last mRS 1-6) and absence of tumor at the last imaging by simple- and multiple linear regression models of pineal cysts and tumors associated with hydrocephalus.

CI, confidence interval; GTR at FU, gross total resection at follow up; Log HR, logarithm of the hazard ratio; mRS, modified Rankin scale; post, postoperative; pre, preoperative; WHO, world health organization.
Values with statistical significance in bold.

Last mRS						
	Univariate model			Multivariate model		
Variable	Log HR	95.0% CI for Log HR	p-value	Log HR	95.0% CI for Log HR	p-value
WHO grade	0.84	0.5 , 1.2	**<0.001**	0.66	0.34 , 0.95	**<0.001**
Female sex	-1.1	-2.1 , -0.05	**0.04**	-	-	0.64
Pre mRS	0.8	0.3 , 1.3	**0.003**	-	-	0.52
Tumor volume	3.946E-5	0 , 0	**0.002**	-	-	0.52
Pre-shunt	1.1	0.04 , 2.2	**0.04**	-	-	0.87
Number of post shunt	0.6	0.2 , 1	**0.004**	-	-	0.69
Number of Shunt surgeries	0.5	0.2 , 0.8	**0.002**	0.30	0.08 , 0.53	**0.01**
Number hydrocephalus procedures	0.5	0.2 , 0.8	**0.002**	-	-	0.43
Major complications	3.3	1.2 , 5.4	**0.003**	3.9	2.2 , 5.7	**<0.001**
Extent of resection	-0.99	-1.6 , -0.4	**0.002**	-0.89	-1.4 , -0.4	**0.001**
GTR at FU	-1.9	-3 , -0.8	**0.001**	-	-	0.60
Tumor free at the last MRI						
GTR at FU	4.6	2.8 , 6.4	**<0.001**			

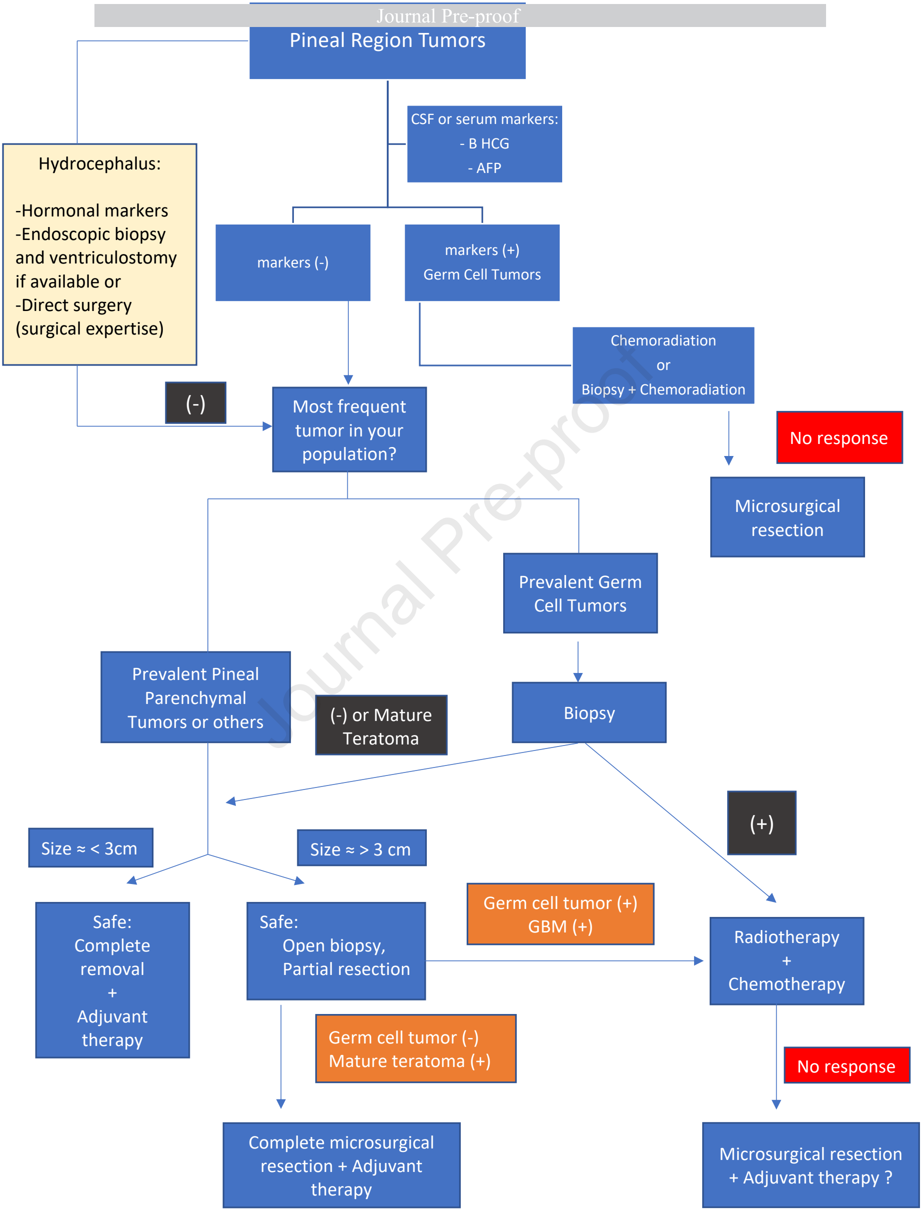
Major complications: aseptic meningitis, surgical bleeding/infarction, tension pneumocephalus that required treatment, pseudomeningocele, and epidural hematoma.

Table 6. Predictors for the overall and disease-specific survival rates obtained by single and multiple Cox regression models of pineal cysts and tumors associated with hydrocephalus.

Log HR, logarithm of the hazard ratio; CI, confidence interval; GTR at FU, gross total resection at follow up; mRS, preoperative modified Rankin scale; MRI, magnetic resonance imaging; post, postoperative; pre, preoperative; WHO, world health organization.
Values with statistical significance in bold.

	Overall mortality					
	Univariate model			Multivariate model		
Variable	Log HR	95.0% CI for HR	p-value	Log HR	95.0% CI for HR	p-value
WHO grade	0.86	1.6 , 3.5	**<0.001**	1.0	1.5 , 5.6	**0.002**
Age	0.31	1 , 1.1	**0.007**	0.05	1.02 , 1.09	**0.005**
Pre mRS	0.81	1.3 , 3.8	**0.003**	-0.62	0.22 , 1.05	0.096
Immediate post mRS	0.79	1.5 , 3.2	**<0.001**	0.95	1.3 , 4.6	**0.003**
Post complications	0.92	1 , 6	**0.042**	1.39	0.1 , 1.1	**0.032**
Tumor at last MRI	0.7	1.3 , 3.1	**0.001**	0.77	1.1 , 4.9	**0.041**
GTR at FU	-0.9	0.17 , 0.99	**0.047**	-1.2	0.1 , 1.1	0.068
	Disease-specific mortality					
WHO grade	1.2	1.7 , 6.1	**<0.001**	2.017	1.8 , 31.6	**0.006**
Immediate post mRS	0.73	1.3 , 3.5	**0.005**	1.516	1.4 , 14.7	**0.011**
Major complications	2.5	3 , 49	**0.001**	2.503	1.5 , 99.8	**0.019**
Tumor at last MRI	1.1	1.8 , 5.1	**<0.001**	1.221	1.3 , 8.9	**0.013**
GTR at FU	-1.4	0.1 , 0.9	**0.027**	-2.712	0.01 , 0.8	**0.035**

Major complications: aseptic meningitis, surgical bleeding/infarction, tension pneumocephalus that required treatment, pseudomeningocele, and epidural hematoma.


Pineal Region Tumors
CSF or serum markers:
- B HCG
- AFP
Hydrocephalus:
-Hormonal markers
-Endoscopic biopsy and ventriculostomy if available or
-Direct surgery (surgical expertise)
markers (-)
markers (+)
Germ Cell Tumors
Chemoradiation
or
Biopsy + Chemoradiation
(-)
Most frequent tumor in your population?
No response
Microsurgical resection
Prevalent Germ Cell Tumors
Prevalent Pineal Parenchymal Tumors or others
(-) or Mature Teratoma
Biopsy
(+)
Size ≈ < 3cm
Size ≈ > 3 cm
Germ cell tumor (+)
GBM (+)
Safe:
Complete removal
+
Adjuvant therapy
Safe:
Open biopsy,
Partial resection
Radiotherapy
+
Chemotherapy
Germ cell tumor (-)
Mature teratoma (+)
No response
Complete microsurgical resection + Adjuvant therapy
Microsurgical resection
+ Adjuvant therapy ?

Title

Management of obstructive hydrocephalus associated with pineal region cysts and tumors and its implication in long-term outcome

Abbreviations and Acronyms

HUH, Helsinki University Hospital; WHO, World Health Organization; DS survival, disease specific survival; mRS, modified Rankin Scale; CSF, cerebrospinal fluid; GCT, germ cell tumor, PPTID, pineal parenchymal tumor of intermediate differentiation; GTR, gross total resection.

Title

Management of obstructive hydrocephalus associated with pineal region cysts and tumors and its implication in long-term outcome

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, and devices described in this article.