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CLINICAL STUDY

Cyproterone acetate and meningioma: a nationwide-wide population based study

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Abstract

Background The study the characteristics of surgical meningiomas in female patients who took CPA and to compare this population to a non-CPA control group.

Materials and methods We processed the French Système National des Données de Santé (SNDS) database to retrieve appropriate cases operated between 2007 and 2017.

Results 1 101 female patients (3.8%) who used to take CPA and underwent a meningioma surgery were extracted from a nationwide population based cohort of 28 924 patients. Median age at CPA prescription was 42 years IQR[36.7–48.9]. The median time between CPA start and surgery was 5.5 years IQR[3.1–7.9]. The median age at surgery was significantly lower in patients who were treated by CPA (47 years, IQR[42–54) compared to the non-CPA population (61 years, IQR[51–70], $p<0.001$). Median CPA dose was 40 g, IQR[19–72]. There was a strong correlation between CPA dose and duration ($r=0.58$, $_{95\%}$CI[0.54–0.62], $p<0.001$). Middle skull base was the most common (39%) location with a anterior skull base insertion being also far more common compared to the usual population with 21.9% of the tumour. This skull base predominance of CPA-associated meningioma is highly significant ($p<0.001$). Increased CPA dose raised the risk of having multiple meningioma surgeries ($p<0.001$) and multiple meningioma locations ($p<0.001$). Tumour grading was not modified by CPA treatment ($p=0.603$). Benign or grade I meningioma accounting for 92%, atypical or grade II for 6.1% and malignant or grade III for 1.9%.

Conclusion In the past 10 years, a significant number of CPA-induced meningiomas have been removed, modifying the global pyramid of age at surgery for female patients. These tumours occur well before the usual age and are preferentially located on the anterior and middle skull base.

Keywords Meningioma · Cyproterone · SNDS · Progestin · Epidemiology

Abbreviations

AMDB	Administrative medical databases
CCAM	Classification Commune des Actes Médicaux
CI	Confidence interval
CNS	Central nervous system
CPA	Cyproterone acetate
ICD	International Classification of Diseases (10th revision)
IQR	Interquartile range
OR	Odds Ratio
PR	Progesterone receptor
RR	Relative risk
SNDS	Système National des Données de Santé
WHO	World Health Organization

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Introduction

Meningiomas are usually non-malignant, slow-growing neoplasms arising from meningothelial cells of the arachnoid. They are the most common intracranial extracerebral tumours accounting for 36.8% in the Central Brain Tumor

Registry of the United States [1]. The 2016 World Health Organisation (WHO) classification of tumours affecting the central nervous system (CNS) recognises three grades of meningiomas [2]. WHO grade I or benign meningiomas (BM) occur for two-thirds in women and have usually a good outcome [3, 4]. WHO grade III or malignant meningiomas (MM) are rare and aggressive neoplasms with a poor prognosis [5]. Behaviour and outcome of atypical—WHO grade II (AM) are intermediate [6, 7]. The vast majority (~90%) of meningioma are benign with malignant forms being rare, accounting only for 1 to 3% [1, 8]. Although grade II meningiomas have been recognised in only about 5%, after changes in diagnostic criteria in the 2007 WHO CNS classification, they nowadays comprise around 10%. In the most recent WHO CNS classification of 2016, no molecular prognostic markers has been introduced for meningioma grading which is still based solely on histological criteria prone to inter observer and sampling bias [2].

Management options include regular monitoring especially for incidental meningioma, symptoms control, surgical excision, radiotherapy and occasionally chemotherapy but, tailored maximal safe resection remains the treatment of choice. Most meningiomas are sporadic and their incidence in France is about 5/100 000 persons per year [3, 4]. Ionizing radiation is the only unequivocal risk factor identified although others have been suspected. Evidence suggests the influence of sexual hormones as meningiomas are known to be hormone-sensitive and usually express progesterone receptors (PR). Despite the abundant expression of PR which are found in 88% of the meningioma, it is unknown, however, how PR expression is regulated, especially since oestrogen receptors are virtually absent in these tumours [9, 10].

A progestogen is a medication that produces effects alike to those of the natural progesterone. Synthetic progestogens or progestins are used alone or in combination with oestrogens most commonly in hormonal birth control and menopausal hormone therapy. They may also be used in the treatment of gynaecological conditions, to support fertility, lower sex hormone levels for various purposes, and for other indications. Previous studies suggest that hormone therapy may play a role in the development of meningioma. Among all progestins available in France, cyproterone acetate (CPA) sold under the brand name Androcur® that has anti-androgenic, progestagenic and antigonadotropic effect is indicated in women solely in severe hirsutism impairing the daily life. Exposure over one year to high dose of CPA has been shown to increase the risk of meningioma [11].

Administrative medical databases (AMDB) are massive repositories of collected healthcare data for various purposes. They may contain medical claims for reimbursement, records of health services, medical procedures, prescriptions, and diagnoses. AMDB provide a variety of already stored data with a constant and often increasing on-going collection process [12]. They encompass very large population and frequently the whole nation, ensuring high statistical power without biases related to the representativity of a sample. AMDB can be used to conduct epidemiological studies and evaluate medical practices. Use of these databases is less expensive than conducting specific surveys in dedicated populations by providing rapid access to data gathered in a standardised format [13].

In that respect, the recent access opening of French nationwide health record database or SNDS (Système National des Données de Santé) is a great opportunity to carry out comprehensive health studies at the country level. The SNDS includes many information such as demographic data, medical and surgical procedure with linked and associated diagnoses or date of death [13]. It is continually evolving towards enrichment by medical information [13]. Around 3 000 patients are operated on for a meningioma each year in France. Very few cohort studies reporting on CPA and meningioma exist and little is known about the natural history of CPA-associated meningiomas. Using this unique database, we aimed at assess the relation between CPA and surgically removed meningioma as to date, such a research has not achieved in France.

Objective

The objective was to assess the characteristics of operated meningiomas in female patients who took CPA and to compare this population to a larger non-CPA control group.

Material and methods

We performed a nationwide population-based descriptive observational and analytic retrospective study. Incidental meningiomas never operated were not considered in this study; only surgically treated tumours were taken into account. Data were extracted from the Système National des Données de Santé (SNDS), the national French medico-administrative database. Patients who underwent the surgical resection of a meningioma between 2007 and 2017 were included. Cases were extracted using an algorithm combining two variables as described previously: the type of the surgical procedure identified by the Common Classification of Medical Acts (CCAM) and the primary diagnosis according to the International Classification of Diseases (ICD-10) as described previously [3, 14, 15]. Meningioma were categorised into 8 anatomical locations according their dural base insertion after further categorisation of the 40 CCAM codes which aimed at described intracranial extracerebral tumour resection. Male patients and those below 18 years

were not considered in this study. The patients who had only a prescription of one CPA box were excluded from this study (n = 56). The female CPA population was compared to a larger non-CPA female population serving as a control group. The 56 patients were completely excluded from the analysis and not transferred into the control group.

Statistical methods

For the description of the cohort presented in Table 1, continuous variables are reported as means and standard deviations or as medians and interquartile ranges (IQR) for non-Gaussian distributed variables; categorical variables are reported as frequencies and proportions. All tests were 2-sided and statistical significance was defined with an alpha level of 0.05 ($p < 0.05$). Analysis was performed with both the SAS Enterprise guide version 7.15, the R programming language and software environment for statistical computing and graphics (R version 4.0.2 (2020–06-22)) [16]. The statistical programme and workflow was written in R Markdown v2 with RStudio® for dynamic and reproducible research [17].

Results

Population description

1 101 women (3.8%) used to take CPA and underwent a meningioma surgery were extracted from a nationwide population based cohort of 28 924 patients who had meningioma surgery between 2007 and 2017. Median age at CPA prescription was 42 years IQR[36.7–48.9]. The median time between CPA start and surgery was 5.5 years IQR[3.1–7.9]. The median age at surgery was significantly lower in patients who were treated by CPA (47 years, IQR[42–54) compared to the non-CPA population (61 years, IQR[51 70], $p < 0.001$) (Table 1 and Fig. 1a, b). When available, treatment indications were *e.g.* ovarian dysfunction (3.1%), endometriosis (2.4%), hypertrichosis (2.5%), leiomyoma of uterus (1.5%). Median

Table 1 Characteristics of the patients (n = 1101)

Variable	No cyproterone n = 16 158	Cyproterone n = 1 101	*p*-value
Age at surgery (continuous)[a]	61, 51–70	47, 42—54	< 0.001
Tumour grading (5 cat.)			
< 40 years	1325 (8.2%)	217 (19.7%)	
< 40 to > 50	2506 (15.5%)	486 (44.1%)	
< 50 to > 60	3828 (23.7%)	256 (23.3%)	
< 60 to > 70	4711 (29.2%)	112 (10.2%)	
> 70	3788 (23.4%)	30 (2.7%)	**< 0.001**
Location			
Cranial convexity	3817 (23.6%)	254 (23.1%)	
Anterior skull base	2038 (12.6%)	241 (21.9%)	
Falx cerebri	1250 (7.7%)	49 (4.5%)	
Middle skull base	3303 (20.4%)	429 (39%)	
Parasagittal	1515 (9.4%)	52 (4.7%)	
Posterior skull base	2147 (13.3%)	64 (5.8%)	
Spine	1977 (12.2%)	11 (1%)	**< 0.001**
Tumour grading			
Benign	14,940 (92.5%)	1013 (92%)	
Atypical	878 (5.4%)	67 (6.1%)	
Malignant	340 (2.1%)	21 (1.9%)	0.6
Dose (g)	–	40, 19–72	
Duration (years)	–	5.2, 2.6—7.7	
Time between cyproterone start and surgery (years)	–	5.5, 3.1—7.9	
Time between cyproterone end and surgery (years)	–	0.2, 0—0.8	
Cyproterone discontinued before surgery	–	534 (48.5%)	
Cyproterone discontinued at last follow-up	–	762 (69.2%)	

p-values displayed in bold reached the statistical significance

[a]Median and *IQR* inter quartile range

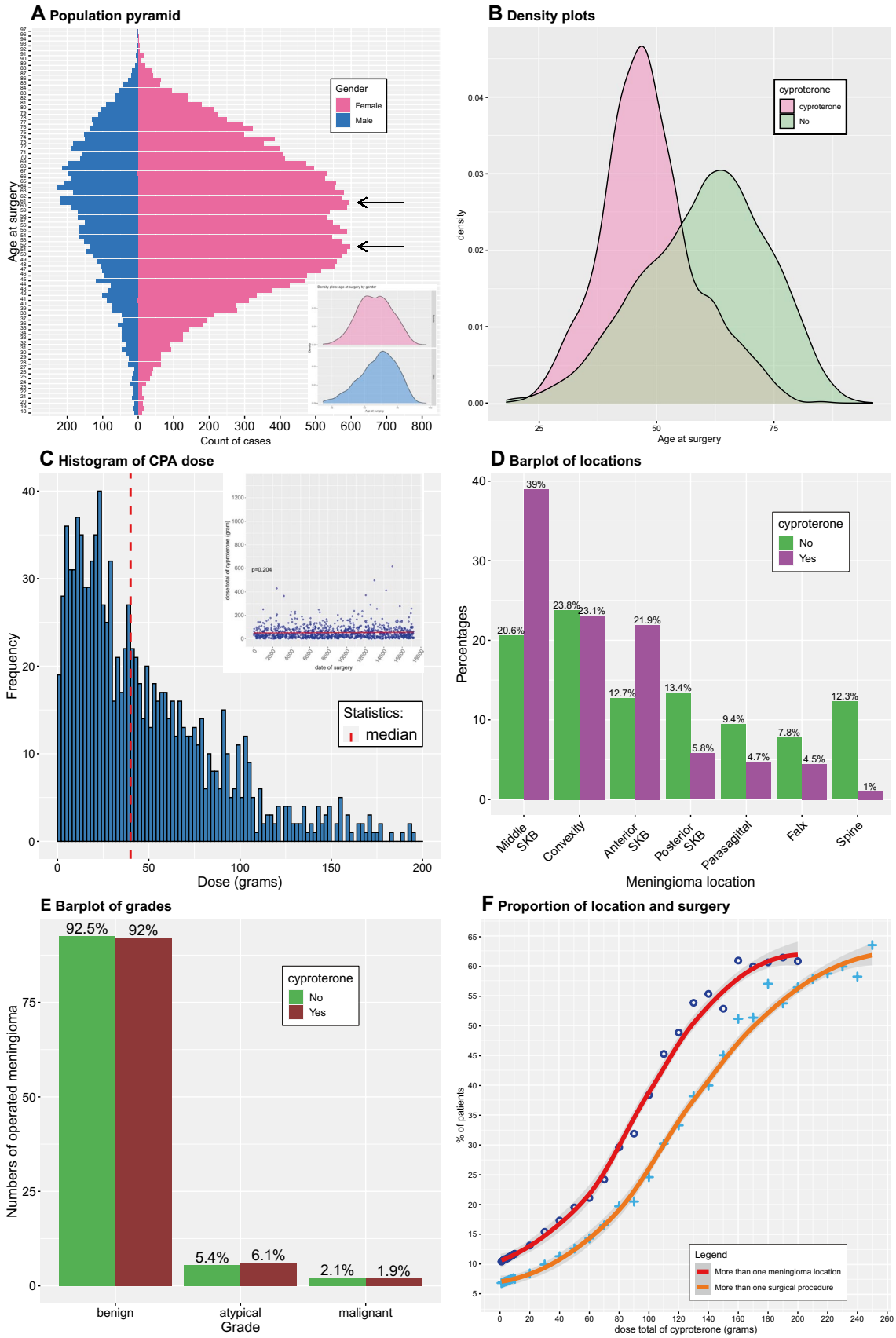

Fig. 1 **a** Population pyramid. **b** Density plots. **c** Histogram of CPA dose. **d** Barplot of locations. **e** Barplot of grades. **f** Proportions of location and surgery

CPA dose was 40 g, IQR[19–72] which correspond to a median treatment duration of 5.2 years, IQR[2.6–7.7]. 356 patients (32.3%) received 60 g of CPA or more. There was a strong correlation between CPA dose and duration. A long duration of CPA uptake correlated with a high dose of CPA ($r = 0.58$, $_{95\%}$CI[0.54—0.62], $p < 0.001$). Middle skull base was the most common (39%) location with anterior skull base insertion being also far more common compared to the usual population with 21.9% of the tumour. This skull base predominance of CPA-associated meningioma is highly significant ($p < 0.001$). (Table 1 and Fig. 1d). A CPA dose of 40 g or more significantly increased the risk of having multiple meningioma surgeries at different times (11.3%) ($p < 0.001$) and multiple meningioma locations (17.3%) ($p < 0.001$) (Fig. 1f).

If CPA was associated with a significant modification of age at meningioma surgery and location however, tumour grading was not modified by CPA treatment ($p = 0.603$). Benign or grade I meningioma accounting for 92%, atypical or grade II for 6.1% and malignant or grade III for 1.9% (Table 1, Fig. 1e).

Discussion

Key results

In this study, we assessed the characteristics of surgically treated meningioma after CPA treatment using the French health insurance national database SNDS. In our main cohort of 28 924 patients, the bimodal shape of the curve for female patients makes us wonder about this unusual features not previously reported in epidemiological studies on meningioma (Fig. 1a) [1, 20, 21]. It appears that this unexpected characteristic might be related to hormonal treatments [22]. Weill et al. identified 253 777 women who used to take at least 3 g of CPA between 2007 and 2014 [22]. The density plots of subfigure 1b confirmed this suspicion and shows a distribution of ages at surgery being well apart and much younger for the female patients who took CPA, with a median age at meningioma surgery 14 years lower compared to non-CPA population ($p < 0.001$). A 30 cases series assert our findings with a reported mean age at surgery of 50 years for CPA-induced meningioma *vs.* 58 years for the controlled group [23]. CPA was the foremost-suspected molecule responsible for this second peak at 51 years visible on the subfigure 1a. Two others molecules chlormadinone and nomegestrol acetate also largely prescribed within the French female population are also suspected to increase the risk of meningioma and will be therefore investigated in the near future [24].We found a median time between CPA treatment start until surgery of 5.5 years, IQR[3.1–7.9] *i.e.* about 66.1 g of CPA for an uninterrupted treatment of 50 mg per day, 20 days per month during 5.5 years. In fact, the median total dose taken by the patient is somewhat lower (40 g, IQR[19–72]) due to periods of treatment discontinuation. Nonetheless, a meningioma may grow only after a sufficient cumulative dose has been reached over enough treatment time. For Portet et al. 86.7% of the 30 patients had a prolonged exposure over 10 years and Bernat et al. found a mean exposure time of 18.6 years with an average dose of 40 g [23, 25]. The patients who used to take 40 g or more of CPA had significantly more meningioma locations (17.3%) *vs.* those having taken less CPA (4%, $p < 0.001$). This is also true for a dose of 60 g (21.1%, *vs.* 5.2%, $p < 0.001$) and if we take into consideration the count of neurosurgical procedures (14.3%) *vs.* those having taken less CPA (3.3%, $p < 0.001$). The resulting curves are sigmoid functions (Fig. 1f).

Limitations

The strengths of the SNDS reside both in the high number of patients and in the exhaustive data available from every hospital in France. The database representativeness is nearly perfect, since it includes the whole country's population of nearly 68 million of inhabitants constituting one of the largest AMDB in the world [13]. However, these data were not initially collected for research purposes and they may therefore be subject to random or systematic measurement errors, which can have consequences when defining study populations, events and covariates. Important variables such as the quality of resection are not recorded in the SNDS [26]. The retrospective nature of this study, together with the lack of clarity regarding treatment rationales without random assignment, needs to be considered when evaluating the results. AMDB-based studies are built upon what is available in them, sometimes limiting chances to explore potential interesting associations. Despite these limitations, the SNDS is an invaluable tool to assess meningioma outcome. It offers an incomparable mean to explore associations with other pathology, medication or combine treatment which has and could not be assessed before. Moreover, use of these databases is less expensive than conducting specific surveys in dedicated populations.

Interpretation

The role of sexual hormones in the development of intracranial meningioma has been proposed as one hypothesis to explain the predominance of such tumours in women. Despite a long time ago suspected link, it was not until recently quantified; prior epidemiologic studies reporting contradictory results [27]. Wigertz et al.were among the first to found an elevated risk of meningioma associated with the use of hormone replacement therapy [28]. An increased risk was found among post-menopausal women for ever use of

hormone replacement therapy (odds ratio (OR) = 1.7 $_{95\%}$CI [1.0—2.8]) and for users of 10 years or more of long-acting hormonal contraceptives (OR = 2.7 $_{95\%}$CI [0.9—7.5]) [28]. The risk of CPA-related meningioma was first suspected in transsexual patients requiring high dose of CPA [29]. Cea-Soriano et al. supported the significantly increased risk of meningioma among three male users of high-dose CPA [27]. Further reports on male-to-female transsexual patients supported these findings [30, 31]. This was comforted by Nota et al. which concluded that cross-sex hormone treatment is associated with a higher risk of meningiomas in transwomen likely linked to CPA [32]. Observations of meningioma, often multiple, among users of high doses of CPA have raised the suspicion that it may promote the rapid growth of pre-existing or new meningioma. It was thus legitimately hypothesised that if CPA stimulates the development of meningioma, its discontinuation should lead to the shrinking of the tumour. Cases studies of meningioma regression after CPA discontinuation sustained this idea either in women or in transwomen [33, 34]. It was therefore suggested that conservative management of CPA-induced meningiomas might be the best option given that spontaneous regression may occur after treatment discontinuation, including improvement of symptoms [35]. Current practice of likely CPA-induced meningioma is treatment withdrawal and regular MRI monitoring (https://www.ema.europa.eu/en/news/restrictions-use-cyproterone-due-meningioma-risk) [25, 33–37].

Generalisability

CPA is indicated for severe hirsutism eventually related to a polycystic ovary syndrome at a dosage of 50 mg per day. In fact, it was widely used in France, often outside its official indication as *e.g.* contraception mean, acne treatment or ovarian dysfunction.

Weill et al. found that around 80% of CPA prescriptions were outside official indications [22]. Presumably, CPA was mostly used as contraception mean in our cohort as only 14.5% of the patients having a related diagnosis of gynaecological or endocrine problem. CPA is also found in smaller quantities (2 mg) in combined oral contraceptives for treating seborrhea, acne, hypertrichosis, and moderate androgen-related alopecia. Weill et al. found a relative risk of meningioma of 6.6 $_{95\%}$CI [0, 1, 4, 11] above 3 g of CPA and a marked dose–effect (adjusted hazard ratio = 21.6 $_{95\%}$CI [5, 8, 10, 43]) above 60 g [22]. For Gil et al. patients exposed to high-dose CPA showed an increased risk of meningioma of 11.4 $_{95\%}$CI[4.3–30.8] [11]. Although the association between CPA and intracranial meningioma development is now established, the underlying mechanisms remain unknown. It was soon noticed that CPA-induced meningiomas likely grown near the skull base and preferentially on the anterior or the middle part [29]. In our study, middle skull base CPA-induced meningiomas were the most common (39%) as opposed to cranial convexity which is the undisputed most usual location in the general population with 23.6% in the main cohort study. For Portet et al. a significant relationship linked CPA and skull base localisation where 86.7% of the meningiomas were inserted [23]. Moreover, Bernat et al. suggested that patients with multiple tumours had used CPA for a longer period of time (mean 20.4 years) than the two patients with only one meningioma (10 years). CPA does not promote the occurrence of aggressive meningiomas, a conclusion supported by Portet et al. study which moreover found a positive association between meningothelial or microcystic histology and CPA [23].

In October 2018, the Agence Nationale de Sécurité du Médicament et des Produits de Santé had issued several recommendations among which the need to follow more rigorous indication of prescription and to perform brain MRI at treatment onset and regularly of the CPA treatment cannot be superseded (severe hirsutism). This guidance was reinforced in July 2019 by the obligation by the prescriber to inform annually the patient about the CPA meningioma-associated risk which in return must fill and co-signed an attestation to get the treatment at the pharmacy. As such, the level of CPA prescription which was authorised in France in 1980 has dramatically decreased.

As conservative management of CPA-induced meningiomas is the recommended attitude given the usual regression after treatment discontinuation, combined with the drastic diminution of CPA prescription, we should observe in the near future, a slight decreased of meningioma resection frequency around 50 years and thus the disappearance of this bimodal distribution.

Conclusion

In the past 10 years, a significant number of CPA-induced meningiomas have been removed, modifying the global pyramid of age at surgery for female patients. These tumours occur well before the usual age and are preferentially located on the anterior and middle skull base.

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Availability of data and material Restricted, the authors do not have permission to share data.Code availability On demand.

Compliance with ethical standrads

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was conducted according to the ethical guidelines for epidemiological research in accordance with the ethical standards of the Helsinki Declaration (2008), to the French data protection authority (CNIL) an independent national ethical committee, authorisation number: 2008538; to the RECORD guidelines for studies conducted using routinely-collected health data and, according to the SAMPL Guidelines [18, 19].

Informed consent Informed consent was not required due to the retrospective nature of the study. The SNDS encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers.

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