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1 **Infant Cancers in France: Incidence and Survival (2000-2014)**

2 **Abstract**

3 Background: On average 185 children are diagnosed each year in France with a cancer in their
4 first year of life, representing 11% of cancers diagnosed in children less than 15 years.

5 Methods: A retrospective population-based observational study was conducted between 2000
6 and 2014 of all infants with a diagnosis of cancer using the National Registry of Childhood
7 Cancers Database.

8 Results: Out of 2,760 cases of primary cancers in infancy, there were mainly neuroblastomas
9 (30.1%), central nervous system (CNS) tumors (16.1%), leukemias (15.3%), retinoblastomas
10 (11.6%), and Wilms tumors (6.9%). Embryonal malignancies accounted for 55.2% of cases.
11 Most diagnoses showed a male excess, particularly for malignant gonadal germ-cell tumors
12 (GCT) with a 17.5 sex-ratio. The annual incidence rate, 242.9 per million infants overall, was
13 stable over the study period for all types of cancer. Most deaths occurred within the first
14 month of life (70.8% of deaths). The 5-year overall survival (5-y OS) was 81.0% (95%CI,
15 79.4-82.4) with large contrasts between diagnoses. The best 5-y OS (>85%) were observed
16 for retinoblastomas, carcinomas, nephroblastomas, GCT, neuroblastomas, and
17 hepatoblastomas. Conversely, the lowest 5-y OS (<65%) were observed for acute myeloid
18 leukemias, CNS tumors, and lymphoid leukemias. We observed no substantial change over
19 time (80.5% [95%CI, 77.7-82.9] in 2000-2004 and 82.6% [95%CI, 80.0-84.9] in 2010-2014)
20 for all cancers combined. The same result has been found whatever the diagnostic group.

21 Conclusion: Our results contribute to better understand these tumors by quantifying their
22 impact on the French population and assessing the burden of some devastating infant cancers.

23

24

25

26 **1. Introduction**

27 Cancer in infants is rare, with about 185 new cases diagnosed annually in France, for an
28 average annual incidence rate of 243 per million [1]. There are substantial differences for
29 these cancers compared to older children, in terms of methods of diagnosis, incidence,
30 anatomical site, histological features, clinical behavior and treatment [1-4]. Prenatal detection
31 is becoming more and more efficient, which raises issues regarding not only the best option
32 during pregnancy and the conditions of delivery for optimal treatment, but also over-diagnosis
33 of possibly spontaneously regressive tumors [4]. Despite predisposing genetic factors in
34 infants frequently playing an important role in etiology of cancer [5], clinical surveillance of
35 an acquired or inherited abnormality of a cancer-predisposing gene can help detect them
36 early. In two third of these early cancers, histological types are embryonal cancers or germ-
37 cell tumors (GCT). The most frequently diagnosed cancers among infants are neuroblastomas,
38 retinoblastomas, lymphoid leukemias, acute myeloid leukemias, nephroblastomas (Wilms
39 tumors), and central nervous system (CNS) tumors. Treatments vary according to center and
40 pathology, and many infants with congenital tumors receive no therapy [6, 7]. The rarity and
41 diversity of infant cancers make it difficult to determine the best treatment and factors
42 influencing survival.

43 The French National Childhood Cancer Registry database provides an unique opportunity to
44 document incidence, clinical features, and outcome of cancers in children aged less than 1
45 year over the 2000-2014 period.

46

47 **2. Methods**

48 **2.1. Population**

49 The cases were obtained from the French National Registry of Childhood Cancers (RNCE)
50 [1]. We identified all children from 0 to 1 year of age, living in mainland France, newly

51 diagnosed with a cancer or a non-malignant tumor of CNS between 2000 and 2014. The
52 diagnoses were coded using third edition of the International Classification of Disease for
53 Oncology (ICDO-3) revised in 2013 [8] and grouped according the third version of the
54 International Classification of Childhood Cancer (ICCC-3) [9]. In the present study, infants
55 with a Langherans cell histiocytosis were not included, mostly because inclusion criteria have
56 changed over the years. We included transient abnormal myelopoiesis (TAM), a borderline
57 entity with same clinical and morphologic features as acute myeloid leukemia, classified
58 9898/1 in the ICDO-3 [8] and not considered in the ICC-3 [9]. Although not included in
59 routine incidence and survival analyses, it was worth describing TAM in the present paper
60 specifically dedicated to infants. The RNCE provided some clinical information on infants
61 with TAM without including them in incidence and survival analyses, as they are not included
62 in the ICC-3 classification [9]. The RNCE provided information on child and cancer
63 characteristics, vital status updated on August 2018, and last contact date. Population data
64 were provided by the French Institute of Statistics and Economic Studies (INSEE) through
65 2014. The number of live births varied overall from 742,337 in 2000 to 756,558 in 2014.

66

67 **2.2. Data analysis**

68 Crude incidence rates (IR) were calculated for the 15-year period, 2000-2014, and based on
69 person-years derived from the INSEE annual estimates of 0-1-year-old children by sex. Time
70 trend in the incidence was estimated by the annual percent change (APC) calculated as the
71 slope of the linear regression used to model the natural logarithm of the IRs as a function of
72 the calendar year [3]. Median length of follow-up was calculated using the inverse Kaplan-
73 Meier method [10]. Survival analysis was performed on a dataset containing all cases
74 diagnosed between January 1, 2000 and December 31, 2014 and followed-up until August 1,
75 2018. The probability of overall survival (OS) was estimated using the Kaplan-Meier methods

76 [11]. The endpoint of interest was death from any cause for OS, with the date of diagnosis
77 acting as the time origin. For the cases diagnosed antenatally, the date of birth was used as the
78 time origin. Survival curves between groups were compared using the log-rank test and the
79 trend in survival over time periods was estimated using the log-rank test for trend [12, 13].
80 Cox models were used to calculate the hazard ratios of death (HR) and their 95% confidence
81 intervals (95%CI) [14]. Statistical tests were two-sided with a significant level of 0.05. All
82 statistical analyses were performed using the SAS version 9.4 (SAS Institute Inc., Cary, North
83 Carolina, USA, 2013).

84

85 **3. Results**

86 **3.1. Description of cases**

87 We identified 2,754 infants with a cancer diagnosed over the 2000-2014 studied period. Four
88 of them were reported with multiple primary cancers (Table 1). The average age at diagnosis
89 was 5.2 months (95%CI: \pm 3.7). Altogether, 525 new cases (19.0% of all cases) were
90 diagnosed in the first month of age (Fig. 1), while from the month two the monthly number of
91 cases remained around 200.

92 The most common diagnostic groups (Table 2) were neuroblastomas (30.1%), CNS tumors
93 (16.1%), leukemias and myelodysplastic syndromes (15.3% with similar frequencies of
94 lymphoid leukemias and acute myeloid leukemias), retinoblastomas (11.6%), and GCT
95 (8.5%). Embryonal malignancies taken as a whole, including Wilms tumors, hepatoblastomas,
96 retinoblastomas, neuroblastomas, and medulloblastomas (ICCC-3 diagnostic subgroups IIIc,
97 IVa, V, VIa1, and VIIa) accounted for 55.2% of cases (Table 2). Most diagnoses showed a
98 male excess (particularly for malignant gonadal GCT, fibrosarcomas, myelodysplastic
99 syndromes and most CNS tumors, with male/female ratios of 17.5, 2.1, 1.8, and 1.4,

100 respectively), but in the extracranial and extragonadal GCT there was a marked female excess
101 with a sex-ratio of 0.5 (Table 2).

102 **Circumstances of diagnosis.** Cancers were diagnosed most often on clinical signs after birth
103 (72.5%), but also by fortuitous detection (14.2%, especially for neuroblastomas 37.7%, for
104 hepatoblastomas 36.8%, and for neuroblastomas 25.7%), routine ultrasonography during
105 pregnancy (9.8%, especially for GCT 41.9% and for neuroblastomas 16.7%), and clinical
106 surveillance in the context of familial or genetic predisposition (3.5%, especially for thyroid
107 carcinomas 62.5% and for retinoblastomas 11.8%). Routine ultrasonography during
108 pregnancy established more frequently the diagnosis in infants younger than 28 days of age
109 (46.6%, especially for neuroblastomas 53.4% and GCT 74.6%).

110 **Basis of diagnosis.** The diagnosis was documented by histology in 87.1% of cases (Table 4).
111 Retinoblastomas detected by fundoscopy (56.7%) and CNS tumors detected by imaging
112 (18.7%) accounted for the majority of cases without histological confirmation.

113 **Predisposition syndromes.** Approximately 9.8% of all infant cases had an inherited cancer
114 predisposition (Table 3): 11.3% of non-CNS solid tumors, 6.8% of CNS tumors and 6.9% of
115 leukemias.

116 **Incidence.** The crude IR of infant cancers was 242.9 per million infants per year (Table 2).
117 Incidence was stable over time for all diagnosis groups, with an overall APC of -0.2%
118 (95%CI: -2.8%; +2.6%), P value = 0.90 (Table 4).

119 **Survival.** Table 5 describes 1-year and 5-year OS by ICCC-3 diagnostic groups and
120 subgroups over the 2000-2014 period. With 4.3% lost to follow-up, the median follow-up
121 time was 10 years and 2 months (0-223 months). At the date of point, 543 of the 2,754 infants
122 had died with a median time after diagnosis of 6.4 months, most of them (n=388) within the
123 first month of life. For all cancers combined, OS was 86.1% (95%CI: 84.7-87.3) at 1 year,
124 and 81.0% (95%CI: 79.4-82.4) at 5 years. The 5-year OS greater than 85% were observed for

125 retinoblastomas, carcinomas, nephroblastomas, GCT, neuroblastomas, and hepatoblastomas
126 whereas 5-year OS was lower than 65% for acute myeloid and lymphoid leukemia or CNS
127 tumors. The 5-year OS did not vary significantly from 2000-2004 to 2010-2014, for any
128 diagnostic group (Table 6). The overall increase was 2.1% for all cancers combined: from
129 80.5% (95%CI, 77.7-82.9) in 2000-2004 to 82.6 % (95%CI, 80.0-84.9) in 2010-2014
130 (p=0.25).

131

132 **3.2. Main specific cancer diagnoses**

133 **Leukemias, myeloproliferative and myelodysplastic diseases.** A total of 360 infant cases
134 were registered with an acute leukemia (Table 8): 173 acute lymphoblastic leukemias (ALL),
135 169 acute myeloid leukemias (AML), and 17 cases with biphenotypic leukemia, and 1 case
136 not adequately classified due to insufficient immunophenotyping data. Overall 5-year survival
137 was very low in neonates aged from 0 to 28 days (8.3% [0.5-31.1], p<0.01).

138 The early B-cell precursor immunophenotype (pro-B) accounted for 44.9% (n=71) of the 158
139 precursor B-cell ALL. Most of them (n=64) were registered as expressing MLL transcript or
140 carrying a cytogenetic abnormality involving 11q23, and 18 of them had CNS involvement.

141 For the precursor B-cell ALL, infants younger than 3 months and infants with rearrangements
142 of the mixed lineage leukemia (MLL) gene in leukemic B-cells had a relatively poor
143 prognosis: HR=5.0 (IC95%: 2.4-10.8; P<0.01) and HR=2.5 (IC95%: 1.3-4.7; P<0.01),
144 respectively. There were only 9 cases of precursor T-cell ALL and 2 cases of Burkitt
145 leukemias.

146 AML was diagnosed in 169 cases, 15 of whom had a Down syndrome (DS). Acquired
147 11q23/MLL rearrangements have been detected in 71 cases with normal constitutional
148 karyotype. The two most frequent cytological AML subtypes were acute monocytic leukemia
149 (AML-M5), in 33 infants as well, 10 of them with DS (one had a transient abnormal

150 myelopoiesis (TAM) in the neonatal period). Neonates (age<29 days) with AML had a higher
151 risk of dying from the disease compared to infants older than 28 days (HR=3.6; IC95%: 2.1-
152 6.3; P<0.01).

153 There were 4 cases of myelodysplastic syndromes and 50 cases of juvenile myelomonocytic
154 leukemias (JMML), 10 of whom identified with Noonan syndrome. There were also 3
155 myeloproliferative syndromes: 1 case of BCR-ABL1-positive chronic myeloid leukemia, and
156 2 cases of essential thrombocythemia.

157 The crude IR of TAM was 4.9 per million infants per year (95%CI: 3.7-6.4). Out of 56 cases
158 of TAM, 47 newborns had a DS and one had a Noonan syndrome. Within the first 3 years of
159 life 14 cases developed an established acute myeloid leukemia, and 2 other cases evolved
160 towards myelodysplastic syndromes including 1 case of refractory anemia with excess
161 megakaryoblasts.

162 **CNS tumors.** Gliomas represented 37.5% (n=166/443) of infant CNS tumors. Optic pathway
163 was the most prevalent location (58.4%), following by infratentorial brain tumors (16.3%, of
164 which 6.6% brain stem gliomas), gliomas of deep midline structures (14.5%), hemispheric
165 gliomas (8.4%) and spinal cord gliomas (2.4%). Optic pathway gliomas were an important
166 subtype associated with NF1 (14.4%). Based on histopathological diagnosis (n=109/166),
167 gliomas were subdivided in astrocytic (75.2%), oligodendroglial (9.2%), oligoastrocytic
168 (7.3%), and unclassifiable (8.3%) tumors. The most common astrocytoma histology in
169 infants was the pilocytic (72.0%), following by other low-grade astrocytomas (15.9%),
170 anaplastic astrocytomas (7.3%), and glioblastomas (4.9%). The 5-year OS for infants with
171 low-grade gliomas (79.3%; 95%CI: 70.1-86.0) was significantly higher than those with high-
172 grade tumors (57.9%; 95%CI: 33.2-76.3; Log-rank P=0.02).

173 One hundred and fourteen cases of intracranial and intraspinal embryonal tumors were
174 identified, especially atypical teratoid/rhabdoid tumors (ATRT, 56.1%) and medulloblastomas

175 (36.0%). Overall, 72.8% of tumors occurred exclusively infratentorially, 24.6% exclusively
176 supratentorially, and 2.6% in the spinal cord. Compared to infants with medulloblastoma,
177 those with ATRT had a relatively poor prognosis: HR=4.0 (IC95%: 2.3-6.8; P<0.001).

178 Sixty-two infants with choroid plexus tumors were included: 53% were benign papillomas (1
179 of whom with Noonan syndrome, Table 3), 23% were atypical papillomas, and 24% were
180 carcinomas (2 of whom with Li-Fraumeni syndrome, Table 3).

181 **Neuroblastoma.** Out of the 831 cases there were 56 cases of spontaneous regression, 45 of
182 whom had a diagnosis by imaging alone. The clinical and biological characteristics at
183 diagnosis of the 831 infants with neuroblastoma are listed in Table 6. The most common
184 primary site was the abdomen (69.7%, especially adrenal gland: 56.3%). For children with
185 INRGSS stages L1 and L2, the 5-year OS was higher than 93%. OS by stage are shown in
186 Table 7 and Fig. 2. Infants with metastatic disease (stage M) had significantly a lower
187 prognosis (5-year OS: 72.7% [95%CI: 63.4-80.1]). Amplification of the MYCN gene was
188 found in 7.0% of the cases and associated with a higher risk of dying from the disease
189 compared to infants without MYCN amplification (HR=14.7; IC95%: 9.1-23.5; P<0.01).

190 **Retinoblastoma.** Three hundred and twenty-one cases were identified, 152 of whom (47.4%)
191 had bilateral retinoblastoma. A familial history of retinoblastoma was recorded for 43 cases
192 (13.4%), including 25 cases with bilateral tumors. The proportion of 13q14 deletion,
193 containing the tumor suppressor gene Rb, was significantly higher in infants with bilateral
194 retinoblastoma (n=19; 12.5%) than in those with unilateral retinoblastoma (n=10; 5.9%;
195 p=0.04). In one infant with retinoblastoma and an interstitial deletion extending to 13q22
196 Hirschsprung disease was reported. Only 3 deaths were observed among children with
197 retinoblastoma (one with pinealoblastoma diagnosed 4 years after, one with associated
198 polymalformative syndrome, and one with associated psychomotor retardation with
199 swallowing disorders).

200 **Wilms tumor.** One hundred and ninety-one cases were identified, and 16.2% of them (n=31)
201 were bilateral. A total of 53.9% of infants had SIOP stage I disease, 14.7% infants with SIOP
202 stage II, 8.4% with SIOP stage III, 1.1% with SIOP stage IV, and 16.2% with SIOP stage V
203 (eleven cases with unknown stage). The proportion of WT1 and WT2 gene deletions varied
204 significantly between infants with unilateral or bilateral Wilms tumor: 0.6% vs 19.4%
205 respectively for WT1, and 2.5% vs 0.0% respectively for WT2. All children with SIOP stage
206 V (bilateral Wilms tumor) were alive at the time of analysis. The 5-year OS for infants with
207 SIOP stage I-II disease (96.8%; 95%CI: 91.8-98.8) was higher, but not significantly different,
208 than those with stage III-IV disease (88.9%; 95%CI: 62.4-97.1; Log-rank P=0.09).

209 **Hepatoblastoma.** Hepatoblastoma was diagnosed in 67 cases, 3 of whom had a
210 predisposition syndrome (2 Beckwith-Wiedemann syndromes, and 1 trisomy 18, Table 3).
211 Five infants (7%) had a metastatic disease.

212 **Extracranial GCT.** There were 199 cases of extracranial GCT. Malignant teratoma (defined
213 by the presence of microfoci of yolk sac tumor or immature cells by histology) was the most
214 diagnosis in this group (61.8%). The most common site for GCT was the sacrococcygeal
215 region (n=97, 48.7%). There were 35 testicular GCT, 22 were intraabdominal, 21 presented in
216 the head and neck, and 10 in the mediastinum. Significant differences between different age
217 groups (0-28 days vs >28 days) were observed in the proportion of sacrococcygeal region
218 sites (86.6% vs 13.4%, respectively, P<0.01), in the proportion of malignant teratomas
219 (78.1% vs 22.0%, respectively, P<0.01), and in the proportion of prenatal diagnoses (96.1%
220 vs 3.2%, respectively, P<0.01). Only 19 deaths were observed among children with
221 extracranial GCT (42% during or immediately after surgery).

222 **Soft-tissue sarcomas.** Three main histological types were distinguished: 33% for
223 rhabdomyosarcoma (especially embryonal sub-types: 81%), 27% for myofibroblastic tumors

224 (especially infantile fibrosarcomas: 96%), and 21% for extrarenal rhabdoid tumors (1 of
225 whom with SMARCB1/INI1 mutation).

226

227 **4. Discussion**

228 This study describes the incidence and the survival of infant tumors in France during the
229 2000-2014 period, based on national population-based cancer registry data. The large number
230 of cases spread throughout the national territory surrogates a real strength and reliability to
231 this work. We showed that the incidence was stable during this period, with an average annual
232 IR of 243.1 per million. A high proportion of infants survived as the 5-year OS was 81.0%
233 (95% CI: 79.4-82.4), stable over time. Most deaths occurred within the first month of life
234 (71.5%).

235 Comparisons between France and the other countries [15] demonstrated variations in infant
236 cancer incidence rates, with the most striking differences: lower for leukemia (compared to
237 North American countries particularly) and higher for neuroblastoma and retinoblastoma. In
238 the United-States (US) there are some differences in incidence rates and temporal trends of
239 childhood leukemia by racial/ethnic background [16]. Barrington-Trimis et al [16] report a
240 higher incidence and increasing rates of ALL among Hispanic white children. Our rates seem
241 to be more similar to those observed in non-Hispanic white infants. Registration practices can
242 induce differences between countries, particularly for spontaneously regressive tumors, like in
243 neuroblastoma or in leukemia (if TAM are registered as leukemias). The high incidence of
244 neuroblastomas in France could be explained by a possible over-diagnosis of spontaneously
245 regressive tumors without histological confirmation (5.4% of infant neuroblastomas in our
246 study). The incidence of retinoblastoma is not distributed equally around the world. Whether
247 these geographical variations are due to ethnic or socioeconomic factors is not well known

248 [17]. TAM has been reported to affect approximately 4% to 10% of DS neonates [18], but the
249 true incidence may be underestimated. In France, 4 new TAM cases are annually diagnosed.
250 Our 5-year OS rates were comparable to those reported in the US during the 2008-2014
251 period [3]. In France, as in other countries, age less than 1 year at diagnosis is a very poor
252 prognostic factor for leukemia and CNS tumors, and a good prognostic factor for
253 neuroblastoma [3, 19]. The good prognosis of infantile neuroblastoma has been attributed to
254 the fact that patients aged less than 1 year have smaller and less aggressive tumors (less
255 metastatic and less MYCN-amplified diseases), which, in some cases, regress spontaneously
256 [20-22]. There are a higher proportion of MYCN-amplified tumors in infants with stage 4
257 disease compared to those without metastatic neuroblastoma (19% vs. 3%) [23, 24].
258 Regarding leukemia, ALL with rearrangements of MLL gene, most often by t(4;11)
259 translocation, are most early precursor-B-ALL immunophenotype particularly prevalent in
260 infants (68% in our study vs 3-5% in older children). They are associated with a high risk of
261 treatment failure and relapse [25, 26], consistent with the poor 5-year OS reported in the
262 present study. In AML, MLL rearrangements are less frequent than in infant ALL and due to
263 other translocations (eg t(9;11), t(10;11), t(11;19)). They are more often present in M4 and
264 M5 cytological subtypes, and they are associated with better 5-year survival [27, 28]. The M7
265 subtype is specific to infancy (20% of cases vs 8% in older children) and still reported poor
266 outcome, particularly in non-DS infants [29, 30]. As regard to CNS tumors, embryonal
267 neoplasms represent a significant source of morbidity and mortality in infants [31, 32]. These
268 aggressive tumors are largely comprised of medulloblastomas, ATRT, and CNS embryonal
269 tumors not specified (formerly known as cPNET) and they are more frequently diagnosed in
270 infants than in older children (25.7% of all CNS tumors vs 18.7%, respectively) [33, 34].
271 Conversely, the most common low-grade glioma (pilocytic astrocytoma), occurs less mainly
272 in infants than in older children (13.3% of all CNS tumors vs 22.5%, respectively) [33, 34].

273 The proportion of infants with cancer attributable to an underlying cancer predisposition
274 syndrome (CPS) is still unclear. Our results indicate that a considerable percentage of infant
275 cancers are due to CPS (11.3% of non-CNS solid tumors, 6.8% of CNS tumors and 6.9% of
276 leukemias), although the RNCE cannot pretend to completeness of CPS registration. One of
277 many advantages of our population-based study is to highlight rare associations, commonly
278 not found in quasi-random case reports, like the association between medulloblastoma and
279 multiple endocrine neoplasia syndrome type 2b or choroid plexus papilloma and Noonan
280 syndrome. Our proportion of neuroblastomas in infants with Sotos syndrome is nevertheless
281 surprising, given that childhood cancer is believed to be much rarer in this syndrome than in
282 some other overgrowth syndromes [35, 36].

283

284 **5. Conclusion**

285 Infants with cancer represent a cohort of children with peculiar clinical and biological
286 features. Epidemiological data on incidence and survival found in this report contribute to our
287 understanding of these tumors by quantifying their impact on the French population and
288 assessing the burden of some devastating infant cancers. Because of their relative rarity,
289 studying infant tumors as part of national studies is essential to understand their etiology,
290 including genetic predisposition syndromes, determine the best treatment approaches, and
291 improve survival and quality of life for those patients.

292

293 **Authors' contributions**

294 All named authors have participated in the study to a sufficient extent to be named as authors.
295 All authors were involved in the study design and analysis plan. All authors critically
296 reviewed the study results, commented on the drafts, and approved the final manuscript.

297

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301

302 **Declaration of Competing Interest**

303 None declared.

304

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311

312 **Ethical Approval**

313 This study was performed at the French National Registry of Childhood Cancer, CRESS
314 Team 7, UMR-S 1153, Inserm, Paris-Descartes University, France. Ethical approval was
315 granted by the French National Commission on Informatics and Freedoms (Number 900183
316 for the French National Registry of Childhood Solid Tumors and Number 998198 for the
317 French National Registry of Childhood Hematological Malignancies), providing all patients
318 have expressed their opposition before registration in the French National Registry of
319 Childhood Cancer database.

320

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420

421 **Table 1.** Characteristics of infants with multiple primary cancers (France, 2000 to 2014)

422

423 **Fig. 1.** Number of cancer cases by month of age at diagnosis (France, 2000 to 2014): All
424 ICCC-3 groups and the main ICCC-3 groups (I. Leukemia, III. CNS tumors, and IV:
425 Neuroblastoma and other peripheral nervous cell tumors)

426 *Abbreviations:* ICCC-3, International Classification of Childhood Cancer, Third Edition;
427 CNS, Central nervous system

428

429 **Table 2.** Number of cases of infant cancers, sex ratio, and annual incidence rates per million
430 children by ICCC-3 diagnostic groups and subgroups: France, 2000 to 2014

431 *Abbreviations:* 95%CI, 95% confidence interval; ASR, age standardized rate; ICCC-3,
432 International Classification of Childhood Cancer, Third Edition; M/F ratio, ratio of male over
433 female cases

434

435 **Table 3.** Pediatric cancer predisposition syndromes by diagnosis (France, 2000 to 2014)

436 * All bilateral retinoblastomas have been considered as heritable.

437 ** Unilateral retinoblastomas with familial history of retinoblastoma and/or any germline Rb
438 mutation have been considered as heritable.

439

440 **Table 4.** Percentage of microscopically verified cases and annual percent change in incidence
441 rate for cancers among infants according to ICCC-3 group: France, 2000 to 2014.

442 *Abbreviations:* 95%CI, 95% confidence interval; APC, annual percent change; ICCC-3,
443 International Classification of Childhood Cancer, Third Edition; MV%, percentage of
444 microscopically verified cases

445 * Linear regression

446

447 **Table 5.** One-year and five-year overall survival (OS) among infants with cancers by ICCC-

448 3 diagnostic groups and subgroups: France, 2000 to 2014

449 *Abbreviations:* 95%CI, 95% confidence interval; OS, overall survival; ICCC-3, International

450 Classification of Childhood Cancer, Third Edition

451 *For infants with many primary cancers, only the first primary cancer was including in the

452 global overall survival analysis

453

454 **Table 6.** Time variation of 5-year overall survival for French infants diagnosed with cancer,

455 by period of diagnosis (2000–2004, 2005–2009, and 2010–2014).

456 *Abbreviations:* 95%CI, 95% confidence interval; 5y OS, five-year overall survival; ICCC-3,

457 International Classification of Childhood Cancer, Third Edition

458 * Log-rank trend test

459 **For infants with many primary cancers, only the first primary cancer was including in the

460 global overall survival analysis

461

462 **Table 7.** Clinical and pathology/biology features of infants with neuroblastoma (France,

463 2000 to 2014, n=831)

464 *Abbreviations:* 95%CI, 95% confidence interval; OS, overall survival; INRGSS, International

465 Neuroblastoma Risk Group Staging System

466 * Log-rank test

467

468 **Fig. 2.** Overall survival curves for infants with neuroblastoma by International Neuroblastoma

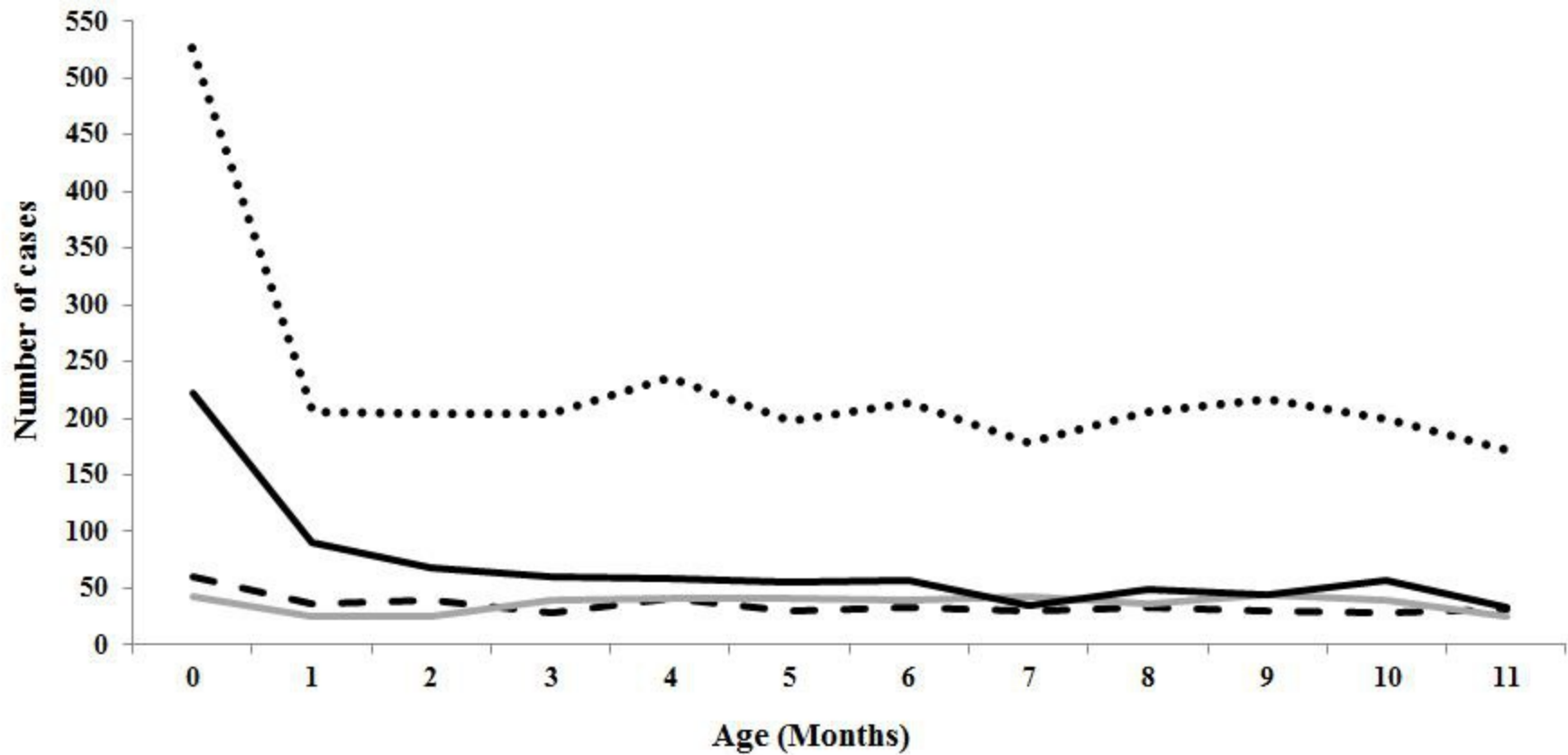
469 Risk Group Staging System (INRGSS): France, 2000 to 2014 (n=831)

470

471 **Table 8.** Clinical and pathology/biology features of infants with acute leukemia (France,
472 2000 to 2014)

473 *Abbreviations:* 95%CI, 95% confidence interval; OS, overall survival; CNS, Central nervous
474 system; MLL, Mixed Lineage Leukemia; ALL, Acute lymphoblastic leukemia; AML, Acute
475 myeloid leukemia; AMKL, Acute megakaryoblastic leukemia

476 * Log-rank test



- - I. Leukemia — III. CNS tumors — IV. Neuroblastoma •••• All groups

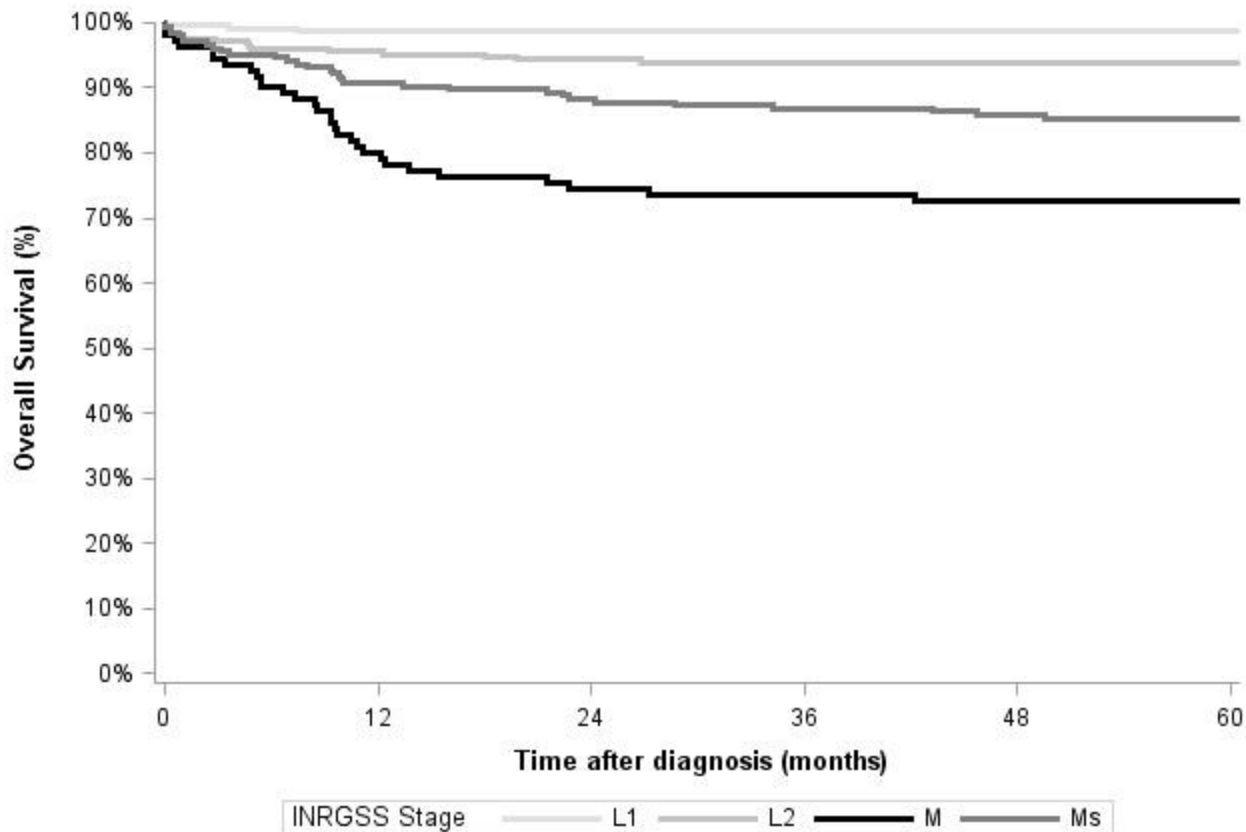


Table 1. Characteristics of infants with multiple primary cancers (France, 2000 to 2014)

Infants	Gender	Genetic abnormalities	Age at diagnosis	Diagnoses	Follow-up: Alive or Dead (age at death)
n°1	Female	Fanconi anemia	10.3 months 10.3 months	Unilateral nephroblastoma Neuroblastoma	Dead (13 months)
n°2	Male	None	9.6 months 9.6 months	Unilateral nephroblastoma Neuroblastoma	Alive
n°3	Female	SMARCB1/INI1	11 days 1.2 month	Extrarenal rhabdoid tumor Unspecified primary brain tumor	Dead (7 months)
n°4	Female	Fanconi anemia	9.5 months 9.5 months 9.6 months 9.8 months	Refractory anemia with excess blasts Rhabdomyosarcoma Sacrococcygeal germ-cell tumor Neuroblastoma	Dead (13 months)

Table 2. Number of cases of infant cancers, sex ratio, and annual incidence rates per million children by ICCC-3 diagnostic groups and subgroups: France, 2000 to 2014

ICCC-3 diagnostic groups and subgroups	Cases		M/F	Incidence rate (/10 ⁶)	
	N	%	Ratio	IR	95%CI
I. Leukemias, myeloproliferative and myelodysplastic diseases	422	15.3	1.1	37.1	[33.7-40.9]
Ia. Lymphoid leukemias	173	6.3	1.0	15.2	[13.0-17.7]
Ia1. Precursor cell leukemias	171	6.2	1.0	15.0	[12.9-17.5]
Ia2. Burkitt leukemia	2	0.1	1.0	0.2	[0.0-0.6]
Ib. Acute myeloid leukemias	169	6.1	1.1	14.9	[12.7-17.3]
Ic. Chronic myeloproliferative diseases	3	0.1	-	0.3	[0.1-0.8]
Id. Myelodysplastic syndrome and other myeloproliferative diseases	54	2.0	1.8	4.8	[3.6-6.2]
Ie. Unspecified and other specified leukemias	23	0.8	1.1	2.0	[1.3-3.0]
II. Lymphomas and reticuloendothelial neoplasms	3	0.1	0.5	0.3	[0.1-0.8]
IIb Non-Hodgkin's lymphomas	3	0.1	0.5	0.3	[0.1-0.8]
IIb2. Mature B-cell lymphomas (except Burkitt lymphoma)	1	0.0	0.0	0.1	[0.0-0.5]
IIb3. Mature T-cell and NK-cell lymphomas	2	0.1	1.0	0.2	[0.0-0.6]
III. Central nervous system tumors	443	16.1	1.4	39.0	[35.4-42.8]
IIIa. Ependymomas and choroid plexus tumor	93	3.4	1.8	8.2	[6.6-10.0]
IIIa1. Ependymomas	31	1.1	1.6	2.7	[1.9-3.9]
IIIa2. Choroid plexus tumor	62	2.2	2.0	5.5	[4.2-7.0]
IIIb. Astrocytomas	132	4.8	1.2	11.6	[9.7-13.8]
IIIc. Intracranial and intraspinal embryonal tumors	114	4.1	1.5	10.0	[8.3-12.1]
IIIc1. Medulloblastomas	41	1.5	1.7	3.6	[2.6-4.9]
IIIc2. cPNET	8	0.3	0.3	0.7	[0.3-1.4]
IIIc3. Medulloepithelioma	1	0.0	-	0.1	[0.0-0.5]
IIIc4. Atypical teratoid/rhabdoid tumor	64	2.3	1.7	5.6	[4.3-7.2]
IIId. Other gliomas	34	1.2	1.3	3.0	[2.1-4.2]
IIId1. Oligodendrogliomas	9	0.3	1.3	0.8	[0.4-1.5]
IIId2. Mixed and unspecified gliomas	24	0.9	1.2	2.1	[1.4-3.1]
IIId3. Neuroepithelial glial tumors of uncertain origin	1	0.0	-	0.1	[0.0-0.5]
IIIe. Other specified intracranial and intraspinal neoplasms	52	1.9	1.6	4.6	[3.4-6.0]
IIIe2. Craniopharyngiomas	5	0.2	0.7	0.4	[0.1-1.0]
IIIe3. Pineal parenchymal tumors	4	0.1	-	0.4	[0.1-0.9]
IIIe4. Neuronal and mixed neuronal-glia tumors	42	1.5	1.6	3.7	[2.7-5.0]
IIIe5. Meningiomas	1	0.0	0.0	0.1	[0.0-0.5]
III f. Unspecified intracranial and intraspinal neoplasms	18	0.7	1.0	1.6	[0.9-2.5]
IV. Neuroblastoma and other peripheral nervous cell tumors	833	30.2	1.2	73.3	[68.4-78.5]
IVa. Neuroblastoma and ganglioneuroblastoma	831	30.1	1.2	73.1	[68.2-78.3]
IVb. Other peripheral nervous cell tumors	2	0.1	0.0	0.2	[0.0-0.6]
V. Retinoblastoma	321	11.6	1.2	28.2	[25.2-31.5]
VI. Renal tumors	215	7.8	1.1	18.9	[16.5-21.6]
VIa. Nephroblastoma and other nonepithelial renal tumors	215	7.8	1.1	18.9	[16.5-21.6]
VIa1. Nephroblastoma	191	6.9	1.0	16.8	[14.5-19.4]
VIa2. Rhabdoid renal tumors	13	0.5	1.2	1.1	[0.6-2.0]
VIa3. Kidney sarcoma	11	0.4	10.0	1.0	[0.5-1.7]
VII. Hepatic tumors	68	2.5	1.3	6.0	[4.6-7.6]
VIIa. Hepatoblastoma	67	2.4	1.3	5.9	[4.6-7.5]
VIIc. Unspecified malignant hepatic tumors	1	0.0	0.0	0.1	[0.0-0.5]

Table 2. (Continued)

ICCC-3 diagnostic groups and subgroups	Cases		M/F	Incidence rate (/10 ⁶)	
	N	%	Ratio	IR	95% CI
VIII. Malignant bone tumors	5	0.2	0.7	0.4	[0.1-1.0]
VIIIa. Osteosarcomas	1	0.0	-	0.1	[0.0-0.5]
VIIIb. Chondrosarcomas	1	0.0	0.0	0.1	[0.0-0.5]
VIIIc. Ewing tumor and related sarcomas of bone	3	0.1	0.5	0.3	[0.1-0.8]
IX. Soft tissue and other extrasosseous sarcomas	175	6.3	1.4	15.4	[13.2-17.9]
IXa. Rhabdomyosarcomas	57	2.1	1.6	5.0	[3.8-6.5]
IXb. Fibrosarcomas, and other fibrous neoplasms	49	1.8	2.1	4.3	[3.2-5.7]
IXb1. Fibroblastic and myofibroblastic tumors	47	1.7	1.9	4.1	[3.0-5.5]
IXb2. Nerve sheath tumors	2	0.1	-	0.2	[0.0-0.6]
IXc. Kaposi sarcoma	1	0.0	0.0	0.1	[0.0-0.5]
IXd. Other specified soft tissue sarcomas	54	2.0	1.2	4.8	[3.6-6.2]
IXd1-2. Ewing tumors and pPNET of soft tissue	8	0.3	3.0	0.7	[0.3-1.4]
IXd3. Extrarenal rhabdoid tumor	37	1.3	1.1	3.3	[2.3-4.5]
IXd4. Liposarcomas	1	0.0	0.0	0.1	[0.0-0.5]
IXd5. Fibrohistiocytic tumors	6	0.2	1.0	0.5	[0.2-1.1]
IXd7. Synovial sarcomas	2	0.1	1.0	0.2	[0.0-0.6]
IXe. Unspecified soft tissue sarcomas	14	0.5	0.8	1.2	[0.7-2.1]
X. Germ-cell tumors, and other neoplasms of gonads	234	8.5	0.9	20.6	[18.0-23.4]
Xa. Intracranial and intraspinal germ cell tumors	34	1.2	1.6	3.0	[2.1-4.2]
Xa2. Intracranial and intraspinal teratomas	32	1.2	1.5	2.8	[1.9-4.0]
Xa4. Intracranial and intraspinal yolk sac tumor	1	0.0	-	0.1	[0.0-0.5]
Xa6. Intracranial and intraspinal tumors of mixed forms	1	0.0	-	0.1	[0.0-0.5]
Xb. Malignant extracranial and extragonadal germ cell tumors	162	5.9	0.5	14.3	[12.1-16.6]
Xb1. Malignant germinomas of extracranial and extragonadal sites	1	0.0	0.0	0.1	[0.0-0.5]
Xb2. Malignant teratomas of extracranial and extragonadal sites	109	3.9	0.5	9.6	[7.9-11.6]
Xb4. Yolk sac tumor of extracranial and extragonadal sites	22	0.8	0.6	1.9	[1.2-2.9]
Xb5. Choriocarcinomas of extracranial and extragonadal sites	5	0.2	1.5	0.4	[0.1-1.0]
Xb6. Other and unspecified malignant mixed germ cell tumors	25	0.9	0.4	2.2	[1.4-3.2]
Xc. Malignant gonadal germ cell tumors	37	1.3	17.5	3.3	[2.3-4.5]
Xc2. Malignant gonadal teratomas	14	0.5	-	1.2	[0.7-2.1]
Xc4. Gonadal yolk sac tumor	12	0.4	-	1.1	[0.5-1.8]
Xc6. Malignant gonadal tumors of mixed forms	11	0.4	4.5	1.0	[0.5-1.7]
Xe. Other and unspecified malignant gonadal tumors	1	0.0	-	0.1	[0.0-0.5]
XI. Other malignant epithelial neoplasms and malignant melanomas	29	1.1	0.5	2.6	[1.7-3.7]
XIa. Adrenocortical carcinomas	18	0.7	0.4	1.6	[0.9-2.5]
XIb. Thyroid carcinomas	8	0.3	0.6	0.7	[0.3-1.4]
XId. Malignant melanomas	3	0.1	0.5	0.3	[0.1-0.8]
XII. Other and unspecified malignant neoplasms	12	0.4	1.4	1.1	[0.5-1.8]
XIIa. Other specified malignant tumors	12	0.4	1.4	1.1	[0.5-1.8]
XIIa3. Pulmonary blastoma and pleuropulmonary blastoma	10	0.4	1.5	0.9	[0.4-1.6]
XIIa6. Other specified malignant tumors	2	0.1	1.0	0.2	[0.0-0.6]
Total	2760	100.0	1.2	242.9	[233.9-252.1]

Abbreviations: 95%CI, 95% confidence interval; IR, incidence rate; ICC-3, International Classification of Childhood Cancer, Third Edition; M/F ratio, ratio of male over female cases; cPNET, central primitive neuroectodermal tumors; pPNET, peripheral primitive neuroectodermal tumors

Table 3. Pediatric cancer predisposition syndromes by diagnosis (France, 2000 to 2014)

Syndromes by diagnosis	Number of infants (n=270)
Beckwith-Wiedemann syndrome	11
Nephroblastoma	4
Neuroblastoma	3
Hepatoblastoma	2
Rhabdomyosarcoma	1
Adrenocortical carcinoma	1
Denys-Drash syndrome	4
Nephroblastoma (including 3 bilateral)	4
Down syndrome	16
Acute myeloid leukemia (1 M7, 2 M0, 1 M5, 1 not specified)	15
Unilateral retinoblastoma	1
Familial mosaic monosomy 7	1
Myelodysplastic syndrome, not specified	1
Fanconi anemia or BRCA2/FANCD1 mutation	2
Unilateral nephroblastoma + neuroblastoma	1
Refractory anemia with excess blasts + rhabdomyosarcoma + germ-cell tumor + neuroblastoma	1
Hereditary retinoblastoma	173
Bilateral retinoblastoma (including 19 with a 13q14 deletion recorded)*	152
Unilateral retinoblastoma (including 10 with a 13q14 deletion recorded)**	21
Li-Fraumeni syndrome	2
Choroid plexus carcinoma	2
Multiple endocrine neoplasia (MEN) type 2 syndrome	6
Thyroid medullary carcinoma (n=1 2a and n=4 2b)	5
Medulloblastoma	1
Neurofibromatosis type 1	19
Optic pathway glioma	14
Intramedullary spinal cord glioma	1
Precursor T-cell lymphoblastic leukemia	1
Neuroblastoma	1
Bilateral retinoblastoma	1
Rhabdomyosarcomas	1
Noonan syndrome	12
Juvenile myelomonocytic leukemia	11
Choroid plexus papilloma	1
INI1 mutation	11
Atypical teratoid rhabdoid tumor	5
Renal rhabdoid tumor	2
Extrarenal rhabdoid tumor (including 1 case with an additional unspecified brain tumor)	4
Sotos syndrome	3
Neuroblastoma	3
Trisomy 18 (Edwards syndrome)	1
Hepatoblastoma	1
Tuberous sclerosis	5
Subependymal giant cell astrocytoma	5
Turner syndrome	1
Neuroblastoma	1
WAGR (Wilms tumor, Aniridia, Genitourinary anomalies, and Retardation) syndrome	3
Bilateral nephroblastoma	3

* All bilateral retinoblastomas have been considered as heritable.

** Unilateral retinoblastomas with familial history of retinoblastoma and/or any germline Rb mutation have been considered as heritable.

Table 4. Percentage of microscopically verified cases and annual percent change in incidence rate for cancers among infants according to ICCC-3 group: France, 2000 to 2014.

ICCC-3 diagnostic groups	N	MV%	APC	95%CI	P-value*
I. Leukemias, myeloproliferative and myelodysplastic diseases	422	99.5	0.0	[-1.1-1.2]	0.96
II. Lymphomas	3	100.0	0.2	[-2.5-2.9]	0.90
III. Central nervous system tumors	443	81.3	0.1	[-1.9-2.1]	0.93
IV. Neuroblastoma and other peripheral nervous cell tumors	833	90.6	0.0	[-0.5-0.5]	0.98
V. Retinoblastoma	321	43.3	-1.6	[-9.5-6.9]	0.71
VI. Renal tumors	215	100.0	0.6	[-4.4-5.9]	0.82
VII. Hepatic tumors	68	97.1	2.9	[-7.7-14.7]	0.62
VIII. Malignant bone tumors	5	100.0	1.7	[-6.6-10.8]	0.70
IX. Soft tissue and other extraosseous sarcomas	175	99.4	1.8	[-6.6-10.9]	0.70
X. Germ-cell tumors, and other neoplasms of gonads	234	96.2	-2.5	[-11.9-8.0]	0.64
XI. Other malignant epithelial neoplasms and malignant melanomas	29	100.0	-4.6	[-16.9-9.6]	0.52
XII. Other and unspecified malignant neoplasms	12	100.0	5.2	[-8.8-21.3]	0.61
Total	2760	87.1	-0.2	[-2.8-2.6]	0.90

Abbreviations: 95%CI, 95% confidence interval; APC, annual percent change; ICCC-3, International Classification of Childhood Cancer, Third Edition; MV%, percentage of microscopically verified cases

* Linear regression

Table 5. One-year and five-year overall survival (OS) among infants with cancers by ICCC-3 diagnostic groups and subgroups: France, 2000 to 2014

ICCC-3 diagnostic groups and subgroups	N	1-year OS		5-year OS	
		%	95%CI	%	95%CI
I. Leukemias, myeloproliferative and myelodysplastic diseases	422	76.0	[71.7-79.8]	60.7	[55.8-65.2]
Ia. Lymphoid leukemias	173	79.1	[72.3-84.5]	55.1	[47.3-62.2]
Ia1. Precursor cell leukemias	171	78.9	[72.0-84.3]	54.6	[46.8-61.7]
Ia2. Burkitt leukemia	2	100.0	-	100.0	-
Ib. Acute myeloid leukemia	169	71.6	[64.2-77.8]	63.9	[56.1-70.6]
Ic. Chronic myeloproliferative diseases	3	100.0	-	100.0	-
Id. Myelodysplastic syndrome and other myeloproliferative diseases	54	83.3	[70.3-90.9]	70.0	[55.8-80.5]
Ie. Unspecified and other specified leukemias	23	65.2	[42.3-80.8]	52.2	[30.5-70.0]
II. Lymphomas and reticuloendothelial neoplasms	3	66.7	[5.4-94.5]	66.7	[5.4-94.5]
IIb Non-Hodgkin's lymphomas	3	66.7	[5.4-94.5]	66.7	[5.4-94.5]
IIb2. Mature B-cell lymphomas (except Burkitt lymphoma)	1	0.0	-	0.0	-
IIb3. Mature T-cell and NK-cell lymphomas	2	100.0	-	100.0	-
III. Central nervous system tumors	443	69.9	[65.3-73.9]	62.0	[57.3-66.4]
IIIa. Ependymomas and choroid plexus tumor	93	80.3	[70.6-87.1]	70.2	[59.7-78.5]
IIIa1. Ependymomas	31	71.0	[51.6-83.7]	48.4	[30.2-64.4]
IIIa2. Choroid plexus tumor	62	85.1	[73.3-92.0]	81.7	[69.4-89.4]
IIIb. Astrocytomas	132	87.9	[81.0-92.4]	80.9	[73.0-86.6]
IIIc. Intracranial and intraspinal embryonal tumors	114	35.1	[26.5-43.8]	25.4	[17.8-33.7]
IIIc1. Medulloblastomas	41	70.7	[54.3-82.2]	53.5	[37.3-67.3]
IIIc2. cPNET	8	12.5	[0.7-42.3]	12.5	[0.7-42.3]
IIIc3. Medulloepithelioma	1	100.0	-	100.0	-
IIIc4. Atypical teratoid/rhabdoid tumor	64	14.1	[6.9-23.7]	7.8	[2.9-16]
IIId. Other gliomas	34	79.4	[61.6-89.6]	73.4	[55.1-85.2]
IIId1. Oligodendrogliomas	9	88.9	[43.3-98.4]	77.8	[36.5-93.9]
IIId2. Mixed and unspecified gliomas	24	75.0	[52.6-87.9]	70.6	[48.0-84.8]
IIId3. Neuroepithelial glial tumors of uncertain origin	1	100.0	-	100.0	-
IIIe. Other specified intracranial and intraspinal neoplasms	52	88.5	[76.1-94.6]	84.6	[71.5-92]
IIIe2. Craniopharyngiomas	5	100.0	-	100.0	-
IIIe3. Pineal parenchymal tumors	4	50.0	[5.8-84.5]	25.0	[0.9-66.5]
IIIe4. Neuronal and mixed neuronal-glioma tumors	42	92.9	[79.5-97.6]	90.4	[76.4-96.3]
IIIe5. Meningiomas	1	0.0	-	0.0	-
IIIf. Unspecified intracranial and intraspinal neoplasms	18	33.3	[13.7-54.5]	26.7	[9.1-48.2]
IV. Neuroblastoma and other peripheral nervous cell tumors	833	93.3	[91.3-94.8]	90.4	[88.1-92.2]
IVa. Neuroblastoma and ganglioneuroblastoma	831	93.4	[91.5-94.9]	90.5	[88.2-92.3]
IVb. Other peripheral nervous cell tumors	2	50.0	[0.6-91.0]	50.0	[0.6-91.0]
V. Retinoblastoma	321	99.4	[97.5-99.8]	99.4	[97.5-99.8]
VI. Renal tumors	215	91.2	[86.5-94.3]	88.3	[83.2-91.9]
VIa. Nephroblastoma and other nonepithelial renal tumors	215	91.2	[86.5-94.3]	88.3	[83.2-91.9]
VIa1. Nephroblastoma	191	97.4	[93.8-98.9]	95.7	[91.7-97.8]
VIa2. Rhabdoid renal tumors	13	15.4	[2.5-38.8]	15.4	[2.5-38.8]
VIa3. Kidney sarcoma	11	72.7	[37.1-90.3]	45.5	[16.7-70.7]
VII. Hepatic tumors	68	88.2	[77.9-93.9]	88.2	[77.9-93.9]
VIIa. Hepatoblastoma	67	88.1	[77.5-93.8]	88.1	[77.5-93.8]
VIIc. Unspecified malignant hepatic tumors	1	100.0	-	100.0	-

Table 5. (Continued)

ICCC-3 diagnostic groups and subgroups	N	1-year OS		5-year OS	
		%	95%CI	%	95%CI
VIII. Malignant bone tumors	5	80.0	[20.4-96.9]	80.0	[20.4-96.9]
VIIIa. Osteosarcomas	1	100.0	-	100.0	-
VIIIb. Chondrosarcomas	1	100.0	-	100.0	-
VIIIc. Ewing tumor and related sarcomas of bone	3	66.7	[5.4-94.5]	66.7	[5.4-94.5]
IX. Soft tissue and other extrasosseous sarcomas	175	74.3	[67.1-80.1]	69.1	[61.7-75.4]
IXa. Rhabdomyosarcomas	57	93.0	[82.4-97.3]	82.5	[69.8-90.2]
IXb. Fibrosarcomas, and other fibrous neoplasms	49	89.8	[77.2-95.6]	89.8	[77.2-95.6]
IXb1. Fibroblastic and myofibroblastic tumors	47	91.5	[78.9-96.7]	91.5	[78.9-96.7]
IXb2. Nerve sheath tumors	2	50.0	[0.6-91.0]	50.0	[0.6-91.0]
IXc. Kaposi sarcoma	1	100.0	-	100.0	-
IXd. Other specified soft tissue sarcomas	54	40.7	[27.7-53.4]	38.9	[26.0-51.5]
IXd1-2. Ewing tumors and pPNET of soft tissue	8	75.0	[31.5-93.1]	75.0	[31.5-93.1]
IXd3. Extrarenal rhabdoid tumor	37	18.9	[8.3-32.8]	16.2	[6.6-29.6]
IXd4. Liposarcomas	1	100.0	-	100.0	-
IXd5. Fibrohistiocytic tumors	6	100.0	-	100.0	-
IXd7. Synovial sarcomas	2	100.0	-	100.0	-
IXe. Unspecified soft tissue sarcomas	14	91.1	[74.8-97.0]	91.1	[74.8-97.0]
X. Germ-cell tumors, and other neoplasms of gonads	234	91.0	[86.6-94.1]	90.6	[86.1-93.7]
Xa. Intracranial and intraspinal germ cell tumors	34	91.1	[74.8-97.0]	91.1	[74.8-97.0]
Xa2. Intracranial and intraspinal teratomas	32	96.9	[79.8-99.6]	96.9	[79.8-99.6]
Xa4. Intracranial and intraspinal yolk sac tumor	1	0.0	-	0.0	-
Xa6. Intracranial and intraspinal tumors of mixed forms	1	0.0	-	0.0	-
Xb. Malignant extracranial and extragonadal germ cell tumors	162	88.9	[82.9-92.9]	88.3	[82.2-92.3]
Xb1. Malignant germinomas of extracranial and extragonadal sites	1	0.0	-	0.0	-
Xb2. Malignant teratomas of extracranial and extragonadal sites	109	89.9	[82.5-94.3]	89.9	[82.5-94.3]
Xb4. Yolk sac tumor of extracranial and extragonadal sites	22	100.0	-	100.0	-
Xb5. Choriocarcinomas of extracranial and extragonadal sites	5	40.0	[5.2-75.3]	40.0	[5.2-75.3]
Xb6. Other and unspecified malignant mixed germ cell tumors	25	88.0	[67.3-96.0]	84.0	[62.8-93.7]
Xc. Malignant gonadal germ cell tumors	37	100.0	-	100.0	-
Xc2. Malignant gonadal teratomas	14	100.0	-	100.0	-
Xc4. Gonadal yolk sac tumor	12	100.0	-	100.0	-
Xc6. Malignant gonadal tumors of mixed forms	11	100.0	-	100.0	-
Xe. Other and unspecified malignant gonadal tumors	1	100.0	-	100.0	-
XI. Other malignant epithelial neoplasms and malignant melanomas	29	96.6	[77.9-99.5]	96.6	[77.9-99.5]
XIa. Adrenocortical carcinomas	18	94.4	[66.6-99.2]	94.4	[66.6-99.2]
XIb. Thyroid carcinomas	8	100.0	-	100.0	-
XId. Malignant melanomas	3	100.0	-	100.0	-
XII. Other and unspecified malignant neoplasms	12	100.0	-	91.7	[53.9-98.8]
XIIa. Other specified malignant tumors	12	100.0	-	91.7	[53.9-98.8]
XIIa3. Pulmonary blastoma and pleuropulmonary blastoma	10	100.0	-	100.0	-
XIIa6. Other specified malignant tumors	2	100.0	-	50.0	[0.6-91.0]
Total*	2754	86.1	[84.7-87.3]	81.0	[79.4-82.4]

Abbreviations: 95%CI, 95% confidence interval; OS, overall survival; ICC-3, International Classification of Childhood Cancer, Third Edition; cPNET, central primitive neuroectodermal tumors; pPNET, peripheral primitive neuroectodermal tumors

*For infants with many primary cancers, only the first primary cancer was including in the global overall survival analysis

Table 6. Time variation of 5-year overall survival for French infants diagnosed with cancer, by period of diagnosis (2000–2004, 2005–2009, and 2010–2014).

ICCC-3 diagnostic groups	2000-2004			2005-2009			2010-2014			P-value*
	n	5-y OS	CI95%	n	5-y OS	CI95%	n	5-y OS	CI95%	
I. Leukemias, myeloproliferative and myelodysplastic diseases	135	57.8	[49.0-65.6]	146	60.0	[51.6-67.5]	141	64.3	[55.7-71.6]	0.30
II. Lymphomas	1	100.0	-	1	100.0	-	1	100.0	-	0.22
III. Central nervous system tumors	140	57.1	[48.4-64.8]	149	64.2	[55.9-71.3]	154	64.4	[56.2-71.5]	0.13
IV. Neuroblastoma and other peripheral nervous cell tumors	283	89.4	[85.2-92.5]	267	89.9	[85.6-93.0]	283	91.8	[87.9-94.5]	0.29
V. Retinoblastoma	111	100.0	-	111	98.2	[93.0-99.5]	99	100.0	-	0.33
VI. Renal tumors	76	85.5	[75.4-91.7]	68	88.2	[77.9-93.9]	71	91.5	[82.2-96.1]	0.27
VII. Hepatic tumors	17	88.2	[60.6-96.9]	25	88.0	[67.3-96.0]	26	88.5	[68.4-96.1]	0.97
VIII. Malignant bone tumors	2	100.0	-	1	100.0	-	2	100.0	-	1.00
IX. Soft tissue and other extrasosseous sarcomas	49	77.6	[63.1-86.9]	62	62.9	[49.7-73.6]	64	68.6	[55.7-78.5]	0.25
X. Germ-cell tumors, and other neoplasms of gonads	88	93.2	[85.5-96.9]	79	86.0	[76.2-92.0]	67	92.5	[83.0-96.8]	0.87
XI. Other malignant epithelial neoplasms and malignant melanomas	12	91.7	[53.9-98.8]	8	100.0	-	9	100.0	-	0.29
XII. Other and unspecified malignant neoplasms	0	-	-	4	100.0	-	8	87.5	[38.7-98.1]	0.48
Total**	912	80.5	[77.7-82.9]	920	79.8	[77.1-82.3]	922	82.6	[80.0-84.9]	0.25

Abbreviations: 95%CI, 95% confidence interval; 5y OS, five-year overall survival; ICCC-3, International Classification of Childhood Cancer, Third Edition

* Log-rank trend test

**For infants with many primary cancers, only the first primary cancer was including in the global overall survival analysis

Table 7. Clinical and pathology/biology features of infants with neuroblastoma (France, 2000 to 2014, n=831)

	n	%	5-year OS (%)	95% CI	P-value*
Gender					
male	461	55.5	90.4	[87.3-92.8]	0.88
female	370	44.5	90.5	[87.0-93.1]	
Age at diagnosis					
0-28 days	219	26.4	93.1	[88.9-95.8]	0.09
29 days-2 months	164	19.7	93.3	[88.2-96.2]	
3-5 months	174	20.9	89.7	[84.1-93.4]	
6-12 months	274	33.0	87.1	[82.5-90.6]	
Primary tumor site					
adrenal	468	56.3	87.8	[84.5-90.4]	0.02
abdominal/retroperitoneal	111	13.4	90.9	[83.8-95.0]	
cervical	32	3.9	96.9	[79.8-99.6]	
thoracic	143	17.2	97.2	[92.7-98.9]	
pelvic	61	7.3	90.0	[79.1-95.4]	
other	16	1.9	93.8	[63.2-99.1]	
INRGSS stage					
L1	247	29.7	98.4	[95.7-99.4]	< 0.01
L2	248	29.8	93.9	[90.1-96.3]	
M	110	13.2	72.7	[63.4-80.1]	
Ms	205	24.7	85.3	[79.7-89.5]	
unknown	21	2.5	100.0	-	
MYCN					
non-amplified	628	75.6	94.9	[92.9-96.4]	< 0.01
amplified	58	7.0	41.2	[28.5-53.5]	
unknown	145	17.4	91.0	[85.1-94.7]	

Abbreviations: 95%CI, 95% confidence interval; OS, overall survival; INRGSS, International Neuroblastoma Risk Group Staging System

* Log-rank test

Table 8. Clinical and pathology/biology features of infants with acute leukemia (France, 2000 to 2014)

	n	%	5-year OS (%)	95% CI	P-value*
Acute lymphoblastic leukemias (n=173)					
Gender					
male	87	50.3	58.5	[47.4-68.1]	0.13
female	86	49.7	51.7	[40.5-61.7]	
Age at diagnosis					
0-28 days	12	6.9	8.3	[0.5-31.1]	<0.01
29 days-2 months	30	17.3	43.3	[25.6-59.9]	
3-5 months	48	27.7	64.6	[49.4-76.3]	
6-12 months	83	48.0	61.8	[50.3-71.4]	
CNS involvement					
CNS negative	140	80.9	56.2	[47.5-64.0]	0.26
CNS positive	33	19.1	50.4	[32.2-66.0]	
ALL subtypes					
Precursor B-cell	158	91.3	54.3	[46.2-61.7]	0.50
Precursor T-cell	13	7.5	58.7	[27.4-80.4]	
Burkitt leukemia	2	1.2	100.0	-	
Precursor B-cell ALL (n=158)					
Gender					
male	81	51.3	56.7	[45.2-66.7]	0.20
female	77	48.7	51.8	[40.1-62.2]	
Age at diagnosis					
0-28 days	12	7.6	8.3	[0.5-31.1]	<0.01
29 days-2 months	28	17.7	39.3	[21.7-56.5]	
3-5 months	47	29.8	63.8	[48.4-75.7]	
6-12 months	71	44.9	62.9	[50.5-73.0]	
CNS involvement					
CNS negative	127	80.4	54.9	[45.8-63.1]	0.44
CNS positive	31	19.6	51.6	[33.1-67.4]	
MLL rearrangement					
negative	50	31.7	71.9	[57.3-82.3]	<0.01
positive	108	68.3	46.1	[36.4-55.1]	
Geil criteria					
Pro-B	71	44.9	43.2	[31.5-54.4]	0.07
Common-B	26	16.5	61.3	[40.0-77.0]	
Pre-B	37	23.4	67.6	[50.0-80.1]	
Mature B	7	4.4	42.9	[9.8-73.4]	
Unknown	17	10.8	64.7	[37.7-82.3]	

Table 8. (Continued)

	n	%	5-year OS (%)	95%CI	P-value*
Acute myeloid leukemias (n=169)					
Gender					
male	88	52.1	61.3	[50.3-70.6]	0.37
female	81	47.9	66.6	[55.2-75.7]	
Age at diagnosis					
0-28 days	28	16.6	35.7	[18.9-53.0]	<0.01
29 days-2 months	29	17.2	69.0	[48.8-82.5]	
3-5 months	35	20.7	74.3	[56.4-85.7]	
6-12 months	77	45.6	67.4	[55.7-76.6]	
CNS involvement					
CNS negative	156	92.3	63.4	[55.3-70.4]	0.68
CNS positive	13	7.7	69.2	[37.3-87.2]	
AML subtypes					
M0	7	4.1	57.1	[17.2-83.7]	0.06
M1	2	1.2	50.0	[0.6-91.0]	
M2	3	1.8	100.0	-	
M3	1	0.6	0.0	-	
M4	5	3.0	80.0	[20.4-96.9]	
M4eo	2	1.2	100.0	-	
M5	33	19.5	69.7	[51.0-82.4]	
M6	4	2.4	25.0	[0.9-66.5]	
M7 (AMKL)	34	20.1	47.1	[29.8-62.5]	
- with Down syndrome	11	32.3	54.5	[22.9-78.0]	
- without Down syndrome	23	67.7	43.5	[23.3-62.1]	
MLL rearrangement	71	42.0	70.4	[58.3-79.6]	
Unknown	7	4.1	57.1	[17.2-83.7]	
Biphenotypic leukemias (n=17) and acute unspecified leukemia (n=1)					
Gender					
male	9	50.0	44.4	[13.6-71.9]	0.89
female	9	50.0	44.4	[13.6-71.9]	
Age at diagnosis					
0-28 days	2	11.1	50.0	[0.6-91.0]	0.01
29 days-2 months	5	27.8	20.0	[0.8-58.2]	
3-5 months	4	22.2	75.0	[12.8-96.1]	
6-12 months	7	38.9	57.1	[17.2-83.7]	
CNS involvement					
CNS negative	16	88.9	50.0	[24.5-71.0]	0.07
CNS positive	2	11.1	50.0	[0.6-91.0]	

Abbreviations: 95%CI, 95% confidence interval; OS, overall survival; CNS, Central nervous system; MLL, Mixed Lineage Leukemia; ALL, Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; AMKL, Acute megakaryoblastic leukemia

* Log-rank test