RESEARCH

Epidemiology of craniopharyngiomas: a population-based study in Malta

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Abstract

Background: Despite being benign tumours, craniopharyngiomas are challenging to manage and can cause significant morbidity and mortality in both the paediatric and adult population. The aim of the study was to analyse the epidemiology of craniopharyngiomas, patient and tumour characteristics through a population-based study in Malta, enabling a better quantification of the disease burden.
Methods: Thorough research was carried out to identify the number of patients who were diagnosed with craniopharyngiomas. Epidemiological data, including both standardised incidence rates (SIR) and prevalence rates, were established in a well-defined population. For incidence estimates, patients who were diagnosed between 2008 and 2019 were included. The background population formed 4.8 million patient-years at risk.
Result: Twenty-nine subjects were identified and included in our study. The overall SIR was 0.3/100,000/year, with a higher SIR for males compared to females (0.4/100,000/year and 0.2/100,000/year, respectively). The highest SIR was recorded in the 10–19 year age group. The estimated prevalence rate amounted to 5.27/100,000 people, with a lower prevalence rate for childhood-onset when compared to the adult-onset category (2.03/100,000 vs 3.24/100,000 people). The median longest tumour diameter was 31.0 mm (IQR 21–41), with a statistically significant difference between childhood- and adult-onset disease; 43.0 mm (IQR 42.5–47.25) vs 27.0 mm (IQR 20.55–31.55) ($P = 0.011$).
Conclusion: Through this population-based study, accurate and up-to-date prevalence and incidence rates for craniopharyngiomas are reported. These provide a clearer reflection of the true health burden of the disease.

Key Words
- craniopharyngioma
- incidence
- prevalence
- epidemiology

Endocrine Oncology (2021) **1**, 9–16

Introduction

Craniopharyngiomas are rare but challenging tumours. Despite being a serious condition, population-based epidemiological data on craniopharyngiomas are limited in other studies (Bunin *et al.* 1998, Haupt *et al.* 2006, Nielsen *et al.* 2011, Zacharia *et al.* 2012). Epidemiological studies enable the researcher to adequately quantify the disease burden, disease severity stratification and utilisation of health care resources (Gruppetta *et al.* 2013). The aim of this study was to analyse variable factors related to craniopharyngiomas, focusing mainly on epidemiology and tumour characteristics by carrying out a population-based study.

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https://doi.org/10.1530/EO-21-0006

Materials and methods

Study population and data collection

Malta is an archipelago of islands situated in the middle of the Mediterranean Sea with almost 500,000 inhabitants. The fact that Malta is an island with a high population density is advantageous when conducting epidemiological studies (Gruppetta *et al.* 2013). Since we only have one central National Health Service hospital to which all patients are referred, the whole Maltese population was taken as the background population for this study.

Permission for data collection was granted through our local institutional review board. To ensure that data collection was accurate and complete, we analysed multiple data sources. Subjects were identified from several hospital databases including the outpatient departments, the neurosurgical registry, the radiology department MRI registry and the neuro-endocrine paediatric and adult clinic records. Furthermore, all MRI scans (c. 100,000) that in any way visualised the parasellar area were reviewed. This multi-method data acquisition allowed for data triangulation. Patients with pituitary pathology other than craniopharyngioma on imaging were excluded from the study. The diagnosis of craniopharyngiomas was done using the most universally accepted radiological characteristics of craniopharyngiomas on MRI (Friedman *et al.* 2003), after discussion with different specialists including experienced neuro-radiologists, neurosurgeons, neuro-endocrinologists and tertiary centre referral specialists. This was confirmed by histology in those patients who were operated. Demographic data including gender, age at presentation, the onset of symptomatology and diagnosis were collected from hospital case notes and clinical records. The cohort was subdivided into patients with childhood-onset craniopharyngioma (presentation at < 20 years of age) and adult-onset (presentation at ≥ 20 years of age).

Data on the population at risk for each calendar year was obtained from the National Statistics Office. For prevalence estimates, patients who were alive and fulfilled the inclusion criteria on 30 June 2019 were included, while to estimate incidence rates, patients diagnosed between the beginning of 2008 and the end of 2018 were selected. During this study period, the annual number of inhabitants in the country varied from 413,609 to 493,579. The background population during this study period gave rise to 4.8 million patient-years at risk.

Tumour characteristics

We studied tumour size, localisation, consistency as well as any involvement of surrounding structures. Findings were obtained by analysing all available imaging techniques, followed by confirmation with neuroimaging and neurosurgery reports. Anteroposterior, craniocaudal and transverse dimensions were measured, enabling us to calculate the median longest tumour diameter as well as to assess any statistically significant differences between childhood-onset and adult-onset patients.

We categorised craniopharyngiomas into four groups based on tumour location and its relation to surrounding structures on MRI, mainly the sellar diaphragm, optic chiasm and mammillary bodies. As shown in Fig. 1, group 1 craniopharyngiomas were strictly intrasellar, group 2 tumours were supra-diaphragmatic and infra-chiasmatic, whilst group 3 tumours were supra-chiasmatic (referred to as group 3A or 3B depending on if they were located anteriorly or posteriorly to the mamillary bodies, respectively). Group 3B tumours were further examined for any evidence of brainstem involvement. This grading system was adapted from Flitsch *et al.* (2011) who suggested a relationship between pre-operative tumour grade and post-operative morbidity (Zoicas & Schöfl 2012, Müller 2014). We also analysed if there was evidence of optic chiasm involvement on imaging, and if present, it was further determined whether the compression was from the superior, inferior or posterior aspect, with the latter resulting in splaying of the chiasm. Tumour consistency was studied, and tumours were characterised as unicystic, multicystic, solid with cystic components or as a predominantly solid lesion.

Statistical analysis

Prevalence figures together with the standardised incidence rates (SIR) were calculated, standardising with the World Health Organization 2001 standard population using the direct method (Ahmad *et al.* 2001). CIs (95% CI) were calculated using Wilson's method. Results were expressed as mean when the data were normally distributed, together with S.D. (± S.D.), whilst median was used when data were not symmetrical. Non-parametric assessments were used. Statistical analyses were carried out using IBM SPSS® Statistics for Windows, Version 25.0 (IBM Corp.). Two-sided *P*-values below 0.05 were considered statistically significant.

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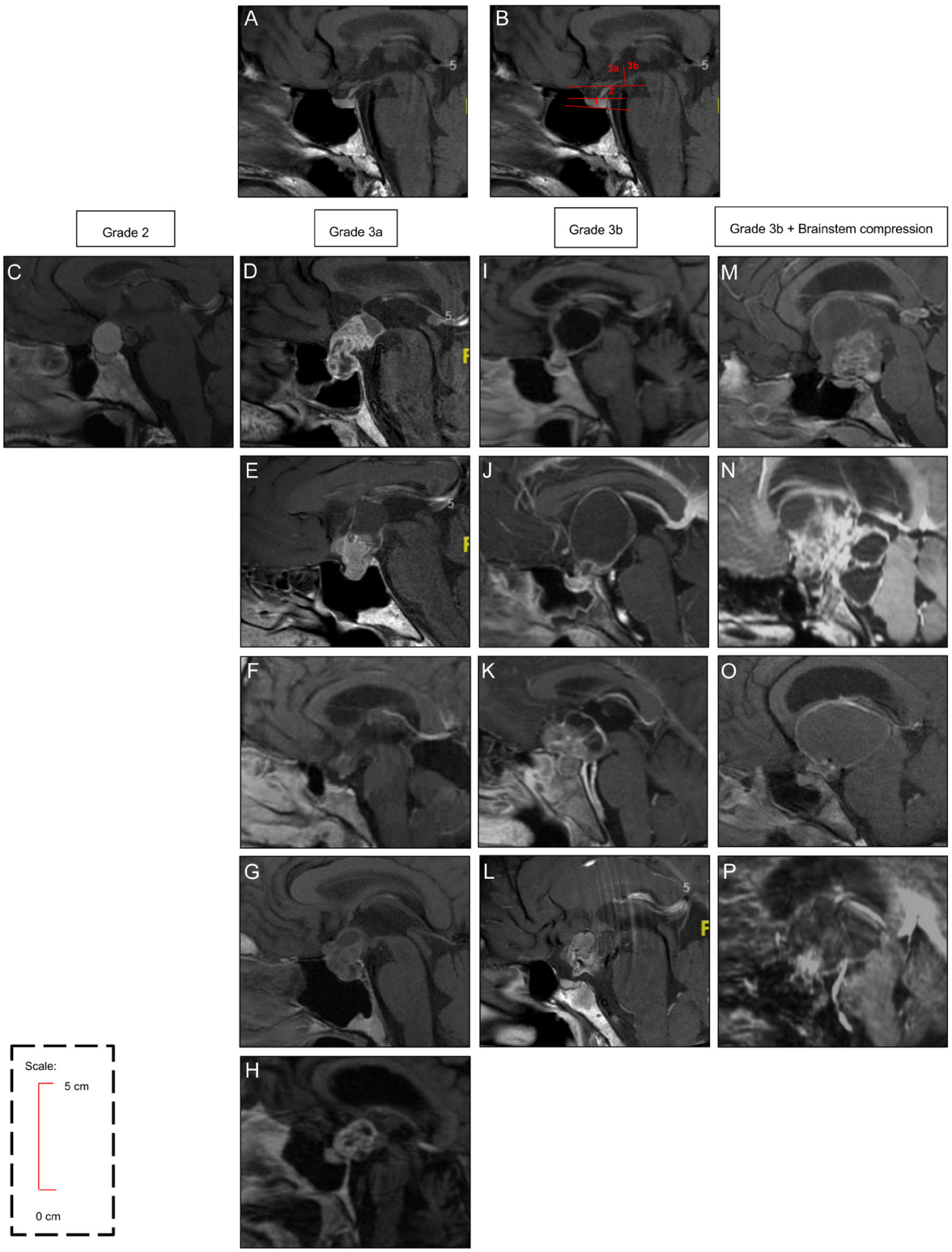

Figure 1
Midline sagittal MR contrast enhanced T1 weighted images. (A) Normal view, (B) classification system of craniopharyngioma. Intra and suprasellar region is divided into three sections. Region 1 is limited intrasellarly, region 2 is beneath the optic chiasm and mamillary bodies, region 3 is above the optic chiasm and mamillary bodies. Region 3 is divided in two: anterior (3A) and posterior (3B) to the mammillary bodies. (C–P) Tumours in our study were classified as explained in (B). (C) Grade 2; (D–H) Grade 3A; (I–L) Grade 3B; (M–P) Grade 3B + brainstem compression.

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Results

Epidemiology

Twenty-nine patients were identified as having craniopharyngioma among the Maltese population, with 26 patients being alive at the end of the study period (30 June 2019). Hence, the estimated prevalence rate amounted to 5.27/100,000 people. The prevalence rate for childhood onset craniopharyngiomas was lower than for the adult-onset category (2.03/100,000 vs 3.24/100,000 people). Females had a lower prevalence rate compared to males (3.31/100,000 and 7.15/100,000 people respectively). For incidence estimates, a total of 13 patients, who were diagnosed between beginning of 2008 and end of 2018, were included. The overall SIR was 0.3/100,000/year, with a higher SIR for the male compared to the female group (0.4/100,000/year and 0.2/100,000/year, respectively). The highest overall SIR was recorded in the 10–19 year age group (SIR of 1.01/100,000/year). From the adult-onset group, the highest SIR was recorded in the 50–59 year group (0.35/100,000/year) (Fig. 2). Further details regarding the prevalence and incidence of craniopharyngiomas are found in Table 1.

Tumour characteristics

We described tumour characteristics in a sub-cohort of 14 consecutive patients for whom all pre- and post-operative imaging were available, allowing for assessment of variations during follow-up. Tumour characteristics varied significantly between patients with childhood-onset and those with adult-onset disease (Table 2). As seen in Fig. 1, the commonest tumour grading was grade 3A (5 patients, 35.7%) followed by grade 3B (4 patients, 28.6%). One patient had a grade 2 tumour (7.1%). No tumours were solely intrasellar (grade 1). The presence of hydrocephalus as well as hypothalamic and/or 3rd ventricle involvement was commoner in patients with childhood-onset disease (5 out of 5 patients, 100% vs 3 out of 9 patients, 33.3%). In 10 patients (71.4%), the optic chiasm was compressed from its posterior aspect, with resultant splaying of the chiasm. Most tumours were multicystic (6 out of 14 patients, 42.9%). Such tumours were present in significantly higher numbers in childhood- compared with adult-onset disease (5 patients, 83.3% vs 1 patient, 16.7%). For the cohort of 14 patients, the median longest tumour diameter was 31.0 mm (IQR 21–41). There was a statistically significant difference between the longest tumour diameter in patients with childhood-onset and those with adult-onset disease ($P = 0.011$) (Table 2).

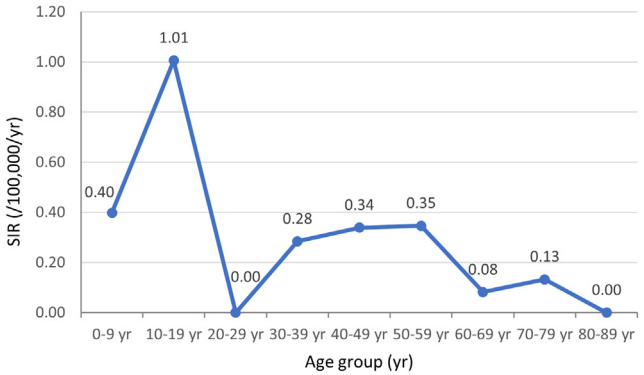

Figure 2
Standardised incidence rates according to 10-year age groups (2008–2018).

Presentation, treatment and follow up

Visual disturbances and symptoms secondary to raised intracranial pressure (ICP) such as headaches, nausea and vomiting were the commonest presenting features, affecting 11 (37.9%) and 10 (34.5%) patients out of 29 patients respectively, followed by endocrine disturbances mainly resultant of hypopituitarism (presenting as menstrual irregularities, decreased libido and erectile dysfunction, lethargy and delayed puberty) as well as abnormal thirst and cognitive impairment, affecting a total of 8 patients (27.6%).

Twenty-four patients (out of the total cohort of 29 patients) required neurosurgical intervention (82.8%). Eleven patients (45.8%) underwent trans-frontal/transcranial surgery whilst 14 patients (58.3%) underwent a trans-sphenoidal approach. Seven patients with childhood-onset disease underwent trans-frontal/transcranial surgery compared to 4 patients with adult-onset disease. All patients had adamantinomatous craniopharyngioma on histology. Fifteen patients out of the total cohort underwent surgery through the trans-frontal/transcranial route whilst 11 patients underwent trans-sphenoidal surgery, with two patients requiring both surgical approaches due to residual tumour or recurrence post-operatively. Sixty percent had been administered radiotherapy post-operatively.

The median follow-up period since the time of diagnosis for the whole cohort of 29 patients was 13.0 years (IQR 5–25); 14.0 years (IQR 4.5–28) for childhood-onset craniopharyngioma and 9.5 years (IQR 5.21–21) for the adult-onset group, with no statistically significant difference in length of follow-up between both groups ($P = 0.674$). The commonest long-term sequalae were pituitary hormone deficiencies (defined as deficiency of one or more of ACTH, GH, TSH, LH, FSH, ADH), present in 27 patients (93.1%). The second most common long-term complication was obesity (BMI > 30 kg/m^2) present in 18 patients (62.1%), followed by cognitive deficits (affecting 5 patients, 17.2%).

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Table 1 Prevalence and incidence of craniopharyngiomas.

	All craniopharyngiomas	**Childhood-onset** (<20 years)	**Adult-onset**
Prevalence estimates (30 June 2019)			
Number of craniopharyngiomas (*n*)	26*	10	16
Overall prevalence (/100,000) (95% CI)	5.27 (3.59–7.72)	2.03 (1.10–3.73)	3.24 (1.99–5.27)
Male (*n*)	18	7	11
Female (*n*)	8	3	5
Prevalence male (/100,000) (95% CI)	7.15 (4.52–11.3)	2.78 (1.35–5.74)	4.37 (2.44–7.82)
Prevalence female (/100,000) (95% CI)	3.31 (1.68–6.53)	1.24 (0.42–3.65)	2.07 (0.88–4.84)
Median age at diagnosis (IQR)	32 (14.5–45)	13 (9.5–15.5)	41.5 (33–51)
No. of patients undergoing surgery	22	9	13
No. of patients undergoing radiotherapy	15	6	9
No. of patients BMI 20–29 kg/m^2 (%)	10 (38.5)	4 (40)	6 (37.5)
No. of patients BMI 30–39 kg/m^2 (%)	13 (50)	4 (40)	9 (56.3)
No. of patients BMI > 40 kg/m^2 (%)	3 (11.5)	2 (20)	1 (6.25)
No. of patients with pituitary hormone deficiencies (%)	25 (96.2)	10 (100)	15 (93.8)
Regrowth/recurrence (out of 23)° (%)	6 (26.09)	2 (8.70)	4 (17.39)
Incidence estimates (2008–2019)			
Number of patients (*n*)	13‡	4	9
Overall SIR (/100,000/year) (95% CI)	0.3 (0.18–0.5)	0.72 (0.35–1.48)	0.19 (0.09–0.39)
Male (*n*)	8	3	5
Female (*n*)	5	1	4
SIR male (/100,000/year) (95% CI)	0.4 (0.21–0.74)	0.10 (0.44–2.38)	0.22 (0.09–0.56)
SIR female (/100,000/year) (95% CI)	0.2 (0.08–0.47)	0.37 (0.1–1.46)	0.15 (0.05–0.45)
Median longest diameter at diagnosis (IQR)	32.1 (23.25–41.5)	43 (42.5–47.25)	27 (20.55–31.55)
Median age at diagnosis (IQR)	41 (17–53)	12 (9.75–14)	51 (41–58)

*out of a cohort of 29 patients, 3 patients passed away by 30 June 2019, and hence could not be included in this study's prevalence estimates. °In 3 patients, regrowth could not be established (follow up scans or comparative imaging was unavailable). ‡All the consecutive patients (*n* = 13) diagnosed between beginning of 2008 and end of 2018 were included for SIR estimation.

Table 2 Tumour characteristics at presentation.

		All craniopharyngiomas (%)	**Childhood-onset** (%)	**Adult-onset** (%)
Number of patients		14*	5	9
Localisation	Confined to sella	0 (0.0)	0 (0.0)	0 (0.0)
	Suprasellar	7 (50.0)	5 (100)	2 (22.2)
	Intra-/supra-sellar extension	6 (42.9)	5 (100)	1 (11.1)
Consistency	Solid	1 (7.1)	0 (0.0)	1 (11.1)
	Cystic with solid components	4 (28.6)	2 (40.0)	2 (22.2)
	Multicystic	6 (42.9)	2 (40.0)	4 (44.4)
	Unicystic	3 (21.4)	2 (40.0)	1 (11.1)
Hydrocephalus		5 (35.7)	5 (100)	0 (0.0)
Hypothalamic/3rd ventricle involvement		8 (57.1)	5 (100)	3 (33.3)
Brainstem compression		4 (28.6)	4 (80.0)	0 (0.0)
Chiasmal compression	Infra-chiasmatic	3 (21.4)	0 (0.0)	3 (33.3)
	Supra-chiasmatic	0 (0.0)	0 (0.0)	0 (0.0)
	Posteriorly + splaying	10 (71.4)	4 (80.0)	6 (66.7)
	Nil	1 (7.1)	1 (20.0)	0 (0.0)
Median longest diameter (mm) (IQR)		31.0 (21–41)	43.0 (42.5–47.25)	24.0 (20–31)

*sub-cohort of 14 consecutive patients for whom all pre- and post-operative imaging were available.

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Seven patients (out of 23, 30.4%) had evidence of tumour regrowth or recurrence during follow-up, with 2 patients having childhood-onset disease and 4 individuals with adult-onset disease. Out of these patients, 3 (42.9%) had undergone sub-total resection through a trans-cranial approach followed by immediate post-operative radiotherapy and 4 individuals (57.1%) were given radiotherapy months after surgical removal in view of recurrence or regrowth. Kaplan–Meier estimates showed no statistically significant difference regarding regrowth and recurrence (Supplementary Fig. 1, see section on Supplementary materials given at the end of this article). Three patients passed away during follow-up. Survival rates were comparable for patients undergoing surgery or surgery with adjuvant radiotherapy.

Discussion

To date, very few epidemiological studies relating to craniopharyngiomas have been published and precise population-based data for craniopharyngiomas are limited (Bunin *et al.* 1998, Haupt *et al.* 2006, Nielsen *et al.* 2011, Zacharia *et al.* 2012). Such data are important to accurately estimate the disease burden and eventual need and utilisation of health care resources. In previous studies, the quoted tumour's epidemiology was obtained from cancer registries or tertiary referral centre patients (Bunin *et al.* 1998, Nielsen *et al.* 2011). Since data obtained from registries and non-population-based studies are pre-collected, necessary information might be subject to under-reporting, inaccessible or miscategorized (Thygesen & Ersbøll 2014). It is therefore possible that the quoted incidence rates are lower than the actual figures. Calculating accurate incidence rates was possible in our study since we had precise and sensitive identification of patients during a well-defined period of time, as well as reliable information about the size and characteristics of the background population. Furthermore, data selection was controlled by the researcher and was not limited by variables recorded in the registers. To our knowledge, this is the first population-based study on craniopharyngiomas quoting both prevalence and incidence rates.

Our estimated prevalence rate amounts to 5.27/100,000 people. To our knowledge, this is a novel finding, since prevalence rates have not been reported in other studies. As shown in Table 3, our SIR of 0.3/100,000/year is higher (approximately double) than rates quoted in the literature. Nielsen *et al.* (2011) carried out a study through which 189 patients with probable craniopharyngioma were identified from different patient registries in Denmark between 1985 and 2004. The standardised incidence rate for craniopharyngiomas during the 20-year study period was 0.19/100,000/year (95% CI 0.16–0.21), with similar rates for males and females (0.17 vs 0.15). They also estimated the worldwide incidence rate by searching literature that contained the terms 'craniopharyngioma', 'incidence' and 'epidemiology', identifying 1232 patients diagnosed with craniopharyngioma between 1935 and 1999. Absolute incidence rates varied between 0.09 and 0.57/100,000/year with no geographical pattern and the weighted summary incidence rate was of 0.13/100,000/year (95% CI 0.12–0.15) for the whole population. The CBTRUS report for 2005–2009 obtained incidence rates from 49 cancer registries (44 NPCR (National Programme of Cancer Registries), and 5 SEER (surveillance, epidemiology and end results), including both malignant and non-malignant brain and CNS tumours. From this registry-based study, Dolecek *et al.* (2012) identified 2680 patients with craniopharyngioma, with an annual incidence rate of 0.18/100,000/year (95% CI 0.18–0.19). Zacharia *et al.* (2012) quote an incidence rate of 0.17 cases per 100,000 person-years from a SEER database over a period of 5 years (2004–2009) which included 644 patients diagnosed with craniopharyngioma. As was noted in the CBTRUS study (Dolecek *et al.* 2012), where only 28.7% (766 patients) from a total cohort of 2680 had childhood-onset craniopharyngioma, in our cohort, adult-onset disease was more frequently prevalent (16 out of 26 patients, 61.5%). In our study, peak incidence rates were observed in the 2nd and 5th decade, similarly to what is quoted in the literature. Dolecek *et al.* (2012) quote peaks in incidence rates between 65–74 years (0.25/100,000/year, 95% CI 0.22–0.28) for the adult population and 5–9 age group (0.26/100,000/year, 95% CI 0.23–0.29). Nielsen *et al.* (2011) quote a peak at ages 5–9 and 40–44 years, and Bunin *et al.* (1998) noted a bimodal age distribution with a peak

Table 3 Standardised incidence rates for present study compared to other literature.

	Present study, 2021	Dolecek *et al.* 2012	Nielsen *et al.* 2011	Bunin *et al.* 1998
Overall SIR (/100,000/year) (95% CI)	0.30 (0.18–0.50)	0.18 (0.18–0.19)	0.16 (0.13–0.18)	0.13
SIR male (/100,000/year) (95% CI)	0.40 (0.21–0.74)	0.18 (0.17–0.19)	0.17 (0.13–0.20)	0.13
SIR female (/100,000/year) (95% CI)	0.20 (0.08–0.47)	0.18 (0.17–0.19)	0.15 (0.12–0.18)	0.12

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incidence in children aged 5–14 years and adults aged 65–74 years. Similar to what was observed in the study by Warmuth-Metz *et al.* (2004) in our population, males were more commonly affected. However, in contrast to our rates, in various other studies, there was no statistically significant difference in incidence rates between genders (De Vries *et al.* 2003, Haupt *et al.* 2006, Jane & Laws 2006, Dolecek *et al.* 2012, Cohen *et al.* 2013, Karavitaki 2014, Wijnen *et al.* 2017, Andereggen *et al.* 2018).

In our local population, multicystic tumours were present in significantly higher numbers in childhood-compared with adult-onset disease, as was also observed in a Bonferroni-corrected *post hoc* analysis carried out by Wijnen *et al.* (2017). In agreement with our results, these researchers concluded that multi-cystic craniopharyngiomas were more commonly seen in patients with childhood-onset when compared to adult-onset disease patients (45% vs 21%, $P = 0.02$). Locally, similarly to what was observed in other studies, hydrocephalus and 3rd ventricle involvement were more frequently observed in patients with childhood-onset disease. In our study, 62.5% of patients with childhood-onset (vs 35.5% of adult-onset) had hydrocephalus, compared to 44% of patients in the study carried out by Karavitaki *et al.* (2014) and 40% of patients with childhood-onset disease in the study by Wijnen *et al.* (2017).

Craniopharyngiomas can arise anywhere along the craniopharyngeal canal but are most commonly seen in the sellar and para-sellar areas (Karavitaki *et al.* 2006). Both locally and in other studies, the majority were intrasellar tumours with suprasellar extension (Table 2) (Petito *et al.* 1976, Hoffman *et al.* 1992, Karavitaki *et al.* 2006). No patients from our cohort had tumours restricted to the intrasellar region. In concordance, in the literature, this was the least common location (5–6%) (Petito *et al.* 1976, Karavitaki *et al.* 2006). By assessing the epidemiology and tumour characteristics of a cohort of 14 patients who were consecutively diagnosed over a 10-year period, we think we obtained a clearer overview of the variations in craniopharyngiomas in a definite population.

Both in our cohort and in other studies, the presentation was usually dominated by non-specific symptoms related to raised intracranial pressure such as headache and visual disturbances and pituitary hormone deficiencies (De Vries *et al.* 2003, Halac & Zimmerman 2005, Karavitaki *et al.* 2005, Wijnen *et al.* 2017, Andereggen *et al.* 2018). Overall survival rates in our cohort were comparable to other studies. Wijnen *et al.* (2017) quote an overall survival rate of 85%, and other recent studies report 10-year survival rates between 40 and 95% (Sherlock *et al.* 2010, Lee *et al.* 2014, Hoffmann *et al.* 2015, Olsson *et al.* 2015, Hoffmann *et al.* 2016, Pan *et al.* 2016). In our cohort, the commonest surgical modality was the trans-sphenoidal approach, targeted at tumour resection whilst preserving hypothalamic function.

Limitations to this study include the retrospective nature of data gathering with certain details being unavailable in some patients. However, due to the scarcity of the condition and the necessity for lengthy follow-up, prospective observational studies would be very challenging and time-consuming. Another limitation was the small sample size, which we tried to mitigate by including all patients diagnosed with craniopharyngioma from a well-defined population. Since there were various health care professionals taking care of these patients, this could result in possible differences when interpreting imaging and investigations. To minimize this, radiological investigations as well as tumour characteristics were all objectively assessed by a single specialist.

Conclusion

This study provides up-to-date and in-depth epidemiological data of craniopharyngiomas in a population. Being the first population-based study in this respect, the resultant rates were about twice the previously quoted figures. We think that these figures and tumour characteristic analysis better represent the health burden of craniopharyngiomas.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/EO-21-0006.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Ethical approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Acknowledgements
The authors would like to thank Professor J Vassallo, Dr MJ Cachia and Dr M Giordano Imbroll, for their assistance and support in this study and acknowledge all the medical staff and healthcare professionals at Mater Dei Hospital who gave invaluable input for this study to be completed.

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Received in final form 1 May 2021
Accepted 28 May 2021
Accepted Manuscript published online 28 May 2021