

## **ANNEX A.**

### **Summary of the literature review of 21<sup>st</sup> century series.**

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Author	N	Mean/Median FU (yr)	Study goal	Treatment recommendations	Outcome parameters	Disease control	Complications or Sequelae
<b>Saint Rose. 2005</b> [1]	66. Retrospective  Aim of GTR in 100% at first surgery (33 STR)  FSRT 18.18%	7 years (mean)	To classify PCPG at presentation to allow rationalization of multimodal therapy to decrease morbidity.	Treatment strategy may be adapted according to the <b>degree of preoperative hypothalamic involvement</b> in order to minimize morbidity.	BMI, HUI index related to hypothalamic types and surgeon experience.	36% recurrence GTR 54% recurrence STR	90% hormonal therapy. Visual function was improved in 68% but worse in 21%.  A degree of hyperphagia 70% of the cases (18% severe leading to morbid obesity)  15% of the children had an impaired neuropsychological evaluation post-operatively.
<b>Thompson. 2005</b> [2]	75 historical/ 48 current  25/48 GTR 23/48 STR 6 STR (<5y) 17 STR+FSRT	5.58 years (mean in current series)	To compare current conservative approach (STR + FSRT) with previous policy (GTR)	<b>Avoidance of radical surgery as a primary curative treatment option</b> is associated with a reduction in post-operative morbidity without subsequent fall in rates of cure.	Degree of hydrocephalus Size of tumor Age less than 5y Signs of hypothalamic disturbance Intra-operative complication Removal of tumor observed to be adherent to hypothalamus	Current series: 48% recurrence GTR 100% recurrence STR alone 17.64% recurrence STR+FSRT	Historical series vs current series: Mortality rates 12% vs 4% Neurological sequelae 67% vs 20% Hormonal impairment 99% vs 92% DI 80% vs 73%

<b>Pierre-Kahn. 2005 [3]</b>	14		Incidence of hypothalamic syndrome after GTR of PCPG	<b>CPG with preop hypothalamic involvement</b> (abnormal BMI, behavioral disturbances, and/or intraventricular extension) <b>are not amenable to “total” resection.</b>	A large defect at the level of the III V floor on post-surgical MRI is a factor of bad prognosis.		At 2-year follow-up, only two children (14.3%) were symptom-free, considered as intellectually normal, and at tending normal schooling. The 12 others presented with at least two of the six symptoms constituting the hypothalamic syndrome
<b>Zuccaro. 2005 [6]</b>	153	A follow up of 1 to 16 years	Results of a radical surgery perspective.	<b>The treatment of choice in CPG in childhood is total resection</b> in order to avoid radiation therapy and recurrence.	Surgeon experience	0% recurrence GTR 51% recurrence STR+RTEF	85% supplemental hormonal therapy. Visual status improved markedly after surgery. Surgical complications:  Subdural hematoma (12%) Seizures (9%) Vascular (6%), Neurological (4%) Infection (4%) Transplanted craniopharyngioma (1%). Shunt malfunction (68%).  Until December 1994, the overall mortality was 12.5%; 7% (2005). 3.2% perioperative deaths.
<b>Puget. 2007 [5]</b>	66	Retrospective: 7 years (median) Prospective: 13.8 months (mean)	A retrospective analysis to identify pre-operative PCPG prognostic factors that would allow stratification of patients, that was applied prospectively to	<b>Multimodal treatment</b> for	Surgeon experience  Hydrocephalus  Pre- and post-operative classification of hypothalamic involvement.	53% recurrence (retrospective series)  Recurrence rate 36% after GTR and 54% after STR, (intergroup	

	Prospective cohort (treatment stratified according to risk factors)		another cohort of patients.		Hyperphagia Neuropsychological dysfunction.		difference was not significant)
<b>Elliott. 2010 [23]</b>	86 Retrospective	9 years (mean)	Overall and progression-free survivals and outcomes in a large series of children who underwent GTR of primary and recurrent CPG performed by a single surgeon.	<b>The treatment of choice in CP in childhood is total resection.</b>	Surgeon experience Risk factors for STR: prior RT, size of the tumor. Risk factors affecting OS and PFS after radical resection of CP were hydrocephalus, VP shunt and size > or equal to 5 cm.	20% recurrence GTR. There was no difference in the rate of recurrence between the primary and the recurrent tumors.	15% died during the study period. Overall operative mortality rate of 3%. Neurological morbidity (53%) Non neurological complications (8%) 78% had DI. 24.6% post-operative hypothalamic dysfunction.
<b>Cavalheiro. 2010 [16]</b>	60 Prospective and multicenter > 60% of the tumor volume was cystic	44 months (mean)	To demonstrate that the use of ICC with INF $\alpha$ is a simple method, with a very low cost, that allows the control of cystic CPG	<b>The use of INF<math>\alpha</math> for the treatment of cystic forms of CPG is efficacious, easy to handle, and available at a low cost; it is also associated with a low morbidity rate.</b>		Disease control was achieved in 78.3% of the patients (they considered disease to be controlled when a tumor decreased more than 50%)	30% of the patients had some kind of side effect due to INF $\alpha$ 2A therapy (headache, palpebral edema, fever, chronic fatigue syndrome and arthritis) Only 13% of patients developed a worsening of endocrine function, no patient developed severe hypothalamic disturbances or

							became obese and the mortality rate was 0%.
<b>Mallucci. 2012 [7]</b>	20  Prospective  Endoscopic drainage of tumor cyst + risk grade and surgical strategy.  Definitive surgery was performed in 4–6 weeks' time.	3 years (median)	To review their management of patients with CPG using a risk stratification system that combines the CCLG guidelines and the Paris staging system.	<b>Re-stratification before and after endoscopic decompression</b> of the cystic component and hydrocephalus.	Hypothalamic syndrome at presentation, hydrocephalus, tumor size and the radiological three-point Paris grading, were combined to produce four subgroups: very high, high, medium and low risk.	GTR (30%), NTR (25%) or STR (45%)	No complications associated with the neuroendoscopic procedures. No surgical-related mortality. Two new visual field defects. No hypothalamic complications.  Post-operative complications: one extradural hematoma, seizure and a cerebrospinal fluid fistula.  47 % patients were deficient in all anterior pituitary hormones and 16 patients had DI.
<b>Cohen. 2013 [17]</b>	33 (2001-2011) 43 (1990-2001) 50 (1975-1989)  Retrospective	4 years (mean)	They aim to compare long-term outcomes of pediatric CP treated over the last decade vs historical series.	Treatment approach to CP has shifted from a goal of “curative” tumor resection to use of <b>minimalistic surgery plus adjuvant treatment to reduce tumor symptoms</b> .	Younger age at diagnosis and degree of hypothalamic involvement.	Recurrence rates were not significantly different among the 3 time periods, shifting from 34% and 30% in the past to 52% in the last decade.	Prevalence of pituitary hormone deficiency has decreased significantly compared with the last decade, including both anterior panhypopituitarism and DI. The prevalence of obesity decreased by 10% and that of severe obesity by 36% ( not significant.)  Survival rate in this series was 97%.

<b>Hoffman. 2014 [15]</b>	120 KPHG2000. 106 KPHG 2007.  Prospective and multicenter	6.78 years (mean) KPHG2000  2.22 years (mean) KPHG2007	To analyzed childhood CPG patients of the studies KPHG 2000/2007.	A trend towards <b>more hypothalamus-sparing surgical strategies</b> in childhood CPG.  <b>FSRT is recommended for treatment and/or prevention of progression after STR</b>	Surgical expertise.	Comparing KPHG 2000 vs 2007, 3-year event free survival rates were higher in patients after GTR (89% vs 77%) when compared to patients after STR (33% vs 32%)	The 3-year overall survival rate in KPHG 2000 was $0.97 \pm 0.015$ . In KPHG 2007, no lethal event was encountered up to now (September 2013)
<b>Amayiri. 2017 [8]</b>	24  Retrospective	4.5 years (median)	To review the experience in the management of pediatric CPG in a LMIC, with emphasis on the QoL.	It is important, to have a <b>locally feasible plan</b> to care of children with CPG. It may be practical <b>to accept less than a GTR to avoid further hypothalamic injury and morbidities.</b>  Multidisciplinary teams and second opinions, from experts.		54% needed multiple surgical resections, with a median of two interventions (range 2–4)	Post-operative complications were mainly related to electrolyte imbalance. Four patients had significant post-operative hypothalamic symptoms.  17% died and 13% were lost to follow-up. One immediate postoperative mortality was due to major cerebral infarction following STR.  At last follow-up, VA stabilized in 33 (69%). Almost all patients were on multiple hormonal supplements. All GTR were overweight or obese. Hyperlipidemia (41%), and liver with fatty changes (67%). 11/17

						<p>patients (65%) were attending school. 53% low self-esteem and difficulties to engage with peers. Two patients had significant behavioral difficulties and attention seeking behaviors.</p>
<b>Fouda. 2020 [18]</b>	45 old era/90 new era Retrospective	10 years (median)	To demonstrate the paradigm shift in management strategies.	Aggressive resection-related <b>morbidities are balanced</b> by the avoidance of radiation-induced morbidities and the contrary.	29% recurrence (new era) 31% recurrence (old era) STR/cyst drainage + FSRT has similar rate of recurrence in comparison with GTR. STR without adjuvant FSRT was associated with a 71% risk of recurrence.	<p>4% patients died.</p> <p>Visual function improved in 13% patients while it deteriorated in 18%</p> <p>Panhypopituitarism was evident in 75%.</p> <p>New-onset DI in 61% patients.</p> <p>Radiation induced moyamoya was 11%. Intracranial aneurysm was evident in 5%.</p> <p>Psychological impairment was documented in 22% and learning disabilities in 28%.</p> <p>New-onset hypothalamic obesity in 34% patients.</p>

							<p>Radiation-induced secondary malignancies were seen 4% patients.</p> <p>Seizures were evident in 15 patients (three had seizures preoperatively).</p> <p>Motor dysfunction was evident in seven patients.</p>
<b>Al Shail. 2020 [25]</b>	35. Retrospective.	156.9 months (median)	To investigate factors related to recurrence of CPG.	Twenty-four patients (70.6%) had GTR. There were 12/35 patients who received radiotherapy.	VP shunt presence at presentation.	Rate of disease recurrence was 42.9% (15 patients)	<p>Probability of 10-year overall survival was observed at <math>0.889 \pm 0.105</math>.</p> <p>Postsurgical panhypopituitarism was observed in nine (25.7%) patients. VP shunt was inserted in 12 (34.3%) patients</p>
<b>Liu. 2020 [24]</b>	28 Retrospective	6.1 years (median)	To review the experience of managing CP over the past 20 years. To investigate patient survival, predictors of outcome, and long-term morbidities.	<p>The treatment approaches were heterogeneous. GTR/NTR in 39% STR 50% and Biopsy+IFN 11% patients.</p> <p>Adjuvant RT 32%</p>	Patients treated in a high-volume center had significantly better outcomes.	43% patients experienced disease progression (median time to progression = 1.4 years)	<p>Among the survivors (n = 25), 60% had chronic visual impairments. Endocrinopathies were present in 92% patients. 64% patients were overweight or obese at their last evaluation, with one patient requiring bariatric surgery.</p>

<b>Enayet. 2021 [9]</b>	130	43.95 months (median)	To report their experience and management strategies for childhood CPG.	Management protocol is presented based on <b>individualized surgical approach</b> (guided by preoperative imaging and intraoperative findings) <b>and tumor genetics</b> (Beta-catenin mutations)	Beta-catenin mutations more than 5% were associated with statistically trending aggressive clinical behavior.	5-year PFS was 52.3%, (34.49% for the follow-up group and 72.25% for the RT group) Median time to progression in the follow-up cohort and the radiotherapy cohort was 20.5 months and 44.3 months, respectively.	Mortality was reported in eight patients (8/137)
	Retrospective						
	65 Surgery “follow up group”						
	71 Surgery+RT “RT group”						
	1 Ommaya+IF						