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Summary

Meningioma is the most common primary intracranial tumour. Despite a consistent literature, there is less than a handful of studies reporting on outcome after meningioma surgery using nationwide administrative medical databases. The recent existence of the French nationwide healthcare database (SNDS) offered us the opportunity to study globally what we have also done locally. The reported incidence of meningioma has varied substantially over time and by the method of identification, from 1 to 8.4 per 100 000 with 5/100 000 in our study. We conclude that the SNDS is a reliable and effective source for studying the epidemiology of surgically treated meningiomas, including the precise location of the tumour asserting the usefulness of such a database to investigate the patients' outcome after meningioma surgery. Based on a single centre retrospective study of 501 patients operated on for a WHO grade I meningioma at Queen Elizabeth University Hospital, Glasgow, Scotland, we found that treatment failure correlated with venous sinus invasion, incomplete resection, and progressing tumour. Shorter survival correlated with increased age and redo surgery for recurrence. We recommend the cumulative incidence competing risk approach in meningioma studies where unrelated mortality may be substantial, as this approach results in more accurate estimates of disease risk and associated predictors. Then, in a multicentre cohort study involving 6 centres in France and in the United Kingdom, we confirmed the poor prognosis associated with malignant meningioma, the treatment of which remains challenging. Patients under 65-yr-old with primary malignant meningioma may live longer after complete resection and postoperative radiotherapy but even with aggressive treatments, local control remains difficult to achieve. Finally, we investigate the nationwide survival after meningioma surgery and search for associated factors using the SNDS. This nationwide study found 28 891 patients of which 75.4% were female. Median age at surgery was 59 years, IQR[49 - 68]. Cranial convexity (24.4%) and middle skull base (21.7%) were the most common locations. 91.2% of the tumours were benign and 2.7% malignant. 7.6% of the patients underwent redo surgery, 9.2% radiotherapy (RT) and 3.2% stereotactic radiosurgery (SRS) for recurrence. Median follow-up was 4.9 years, IQR[2.5-7.6]. At data collection, 8.3% were dead. 191 patients died within a month of surgery and 623 within a year. Overall survival rates at 5 years was: 92.6%, $_{95\%}$CI[92.2-92.9]. In the multivariable analysis, gender (HR=0.6, $_{95\%}$CI[0.55-0.65], p<0.001), age at surgery (HR=1.07, $_{95\%}$CI[1.07-1.07], p <0.001), type 2 neurofibromatosis (HR=4.18, $_{95\%}$CI[2.88-6.07], p<0.001), parasagittal (HR=1.18, $_{95\%}$CI[1.03, 1.35], p=0.017) or falx cerebri location (HR=1.18, $_{95\%}$CI[1.02-1.37], p=0.031), atypical (HR=1.32, $_{95\%}$CI[1.14-1.54], p<0.001) or malignant (HR=2.97, $_{95\%}$CI[2.56, 3.45], p<0.001), redo surgery (HR=2, $_{95\%}$CI[1.79, 2.24], p<0.001) or RT for recurrence (HR=2.14, $_{95\%}$CI[1.93, 2.37], p<0.001) were established as independent prognostic factors of survival. After removal of meningioma, survival of patients presenting no co-morbidities is long and outcome is better in women, younger adults, and patients with convexity and benign tumour. Once the tumour had relapsed, cure is unlikely and none of the treatment studied succeed to improve the survival. This study on meningioma using the SNDS is the first of its kind. Despite some limitations, the SNDS is an invaluable tool to assess meningioma outcome. It offers incomparable means to explore associations with other pathology, medication or other surgical treatment which has and could not be assessed before.

Keywords: Meningioma; Survival; Predictors; Database; SNDS

Résumé

Les méningiomes sont les tumeurs intracrâniennes primitives les plus fréquentes. Malgré une importante littérature sur le sujet, il n'y a que quelques publications sur le devenir des patients opérés de méningiomes utilisant les bases médico-administratives. La mise à disposition récente du système national de santé (SNDS), la base médico-admini-strative nationale française nous a offert l'opportunité d'étudier globalement ce qui se fait généralement localement. L'incidence des méningiomes varie de manière substantielle en fonction de la méthodologie utilisée de 1 à 8.4 pour 100 000 avec une incidence de 5/100 000 dans notre étude. Fort de cette étude montrant que le SNDS est une source fiable pour étudier l'épidémiologie des méningiomes opérés, y compris la localisation précise de l'insertion tumorale nous avons décidé d'évaluer la survie à long terme des ces patients. Basés sur une étude monocentrique de 501 patients opérés d'un méningiome de grade I à l'hôpital Universitaire de Glasgow en Écosse, nous avons trouvés que l'échec du traitement chirurgical était corrélé à l'invasion d'un sinus veineux, la résection incomplète de la tumeur et une progression de son grade histopathologique. Une survie réduite des patients était en relation avec un âge avancé et une nouvelle chirurgie d'éxérèse. Suite à l'utilisation de cette méthode statistique originale dans cette étude, nous recommandons l'utilisation de l'incidence cumulée en présence de risques compétitifs car cette approche est plus précise pour l'analyse de la survie des patients opérés de méningiomes qui ont souvent une cause de décès non en relation avec ce type de tumeur. Ensuite, dans une étude multicentrique sur 6 centres français et anglais, nous avons confirmé le mauvais pronostic associé à un diagnostic de méningiome malin, dont le traitement reste problématique. Les patients de moins de 65 ans avec un méningiome malin primitif réséqué complètement suivi d'une radiothérapie sont ceux qui vivent le plus longtemps mais même avec une combinaison de traitement aggressifs, le contrôle tumoral reste difficile à obtenir. Finalement, nous avons étudié la survie à long terme des patients opérés d'un méningiome ainsi que les facteurs pronostiques associés, en utilisant le SNDS. Cette étude nationale a identifié 28 891 patients dont 75.4% de femmes. L'âge médian à la chirurgie était de 59 ans EI[49-68]. Les méningiomes étaient le plus souvent localisés sous la convexité crânienne dans 24.4% ou implantés sur l'étage moyen de la base du crâne dans 21.7%. 91.2% des tumeurs étaient considérées comme bénignes et 2.7% malignes. 7.6% des patients ont du être réopérés pour une récidive, 9.2% ont bénéficié d'une radiothérapie et 3.2% d'une radiochirurgie. Le suivi médian était de 4.9 ans, EI[2.5-7.6]. A l'analyse des données, 8.3% des patients étaient décédés avec 191 décès dans le mois et 623 dans l'année suivant l'intervention. La survie globale à 5 ans était de 92.6%, $IC_{95\%}$[92.2-92.9]. Le sexe (HR=0.6, $IC_{95\%}$[0.55-0.65], p<0.001), l'âge à la chirurgie (HR=1.07, $IC_{95\%}$[1.07-1.07], p<0.001), une neurofibromatose de type 2 (HR=4.18, $IC_{95\%}$[2.88-6.07], p<0.001), la localisation (HR=1.18), un grade élevé (HR=2.97, $IC_{95\%}$[2.56-3.45], p<0.001), une nouvelle exérèse (HR=2, $IC_{95\%}$[1.79-2.24], <0.001) ou une radiothérapie (HR=2.14, $IC_{95\%}$[1.93-2.37], p <0.001) étaient des facteurs indépendants associés à la survie. Après chirurgie, les patients de sexe féminin, jeune, n'ayant pas de comorbidités, et un méningiome bénin de la convexité ont une survie significativement prolongée. En cas de récidive de la tumeur, la guérison est dès plus incertaine et ni une nouvelle chirurgie ou une radiothérapie améliore le pronostic vital. Malgré ses limitations, cette recherche originale montre que le SNDS est un outil unique et incomparable pour étudier la devenir des patients opérés d'un méningiome. Il permet d'explorer l'influence de nombreux facteurs comme les pathologies associées, les traitements médicaux et chirurgicaux, ce qui n'était pas possible auparavant.

Mots-clés: Méningiome; Survie; Facteurs de risque; Base de données; SNDS

Scientific production in relation with the doctorat

Peer-rewieved publications

1. Malignant Meningioma: An International Multicentre Retrospective Study.
   Champeaux C, Jecko V, Houston D, Thorne L, Dunn L, Fersht N, Khan AA, **Resche-Rigon M.**
   Neurosurgery. 2019 Sep 1;85(3):E461-E469. doi: 10.1093/neuros/nyy610

2. Intracranial WHO grade I meningioma: a competing risk analysis of progression and disease-specific survival.
   Champeaux C, Houston D, Dunn L, **Resche-Rigon M.**
   Acta Neurochir (Wien). 2019 Nov 9. doi: 10.1007/s00701-019-04096-9

3. Epidemiology of meningiomas. A nationwide study of surgically treated tumours on French medico-administrative data.
   Champeaux C, Weller J, Katsahian S.
   Cancer Epidemiol. 2019 Feb;58:63-70. doi: 10.1016/j.canep.2018.11.004. Epub 2018 Nov 24

Publications under consideration in peer-rewieved medical journals

1. Meningioma: a nationwide study on overall survival.
   C. Champeaux, J. Weller, S. Froelich, M. Resche-Rigon
   Submitted to *Acta Neurochirurgica*

2. Neurofibromatosis type 2: a nationwide population-based study focused on survival after meningioma surgery.
   C. Champeaux, J. Weller, M. Resche-Rigon
   Submitted to *Neurological Sciences*

3. Tamoxifen. A treatment for aggressive meningioma? A nationwide population-based matched cohort study.
   C. Champeaux, J. Weller, M. Resche-Rigon
   Submitted to *Oncoscience*

Oral presentations

1. Malignant Meningioma: an international multicentre retrospective study
   Congrès de la SFNC de Strasbourg, vendredi 29 mars 2019 à 9:42:00

Posters

1. Poster pour le 2nd congrès "le SNDS pour la recherche en santé" Rennes, 24 & 25 mai 2019: Meningioma: an 8-year nationwide study on outcome and associated predictors

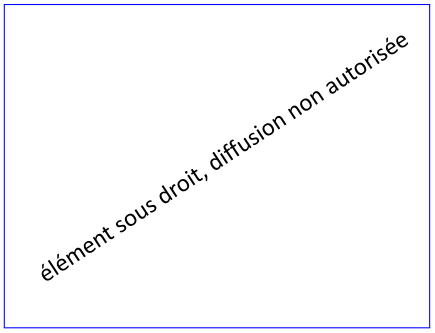
2. Poster pour les journées de l'école doctorale Pierre Louis de santé publique (ED 393) de Saint-Malo en Octobre 2019: A nationwide study of surgically treated tumours on French medico-administrative data

3. Poster pour le congrès de la SFNC de Strasbourg en mars 2019: Epidemiology of meningiomas. A nationwide study of surgically treated tumours on French medico-administrative data

4. Poster pour les journées de l'école doctorale Pierre Louis de santé publique (ED 393) de Saint-Malo en Octobre 2018 : Malignant Meningioma: An International Multicentre Retrospective Study

Vi Veri Universum vivus vici.

Aleister Crowley (1875-1947) in The Cry of the 4th Aethyr



4 Introduction

4.1 Preamble

The meninges are the three membranes surrounding the brain and the spinal cord. In mammals, the meninges are the dura mater, the thick outermost layer, the arachnoid, and the pia mater.

Figure 1 – On this anatomical representation, the dura mater coating all the inner cranium and its great fold, the falx cerebri are displayed as a white membrane. From Atlas and Text-book of Human Anatomy Volume III by Dr. Johannes Sobotta

Cerebrospinal fluid flows in the subarachnoid space between the arachnoid and the pia mater which constitute the leptomeninges. The primary function of the meninges is to protect the central nervous system (CNS).

Meningiomas which are thought to arise from the meningothelial cells of the arach-

noid layer are the most common intracranial extracerebral tumours. Harvey Cushing first used the term “meningioma” in a 1922 publication describing tumours that originate from the meningeal, i.e. dural, coverings of the brain and spinal cord. Meningiomas can occurs anywhere along the CNS. They are highly diverse tumours with respect to localisation, clinical presentation, radiological aspects and histology.

Ionizing radiation is the only unequivocal risk factor identified although others have been suspected. Evidence suggest the influence of sexual hormones as meningiomas are known to be hormone-sensitive and usually express progesterone receptors but rarely oestrogen receptors. Hormone exposure has been implicated in the development of meningioma as evidenced by a female preponderance or tumour growth during pregnancy [48]. Exposure over one year to high dose of cyproterone acetate which has anti-androgenic, progestagenic and antigonadotropic effect, has been shown to increase the risk of meningioma [26].

Figure 2 – Artist illustration of cranial meninges [2]

Neurofibromatosis (NF) type 2 (NF2) is a rare autosomal-dominant multiple neoplasia syndrome resulting from mutations of the NF2 tumour suppressor gene located on chromosome 22q12. NF2 patients are predisposed to develop CNS lesions, meningiomas included. The cumulative incidence of meningiomas was shown to be close to 80% by 70 years of age in a cohort of 411 patients with proven NF2 mutation [28].

Certain subtypes of meningioma display an aggressive behaviour and are associated with an increased risk of recurrence and unfavourable prognosis. The 2016 World Health Organisation (WHO) classification of tumours affecting the CNS recognised three

[2] http://vanat.cvm.umn.edu/neurHistAtls/pages/men1.html

histological grades of meningioma and distinguishes 15 histological variants: the common type (WHO grade I), the atypical or intermediate type (grade II) and the anaplastic or malignant type (grade III) [37].

Almost all meningiomas are sporadic and their incidence in France is about 5/100 000 persons per year [54, 16]. Females are affected by meningiomas far more frequently ($^3/_4$) than males ($^1/_4$). The majority ($\approx$ 90%) of meningiomas are located intracranially, but around 10% are found in the spinal meninges. Meningiomas occur primarily in elderly patients, with increased incidence in individuals above 60 years. These tumours are exceedingly rare in children, representing 0.4–4.1% of all paediatric tumours. Meningioma is one of the cytogenetically best-studied solid tumours. The most frequent chromosomal aberration in meningiomas is monosomy 22, which, however, has been shown to be an isolated anomaly not relevant for prognosis [34].

4.2 Management of meningioma

Nowadays, numerous intracranial tumours, meningioma included, are fortuitously discovered on computed tomography (CT) or magnetic resonance imaging (MRI) scanner requested for likely unrelated symptoms or systematic scan. A meningioma can be difficult to diagnose because the tumour is often slow growing. Related symptoms may also be subtle and mistaken for other health conditions or written off as normal signs of aging. Decision to treat a meningioma is based mainly on one criterion: is the tumour symptomatic? Common symptoms include headache, seizures and progressive neurological deficit [54]. Asymptomatic tumours which are increasingly discovered incidentally are preferentially managed conservatively with a regular MRI monitoring. Incidental, asymptomatic, radiographically presumed meningiomas appear to behave less aggressively, may be observed, and treatment withheld until symptoms develop,

sustained growth occurs, or concerns of encroachment on sensitive structures arise. Generally, surgery aiming for gross total resection is the primary treatment for meningioma. It also serves to establish a histological diagnosis which guides all subsequent decision-making. Current guidelines recommend gradual treatment regimens depending on tumour grade and the extent of resection as defined by Donald Simpson [49, 27].

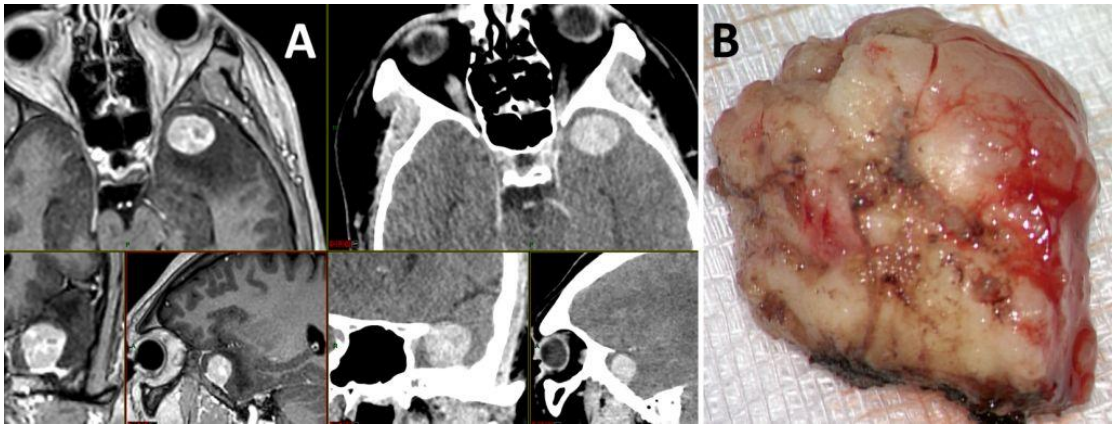


Figure 3 – Twenty-six-year old man, inaugural grand mal seizure, WHO grade I meningothelial meningioma inserted on the temporal fossa floor. (A) MRI (left) and CT (right) scans images with contrast and (B) macroscopic appearance after removal

However, treatment strategies varies according to factors such as clinical presentation, age, tumour location, size, and associated pathology. Incidental, asymptomatic presumed meningiomas which appear to behave less aggressively, may be observed, and treatment withheld until symptoms develop, sustained growth occurs, or concerns of encroachment on sensitive structures arise.

Treatment options include observation with radiological follow-up, radiation therapy, surgery or combinations of these alternatives. Complete surgical excision is the treatment of choice in all types meningioma. Maximal surgical excision remains the mainstay of treatment for all grades of cranial and spinal meningioma, but cranial stereotactic radiosurgery (SRS) are increasingly used especially for small lesion deep seated. Surgery for large and often hypervascular meningioma is still challenging be-

cause of encountering significant intraoperative bleeding. Preoperative embolisation of the feeding vessels may be one of the solutions to reduce such bleeding, facilitate resection, and shorten operating time.

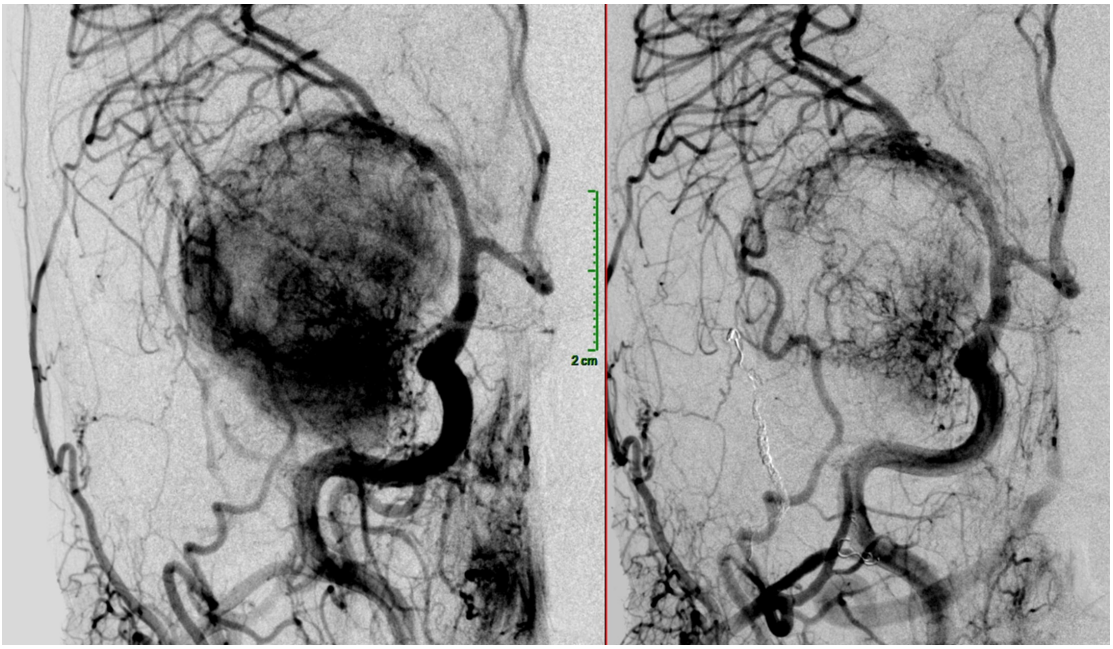


Figure 4 – Appearence of a middle skull base meningioma before the endovascular treatment (left) and after (right). There is a significant reduction of the iodinated contrast uptake on the digital subtraction angiography anterioposterior views.

Surgical approach is based on skull flap cutting to expose the dural insertion of the tumour given its origin outside of the brain parenchyma. Principles include: a tailored keyhole craniotomy to minimise exposure of other structures and brain injury; if necessary, a careful and progressive displacement of anatomical structures to reach the meningioma; coagulation and/or section of the infiltrated dura mater; debulking of the meningioma respecting the arachnoid plane; preservation of the surrounding arteries, veins and nerves for skull base meningiomas; meticulous but gentle haemostasis; reconstruction and closure of the dura mater ideally with pediculated epicranium; anatomical osteosynthesis of bone flat; skin closure as usual. The goal is a total removal (Simpson grade I/II) at first surgery or maximal safe resection if the meningioma can't be fully resected [49]. Extent of resection is the most powerful factor which correlates to the

survival and the relapse but, treatment paradigms vary among surgeons, institutions and countries. Further optimal management is difficult to establish. Owing to a lack of prospective, randomised trials, standardised treatment guidelines are difficult to formulate.

After resection, unless the histopathology showed a malignant meningioma (MM), a clinical and radiological follow-up is usually applied. Basically, the treatment of relapse is based on repeated surgery and/or RT [2].

When total resection cannot be achieved, RT or SRS may be helpful in case of meningioma remnant progression. Radiation therapy or radiotherapy (RT) is a therapy using ionizing radiation to control or kill tumoral cell. Photon (X or gamma rays) or charged particle such as proton damages the cell DNA by ionization of the atoms. Of the different types of RT, External Beam RadioTherapy (EBRT) is the most commonly used to treat intracranial tumour. There are many types of EBRT such as intensity modulated radiation therapy (IMRT) or protontherapy available in three centres in France, one near Paris in Orsay, another in Nice and a recent one in Caen.

The role of post-operative radiotherapy (RT) as a standard adjuvant treatment remain controversial for grade II meningioma. Grade III tumours require radical surgery and adjuvant RT due to their aggressive clinical course. Irrespective of surgical extent, fractionated RT (> 54 Gy) is recommended. No randomised essay on adjuvant RT after WHO grade III meningioma surgery has been or is currently undertaken, mainly due to the rarity of these tumour. Nevertheless, most neuro-oncologists and neurosurgeons regards RT as the standard postoperative treatment.

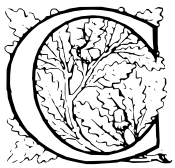
Chemotherapy is considered experimental in the context of meningioma as only limited evidence exist. As such, their use is only recommended in anaplastic cases and preferentially in the context of clinical trials [29].

4.3 Objectives

The main objectives of this work are to describe the characteristics of operated meningiomas in France and to investigate clinical and pathological factors associated with disease progression and overall survival. Firstly, we will assess the epidemiology of operated meningiomas in France using the National Healthcare database and to compare our findings with published results. Secondly, we will investigate clinical and pathological factors associated with cumulative incidence of benign meningioma disease progression or related mortality using a competing risk analysis in the presence of unrelated causes of death based on a single centre retrospective study from the Queen Elizabeth University Hospital, Glasgow, Scotland. Third, we will described the clinical and pathological prognostic factors associated with overall survival of malignant meningioma based on a multicentre cohort study involving 6 centres in France and in the United Kingdom. Finally, we will present a French nationwide study on OS prognostic factors using the "Système National des Données de Santé (SNDS)".

5 Epidemiology of meningiomas

5.1 Introduction



lassical epidemiologic studies seek to acquire data on sufficiently large and representative sample of subjects to provide meaningful, valid and generalisable findings. Most of the time, it implies to implement expensive large cohort studies with a long follow up and dedicated to one particular research question. Since scientific research is often limited in resources, cost-effective alternatives of traditional observational studies have been suggested. Nowadays, in the era of computerisation, most information systems, medical and others, are being set up for digital collection and storage.

5.1.1 Healthcare data

Administrative medical databases (AMDB) are massive repositories of data collected in healthcare for various purposes. Such databases are maintained in hospitals, health maintenance organisations and health insurance organisations. They may contain medical claims for reimbursement, records of health services, medical procedures, prescriptions, and diagnoses information. Such databases provide a variety of already stored data with a constant and often increasing on-going collection process. Due to this data availability, their use in epidemiological research has become increasingly popular [25].

Routinely collected health data, obtained for administrative and clinical purposes without specific a priori research goals, are increasingly used for research in many countries [51]. These databases which present numerous advantage, can be used to conduct epidemiological studies and evaluate medical practices. They encompasses very large

population and often the whole nation, ensuring high statistical power without biases related to the representativity of a sample, thereby allowing more detailed analyses of subgroups. Use of these databases is less expensive than conducting specific surveys in dedicated populations by providing rapid access to data collected in a standardised format [51]. Usefulness of such databases in epidemiological study has been recognised and demonstrated during the past years [25, 15].

Such data not initially collected for research purposes, may be subject to random or systematic errors leading to incorrect definition of populations, exposures or events. However, research involving these databases suffers from the same usual biases which may be broadly classified as either selection or information bias family which occurs due to imperfect data collection and is mainly expressed in misclassification of the exposure, outcome or both [25].

5.1.2 In France

The French health care system is based on universal coverage by one of several health care insurance plans. The Système National d'Information Inter Régimes de l'Assurance Maladie (SNIIRAM) database merges anonymous information of reimbursed claims from all these plans. The SNIIRAM is linked to the national hospital-discharge summaries database (Programme de Médicalisation des Systèmes d'Information (PMSI)) and the national death registry (CépiDc). The PMSI gathered discharge abstracts from all hospitals in France, public and private, including overseas departments. The SNIIRAM that merge anonymously the above-mentioned databases has continued to grow and extend to become the Système National des Données de Santé (SNDS) or national health data system [23].

The 2016 health system modernisation act created the SNDS (http://www.snds.gouv.fr/) which comprises individual information on the sociodemographic and medical characteristics of beneficiaries and all hospital care and office medicine reimbursements. This system covers almost the entire French population and all of their health care expenditure. This database was initially elaborated for the purposes of monitoring and analysis of health care reimbursements. It is continually evolving towards enrichment by medicalised information, as well as simplification of its architecture [51]. Throughout the SNDS and over the years, a patient is identified by the very same pseudonymisation number, regardless the institution to which he or she was admitted. The SNDS includes demographic data, health care encounters such as physician or paramedical visits, medicines, medical devices, lab tests (without results); chronic medical conditions (ICD-10 codes); hospitalisations with ICD-10 codes for primary, linked and associated diagnoses, date and duration, procedures, diagnostic-related groups, and cost coding; date and cause of death [51]. The database representativeness is near perfect, since it essentially includes the whole country's population. It is estimated that the SNDS covers 97.2% of the French population. The SNDS provides a wealth of information from private and public institutions that can be used for public health purposes. Access is granted to researchers after motivated request to the institut national des données de santé - National Institut of Health Data INDS and approval of the French data protection authority (CNIL). France has now an extensive AMDB which has started to issued numerous publica-

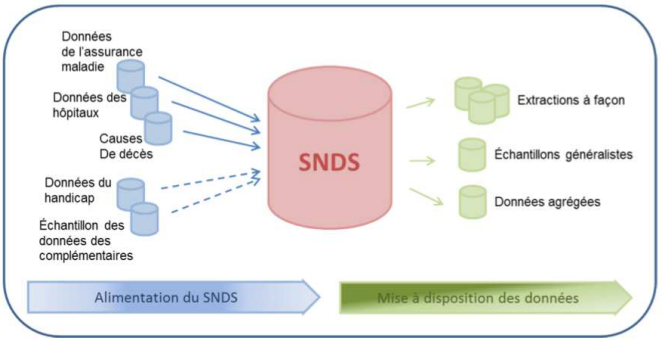


Figure 5 – Schematic representation of the SNDS [3]

[3] https://www.indsante.fr/fr/les-composantes-du-snds

tions. However, use of the SNDS database is uneasy due to its large volume and complex organisation. Thus, analysis of these data requires dedicated skills and necessary training. Dictionaries of variables (http://dico-snds.health-data-hub.fr/; https://documentation-snds.health-data-hub.fr/) are available.

5.2 Methods

5.2.1 Data sources

This observational retrospective cohort study on meningioma was achieved using healthcare data extracted from the SNDS. The extraction was realised by a team of the Caisse National d'Assurance Maladie (CNAM) (Marjorie Boussac, Julius Kemme, and EL Mehdi GABBAS) which hosts and manage the database after dedicated request (https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees). Access to the data extraction is available via a protected website.

5.2.2 Period considered

The SNDS allows only data extraction covering a period of 10 years or less. Incidental meningioma never operated were not considered in this study; only surgically treated meningioma were taken into account.

5.2.3 Identification of the cases

Direct identification of patients who underwent a surgery for meningioma is not possible. Therefore, we used an algorithm combining two variables: 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). This algorithm was transmitted to the extraction team of the CNAM. Patients with a negative survival were excluded likely corresponding to wrong anonymous number.

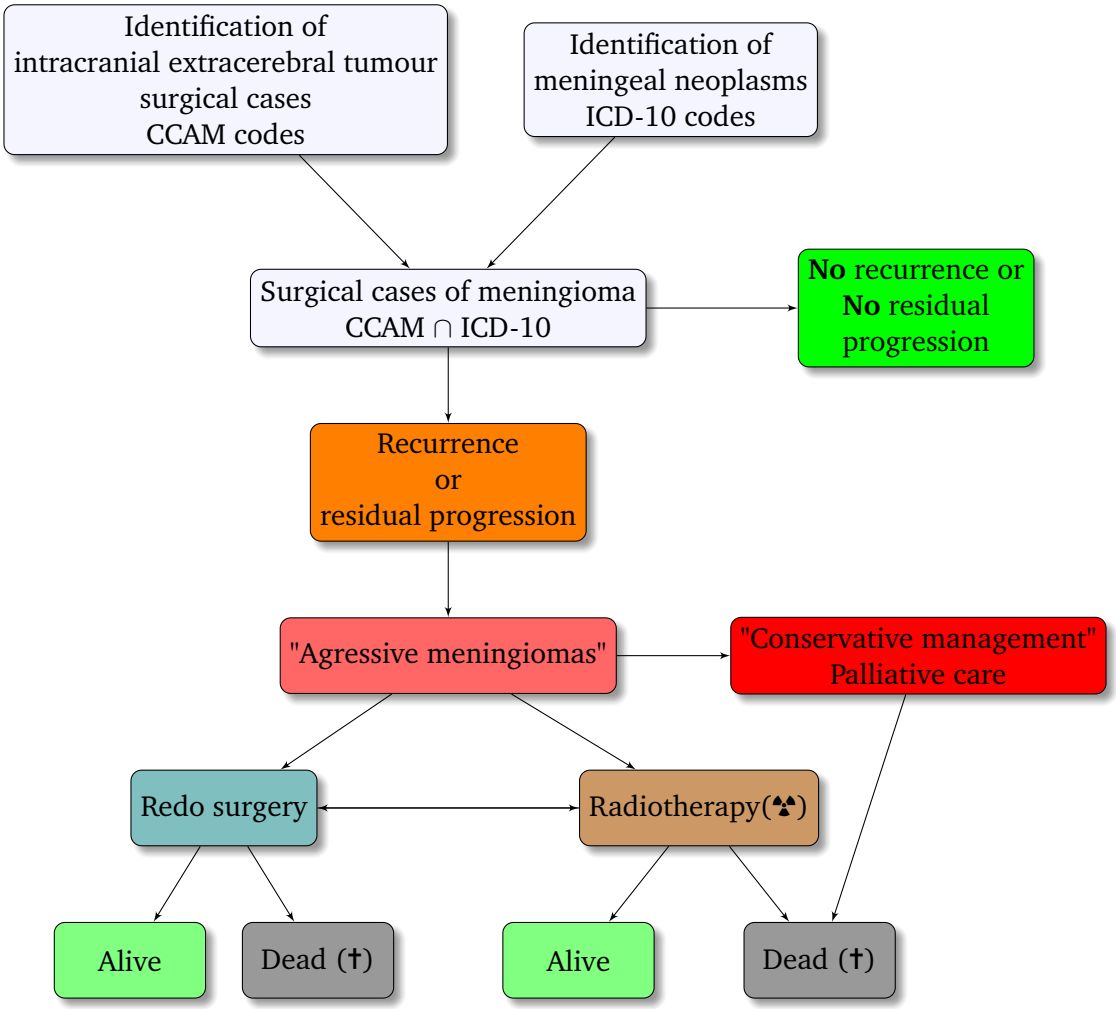


Figure 6 – Diagram of patients' selection and evolution possibilities

5.2.4 Selection of the patients

5.2.5 According to the surgical procedure

The patients who underwent at least one surgical procedure for the resection of an intracranial extracerebral tumour between 2007 and 2017, were included. Such procedures are identified by CCAM codes. The CCAM which aims to describe more precisely medical and surgical procedures on a common basis, both for hospital and

ambulatory care. The CCAM is fully comprehensive as it contains details of each of the 7 200 procedures and services, corresponding to only one label and one code. The full list of the 40 CCAM codes used for the study are given below[4]. However, some of the surgical acts may not correspond to the resection of a meningioma but, to a different type of neoplasm. For example, procedures ACFA005 & ACFA010 are likely performed for a vestibular schwannoma.

The procedures are listed in two sets. The first set includes those which are are usually performed for resection of a meningioma (high probability > 90%). For the others it may also be performed for other histological type of tumours.

- ACFA001: Exérèse de tumeur de l'étage antérieur de la base du crâne, par craniotomie frontale unilatérale
- ACFA002: Exérèse de tumeur extraparenchymateuse de la convexité du cerveau sans atteinte de sinus veineux dural, par craniotomie
- ACFA008: Exérèse de tumeur extraparenchymateuse de la convexité du cervelet sans atteinte de sinus veineux dural, par craniotomie
- ACFA011: Exérèse de tumeur de l'étage moyen de la base du crâne, par craniotomie
- ACFA013: Exérèse de tumeur du tiers interne de l'étage moyen de la base du crâne intéressant l'angle sphéno-orbitaire, par craniotomie
- ACFA015: Exérèse de tumeur de l'étage antérieur de la base du crâne, par craniotomie frontale bilatérale
- ACFA018: Exérèse de tumeur extraparenchymateuse de la convexité du cervelet envahissant un sinus veineux dural, par craniotomie
- ACFA028: Exérèse de tumeur extraparenchymateuse de la convexité du cerveau envahissant un sinus veineux dural, par craniotomie
- ABFA005: Exérèse de lésion d'un ventricule latéral cérébral, par craniotomie
- ABFA008: Exérèse de tumeur de la tente du cervelet, par craniotomie sous tentorielle
- ABFA009: Exérèse de tumeur de l'incisure de la tente, par craniotomie sus tentorielle
- ABFA010: Exérèse de tumeur de la faux du cerveau, par craniotomie

The second list includes the surgical procedures that likely described a meningioma resection as it may also be performed for other histological type of tumours.

- ACFA003: Exérèse de tumeur de la pointe du rocher, par abord translabyrinthique
- ACFA004: Exérèse de tumeur du clivus, par craniotomie

[4] ACFA017 & ACFA021 are deprecated

- ACFA005: Exérèse de tumeur de l'angle pontocérébelleux et/ou du méat acoustique interne [conduit auditif interne], par abord rétrolaby-rinthique présigmoïdien.
- ACFA006: Exérèse de tumeur de la pointe du rocher sans déroutement du nerf facial, par abord transpétreux
- ACFA007: Exérèse de tumeur de l'angle pontocérébelleux et/ou du méat acoustique interne [conduit auditif interne], par abord translabyrinthique
- ACFA009: Exérèse de tumeur de la pointe du rocher, par abord suprapétreux
- ACFA010: Exérèse de tumeur de l'angle pontocérébelleux et/ou du méat acoustique interne [conduit auditif interne], par abord infra-occipital rétrosigmoïdien
- ACFA012: Exérèse de tumeur de l'angle pontocérébelleux et/ou du méat acoustique interne [conduit auditif interne], par abord supra-pétreux
- ACFA014: Exérèse de tumeur de l'angle pontocérébelleux et/ou du méat acoustique interne [conduit auditif interne], par deux abords
- ACFA016: Exérèse de tumeur de la région pétroclivale sans déroute-ment du nerf facial, par abord transpétreux
- ACFA019: Exérèse de tumeur du foramen magnum avec déroutement de l'artère vertébrale, par craniotomie
- ACFA020: Exérèse de tumeur du clivus, par abord transoral ou nasosphénoïdal
- ACFA022: Exérèse de tumeur de la région optochiasmatique et/ou hypothalamique, par craniotomie
- ACFA023: Exérèse de tumeur du foramen jugulaire, par craniotomie
- ACFA024: Exérèse de tumeur du foramen magnum sans déroutement de l'artère vertébrale, par craniotomie
- ACFA025: Exérèse de tumeur de la région pétroclivale avec déroute-ment du nerf facial, par abord transpétreux
- ACFA026: Exérèse de tumeur de l'étage antérieur de la base du crâne, par craniotomie frontale bilatérale et abord ethmoidal
- ACFA027: Exérèse de tumeur de l'angle pontocérébelleux et/ou du méat acoustique interne [conduit auditif interne], par abord transotique
- ACFA029: Exérèse de tumeur de la pointe du rocher avec déroutement du nerf facial, par abord transpétreux
- ABFA002: Exérèse de lésion du troisième ventricule, par craniotomie
- ABFA006: Exérèse de lésion du quatrième ventricule, par craniotomie
- ABFC001: Exérèse de lésion du troisième ventricule, par vidéochirurgie intracrânienne
- ABFC002: Exérèse de lésion d'un ventricule latéral cérébral, par vidéo-chirurgie intracrânienne
- AFFA001: Exérèse de tumeur intradurale extraspinale sans reconstruction vertébrale, par abord antérieur ou antérolatéral
- AFFA005: Exérèse de tumeur épidurale rachidienne avec ostéosynthèse vertébrale, par abord postérieur
- AFFA007: Exérèse de tumeur intradurale extraspinale, par abord posté-rieur ou postérolatéral
- AFFA009: Exérèse de tumeur intradurale extraspinale avec reconstruction vertébrale, par abord antérieur ou antérolatéral
- AFFA010: Exérèse de tumeur épidurale rachidienne, par abord postérieur

Missing date of surgery or redo surgery were imputed using the month and year of hospitalisation date and the delay of surgery. If a patient had several reoperations, only the first one was taken into account.

5.2.5.1 Tumour location

Meningiomas may growth from everywhere there are meningothelial cells, including from inside the ventricle. However, they usually arise from some typical locations such as the cranial convexity. The CCAM enables to know the site of the tumour origin. Some locations *e.g.* petroclival are infrequent, making them unsuitable for statistical analysis. Therefore, a simplified and practical classification of eight categories was designed (table 1) to be use in the statistical analysis.

Table 1 – Category of meningioma location and related CCAM codes

Category number	"Classical" meningioma location	CCAM codes
1	Cranial convexity	ACFA002[1] & ACFA008[2]
2	Parasagittal	ACFA018[2] & ACFA028[1]
3	Falx cerebri	ABFA010
4	Anterior skull base	ACFA001/-15/-26
5	Middle skull base	ACFA011/-13/-22
6	Posterior skull base	ACFA003/-04/-05/-06/-07/-09/-10 -12/-14/-16/-19/-20/-23/-24/-25 -27/-29/ ABFA008/ ABFA009
7	Spine	AFFA001/ AFFA005/ AFFA007 AFFA009/ AFFA010
8	Intraventricular	ABFA002/ ABFA005/ ABFA006 ABFC001/ ABFC002

[1] supratentorial
[2] infratentorial

We can summmarise further these categories into two news ones, intraventricular tumours excluded. Cranial convexity, parasagittal and falx cerebri locations are merged

into a new broader "convexity" class and, anterior, middle, posterior skull base and spine into the "skull base" class.

- Locations
  - "**Convexity**"
    1. cranial convexity
    2. parasagittal
    3. falx cerebri
  - "**Skull base**"
    4. anterior skull base
    5. middle skull base
    6. posterior skull base
    (7. spine)

A MRI example of some category given above is provided in the figure below 7.

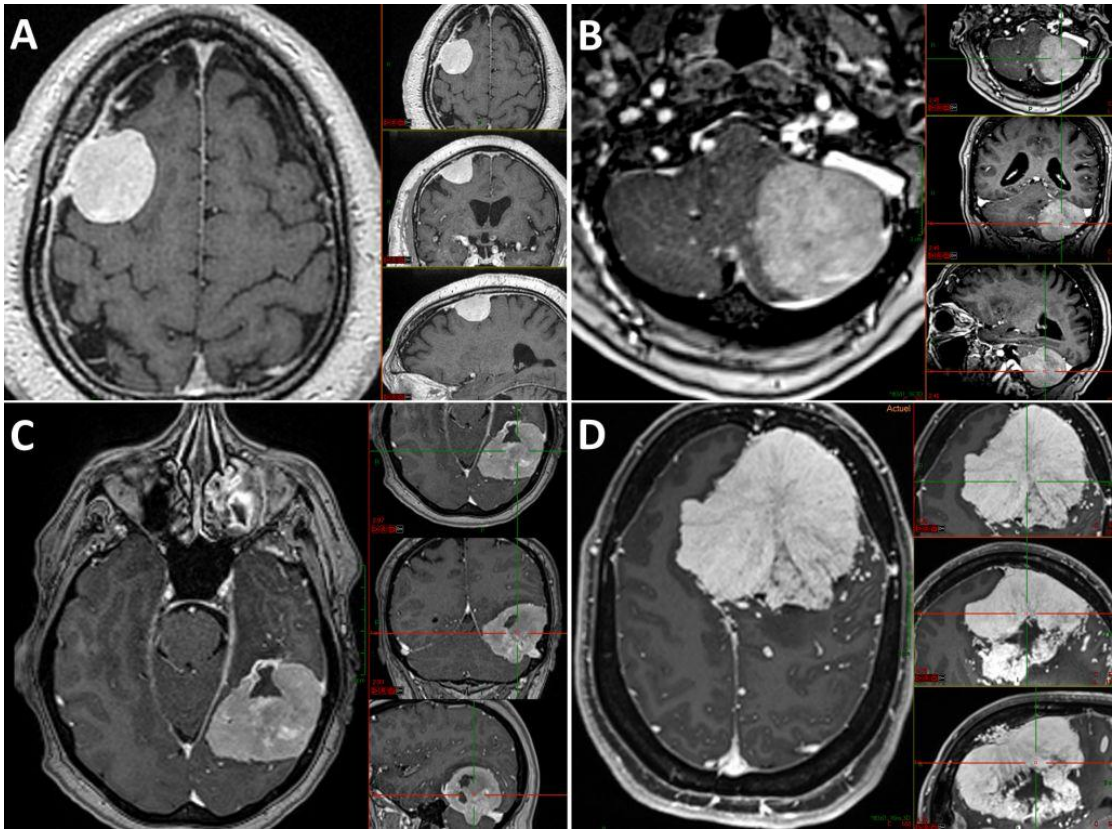


Figure 7 – MRI images of 4 meningioma locations. A: supratentorial convexity (ACFA002) B: infratentorial/cerebellar convexity (ACFA008), 1C: tentorium cerebelli (ABFA008), 1D: parasagittal/ falx cerebri (ACFA028/ABFA010)

5.2.6 According to the International Classification of Diseases

According to the International Classification of Diseases (ICD-10), neoplasm of meninges or meningioma are identified by dedicated codes:(http://apps.who.int/classifications/icd10/browse/2010/en). WHO grade I (benign) meningiomas were considered as corresponding to the D32, grade II (atypical) to D42 and grade III (malignant) to C70.

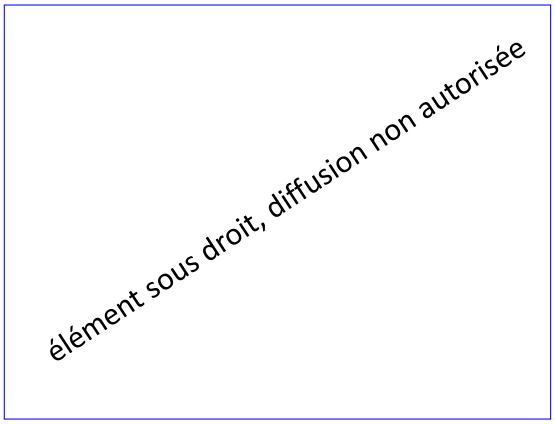
- D32: **Benign** neoplasm of meninges ≅ WHO grade I
- D42: Neoplasm of **uncertain or unknown behaviour** of meninges ≅ WHO grade II
- C70: **Malignant** neoplasm of the meninges ≅ WHO grade III

In the ICD-10, the last digit placed after the dot refers to the anatomical location, (*e.g.* D32.1 means benign neoplasm of **spinal** meninges).

- XXX.0: Cerebral meninges
- XXX.1: Spinal meninges
- XXX.9: Meninges, unspecified

Obest plerumque iis qui discere
volunt auctoritas eorum qui docent.

Michel Eyquem de Montaigne, Essais, livre I, chapitre 26



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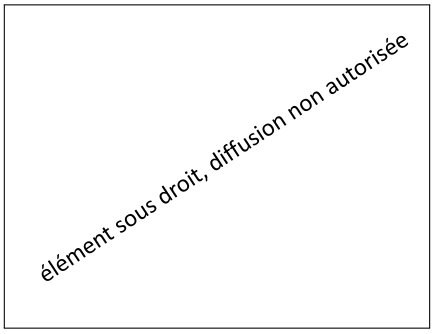
5.4 Conclusion

The reported incidence of all grades of meningioma has varied substantially over time and by the method of meningioma identification, from 1 to 8.4 per 100 000. The PMSI database is a reliable and effective source for studying the epidemiology of surgically treated meningiomas, including the precise location of the tumour. Our findings comfort previous studies and are comparatively correlated. This may assert the usefulness of such a database to investigate the patients' outcome after meningioma surgery.

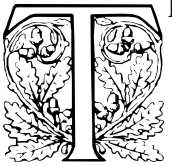
Das Leben ohne Musik ist einfach ein Irrtum, eine Strapaze, ein Exil.

Friedrich Wilhelm Nietzsche



6 Benign meningioma

6.1 Introduction



he majority of meningiomas are benign. With more uniform adoption of the current WHO 2016 standards, approximately 80% to 90% are grade I. Benign or WHO grade I meningiomas occur most often in women and are associated with a relatively good prognosis [54].

Competing risk analysis refers to a special type of survival analysis that aims to correctly estimate marginal probability of an event in the presence of competing events. Traditional methods to describe survival process, such Kaplan Meier product-limit method, are not designed to accommodate the competing nature of multiple causes to the same event, therefore they tend to produce inaccurate estimates when analysing the marginal probability for cause-specific events. As an work-around, Cumulative Incidence Function (CIF) was proposed to solve this particular issue by estimating the marginal probability of a certain event as a function of its cause-specific probability and overall survival probability. This method hybridizes the idea of product-limit approach and the idea of competing causal pathways, which provides a more interpretable estimate for the survival experience of multiple competing events for a group of subjects [30]. Like many analyses, the competing risk analysis includes a non-parametric method which involves the use of a modified Chi-squared test to compare CIF curves between groups, and a semi-parametric approach which model the CIF based on a subdistribution hazard function [24].

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6.3 Conclusion

Patients with WHO Grade I meningioma have lengthy survival expectations, and hence long-term studies are required to understand the risks of progression and death. Benign meningioma treatment failure correlated with venous sinus invasion, incomplete resection, and progressing tumour; shorter survival correlated with increased age and redo surgery for recurrence.

In standard survival data, subjects are supposed to experience only one type of event over follow-up, on the contrary to real life where subjects can potentially experience different events. As a result, we call the probability of these events as "competing risks", in a sense that the probability of each competing event is somehow regulated by the other competing events. Up to date, the most popular alternative approach to analyse competing event data is called the Cumulative Incidence Function (CIF), which estimates the marginal probability for each competing event.

We recommend the cumulative incidence competing risk approach in benign meningioma studies where unrelated mortality may be substantial, as this approach results in more accurate estimates of disease risk and associated predictors. Grade I tumour that can be totally resected should be followed by observation. A totally resected benign tumour is very unlikely to recur after 5 years but, if excision is incomplete, late regrowth or slow progression of residual tumour may be missed if follow-up is not long enough.

In the SNDS, available causes of death are currently available for the years 2013 to 2015. For these years, a study investigating factors associated with cumulative incidence of meningioma disease progression or related mortality using CR analysis in the presence of unrelated causes of death using the French National Healthcare database is under writing.

7 Malignant meningioma

7.1 Introduction

Historically, malignant meningiomas have been defined by the WHO based on histologic characteristics. As early as 1979, the WHO offered preliminary criteria that distinguished Grade II and Grade III meningiomas from their benign counterparts by specifying that these higher grade meningiomas displayed anaplastic features. The behaviour and outcome of WHO Grade II meningiomas also called atypical are intermediate as they show a greater tendency to recur compared to grade I [13, 14, 11]. They are histologically characterized by increased mitotic activity of 4 or more mitoses per 10 HPFs and/or three or more of the following features: increased cellularity, small cells with high nuclear to cytoplasm ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth, and foci of spontaneous or geographic necrosis. WHO grade III also named malignant meningiomas are associated with aggressive growth patterns reflecting their clinical and histopathological features of malignancy and can even spread by metastatic dissemination [20, 18]. Their very low incidence of less than 5 cases for 1 000 000 persons per year, *i. e.* 1% to 3% of all meningiomas, make it difficult to study their behaviour [22]. Consequently, with such rarity, firm conclusions regarding optimal treatment are problematic. Malignant meningioma is a highly aggressive and often fatal variant that may be encountered in patients either de novo or from the malignant progression of lower grade meningiomas of any subtype. They have a poor prognosis with reported five-year survival rates of 28 - 61 % [31, 20]. Histologically, it is defined by overt cellular anaplasia and/or excessive mitotic activity of 20 mitoses or more per 10 high-power fields (HPF).

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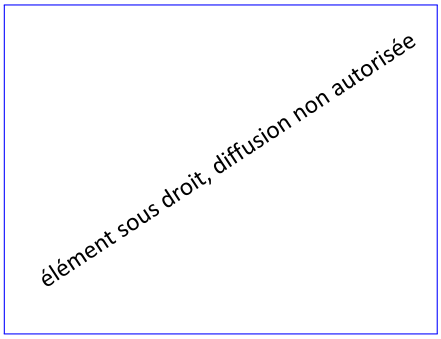
7.3 Conclusion

Malignant meningiomas remain a rare clinical entity that is relatively poorly understood and very difficult to treat. Indeed, the scarcity of these lesions makes their study problematic; not only have extremely few prospective studies been undertaken, but even established retrospective studies are marked by small sample sizes. Malignant meningiomas are aggressive tumours with considerably poorer local control and overall survival than lower grade meningioma with median overall survival has been less than 2 to 3 years. There is little discrepancy in recommendations for aggressive treatment, typically including surgery and radiation therapy. This large series confirms the poor prognosis associated with MM, the treatment of which remains challenging. Patients under 65-yr-old with primary MM may live longer after complete resection and post-operative radiotherapy. Even with aggressive management, local control remains difficult to achieve, and metastasis, although uncommon, can occur. Improved treatment paradigms are needed.

Everything changes and nothing stands still.

Heraclitus of Ephesus



8 Nationwide study on overall survival

The focus of this study is on large symptomatic meningiomas that undergo surgery. Indeed the grade of an incidental, observed untreated meningioma is unknown, and its natural history may differ considerably from the larger, symptomatic tumours selected for definitive treatment. The existence of a French nationwide healthcare database offered us the opportunity to study globally what is usually done locally. To date, such a research on meningiomas outcome has never been achieved in France. The main surgical act of meningioma removal such as ACFA002, may be associated to others such as those described below.

8.1 Acts associated to the main surgery

8.1.1 Embolisation

The main surgical act of meningioma removal such as ACFA002, may be associated to other such as a preoperative endovascular treatment. An example of such procedure of embolisation is displayed below on figure 4.

- EASF002: Occlusion intraluminale d'un vaisseau intracrânien afférent à une tumeur, par voie vasculaire transcutanée
- EASF003: Occlusion intraluminale de plusieurs vaisseaux intracrâniens afférents à une tumeur, par voie vasculaire transcutanée
- EASF012: Occlusion intraluminale d'un vaisseau intracrânien, par voie vasculaire transcutanée
- EASF014: Embolisation sélective ou hypersélective unilatérale ou bilatérale de branche de l'artère carotide interne, par voie artérielle transcutanée
- EBSF003: Embolisation sélective ou hypersélective unilatérale ou bilatérale de branche de l'artère carotide externe, par voie artérielle transcutanée

- EBSF004: Embolisation suprasélective unilatérale ou bilatérale de branche de l'artère carotide externe, par voie artérielle transcutanée

8.1.2 Neuronavigation

Despite a deep neuroanatomical knowledge being the best neuronavigator, more and more neurosurgeons employ intraoperative technological adjuncts. Neuronavigation may be useful for deep-seated lesions or to delinate sclap incision and tailored bone flat cutting of lesion of the convexity.

- ACQP002: Repérage de structure nerveuse et/ou osseuse et guidage peropératoires assistés par ordinateur [Navigation]

8.1.3 Duraplasty

Usually, resection of an meningioma involved the removal of its dura mater insertion. In these case, a reconstruction of the dura mater (duraplasty) is best achieved with surrounded pediculated pericranium or synthetic material. An pictural example of such procedure of duraplasty with epicranium is shown below on figure 8.

- AGMA001: Réparation de perte de substance durale de plus de 10 cm^2 par greffe ou substitut, au cours d'une intervention intracrânienne ou intrarachidienne.

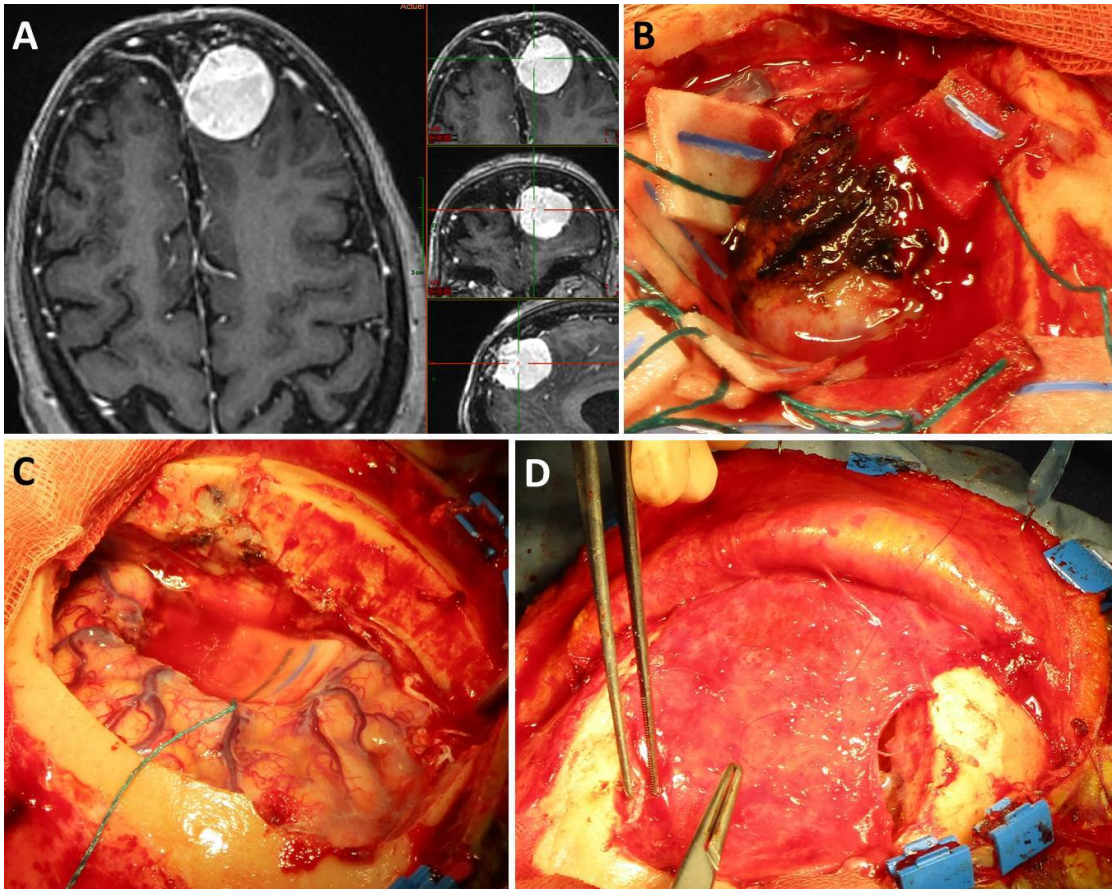


Figure 8 – Removal of a left parasagittal meningioma followed by a pediculated pericranium duraplasty. A: MRI of the tumour, B: surgical view of the tumour, after tumour resection (C) and of the duraplasty (D).

As a duraplasty is most likely achieved after complete removal of the tumour, *id est* after its dura mater meningeal insertion removal.

8.1.4 Cranioplasty

- LAMA009: Cranioplastie de la voûte

8.1.5 Cerebro spinal fluid shunt

- ABCA002: Dérivation péritonéale ou atriale du liquide cérébrospinal ventriculaire, par abord direct

8.1.6 According to radiotherapy

As for surgery, the patients who underwent RT can be identified by dedicated CCAM acts. Each acts refer to a specific type of EBRT or technic or to a given dose measured in gray (Gy). The gray is defined as the absorption of one joule of radiation energy per kilogram of matter: $1\mathrm{Gy} = 1\frac{\mathrm{J}}{\mathrm{kg}} = 1\frac{\mathrm{m}^2}{\mathrm{s}^2}$. For RT, there are hundreds of CCAM codes which are summarised below.

- ZZMK001/ 002/ 011/ 013/ 014/ 016/ 017/ 018/ 019/ 020/ 022/ 024/ 025/ 026/ 027/ 028 (préparation à une irradiation externe...)
- ZZMK019/ 020/ 022/ 025/ 027/ (reprise de préparation à une irradiation externe...)
- AGMP001 (préparation à une irradiation externe du névraxe [irradiation craniospinale])
- ZZMP012 (préparation à une irradiation intracrânienne en conditions stéréotaxiques en dose unique, avec pose de cadre effractif)
- ZZMP016 (...)
- ZZNL0.. (séances d'irradiation externe...)
- ZANL001 (...)
- AZNL001 (séances d'irradiation externe du névraxe [irradiation craniospinale])

As for the surgical procedures, certain of these codes are most likely involved in meningioma irradiation. Stereotaxy is a localisation method of intracranial tumours in which a three-dimensional coordinate system is used often based on a reference framed fixed on the patient head. RT involving stereotaxy erroneously named Stereotactic RadioSurgery (SRS) applies the methodology of stereotaxy to EBRT. SRS is defined as the targeted delivery of an ionizing radiation dose using stereotactic localisation. Traditionally this is carried out in a single session but revised definition of SRS includes both traditional single dose as well as multi-session SRS up to 5 fractions (2-5 doses). There are 7 CCAM codes describing SRS.

- ZZMP012: préparation à une irradiation intracrânienne en conditions stéréotaxiques en dose unique, avec pose de cadre effractif.
- ZZMP016: préparation à une irradiation externe en conditions stéréotaxiques...
- ZZNL058: séance d'irradiation externe en conditions stéréotaxiques...
- ZZNL059: séance d'irradiation externe en conditions stéréotaxiques par machine dédiée...

- ZANL001: irradiation externe intracrânienne en conditions stéréotaxiques avec cadre effractif, en dose unique
- ZZNL049: irradiation externe en conditions stéréotaxiques par machine...
- ZZNL055: irradiation externe en conditions stéréotaxiques par machine dédiée...

Analysis of the RT was quite complexe as involving hundreds of labels. Furthermore, following Dr Christine Piedbois-Levy advice, expert radiotherapist in neuro-oncology, all RT acts involving a field of 300 cm^2 or more were excluded as not corresponding to an intracranial RT.

8.1.7 Outcomes

Because death is the most untoward event, the main outcome of interest of our study is the survival (OS) of the patients. OS was defined as the length of time between the first surgery for meningioma and the death of the patient regardless the cause or its last follow-up for alive patient.

8.1.8 Statistical methods

Central tendencies were presented as means $\pm$ SD, or median and interquartile range if skewed. Overall survival (OS) was measured from the date at meningioma first surgery to the date of last follow-up or death [32]. We used a time-to-event framework with Kaplan–Meier method to estimate OS and the Mantel Cox log-rank test to compare survival curves. We censored records at the end of a participant's registration, the last date of SNDS data collection, or death. Survival functions were assessed by the Kaplan-Meier method and, the Mantel Cox log-rank test was used to compare different survival functions according to clinical and therapeutic factors. A univariable Cox regression was subsequently run on clinical and pathological criteria to estimate mortality hazard ratios (HRs). Independent prognostic factors with a p-value <0.20 were assessed using a multivariable Cox model. A complete cases analyse was performed. A

p-value <0.05 was considered as statistically significant. Analyses were performed with the R programming language and software environment for statistical computing and graphics (R version 3.6.3 (2020-02-29)). Dedicated package were used when necessary [41, 50].

The statistical program and workflow was written in LaTeXwith Miktex and RStudio® for dynamic and reproducible research [43].

This study was be conducted according to the ethical guidelines for epidemiological research in accordance with the ethical standards of the Helsinki Declaration (2008) and the French data protection authority (CNIL), authorisation number: 2008538.

The REporting of studies Conducted using Observational Routinely-collec-ted health Data (RECORD) statement, an extensions of STROBE, was followed to ensure best research practices [6, 38].

Meningioma: a nationwide study on overall survival.

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Abbreviations list

AMDB: Administrative medical databases

CCAM: Classification Commune des Actes Médicaux

CI: Confidence Interval

CNS: Central Nervous System

GTR: Gross Total Resection

ICD: International Classification of Diseases

IQR: Interquartile Range

HR: Hazard Ratio

SNDS: Système National des Données de Santé

WHO: World Health Organization

Abstract

Background

There are very few nationwide studies on meningioma outcome, the most common primary intracranial tumour.

Methods

We processed the French Système National des Données de Santé (SNDS) database using an algorithm combining the type of surgical procedure and the International Classification of Diseases to retrieve all cases of meningiomas operated between 2007 and 2017. A survival analysis was performed.

Results

This nationwide study found 28 891 patients of which 75.4% were female. Median age at surgery was 59 years, IQR[49 - 68]. Cranial convexity (24.4%) and middle skull base (21.7%) were the most common locations. 91.2% of the tumours were benign and 2.7% malignant. 7.6% of the patients underwent redo surgery, 9.2% radiotherapy (RT) and 3.2% stereotactic radiosurgery (SRS) for recurrence. Median follow-up was 4.9 years, IQR[2.5 - 7.6]. At data collection, 8.3% were dead. 191 patients died within a month of surgery and 623 within a year. Overall survival (OS) rates at 5 years was: 92.6%, 95%CI[92.2, 92.9].

In the multivariable analysis, gender (HR= 0.6, 95%CI[0.55, 0.65], p <0.001), age at surgery (HR= 1.07, 95%CI[1.07, 1.07], p <0.001), type 2 neurofibromatosis (HR= 4.18, 95%CI[2.88, 6.07], p <0.001), parasagittal (HR= 1.18, 95%CI[1.03, 1.35], p= 0.017) or falx cerebri location (HR= 1.18, 95%CI[1.02, 1.37], p= 0.031), atypical or (HR= 1.32, 95%CI[1.14, 1.54], p <0.001) malignant (HR= 2.97, 95%CI[2.56, 3.45], p <0.001), redo surgery (HR= 2, 95%CI[1.79, 2.24], p <0.001) or RT for recurrence (HR= 2.14, 95%CI[1.93, 2.37], p <0.001) were established as independent prognostic factors of the OS.

Conclusion

Using this unique database, we found that outcome after meningioma surgery is better in women, younger adults, and patients with convexity and benign tumour.

Keywords: Meningioma; Outcome; Database; SNDS; Survival

INTRODUCTION

Meningiomas are a group of mostly non-malignant, slow-growing neoplasms thought to arise from the meningothelial cells of the arachnoid layer. They are the most common intracranial extracerebral tumours accounting for 36.8% in the CBTRUS [22]. The 2016 World Health Organization (WHO) classification of tumours affecting the central nervous system (CNS) recognises three grades of meningiomas[18]. WHO grade I or benign meningiomas occur for two-thirds in women and have usually a good outcome [8, 35]. malignant or malignant are rare and aggressive neoplasms with a poor prognosis [7, 9]. Behaviour and outcome of atypical - WHO grade II meningiomas, are intermediate [4, 5]. Management options include regular monitoring especially for incidental meningioma, symptom control, surgical excision, radiotherapy (RT), and stereotactic radiosurgery (SRS). Complete surgical resection is the treatment of choice for all meningiomas. Further optimal management is difficult to establish; the role of post-operative RT as standard adjuvant treatment remaining controversial apart for malignant [4, 5, 9].

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. Such databases provide a variety of already stored data with a constant and often increasing on-going collection process [11]. They encompasses very large population and often 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 [31].

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 [31]. The database representativeness is nearly perfect, since it includes the whole country's population. It is continually evolving towards enrichment by medicalised information, as well as simplification of its architecture [31]. To date, such a research has never been achieved in France where around 3 000 patients are operated on for a meningioma each year.

OBJECTIVE

The aim of this study was to investigate overall survival (OS) of patients operated on for a meningioma and search for associated factors using the French National Healthcare (SNDS) database.

MATERIAL AND METHODS

We performed a nationwide descriptive observational and analytic retrospective study. Incidental meningioma 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. All patients who underwent the surgical resection of a meningeal tumour between 2007 and 2017 were included. Direct identification of patients who underwent a surgery for meningioma is not possible. Therefore, we used an algorithm combining two variables: 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 decribed previously [8]. Meningioma were categorised into 8 anatomical locations acccording their dural base insertion after further categorisation of the 40 CCAM codes which aimed at described intracranial extracerebral tumour resection. Benign meningiomas were considered as corresponding to the D32 ICD-10 codes, atypical to D42 and malignant to C70.

Statistical methods

Continuous variables are reported as means and standard deviations or as medians and interquartile ranges (IQR); categorical variables are reported as frequencies and proportions. Overall survival (OS) was measured from the date at meningioma first surgery to the date of last follow-up or death [12]. We used the Kaplan–Meier method to estimate the OS and the Mantel Cox log-rank test was used to compare survival curves. Cox proportional hazards regression was implemented to identify predictors of death and, to estimate Hazard Ratio (HR) with 95% Confidence Intervals (95% CI) [29]. 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 the R programming language and software environment for statistical computing and graphics (R version 3.6.3 (2020-02-29)) and the survival package among others [24, 30]. The statistical programme and workflow was written in R Markdown v2 with RStudio® for dynamic and reproducible research [25].

Compliance with ethical standards

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 [16, 21]. Informed consent was not required due to the retrospective nature of the study.

RESULTS

Population description

A total number of 28 891 meningiomas were surgically treated over a 10-year period (table. 1). As expected, meningioma surgery was 3 times more common in women than men (75.4% *vs.* 24.6%). Median age at surgery was 59 years IQR[49 - 68] and 0.41% were under 18 years. Most of the patients were in the seventh decade of age 25.4. 184 patients had an associated diagnosis of type 2 neurofibromatosis. Cranial convexity was the most common (24.4%) location followed by middle skull base (21.7%) (sphenoïd wing). Spinal tumours accounted for 9.8%. Benign meningioma represent 91.2%, atypical 6.1% and malignant 2.7% (table 1). These patients had a significant number of associated procedure such as CSF shunt insertion for 1.9 or cranioplasty in 6.2.

Overall survival

At data collection, 2 388 patients were dead (8.3%). The median age at death was 73.1 years, IQR [63.7 - 80.9] considering the whole cohort and was significantly lower for NF2 patients with a median age at death of 41 years, IQR [32.2 - 50]. 191 patients died within a month of surgery and 623 within a year. OS rates at 5 years was: 92.6%, $_{95\%}$CI[92.2 - 92.9] (fig. 1A).

In the multivariable analysis, gender, (HR= 0.6, 95%CI[0.55, 0.65], p <0.001), age at surgery (HR= 1.07, 95%CI[1.07, 1.07], p <0.001), type 2 neurofibromatosis (HR= 4.18, 95%CI[2.88, 6.07], p <0.001), parasagittal (HR= 1.18, 95%CI[1.03, 1.35], p= 0.017) or falx cerebri location (HR= 1.18, 95%CI[1.02, 1.37], p= 0.031), atypical or (HR= 1.32, 95%CI[1.14, 1.54], p <0.001) malignant (HR= 2.97, 95%CI[2.56, 3.45], p <0.001), redo surgery (HR= 2, 95%CI[1.79, 2.24], p <0.001) or radiotherapy for recurrence (HR= 2.14, 95%CI[1.93, 2.37], p <0.001) were established as independent prognostic factors of the OS (table 2 & 3 and figures 1 & 2). OS after surgery is better in women, younger adults, and patients with convexity and benign meningioma. Treatment of recurrence failed to improve the survival.

DISCUSSION

Studies relying on AMDB are useful for evaluating treatment strategies as they offer another insight compared to results of selected retrospective data. AMDB allow inclusion of large patients' groups that may be ineligible for trials due to older age and comorbidities. Studies bases on AMDB are made of what is available in themselves, sometimes limiting the potential to explore interesting associations. However, for variables included, it is possible to collect large amounts of data in a population-based setting. In contrast to malignant neoplasms, outcome data on benign tumours such as meningioma are scarce as they are logically not considered as "cancer" and thus, rarely registered. Also, this kind of research is valuable in the field of neurosurgery where significant variations in clinical practices exist. Up-to-date and detailed population-based data on outcome after meningioma surgery is sparse; most studies reporting on hospital cohorts or on selected samples. Reported nationwide studies on outcome after surgery for meningioma are summarised in the table 4.

Strengths and 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 SNDS which covers 97.2% of the French population *i.e.* around 68 millions inhabitants constitutes one of the largest AMDB in the world [31]. Compiled from a number of institutions, its accuracy is limited by inconstancies in data collection and recording. Moreover, important variables are missing such as the quality of resection [28]. Despite some limitations, the SNDS is an invaluable tool to assess meningioma outcome. It offers an uncomparable mean to explore associations with other pathology, medication or combine surgical treatment which has and could not be assessed before. The retrospective nature of this study, together with the lack of clarity regarding treatment rationales and non-homogenous management strategies without random assignment, needs to be considered when evaluating the results.

Post-operative mortality

Very few studies assessed the peri-operative time. Corell *et al.* found a post-operative 30-day mortality of 1.5% *vs.* 0.66% in our study. Meling *et al.* observed a 30-day mortality of 1.9% and its significant reduction as well as of neurologic morbidity over the time [20].

Overall Survival

Despite having a mostly indolent behaviour, outcome of patients treated for meningioma may occasionally be poor. Only a few studies have reported nationwide or large cohort meningioma OS. Five-year ranges from 83% to 95.8% in previous studies *vs.* 92.6% in our cohort [13, 14, 20, 22, 27, 33]. Brodbelt *et al.* & Meling *et al.* observed that OS outcomes for surgically treated patients have increased over the time [3, 20].

Factors affecting the survival

Our results show that OS is influenced by factors such as gender, age at surgery, or grade [19, 27]. Surprisingly, Corell *et al.* observe that symptomatic patients before the intervention had a worse OS. Unsurprisingly, asymptomatic patients were younger and presented with smaller tumours than the symptomatic group [10].

Gender

Gender was associated to OS. Males had an increased risk of death compared with females in most nationwide studies on the subject with a HR of 1.44 $_{95\%}$CI[1.37-1.52] for Yang *et al.* [34]. Improved survival of females has already been described for many tumours and has been attributed to fewer comorbidities and higher clinical performance [33].

Age at surgery

Without surprise, OS after meningioma surgery is better for younger adults [3, 33]. For Brodbelt *et al.* there was a significant reduction in 5-year net survival over the age of 69 years, to less than 83% in men and 87% in women. This means that 27% of men age 70 to 79 years who had surgery for a cranial meningioma died within 5 years over and above what would be expected for their age, and hence may be attributable to their meningioma, treatment, or complications thereof [3].

Neurofibromatosis

Neurofibromatosis type 2 is an autosomal-dominant multiple neoplasia syndrome that results from mutations in the NF2 tumour suppressor gene located on chromosome 22q. It has a frequency of one in 25 000 livebirths and nearly 100% penetrance by 60 years of age. Patients are predisposed to development of lesions of the CNS. Intracranial meningiomas are present in 45-58% of patients and spinal meningiomas are present in about 20% [1]. Intracranial meningiomas are frequently multiple and they develop at a younger age. NF2

patients have a significant reduce life expectancy with a median age at death of 41 years, IQR [32.2 - 50] in our study.

Grading

Impaired survival of benign meningioma has been reported with relative survival ranging from 79.5% in Eastern Europe to 93.4% in Northern Europe [10, 13, 33]. In a previous study solely dedicated to benign meningioma, we found a risk of recurrence or meningioma-related death at 5 years of 16.2%, $_{95\%}$CI[12.5 - 20] and a 5-year OS of 86.1% $_{95\%}$CI[82.8 - 89.6] [6]. For atypical meningioma, 5-year OS spans from 75.9% to 93.6%, encompassing our result of 90.6% [26, 33]. Our proportions of benign (91.2%), atypical (6.1%) and malignant (2.7%) are close to those of Kshettry *et al.*: 94.6%, 4.2%, 1.2% & Meling *et al.*: 92.5%, 5.3%, 2.2% [15, 20]. Although atypical meningiomas have traditionally been recognised in only about 5%, after changes in diagnostic criteria with the 2007 and 2016 WHO CNS classifications, their incidence has increased [3, 18, 32]. For Zouaoui *et al.*, of 13 038 newly diagnosed and histologically confirmed meningiomas in France between 2006-2010, rate of atypical was 8.5% *id est* slightly higher (+ 2.4%) compared to our findings[35].

Location

One of the advantages of the SNDS which uses the CCAM classification is to provide precise location of the dural insertion, an invaluable feature. The majority of meningiomas are situated intracranially (~ 90%) and convexity is the most common location with one fourth (24.4%) of the tumours. By definition, parasagittal and meningioma of the falx invade or reach at least one wall of the superior sagittal sinus (SSS). Because of their location close to the SSS, associated bridging veins and frequent closeness to eloquent areas, radical surgery without permanent deficits may be difficult to achieve. On contrary to its last two thirds, the frontal part of the SSS can usually be removed with minimal complication. Since the seminal

publication of Donald Simpson in 1957, there is general agreement about the importance of completeness of resection which is the most powerful predictor of recurrence and survival [6, 28]. A complete resection is usually achievable when the tumour is located on the convexity. It is likely more difficult for tumours infiltrating surrounding neural and vascular structures. As such, parasagittal and meningioma of the falx are associated with an increase risk of recurrence and thus a reduce survival. In addition, skull-base tumour such as cavernous or petroclival meningiomas and those with bone invasion are less likely completely resected. For Pettersson *et al.* total recurrence rate of parasagittal meningioma was 47% after 25 years and non-radical treatment correlated with recurrence, increased morbidity and tumour-related mortality [23]. Despite being not available in the SNDS, completeness of resection may be approximate from its dural implantation: likely complete for meningioma of the convexity but not for parasagittal meningioma. Gross total resection (GTR) *id est* Simpson grade I, II or III resection, was achieved in 96.7% for convexity tumour [17]. 9.8% of the meningiomas were removed out of the spine *vs.* 7.7% for Brodbelt *et al.*. In our study, spinal meningioma failed from short to be associated with an increase survival (HR= 0.86, $_{95\%}$CI[0.74, 1.01], p= 0.0584) as found by Brodbelt *et al.* where patients with spinal meningiomas did better in all grades, gender and ages.

Treatment of recurrence

Despite a generally indolent biological behaviour, the outcome of patients treated for meningioma may occasionally be poor and in this study, the patients who needed reoperation or RT for recurrence or residual progression, did not demonstrated improve survival. On the contrary, the patients who need redo surgery for recurrence had an impaired survival by nearly two times. Once the tumour relapse, cure is even more unlikely. However, many confounding factors or statistical interactions such as the grade and the lack of treatment indication needs to be considered when evaluating the results. It is likely that patients who

received RT had a worse prognosis at the time of diagnosis considering other factors and consequently, also had a worse survival rate. However, for Rydzewski *et al.* GTR and adjuvant RT are highly associated with improved survival, especially for the 11.1% of patients with atypical meningioma.

Perspectives

In 2017, the first accesses to the SNDS were granted and since, causes of death are progressively integrated to the database. Once fully available, interpretation of OS of patients with meningioma confounded by deaths from other causes may be addressed. In a study examining time to death attributable to meningioma, unrelated deaths such as those due to cancer (e.g. lung) or cardiovascular disease are competing risks (CR) [6]. Thus, by eliminating the effect of competing causes of mortality, we may assess the cause-specific or the relative survival which is defined as the ratio of the observed survival in the patient group and the expected survival in a sex- and age-matched disease-free population [2, 33]. Age and grade have been constantly reported as uppermost predictors of outcome. Therefore, a dedicate age-stratified analysis by grade may be a rational option to further explore predictors of the outcome of patients.

CONCLUSION

Despite its lack of resection assessment, using this unique database, we found that outcome after meningioma surgery is better in women, younger adults, and patients with convexity and benign tumour.

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Conflict of interest

None. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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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.

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Table captions

Table 1. Characteristics of the patients

Table 2. Univariable Cox regression for meningioma overall survival

Table 3. Multivariable Cox regression for meningioma overall survival

Table 4. Literature review of AMDB nationwide studies on meningioma

Figure captions

Figure 1. Kaplan-Meier OS curves comparison (1/2)

Figure 2. Kaplan-Meier OS curves comparison (2/2)

Figure 1

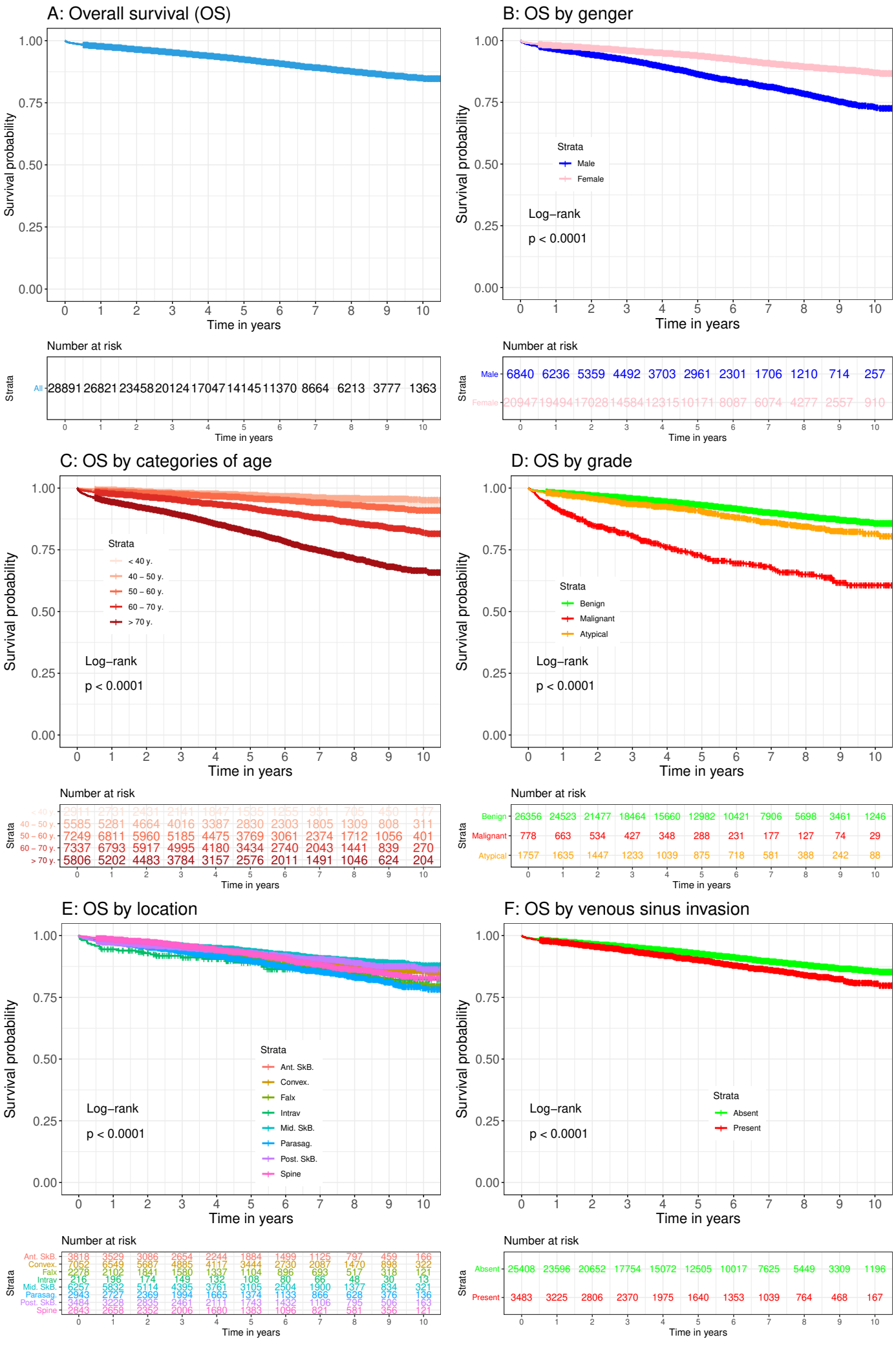

A: Overall survival (OS)
Survival probability
Time in years
Number at risk
All 28891 26821 23458 20124 17047 14145 11370 8664 6213 3777 1363
B: OS by genger
Strata
Male
Female
Log−rank
p < 0.0001
Male 6840 6236 5359 4492 3703 2961 2301 1706 1210 714 257
Female 20947 19494 17028 14584 12315 10171 8087 6074 4277 2557 910
C: OS by categories of age
< 40 y.
40 – 50 y.
50 – 60 y.
60 – 70 y.
> 70 y.
40 – 50 y. 5585 5281 4664 4016 3387 2830 2303 1805 1309 808 311
50 – 60 y. 7249 6811 5960 5185 4475 3769 3061 2374 1712 1056 401
60 – 70 y. 7337 6793 5917 4995 4180 3434 2740 2043 1441 839 270
> 70 y. 5806 5202 4483 3784 3157 2576 2011 1491 1046 624 204
D: OS by grade
Benign
Malignant
Atypical
Benign 26356 24523 21477 18464 15660 12982 10421 7906 5698 3461 1246
Malignant 778 663 534 427 348 288 231 177 127 74 29
Atypical 1757 1635 1447 1233 1039 875 718 581 388 242 88
E: OS by location
Ant. SkB.
Convex.
Falx
Intrav
Mid. SkB.
Parasag.
Post. SkB.
Spine
Ant. SkB. 3818 3529 3086 2654 2244 1884 1499 1125 797 459 166
Convex. 7052 6549 5687 4885 4117 3444 2730 2087 1470 898 322
Falx 2278 2102 1841 1580 1337 1104 896 693 517 318 121
Intrav 216 195 174 149 132 108 80 66 48 30 13
Mid. SkB. 6257 5832 5114 4395 3761 3105 2504 1900 1377 834 321
Parasag. 2943 2727 2369 1994 1665 1374 1133 866 628 376 136
Post. SkB. 3484 3228 2835 2461 2111 1743 1432 1106 795 506 163
Spine 2843 2658 2352 2006 1680 1383 1096 821 581 356 121
F: OS by venous sinus invasion
Absent
Present
Absent 25408 23596 20652 17754 15072 12505 10017 7625 5449 3309 1196
Present 3483 3225 2806 2370 1975 1640 1353 1039 764 468 167

Figure 2

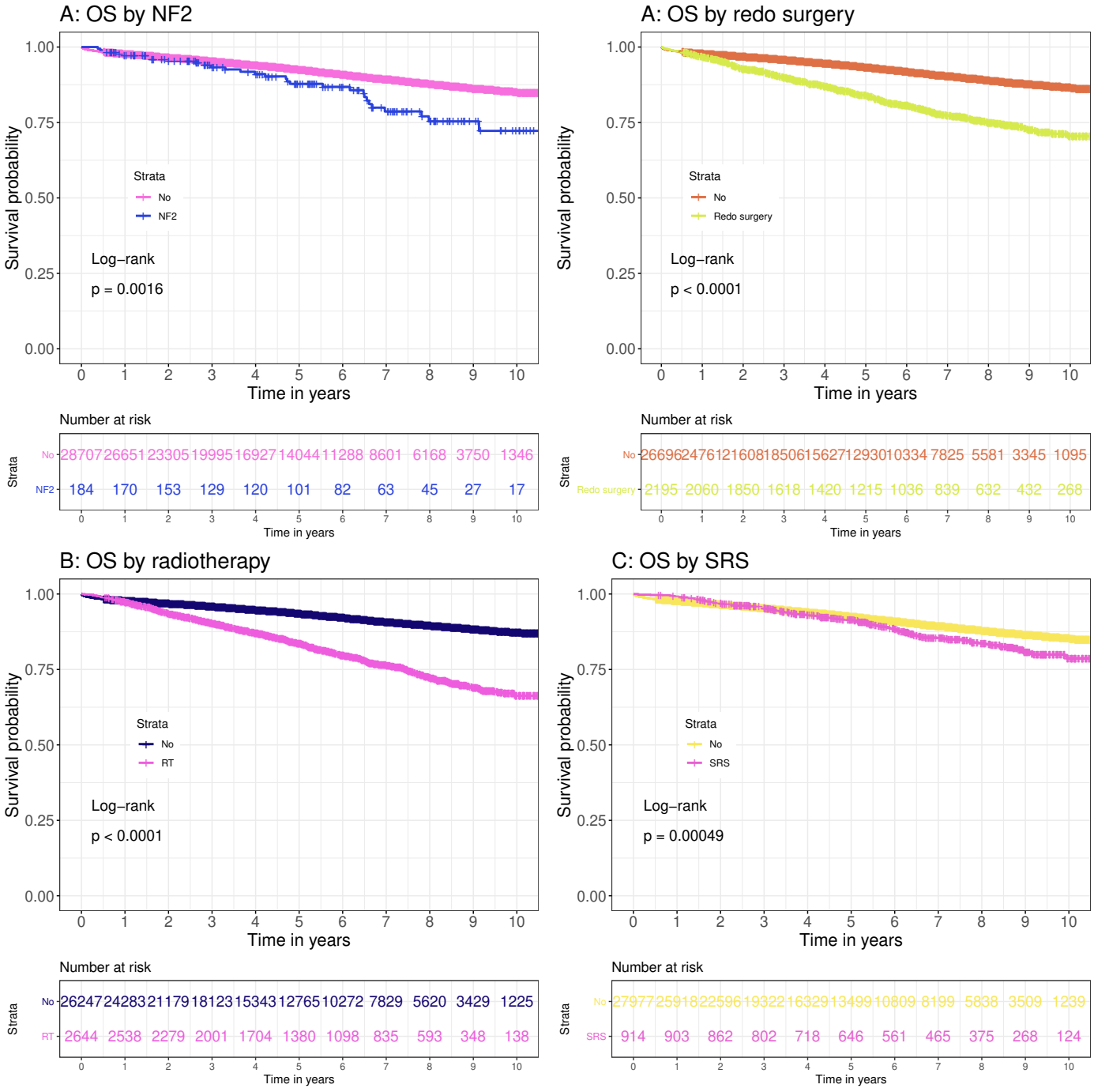


Figure 1: Kaplan-Meier OS curves comparison (2/2)

Table 1

Table 1. Characteristics of the 28 891 patients

Characteristics	*n* or median	% or IQR[1]
Gender female	20 947	75.4%
Median age at surgery	59 years	IQR[49 - 68]
Age at surgery		
• <50 y.	8 496	29.4%
• > 50 y. - < 60 y.	7 249	25.1%
• > 60 y. - < 70 y.	7 337	25.4%
• > 70 y.	5 806	20.1%
Neurofibromatosis (NF2)	184	0.6%
Location		
• cranial convexity	7 052	24.4%
• Middle skull base	6 257	21.7%
• Anterior skull base	3 818	13.2%
• Posterior skull base	3 484	12.1%
• Parasagittal	2 943	10.2%
• Falx cerebri	2 278	7.9%
• Intraventricular	216	0.7%
• Spine	2 843	9.8%
Skull base *vs.* others[2]	13 559	52.5%
Pre-operative embolisation	1 356	4.7%
Venous sinus invasion	3 483	12.1%
Dura mater reconstruction	6 323	21.9%
Cranioplasty	1 780	6.2%
CSF shunt	562	1.9%
Tumour grading		
• Benign	26 356	91.2%
• Atypical	1 757	6.1%
• Malignant	778	2.7%
Redo surgery for recurrence	2 195	7.6%
RT for recurrence	2 644	9.2%
SRS for recurrence	914	3.2%

[1] IQR: Inter Quartile Range
[2] Spinal & intraventicular meningioma excluded

Table 2. Univariable Cox regression for meningioma overall survival (OS)

Variable	Overall survival (OS)		
	HR[a]	[95 %CI][b]	*p*-value
Gender (female)	0.46	0.42, 0.49	<**0.001**
Age at diagnosis (continuous)	1.06	1.06, 1.07	<**0.001**
Age at diagnosis (5 categories) (ref. < 40 y.)			
• > 40 y. - < 50 y.	0.77	0.6, 0.98	**0.04**
• > 50 y. - < 60 y.	1.28	1.03, 1.58	**0.03**
• > 60 y. - < 70 y.	2.64	2.15, 3.24	<**0.001**
• > 70 y. - < 100 y.	5.98	4.9, 7.28	<**0.001**
Neurofibromatosis	1.79	1.24, 2.58	<**0.001**
Location (ref. convexity)			
• Anterior skull base	0.92	0.8, 1.06	0.26
• Falx cerebri	1.3	1.12, 1.51	<**0.001**
• Intraventricular	1.48	1, 2.2	**0.05**
• Middle skull base	0.83	0.73, 0.94	<**0.001**
• Parasagittal	1.43	1.25, 1.63	<**0.001**
• Posterior skull base	0.94	0.81, 1.09	0.41
• Spine	1.05	0.91, 1.22	0.5
Skull base meningioma *vs.* other	0.76	0.7, 0.83	<**0.001**
Pre-operative embolisation	1.34	1.14, 1.57	<**0.001**
Venous sinus invasion	1.37	1.23, 1.53	<**0.001**
Dura mater reconstruction	1.09	0.99, 1.19	0.09
Cranioplasty	1.24	1.07, 1.44	<**0.001**
CSF shunt	3.54	3, 4.18	<**0.001**
Tumour grading (ref. benign)			
• Atypical	1.42	1.23, 1.65	<**0.001**
• Malignant	4.11	3.55, 4.75	<**0.001**
Reoperation	2.44	2.2, 2.7	<**0.001**
RT	2.74	2.49, 3.02	<**0.001**
SRS	1.36	1.14, 1.62	<**0.001**

[a] Hazard Ratio
[b] 95 % Confidence Interval
[d] Not Applicable
p-values displayed in **bold** reached the statistical significance.

Table 3

Table 3. Multivariable Cox regression for meningioma overall survival (OS)

Variable	Overall survival (OS)		
	HR[a]	[95 %CI][b]	*p*-value
Female gender	0.6	0.55, 0.65	<**0.001**
Age at surgery (continuous)	1.07	1.07, 1.07	<**0.001**
Neurofibromatosis	4.18	2.88, 6.07	<**0.001**
Location (ref. convexity)			
• Falx cerebri	1.18	1.02, 1.37	**0.03**
• Parasagittal	1.18	1.03, 1.35	**0.02**
• Spine	0.86	0.74, 1.01	0.06
Grade (ref.: benign)			
• Grade II	1.32	1.14, 1.54	<**0.001**
• Grade III	2.97	2.56, 3.45	<**0.001**
Reoperation	2	1.79, 2.24	<**0.001**
Radiotherapy	2.14	1.93, 2.37	<**0.001**

[a] Hazard Ratio
[b] 95 % Confidence Interval
[d] Not Applicable
p-values displayed in **bold** reached the statistical significance.

Table 4

Table 1: literature review

Author country year	Period considered *n*	% of female age	% by grade I, II, III	5-year survival all grades, I, II, III	Significant factors
Present study	2008-2017 10 years 28 891	75.4% 59 ±13.8 years	91.2% 6.1% 2.7%	92.6% 93.3% 90.6% 72.4%	Gender age NF2 location grade redo surgery RT
Brodbelt UK 2019	1999-2013 15 years 15 417	70.1% 57.5 ±14.4 years	79.5% 18.4% 2.1%	90% 80%[1] 30%	Gender age spine grade
Ostrom USA 2017	2010–2014 4 years 112 582	73.1% 66 years	81.3% 16.9% 1.7%	all grades: 86.7% NA[2]	Age spine grade
Corell Sweden 2019	2009–2015 6 years 2 324	70.5% 58.7 ±13.5 years	87.6% NA[1]	graphical representation	Grade symptoms
Holleczek Saarland 2019	2000-2015 15 years 992	72% 63 years	70% 28% 3%	OS:85% OS:87.6%, RS:96.8%[3] OS:85.7%, RS:95.6% OS:50%, RS:61.2%	Gender age grade
Rydzewski USA 2018	2004-2014 10 years 70 092	69.8% NA	86.1% 11.1% 2.8%	85.5% 75.9% 55.4%	Grade GTR RT
Woehrer Austria 2014	2005-2010 6 years 2 149	74.4% 60.05 ±14.2 years	89.1% 10.9% NA%	I: OS:89.6%, RS:96% II: OS:80.6%, RS:86.9% NA	Grade histology
McCarthy USA 1998	1989-1992 25 years 9 000	71.2% 61.3 years	90.5% 1.7% 7.8%	69% 70% 75% 55%	Age grade size
Sankila Finland 1992	1959-1984 25 years 1 986	69.9% 53 years	94.3% 4.7% 1%	all grades 83% NA	Gender age

[1] Net survival
[2] Not Available
[3] RS: Relative survival (≈ net survival)

8.3 Conclusion

Meningioma are highly diverse tumours with respect to localisation, clinical presentation, radiological aspects and histology. Many factors influence their growth and outcome after surgery which remain the most powerful predictors of recurrence and survival. Once the tumour relapse, cure is unlikely. However, detailed and stratified sub analysis by grade and age for example are further needed to circumvent confounding factors and statistical interactions of the many predictors influencing the outcome. In that respect, large database are needed to provide enough unselected patients ensuring high statistical power and unbiased samples. This study on meningioma using the SNDS is the first of its kind. Despite some limitations such as imprecise tumour grading and the absence of resection quality information, the SNDS is an invaluable tool to assess meningioma outcome. It offers incomparable means to explore associations with other pathology, medication or other surgical treatment which has and could not be assessed before. Despite its lack of resection assessment, using this unique database, we found that outcome after meningioma surgery is better in women, younger adults, and patients with convexity and benign tumour.

9 Discussion

tudies relying on administrative medical databases (AMDB) are useful for evaluating treatment strategies as they offer another insight compared to results of selected retrospective data. This kind of research is valuable in the field of neurosurgery where significant variations in clinical practices exist. AMDB allow inclusion of large patients' groups that may be ineligible for inclusion in trials due to older age and co-morbidities. Additionally, these studies allow monitoring of trends, costs, and complications of surgical procedures in a real-world setting. Meningioma is the most common intracranial tumour however, compared to the glial tumours, they are relatively understudied. Up-to-date and detailed population-based data on outcome is sparse; most studies reporting on hospital cohorts or on selected samples.

9.1 Strengths and limitations

The strengths of the PMSI and SNDS databases reside both in the high number of patients and in the exhaustive data available from every hospital in France. Quality control is carried out a posteriori by medical inspectors on samples. However, these databases have some limitations in their use. Even if coding rules are national, there may be differences between establishments. The algorithm we used to identify surgically treated meningioma cannot be formally validated, and some patients may not have been identified. The PMSI database has been created for payment purposes. Its main limitation is the lack of case validation. The anonymisation makes it difficult to match clinical cohort to perform such a validation, as only events accompanying the diagnosis or complicating the disease are encoded. The SNDS database which covers 97.2% of the French population *i.e.* around 68 millions inhabitants constitutes one of the largest med-

ical administrative database in the world has some limitations [51]. Limitations of this study are inherent to a retrospective database analysis. Specifically, as data in the SNDS are compiled from a number of institutions, its accuracy is limited by inconstancies in data collection and recording. Using this database is far from being straightforward for non-expert data scientists as its use stays delicate due the complexity of the data organisation. Important variables are missing within the database, for example, histopathological details such meningioma subtype or quality of resection according the Simpson grade [49]. Another limitation is the absence of clinical information and biological results [47]. The retrospective nature of this study, together with the lack of clarity regarding treatment rationales and non-homogeneous management strategies without random assignment, needs to be considered when evaluating the results.

9.2 Selection bias

The ICD-10 formal diagnosis we used refer to "neoplasm of meninges". Meningioma is the most common meningeal tumour subtype, comprising more than 95% of the cases. However, the main differential diagnosis of meningioma are tumours of the solitary fibrous/haemangiopericytoma group (SFT/HPC) [37]. Some others neoplasms or cancer metastasis described as dural metastatis may exceptionally present as meningeal tumour [36].

The 2007 WHO classification of tumours of the CNS distinguished meningeal HPCs from SFT given their distinct clinicopathologic behaviour. HPCs are now considered as the aggressive form of SFT. Indeed, it has recently been demonstrated that both SFTs and HPCs, including those occurring in the neuraxis, share inversions at 12q13, fusing the NAB2 and STAT6 genes. This leads to a nuclear expression of STAT6 that can be detected by immunohistochemistry for a formal diagnosis [19, 12].

Therefore, in the 4th edition of the WHO classification of tumours of soft tissue and bone (2013), these neoplasms are no longer separate entities. It has become clear that meningeal SFTs and HPCs are overlapping, if not identical. For this reason, the 2016 WHO classification of CNS tumours has merged both neoplasms under the same category [19, 12]. SFT and HPC show high risks of recurrence rates and are known metastasise systemically. Intracranial SFT and HPC are meningeal tumour that often display a meningioma like appearance on the MRI. They often presenting as a large and locally aggressive dural mass, frequently extending through the skull vault. They are difficult to distinguish on imaging from the far more common meningioma but are treated similarly. As for meningioma complete surgical excision is the treatment of choice of HPC and SFT. Further optimal management is difficult to establish. Which patients might benefit from radiotherapy and what the optimal time to deliver it following surgery remains unclear. The rarity of these tumours which incidence is thought to be less than six cases for 1 000 000 habitants per year, make it difficult to study their behaviour [22]. Thus, it is very likely that our cohort integrate most of the SFT/HPC operated over the same period. Although meningioma and HPCs/SFTs are different types of meningeal tumours, one may legitimately think that they should follow approximately the same rule after resection. Indeed, it has been shown that extent of resection is the most powerful prognostic factor for recurrence of HPC/SFT. Most cohort studies have confirmed the effect of complete surgery on PFS and OS [19, 12]. Users of the SNDS for epidemiological studies, must bear in mind that inherent errors are

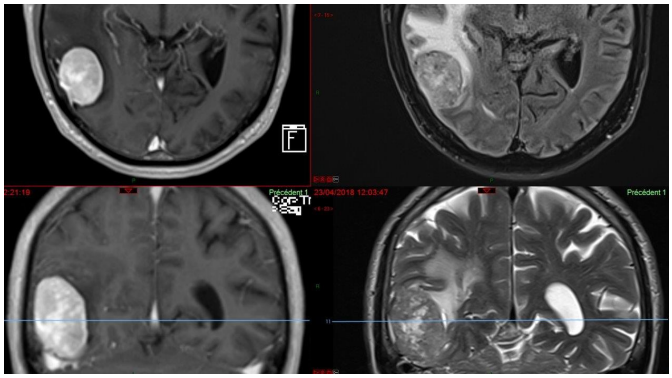


Figure 9 – MRI appearance of an haemangiopericytoma preoperatively mistaken for a meningioma

possible. Some of its limitations may be usefully circumvent by joined analysis of other data sources such as from matched surveys or registries [51].

9.3 Outcome

round 3 000 patients are diagnosed with meningioma each year in France and numbers have been increasing year-on-year. There are very few nationwide studies on outcome after meningiomas surgery.

Despite having a mostly indolent behaviour, outcome of patients treated for meningioma may occasionally be poor. Only a few studies have reported nationwide or large cohort meningioma OS. Five-year ranges from 83% to 95.8% in previous studies [45, 52, 40, 34, 46].

9.3.1 Factors affecting the outcome

9.3.1.1 Gender

Male gender was associated with a reduced OS. Males had an increased risk of death compared with females in most nationwide studies on the subject with a HR of 1.44 $_{95\%}$CI [1.37-1.52] for Yang *et al.* [53].

9.3.1.2 Age at surgery

Without surprise, OS after meningioma surgery is better for younger adults [10, 52]. For Brodbelt *et al.* there was a significant reduction in 5-year net survival over the age of 69 years, to less than 83% in men and 87% in women. This means that 27% of men age 70 to 79 years who had surgery for a cranial meningioma died within 5 years over and above what would be expected for their age, and hence may be attributable to their meningioma, treatment, or complications thereof [10]. An age-stratified analysis of OS after meningioma surgery is planned

9.3.1.3 Comorbidities

None of the nationwide studies on meningioma assessed the influence of comorbidities on the OS. However, three computes the net survival which under certain assumptions may be interpreted as the probability of surviving cancer in the absence of any other causes of death [10, 52, 34]. For estimation of net cancer survival, either cause-specific survival or relative survival analysis methods can be used. Cause-specific survival analysis takes a specific cause of death as the end point of interest and all the other causes of death are treated as independent censoring [9]. A dedicated study on CSS on this cohort his under writting.

9.3.1.3.1 Neurofibromatosis

Neurofibromatosis type 2 is an autosomal-dominant multiple neoplasia syndrome that results from mutations in the NF2 tumour suppressor gene located on chromosome 22q. It has a frequency of one in 25 000 livebirths and nearly 100% penetrance by 60 years of age. Patients are predisposed to development of lesions of the CNS. Intracranial meningiomas are present in 45-58% of patients and spinal meningiomas are present in about 20% [3]. Intracranial meningiomas are frequently multiple and they develop at a younger age. Some authors found that NF2 meningiomas may have heightened proliferative activity and a greater rate of atypical and anaplastic grades than do sporadic meningiomas on contrary to our findings [3]. A dedicated analysis of NF2 patients outcome has been achieved and is under consideration in a peer-rewieved medical journal.

9.3.1.4 Quality of resection

Since the seminal publication of Donald Simpson in 1957, there is general agreement about the importance of completeness of resection [49]. For all grades of meningioma, extent of resection has been shown to affect the risk of recurrence and the

OS. Quality of resection according the Simpson grade are unfortunately non available within the SNDS. This information may be found in the operative record or in the post-operative MRI report and extracted using text mining of unstructured data [4].

9.3.1.5 Location

A Simpson grade I or II resection is usually achieved when the tumour is located on the convexity. It is often more difficult for tumours on the skull base that infiltrate surrounding neural and vascular structures. Thus, skull base location is a risk factor for incomplete resection, and sub-totally removed meningiomas may continue to grow. Cranial meningiomas can be broadly divided into skull base tumours and non-skull base. Skull base meningioma are less common, have a higher recurrence rate and worse PFS, but are more likely benign, have a slower growth rate [10]. In our study, spinal meningioma were associated OS was not significantly increased. For Brodbelt *et al.* patients with spinal meningiomas did better in all grades, gender and ages [10].

9.3.1.6 Associated surgical acts

9.3.1.6.1 CSF shunting

Patients with intracranial tumours are at risk of developing hydrocephalus due to CSF pathways obstruction or impaired resorption. Meningioma predisposes patients to hydrocephalus which may require a permanent CSF diversion such as ventriculoperitoneal (VP) shunts or endoscopic third ventriculostomy. CSF shunting reduced the morbidity and mortality of hydrocephalus. However, it is associated with potential complications including shunt failure due to obstruction, infections, and mechanical problems which may require repeated surgeries in case of VP shunt failure [7]. In our analyse, CFS shunting was associated to an increased risk of reduce OS. A dedicated study on the incidence of permanent shunting among patients operated on for a meningioma has

been considered.

9.3.1.6.2 Cranioplasty

In 25%-50% of cases, meningioma have an influence on surrounding cranial vault with usually hyperostotic changes. Various causes have been proposed for hyperostosis of which tumour invasion into the bone. The surgical decision to remove or replace the hyperostotic flap is controversial [8]. Some recommend to replace it with synthetic materials owing to the possibility of tumour invasion and to reduce the associated risk of recurrence. A recent study showed that meningioma recurrence was unlikely when autologous cranioplasty was done with the refashioned hyperostotic bone [8]. Surgical site infection is an inherent risk and complication after elective intracranial tumour surgery. Risk factors of bone flap infection include RT, re-operations, prolonged operative times and CSF leak. The neuro-oncological patient usually satisfies one or more of these criteria. Usual management involved debridement and explantation of the infected bone flap followed by a prolonged targeted antibiotic therapy. Reasons for cranioplasty include protection against trauma and restoration of the appearance among others. Influence of a cranioplasty insertion after meningioma surgery either to prevent a recurrence or after bone flap infection on the survival was never previously assessed. A dedicated study to examine the characteristics and outcome of the patients of our cohort who underwent a cranioplasty after meningioma removal is planned.

9.3.1.7 Histopathological grading

Histological grading is one of the most powerful predictor of TTP, PS and OS as found in most reported studies [10, 52].

Impaired survival of benign meningioma has been reported with relative survival ranging from 79.5% in Eastern Europe to 93.4% in Northern Europe [52, 21, 34]. In a previous study solely dedicated to grade I meningioma, we found a risk of recurrence

or meningioma-related death at 5 years of 16.2%, $_{95\%}$CI[12.5 - 20] and a 5-year OS of 86.1% $_{95\%}$CI[82.8 - 89.6] [17]. Our findinds is supported by those of van Alkemande *et al.* who observed in the long term, a challenged survival with WHO grade I meningioma with a majority of patients have long-term neurological deficits [1]. WHO grade I meningiomas have typically a mitosis count of less than 4 per 10 HPFs. In common with other intracranial neoplasms such as gliomas, the microscopic characteristics of meningiomas are not fixed and may evolve. As only certain meningiomas undergo transformation, there might be a combination of genetic predispositions and external factors influencing this transformation, which is associated with a worse outcome. For Bodbelt et al. who assessed the net survival, in patients with grade I, 19% of people are dead at 10 years over what one would expect without the disease *id est* a substantial reduction in survival for a "benign" condition.

For grade II, 5-year OS spans from 75.9% to 93.6% [44, 52]. In case cohort studies, 5-year OS range from 35 to 89.1% with medians extending from 4.75 to 11.2 years [13, 14, 11]

Malignant meningioma have a 5-year survival ranging from 30% to 55.4% [10, 18, 34]. In Sant *et al.* study, MM constituted 8.8% (1 110 cases) of all meningiomas, with 5-year relative survival of 72.7% [46].

In a previsous study dedicated solely to MM, we found a median OS of 2.9 years, $_{95\%}$CI[2.4, 4.5] *vs.* 4.1 years for Holleczek *et al.*. Obviously, the aggressive behaviour of meningioma cannot be accounted for by histological features alone. Orton *et al.* in a dedicated study on grade III using the USA NCDB found on 755 patients a 5-year OS rate of 41.4% with GTR and RT associated with improved survival [39].

9.3.1.8 Treatment of recurrence

In this study, the patients who needed reoperation or irradiation for recurrence did

not demonstrated improve survival.

In previous studies dedicated to grade II meningioma, we showed that redo surgery did not increase the survival. On the contrary, the patients who need redo surgery for recurrence had an impaired survival by nearly three times [13, 14, 11].

Modern (RT) is becoming increasingly important in the treatment of meningiomas. RT can be performed as stereotactic radiosurgery (SRS) or as conventional fractionated EBRT. In case of MM (WHO grade III), adjuvant RT is generally recommended, regardless of the extent of surgical resection. This has been shown to improve local tumour control and recurrence rates [18, 20]. We could no demonstrated any favourable effect of RT on OS. a dedicated study on effectiveness of RT on atypical and malignant meningioma is planned.

For atypical meningioma, findings are mixed and continue to be controversial. For grade II meningioma, most neurosurgeons would not advocate adjuvant RT if the tumour was completely excised. These practices are generally in agreement with RT after the first recurrence, whether re-operated on or not [13, 14, 11]. For some authors, the patients who received adjuvant RT demonstrated a significantly longer PFS rate [33]. Kaur et al. reported a median 5-year PFS after adjuvant RT of 54.2% and a median 5-year OS of patients with atypical meningioma treated by RT of 67.5%, ranging from 51% to 100% [35]. Moreover, no study was able to demonstrate a statistically significant improvement in any of the clinical outcomes with adjuvant RT for WHO grade II meningioma. Systematic post-operative RT irrespective of the resection extent failed to demonstrate its usefulness. Therefore, they recommend careful consideration of the side effects and, if possible, application within research protocols. No randomised clinical trials have been performed but there is an ongoing trial "the RT versus observation following surgical resection of atypical meningioma (ROAM trial)" which may provide more information in the future on the usefulness of RT for completely resected menin-

gioma [13, 14, 11]. We are considering to evaluate the meningioma control after proton therapy *vs.* standard EBRT.

No clinical trial validating the effectiveness of RT in grade III has been achieved. However, reported results suggest that patients may live longer after adjuvant RT. According to Kaur et al., median five-year overall survival after radiotherapy was 55.6% and reported rates ranged from 27% to 80.8%. However, given the lack of a non-irradiated control group in most of the studies, the prognostic impact of adjuvant radiotherapy could not be reliably be assessed [35]. Thus, in case of WHO grade III meningioma diagnosis, RT is conventionally given as an adjuvant treatment within the months after the surgery to prevent recurrence. In previous grade III cohort studies, we showed the value of adjuvant RT for improving the survival [18, 20]. For Rydzewski *et al.* there is a trend for both GTR and RT being significant factors of survival for MM.

The French Brain Tumour Database (FBTDB) is a national histological database of all primary CNS tumour (PCNST in France). It is based on a network of all neurosurgeons, pathologists and neuro-oncologists involved in PCNST, in collaboration with all the societies focused on PCNST. The FBTDB's main objective is to prospectively record all histologically-proven cases of PCNST diagnosed in France, meningioma included [5, 42, 22]. As the SNDS authorise database merging, it would be of great value to merge both databases for further research.

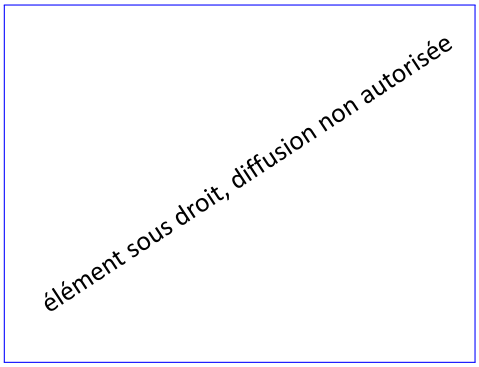
10 Conclusion

eningioma are highly diverse tumours with respect to localisation, clinical presentation, radiological aspects and histology. Many factors influence their growth and outcome after surgery which remain the most powerful predictors of recurrence and survival. Once the tumour relapse, cure is unlikely. WHO grade I meningioma treatment failure correlated with venous sinus invasion, incomplete resection, and progressing tumour; shorter survival correlated with increased age and redo surgery for recurrence. We recommend the cumulative incidence competing risk approach in WHO grade I meningioma studies where unrelated mortality may be substantial, as this approach results in more accurate estimates of disease risk and associated predictors. We confirms the poor prognosis associated with malignant meningioma, the treatment of which remains challenging. Patients under 65-yr-old with primary malignant meningioma may live longer after complete resection and postoperative radiotherapy. However, even with aggressive treatments, local control remains difficult to achieve. Detailed and stratified sub analysis by grade and age for example are needed to circumvent confounding factors and statistical interactions of the many predictors influencing the outcome. So far, most published studies reported findings of hospital cohorts or used otherwise selected samples of patients. In that respect, large database are needed to provide enough unselected patients ensuring high statistical power and unbiased samples. The SNDS database is a reliable and effective source for studying the epidemiology of meningiomas, including the precise location of the tumour. Our findings comfort previous studies and are comparatively correlated which enable to investigate the patients' outcome. This work presents a nationwide population-based data on the burden of meningiomas and derived unselected outcome measures of men-

ingioma patients in terms of overall survival up to 10 years after diagnosis. After removal of meningioma, survival of patients presenting no comorbidities is long and outcome is better in women, younger adults, and patients with convexity and benign tumour. Once the tumour had relapsed, cure is unlikely and none of the treatment studied succeed to improved the survival. This study on meningioma using the SNDS is the first of its kind. Despite some limitations, the SNDS is an invaluable tool to assess meningioma outcome. It offers incomparable means to explore associations with other pathology, medication or other surgical treatment which has and could not be assessed before.

Unthinking respect for authority is the greatest enemy of truth.

$$R_{\mu\nu} - \frac{1}{2}R\,g_{\mu\nu} + \Lambda g_{\mu\nu} = \frac{8\pi G}{c^4}T_{\mu\nu}$$



11 Appendix

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Compliance with ethical standards

In accordance with the French regulations, this project was approved by the French data protection authority (CNIL), authorisation number: 2008538.

Conflicts of interest

The authors declare that they have no conflict of interest.

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11.3 List of abbreviations

AMDB: Administrative Medical DataBase

CCAM: Classification Commune des Actes Medicaux (Common Classification of Medical Acts)

CépiDc: Centre d'épidémiologie des causes médicales de Décès (National death registry)

CNIL: Commission Nationale de l'Informatique et des Libertés (French data protection authority)

CNS: Central Nervous System

CSF: CerebroSpinal Fluid

FBTDB: French Brain Tumour Database

GTR: Gross Total Resection

HPC: Haemangiopericytoma

HPF: High-Power Field ($\times$ 400)

INDS: Institut National des Données de Santé

MM: Malignant Meningioma

OS: Overall Survival

PCNST: Primary Central Nervous System Tumours

PFS: Progression-Free Survival

PMSI: Programme de Médicalisation des Systèmes d'Information

RT: RadioTherapy

SD: Standard Deviation $\sigma = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(x_i - \bar{x})^2}$

SFT: Solitary Fibrous Tumour

SNDS: Système National des Données de Santé

SNIIRAM: Système National d'Information Inter Régimes de l'Assurance Maladie

SRS: Stereotactic RadioSurgery

STR: Sub Total Resection

TR: Total Resection

TTP: Time to Pogression

VP: VentriculoPeritoneal (shunt)

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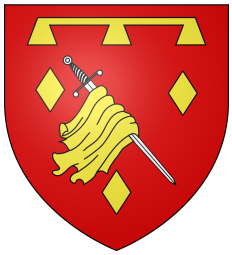

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LISTE DES ELEMENTS SOUS DROITS

Liste de tous les éléments retirés de la version complète faute d'en détenir les droits

(Annexe séparée accompagnant obligatoirement la version de diffusion)

Illustrations, figures, images...

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