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Review

# Childhood cancer survival in France, 1990–1999

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ABSTRACT

The aim of this study was to describe the overall survival after childhood cancer in France using follow-up data from regional population-based registries. The survival of children (aged under 15 years) diagnosed with a cancer during 1990–1999 was analysed. For all cancers, the survivals were, respectively, 90.3% [89.4–91.3] at 1-year, 75.2% [73.8–76.6] at 5 years and 72.2% [70.7–73.7] at 10 years. During the 1990s, the average improvement in the 5-year survival was +1.2% per year. Adjusted for gender, age, area of residence and stage, children with cancer diagnosed between 1995 and 1999 had a 0.80 reduced risk of dying compared with those whose cancer had been diagnosed between 1990 and 1994. The increase of survival at the population level reflects a global improvement in childhood cancer care. The Paediatric Registries, in association with the French Society of Childhood Cancer, are now collecting data to quantify on a national basis the other events, at least relapse and second cancers.



## 1. Introduction

Approximately 1600 children, aged less than 15 years, are diagnosed annually with a cancer in France, which corresponds to an annual incidence rate of 138 per million.[1] Cancer remains the second cause of death in children aged from 0 to 14 years after non-intentional injuries, representing 350 deaths each year.[2]

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The national registration of childhood cancer began in France in 1990 for haematopoietic malignancies and in 1999 for solid tumours. The objective of the present study was to estimate the overall survival (OS) after childhood cancer in the French population during the 1990–1999 period. We used the French Regional Paediatric Cancer Registries, which covered a quarter of the French territory at this period and allowed us to study survival according to characteristics at diagnosis, irrespective of inclusion in clinical trials.

## 2. Patients and methods

All cancers in children from five regional population-based cancer registries of several French administrative areas (French regional areas of Auvergne-Limousin, Bretagne, Lorraine, Rhône-Alpes and French departmental area of Val-de-Marne) were included. Altogether, the registries cover 24% of the French paediatric population and about the same proportion of French territory. The five population-based cancer registries identified cases using both active search procedures in hospital departments and mailed questionnaires to public and private hospitals, specialised practitioners and pathologists, following international recommendations.[3] Each case was attributed a morphology code and a topography code as per the International Classification of Diseases for Oncology (ICD-O). All morphology codes have been converted into the third edition of ICD-O.[4]

The cases consist of children with an incident tumour diagnosed between 1990 and 1999, aged 0–14 years and residing, at diagnosis, in the administrative areas covered by the French regional Childhood Cancer Registries. All malignancies with an ICD-O behaviour code of '/3' were included. Benign tumours, tumours of uncertain malignancy or *in situ* carcinomas (ICD-O morphology behaviour code '/0', '/1' or '/2') were excluded, except for 'Central nervous system and miscellaneous intracranial and intraspinal neoplasms' (group III of the third edition of the International Classification of Childhood Cancer (ICCC)), in line with international recommendations.[5] Myelodysplastic syndrome and other myeloproliferative diseases (subgroup Id of the ICCC), not homogeneously recorded by all paediatric registries, were excluded. As recommended, lymphomas with bone-marrow involvement greater than 25% were coded as leukaemias whereas those with lower bone-marrow involvement were coded as stage IV lymphomas.[6]

The data available for each case were gender, date and place of birth, date and place of diagnosis, tumour morphology and topography, stage at diagnosis (metastatic or not), vital status and date of last contact.

Analyses were performed with all cases diagnosed between 1st January 1990 and 31st December 1999, and followed up until 1st January 2006. The end-point of interest was death from any cause for the estimation of the proportion of OS. French Paediatric Registries attempt to follow up all cases till death. Vital status was obtained at the time of analysis by active search in medical records and by matching the Childhood Cancer Registry 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. Children who were last known alive less than 5 years after diagnosis were considered as lost to follow up at 5 years. Median length of follow up was calculated using the inverse Kaplan–Meier method.[7] The proportion of OS was estimated using Kaplan–Meier methods.[8]

Survival curves were compared using the log-rank test[9] and the trend in survival over time periods was estimated using the log-rank test for trend.[10] The percent change in cumulative probability (PCCP) was the relative difference of 5-year survival proportions between time periods. The average annual percent change (AAPC) in 5-year survival was calculated as the slope of the linear regression used to model the natural logarithm of the 5-year survival proportion as a function of the calendar year.[11] Finally, the risks of death according to age, gender, stage, area of residence and period were estimated by hazard ratios (HR) and their 95% confidence intervals (95% CI) using Cox proportional hazards regression models.[12] Reference categories were selected logically as the first category (localised/stages I–III tumours and period 1990–1994) or as the modal category (1–4-year age group), or arbitrarily (boys and Lorraine region). Statistical tests were two-sided (significance at 5%).

All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., 1996).

## 3. Results

### 3.1. Survival

Overall, 3566 cases of childhood cancer were included during the 1990–1999 period (402 in 'Auvergne-Limousin', 667 in 'Bretagne', 608 in 'Lorraine', 1530 in 'Rhône-Alpes' and 359 in 'Val-de-Marne') with a median follow up of 10 years and 4 months, and 1.8% and 8.2% lost to follow up at 5 and 10 years, respectively. Table 1 describes the overall survivals at 1, 5 and 10 years. For all cancers combined, overall survivals ranged from 90.3% [89.4–91.3] at 1-year to 72.2% [70.7–73.7] at 10 years. The best survivals were observed for Hodgkin's and Burkitt's lymphomas, retinoblastomas, malignant gonadal germ-cell tumours and thyroid carcinomas, for which 5-year OSs were higher than 90%. Conversely, the lowest survivals were observed for central nervous system (CNS) embryonal tumours and acute non-lymphoblastic leukaemia (ANLL), with 5-year OSs of 48.6% and 51.3%, respectively. For most diagnostic groups, around 35% of the deaths had occurred within 1-year and 90% within 5 years after diagnosis. Five-year survival was significantly lower for T-cell acute lymphoblastic leukaemia (ALL) than for B-precursor ALL (65.9% [57.6–74.2] versus 84.1% [81.3–86.9]; $p < 0.01$). Within CNS tumours, the lowest survivals were observed for central primitive neuro-ectodermal tumours (cPNET), particularly for supratentorial site, and for other gliomas.

### 3.2. Demographic characteristics

The OS did not differ significantly according to gender for any site of cancer (Table 2). Survival was strongly related to age, with the lowest 5-year survivals observed in children below 1-year of age with leukaemia (37.5% [25.6–49.4]) and with CNS tumours (45.0% [32.4–57.6]). Conversely, survival was

**Table 1 – Overall survival (OS) for French children diagnosed with cancer during the period 1990–1999, by type of tumour**

| Tumour types | Number of cases | Lost to follow-up at 5 years (%) | Median length of follow-up (years) | 1-year OS % (95% CI) | 5-year OS% (95% CI) | 10-year OS% (95% CI) |
|---|---|---|---|---|---|---|
| Leukaemia | 1056 | 1.5 | 10.1 | 96.6 [88.8–92.4] | 74.4 [71.8–77.1] | 71.5 [68.7–74.3] |
| Acute lymphoblastic leukaemia (ALL) | 832 | 1.8 | 10.2 | 93.6 [91.9–95.3] | 80.5 [77.8–83.2] | 77.1 [74.2–80.0] |
| B-precursor ALL | 646 | 1.4 | 10.2 | 94.7 [93.0–96.4] | 84.1 [81.3–86.9] | 81.2 [78.1–84.3] |
| T- cell ALL | 126 | 1.6 | 10.1 | 92.9 [88.4–97.3] | 65.9 [57.6–74.2] | 60.8 [52.0–69.6] |
| Other specified or unspecified ALL | 60 | 6.7 | 9.6 | 81.4 [71.5–91.3] | 76.1 [65.2–87.0] | 67.5 [54.8–80.2] |
| Acute non-lymphoblastic leukaemia (ANLL) | 183 | 0.5 | 9.8 | 77.6 [71.6–77.6] | 51.3 [44.0–58.5] | 50.1 [42.8–57.4] |
| Lymphomas | 430 | 1.9 | 10.1 | 94.9 [92.8–97.0] | 89.3 [86.4–92.2] | 86.8 [83.5–90.1] |
| Hodgkin's disease | 154 | 0.6 | 9.5 | 99.4 [98.1–100.0] | 96.1 [93.0–99.2] | 95.3 [91.9–98.7] |
| Non-Hodgkin's lymphoma | 137 | 2.2 | 10.7 | 92.0 [87.4–96.5] | 79.8 [73.4–86.3] | 75.2 [68.2–82.3] |
| Burkitt's lymphoma | 122 | 2.5 | 10.9 | 93.4 [89.0–97.8] | 93.4 [89.0–97.8] | 92.2 [87.2–97.2] |
| Central nervous system (CNS) tumours | 797 | 2.6 | 10.6 | 82.2 [79.6–84.9] | 64.8 [61.4–68.1] | 61.3 [57.9–64.8] |
| Ependymoma | 103 | 2.9 | 10.5 | 81.6 [74.1–89.0] | 60.8 [51.3–70.3] | 55.1 [45.2–64.9] |
| Astrocytoma | 333 | 3.6 | 10.6 | 86.6 [83.0–90.3] | 77.8 [73.3–82.3] | 75.2 [70.5–80.0] |
| Embryonal tumours | 158 | 1.2 | 9.6 | 76.0 [69.3–82.6] | 48.6 [40.7–56.4] | 43.4 [35.5–51.3] |
| Medulloblastoma | 117 | 1.7 | 9.6 | 82.9 [76.1–89.7] | 56.2 [47.2–65.2] | 52.4 [43.2–61.6] |
| Supratentorial central primitive neuro-ectodermal tumours (cPNET) | 41 | 0.0 | 9.1 | 53.7 [38.4–69.0] | 26.8 [13.3–40.3] | 17.6 [5.2–30.0] |
| Other gliomas | 93 | 3.2 | 9.8 | 64.2 [54.4–74.0] | 31.5 [21.9–41.0] | 30.1 [20.7–39.6] |
| Other specified CNS tumours | 96 | 0.0 | 11.3 | 96.9 [93.4–100.0] | 88.5 [82.2–94.9] | 84.9 [77.5–92.2] |
| Sympathetic nervous system tumours | 315 | 1.3 | 11.1 | 89.5 [86.1–92.9] | 69.8 [64.7–74.9] | 67.8 [62.7–73.0] |
| Neuroblastoma | 309 | 1.3 | 11.0 | 89.6 [86.3–93.0] | 69.9 [64.7–75.0] | 67.9 [62.6–73.1] |
| Retinoblastoma | 101 | 1.0 | 10.2 | 99.0 [97.1–100.0] | 97.0 [93.6–100.0] | 97.0 [93.6–100.0] |
| Renal tumours | 226 | 1.3 | 10.4 | 94.6 [91.7–97.6] | 86.6 [82.1–91.1] | 85.7 [81.1–90.3] |
| Wilm's tumour | 218 | 1.4 | 10.4 | 94.4 [91.4–97.5] | 87.0 [82.5–91.5] | 86.1 [81.4–90.7] |
| Hepatic tumours | 39 | 0.0 | 11.3 | 84.6 [73.3–95.9] | 71.8 [57.7–85.9] | 71.8 [57.7–85.9] |
| Hepatoblastoma | 33 | 0.0 | 11.2 | 81.8 [68.7–95.0] | 75.8 [61.1–90.4] | 75.8 [61.1–90.4] |
| Malignant bone tumours | 191 | 0.5 | 9.8 | 94.2 [90.9–97.5] | 71.6 [65.2–78.0] | 64.5 [57.5–71.4] |
| Osteosarcoma | 92 | 1.1 | 10.4 | 95.6 [91.4–99.8] | 68.1 [58.6–77.7] | 61.0 [50.8–71.2] |
| Ewing's sarcoma | 86 | 0.0 | 9.6 | 94.2 [89.3–99.1] | 74.4 [65.2–83.6] | 66.3 [55.9–76.6] |
| Soft-tissue sarcomas | 190 | 1.1 | 10.7 | 92.6 [88.9–96.3] | 67.7 [61.1–74.4] | 65.0 [58.1–71.9] |
| Rhabdomyosarcoma | 108 | 1.9 | 10.9 | 95.3 [91.3–99.3] | 64.5 [55.4–73.5] | 62.0 [52.6–71.4] |
| Non-rhabdomyosarcoma | 82 | 0.0 | 10.5 | 92.7 [87.0–98.3] | 72.0 [62.2–81.7] | 70.5 [60.5–80.4] |
| Germ-cell tumours | 119 | 2.5 | 10.9 | 92.4 [87.7–97.2] | 83.9 [77.3–90.6] | 79.8 [72.3–87.2] |
| Intracranial and intraspinal germ-cell tumours | 37 | 0.0 | 10.5 | 86.5 [75.5–97.5] | 78.4 [65.1–91.6] | 70.0 [53.8–86.2] |
| Malignant gonadal germ-cell tumours | 42 | 2.4 | 11.2 | 100.0 | 90.4 [81.5–99.3] | 87.9 [77.9–97.9] |
| Carcinomas | 95 | 6.3 | 8.8 | 96.8 [93.2–100.0] | 86.8 [79.9–93.8] | 81.2 [72.7–89.6] |
| Thyroid carcinoma | 34 | 8.8 | 8.3 | 100.0 | 100.0 | 96.8 [90.6–100.0] |
| All tumours | 3566 | 1.8 | 10.3 | 90.3 [89.4–91.3] | 75.2 [73.8–76.6] | 72.2 [70.7–73.7] |

95% CI: 95% confidence interval.

much better in neuroblastoma diagnosed before the age of 1-year than in those diagnosed later (85.5% [79.1–91.8] for <1-year, 63.1% [55.6–70.6] for 1–4 years, 47.8% [27.4–68.3] for 4–9 years and 44.4% [12.0–76.9] for 10–14 years).

### 3.3. *Stage*

On average, 15% of lymphomas and solid tumours were classified as stage IV or metastatic. The distribution of metastatic

**Table 2 – Five-year overall survivals for French children diagnosed with cancer, by gender, age and stage at diagnosis (1990–1999)**

| Tumour types | Gender (%, 95% CI) | | Age group (%, 95% CI) | | | | Stage at diagnosis (%, 95% CI)[a] | |
|---|---|---|---|---|---|---|---|---|
| | Boys ($n$ = 1928) | Girls ($n$ = 1638) | <1-year ($n$ = 388) | 1–4 years ($n$ = 1239) | 5–9 years ($n$ = 967) | 10–14 years ($n$ = 972) | Stage I, II, III/not metastatic ($n$ = 2140) | Stage IV/metastatic ($n$ = 370) |
| Leukaemia | 73.0 [69.3–76.7] | 76.2 [72.4–79.9] | 37.5 [25.6–49.4] | 79.4 [75.7–83.1] | 79.3 [74.8–83.9] | 67.8 [61.7–74.0]** | – | – |
| ALL | 79.1 [75.4–82.9] | 82.5 [78.6–86.3] | 23.8 [5.6–42.0] | 83.4 [79.7–87.0] | 84.2 [79.5–88.8] | 75.4 [68.8–82.0]** | – | – |
| B-precursor ALL | 83.6 [79.5–87.6] | 85.0 [81.1–88.9] | 29.4 [7.7–51.1] | 87.2 [83.7–90.7] | 86.4 [81.3–91.5] | 78.8 [71.0–86.7]** | – | – |
| T-cell ALL | 66.3 [56.5–76.1] | 64.9 [49.5–80.2] | 0.0 | 50.0 [34.1–65.9] | 77.3 [64.9–89.7] | 69.8 [46.1–83.5]** | – | – |
| ANLL | 44.6 [33.9–55.3] | 56.8 [47.1–66.6] | 43.2 [27.3–59.2] | 55.3 [41.1–69.5] | 60.9 [47.8–73.9] | 42.2 [27.8–56.6] | – | – |
| Lymphomas | 89.0 [85.4–92.6] | 89.9 [84.9–94.9] | 60.0 [17.1–100.0] | 87.6 [79.6–95.6] | 91.8 [87.7–95.9] | 89.4 [85.0–93.8]** | 90.1 [87.0–93.2] | 84.6 [75.8–93.4]* |
| Hodgkin's disease | 97.9 [95.1–100.0] | 93.0 [86.3–99.6] | – | 100.0 | 97.9 [93.8–100.0] | 94.9 [90.5–99.3] | 97.0 [94.1–99.9] | 90.0 [76.8–100.0]* |
| Non-Hodgkin's lymphoma | 76.3 [67.5–85.2] | 83.3 [72.8–93.9] | 0.0 | 72.9 [55.7–90.0] | 89.5 [81.5–97.4] | 75.0 [63.2–86.8]** | 80.5 [73.2–87.8] | 70.8 [52.6–89.0] |
| Burkitt's lymphoma | 91.5 [85.8–97.1] | 100.0 | – | 100.0 | 89.1 [81.4–96.7] | 96.9 [90.8–100.0]*** | 93.1 [88.2–98.0] | 94.7 [84.7–100.0] |
| CNS tumours | 66.4 [61.8–70.9] | 63.0 [58.1–67.9] | 45.0 [32.4–57.6] | 64.5 [58.4–70.6] | 65.6 [59.9–71.4] | 69.6 [63.7–75.6]** | 67.1 [63.7–70.5] | 29.2 [16.3–42.1]** |
| Ependymoma | 64.8 [51.6–77.9] | 56.9 [43.3–70.5] | 45.5 [24.6–66.3] | 63 [49.1–77.0] | 63.0 [39.5–86.6] | 71.4 [50.2–92.7] | 64.8 [55.0–74.6] | 27.3 [1.0–53.6]** |
| Astrocytoma | 79.7 [73.6–85.8] | 75.8 [69.1–82.4] | 69.2 [44.1–94.3] | 88.7 [82.3–95.0] | 77.1 [69.1–85.2] | 70.1 [61.6–78.5]** | 78.4 [73.9–82.9] | 40.0 [0.0–82.9]** |
| Embryonal tumours | 48.4 [38.5–58.2] | 48.9 [36.1–61.7] | 28.6 [4.9–52.2] | 32.7 [19.5–45.8] | 58.3 [46.2–70.3] | 62.9 [45.4–80.3]** | 52.5 [43.9–61.1] | 31.0 [14.2–47.8] |
| Medulloblastoma | 55.8 [44.6–67.1] | 56.9 [41.8–71.9] | 50.0 [11.0–89.0] | 34.4 [17.9–50.9] | 64.6 [51.8–77.4] | 67.4 [48.8–86.0]* | 62.8 [52.9–72.7] | 32.0 [13.8–50.2]* |
| Supratentorial cPNET | 25.0 [7.7–42.3] | 29.4 [7.7–51.1] | 12.5 [0.0–35.2] | 29.4 [7.7–51.1] | 27.3 [1.0–53.5] | 40.0 [0.0–80.0]* | 27.0 [12.7–41.3] | 25.0 [0.0–67.3] |
| SNS tumours | 67.8 [60.6–74.9] | 72.0 [64.8–79.2] | 85.5 [79.1–91.8] | 62.3 [54.8–69.8] | 47.8 [27.4–68.3] | 61.5 [35.1–88.0]** | 85.5 [80.5–90.6] | 46.7 [38.1–55.4]** |
| Neuroblastoma | 68.0 [60.8–75.3] | 71.8 [64.6–79.0] | 85.5 [79.1–91.8] | 63.1 [55.6–70.6] | 47.8 [27.4–68.3] | 44.4 [12.0–76.9]** | 85.7 [80.6–90.8] | 47.1 [38.4–55.8]** |
| Retinoblastoma | 96.3 [91.3–100.0] | 97.8 [93.6–100.0] | 100.0 | 94.2 [87.9–100.0] | 100.0 | 100.0 | 96.9 [93.4–100.0] | 100.0 |
| Renal tumours | 82.4 [74.6–90.2] | 89.5 [84.3–94.7] | 83.3 [71.2–95.5] | 89.3 [84.0–94.6] | 86.1 [75.7–96.4] | 71.4 [47.8–95.1] | 89.2 [84.9–93.6] | 69.0 [52.1–85.8]** |
| Wilm's tumour | 82.6 [74.5–90.6] | 90.0 [84.8–95.2] | 83.3 [71.2–95.5] | 89.3 [84.0–94.6] | 85.7 [75.1–96.3] | 71.4 [38.0–100.0] | 88.9 [84.4–93.4] | 74.1 [57.5–90.6]** |
| Hepatic tumours | 74.1 [57.5–90.6] | 66.7 [40.0–93.3] | 90.9 [73.9–100.0] | 72.7 [54.1–91.4] | 50.0 [0.0–100.0] | 25.0 [0.0–67.4] | 78.1 [63.8–92.5] | 42.9 [6.2–79.5]*** |
| Hepatoblastoma | 78.3 [61.4–95.1] | 70.0 [41.6–98.4] | 90.9 [73.9–100.0] | 71.4 [52.2–90.6] | 0.0 | –*** | 81.5 [66.8–96.1] | 50.0 [10.0–90.0] |
| Malignant bone tumours | 71.4 [62.8–80.1] | 71.8 [62.2–81.3] | 100.0 | 68.8 [46.0–91.5] | 66.0 [52.4–79.5] | 73.8 [66.1–81.5] | 76.7 [70.2–83.2] | 40.7 [22.2–59.3]** |
| Osteosarcoma | 72.2 [60.3–84.2] | 67.6 [52.5–82.7] | – | 50.0 [0.0–100.0] | 64.3 [39.2–89.4] | 69.3 [58.9–79.9] | 73.1 [63.2–82.9] | 38.5 [12.0–64.9]* |
| Ewing's sarcoma | 76.7 [64.1–89.4] | 72.1 [58.7–85.5] | 100.0 | 76.9 [54.2–99.6] | 64.5 [47.7–81.3] | 82.9 [71.4–94.4] | 80.8 [71.8–89.9] | 46.2 [19.0–73.3]** |
| Soft-tissue sarcomas | 67.3 [58.5–76.0] | 68.4 [58.1–78.6] | 60.1 [40.9–79.3] | 80.8 [70.0–91.5] | 63.2 [50.6–75.7] | 63.6 [50.9–76.4]*** | 78.1 [71.6–84.6] | 20.6 [7.0–34.2]** |
| Rhabdomyosarcoma | 67.7 [56.1–79.4] | 60.0 [45.7–74.3] | 44.4 [12.0–76.9] | 78.1 [65.4–90.7] | 62.2 [46.5–77.8] | 50.0 [28.1–71.9]*** | 75.0 [65.9–84.0] | 15.8 [0.0–32.2]** |
| Non-rhabdomyosarcoma | 66.7 [53.3–80.0] | 79.4 [65.8–93.0] | 68.8 [46.0–91.5] | 90.9 [73.9–100.0] | 65.0 [44.1–85.9] | 71.4 [56.5–86.4] | 82.1 [72.9–91.3] | 26.7 [4.3–49.1]** |
| Germ-cell tumours | 79.7 [68.4–90.9] | 87.0 [79.0–94.9] | 74.8 [57.3–92.3] | 86.2 [73.7–98.8] | 76.9 [54.0–99.8] | 88.7 [80.2–97.2] | 88.4 [82.2–94.6] | 53.3 [28.1–78.6]** |
| Gonadal germ-cell tumours | 81.9 [63.4–100.0] | 96.0 [88.3–100.0] | 100.0 | 100.0 | 100.0 | 84.0 [69.6–98.4] | 97.2 [91.8–100.0] | 50.0 [10.0–90.0]** |
| Carcinomas | 87.3 [77.8–96.8] | 86.3 [76.2–96.5] | 100.0 | 75.0 [45.0–100.0] | 88.5 [76.2–100.0] | 87.4 [78.6–96.1] | 87.4 [80.0–94.7] | 83.9 [63.4–100.0] |
| Thyroid carcinoma | 100.0 | 100.0 | – | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| All tumours | 74.8 [72.9–76.7] | 75.7 [73.6–77.8] | 69.9 [65.3–74.5] | 76.3 [73.9–78.6] | 76.2 [73.5–78.9] | 75 [72.2–77.7]*** | 79.7 [78.0–81.4] | 51.7 [46.6–56.8]** |

Log-rank test: * <0.05; ** <0.01; *** <0.10; 95% CI: 95% confidence interval.
a Leukaemia excluded.

tumours ranged from 3% for retinoblastoma to 41% for neuroblastoma. For all cancers combined (leukaemia excluded), 5-year OS was 79.7% [78.0–81.4] for localised stages and 51.7% [46.6–56.8] for advanced stages ($p < 0.01$) (Table 2).

### 3.4. *Time trends in survival*

All cancers combined, the 5-year OS increased from 72.4% [70.3–74.6] for the 1990–1994 period to 77.7% [75.8–79.6] for the 1995–1999 period ($p < 0.01$). The increase in survival was significant for ALL, ANLL and Ewing's tumour (Table 3). Increase in 1-year survival was particularly marked for ANLL (from 67.1% [56.5–77.7] for the 1990–1994 period to 82.2% [75.0–89.5] for the 1995–1999 period), compared to ALL (from 92.4% [89.7–95.0] to 94.5% [92.4–96.6], respectively) and Ewing's tumour (from 88.6% [78.0–99.1] to 98.0% [94.2–100.0], respectively).

The average improvement in the 5-year survival during the 1990s was +1.2% per year ($p = 0.02$) for all cancers taken as a whole, and was +1.5% per year ($p = 0.04$) for leukaemia and +4.8% per year ($p = 0.02$) for malignant bone tumours.

For the 10–14 age group, the average improvement in the 5-year survival during the 1990s was +1.9% per year ($p = 0.02$).

Between the two periods the proportion of metastatic cancer at diagnosis did not change.

### 3.5. *Multivariate analysis*

The previous results remained in the multivariate analyses including age, gender, area of residence, period and stage

**Table 3 – Evolution of 5-year overall survival (OS) for French children diagnosed with cancer between the two halves of the study periods (1990–1994 and 1995–1999)**

| Tumour types | 1990–1994 | | 1995–1999 | | *p*-Value |
|---|---|---|---|---|---|
| | *n* | 5-year OS (95% CI) | *n* | 5-year OS (95% CI) | |
| Leukaemia | 489 | 70.3 [66.2–74.4] | 567 | 78.2 [74.8–81.6] | <0.01 |
| ALL | 393 | 76.7 [72.5–80.9] | 439 | 84.1 [80.7–87.5] | <0.01 |
| B-precursor ALL | 302 | 80.8 [76.4–85.2] | 344 | 87.4 [83.9–90.9] | <0.01 |
| T-cell ALL | 62 | 58.1 [45.8–70.4] | 64 | 73.4[62.5–84.2] | 0.13 |
| ANLL | 76 | 42.1 [31.0–53.2] | 107 | 57.8 [48.4–67.2] | 0.05 |
| Lymphomas | 204 | 88.2 [83.8–92.6] | 226 | 90.2 [86.3–94.1] | 0.91 |
| Hodgkin's disease | 63 | 95.2 [89.9–100.0] | 91 | 96.7 [93.0–100.0] | 0.94 |
| Non-Hodgkin's lymphoma | 73 | 76.7 [67.0–86.4] | 64 | 81.1[71.5–90.7] | 0.76 |
| Burkitt's lymphoma | 60 | 94.9 [89.3–100.0] | 62 | 91.9 [85.1–98.7] | 0.29 |
| CNS tumours | 395 | 64.2 [59.4–69.0] | 402 | 65.3 [60.6–70.0] | 0.89 |
| Ependymoma | 46 | 60.4 [46.1–74.6] | 57 | 61.1 [48.4–73.9] | 0.74 |
| Astrocytoma | 167 | 74.5 [67.9–81.2] | 166 | 81.0 [75.0–87.1] | 0.14 |
| Embryonal tumours | 78 | 43.6 [32.6–54.6] | 80 | 53.6 [42.6–64.5] | 0.29 |
| Medulloblastoma | 57 | 50.9 [37.9–63.9] | 60 | 61.5 [49.2–73.9] | 0.30 |
| Supratentorial cPNET | 21 | 28.6 [9.3–47.9] | 20 | 30.0 [9.9–50.1] | 0.90 |
| SNS tumours | 170 | 67.0 [59.9–74.1] | 145 | 73.1 [65.8–80.3] | 0.54 |
| Neuroblastoma | 166 | 66.8 [59.6–74.0] | 143 | 73.4 [66.1–80.6] | 0.49 |
| Retinoblastoma | 48 | 93.6 [86.6–100.0] | 53 | 100.0 | 0.06 |
| Renal tumours | 101 | 84.0 [76.8–91.2] | 125 | 88.7 [83.1–94.3] | 0.30 |
| Wilm's tumour | 96 | 85.3 [78.1–92.4] | 122 | 88.4 [82.7–94.1] | 0.48 |
| Hepatic tumours | 20 | 70.0 [49.9–90.1] | 19 | 73.7 [53.9–93.5] | 0.86 |
| Hepatoblastoma | 17 | 70.6 [48.9–92.2] | 16 | 81.3 [62.1–100.0] | 0.52 |
| Malignant bone tumours | 87 | 65.5 [55.5–75.5] | 104 | 76.7 [68.5–84.9] | 0.03 |
| Osteosarcoma | 45 | 68.9 [55.4–82.4] | 47 | 69.6 [56.3–82.9] | 0.49 |
| Ewing's sarcoma | 35 | 62.9 [46.8–78.9] | 51 | 82.4 [71.9–92.8] | 0.01 |
| Soft-tissue sarcomas | 95 | 69.2 [59.8–78.5] | 95 | 66.3 [56.8–75.8] | 0.63 |
| Rhabdomyosarcoma | 51 | 66.0 [52.9–79.1] | 57 | 63.2 [50.6–75.7] | 0.86 |
| Non-rhabdomyosarcoma | 44 | 72.7 [59.6–85.8] | 38 | 71.1 [56.6–85.5] | 0.74 |
| Germ-cell tumours | 57 | 82.3 [72.3–92.2] | 62 | 85.5 [76.7–94.2] | 0.78 |
| CNS germ-cell tumours | 17 | 70.6 [48.9–92.2] | 20 | 85.0 [69.4–100.0] | 0.40 |
| Gonadal germ-cell tumours | 22 | 90.9 [78.9–100.0] | 20 | 90.0 [76.8–100.0] | 0.80 |
| Carcinomas | 34 | 84.9 [72.6–97.1] | 61 | 88.0 [79.6–96.3] | 0.33 |
| Thyroid carcinoma | 9 | 100.0 | 25 | 100.0 | 1.00 |
| All tumours | 1702 | 72.4 [70.3–74.6] | 1864 | 77.7 [75.8–79.6] | <0.01 |

*p*-Value: log-rank test for trend.
95% CI: 95% confidence interval.

**Table 4 – Multivariate estimation of hazard ratios for death within 5 years after childhood cancer, adjusted for age, gender, area of residence, period and stage**

| | HR [95%CI] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | All tumours[a] (*n* = 2510) | Leukaemia (*n* = 1056) | Lymphomas (*n* = 430) | CNS tumours (*n* = 797) | SNS tumours (*n* = 315) | Renal tumours (*n* = 226) | Malignant bone tumours (*n* = 191) | Soft-tissue tumours (*n* = 190) |
| Gender | | | | | | | | |
| Boys | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| Girls | 0.99 [0.87–1.13] | 0.85 [0.68–1.07] | 0.77 [0.42–1.38] | 1.07 [0.85–1.35] | 1.14 [0.77–1.71] | 0.81 [0.39–1.65] | 1.19 [0.73–1.95] | 1.07 [0.64–1.81] |
| Age group | | | | | | | | |
| <1-year | 1.28 [1.04–1.59] | 4.79 [3.32–6.91] | 8.69 [2.27–33.2] | 1.78 [1.19–2.67] | 0.41 [0.24–0.69] | 2.06 [0.76–5.57] | – | 2.76 [1.15–6.65] |
| 1–4 years | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| 5–9 years | 1.07 [0.91–1.26] | 1.05 [0.77–1.41] | 0.74 [0.34–1.60] | 0.96 [0.73–1.28] | 0.98 [0.54–1.78] | 1.30 [0.53–3.18] | 0.91 [0.36–2.35] | 1.81 [0.87–3.78] |
| 10–14 years | 1.16 [0.98–1.36] | 1.80 [1.34–2.41] | 0.90 [0.42–1.95] | 0.91 [0.67–1.23] | 0.81 [0.32–2.04] | 2.36 [0.75–7.43] | 0.68 [0.28–1.64] | 1.91 [0.91–4.04] |
| Area of residence | | | | | | | | |
| Auvergne-Limousin | 1.39 [1.10–1.74] | 1.65 [1.09–2.47] | 1.22 [0.47–3.15] | 1.10 [0.70–1.72] | 1.74 [0.91–3.33] | 0.81 [0.19–3.50] | 2.33 [0.92–5.92] | 2.20 [0.92–5.28] |
| Bretagne | 1.15 [0.93–1.42] | 1.23 [0.85–1.77] | 1.11 [0.43–2.85] | 1.08 [0.74–1.58] | 1.00 [0.52–1.94] | 1.11 [0.34–3.61] | 1.08 [0.46–2.57] | 1.28 [0.53–3.09] |
| Lorraine | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| Rhône-Alpes | 1.05 [0.88–1.27] | 0.86 [0.61–1.20] | 1.14 [0.52–2.49] | 1.01 [0.73–1.41] | 1.35 [0.77–2.39] | 1.11 [0.39–3.13] | 1.64 [0.78–3.47] | 1.67 [0.76–3.69] |
| Val-de-Marne | 0.98 [0.76–1.27] | 0.93 [0.58–1.49] | 1.01 [0.31–3.31] | 1.19 [0.75–1.88] | 1.15 [0.54–2.49] | 0.78 [0.18–3.33] | 1.11 [0.40–3.11] | 0.91 [0.33–2.47] |
| Stage at diagnosis | | | | | | | | |
| Localised/stages I–III | Ref. | – | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| Metastatic/stage IV | 2.54 [2.17–2.97] | – | 2.01 [1.08–3.73] | 2.72 [1.90–3.89] | 5.12 [3.21–8.19] | 4.21 [190–9.34] | 3.36 [1.88–5.99] | 6.59 [3.66–11.87] |
| Period | | | | | | | | |
| 1990–1994 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| 1995–1999 | 0.80 [0.71–0.91] | 0.65 [0.51–0.82] | 1.04 [0.60–1.79] | 0.95 [0.76–1.20] | 0.87 [0.58–1.31] | 0.76 [0.37–1.56] | 0.63 [0.38–1.05] | 1.16 [0.70–1.91] |

HR: hazard ratio and 95% CI: 95% confidence interval.
a Leukaemia excluded.

(Table 4). Risk of death of infants with leukaemia, lymphomas and CNS tumours was multiplied by a factor of 5, 9 and 2, respectively, compared to children aged 1–4 years with the same type of cancer. Children with metastatic or stage IV cancer at diagnosis were at a significantly higher risk of dying than those with localised cancers, with HR ranging from 2.0 for lymphomas to 6.6 for soft-tissue sarcomas. The adjusted HRs for those residing in 'Auvergne-Limousin' compared to the reference region ('Lorraine') were 1.4 for all cancers and 1.7 for leukaemia. Children with cancer diagnosed from 1995 to 1999 had a lower risk of dying (HR = 0.81 [0.72–0.92]) than those diagnosed in the previous period and the reduction in mortality was slightly greater for leukaemia (HR = 0.66 [0.53–0.84]) than the other localisations.

## 4. Discussion

The present paper reports the survival of all childhood cancers in a part of France, based on paediatric registries. Although the National Registry of Childhood Leukaemia and Lymphoma includes all cases of leukaemia and lymphoma since 1990, we cannot present survival data on the whole country for all cancer groups and subgroups, because the National Registry of Childhood Solid Tumours was created in 1999 and its available follow up period is not sufficiently long. The present population-based study showed evidence that survival after childhood cancer has improved on average by 1.2% per year during the 1990s in France. The improvement was particularly apparent for leukaemia, for which the risk of death was 1.5-fold lower in the second half of the 1990s than in the first half. Age lower than 1-year at diagnosis was a factor of very poor prognosis for leukaemia, lymphoma and CNS tumours, but of good prognosis for neuroblastoma.

### 4.1. *Quality of data*

The population-based design prevented the results from being distorted by selection criteria necessary for inclusion in clinical trials. The OS estimates were all the more reliable since the number of children lost to follow up by the paediatric registries was very small. Survival is a robust indicator of the efficacy of cancer treatment, and a major indicator of cancer burden at the population level.[13] Moreover, high resolution studies, including standardised information on stage at diagnosis and adjusting for staging procedures in stage-specific comparisons, are necessary to conclude that the survival increases are more due to an improvement of treatment both in localised and advanced stages than an improvement of diagnosis procedures.[14] Unfortunately, French Paediatric Registries were not able to routinely register other events than death with active procedure. One of the aims of the National Registries will be, for the next decade, to register all the events, i.e. not only deaths but also relapse and second cancers.

The French Childhood Cancer Registries used identical procedures of case identification, classification, staging and follow up, to analyse and to compare survival for these rare cancers across five French geographic areas.

### 4.2. *Survival by cancer types*

For all cancers pooled, the French 5-year survivals were similar to those reported in Europe[15–26] and in the United States[11] (Table 5). Survival after childhood acute leukaemia and non-Hodgkin's lymphoma was also similar to that published at a national scale in France for the same period.[27] National survivals for ANLL were a little higher, but not significantly, than in the present study. The distribution of acute myeloid leukaemia subtypes was very similar in the two studies. We observed higher 5-year survivals (76%) for hepatoblastoma than that reported in Europe (63%) and in the United States (61%). Our estimation, although based on a small number ($n$ = 33 cases), was of the same order of magnitude as those provided by clinical trials.[28–32] Stiller and colleagues showed noticeable inter-country variations with lowest 5-year survivals in Eastern Europe (52% [38–64]) and highest survivals in the North (84% [67–92]).[26] Of the East European countries represented in this ACCIS study, only Hungary entered patients in the SIOPEL trials. Stiller and colleagues suggested that the poorer prognosis in the East was a consequence of the lack of access to modern therapy in some countries of the region.[26]

### 4.3. *Demographic and clinical factors*

As previously observed in several population-based European or American series,[27,33,34] survival after childhood cancer did not depend on gender.

Age was confirmed a major factor in childhood survival. The poor survival of infants with acute leukaemia is consistent with the findings of most registry-based studies[16,27,34,35] and clinical trials.[36] For lymphoma, small numbers preclude precise studies in children less than 1-year-old. However, the SEER programme reported lowest 5-year survivals in infants (49.7%) versus 82.9% for 1–4 years, 88.7% for 5–9 years and 88.0% for 10–14 years.[34] The poor survival of infants with CNS tumours is reported by most cancer registry-based studies.[21,34] Age at diagnosis, histology and extent of the tumour have been described as the most relevant predictors of survival in CNS tumours, together with anatomic site and type of treatment, which were not homogeneously available in our registries.[37] The prognosis of neuroblastoma is also known to depend on age, extent of disease at diagnosis, and expression of the N-Myc in tumour cells. Independent of the stage at diagnosis, age less than 1-year at diagnosis of neuroblastoma was confirmed to be a good prognostic factor.[23,33,34,38]

The tendency we observed for lower survival of leukaemia cases is more frequent in the 'Auvergne-Limousin' region than in other French areas and may be due to chance or a true heterogeneity in access to health care. Actually, there are some contrasts between the French regions. 'Val-de-Marne', in the 'Paris' area, is a highly urban area, while 'Auvergne and Limousin' belong to the most rural areas (average population densities around 50 inhabitants/km$^2$), while the other geographic sites are average areas in terms of rural status. One cannot rule out that the ease of access to medical care and low density of health care may influence survival in rural places. Caution must be exercised when interpreting

differences in survival in the total absence of information on cytogenetic factors (e.g. hypodiploidy, t(9;22)(q34;q11.2), t(4;11)(q21;q23), t(1;19)(q23;p13.3) for B-precursor ALL).[39]

### 4.4. *Survival trends*

For all cancers combined, the 5-year OS increased from 72.4% to 77.7% during the 1990s, with a PCCP of 7.3%. This positive trend has been reported in Europe with an increase from 71% to 75% and a PCCP of 5.6%,[40] and in the United States with an increase from 75.4% to 79.4% and a PCCP of 5.3%.[34] In our study, the improvement was particularly important for ANLL and Ewing's tumour (PCCP: 37.3% and 31.0%, respectively).

Regarding acute leukaemia, the positive trends have already been reported in France on a national scale[27] and were attributed to changes in therapeutic patterns: combination chemotherapies, large scale use of bone-marrow transplants for acute non-lymphoblastic leukaemia and adaptation of treatment intensity.[41,42] For childhood acute myeloblastic leukaemia, drug intensification at induction and post-remission may have contributed to the improvement in outcome.[43–47] Moreover, during the last two decades, early deaths from childhood cancer have decreased considerably, especially for

**Table 5 – Five-year survivals for children with cancer aged 0–14 years at diagnosis in France (data from National Registry of Childhood Haematological Malignancies), in Europe (data from ACCIS project) and in the United States (data from SEER programme)**

| Tumour types | Our study (1990–1999) %–95% CI | France[a] (1990–2000) %–95% CI | Europe[b] (1988–1997) %–95% CI | United States[c] (1985–1999)% |
|---|---|---|---|---|
| Leukaemia | 74.4 [71.8–77.1] | – | 73 [72–74] | 74.4 |
| ALL | 80.5 [77.8–83.2] | 82 [80–83] | 79 [78–79] | 81.8 |
| B-precursor ALL | 84.1 [81.3–86.9] | 85 [84–85] | – | – |
| T-cell ALL | 65.9 [57.6–74.2] | 67 [63–71] | – | – |
| Other specified or unspecified ALL | 76.1 [65.2–87.0] | 63 [52–74] | – | – |
| ANLL | 51.3 [44.0–58.5] | 58 [54–61] | 49 [47–51] | 41.1 |
| Lymphomas | 89.3 [86.4–92.2] | – | 84 [83–85] | 83.4 |
| Hodgkin's disease | 96.1 [93.0–99.2] | – | 93 [92-94] | 93.6 |
| Non-Hodgkin's lymphomas | 79.8 [73.4–86.3] | 77 [76–79] | 77.1 | |
| Burkitt's lymphomas | 93.4 [89.0–97.8] | 81 [78–84] | – | |
| CNS tumours | 64.8 [61.4–68.1] | – | 64 [63-65] | 66.4 |
| Ependymoma | 60.8 [51.3–70.3] | – | 58 [55–61] | 58.2 |
| Astrocytoma | 77.8 [73.3–82.3] | – | 75 [73–76] | 78.2 |
| Embryonal tumours | 48.6 [40.7–56.4] | – | 49 [47–51] | 56.6 |
| Medulloblastoma | 56.2 [47.2–65.2] | – | 57 [54–60] | 53.1 |
| Supratentorial cPNET | 26.8 [13.3–40.3] | – | 84 [82-87] | – |
| SNS tumours | 69.8 [64.7–74.9] | – | 59 [58–61] | 66.0 |
| Neuroblastoma | 69.9 [64.7–75.0] | – | 59 [57–61] | 66.0 |
| Retinoblastoma | 97.0 [93.6–100.0] | – | 93 [91–94] | 94.7 |
| Renal tumours | 86.6 [82.1–91.1] | – | 84 [82–85] | 90.4 |
| Wilm's tumour | 87.0 [82.5–91.5] | – | 83 [82–85] | 90.6 |
| Hepatic tumours | 71.8 [57.7–85.9] | – | 57 [52–62] | 55.8 |
| Hepatoblastoma | 75.8 [61.1–90.4] | – | 63 [57–68] | 61.0 |
| Malignant bone tumours | 71.6 [65.2–78.0] | – | 61 [59-63] | 67.5 |
| Osteosarcoma | 68.1 [58.6–77.7] | – | 59 [56–62] | 66.9 |
| Ewing's sarcoma | 74.4 [65.2–83.6] | – | 62 [58–65] | 64.7 |
| Soft-tissue sarcomas | 67.7 [61.1–74.4] | – | 65 [63–66] | 73.1 |
| Rhabdomyosarcoma | 64.5 [55.4–73.5] | – | 63 [60–65] | 68.2 |
| Germ-cell tumours | 83.9 [77.3–90.6] | – | 4 [82–86] | 86.7 |
| CNS germ-cell tumours | 78.4 [65.1–91.6] | – | – | 74.1 |
| Gonadal germ-cell tumours | 90.4 [81.5–99.3] | – | – | 98.1 |
| Carcinomas | 86.8 [79.9–93.8] | – | 89 [87–90] | 89.2 |
| Thyroid carcinoma | 100.0 | – | 98 [94–99] | 97.3 |
| All tumours | 75.2 [73.8–76.6] | – | 72 [72–72] | 74.7 |

95% CI: 95% confidence interval.
a Data from Ref. [27].
b Data from Refs. [15–26].
c Data from Ref. [11].

acute myeloid leukaemia. This was probably due to both an increased awareness of the potential problems and side-effects of chemotherapy and improved management and supportive care for critically ill children, including improved in-patient care, the use of total parenteral nutrition and the early use of broad-spectrum antibiotics and anti-fungal agents.[48,49]

For Ewing's tumour, the late 1970s and the early 1980s saw a dramatic change from local therapy alone to local treatment plus systemic chemotherapy. The outcomes continued to improve during the following decade with the use of some drugs currently believed to be most active against Ewing's tumour, namely vincristine, actinomycin D, cyclophosphamide or ifosfamide and doxorubicin.[50] During the 1990s, the use of high-dose therapy (melphalan-based combined with such agents as busulfan, etoposide or 1,3-bis(2-chloroethyl)-1-nitrosurea) with stem cell rescue seems to be promising for the treatment of high-risk primary Ewing's sarcoma patients (bulky primaries, metastatic diseases and so).[51–58]

Besides, better access to a care system may also have contributed to the global increase in OS, although changes may have been heterogeneous over the country during the 1990s.

## 5. Conclusion

The increase in OS at the population level reflects a global improvement in childhood cancer care, including combined modality targeted treatment, dose-intensive chemotherapy, risk-adapted/response-driven treatment and, possibly, better access to care system. The French Paediatric registries, in association with the French Society of Childhood Cancer, are now collecting data to quantify on a national basis the other events, at least relapse and second cancers, which need to be evaluated in the global burden of cancer in the childhood population.

## Conflict of interest statement

None declared.

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