CRANIOPHARYNGIOMA IN THE ELDERLY: A MULTICENTER AND NATION-WIDE STUDY IN SPAIN

Pedro Iglesias[a], Ignacio Nocete[a], María Dolores Moure Rodríguez[b], Eva Venegas-Moreno[c], Jessica Ares[d], Betina Biagetti[e], Víctor Rodríguez Berrocal[f], Fernando Guerrero-Pérez[g], Almudena Vicente[h], Rocío Villar-Taibo[i], Fernando Cordido[j], Miguel Paja[k], Mariela Glerean[l,m], Natividad González Rivera[n], Elena Dios Fuentes[c], Concepción Blanco[o], Cristina Alvarez-Escolá[p], Tomás Martín[n], Susan M Webb[m], Ignacio Bernabeu[i,] Carles Villabona[g], Alfonso Soto-Moreno[c], Sonia Gaztambide[b,q], and Juan José Díez[a,r]

[a]Department of Endocrinology, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain. Instituto de Investigación Sanitaria Puerta de Hierro Segovia de Arana (IDIPHISA).

[b]Department of Endocrinology, Hospital Universitario Cruces, Biocruces Bizkaia, EndoERN, Cruces Barakaldo.Bizkaia, Spain

[c]Department of Endocrinology, Hospital Universitario Virgen del Rocío, Sevilla, Spain

[d]Department of Endocrinology, Hospital Universitario Central de Asturias, Oviedo, Spain

[e]Department of Endocrinology, Universitari Vall d'Hebron, Barcelona, Spain

[f]Department of Neurosurgery, Hospital Universitario Ramón y Cajal, Madrid, Spain

[g]Department of Endocrinology, Hospital de Bellvitge (L'Hospitalet de Llobregat), Barcelona, Spain

[h]Department of Endocrinology, Hospital Virgen de la Salud, Toledo, Spain

[i]Department of Endocrinology, Complexo Hospitalario Universitario de Santiago de Compostela, Spain

[j]Department of Endocrinology, Complejo Hospitalario Universitario A Coruña, Spain. Facultad de Ciencias de la Salud, Universidad de A Coruña, Spain.

[k]Department of Endocrinology, Hospital Universitario de Basurto, Bilbao, Spain

[l]Department of Endocrinology, Hospital Italiano de Buenos Aires, Argentina (present address)

[n]Department of Endocrinology, Hospital Universitario Virgen de la Macarena, Sevilla, Spain

[o]Department of Endocrinology, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, Spain

[p]Department of Endocrinology, Hospital Universitario La Paz, Madrid, Spain

[m]Department of Endocrinology, Hospital Sant Pau, Dept Medicine/Endocrinology, IIB-Sant Pau, Research Center for Pituitary Diseases, Barcelona, Spain; Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER, Unidad 747), ISCIII; Universitat Autònoma de Barcelona, Barcelona, Spain

[q]UPV-EHU, CIBERDEM, CIBERER

[r]Department of Medicine, Universidad Autónoma de Madrid, Spain

Running title: **Craniopharyngioma in the elderly**

Key-words: Craniopharyngioma, elderly, diabetes insipidus, hypopituitarism, visual field defects, neurosurgery, therapeutic outcome.

Correspondence:
Dr. Pedro Iglesias
Department of Endocrinology
Hospital Universitario Puerta de Hierro Majadahonda
Calle Manuel de Falla 1
28222 Madrid
Spain
e-mail: piglo65@gmail.com

ABBREVIATIONS

ACP, Adamantinomatous craniopharyngioma; **DI**, diabetes insipidus**; EET**, Endoscopic endonasal transsphenoidal; **CP**, Craniopharyngioma; **CT**, computed tomography; **MRI**, magnetic resonance imaging (MRI); **MT**, Microscopic transsphenoidal; **PCP**, papillary craniopharyngioma; **PD**, Progressive disease; **PR**, Partial response; **TC**, tumor cure; **SD**, stable disease

ABSTRACT

Background. Craniopharyngioma (CP) is a rare tumor in the elderly whose clinical features and prognosis are not well known in this population.

Aim. To evaluate the clinicopathological features and therapeutic outcomes of CP diagnosed in the elderly.

Patients and Methods. A retrospective, multicenter, national study of CP patients diagnosed over the age of 65 years and surgically treated was performed.

Results. From a total of 384 adult CP patients, we selected 53 (13.8%) patients [27 women (50.9%), mean age 72.3 ± 5.1 years (range 65-83 yr)] diagnosed after the age of 65 years**.** The most common clinical symptoms were visual field defects (71.2%) followed by headache (45.3%). Maximum tumor diameter was 2.9 ± 1.1 cm. In most patients, the tumor was suprasellar (96.2%) and mixed (solid-cystic) (58.5%). The surgical approach most commonly used was transcranial surgery (52.8%) and more than half of the patients (54.7%) underwent subtotal resection (STR). Adamantinomatous CP (ACP) and papillary CP (PCP) were present in 51% and 45.1%, respectively, with mixed forms in the remaining. Surgery was accompanied by an improvement in visual field defects and in headaches; however, pituitary hormonal hypofunction increased, mainly at the expense of an increase in the prevalence of diabetes insipidus (DI) (from 3.9% to 69.2%). Near-total resection (NTR) was associated with a higher prevalence of DI compared with subtotal resection (87.5 vs 53.6%, p=0.008). Patients were followed for 46.7±40.8 months. Mortality rate was 39.6% with a median survival time of 88 (95% CI, 57-118) months. DI at last visit was associated with a lower survival.

Conclusion. CP diagnosed in the elderly shows a similar distribution by sex and histologic forms than that diagnosed at younger ages. At presentation visual field alterations and headaches are the main clinical symptoms which improve substantially with surgery. However, surgery, mainly NTR, is accompanied by worsening of pituitary function, especially DI, which seems to be a predictor of mortality in this population.

INTRODUCTION

Craniopharyngioma (CP) is a non-glial intracranial tumor developed from embryonic remnants of the craniopharyngeal duct (Rathke's pouch), which explains its selar or suprasellar location [1]. It is a very rare tumor with an overall age-adjusted incidence rate of 1.7-1.9 cases per 1 million person-years without gender predominance [2,3].

CP represents <1% of all CNS tumors; however, in children, CP is the most common non-glial intracranial tumor (~10% of brain tumors), with an annual incidence of 2.1-3.8 cases per 1 million children [2-6].

Although CP can develop at any age, its distribution usually depends on the histological type. Adamantinomatous CP (ACP) has a bimodal distribution with peak incidences between 5 and 14 years in children and 45-60 years in adults [2,3,7]. However, papillary CP (PCP) appears almost exclusively in adults, with a mean age of 45-50 years [7].

CP can be accompanied by neuro-ophthalmological and endocrinological symptoms due to compression of neighboring structures and involvement of the pituitary hypothalamic axis [8]. Such symptoms may be related to the location of the tumor and the age of the patient. Older patients can develop depressive symptoms and cognitive disorders that could make diagnosis difficult and delayed.

To the best of our knowledge, there are no published series that have studied in detail CP diagnosed in advanced age. Given the paucity of information on CP in this population [9-12] and the progressive aging of the population, and therefore a probable increase in the incidence of this tumor in the future, we believe of interest to appraise better the clinical behavior and therapeutic response of CP in this population. Therefore, the objective of the present study was to analyze the clinicopathological features, used therapies and outcomes in a large series of elderly patients diagnosed with CP over the age of 65 years.

PATIENTS AND METHODS

A retrospective, multicenter, national study of patients diagnosed with CP over the age of 65 years, and treated surgically, encompassing the last two decades (from 1996 to 2019). The project received a favorable evaluation from the board of directors of the Spanish Society of Endocrinology (SEEN) and was disseminated to all members of the Neuroendocrinology Task Force of the SEEN, a working group that includes most of the endocrinologists who are experts in neuroendocrinology. All members had the opportunity to review the protocol and suggest modifications. After several rounds of emails and discussion sessions, a final version of the protocol was approved by the 24 investigators from 15 centers who were interested in participating.

Clinical data, hormonal workup, imaging tests and therapeutic outcomes were recorded in each patient. CP diagnosis was established with the histological demonstration of the tumor after surgery. Near-total resection (NTR) was defined as > 90% resection of tumor volume and subtotal resection (STR) was defined as the removal of 25-90% of tumor volume based on the post-surgical MRI findings.

In every patient the following parameters were analyzed: sex, age at diagnosis, personal background (cranio-cervical radiotherapy, diabetes, hypertension, and hyperlipidemia), clinical manifestations at diagnosis, tumor features, therapies used, surgical complications, and therapeutic outcomes.

Type and number of pituitary deficiencies were also registered. Hypopituitarism was defined as deficient secretion of one or more pituitary hormones diagnosed by criteria of routine clinical practice. The diagnosis of hypopituitarism was made based on the baseline hormonal values [thyrotropin, TSH; free thyroxine, FT4; follicle stimulating hormone, FSH; luteinizing hormone, LH; testosterone (men), 17-beta-estradiol (women); cortisol; and insulin-like growth factor type 1, (IGF 1) and PRL]. Hormonal measurements were performed in each laboratory using standard radioimmunoassay, immunoradiometric assay or enzymoimmunometric assay methods, with their respective reference ranges. Hormonal status was evaluated at diagnosis, up to 3 months after surgery, and again at their last clinical visit.

Tumor response evaluation criteria used at the last clinical visit were: Tumor cure (TC) when the last imaging study was negative; Partial response (PR): a reduction of at least 30% of the initial largest tumor diameter in the last 6 months; Progressive disease (PD): tumor progression of at least 20% of the largest diameter in the last 6 months; and stable disease (SD): neither PR nor PD.

Patient's data were obtained under the standard medical care conditions. The patient's confidential information was protected according to national law and the study was approved by the local ethics committee of the hospital Puerta de Hierro Majadahonda, Madrid. Spain.

Statistical analysis

Qualitative data are presented as the number of patients and the percentage in parenthesis or the number of patients with the feature / total number of patients with available information and relevant percentage in parenthesis. Quantitative data are expressed as mean ± SD for normally distributed data or as median (interquartile range) for nonparametric data. Kolmogorov- Smirnov test was used to check the normal distribution of the quantitative variables. The Student t-test was used for mean comparisons between two groups of subjects for normally distributed data, and the Mann-Whitney test was employed for nonparametric data. For ratio comparisons the χ^2 test was used. Survival time was estimated by the Kaplan-Meier method; the log rank test was used to compare arms. The

expected mortality by age, gender, and year of calendar of mortality was calculated for each patient according to data obtained from the Spanish National Statistical Institute [13]. Standardized mortality ratio (SMR) was defined as the number of observed deaths/number of expected deaths in an age- and gender-matched population using the Spanish population as the reference. Estimated 95% confidence interval (CI) for the SMR was calculated using an open source SMR OpenEpi calculator, version 3 [14]. Unadjusted and stepwise multivariate Cox regression models were used to assess the effects of several quantitative (age and maximal tumor diameter) and qualitative (sex, diabetes, hypertension, dyslipidemia, clinical signs and symptoms, hormonal deficits, tumor composition, calcifications, sellar involvement, surgical approach, surgical resection type, histological tumor type, and radiotherapy) variables on the risk of death. Hazard ratios (HRs) and their 95% confidence intervals (CIs) for mortality were estimated. Differences were considered significant when $p < 0.05$.

RESULTS

Clinical data and imaging studies

From a total of 384 adult CP patients, we selected 53 (13.8%) patients [27 women (50.9%), mean age 72.3 ± 5.1 years (range 65-83 yr)] diagnosed after the age of 65 years (table 1). According to age range, 18 (34%) were in the range 65-69 years, 23 (43.4%) patients in the range 70-75 years, and 12 (22.6%) were over 75 years old. No significant differences in age between men and women were found (72.1 ± 5.2 vs 72.4 ± 5.2 yr). No patient had a history of prior cranial radiation therapy. Diabetes mellitus, hyperlipidemia, and hypertension was present in 22 (41.5%), 32 (60.4%) and 33 (62.3%) patients, respectively. According to sex, women showed larger tumors (3.2 ± 1.2 vs 2.6 ± 0.9 cm, p=0.045) and a higher prevalence of diabetes mellitus (55.5% vs 26.9%, p=0.033) and sellar involvement (63 vs 34.6%, p=0.036) compared to men (table 1).

Median time from the onset of symptoms to the diagnosis of CP was 4 months (2-7.5 mo). The diagnosis of CP was incidental in 13 (24.5%) patients. The most prevalent clinical symptoms at diagnosis were visual field defects (mainly hemianopsia), followed by headache, memory disturbances, disorientation, sleep disorders, and behavioral disturbances (figure 1).

Gonadotropin deficiency was the most prevalent pituitary hormonal deficiency at diagnosis followed by thyrotropin, GH, ACTH and antidiuretic hormone (ADH) (figure 2). Hyperprolactinemia at diagnosis was present in 16/46 (34.8%).

Imaging techniques used were cranial computed tomography (CT) in 34/52 (65.4%) and pituitary magnetic resonance imaging (MRI) in 51/53 (96.2%) patients. Maximum tumor diameter was 2.9 ± 1.1 cm. In most patients (31, 58.5%) the tumor was mixed (solid-cystic), in 19 (35.8%) cystic and in 3 (5.7%) solid. Calcifications within the tumor were present in 19/52 (36.5%) patients. Tumor location was suprasellar in most patients (51, 96.2%). Of these, 26 (49.1%) patients had sellar involvement.

Two patients (3.8%) presented atypical locations (one ventricular and one sphenoid). Chiasmatic compression was present in 43 (81.1%) patients. Lastly, 8 (15.1%) patients showed hydrocephalus.

Treatment outcomes and pathological results

The surgical approach most commonly used was transcranial surgery (28, 52.8%) followed by endoscopic endonasal transsphenoidal (EET) surgery (22, 41.5%), and microscopic transsphenoidal (MT) surgery (3, 5.7%).

We did not find any significant difference in age at diagnosis, sex, maximum tumor diameter, presence of calcifications, chiasmatic compression, tumor composition and type of resection between transcranial and transsesphenoidal approaches. Only the presence of sella turcica involvement by the tumor was statistically different between both surgeries (64.0% vs 37.5%, transsesphenoidal vs transcranial, p=0.037).

More than half of the patients (29, 54.7%) underwent STR and the remaining (24, 45.3%) NTR. A significantly higher prevalence of DI after surgery in patients who underwent NTR was observed (87.5 vs 53.6%, p=0.008) (table 2).

In more than half of the patients (31, 58.5%) the tumor was mixed (solid-cystic), in 19 (35.8%) cystic and in 3 (5.7%) solid. Calcifications within the tumor were present in 19/52 (36.5%) patients. Tumor location was suprasellar in most patients (51, 96.2%). Of these, 26 (49.1%) had sellar involvement. Two patients (3.8%) presented atypical locations (one ventricular and one within the sphenoid). Chiasmatic compression was present in 43 (81.1%) patients and 8 (15.1%) showed hydrocephalus.

Histological type of the CP was available in 51 (96.2%) tumors. The most common form was adamantinomatous CP (ACP) (26/51, 51%) followed by papillary CP (PCP) (23/51, 45.1%) and mixed forms (2/51, 3.9%). No significant differences between ACP and PCP in sex, age at diagnosis, maximum tumor diameter, presence of calcifications, sellar involvement or type of resection were found.

BRAF V600E and CTNNB1 gene mutations were available in 22 (41.5%) and 20 (37.7%) patients, respectively. Mutations for BRAF V600E and CTNNB1 were positive in 5/22 (22.7%, all of them PCP; one of these with a double BRAF V600 and CTNNB1 gene mutation) and 5/20 (25%, 4 of them ACP), respectively. No significant differences in age, sex, clinical characteristics and pituitary function at diagnosis, maximal tumor diameter, type of resection and surgical approach between patients with positive and negative gene mutations were found.

After surgery, a reduction in the prevalence of hemianopia (18/51, 35.3%), headaches (15/52, 28.8%), memory disturbances (14/46, 30.4%), disorientation (11/49, 22.4%), sleep disorders (7/48, 14.6%), and behavioral disturbances (9/47, 19.1%) was observed with respect to time of the diagnosis (figure

1). The prevalence of depression was unchanged; however, the prevalence of hyperphagia (11/52, 21.2%), nausea/vomiting (9/52, 17.3%), changes in body temperature (6/52, 11.5%) and adipsia/hypodipsia (4/51, 7.8%), increased (figure 1).

On the other hand, the prevalence of pituitary hormonal hypofunction increased for all hormones after surgery, mainly at the expense of DI (from 3,9% to 69.2%) and secondary adrenal insufficiency (from 23.5% to 69.2%) (figure 2). Hyperprolactinemia slightly decreased to 13/44 (29.5%).

Imaging studies after surgery were available in 49/53 patients (92.4%). There were 21/49 (42.9%) cured patients, 24/49 (49.0%) with tumor persistence and 4/49 (8.2%) recurrences. Only 6/49 patients (12.2%) with tumor persistence after first surgery underwent a second surgery (1 EET and 5 transcranial approach, 5 STR and 1 NTR, mean time between both surgeries, 66.6 ± 64.3 mo, range 9-139 mo).

Radiotherapy was used in 10 (18.9%) patients, 2 of them after a second surgery [3 conventional radiotherapy and 7 fractionated stereotactic radiotherapy, mean dose 48.8 ± 4.5 Gy (range, 38-54)]. Lastly, intracavitary chemotherapy with alpha interferon was used in one patient.

Long-term follow-up

At last clinical visit, 48/53 (90.6%) patients could be evaluated after a follow-up period of 46.7±40.8 months (1-167). At this time, the only clinical symptom that improved significantly with respect to baseline and after surgery was headache (3/45, 6.7%). Compared to the post-surgical evaluation some clinical symptoms (visual fields, memory disturbances, disorientation, sleep disorders, and behavioral disturbances) worsened slightly whereas others (hyperphagia, nausea/vomiting, hypo/hyperthermia, and adipsia/hypodispsia) improved slightly. Lastly, depressive symptoms were not modified (figure 1). The prevalence of hormonal deficiencies at the last clinical visit was similar or slightly higher than that observed at the postoperative evaluation (figure 2). DI insipidus at last visit was associated with surgical resection type [17/19 (89.5%) vs 16/28 (57.1%), NTR vs STR, p=0.017]. Lastly, hyperprolactinemia remained stable 14/44 (31.8%).

Most patients (22/51, 43.1%) showed TC, 7/51 (13.7%) PR, 18/51 (35.3%) SD, and 4/51 (7.8%) PD (p=0.01). We did not find significant differences between the clinical tumor response and the surgical approach. However, histological type did influence the type of clinical response. In this sense, TC was the clinical response more commonly observed in PCP (16/22, 72,7%), while SD (12/25, 48%) was preferably detected in ACP. Lastly, PD was only found in ACP patients (4/25, 16%) (p=0.009) (figure 3).

During the study 19/48 (39.6%) patients died. Only one patient died within 30 days after surgery (29th day). We did not find significant differences in age at diagnosis, sex, tumor size, sella turcica

involvement, chiasmatic compression, pituitary hormone deficiency, surgical resection type, surgical approach, histological type, and radiotherapy among patients who died and survived.

Of the 19 patients who died, we found out the cause of death in 15/19 (78.9%). The most common causes of death (11/15, 73.3%) were those related to the tumor and / or its treatments (cause-specific mortality) and perioperative complications [systemic infection (n=3), post-surgical bleeding (n=2), radionecrosis (n=1), anaplastic astrocytoma (n=1), late hydrocephalus (n=1), tumor progression n=1), aspiration and respiratory failure after postoperative seizures (n=1) and sudden death (n=1)]. Other causes were cancer (2/15, 13.3%), cardiovascular disease (1/15, 6.7%) and complication of urological surgery (1/15, 6.7%). SMR was 12.2 (95% CI 11.8-29.1). SMR for women (14.3, 95% CI 7.0-26.3) was higher than for men (10.8, 95% CI 5.5-19.2).

Kaplan-Meier analysis showed a median survival time of 88 (95% CI, 57-118) months for all-cause mortality (figure 4A). The overall survival rates at 1 and 5 years was 87% and 64%, respectively. Cause-specific mortality in our patients was earlier than all-cause mortality. In this setting, median survival time for cause-specific mortality was 43 (95% CI, 0-109) months, with median survival at 1 and 5 years of 60% and 35%, respectively (figure 4B). Patients with DI at last visit showed a lower survival probability than those without DI (Log Rank 8.4, p=0.004) (figure 4C).

Unadjusted and stepwise multivariate Cox regression models showed that cause-specific mortality was not influenced by sex, age at diagnosis, maximal tumor diameter, surgical approach, type of surgical resection, and radiotherapy. Only DI at last clinical visit was significantly related to cause-specific mortality (HR, 11.6, 95% CI, 1.3-102, p=0.027).

DISCUSSION

The present study reports the first series reviewed in detail of CP in elderly patients surgically treated with a long follow-up period. Our work shows that this tumor is equally distributed between men and women. The most prevalent clinical characteristics at diagnosis in this population were those derived from alterations in the visual fields, headache and hormonal deficiencies. All of them improve with surgery, except for hormonal deficiencies, which worsened dramatically, mainly at the expense of ADH deficiency. The latter is important since the development of DI during the clinical follow-up constitutes an independent predictor of mortality in this population.

Most series [3,7,15-19], although not all [2,4], have shown that the incidence of CP in the elderly is low. For example, only 28 (2.8%) of 1002 CF patients were diagnosed in the 61-70 age range [15]. In another series of 125 patients, the oldest patient was a 60-year-old man [16]. However, in US population a bimodal distribution by age was noted with peak incidence rates in children (aged 5-14 years) and among older adults (aged 65-74 years) [4]. In a Danish population, the age range of 65-69 years presented the third incidence rate (2.62 per million per year) in frequency after the age

ranges of 5-9 years (3.49 per million per year) and 40-44 years (2.86 per million per year) [2]. From the data derived from our study, it seems that in our country CP is diagnosed in elderly patients in a low percentage, around 14% of the adult population with CP, mainly in the range 70-75 years, and, as previously reported in the general population [2,4,17], no gender differences are observed.

Most CP have a suprasellar component [8]. This has been reported in both children and adults in approximately 95% [5]. In our series, this location was also very common, being present in around 96% of patients. Although a prevalence of 5-6% of purely intraselar CP has been reported in children and adults [5,20], in our elderly population we did not find any case. Lastly, atypical location was also present in our series although the percentage was very low (<4%).

A delay in the diagnosis of CP from the onset of symptoms has been reported in both children [12 months (0.5-60)] and adults [12 months (0.5-240)] [5]. However, in our elderly population this period of time was relatively short [4 months (2-7.5)]. This could be related to a greater and earlier visual impairment that would make it more easily detectable. Another interesting finding of our study was that in approximately 25% of the patients the diagnosis of CP was incidental. This percentage contrasts with that obtained in children, which is usually <2% [21]. These differences could be explained by the greater number of imaging tests carried out in the elderly population.

As occurs in other population groups of different ages, the presenting clinical features in the elderly with CP are visual disturbances and headaches. However, our data support that the distribution percentage varies according to age. Headaches at diagnosis are usually more prevalent in children (78%) than in adults (56%), while visual field defects prevail in adults (60%) compared to children (46%) [5]. In our elderly CP patients the main presenting clinical features were visual field defects (71.2%) followed by headaches (45.3%), indicating that as age advances, the presenting clinical features change over time, increasing visual field defects and decreasing headaches.

Compared with other studies, anterior pituitary hypofunction at presentation in the elderly seems less compromised than that which appears in both children and adults [5,22]. Moreover, while in elderly patients the main hormonal deficiency is that of gonadotropins (50%), in children and adults it is GH deficiency, which appears in 100% and 86%, respectively [5]. We have to take into account that the fact of not having performed GH stimulation tests might underestimate the prevalence of GH deficiency in our study. Another difference with CP in children and adults is the lower prevalence of DI at diagnosis in the elderly. In our study, only 4% of the patients presented ADH deficiency, while this prevalence has been reported in 22% and 17% of children and adults with CP, respectively [5]. The explanation for this finding is not clear, although it would imply less initial involvement of the hypothalamic-neurohypophyseal area in the elderly population. Hyperprolactinemia at diagnosis was present in approximately one third of the patients and remained stable throughout the follow-up.

The surgical approach in CP varies according to the extent of the tumor. It is generally accepted that sellar CP are subsidiary to the transsphenoidal approach. However, some authors have used this surgical approach in CP with suprasellar extension, although this is usually associated with increased incidence of hormonal deficiencies and neurological complications [23,24]. Compared to the transcranial approach, the transsphenoidal approach prevents craniotomy, brain retraction, and reduces neurovascular manipulation, and with the aid of endoscope allows better visualization of arterial perforators [8]. Besides, EET approaches have shown significantly greater rates of gross total resection, improved visual outcome, and a trend towards fewer recurrences compared to transcranial and microscopic transphenoidal approaches. On the other hand the rate of CSF leak is higher than transcranial approaches [25]. EET surgery has also demonstrated to be safe and effective approach for removing CP in children, and may be performed regardless of the size of the nasal cavity, pneumatization of the sphenoid sinuses, and location or extension of the tumors [26]. In our CP elderly population the most common used surgical approach was transcranial followed by transsphenoidal, mainly EET surgery. In our series, sella turcica involvement by the tumor was the only significant determining factor to perform a transsphenoidal approach.

The surgical strategy in CP depends on the location and extent of the tumor. When CP does not affect the optic structures and/or the hypothalamus, gross total resection seems to be the treatment of choice. In the opposite case, the surgical strategy is more controversial, since gross total resection may be accompanied by a higher probability of surgical complications, mainly hypothalamic, while STR can be associated with a greater probability of tumor recurrence. In the latter case, adjuvant treatment with radiotherapy or a second surgery can be considered, although the therapeutic consequences of combined treatment with surgery and radiotherapy is still a subject of debate [8]. The extent of surgical resection used in the treatment of CP varies according to the authors. While some report that complete surgical removal can be achieved with reasonable safety in more than 70% of children and adults [27], others prefer STR, which was used in 83% of children and 81% of adults [5]. In our elderly patients STR was used in more than half of the patients (54.7%). No significant differences in the reduction of the main symptoms at diagnosis such as visual field defects and headaches or in the adenohypophyseal hypofunction, between STR and NTR were found. Although NTR was associated with a higher number of patients with TC, the development of postsurgical DI was also higher compared to STR.

Two different histological forms of CP have been described. The more common form is ACP composed of a complex mixture of adamantinoma-like epithelium, microcalcifications, necrotic debris, fibrosis, and micro- or macrocysts. The second form is PCP composed of mature squamous epithelium and are unaccompanied by fibrocalcific and degenerative changes [7]. ACP affect all age groups with a peak incidence during childhood and early adolescence. However, PCP are mostly restricted to adults [1]. Despite morphological and pathological differences, no significant differences between both entities in relation to resectability, radiotherapy efficacy and overall survival have been reported [7]. The percentage distribution of the 2 types of tumors in our elderly population was very

similar, although slightly higher for ACP. In our series, ACP was the most common histological form as previously reported by others [7]. Besides, no significant differences in several clinical variables between both histological types. In relation to resectability, contrary to what has been described in some studies in children and adults [7], the histological type in elderly CP patients did influence the type of clinical tumor response to surgery. In this sense, TC was more frequently observed in PCP while SD in ACP patients. This could be due to the different composition of the tumor that would offer better resectability in PCP. Lastly, only ACP showed progression. These findings would indicate a greater difficulty in controlling the disease in ACP compared with PCP in the elderly population with CP.

As reported by others in both children and adults [5,28,29], our series showed a postoperative improvement in visual field defects and headaches. However, the neuropsychiatric symptoms (disorientation, behavioral alterations, and depression) did not change substantially, while pituitary deficiencies and symptoms derived from hypothalamic involvement (hyperphagia, hypo-hyperthermia, and adipsia/hypodispsia) increased. The hormonal deficiency that increased the most after surgery was ADH. DI increased from 4% in the preoperative period to 70%, which was maintained over time, as was the case with the rest of the anterior pituitary hormonal deficiencies. DI at last visit was more frequently associated with NTR compared with STR. All these results should always be taken into account when making decisions about the type of surgical resection in elderly population, individualizing in each patient.

CP is associated with high risk mortality even after surgery, radiotherapy and hormone replacement therapy [30-32]. The mortality rate associated with CP is approximately 3 to 5 times that of the general population [8]. It is necessary to distinguish the population according to age. In this setting, the overall survival rate in children with CP ranges from 83 to 96% and 65 to 100% at 5 and 10 years, respectively. While in adults or mixed populations (adults and children) the overall survival rate varies between 54 to 96%, 40 to 93% and 66 to 85% at 5, 10 and 20 years, respectively [8]. In our series of elderly patients, after a follow-up period of 46.7 ± 40.8 months (1-167), the mortality rate was very high (~40%) with a median survival time of 88 (95% CI, 57-118) months and an overall survival rate of 87% and 64% at 1 and 5 years, respectively.

SMR for CP patients seems to vary according to age at diagnosis. Higher SMR values in CP patients with childhood-onset compared to those with adult-onset have been reported [17 (6.3–37) vs 3.5 (2.6–4.6)] [33]. In our elderly population SMR was very high although slightly lower than that observed in CP patients with childhood-onset disease [33]. Moreover, SMR was higher in women than in men, as it has been described in younger populations [30,31].

Several risk factors for excess mortality have been reported in CP patients, among them are female sex, childhood-onset disease, hydrocephalus, tumor recurrence, high body mass index and panhypopituitarism [32]. We did not identify risk factors for excess of all-cause mortality, such as age at diagnosis, sex, tumor size, sella turcica involvement, chiasmatic compression, pituitary hormone

deficiency, surgical resection type, surgical approach, histological type, and radiotherapy. However, when we considered only cause-specific mortality, which was responsible for 73% of the known causes of death in our population, we found a lower median survival time [43 (95% CI, 0-109) months], with a median survival at 1 and 5 years of 60% and 35%, respectively, indicating that CP and / or its treatments contribute by itself to increased mortality rate in the elderly.

DI develops when there is an extensive damage to magnocellular cells of the hypothalamus (supraoptic and paraventricular nuclei), especially if the pituitary stalk is sectioned or directly there is involvement of the median eminence. DI has been considered as a risk factor for mortality in different clinical situations. It has been associated with increased mortality in adults with hypopituitarism [34], and in GH-deficient patients regardless of the number of additional pituitary hormone deficits [35]. Acute DI insipidus has been related to significantly increased mortality in severe head injury [36]. In addition the association of adipsia with DI significantly increases mortality [37]. DI has also been described as a negative prognostic factor for mortality in CP patients with childhood-onset disease [33]. In our series DI was related to cause-specific mortality. This association could be related to greater hypothalamic damage induced by surgery associated with the consequences of ADH deficiency.

From an epidemiological point of view the sample here studied would correspond to approximately a quarter of the total adult population with CP in our country (1.5 x 47 x 23 = 1621 CP patients; 384/1621 x100= 23.7%). This percentage would correspond to a subsample of the total CP population of Spain, which must be taken into account when interpreting the results.

The main limitations of our study are: 1) the vague formulation for inclusion of the participating endocrinologists; 2) the information on evaluation of different symptoms such as depression, disorientation or sleep disorders was not clearly objective (questionnaires); it was based on the clinical criteria of their responsible physicians and clinical data obtained from the patient's medical records, 3) the absence of GH stimulation tests for the diagnosis of GH deficiency, and 3) the fact of having studied a subsample (~25%) of the estimated population of adult PC patients in our country. On the other hand, the main strengths of the study are 1) first study to analyze in detail the surgically intervened PC in the elderly and 2) mostly both histology and genetic evaluations were performed.

In conclusion, CP is diagnosed in patients older than 65 years in ~14% of adult CP patients with a mean age at diagnosis of 72 years with no gender differences. CP diagnosed in the elderly negatively affects survival. Tumor size, histologic type, surgical resection type, and radiotherapy treatment do not appear to influence mortality. In these patients, DI should be considered as a risk factor for mortality, therefore it would be advisable to avoid this surgical complication if possible.

Statement of Ethics

This study was approved on September 23, 2019, by the local ethics committee of the hospital Puerta de Hierro Majadahonda, Madrid. Spain.

Disclosure Statement

The authors have declared that no conflict of interest exists.

Funding Sources

No funding

Author Contribution

P.I. and J.J.D.: both devised the manuscript concept and contributed to manuscript preparation, editing and review. All authors contributed to generation of original data and participated in manuscript editing and review.

References

1 Muller HL, Merchant TE, Warmuth-Metz M, Martinez-Barbera JP, Puget S: Craniopharyngioma. Nat Rev Dis Primers 2019Nov 7;5(1):75,019-0125-9.

2 Nielsen EH, Feldt-Rasmussen U, Poulsgaard L, Kristensen LO, Astrup J, Jorgensen JO, Bjerre P, Andersen M, Andersen C, Jorgensen J, Lindholm J, Laurberg P: Incidence of craniopharyngioma in Denmark (n = 189) and estimated world incidence of craniopharyngioma in children and adults. J Neurooncol 2011Sep;104(3):755-63.

3 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 Oncol 2012Aug;14(8):1070-8.

4 Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM: The descriptive epidemiology of craniopharyngioma. J Neurosurg 1998Oct;89(4):547-51.

5 Karavitaki N, Brufani C, Warner JT, Adams CB, Richards P, Ansorge O, Shine B, Turner HE, Wass JA: Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. Clin Endocrinol (Oxf) 2005Apr;62(4):397-409.

6 Makino K, Nakamura H, Yano S, Kuratsu J, Kumamoto Brain Tumor Group: Population-based epidemiological study of primary intracranial tumors in childhood. Childs Nerv Syst 2010Aug;26(8):1029-34.

7 Crotty TB, Scheithauer BW, Young WF,Jr, Davis DH, Shaw EG, Miller GM, Burger PC: Papillary craniopharyngioma: a clinicopathological study of 48 cases. J Neurosurg 1995Aug;83(2):206-14.

8 Muller HL: Craniopharyngioma. Endocr Rev 2014Jun;35(3):513-43.

9 Russell RW, Pennybaker JB: Craniopharyngioma in the elderly. J Neurol Neurosurg Psychiatry 1961Feb;24(:1-13.

10 Lederman GS, Recht A, Loeffler JS, Dubuisson D, Kleefield J, Schnitt SJ: Craniopharyngioma in an elderly patient. Cancer 1987Sep 1;60(5):1077-80.

11 García Yllán V, García Yllán LM, Sifontes Estrado M: Craneofaringioma en la tercera edad. Revista Electrónica Dr. Zoilo E. Marinello Vidaurreta 2014;39(11).

12 Walker A, Torabi R, Punsoni M, Stopa E, Doberstein C: De novo adantinomatous craniopharingioma presenting anew in an elderly patient with previous normal CT and MRI studies: a case report and implications in pathogenesis. Interdisciplinary Neurosurgery:Advanced Techniques and Case Management 2 2015:149-51.

13 Spanish National Statistical Institute National results, by autonomous communities and provinces Series since 1991 Mortality tables by year, sex, age and functions. .

14 Soe MM, Sullivan KM, Emory University, Atlanta, Georgia, USA; SMR OpenEpi calculator, version 3.

15 Banna M: Craniopharyngioma: based on 160 cases. Br J Radiol 1976Mar;49(579):206-23.

16 Manaka S, Teramoto A, Takakura K: The efficacy of radiotherapy for craniopharyngioma. J Neurosurg 1985May;62(5):648-56.

17 Sorva R, Heiskanen O: Craniopharyngioma in Finland. A study of 123 cases. Acta Neurochir (Wien) 1986;81(3-4):85-9.

18 Paja M, Lucas T, Garcia-Uria J, Salame F, Barcelo B, Estrada J: Hypothalamic-pituitary dysfunction in patients with craniopharyngioma. Clin Endocrinol (Oxf) 1995May;42(5):467-73.

19 Chan D, Cheng Y, Lee M, Pang V, Wong C: Treatment outcome of craniopharyngioma: 18-Year experience at a Hong Kong regional neurosurgical centre. Surgical Practice, 2017, 21(2), 7 - 81 2017;21(2):76-81.

20 Harwood-Nash DC: Neuroimaging of childhood craniopharyngioma. Pediatr Neurosurg 1994;21 Suppl 1(:2-10.

21 Boekhoff S, Bison B, Eveslage M, Sowithayasakul P, Muller HL: Craniopharyngiomas presenting as incidentalomas: results of KRANIOPHARYNGEOM 2007. Pituitary 2019Oct;22(5):532-41.

22 Jensterle M, Jazbinsek S, Bosnjak R, Popovic M, Zaletel LZ, Vesnaver TV, Kotnik BF, Kotnik P: Advances in the management of craniopharyngioma in children and adults. Radiol Oncol 2019Oct 25;53(4):388-96.

23 Jane JA,Jr, Kiehna E, Payne SC, Early SV, Laws ER,Jr: Early outcomes of endoscopic transsphenoidal surgery for adult craniopharyngiomas. Neurosurg Focus 2010Apr;28(4):E9.

24 Park HR, Kshettry VR, Farrell CJ, Lee JM, Kim YH, Won TB, Han DH, Do H, Nyguist G, Rosen M, Kim DG, Evans JJ, Paek SH: Clinical Outcome After Extended Endoscopic Endonasal Resection of Craniopharyngiomas: Two-Institution Experience. World Neurosurg 2017Jul;103(:465-74.

25 Komotar RJ, Starke RM, Raper DM, Anand VK, Schwartz TH: Endoscopic endonasal compared with microscopic transsphenoidal and open transcranial resection of craniopharyngiomas. World Neurosurg 2012Feb;77(2):329-41.

26 Schelini JC, Cavalheiro S, Dastoli PA, Hirai ER, Atallah C, Costa M, Nicacio J, Capellano AM, Silva N, Zymberg S, de Paula Santos R: Endoscopic endonasal transsphenoidal approach for pediatric craniopharyngiomas: A case series. Int J Pediatr Otorhinolaryngol 2020Mar;130(:109786.
27 Mortini P, Losa M, Pozzobon G, Barzaghi R, Riva M, Acerno S, Angius D, Weber G, Chiumello G, Giovanelli M: Neurosurgical treatment of craniopharyngioma in adults and children: early and long-term results in a large case series. J Neurosurg 2011May;114(5):1350-9.
28 Caldarelli M, Massimi L, Tamburrini G, Cappa M, Di Rocco C: Long-term results of the surgical treatment of craniopharyngioma: the experience at the Policlinico Gemelli, Catholic University, Rome. Childs Nerv Syst 2005Aug;21(8-9):747-57.
29 Elliott RE, Jane JA,Jr, Wisoff JH: Surgical management of craniopharyngiomas in children: meta-analysis and comparison of transcranial and transsphenoidal approaches. Neurosurgery 2011Sep;69(3):630,43; discussion 643.
30 Crowley RK, Hamnvik OP, O'Sullivan EP, Behan LA, Smith D, Agha A, Thompson CJ: Morbidity and mortality in patients with craniopharyngioma after surgery. Clin Endocrinol (Oxf) 2010Oct;73(4):516-21.
31 Erfurth EM, Holmer H, Fjalldal SB: Mortality and morbidity in adult craniopharyngioma. Pituitary 2013Mar;16(1):46-55.
32 Qiao N: Excess mortality after craniopharyngioma treatment: are we making progress? Endocrine 2019Apr;64(1):31-7.
33 Olsson DS, Andersson E, Bryngelsson IL, Nilsson AG, Johannsson G: Excess mortality and morbidity in patients with craniopharyngioma, especially in patients with childhood onset: a population-based study in Sweden. J Clin Endocrinol Metab 2015Feb;100(2):467-74.
34 Jasim S, Alahdab F, Ahmed AT, Tamhane S, Prokop LJ, Nippoldt TB, Murad MH: Mortality in adults with hypopituitarism: a systematic review and meta-analysis. Endocrine 2017Apr;56(1):33-42.
35 Gaillard RC, Mattsson AF, Akerblad AC, Bengtsson BA, Cara J, Feldt-Rasmussen U, Koltowska-Haggstrom M, Monson JP, Saller B, Wilton P, Abs R: Overall and cause-specific mortality in GH-deficient adults on GH replacement. Eur J Endocrinol 2012Jun;166(6):1069-77.
36 Hadjizacharia P, Beale EO, Inaba K, Chan LS, Demetriades D: Acute diabetes insipidus in severe head injury: a prospective study. J Am Coll Surg 2008Oct;207(4):477-84.
37 Arima H, Wakabayashi T, Nagatani T, Fujii M, Hirakawa A, Murase T, Yambe Y, Yamada T, Yamakawa F, Yamamori I, Yamauchi M, Oiso Y: Adipsia increases risk of death in patients with central diabetes insipidus. Endocr J 2014;61(2):143-8.

Legend for the figures

Figure 1. Percentage distribution of clinical symptoms at diagnosis, after surgery, and at the end of follow-up in elderly patients with craniopharyngiomas.

Figure 2. Percentage distribution of pituitary hormonal deficiencies at diagnosis, after surgery and at last visit in elderly patients with craniopharyngioma.

Figure 3. Percentage distribution of the clinical response at the end of clinical follow-up according to the histological type in elderly patients with craniopharyngioma.

Abbreviations: ACP, Adamantinomatous craniopharyngioma; MCP, mixed craniopharyngioma; PCP, papillary craniopharyngioma; PD, Progressive disease; PR, Partial response; SD, Stable disease; TC, tumor cure. Chi-square test, p=0.009

Figure 4. Kaplan-Meier survival analysis in elderly patients undergoing surgery for craniopharyngioma. All-cause mortality (left). Cause-specific mortality (center). Cause-specific mortality according to the presence of diabetes insipidus at last clinical visit (right).

Table 1. Clinical characteristics of elderly patients with craniopharyngioma according to sex.

	Women	**Men**	**Total**
Number of patients, n (%)	27 (50.9)	26 (49.1)	53 (100)
Age at diagnosis (yr)	72.4 ± 5.2	72.1 ± 5.2	72.3 ± 5.1
Diabetes mellitus, n (%)	15/27 (55.5)	7/26 (26.9)*	22/53 (41.5)
Hypertension, n (%)	18/27 (66.7)	15/26 (57.7)	33/53 (62.3)
Hyperlipidemia, n (%)	18/27 (66.7)	14/26 (53.8)	32/53 (60.4)
Max. tumor diameter (cm)	3.2 ± 1.2	2.6 ± 0.9*	2.9 ± 1.1
Calcifications, n (%)	11/26 (42.3)	8/26 (30.8)	19/52 (36.5)
Sella turcica involvement, n (%)	17/27 (63.0)	9/26 (34.6)*	26/53 (49.0)
Chiasmatic compression, n (%)	20/27 (74.1)	23/26 (88.5)	43/53 (81.1)
Tumor composition, n (%)			
Solid	1/27 (3.7)	2/26 (7.7)	3/53 (5.7)
Cystic	12/27 (44.4)	7/26 (26.9)	19/53 (35.8)
Mixed (solid-cystic)	14/27 (51.8)	17/26 (65.4)	31/53 (58.5)
Pituitary hypofunction, n (%)			
Gonadotropin	13/26 (50.0)	13/26 (50.0)	26/52 (50)
GH	7/23 (30.4)	7/25 (28.0)	14/48 (29.2)
TSH	9/26 (34.6)	11/25 (44.0)	20/51 (39.2)
ACTH	5/25 (20.0)	7/26 (26.9)	12/51 (23.5)
Diabetes insipidus	1/25 (4.0)	1/26 (3.8)	2/51 (3.9)
Hemianopsia, n (%)	17/26 (65.4)	20/26 (76.9)	37/52 (71.1)
Headache, n (%)	11/27 (40.7)	13/26 (50.0)	24/53 (45.3)
Resection type, n (%)			
Partial or subtotal resection	15/27 (55.5)	14/26 (53.8)	29/53 (54.7)
Near- total resection	12/27 (44.4)	12/26 (46.1)	24/53 (45.3)
Surgical approach, n (%)			
Transsphenoidal	13/27 (48.1)	12/26 (46.1)	25/53 (47.2)
Transcranial	14/27 (51.8)	14/26 (53.8)	28/53 (52.8)
Histological type, n (%)			
PCP	11/26 (42.3)	12/25 (48)	23/51 (45.1)
ACP	15/26 (57.7)	11/25 (44)	26/51 (51.0)
MCP	0/26 (0)	2/25 (8)	2/51 (3.9)
Radiotherapy (n, %)	4/27 (14.8)	6/26 (23.1)	10/53 (18.9)

Abbreviations: **ACP**, Adamantinomatous craniopharyngioma; **MCP**, Mixed craniopharyngioma; **PCP**, papillary craniopharyngioma.

Data are presented as the number of patients with the feature / total number of patients with available information, and the percentage in parenthesis.

Women vs men, *p<0.05

Table 2. Clinical characteristics according to the type of surgery in elderly patients with craniopharyngioma.

	Subtotal resection (STR)	**Near-total resection (NTR)**
Number of patients, n (%)	29/53 (54.7)	24/53 (45.3)
Age at diagnosis (yr)	72.6 ± 5.5	72.0 ± 4.7
Sex (M), n (%)	14/29 (48.3)	12/24 (50.0)
Max. tumor diameter (cm)	2.8 ± 1.1	2.9 ± 1.0
Calcifications, n (%)	11/29 (37.9)	8/23 (34.8)
Sella turcica involvement, n (%)	14/29 (48.3)	12/24 (50.0)
Chiasmatic compression, n (%)	23/29 (79.3)	20/24 (83.3)
Tumor composition, n (%)		
Solid	2/29 (7.0)	1/24 (4.2)
Cystic	13/29 (44.8)	6/24 (25.0)
Mixed (solid-cystic)	14/29 (48.2)	17/24 (70.8)
Pituitary hypofunction after surgery, n (%)		
Gonadotropin	21/29 (72.4)	19/23 (82.6)
GH	14/29 (48.3)	14/23 (60.9)
TSH	20/29 (69.0)	20/23 (87.0)
ACTH	18/29 (62.1)	18/23 (78.3)
Diabetes insipidus	15/28 (53.6)	21/24 (87.5)*
Hemianopsia, n (%)	11/28 (39.3)	7/23 (30.4)
Headache, n (%)	11/29 (37.9)	4/23 (17.4)

Data are presented as the number of patients with the feature / total number of patients with available information, and the percentage in parenthesis.

*p=0.008