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Incidence and survival of children with central nervous system primitive tumors in the French National Registry of Childhood Solid Tumors

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Background. Central nervous system (CNS) tumors are the second most common childhood malignancy. The French National Registry of Childhood Solid Tumors (NRCST) makes it possible to describe this variety of distinct tumor types and to provide incidence and survival data in France on a nationwide basis.

Methods. All children aged 0–14 years, who were registered with a primary CNS tumor in the NRCST of France between 2000 and 2008, were identified. Tumors were classified according to the International Classification of Childhood Cancer, third edition.

Results. Approximately 57% of pediatric CNS tumors were gliomas, with astrocytomas of the pilocytic type predominating. Distributions of subtypes by age showed that primitive neuroectodermal tumors and ependymomas mainly occurred in children aged <5 years. The mean annual incidence rate of CNS tumors was 39 per million. No statistically significant change in time trends of incidence rate was observed during 2000–2008. For all tumors combined, overall survival was 84.8% (95% CI, 83.7%–85.9%) at 1 year and 72.9% (95% CI, 71.5%–74.3%) at 5 years. Survival time trends were studied in a multivariate analysis observing a reduction in the risk of death in periods of diagnosis 2003–2005 (HR = 0.8; 95% CI, 0.7–0.9) and 2006–2008 (HR = 0.7; 95% CI, 0.6–0.9) compared with 2000–2002.

Conclusions. The stable incidence rates during the last 10 years could indicate that major changes in environmental risk factors are unlikely, but the ongoing need for population-based surveillance remains relevant. Results indicate a positive trend in the survival probability still persistent in the 2000s.

Keywords: children, CNS tumor, incidence, population-based study, survival.

In France, as in other developed countries, primary tumors of the central nervous system (CNS) represent the second most frequent neoplasm after leukemia and the leading cause of cancer-related death in childhood. They account for ~25% of malignancies in children <15 years of age at diagnosis.[1] This group of tumors, however, cannot be considered as a single entity because it is composed of different diagnostic categories, the largest being astrocytomas, ependymomas, central primitive neuroectodermal tumors (cPNETs, including medulloblastomas), and other gliomas.[2] In line with the third version of the International Classification of Childhood Cancer (ICCC-3),[3] the CNS tumors include tumors of cranial and paraspinal nerves. Intracranial tumors account for ~90% of all CNS tumors in children. The proportion of cases without histological confirmation of diagnosis is larger than that of other childhood cancers. In our previous study, the diagnosis was documented by cytology/histology in 86% of CNS tumor cases versus 94% of all cancer cases.[1] Contrary to the general rule of cancer registry recommendations, some nonmalignant neoplasms are also included in the CNS group because it is difficult to establish a borderline between benign and malignant neoplasms in the case of ependymomas, some gliomas, and miscellaneous or unspecified intracranial and intraspinal neoplasms.[3] Many cancer registries routinely include nonmalignant CNS tumors.

We report incidence and survival analyses from the French National Registry of Childhood Solid Tumors, in which the CNS tumors have been classified according to the ICCC-3.[3]

Materials and Methods

Population Covered

We identified children with a diagnosis of CNS tumor who were registered in the French National Registry of Childhood Solid Tumors, a population-based

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tumor registry containing data on mainland France. Population data were provided by the French Institute of Statistics and Economic Studies for each year until 2008. The number of births increased slightly until 2002, and the child population was rather stable over that period, varying overall from 11 113 855 children aged <15 years in 2000 to 11 369 876 children in 2008. For a given year, person-years were computed by years of age and sex as the mean of the populations in each year and the next year.

Case Registration

All cases of children (aged 0–14 years) with CNS tumors diagnosed in mainland France between 2000 and 2008 are included. In line with the recommendations of the European Network of Cancer Registries[4] and the ICCC-3,[3] benign or borderline tumors of CNS are also recorded. According to the third edition of the International Classification of Disease – Oncology (ICDO-3),[5] a CNS tumor is defined as a lesion with the following topography code: C70.0-9, C71.0-9, C72.0-9, and C75.1-3. Lacour et al.[1] have previously described the methodology of case registration for the French National Registry of Childhood Solid Tumors.

Data Collection

The registration form includes identification data (first and last names, sex, date and place of birth, address at diagnosis), diagnostic data (incidence date, basis of diagnosis, method of first detection, site of primary tumor, histological type, immunophenotype and genetics, metastasis at diagnosis, laterality, histological grade according to the WHO grading system), patient pathway from diagnosis to treatment, initial treatment (date of treatment initiation, cancer treatment type), vital status, and last contact date. The diagnoses are coded using the ICDO-3[5] and further grouped using the ICCC-3.[3] The diagnosis of CNS tumors could be fortuitous, related to the exploration of symptoms, or related to the surveillance of predisposing conditions (such as neurofibromatosis, tuberous sclerosis, etc.) regardless of whether the patients underwent treatment or not. Vital status was obtained at the time of analysis by actively searching in medical records and by matching the French National Registry of Childhood Solid Tumors files and the central population register (RNIPP) sorted by date and place of birth to obtain the mention of death and the date of death.

Data Analysis

All data were retrieved, tabulated by tumor type, and categorized using the ICCC-3 levels: 12 main diagnostic groups, 47 diagnostic subgroups, and 2–11 divisions of selected subgroups.[3] The incidence rates (IRs) were calculated for the 9-year period 2000–2008 and were based on person-years derived from the Institute of Statistics and Economic Studies' annual estimates of population by age and sex. Crude and age-specific IRs were calculated, and age-standardized rates were estimated by the direct method using the world population for the age groups under 15 years.[6] Cumulative rates, defined as the sum of the age specific IRs over each year of age from 0 to 14 years, were also calculated.[6] Time trend in the incidence was estimated by the conventional annual percent change calculated as the slope of the linear regression used to model the natural logarithm of the IRs as a function of the calendar year.[7] Median length of follow-up was calculated using the inverse Kaplan–Meier method.[8] Survival analysis was performed on a dataset containing all cases diagnosed between January 1, 2000, and December 31, 2008, and followed up until October 1, 2011. The probability of overall survival was estimated using the Kaplan–Meier method.[9] The endpoint of interest was death from any cause for OS, with the date of diagnosis acting as the time origin. Survival curves between groups were compared using the log-rank test,[10] and the trend in survival over time periods was estimated using the log-rank test for trend.[11] The risks of death according to age, sex, grade, stage, and period were estimated by hazard ratios (HRs) and their 95% confidence intervals (95% CI) using Cox proportional hazards regression models.[12] Reference categories were selected logically as the first category (benign tumor, not metastatic, low-grade/WHOI-II, and period 2000–2002) or as the modal category (1–4-year age group), or arbitrarily (boys, infratentorial brain). Statistical tests were 2-sided with a significance level of 0.05. All statistical analyses were performed using SAS version 9.3 (SAS Institute).

Results

Population Description

Between January 1, 2000, and December 31, 2008, there were 3 886 children (2 118 boys and 1 768 girls) younger than aged 15 years diagnosed with a CNS tumor in France. The most common CNS tumors were pilocytic astrocytomas (21.8%), followed by medulloblastomas (13.7%), other astrocytic tumors (13.0%), unspecified malignant gliomas (6.8%), and ependymomas (6.5%). The more detailed diagnostic subgroups are described by age group in Table 1.

The mean age at diagnosis was 7.0 ± 4.4 years for the whole patient group. There were differences in the distribution by histological type according to the age group (Table 1): atypical teratoid/rhabdoid tumors, choroid plexus tumors, and other neuronal-glial tumors were more common before 1 year of age (10.2% vs 1.9%, 12.3% vs 2.0%, and 4.6% vs 0.5%, respectively); germ cell tumors, oligodendrogliomas, dysembryoplastic neuroepithelial tumors, gangliogliomas, and meningiomas were more common after 10 years of age (9.7% vs 4.0%, 5.5% vs 3.6%, 5.8% vs 3.6%, and 3.0% vs 0.9%, respectively); ependymomas and central primitive neuroectodermal tumors (c-PNETs) were more frequent in the 1-4-year age group (9.2% and 4.0%), and medulloblastomas, unspecified gliomas, and craniopharyngiomas were more frequent in the 5-9-year age group (17.0%, 8.5%, and 6.9%, respectively).

Sex Ratio

More boys were affected with CNS tumors than girls (Table 2). The M:F ratio was 1.2 for the whole material, close to 1.0 for astrocytomas, other gliomas, meningiomas, craniopharyngiomas, and unspecified tumors, but the M:F ratio was between 1.3 and 1.6 for ependymomas, choroid plexus tumors, embryonal tumors, pituitary adenomas, germ cell tumors, and sarcomas, and M:F ratio of 2.5 for melanomas.

Annual Incidence

There were ~11.2 million children aged <15 years in France. The overall annual age-standardized incidence of brain tumors in this age group was 39.0 per 1 000 000 children (Table 2), 41.5 for boys and 35.9 for girls. The ASR was a little higher for children aged 1 to 5 years (44.6 per million) and declined slightly in older age groups (37.9 and 33.4 per million in the 5–9-year and 10–14-year age groups, respectively).

Temporal Trends in the Incidence

The incidence was stable during the 2000–2008 period with a nonsignificant conventional annual percent change of −0.2% (95% CI, −2.9%– 2.6%), $P = .90$.

Table 1. Distribution of CNS tumor histologic types by age group (French National Registry of Childhood Solid Tumors, 2000–2008)

Histologic types according to the ICDO-3[5]	<1 year		1–4 years		5–9 years		10–14 years	
	n	%	*n*	%	*n*	%	*n*	%
Pilocytic astrocytomas (M9421)	38	13.4	268	22.3	294	23.3	248	21.7
Other astrocytomas (M9384,M9400–4411, M9420, M9423-9424)	11	3.9	60	5.0	77	6.1	81	7.1
Malignant gliomas (M9380, M9381, M9430, M9444)	37	13.0	203	17.0	150	11.9	85	7.5
Glioblastomas (M9440-9442)	3	1.1	8	0.7	27	2.1	27	2.4
Mixed gliomas (M9382)	3	1.1	14	1.2	27	2.1	22	1.9
Oligodendrogliomas (M9450, M9451)	8	2.8	36	3.0	55	4.4	63	5.5
Medulloblastomas (M9470-9472, M9474)	31	10.9	162	13.5	215	17.0	125	10.9
Central primitive neuroectodermal tumors (M9473)	7	2.5	47	3.9	33	2.6	22	1.9
Atypical teratoid/rhabdoid tumors (M9508)	29	10.2	55	4.6	9	0.7	4	0.4
Ependymomas (M9383, M9391-9394)	17	6.0	110	9.2	71	5.6	53	4.6
Choroid plexus tumors (M9390)	35	12.3	51	4.3	10	0.8	11	1.0
Germ cell tumors (M9060-9105)	20	7.0	44	3.7	45	3.6	111	9.7
Craniopharyngiomas (M9350-9352)	2	0.7	39	3.3	87	6.9	56	4.9
Dysembryoplastic neuroepithelial tumors (M9413)	7	2.4	28	2.3	51	4.0	66	5.8
Gangliogliomas (M9505)	3	1.1	28	2.3	41	3.2	64	5.6
Meningiomas (M9530-9539)	1	0.4	9	0.8	16	1.3	34	3.0
Others tumors	32	11.2	35	2.9	55	4.4	70	6.1
Total	**284**	**100.0**	**1197**	**100.0**	**1263**	**100.0**	**1142**	**100.0**

ICDO-3: third edition of International Classification of Disease – Oncology.

Survival by ICCC-3 Diagnosis Groups

At the end time, 1 098 children had died with a median time after diagnosis of 12 months (min-max: 0–131 months). With 7.5% lost to follow-up, the length of follow-up ranged from 0 to 11 years, with a median follow-up of 6 years and 10 months. Table 2 describes the OSs at 1 and 5 years by ICCC-3 diagnostic groups and subgroups. For all tumors combined, OS was 84.8% (95% CI, 83.6–85.9) at 1 year and 72.9% (95% CI, 1.5–74.3) at 5 years. The best survivals were observed for pituitary adenomas, craniopharyngiomas, neuronal-glial tumors, meningiomas, and germ cell tumors, for which the 5-year OSs were higher than 90%. Conversely, the lowest survivals were observed for c-PNETs, medulloepitheliomas, atypical teratoid/rhabdoid tumors, mixed and unspecified gliomas, gliomatosis cerebri, and melanomas, for which the 5-year OSs were lower than 35%. The 5-year OSs were close to 50% for oligodendroglioma, unspecified tumors, and sarcomas, and close to 65%–70% for ependymomas, choroid plexus tumors, medulloblastomas, and pineal parenchymal tumors.

Univariate Survival Analysis

During the 2000–2008 period studied, there was no variation of survival by sex. During the same period, a more favorable prognosis was significantly suggested for older children, aged 10–14 years, especially for ependymomas and choroid plexus tumors, astrocytomas (IIIa diagnostic subgroup), c-PNET (IIIc diagnostic subgroup), and other specified tumors (IIIe diagnostic subgroup including 23 pituitary adenomas, 184 craniopharyngiomas, 28 pineal parenchymal tumors, 332 mixed neuronal-glial tumors, and 60 meningiomas). Conversely, for other gliomas (IIId diagnostic subgroup especially including 162 oligodendrogliomas and 329 mixed gliomas), the highest survival was observed in the 0-1-year age group ($P < .001$). For all tumor types, high-grade (WHO III and IV) and metastatic tumors were associated with worse survival. Compared with the supratentorial tumor site, the infratentorial tumor sites were associated with worse survival for ependymomas and choroid plexus tumors, other gliomas, and other specified tumors (IIIe diagnostic group including especially mixed neuronal-glial tumors, craniopharyngiomas, and meningiomas) and with better survival for astrocytomas and c-PNETs.

Temporal Trends in the Survival

A comparison of OSs in the 2000–2002 period with those from earlier time periods (2003–2005 and 2006-2008) indicated that substantial survival gains were achieved for all tumors pooled (Table 3), with 68.4% (95% CI, 65.6–70.9), 73.2% (95% CI, 70.6–75.5), and 74.5% (95% CI,71.8–77.0), respectively, at 5 years ($P < .001$). The same time trends were observed for ependymomas and choroid plexus tumors in the subgroup analysis.

Multivariate Survival Analysis

Table 4 presents results of the multivariate analyses of age, sex, tumor location, grade, stage, and period of diagnosis. We observed a statistically significant reduction of the HR for all tumors pooled in more recent periods compared with 2000–2002. Analysis by diagnostic subgroup confirmed the results only for ependymomas, choroid plexus tumors, and c-PNETs. Analysis by age, sex, tumor location, grade, and stage confirmed the results of univariate analyses.

Table 2. Number of cases of childhood CNS tumors, sex ratio, annual incidence rates per million children, 1-year and 5-year overall survivals by ICCC-3 diagnostic groups and subgroups (French National Registry of Childhood Solid Tumors, 2000–2008)

Diagnosis according to the ICCC-3[3]	*n*	%	Sex-ratio	Incidence (/10^6)		Overall Survival (CI 95%)	
				ASR	Cumulative	1-year OS	5-year OS
III. CNS and miscellaneous intracranial and intraspinal neoplasms	**3 649**	**93.8**	**1.2**	**36.7**	**542.1**	**84.3 (83.1–85.4)**	**71.9 (70.4–73.4)**
IIIa. Ependymomas and choroid plexus tumors	358	9.1	1.4	3.8	53.2	86.6 (82.6–89.7)	68.4 (63.1–73.1)
IIIa1. Ependymomas	251	6.5	1.3	2.6	37.3	88.4 (83.8–91.8)	67.1 (60.7–72.7)
IIIa2. Choroid plexus tumors	107	2.8	1.4	1.2	15.9	82.1 (73.4–88.2)	71.3 (61.5–79.0)
IIIb. Astrocytomas	1355	34.9	1.0	13.7	201.3	92.5 (91.0–93.7)	87.1 (85.1–88.8)
IIIc. Intracranial and intraspinal embryonal tumors	746	19.2	1.5	7.7	111.0	75.2 (71.9–78.1)	53.6 (49.9–57.2)
IIIc1. Medulloblastomas	534	13.7	1.8	5.4	79.4	86.5 (83.3–89.1)	64.7 (60.4–68.7)
IIIc2. c-PNET	109	2.8	1.0	1.1	16.2	57.8 (48.0–66.4)	34.3 (25.5–43.3)
IIIc3. Medulloepitheliomas	6	0.2	0.2	0.1	0.9	50.0 (11.0–80.4)	33.3 (0.0–67.6)
IIIc4. Atypical teratoid/rhabdoid tumors	97	2.5	1.1	1.1	14.4	34.0 (24.8–43.4)	16.4 (9.9–24.5)
IIId. Other gliomas	498	12.8	1.0	4.9	74.0	60.8 (56.3–64.9)	35.4 (31.1–39.6)
IIId1. Oligodendrogliomas	162	4.2	1.3	1.6	24.0	72.1 (64.5–83.0)	51.1 (43.1–58.6)
IIId2. Mixed and unspecified gliomas	329	8.5	0.9	3.3	48.9	55.6 (50.1–60.8)	27.8 (23.0–32.8)
IIId3. Neuroepithelial glial tumors of uncertain origin	7	0.2	0.4	0.1	1.0	42.9 (9.8–73.4)	28.6 (4.1–61.2)
IIIe. Other specified intracranial and intraspinal neoplasms	627	16.1	1.3	6.0	93.0	97.0 (95.3–98.0)	94.2 (92.0–95.8)
IIIe1. Pituitary adenomas and carcinomas	23	0.6	1.6	0.2	3.4	100.0 (–)	100.0 (–)
IIIe2. Tumors of the sellar region (craniopharyngiomas)	184	4.7	1.2	1.8	27.4	97.3 (93.6–98.9)	96.2 (92.1–98.2)
IIIe3. Pineal parenchymal tumors	28	0.7	0.6	0.3	4.2	85.7 (66.3–94.4)	67.1 (46.2–81.3)
IIIe4. Neuronal and mixed neuronal-glial tumors	332	8.5	1.4	3.2	49.2	97.9 (95.6–99.0)	95.1 (92.1–97.0)
IIIe5. Meningiomas	60	1.5	1.0	0.6	8.9	95.0 (85.3–98.4)	93.1 (82.6–97.4)
IIIf. Unspecified intracranial and intraspinal neoplasms	65	1.7	1.0	0.6	9.6	64.6 (51.7–74.9)	57.7 (44.7–70.7)
Xa. Intracranial and intraspinal germ cell tumors	**220**	**5.7**	**1.6**	**2.1**	**32.5**	**95.4 (91.7–97.5)**	**92.1 (87.5–95.0)**
Xa1. Intracranial and intraspinal germinomas	85	2.1	2.5	0.8	12.5	100.0 (–)	97.4 (90.0–99.3)
Xa2. Intracranial and intraspinal teratomas	83	2.1	1.0	0.9	12.3	98.8 (91.8–99.8)	97.5 (90.5–99.4)
Xa3. Intracranial and intraspinal embryonnal carcinoma	2	0.1	1.0	0.0	0.3	50.0 (0.0–91.0)	50.0 (0.0–91.0)
Xa4. Intracranial and intraspinal yolk sac tumors	10	0.3	2.3	0.1	1.5	70.0 (32.9–89.2)	60.0 (25.3–82.7)
Xa5. Intracranial and intraspinal choriocarcinomas	14	0.4	1.3	0.1	2.1	92.9 (59.1–99.0)	84.4 (50.4–95.9)
Xa6. Intracranial and intraspinal tumors of mixed forms	26	0.7	1.6	0.2	3.8	88.5 (68.4–96.1)	80.4 (59.1–91.4)
IX. Intracranial and intraspinal sarcomas	**10**	**0.3**	**1.5**	**0.1**	**1.5**	**70.0 (32.9–89.2)**	**50.0 (18.4–75.3)**
XId. Intracranial and intraspinal Malignant melanomas	**7**	**0.1**	**2.5**	**0.1**	**1.0**	**28.6 (0.1–61.2)**	**0.0 (–)**
Total	**3886**	**100.0**	**1.2**	**39.0**	**577.2**	**84.8 (83.6–85.9)**	**72.9 (71.5–74.3)**

Abbreviations: ARS, age-standardized rates; c-PNET, central primitive neuroectodermal tumors; ICCC-3, third version of the International Classification of Childhood Cancer; OS, overall survival.

Discussion

This study describes the incidence and the survival of childhood CNS tumors in France during the period 2000–2008, based on national population-based cancer registry data. We showed that the incidence was stable during this period, with average annual age-standardized rates of 39.0 per million. We demonstrated that the high proportion of deaths had occurred within 1 year from diagnosis and that the 5-year survival improved over time to reach 74.5% (95% CI, 71.8–77.0) at the end of the period. We also noted an age-specific incidence of CNS tumors by subtype and variations in survival between age at diagnosis, histological type, location, stage, and grade of tumor.

CNS tumors in children are a heterogeneous group, with more than 100 histological rare and distinct entities. Variations in classification and registration practices complicate the characterization of incidence, survival, and temporal trends data.[13–15] Recent publications in the Nordic European countries, in Canada, and in the United States covering the same period have reported comparable incidence rates from 40 to 42 per million.[15–20] The completeness of the French National Registry of Childhood Solid Tumors, due to national coverage and compulsory registration of both benign and malignant tumors based to various sources of notification, provides a nonbiased and valid view of the situation in France during the period studied.[1] In our study, no variation in incidence has been shown during the last 10 years in France. Conversely, several studies analyzing incidence during the last 30–40 years have observed a significant increase from +0.7% to +5.7%, particularly during the 1975–1990 period and especially for astrocytomas, due to differences in registration

Table 3. Five-year overall survival among children with CNS tumors by ICCC-3 diagnostic groups (French National Registry of Childhood Solid Tumors, 2000–2008)

	Diagnostic Groups According to the ICCC-3[3]						
	III- CNS	IIIa- Ependymomas and Choroid Plexus Tumors	IIIb- Astrocytomas	IIIc- Embryonal Tumors	IIId-Other Gliomas	IIIe-Other Specified Tumors	Xa-Germ Cell Tumors
	5-y OS (95% CI)	5-y OS (95% CI)	5-y OS (95% CI)	5-y OS (95% CI)	5-y OS (95% CI)	5-y OS (95% CI)	5-y OS (95% CI)
Sex							
Boys	72.2 (70.1–74.1)	70.1 (63.1–76.0)	86.2 (83.3–88.6)	54.4 (49.6–59.0)	35.9 (29.9–42.0)	95.9 (93.2–97.6)	90.9 (84.5–94.7)
Girls	71.7 (69.4–73.8)	66.0 (57.7–73.1)	88.0 (85.2–90.3)	52.6 (46.7–58.1)	34.9 (29.1–40.8)	91.9 (88.0–94.6)	93.9 (85.8–97.4)
Age							
<1 year	59.6 (53.2–65.3)	63.5 (48.3–75.4)	76.7 (65.5–84.7)	32.2 (21.3–43.6)	75.0 (50.0–88.7)	76.5 (57.0–88.1)	85.0 (60.4–94.9)
1–4 years	68.6 (65.8–71.2)	60.2 (52.0–67.4)	93.3 (90.5–95.3)	35.1 (29.4–40.9)	41.1 (32.5–49.5)	93.0 (86.5–96.4)	90.9 (77.6–96.5)
5–9 years	71.6 (68.9–74.1)	78.1 (67.1–85.8)	85.0 (81.3–88.1)	65.2 (58.9–70.8)	22.3 (16.6–28.5)	94.2 (90.1–96.6)	92.9 (79.6–97.7)
10–14 years	79.3 (76.6–81.7)**	80.7 (68.5–88.6)**	83.9 (79.7–87.3)**	76.7 (68.9–82.8)**	41.7 (33.9–49.3)**	96.8 (93.7–98.4)**	93.5 (86.8–96.8)
Grade							
Low grade	91.4 (90.1–92.6)	79.3 (72.9–84.3)	93.9 (92.2–95.2)	–	70.2 (61.5–77.3)	96.7 (94.8–97.9)	–
High grade	45.7 (42.8–48.5)	50.8 (42.0–59.0)	21.6 (15.0–28.9)	–	23.1 (16.8–30.0)	53.0 (36.2–67.3)	–
Unknown	61.2 (56.8–65.3)**	88.9 (43.3–98.4)**	97.3 (93.7–98.9)**	–	22.5 (17.1–28.5)**	100.0 (–) **	–
Site							
Supratentorial	72.7 (69.7–75.4)	71.3 (63.6–77.7)	77.4 (72.8–82.1)	28.1 (19.5–37.3)	56.7 (48.8–63.9)	97.6 (94.7–98.9)	95.2 (82.3–98.8)
Infratentorial	63.5 (61.1–65.9)	60.1 (49.9–68.9)	87.2 (84.1–89.7)	60.4 (56.2–64.2)	19.4 (14.8–24.5)	88.3 (71.8–95.4)	83.9 (57.9–94.5)
Unspecified	83.7 (81.3–85.8)**	73.7 (62.5–82.0)*	91.8 (89.1–93.9)**	27.1 (16.1–39.2)**	43.4 (31.4–54.9)**	92.3 (88.8–94.7)*	92.2 (86.7–95.5)
Stage							
Not metastatic	74.0 (72.5–75.5)	70.5 (65.2–75.1)	87.8 (85.9–89.5)	56.8 (52.5–60.9)	35.4 (31.2–39.7)	94.7 (92.6–96.2)	91.8 (82.2–94.8)
Metastatic	43.3 (36.8–49.5)**	10.3 (0.0–35.5)**	45.8 (25.6–64.0)**	44.2 (36.9–51.3)**	33.3 (0.1–67.6)	63.6 (29.7–84.5)**	75.0 (12.8–96.1)
Period							
2000–2002	68.4 (65.6–70.9)	58.3 (48.8–66.7)	84.2 (80.4–87.3)	51.1 (44.8–57.0)	30.8 (23.8–38.1)	93.1 (88.4–95.9)	89.4 (80.0–94.6)
2003–2005	73.2 (70.6–75.5)	66.0 (56.9–73.6)	90.3 (87.2–92.7)	52.6 (46.2–58.4)	38.0 (30.8–45.2)	94.9 (91.1–97.2)	90.8 (81.6–95.5)
2006–2008	74.5 (71.8–77.0)##	82.3 (73.4–88.5)##	86.8 (83.2–89.7)	57.6 (50.6–64.0)	37.7 (30.2–45.1)	94.3 (90.1–96.7)	97.0 (88.5–99.2)

Abbreviations: 5-y OS, 5-year overall survival; c-PNET, central primitive neuroectodermal tumors; NOS, not otherwise specified; ICCC-3, third version of the International Classification of Childhood Cancer.

test Logrank: *P value <.05, **P value <.01; test Log-rank trend: #P value <.05, ##P value <.01.

Low grade: Astrocytic tumors: M94003, M94203, M94113, M94503, M94211, M94103, M93841; Choroid plexus tumors: M93900; Ependymal tumors: M93913, M93941, M93933, M93831; Glial tumors of uncertain origin: M94441; Meningiomas: M95340, M95391, M95381, M95320, M95300, M95310, M95330, M95370; Mixed tumors: M93823; Neuronal and neuronal-glial tumors: M95061, M95061, M94121, M94130, M94930, M94920, M95051, M86801; Pineal parenchymal tumors: M93611; Tumors of the sellar region: M93501, M93511, M93521, M95820.

High grade: Astrocytic tumors: M94013, M94413, M94403, M94423, M94513; Choroid plexus tumors: M93903; Embryonal tumors: M95083, M94713, M94743, M94703, M94703, M95013, M94723, M94733, M94733; Ependymal tumors: M93923; Glial tumors of uncertain origin: M93813; Meningiomas: M95303, M95383; Mixed tumors: M93823; Neuronal and neuronal-glial tumors: M95053; Pineal parenchymal tumors: M93623, M93623.

Table 4. Results of multivariate analysis of survival of children with CNS tumors by ICCC-3 diagnostic groups (French National Registry of Childhood Solid Tumors, 2000–2008)

	Diagnostic Groups According to the ICCC-3[3]						
	III- CNS	IIIa-Ependymomas and choroid plexus tumors	IIIb-Astrocytomas	IIIc-Embryonal tumors	IIId-Other gliomas	IIIe- Other specified tumors	Xa-Germ cell tumors
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Sex							
Boys	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Girls	1.1 (1.0–1.3)	1.1 (0.8–1.6)	1.0 (0.8–1.4)	1.1 (0.8–1.3)	0.9 (0.8–1.2)	1.7 (0.9–3.3)	0.8 (0.3–2.0)
Age							
<1 year	1.3 (1.1–1.7)	0.9 (0.5–1.6)	2.3 (1.3–4.0)	1.4 (0.9–1.9)	0.4 (0.2–0.9)	3.6 (1.3–10.3)	1.5 (0.3–6.9)
1–4 years	Ref	Ref	Ref	Ref	Ref	Ref	Ref
5–9 years	0.9 (0.7–1.0)	0.6 (0.4–1.1)	1.2 (0.8–1.8)	0.4 (0.3–0.6)	1.6 (1.2–2.1)	0.9 (0.4–2.0)	1.0 (0.2–4.3)
10–14 years	0.7 (0.6–0.8)	0.5 (0.3–0.9)	1.2 (0.8–1.8)	0.3 (0.2–0.4)	1.3 (0.9–1.7)	0.6 (0.2–1.5)	0.9 (0.3–3.3)
Grade							
Low grade	Ref	Ref	Ref	–	Ref	Ref	–
High grade	7.0 (5.9–8.3)	2.5 (1.7–3.8)	23.2 (16.7–32.3)	–	4.2 (3.0–6.1)	16.5 (8.0–33.9)	–
Unknown	5.9 (4.8–7.3)	0.6 (0.1–4.2)	0.7 (0.3–1.5)	–	2.9 (2.0–4.1)	1.1 (0.1–8.6)	–
Site							
Supratentorial	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Infratentorial	0.9 (0.8–1.1)	1.6 (1.0–2.4)	1.3 (0.9–1.8)	0.4 (0.3–0.6)	2.3 (1.7–3.0)	5.5 (1.8–16.7)	1.9 (0.3–10.4)
Unspecified	0.5 (0.4–0.6)	0.9 (0.6–1.6)	0.8 (0.5–1.2)	1.0 (0.7–1.5)	1.6 (1.1–2.3)	1.2 (0.6–2.7)	1.1 (0.3–4.1)
Stage							
Not metastatic	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Metastatic	1.3 (1.1–1.5)	2.2 (1.1–4.2)	5.9 (3.2–10.7)	1.5 (1.2–1.9)	0.7 (0.3–2.0)	1.2 (0.4–4.0)	1.8 (0.2–14.5)
Period							
2000–2002	Ref	Ref	Ref	Ref	Ref	Ref	Ref
2003–2005	0.8 (0.7–0.9)	0.7 (0.4–1.0)	0.6 (0.4–0.9)	0.8 (0.6–1.1)	0.9 (0.7–1.2)	1.2 (0.5–2.5)	0.8 (0.3–2.3)
2006–2008	0.7 (0.6–0.9)	0.3 (0.2–0.6)	0.7 (0.5–1.1)	0.7 (0.6–0.9)	0.9 (0.7–1.2)	1.0 (0.5–2.4)	0.3 (0.1–1.3)

Abbreviations: c-PNET: central primitive neuroectodermal tumors; NOS: not otherwise specified; ICCC-3: third version of the International Classification of Childhood Cancer.
Cox proportional hazards regression.
Low grade: Astrocytic tumors: M94003, M94203, M94113, M94503, M94211, M94103, M93841; Choroid plexus tumors: M93900; Ependymal tumors: M93913, M93941, M93933, M93831; Glial tumors of uncertain origin: M94441; Meningiomas: M95340, M95391, M95381, M95320, M95300, M95310, M95330, M95370; Mixed tumors: M93823; Neuronal and neuronal-glial tumors: M95061, M95061, M94121, M94130, M94930, M94920, M95051, M86801; Pineal parenchymal tumors: M93611; Tumors of the sellar region: M93501, M93511, M93521, M95820.
High grade: Astrocytic tumors: M94013, M94413, M94403, M94423, M94513;Choroid plexus tumors: M93903;Embryonal tumors: M95083, M94713, M94743, M94703, M94703, M95013, M94723, M94733, M94733; Ependymal tumors: M93923; Glial tumors of uncertain origin: M93813; Meningiomas: M95303, M95383; Mixed tumors: M93823; Neuronal and neuronal-glial tumors: M95053; Pineal parenchymal tumors: M93623, M93623.

Table 5. Five-year survival rates by types of CNS tumors among children in Europe, in Australia, and the United States

Diagnostic Groups According to the ICCC-3[3]	Europe				United States[d]	Australia[e]
	France (2000–2008) % (95% CI)	Germany[a] (2001–2010) %	Sweden[b] (1984–2005) % (95% CI)	Great Britain[c] (2001–2005)%	(2002–2008)%	(1995–2004)% (95% CI)
III-CNS tumors	**71.9 (70.4–73.4)**	**76**	**76 (75–77)**	**71**	**71.1**	**70.8 (68.3–73.2)**
IIIa-Ependymoma and choroid plexus tumor	68.4 (63.1–73.1)	80	72 (68–76)	67	69.6	68.6 (59.6–76.0)
IIIb-Astrocytoma	87.1 (85.1–88.8)	80	84 (83–85)	81	84.3	77.9 (74.5–80.9)
IIIc-Embryonal tumors	53.6 (49.9–57.2)	66	61 (58–64)	56	59.8	50.5 (44.2–56.5)
Medulloblastoma	65.7 (60.4–68.7)	–	63 (59–67	–	–	–
Supratentorial cPNET	34.3 (25.5–43.3)	–	47 (40–54)	–	–	–
IIId-Other gliomas	35.4 (31.1–39.6)	42	44 (40–48)	44	52.1	53.8 (45.8–61.02)
Oligodendroglioma	51.1 (43.1–58.6)	–	78 (71–85)	–	–	–
Mixed and unspecified gliomas	27.8 (23.0–32.8)	–	42 (36–48)	–	–	–
Neuroepithelial glial tumors	28.6 (4.1–61.2)	–	12 (6–18)	–	–	–
Xa-CNS Germ-cell tumors	**92.1 (87.5–95.0)**	**90**	–	–	**84.7**	**84.5 (72.8–91.5)**

[a]Data from Ref. [24].
[b]Data from Ref. [19].
[c]Data from Ref. [25].
[d]Data from Ref. [18].
[e]Data from Ref. [23].
From 68.4% (95% CI, 65.6–70.9) in 2000–2002, ICCC-3: third version of the International Classification of Childhood Cancer.

and diagnostic technologies implemented in the mid 1980s and not representing real differences in incidence.[15,18,21] Rates for CNS tumors have been stable since 1990 in the United States and the Nordic European countries.[15,19,22]

Our 5-year overall survival rates for French children with CNS tumors were comparable to those reported in other European countries, Australia, and the United States during the same period[18,19,23–25] (Table 5), except for intracranial and intraspinal germ-cell tumors with a lower survival probability in the United States and in Australia (84.7%, 84.5% vs 92.1%, respectively) and for other gliomas with a higher survival probability (greater than 50% in the United States and Australia and between 42% and 44% in Germany, Sweden, and Great Britain vs 35.4% in our study). It is difficult to compare our results with other studies because selection criteria are not the same; some suggest different analyses to describe the epidemiology of CNS germ cell tumors (pineal vs nonpineal analysis), including only a behavior code of 3 (ie, malignant).[5,26,27] In our series of CNS germ cell tumors, 36% of tumors were mature teratomas ($n = 79$), and 64% were malignant (85 germinomas, 4 immature teratomas, 2 embryonal carcinomas, 10 yolk sac tumors, 14 choricarcinomas, and 26 mixed germ cell tumors). Survival rates did differ by biological behavior and histology, with mature teratomas having the highest 5-year overall survival (100%), and immature teratomas having the lowest 5-year overall survival (50%), 97.4% for germinomas, 84.4% for choriocarcinomas, and 80.4% for mixed germ cell tumors. Gliomas comprise a broad, heterogeneous spectrum of CNS tumors, depending on the registry and the histological criteria used.[28] According to the third version of the ICCC,[3] astrocytomas are grouped with glioblastomas and optic nerve gliomas (IIIb diagnostic group). Differences in the 5-year overall survival have been observed between low-grade astrocytomas (93% ± 1%), high-grade astrocytomas (28% ± 5%) and optic nerve/chiasma gliomas (91% ± 3%).[19] Discordance between institutional diagnosis of high-grade glioma and a central review, which favored the diagnosis of low-grade glioma, was observed in 15%–30% of reviewed cases, and this proportion could be different between countries.[29,30]

Moreover, recent microarray analyses used an unsupervised approach to identifying different molecular subtypes of CNS tumors after grouping for metastatic status, histology, and/or survival, especially for medulloblastomas.[31] Our diagnostic subgroup analysis cannot study outcome for new CNS classifications including distinct genetic profiles. In conclusion, differences in survival could be explained by differences in distribution of anatomical site, histological type, tumor grade, biological behavior, and/or molecular classification.

Our 5-year overall survival rate improved significantly during the 2000s, from 68.4% (95% CI, 65.6–70.9) in 2000–2002, 73.2% (95% CI, 70.6–75.5) in 2003–2005, to 74.5% (95% CI, 71.8–77.0) in 2006–2008. During the 1990s, Desandes et al.[32] reported a 5-year overall survival rate of French children with CNS tumor of 64.8% (95% CI, 61.4–68.1). Our survival time trends showed a reduction in the risk of death during the 2000s : HR of 0.8 (95% CI, 0.7–0.9) for the 2003–2005 period and HR of 0.7 (95% CI, 0.6–0.9) for the 2006–2008 period compared to the 2000–2002 period. These results should be interpreted with caution because biases may have been introduced to the difficulty of identifying an event, as the death, in patients with shorter follow-up (patients included in more recent time periods), and the increasing probability of observing an event with longer follow-up (patients diagnosed in the earlier time periods).

Our analysis by histological groups showed improvement in the 5-year overall survival, especially for ependymomas from 58.3% in 2000–2002 to 82.3% in 2006–2008. As shown by Koshy et al.,[33] postoperative radiation (PORT) improves survival in children with intracranial ependymomas. The 3-year overall survival was significantly improved for patients younger than aged 3 years who received PORT compared with those who did not (81% vs 56%, respectively; $P = .005$). In our study, the proportion of children with ependymomas treated by PORT has significantly improved from 7.8% in 2000–2002 to 29.7% in 2006–2008. As all studies are based on a cancer registry database, our study is also limited by the lack of complete data about treatment. No information was available on chemotherapy (type of drugs, number of cycles, ...), surgery (complete or incomplete resection, ...), and radiotherapy technique (total dose, fraction size, radiation volume, ...). Indeed, it is difficult to establish a causal relationship between radiation therapy and good prognosis.

The basic prognostic factors revealed by this study were similar to those reported by other studies.[19,34] c-PNET showed the poorest prognosis. The patient's sex is not a prognostic factor whereas age is, with the worst prognosis being among infants compared with older children. Young children have a higher proportion of malignancies in the cerebellum and brain stem, and their prognosis remains poor despite advances in treatment. However, caution should be taken with clinical series that report better survival than population-based studies.[35] It is important to review the outcome data and study of basic prognostic factors at the populational level, but our study has limitations including the lack of detailed clinical and treatment data that may impact survival. The ongoing collection of precise treatments for all cases included in the national registry will allow us to better describe outcome according to the treatment and to know their long-term effects.

In conclusion, this study confirms results from recent publications in which the incidence of CNS tumors is stable and close to 40 per million. The overall survival still improves over time and is approximately 73% at 5 years. The ongoing need for population-based surveillance remains relevant to analyzing major changes in environmental risk factors. Insights from population-based incidence and survival analyses provide an opportunity to better understand the impact of site and histological patterns on outcomes associated with CNS tumors and inform future research.

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