Incidence and survival rates for adult malignant neuro-epithelial brain tumors in the Somme county (France): A retrospective, population-based study from 2003 to 2013

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Incidence and survival rates for adult malignant neuro-epithelial brain tumors in the Somme county (France): A retrospective, population-based study from 2003 to 2013

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ABSTRACT

Aims: To describe the incidence and survival rates for neuro-epithelial primary brain tumors (NPBTs) in adults in the Somme county between 2003 and 2013.
Methods: By analyzing the Somme Cancer Registry, we calculated the age-standardized incidence rates (ASRs) for NPBTs. Independent effects of age, gender and period of diagnosis on the incidence were evaluated in a Poisson regression analysis. A Cox proportional hazards model was used to adjust the overall survival rates for age, gender, histologic group and period.
Results: Of the 257 registered NPBTs, 193 (75.1%) were astrocytic tumors. The subpopulations most affected by NPBTs were men (incidence rate ratio (IRR) [95% confidence interval (CI)] females/males = 0.7 [0.55–0.90], $p < 0.001$) and the elderly (IRR [95% CI] = 1.02 [1.01–1.03] per year increment, $p < 0.001$). The ASR [95% CI] was 4.5 [3.9–5.1] cases per 100,000 person-years. The increase in incidence [95%CI] between 2003 and 2013 was estimated to be 7.6% [3.4–11.2%] per year ($p < 0.001$). Survival improved significantly between the 2003–2008 period and the 2009–2013 period (hazard ratio [95%CI] = 0.70 [0.50–0.96], $p = 0.03$).
Conclusion: We observed an increase in the incidence of NPBTs and in survival rates between 2009 and 2013. These increases might have been due to broader, earlier access to diagnostic tools and/or improvements in treatment procedures.

1. Introduction

Neuro-epithelial primary brain tumors (NPBTs) are rare. In 2009, they accounted for just 2% (n = 4491) of all malignant tumors in adults in France (a country with 64.7 million inhabitants at that time) [1]. The prognosis is poor, with a five-year survival rate of 19% [2]. Although the incidence of NPBTs has increased in all age groups, the elderly seem to have been particularly affected [3–6]. This trend has mainly been imputed to population ageing and improved diagnostic procedures (such as medical imaging [7] or neurosurgical biopsies) but is not observed worldwide or at all time points. The overall incidence of malignant brain tumors (all histologic types) increased by 1.1% a year between 1980 and 2012 in adults in France [8] but decreased by 3.1% a year between 2008 and 2010 in adults in the United States [9].

Data on NPBTs from European population-based studies are scarce, and most of the published studies were performed in Scandinavia [10–12]. The survival rate varies from one type of neuro-epithelial tumor to another. For astrocytic tumors (which have the worst prognosis), the number of therapeutic options has increased over the last decade with the emergence of novel procedures for surgery, radiation therapy, chemotherapy and targeted therapy, and combinations thereof.

The primary objective of the present study was to describe the age-standardized incidence rates (ASRs) for NPBTs in the Somme county of France (by age and by gender) and to assess changes in these parameters between 2003 and 2013. The secondary objectives were to describe the overall survival rates and the treatments administered to patients with grade IV astrocytic tumors (the most incident and lethal histologic subtype).

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Table 1
Incidence by gender and histologic subtype (according to the WHO 2007 classification).

Histologic subtype	Both genders					Women					Men					Gender ratio (M/F)
	n	%	CR	ASR	[95%CI]	n	%	CR	ASR	[95%CI]	n	%	CR	ASR	[95%CI]	
Astrocytic tumors	193	75.08	4.2	3.0	2.5 – 3.5	76	71.7	3.2	2.2	1.7 – 2.9	117	77.5	5.3	3.8	3.1–4.7	1.5
Oligodendroglial tumors	20	7.79	0.4	0.5	0.3 – 0.7	8	7.6	0.5	0.5	0.2 – 0.1.0	12	7.9	0.5	0.6	0.3 – 1.1	1.5
Oligoastrocytic tumors	29	11.28	0.8	0.7	0.5 – 1.1	15	14.2	0.9	0.9	0.5 – 1.6	14	9.3	1	1	0.5 – 1.7	0.9
Ependymal tumors	5	1.95	0.1	0.1	0 – 0.3	2	1.9				3	2.0				
Neuronal and mixed neuronal-glial tumors	5	1.95	0.1	0.1	0 – 0.3	3	2.8				2	1.3				
Embryonal tumors	4	1.56	0.1	0.1	0 – 0.3	1	0.9				3	2				
Other neuro-epithelial tumors	1	0.39				1	0.9				0	0				
Total	**257**	**100**	**5.7**	**4.5**	**3.9 – 5.1**	**106**	**100**	**4.6**	**3.4**	**2.8 – 4.3**	**151**	**100**	**6.8**	**5.5**	**4.6 – 6.6**	**1.4**

The bold values corresponds to the results of the whole population described in thus study.
ASR: age-standardized incidence rate, CI: confidence interval, CR: crude incidence rate.

2. Materials and methods

The Somme Cancer Registry (SCR) is a population-based cancer registry located in the Somme county of northern France (population in 2014: 571,461). The SCR's main information sources are public- and private-sector hospitals and, in particular, the latter's central laboratories and pathology departments. Malignant, borderline and benign brain tumors are registered.

2.1. Data selection

The present study's data were extracted from the SCR database. We selected adult patients (≥18 years of age) who had been diagnosed with a malignant NPBT between January 1st, 2003, and December 31st, 2013. The International Classification of Disease for Oncology (3rd edition) [13] was used to code the tumors in terms of their morphology and topography (code C71). The tumors were sorted into histologic subgroups according to the 2007 World Health Organization (WHO) classification [14] for tumors of the central nervous system (CNS). Benign tumors, cases lacking histologic confirmation, meningeal, soft tissue and spinal cord tumors, and primary brain lymphomas were excluded from the study. For grade IV astrocytic tumors, the treatment provided was determined by inspection of the patient's medical files.

2.2. Statistical analysis

Incidence was calculated both as crude rate (CR) and as a world ASR for both genders and for men and women separately. We examined the period ranging from 2003 to 2013 and then each year within this period. The incidence rate was calculated as the number of new NPBT cases for 100,000 person-years for each year and (for five-year age groups) according to the age at diagnosis. Census data on the Somme county's population for each time period was obtained from the French National Institute of Statistics and Economic Studies (*Institut National de la Statistique et des Études Économiques*) [15].

To define whether the incidence of NPBTs decreased or increased over time, we applied a Poisson regression model (adjusted for age, gender and period) after confirming the absence of overdispersion.

Overall survival was calculated from the date of diagnosis and the censoring date was either January 15th, 2016, the date of last follow-up or the death date (whichever occurred first).

The Kaplan-Meier method was used to estimate survival. A log-rank test was used to compare survival among the different histologic subgroups. We did not include neuronal, embryonal and mixed tumors in this analysis, given the small sample size in these subgroups. A Cox proportional hazards model was built to assess the effect of gender, age, histologic subtype and period (2003–2008 or 2009–2013) on survival, after verification of the proportionality assumption.

Descriptive statistics were used to evaluate first-, second- and third-line treatments for grade IV astrocytic tumors. The results are presented as frequencies (i.e. proportion of percentage of glioblastomas treated with a given modality).

3. Results

A total of 257 new cases were reported by the SCR between 2003 and 2013. The median (interquartile range) follow-up time was 17 (31) months. 97 patients (38%) were alive on January 15th, 2016. The mean age was 55.7, and males accounted for 151 cases (58.7%).

According to the 2007 WHO classification, the histologic subgroups were distributed as follows: 193 (75.1%) astrocytic tumors, 29 (11.3%) oligoastrocytic tumors, 20 (7.8%) oligodendroglial tumors, 5 (1.9%) ependymal tumors, 5 (1.9%) neuronal and mixed neuronal-glial tumors, 4 (1.6%) embryonal tumors and 1 (0.4%) chordoid glioma of the third ventricle (classified in the "other types of neuro-epithelial tumors" group). The most frequent astrocytic tumors were glioblastomas, followed by diffuse astrocytomas.

3.1. Incidence

During the period 2003–2013, the CR for NPBTs (all types) among adults in the Somme county was 5.7 cases per 100,000 person-years, and the ASR [95% CI] was 4.5 [3.9–5.1] per 100,000 person-years. For women and men, the CR was respectively 4.6 and 6.8 per 100,000 person-years, and the ASR [95% CI] was 3.4 [2.8–4.3] and 5.5 [4.6–6.6] person-years respectively. The overall gender ratio (M/F) was 1.4 (Table 1). The highest incidence was found for astrocytic tumors (ASR [95%CI]: 3.0 [2.5–3.5] per 100,000 person-years), followed by oligoastrocytic tumors (0.7 [0.5–1.1] per 100,000 person-years) and oligodendroglial tumors (0.5 [0.3–0.7] per 100,000 person-years).

Age-specific incidence rates by gender are described in Fig. 1. The number of cases rose progressively from the age of 30 onwards, and the age-specific incidence rate [95%CI] peaked at 14.2 [12.4–15.7] per 100,000 person-years in the 60–64 age group. For NPBT cases as a whole, 82 (31.9%) occurred in patients aged 65 or over. These age trends were observed for both men and women.

The age-adjusted incidence increased significantly from 2003 to 2013. In the multivariate analysis of the incident cases adjusted for age group, year period and gender, this variation over time translates into an annual increase [95%CI] of 7.6% [3.4–12.0]. Similarly, the number of incident cases rose significantly per year of age (incidence rate ratio (IRR) [95%CI] = 1.02 [1.01–1.03]; p = 0.006) and with male gender ($IRR_{F/M}$ = 0.70 [0.55–0.90]) (Table 2).

3.2. Survival

The median [95%CI] overall survival (from the date of histologic diagnosis onwards) was 19 [16–25] months. The patients with the best 5-year overall survival rates [95%CI] were those diagnosed with embryonal tumors (100% [100–100]), followed by those with

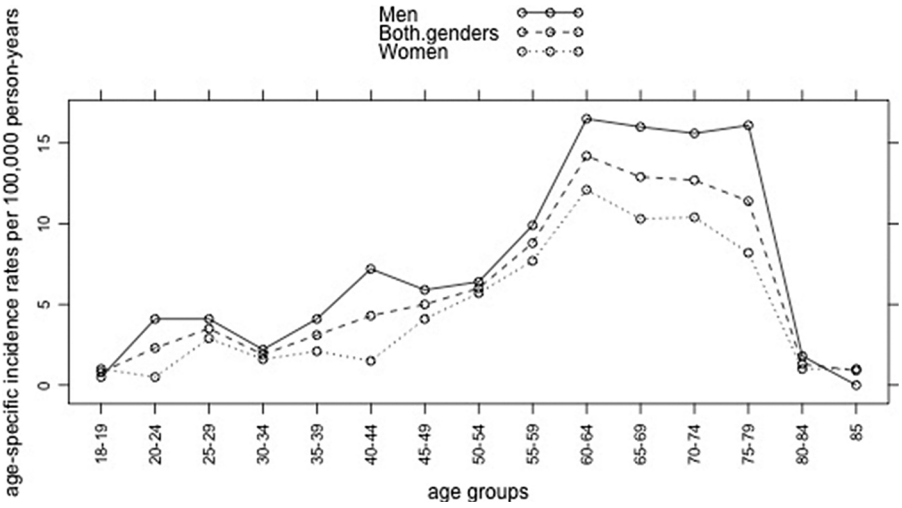

Fig. 1. Age-specific incidence rates by gender.

Table 2
The results of a multivariate analysis of incident cases by age, period and gender.

	Incidence rate ratio	95%CI	p	APC	95%CI
Period[a]	1.07	1.03–1.12	< **0.001**	7.6	3.4–12.0
Age	1.02	1.01–1.03	**0.006**		
Gender (F/M)	0.70	0.55–0.90	< **0.001**		

The bold values correspond to the significance of the confidence interval given for period age and gender.
CI: confidence interval; APC: annual percentage change.
[a] Each period is defined as a calendar year.

Table 3
The results of a multivariate analysis of survival by age, gender, period and histologic subgroup (using astrocytic tumors as the reference subgroup).

	HR	95%CI	p value
Age	1.03	1.02–1.04	< 0.0001
Gender (F/M)	1.12	0.81–1.54	0.50
Oligodendroglial tumors	0.13	0.04–0.40	< 0.001
Oligoastrocytic tumors	0.44	0.25–0.81	0.007
Period (B/A)	0.70	0.50–0.96	0.03

HR: hazard ratio; CI: confidence interval; Period A: 2003–2008, Period B: 2009–2013.

oligodendroglial tumors (84.7% [70.2–100]). Astrocytic tumors presented the worst survival rates, with a 5-year overall survival rate [95%CI] of 19% [13.2–27.4]. The Kaplan-Meier survival curves for the three main histologic subgroups differed significantly from each other (log rank test: $p < 0001$). Oligodendroglial and oligoastrocytic tumors were associated with a better prognosis than astrocytic tumors, with a relative risk reduction in death of 87% (hazard ratio (HR) [95%CI] = 0.13 [0.04–0.40]; $p < 0.001$) and 56% (HR = 0.44 [0.25–0.81]; $p < 0.007$), respectively. Survival has increased since 2009 ($HR_{2003\text{-}2008/2009\text{-}2013}$ = 0.70 [0.50-0.96]; $p < 0.03$). The median [95%CI] overall survival time was 14 months [10–22] between 2003 and 2008 and 20 months [16–36] thereafter. Age had an independent, negative effect on survival (HR [95%CI] = 1.03 [1.02–1.04] per year of age; $p < 0.0001$) (Table 3).

3.3. Treatment

The first-, second- and third-line treatments given to the 159 patients with grade IV astrocytic tumors (i.e. glioblastomas, including giant cell glioblastomas) are summarized in Fig. 2. Data were missing for 3 (1.9%) of the 159 patients. In terms of first-line treatments, 72 (45.3%) patients underwent complete macroscopic resection and 31(19.5%) underwent partial macroscopic resection. The remaining 35.2% of the cases were diagnosed on the basis of a biopsy alone. The Stupp protocol (introduced in the Somme county in 2006) was applied in 60.4% cases. This protocol is based on a combination of radiotherapy and daily chemotherapy with temozolomide, and is generally followed by six cycles of adjuvant chemotherapy with temozolomide (5 days a month). Twenty-one cases treated with the Stupp protocol (13.2%) received more than the usual six adjuvant temozolomide cycles. The physicians mostly justified this choice by the persistence of residual tumor tissue after six cycles. Bevacizumab (an antiangiogenic therapy for glioblastoma introduced in 2010 in the Somme county) was given to 21 (13.2%) patients; it was combined with either temozolomide and radiotherapy (according to the AVAGLIO protocol [16]) or neoadjuvant temozolomide alone. Eleven patients (6.9%) received carmustine implants (9 after complete macroscopic resection and 2 after partial macroscopic resection), followed by the Stupp protocol in 10 cases (Fig. 2**a**).

Seventy-seven (48.4%) patients received second-line treatment: 47 (29.6%) received bevacizumab (administered in combination with chemotherapy in 29 (18.2%) cases and administered alone as a symptomatic anti-edema treatment in 15 (9.4%) cases) (Fig. 2**b**).

Twenty-five (15.7%) patients initiated a third line treatment. Bevacizumab (usually combined with chemotherapy) was administered to 16 (10.1%) patients (Fig. 2**c**).

4. Discussion

Our data showed an ASR of 4.5 per 100,000 person-years for NPBTs in the Somme county of northern France. Over the 11-year study period, we observed a mean annual increase of 7.6%. Age and gender had independent effects on the incidence of NPBTs. Our data also revealed an increase over time in survival for patients with NPBTs – particularly since 2009. Lastly, our results showed that the most frequently administered first-line therapies were surgery and/or the Stupp protocol and that the most frequently administered second- or third-line treatment was bevacizumab (alone or combined with other therapies).

The SCR population-based cancer registry provides exhaustive, reliable information on the incidence and survival of NPBT among the 571,000 inhabitants living in the Somme county. Our study thus constitutes an accurate, up-to-date description of the incidence of NPBTs in this area between 2003 and 2013. Although our sample may not be representative on the French national or European scale, the present study is (to the best of our knowledge) the first to use data from a population-based cancer registry to describe the epidemiology of NPBT in France over the last decade. The most recently published literature data covered a period ending in 2002 [17].

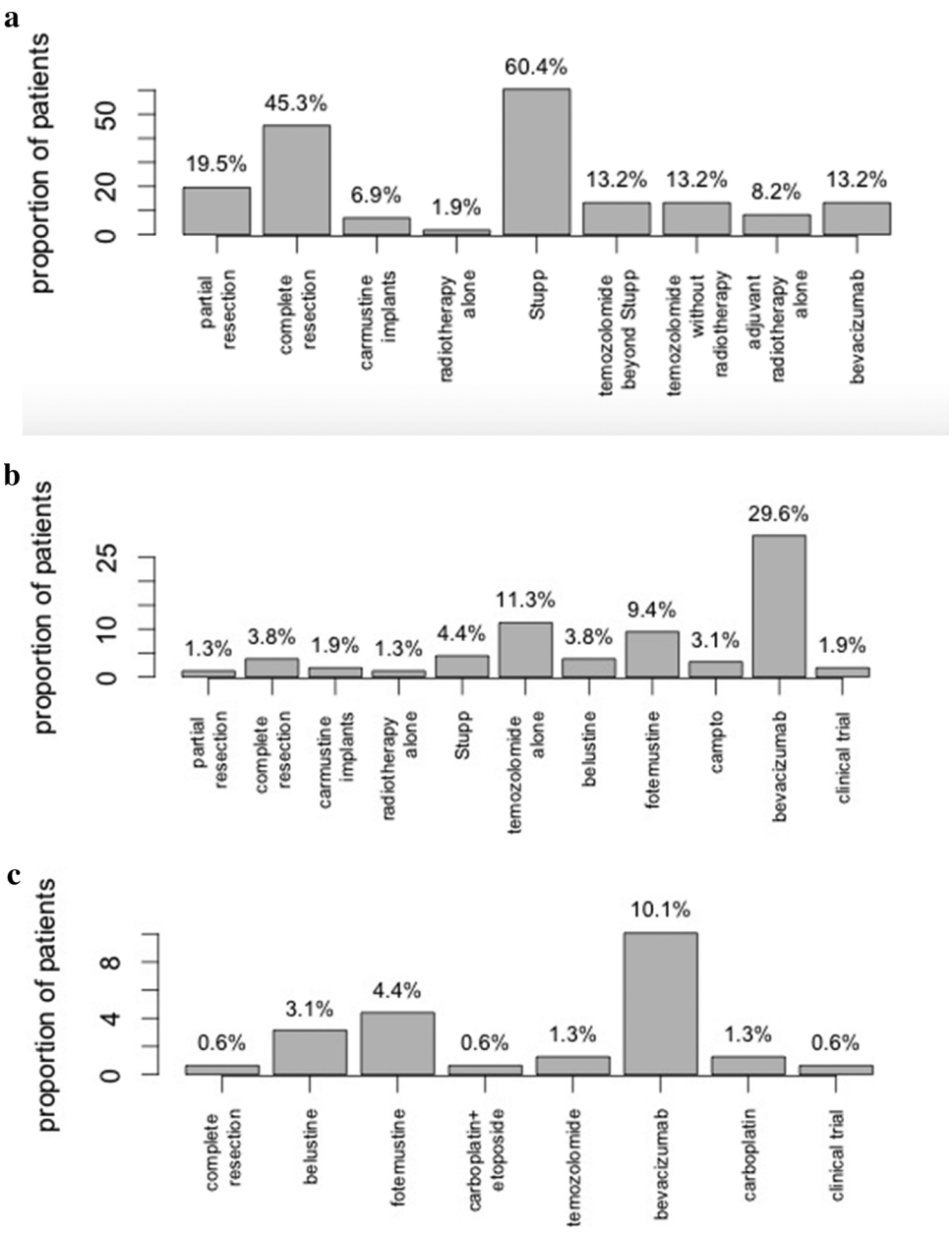

Fig. 2. (a) Distribution of first-line treatments in the 159 patients with glioblastomas. (b) Distribution of second-line treatments in patients with glioblastoma (77 ou of 159). (c) Distribution of third-line treatment in patients with glioblastoma (25 out of 159).

Our work focused exclusively on tumors with histologic confirmation, although 10.8% of the brain tumors registered in the SCR over the 11-year study period were undefined. A previous study of central nervous system tumors in the Somme county (1988–1997) reported that 11.2% were undefined [18], and a recent study in Girona (Spain) reported a value of 41% [19]. These disparities between registries probably reflect differences in diagnostic practice. Over the last decade, oncogeriatric units have been implemented in most cancer centers in the Somme, and physicians have been encouraged to refer their patients to an expert center for diagnosis.

The overall characteristics of neuro-epithelial brain tumors included in the SCR during the 11-year study period are consistent with the findings of most other studies in this field. The overall incidence increased dramatically with age, and men had a significantly higher risk of developing these tumors [20–22].

The observed increase in ASR rates may be due to (amongst other things) population aging, better access to diagnosis tools for elderly patients, and improvements in neurosurgery. Nevertheless, we cannot rule out the occurrence of changes in potential risk factors. However, neither the SCR's registration procedure nor the use of imaging technologies changed significantly during the study period.

The more pronounced increase in incidence in men than in women suggests the involvement of gender-related factors. Some studies have reported a protective effect of menopause or bilateral oophorectomy [23], although the increased use of hormones by women since the 1960s (with the introduction of oral contraception, hormone replacement therapy, and sterility treatments) may also account for this effect.

With regard to the survival of patients with ependymal, embryonal neuronal and mixed-neuronal glial tumors, our results corroborate the literature data [17]. However, the small number of cases prevented us from computing survival estimates for these particular NPBTs. Despite this limitation, our work revealed a significant increase in overall survival from 2003 to 2013 for all other NPBTs and confirmed the significantly poorer prognosis for astrocytic tumors.

Survival of NPBTs has not improved in Europe from 1988 to 2002, which suggests that treatment procedures have not progressed during this period [24]. Visser et al. described an increase in 1-year relative survival of 10–12% in most European regions from 2002 to 2007 −

particularly in central and northern Europe [25]. This trend was confirmed in our study, and suggests that therapeutic progress has indeed been achieved over the past decade [26]. However, elderly patients have not benefited from this increase in survival; despite the use of more interventional treatments in this age group, under-treatment may still be a concern. This increased over time in survival should be interpreted with caution, since a lead-time bias (due to earlier diagnosis) may be present.

Since 2006, the standard of care for glioblastoma in the Somme county has been the most extensive, well-tolerated surgical resection possible, followed by a combination of radiotherapy and temozolomide chemotherapy. Moreover, antiangiogenic treatment with bevacizumab was introduced in 2010. These clinical practices concord with the guidelines issued by the European Society of Medical Oncology) guidelines [27] and those issued by the Association of French-speaking Neuro-oncologists (*Association des Neuro-oncologues d'Expression Française*) [28]. Compliance with guidelines and the enhancement of supportive care may have contributed to increase in survival observed over recent years. It is nevertheless important to note that very few patients are included in clinical trials. This may be due to the frailty of the few patients who are still eligible for systemic treatment after first-line therapy.

In conclusion, our data showed that incidence of NPBTs increased between 2003 and 2013 in the Somme county (particularly among the elderly). This trend is perhaps due to the increased use of diagnostic imaging and surgery, especially among elderly patients. The recent development of oncogeriatric units may have favored the adoption of a less conservative attitude to the treatment of elderly and/or frail patients.

Declaration of conflicts of interest

D. Bello Roufai declares potential conflicts of interest through her relationships with Sanofi Adventis, Sandoz, Novartis, Amgen and Chugai (reimbursement of symposium expenses).

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