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Epidemiological analysis of adult-type diffuse lower-grade gliomas and incidence and prevalence estimates of diffuse IDH-mutant gliomas in France

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Highlights

- The main factors that impact glioma overall and diffuse lower-grade glioma incidences are reviewed
- Estimate of the 2024 French glioma incidence is 6.6/100,000 person-years
- For the first time we provided incidence and prevalence estimates of diffuse IDH-mutant glioma in France
- French incidence estimates of diffuse IDH-mutant gliomas are 1, 0.5, 0.3, 0.2, for all grade, grade 2, grade 3, grade 4 /100,000 person-years, respectively
- Grade 2 IDH-mutant glioma prevalence would be greater than 6.57/100,000 persons

Abstract

Background

The recent advent of anti-IDH therapies and changes in the WHO classification of gliomas implies estimating the number of patients who could benefit (or not) from anti-IDH treatment. As published data on the current incidence of different subtypes of IDH-mutant gliomas (based on the latest histomolecular WHO classification) are lacking in many countries. The present analysis aims to review the main factors impacting the incidence of gliomas and lower-grade gliomas and to estimate the incidence and prevalence of IDH-mutant gliomas in France.

Methods

Our analysis was based on data from the French Brain Tumor DataBase and literature.

Results

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Case definition, recording methods, histological classifications, age, sex, ethnicity, ancestry, environment, genetics, etc., impact the incidence of gliomas overall and lower-grade gliomas. In France, for the year 2024, the incidence estimates of all gliomas and all adult-type diffuse IDH-mutant gliomas are 6.6/100,000 and 1/100,000 person-years, respectively. The incidence estimates of grades 2, 3, and 4 diffuse IDH-mutant gliomas are 0.5, 0.3, 0.2 per 100,000 person-years, respectively. Of note, the incidence estimate of grade 3 diffuse IDH-mutant glioma versus grade 2 or 4 is slightly more difficult to assess due to the possible variability in histological criteria to define tumor grade. The prevalence of diffuse IDH-mutant grade 2 glioma would be more than 6.57/100,000 persons.

Discussion/Conclusion

Our epidemiological analysis provides estimates of potential number of patients, but large prospective real-world studies are required to determine the positioning of anti-IDH treatments among all therapeutic strategies [surgery(ies), chemotherapy(ies), radiotherapy(ies), clinical/radiological follow-up, etc.].

Keywords: IDH-mutant astrocytoma; IDH-mutant and 1p/19q codeleted oligodendroglioma; IDH-mutant glioma; incidence; prevalence; survival

Abbreviations:

ANOCEF, Association des Neuro-Oncologues d'Expression Française; CBTRUS, Central Brain Tumor Registry of the United States; CNS, central nervous system; INCa, Institut National du Cancer; INSEE, Institut National de la Statistique et des Etudes Economiques; FBTDB, French Brain Tumor DataBase; FRANCIM (réseau français des registres des cancers), French Cancer Registry Network; IDH, Isocitrate dehydrogenase; OBTS, Ohio Brain Tumor Study; RnhTPSNC, Recensement national histologique des Tumeurs Primitives du Système Nerveux Central; SFNC, Société Française de Neurochirurgie; SPF, Santé Publique France; TCGA, The Cancer Genome Atlas; WHO, World Health Organization.

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Introduction

The 2021 WHO classification of primary central nervous system (CNS) tumors [1] distinguished diffuse adult-type gliomas and separated them into IDH-mutant and IDH-wildtype gliomas (glioblastoma, grade 4). IDH-mutant gliomas include IDH-mutant astrocytomas (grades 2, 3, and 4) and oligodendrogliomas (IDH-mutant and 1p/19q-codeleted, grades 2 and 3). If epidemiological data allow estimates of the incidence and prevalence of diffuse grade 2 gliomas or diffuse grade 2 + grade 3 gliomas (often denominated as Low-Grade Glioma or Lower-Grade Glioma, respectively) [2-4], the changes in WHO classifications over the past decades (2007, 2016 and 2021 classifications) do not currently allow for precise population-based data regarding IDH-mutant gliomas epidemiology.

Recently, anti-IDH molecules have been developed. In particular, vorasidenib a dual inhibitor of the mutant IDH1 and IDH2 enzymes, was evaluated in patients diagnosed with diffuse grade 2 IDH-mutant glioma. In a double-blind phase 3 clinical trial (NCT04164901, number of included patients: 331, median follow-up: 14.2 months), patients were randomized to receive either vorasidenib, or placebo. Progression-free survival was 27.7 months in patients who received vorasidenib, versus 11.1 months in those who received placebo (hazard ratio, 0.26; 95% CI, 0.15 to 0.43; $p<0.001$) [5]. Given these promising results, it is imperative from a public health perspective to ascertain the number of patients who could potentially benefit from such treatment, considering that the median survival of patients with diffuse grade 2 IDH-mutant gliomas can extend to nearly 20 years in certain cohorts of selected patients [6]. Better knowledge of the incidence and prevalence of these tumors is therefore essential.

The primary objective of this study was to estimate the incidence of adult-type diffuse IDH-mutant gliomas in France in 2024, with an emphasis on grade 2 IDH-mutant gliomas. However, to elucidate the incidence variations of diffuse lower-grade gliomas, we first examined the factors that may influence the incidence of gliomas in general and diffuse lower-grade gliomas.

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Methods

In the absence of published population data on the current incidences of the different types and subtypes of gliomas based on the latest histomolecular classification of CNS tumors (2021 WHO classification) in many countries including France, the present epidemiological analysis was established on the basis of *i)* published and unpublished data from the French Brain Tumor DataBase (FBTDB) (Recensement national histologique des Tumeurs Primitives du Système Nerveux Central - RnhTPSNC), *ii)* an analysis of complementary French and international literature, and *iii)* the experiences and knowledge of the authors (all experts in the field). The FBTDB has identified and recorded patients with newly diagnosed and histologically confirmed primary CNS tumors since 2006 in France. FBTDB is based on a network of all neurosurgeons, pathologists, and neuro-oncologists involved in the management of patients with primary CNS tumors, in collaboration with all societies focused on these tumors (Société Française de Neurochirurgie (SFNC) et Club de Neuro-Oncologie of SFNC, Société Française de Neuropathologie and Association des Neuro-Oncologues d'Expression Française –ANOCEF). FBTDB is one of the largest clinical databases for primary CNS tumors in Europe, and its methodology has previously been published [3,7-14].

FBTDB data are exhaustive until the beginning of 2016. The updated 2016 WHO classification was gradually applied in France, and case recording was impeded by the COVID-19 pandemic. It was not possible to get precise data for all subtypes of gliomas, and cases recording since the last WHO (2021) classification is still on going. Therefore, the recent presented data are estimates.

The French population numbers (denominator) were obtained from the National Institute of Statistics and Economic Studies (INSEE) [15]. In this context, the French incidence estimates are presented as crude rates. Notably, the structure of the French population closely approximates that of the European reference population.

The analysis of the variation factors of the incidence of gliomas in general, and of lower-grade gliomas in particular, was carried out using data from the main brain tumor registries (e.g., Central

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Brain Tumor Registry of the United States (CBTRUS), Belgian registry, Scandinavian registries, Gironde Registry) [for example: 4,16-22] and FBTDB works.

Results

Glioma incidence variations

The incidence of gliomas varies depending on the case definition, census methodologies, population characteristics (age, sex, ethnicity, ancestry, etc.), histological classification, and environmental and genetic factors, among other variables (Table 1).

Various cancer registries employ different criteria for recording tumors. Some registries exclusively document malignant tumors, while others include malignant tumors, benign tumors, and tumors classified as intermediate (or borderline) [38]. An example of the latter category is pilocytic astrocytoma, which is designated as "/1" in the International Classification of Diseases for Oncology [39]. Most tumor registries are intended to identify and record cases with histological confirmation and cases without histological confirmation (primarily based on clinical and/or radiological criteria). This process presents two primary challenges. First, particularly for gliomas, it is not feasible to definitively diagnose a glioma based solely on clinical and/or radiological criteria (differential diagnoses with certain other neuroepithelial tumors, brain metastases, cerebral lymphomas, neurological diseases, etc., which can mimic high- or low-grade gliomas), and it is often even more challenging to specify the precise subtype of glioma when suspected. Second, there are a few countries where brain tumors, particularly gliomas, are classified as notifiable diseases (a condition that, when diagnosed, requires health providers, typically by law, to report to public health officials). In the absence of mandatory reporting to health authorities, it is exceedingly difficult for registries to identify cases without histology because registries must identify cases across numerous medical centers. In practice, the most effective national registries regarding the epidemiology of gliomas are those with mandatory reporting requirements (e.g., USA and Scandinavian countries). Without mandatory reporting, some registries exclusively record histological cases (e.g., FBTDB). Other registries record cases in a restricted

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geographical area where medical care is predominantly provided within the geographical area itself (for example, in France: FRANCIM departmental registries [Le réseau FRANCIM - Registre des cancers | Loire-Atlantique et Vendée - Association EPIC-PL (registre-cancers-44-85.fr)] and, specifically, the specialized registry for the Gironde department [Registre des tumeurs du système nerveux central de la Gironde (u-bordeaux.fr)]).

Among the factors affecting the incidence of different subtypes of glioma, the histological classification variations are major confounding factors.

Glioma histological classifications according the different CNS WHO classifications

Since the first edition of the histological classification of CNS tumors published in 1979 [40], the WHO has published several classifications and/or updates [41-44]. Fig. 1 shows all histological subtypes of gliomas according to the 2007, 2016, and 2021 WHO classifications. Among the aforementioned WHO classifications, there exist substantial modifications: primarily, the introduction and subsequent development of molecular biology to characterize numerous tumors and their subtypes (e.g., gliomas), and secondarily, the differentiation of diffuse gliomas into "adult type" and "pediatric type." The 2021 WHO classification categorizes diffuse adult-type gliomas into IDH-mutant gliomas [IDH-mutant astrocytomas (grades 2, 3, and 4), oligodendrogliomas (IDH-mutant and 1p/19q-codeleted, grade 2 and 3)], and IDH-wildtype gliomas (glioblastoma, grade 4). A French publication elucidates the principal modifications of the 2021 WHO classification [45], while an editorial published in the Neuro-Oncology review explicates several implications for cancer registries [46].

With regard to descriptive epidemiology, these modifications disrupt the incidence of various subtypes of diffuse gliomas. Between the 2007, 2016, and 2021 WHO classifications, there was a progressive and ultimately complete elimination of oligoastrocytomas and anaplastic oligoastrocytomas. Similarly, grades 2, 3, and 4 IDH-wildtype astrocytomas were eliminated, while grade 4 IDH-mutant astrocytomas emerged. Diffuse midline gliomas are now characterized by molecular pathology and categorized as pediatric-type diffuse high-grade gliomas, among other

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changes. These modifications in histological classification partially account for the increased incidence of glioblastomas and the decreased incidence of diffuse lower-grade gliomas. Therefore, all adult-type diffuse lower-grade gliomas are classified as IDH-mutant gliomas.

Evolution of diffuse lower-grade glioma incidence according to time, countries and histological classifications

Twenty-five years ago, the variability in histological grading of diffuse gliomas was substantial, and the reproducibility was notably poor [47,48]. Moreover, medical practices implemented in the past, such as the "wait and see" approach for diffuse grade 2 glioma (with no histological confirmation), could potentially alter the incidence and prevalence of diffuse lower-grade gliomas [49]. In numerous countries, the histological distribution of glioma subtypes exhibits significant heterogeneity [50].

Currently, the contributions of molecular biology and the development of imaging techniques have made it possible to improve the grading of diffuse gliomas. However, intratumoral heterogeneity, surgical sampling methods, quality of surgical resection (biopsy, partial, total, or supratotal resection), and histological criteria can further modify the incidence and grading of the different subtypes of diffuse gliomas (even within the group of diffuse IDH-mutant gliomas).

In France, very little epidemiological work has been carried out on diffuse lower-grade gliomas (diffuse grade 2 and 3 gliomas), apart from FBTDB. The first study carried out in France (study period: 2006-2009) was that of Darlix et al. [51] (Table 2) and gave incidence rates for diffuse grade 2 and 3 gliomas probably a little overestimated for the following reasons: 1) We had just finished the so-called “wait and see” period where diffuse low-grade gliomas (+/- diffuse grade 3 glioma) had been monitored without histological diagnosis, and classified in the registries as brain tumor without precision or even not listed. That had created a "reservoir" of patients and had probably slightly increased the incidence rate of patients operated on over a period of several years. 2) At that time, the tumor samples sent to pathologists by surgeons were sometimes still small and therefore could miss more aggressive tumor contingents. Furthermore, the impact of the Daumas-Duport classification

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[48] on the classification of astrocytomas versus oligodendrogliomas in France resulted in a much higher rate of oligodendroglial tumors in France than in the USA. Later, the distribution of gliomas in France according to their grades and histological subtypes was detailed in a publication by Darlix et al. 2017 [3], and then updated in the South-West report carried out by the FBTDB for two patient associations [ARTC: Association pour la Recherche sur les Tumeurs Cérébrales, and Ligue Contre Le Cancer - Comité Pyrénées Atlantique] [Bauchet, 2020]* (** Of note, t*his report is available upon request at: recensement.tumeurspsnc@gmail.com).

In summary, the French incidences of diffuse lower-grade gliomas were 1.722 (diffuse grade 2 gliomas= 0.792 + diffuse grade 3 gliomas= 0.930) and 1.493 (diffuse grade 2 gliomas= 0.707 + diffuse grade 3 gliomas= 0.786) per 100,000 person-years for the 2006-2011 and 2006-2015 periods, respectively.

Regarding diffuse grade 2 and 3 gliomas in USA, a work carried out by Bauchet and Ostrom, 2019 [4] on the all American population (period 2010-2014) based on data from the CBTRUS, showed that the incidence of diffuse grade 2 gliomas was (0.48+0.24=0.72) and the incidence of diffuse grade 3 gliomas was (0.4+0.11=0.51) (per 100,000 person-years) (see Table 3). Note, that oligoastrocytic tumors were not included in this study.

At country level, very limited data regarding the incidence of diffuse IDH-mutant glioma are available. The last CBTRUS and Belgium Cancer Registry reports analyzed the distribution of brain tumor molecular markers for the selection of histologically confirmed gliomas for the periods 2018-2020 and 2017-2019, respectively (see Table 4).

French estimates

Published data regarding brain tumor epidemiology are limited in France. The National French Institute of Cancer (INCa) published general data regarding malignant brain tumors and glioblastomas only [52]. Only two French organizations published incidence data regarding glioma subtypes: the Gironde CNS tumor registry and FBTDB. The Gironde CNS tumor registry provides data from an area of

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approximately 1.5 million inhabitants [21,22], and the last publication regarding diffuse glioma subtypes analyzed the 2000-2012 period. FBTDB provides data for confirmed histological cases only but from an area of approximately 65 million inhabitants. Table 5 shows the glioma incidence reported for the 2006-2011 and 2011-2015 periods by FBTDB and the estimates for the years 2020 and 2024.

The FBTDB currently does not have precise data in the French Overseas Territories (2024 population: 2 230 472 inhabitants). As a first approximation, if we consider the same value of incidence, the number of patients with newly diagnosed and histologically confirmed glioma would be around 4513 in 2024 for the whole of France and 4307 for patients aged 12 years or older.

The estimated incidence of diffuse grade 2 IDH-mutant gliomas in metropolitan France is 0.5/100,000 inhabitants per year. The estimated incidence of diffuse grade 3 IDH-mutant glioma is slightly more difficult to assess owing to the possible variability in histological criteria [53,54] and is approximately 0.3/100,000 inhabitants per year.

Diffuse grade 4 IDH-mutant astrocytoma has been introduced in the 2021 WHO classification, and we do not have sufficient data in the FBTDB to estimate its incidence. Glioblastoma, IDH-mutant was introduced by the 2016 WHO classification; however, this diagnosis was not applied uniformly between 2016 and 2020 in France. Therefore, FBTDB cannot produce an estimated incidence of diffuse grade 4 astrocytoma. There are no data yet regarding the incidence of grade 4 IDH-mutant astrocytoma at the level of an entire country, but there are some data in the international literature. In a series of 2456 cases of glioblastoma according to the 2007 WHO classification, IDH-mutant glioblastomas (2016 WHO classification) accounted for 4% of all glioblastomas [55]. In the latest CBTRUS report, it was estimated that diffuse grade 4 IDH-mutant astrocytoma accounted for about 3.3%, and diffuse grade 4 astrocytoma not otherwise specified (NOS) for 13.7% of the all diffuse grade 4 astrocytomas [16]. In metropolitan France, the estimated glioblastoma incidence (crude rate) by the French Institute of Cancer was 5.368 per 100,000 person-years [52], the FBTDB estimated that the incidence of glioblastoma in 2024 was slightly lower (about 4.5/100,000 person-years). Therefore, the estimated incidence of diffuse grade 4 IDH-mutant astrocytoma in metropolitan France is

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approximately 0.2/100,000 person-years. Moreover, the quality and/or quantity of the tumor samples can modify the grading (grade 4 vs. grade 3).

In practice, the incidence of diffuse adult-type IDH-mutant gliomas (grade 2,3,4) can be estimated at approximately 1 per 100,000 inhabitants per year.

Diffuse IDH-mutant gliomas are very rare in the pediatric population, and when they exist, they are mostly found in the adolescent population [1]. In metropolitan France, for the year 2024, the estimated numbers of patients aged ≥ 12 years with an incident diagnosis of diffuse grade 2 and 3 IDH-mutant gliomas are 331 and 198, respectively. Considering the same estimates, the numbers of new patients across France in 2024 would be 342 and 205, respectively.

Diffuse lower-grade glioma prevalence estimates and approximation of the diffuse IDH-mutant glioma prevalence

Diffuse lower-grade glioma prevalence estimates

Prevalence is a statistic of primary interest in public health because it identifies the level of burden of disease or health-related events on the population and health care system. Prevalence represents new and pre-existing cases alive on a certain date, in contrast to incidence which reflects new cases of a condition diagnosed during a given period of time. Prevalence is a function of both the incidence of the disease and survival (Cancer Prevalence Statistics Overview). Obtaining complete prevalence data is challenging, as it necessitates registry data collected over a sufficiently extended period to capture all prevalent cases of the disease.

Publications regarding the prevalence of glioma subtypes are very rare and refer to the old WHO classifications, not that of 2021. One of the first approximations of the prevalence of diffuse grade 2 gliomas was 9/100,000 [2]. It was published when “the wait-and-see period” was finished, which artificially and slightly increased the incidence of operated grade 2 diffuse glioma patients, and thus increased the prevalence.

Journal Pre-proof

In USA, Zhang et al. [56] used incidence data from CBTRUS and survival data from 18 SEER registries for the years 1975-2010, and estimated prevalence of main diffuse glioma subtypes (Table 6). The prevalence estimate of diffuse grade 2 gliomas (diffuse astrocytomas + oligodendrogliomas + grade 2 oligoastrocytomas, a part of oligoastrocytic tumors) was between 6.52 and 7.82 per 100,000 persons. Similarly, the prevalence estimate of diffuse grade 3 glioma was between 2.3 and 3.6 per 100,000.

Another way to estimate prevalence is to use an estimate of survival. If the average duration of disease and the population of patients are stationary, the prevalence (*P*) can be estimated by the incidence (*I*) and the mean duration of disease (*D*) using the following equation: $P \approx I \times D$. For diseases that have no cure, the duration of the disease is the survival time. Unfortunately, the mean overall survival is rarely available for gliomas. The median overall survival is usually shorter than the mean overall survival in cancer but might be used as a very first approximation, or at least as a lower value. Using this crude approximation and the values of incidence and median survival from Table 6, we estimated that the prevalence of diffuse grade 2 gliomas and diffuse grade 3 gliomas was superior to 6.24/100,000 and superior to 1.67/100,000, respectively. Furthermore, the prevalence of diffuse lower-grade gliomas was greater than 8/100,000.

A recent study by Neff et al. [57] counted 30,633 patients with diffuse grade 2 or grade 3 astrocytomas, and 24,710 patients with diffuse grade 2 or grade 3 oligodendrogliomas in USA in 2019. The 2019 US population was 328,329,953 (États-Unis - Population totale | Statistiques (usherbrooke.ca)). The prevalence rates for diffuse and anaplastic astrocytomas, and oligodendroglial tumors were 9.33 and 7.53 /100,000, respectively. Therefore, the prevalence rate of diffuse lower-grade gliomas was 16.86 /100,000.

Approximation of the diffuse IDH-mutant glioma prevalence

There is no population data yet to provide a precise answer. Regarding oligodendrogliomas according to the 2021 WHO classification, the survival CBTRUS data from the years 2016-2020

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approach the current definition involving a 1p/19q codeletion (codel) and therefore an IDH 1/2 mutation. However, the survival of diffuse grade 2 and grade 3 astrocytomas does not reflect these of diffuse grade 2 and grade 3 IDH-mutant astrocytomas because diffuse grade 2 and grade 3 astrocytomas included diffuse grade 2 and grade 3 IDH-wildtype astrocytomas in the past WHO classifications. Moreover, glioblastoma IDH-mutant (2016 WHO classification) is now classified as grade 4 IDH-mutant astrocytoma. Therefore, it is difficult to estimate the prevalence of IDH-mutant astrocytomas. Here, we present the survival results of recent studies.

Gittleman et al. [58] analyzed the survival of diffuse lower-grade gliomas (diffuse grade 2 and grade 3 gliomas) from The Cancer Genome Atlas (TCGA) and the Ohio Brain Tumor Study (OBTS) data [238 patients in TCGA, and 98 patients in the OBTS]. Stratifying by molecular subtype, survival analysis showed a significant difference (p<0.001), with the IDH-mutant and codel subtype having the best survival (median survival = 134.3 months; 95% CI: 95.6–median survival not reached [NR] months), followed by the IDH-mutant non-codel subtype (median survival = 75.2 months; 95% CI: 57.9–NR months), and the IDH wildtype having the worst survival (median survival = 19.9 months; 95% CI: 12.8–34.0 months). In a series of the German Glioma Network including 258 patients with IDH-mutant astrocytomas (114 WHO grade 2, 73 WHO grade 3, 71 WHO grade 4), the median overall survival was not reached for grade 2 (median follow-up 10.4 years), 8.1 years (95% CI 5.4–10.8) for grade 3, and 4.7 years (95% CI 3.4–6.0) for grade 4 [59]. In a 20-year retrospective cohort of 392 patients with IDH-mutant grade 2 gliomas, Hervey-Jumper et al. [6] analyzed the progression-free survival (PFS) and the overall survival (OS). The median PFS (and 95% confident intervals) were: 5.70 (4.95 - 8.02), 11.69 (9.29 - 17.70), 8.65 (7.34 to 9.70) years, for IDH-mutant astrocytoma, oligodendroglioma, and both tumor types, respectively. The median OS (and 95% confident intervals) were: 13.1 (11.5 - 18.6), not available - NA (22.2 - NA), and 19.9 (18.0 - NA) years, for IDH-mutant astrocytoma, oligodendroglioma, and both tumor type, respectively. Of course, these series included selected patients, and the survival of all IDH-mutant glioma patients in a population-based study would not be as long.

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Considering CBTRUS 2016-2020 data (survival and incidence) for oligodendrogliomas (grade 2) and considering that 60% of diffuse grade 2 astrocytomas are IDH-mutant and with a median survival of 10 years, the prevalence of diffuse grade 2 IDH-mutant gliomas would be at least: 6.57 / 100,000 persons. As specified above, the mean survival is generally lower than the median survival. Therefore, the prevalence of diffuse grade 2 IDH-mutant gliomas is probably higher than 6.57 / 100,000 persons. This result is in perfect agreement with the latest data published by Neff et al. [57].

Discussion

In this paper, we have reviewed the main factors that affect the incidence of gliomas in general and the incidence of diffuse lower-grade gliomas in particular (e.g., case definition, census methods, characteristics of the studied population (age, sex, ethnicity, ancestry, etc.), histological classifications, environmental and genetic factors, etc.). We estimated the 2024 French incidence of all gliomas (6.6 /100,000 person-years). We then provided French incidence estimates (per 100,000 person-years) of diffuse IDH-mutant gliomas (1, 0.5, 0.3, and 0.2, for all grades, grade 2, grade 3, and grade 4, respectively). Additionally, we estimated that the prevalence of diffuse grade 2 IDH-mutant gliomas may be superior than 6.57 per 100,000 persons.

The estimate of the 2024 French glioma incidence is in good accordance with data from Western countries [16,18,19]. The observed rate is marginally higher than that of the United States, slightly lower than that of Scandinavian countries, and approximately equivalent to that of Belgium. Of note, in France, substantial variations in incidence exist among certain departments. In particular, the incidence of gliomas and glioblastomas seems higher in the far southwest [Bauchet, 2020]*, just as the mortality rate of CNS cancer (mainly linked to mortality due to gliomas) is also more marked in the far southwest of France [Rapport Santé Publique France: Estimations régionales et départementales de l'incidence et de la mortalité par cancer en France, 2007-2016 (santepubliquefrance.fr)]. The estimated incidence of diffuse IDH-mutant gliomas in France is

Journal Pre-proof

consistent with the limited data published in the literature [16,18,59-61]. Data regarding diffuse lower-grade glioma prevalence are limited, but we found an increase between the first and the last publications [57]. This is mainly explained by the increase in the duration of registration of cases by brain tumor registries.

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Limitations

Our study has several limitations. First, owing to incomplete data collection across the entire population, we provided French estimates based on partial results from selected centers while considering the overall observed trends. Second, we discussed literature data obtained through diverse methodologies, noting that population-based study data remains limited. Third, and perhaps most significantly, we presented statistical data without addressing clinical relevance. Indeed, in light of the recent introduction of anti-IDH therapies and modifications to WHO classifications of gliomas, we have provided estimates of the incidence and prevalence of diffuse IDH-mutant glioma; however, we cannot specify for which patients this novel treatment may be proposed. The diagnosis, prognostic factors, surgical management, chemotherapy, and/or radiotherapy management for diffuse lower-grade gliomas have changed over time [6,49,53,62-68]. Currently, the timing of adjuvant therapy after surgery remains controversial and varies across healthcare facilities [61]. Furthermore, considering the long life expectancy of patients (median survival reaching 20 years in certain series), the prescription of a new treatment, whatever it may be, must not (or very little) compromise their quality of life. Indeed, in the study of 600 grade 2 IDH-mutant gliomas patients from Ng et al. [69] the median overall survival was over 20 years, the median overall survival with Karnofsky performance status ≥80% was 14.7 years, and the rate of return to work was 93.7%.

Finally, the optimal timing for administering anti-IDH treatment to patients with diffuse IDH-mutant gliomas remains unclear. Should it be administered before or after the surgery? Between the two surgical interventions for low-risk patients (and how is a low-risk patient defined in 2024)? Prior

Journal Pre-proof

to or during chemotherapy? Given the diverse clinical, radiological, and biological scenarios as well as the variability in medical-surgical care across institutions, only a comprehensive real-world study can adequately address these questions.

Conclusion

This study presents the incidence and prevalence estimates for diffuse IDH-mutant gliomas. However, only large-scale observational and prospective real-life clinical studies are needed to elucidate the optimal strategies for the utilization of anti-IDH treatments.

Author contributions

Conception and design: LB; Analysis and interpretation of data: LB, VR, BM, AD; Writing and reviewing the article: all authors.

Ethical approval

The ethical committee approval was not required given the article type (review).

Conflict of interest

LB, AD: advisory board for Servier; BM: consultant for Servier.

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collaborators

Neurosurgeons and other doctors:

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Table 1. Main factors impacting the glioma incidence

Factor	Value or trend of the incidence (examples)	Reference population	Reference
Country / Area	5.9[a] in USA	US standard population	Miller et al. 2021 [23]
	7.7[a] in Gironde (French area)	Crude rate, unchanged when standardizing on the French population	Pouchieu et al. 2018 [22]
	Other countries, see:		Ostrom et al. 2014 [17]
Sex	Men: 8.6[a] ; Women: 6.0[a] in Nordic countries (Sweden, Norway, Finland and Denmark)	European standard population	Deltour et al. 2012 [19]
Age	Incidence increases with age 20-34 years: 2.74[a] ; 75-84 years : 18.82[a] in USA	US standard population	Ostrom et al. 2023 [16]
Race/Ethnicity	White: 6.33[a] ; Black : 3.5[a] in USA	US standard population	Ostrom et al. 2023 [16]
Genetic and family history	Incidence increases: -Mendelian cancer syndromes (neurofbromatosis types I and II, tuberous sclerosis, Li Fraumeni, etc.) -specific genes and/or single nucleotide polymorphisms (SNPs) -European ancestry -about 5% of glioma are familial		Ostrom et al. 2021 [24] Ostrom et al. 2019 [25] Melin et al. 2017 [26] Labreche et al. 2018 [27] Bauchet and Sanson 2023 [28] Nakase et al. 2024 [29] Wrensch et al. 1997 [30] Choi et al. 2023 [31]
Environment	Incidence increases: with Ionizing radiation. Many environmental risk factors are suspected and still under investigation, but with no conclusive results yet (e.g., pesticides, solvents, nonionizing radiation, virus, etc.).		Sadetzki et al. 2005 [32] Ostrom et al. 2014 [17] Ostrom et al. 2019 [25] Carles et al. 2020 [33] Baldi et al. 2021 [34]
virus varicella zoster infection	Incidence decreases		Amirian et al. 2016 [35] Ostrom et al. 2019 [25] Ostrom et al. 2021 [24]
Allergies and other atopic conditions	Incidence decreases		Schwartzbaum et al. 2012 [36] Amirian et al. 2016 [37] Ostrom et al. 2019 [25] Ostrom et al. 2021 [24]

[a] per 100,000 person-years

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Table 2. Diffuse lower-grade glioma incidences in France, period 2006-2009: standardized rates and international comparisons (Age-sex adjusted incidence rates, per 100,000 with 95 % confidence intervals, to Europe, USA and World standard population), adapted from Darlix et al. 2014 [51]

Histology From 2007 WHO classification	Reference population			
	France	Europe	USA	World
All diffuse grade 2 and 3 gliomas	19.4 [18.8-19.9]	19.8 [19.2-20.4]	18.8 [18.2–19.3]	16 [15.5–16.4]
All diffuse grade 2 and 3 gliomas excluding NOS gliomas	18.8 [18.3–19.3]	19.2 [18.6–19.8]	18.2 [17.7–18.7]	15.5 [15.0–16.0]
All diffuse grade 2 gliomas	8.5 [8.1–8.9]	8.6 [8.3–9.0]	8.3 [8.0–8.7]	7.6 [7.3–8.0]
All diffuse grade 3 gliomas	10.0 [9.7–10.4]	10.3 [9.9–10.7]	9.6 [9.3–10.0]	7.6 [7.3–8.0]

NOS: not otherwise specified

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Table 3. Annual age-adjusted incidence rates (IR) (reference population: US Population), and 95% confidence intervals for selected diffuse WHO grade II and grade III glioma histologies in the United States, 2010–2014, adapted from Bauchet and Ostrom (2019) [4]

	Diffuse Astrocytoma		Anaplastic Astrocytoma		Oligodendroglioma		Anaplastic Oligodendroglioma	
	age-adjusted IR	95% CI	age-adjusted IR	95% CI	age-adjusted IR	95% CI	age-adjusted IR	95% CI
Overall	0.48	0.47–0.49	0.40	0.39–0.41	0.24	0.23–0.25	0.11	0.10–0.11
Sex								
Males	0.55	0.54–0.57	0.46	0.44–0.47	0.28	0.26–0.29	0.12	0.11–0.13
Females	0.42	0.41–0.43	0.35	0.33–0.36	0.21	0.20–0.22	0.09	0.09–0.10
Age								
0–14	0.25	0.23–0.27	0.10	0.09–0.11	0.04	0.03–0.04	—a	—a
15–39	0.44	0.42–0.46	0.30	0.29–0.32	0.28	0.27–0.30	0.09	0.08–0.10
≥40	0.64	0.62–0.66	0.63	0.61–0.65	0.31	0.30–0.32	0.17	0.16–0.18
Race								
White	0.53	0.51–0.54	0.44	0.43–0.45	0.27	0.26–0.28	0.12	0.11–0.12
Black	0.29	0.26–0.31	0.21	0.19–0.23	0.11	0.10–0.13	0.05	0.04–0.06
AIAN	0.28	0.21–0.37	0.21	0.15–0.29	0.13	0.09–0.19	—a	—a
API	0.28	0.25–0.32	0.23	0.20–0.27	0.16	0.13–0.19	0.10	0.08–0.12

AIAN, American Indian/Alaska Native; API, Asian Pacific Islander; CI, confidence interval.

a: Rates are not presented when fewer than 16 cases were reported.

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Table 4. Distribution of brain molecular markers for select histopathologically-confirmed glioma in the CBTRUS Statistical Report (US Cancer Statistics – NPCR and SEER, 2018-2020) adapted from Ostrom et al. 2023 [16] and in the Belgian Cancer Registry report (2017-2019) adapted from Pinson et al. 2024 [18].

US data			**Belgium data**		
Histology	N	P%/s	**Histology**	N	P%/g
Diffuse Astrocytoma			**Astrocytoma, IDH-mutated**	**181**	
Diffuse astrocytoma, IDH-mutant	1701	43.8	grade 2	68	37.6
Diffuse astrocytoma, IDH-wildtype	1337	34.4	grade 3	38	21.0
Diffuse astrocytoma, IDH Status Unknown	845	21.8	grade 4	75	41.4
Anaplastic Astrocytoma			**Astrocytoma, IDH-wildtype**	**100**	
Anaplastic astrocytoma, IDH-mutant	1695	44.3	grade 2	44	44.0
Anaplastic astrocytoma, IDH-wildtype	1696	44.4	grade 3	56	56.0
Anaplastic astrocytoma, IDH Status Unknown	433	11.3	**Astrocytoma, NOS**	**77**	
			grade 2	46	59.7
			grade 3	31	40.3
Oligodendroglioma			**Oligodendroglioma, IDH-mutated and 1p/19q codeleted**	**99**	
Oligodendroglioma, IDH-mutant and 1 p/19q co-deleted	1836	91.5	grade 2	61	61.6
Oligodendroglioma, NOS	171	8.5	grade 3	38	38.4
Anaplastic Oligodendroglioma			**Oligodendroglioma, NOS**	**31**	
Anaplastic oligodendroglioma, IDH-mutant and 1 p/19q co-deleted	958	93.1	grade 2	15	48.4
Oligodendroglioma, anaplastic	71	6.9	grade 3	16	51.6
Glioblastoma			**Glioblastoma**	**1677**	
Glioblastoma, IDH-wildtype	29,066	78.5	Glioblastoma, IDH-wildtype*	1118	
Glioblastoma, IDH Status Unknown	6068	16.4	Glioblastoma NOS	559	
Giant cell glioblastoma	229	0.6			
Gliosarcoma	757	2			
Glioblastoma, IDH-mutant	919	2.5			

P%/s: percentage by IDH status; P%/g: percentage by grade; NOS: not otherwise specified

*In the Belgian Cancer Registry, Giant cell glioblastoma and Gliosarcoma are included in Glioblastoma, IDH-wildtype

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Tableau 5. Incidence and number of patients with newly-diagnosed and histologically confirmed glioma in metropolitan France*

Years	**2006-2010**	**2011-2015**	**2016-2020**	**2024**
Incidence (per 100 000 person-years)	6.08[a]	6.21[a]	6.47[b]	6.60[b]
Average number of patients/year	3778	3956	4195[b]	4365[b]
Average number of patients (aged ≥ 12 years) per year	3610	3769	4002[b]	4166[b]

*: metropolitan France (2024 population: 66 142 961 inhabitants) includes mainland France and nearby islands in the Atlantic Ocean and Mediterranean Sea, and excludes overseas territories;

a: crude rate; b: estimates.

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Table 6. Count and prevalence estimates, median age (in years), incidence and median survival (in months) of main subtypes of diffuse gliomas in USA, adapted from Zhang et al. 2017 [56], Ostrom et al. 2023 [16], and Neff et al. 2023 [57].

	2010 prevalence estimates from Zhang et al. 2017[a]		**Data extracted from the 2016-2020 CBTRUS report, Ostrom et al. 2023[a]**					**Counts in 2019, from Neff et al. 2023[a]**
	Count	Prevalence[b]	Median age	Incidence[c]	95% CI	Median survival	95% CI	Count
Diffuse astrocytoma	11,644	3.76	45	0,44	0,43 – 0,45	63	60 - 66	30,633
Anaplastic astrocytoma	4,933	1.59	52	0,39	0,38 – 0,40	21	20 - 21	
Oligodendroglioma	8,523	2.76	44	0,23	0,22 – 0,23	205	196 - 209	24,710
Anaplastic oligodendroglioma	2,201	0.71	49	0,11	0,10 – 0,11	108	101 - 116	
Oligoastrocytic tumors	4,017	1.30	47	0,01	0,01 – 0,02	113	107-120	
Glioblastoma	19,972	6.46	66	3,27	3,24 – 3,29	8	8-9	24,688

[a] The study periods and methodologies used in each of these works are not exactly the same. For more details, see each of these publications.

[b] per 100,000 persons

[c] per 100,000 person-years

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Title of Figure 1:

Fig. 1. Glioma histological classifications according to the 2007, 2016 and 2021 CNS WHO classifications, adapted from Louis et al. 2007 [43], Louis et al. 2016 [44] and WHO Classification of Tumours Editorial Board 2021 [1]

Legend of Figure 1:

NOS: not otherwise specified

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WHO 2007

Astrocytic tumours	
Pilocytic astrocytoma	9421/1[1]
Pilomyxoid astrocytoma	*9425/3**
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Diffuse astrocytoma	9400/3
Fibrillary astrocytoma	9420/3
Gemistocytic astrocytoma	9411/3
Protoplasmic astrocytoma	9410/3
Anaplastic astrocytoma	9401/3
Glioblastoma	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Gliomatosis cerebri	9381/3
Oligodendroglial tumours	
Oligodendroglioma	9450/3
Anaplastic oligodendroglioma	9451/3
Oligoastrocytic tumours	
Oligoastrocytoma	9382/3
Anaplastic oligoastrocytoma	9382/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Cellular	9391/3
Papillary	9393/3
Clear cell	9391/3
Tanycytic	9391/3
Anaplastic ependymoma	9392/3

WHO 2016

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion–positive	9396/3*
Anaplastic ependymoma	9392/3

WHO 2021

Adult-type diffuse gliomas	
	Astrocytoma, IDH-mutant
9400/3	Astrocytoma, IDH-mutant, grade 2
9401/3	Astrocytoma, IDH-mutant, grade 3
9445/3	Astrocytoma, IDH-mutant, grade 4
	Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
9450/3	Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, grade 2
9451/3	Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, grade 3
9440/3	Glioblastoma, IDH-wildtype
Paediatric-type diffuse low-grade gliomas	
9421/1	Diffuse astrocytoma, MYB- or MYBL1-altered
9431/1	Angiocentric glioma
9413/0	Polymorphous low-grade neuroepithelial tumour of the young
9421/1	Diffuse low-grade glioma, MAPK pathway–altered
Paediatric-type diffuse high-grade gliomas	
9385/3	Diffuse midline glioma, H3 K27–altered
9385/3	Diffuse hemispheric glioma, H3 G34–mutant
9385/3	Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
9385/3	Infant-type hemispheric glioma
Circumscribed astrocytic gliomas	
9421/1	Pilocytic astrocytoma
9421/3*	High-grade astrocytoma with piloid features
9424/3	Pleomorphic xanthoastrocytoma
9384/1	Subependymal giant cell astrocytoma
9444/1	Chordoid glioma
9430/3	Astroblastoma, MN1-altered
Ependymal tumours	
9391/3	Supratentorial ependymoma, NOS
9396/3	Supratentorial ependymoma, ZFTA fusion–positive
9396/3	Supratentorial ependymoma, YAP1 fusion–positive
9391/3	Posterior fossa ependymoma, NOS
9396/3	Posterior fossa group A (PFA) ependymoma
9396/3	Posterior fossa group B (PFB) ependymoma
9391/3	Spinal ependymoma, NOS
9396/3	Spinal ependymoma, MYCN-amplified
9394/1	Myxopapillary ependymoma
9383/1	Subependymoma

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