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Cancer survival among adolescents in France

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ARTICLE INFO

Article history:
Received 16 June 2005
Received in revised form 1 July 2005
Accepted 6 July 2005
Available online 4 January 2006

Keywords:
Adolescent
Cancer
Survival
Epidemiology

ABSTRACT

Cancer is the third most significant cause of mortality in French adolescents. The aim of this study was to investigate survival of adolescents with cancer. Overall (OS), disease-specific (DSS) and event-free survival (EFS) were used for the outcome analysis of adolescents (15–19 years) with cancer, recorded by nine French population-based registries during the 1988–1997 period. Five-year OS, DSS and EFS were, respectively, 74.0% (70.7–77.4), 74.5% (71.2–77.9), and 69.0% (65.4–72.5). Five-year DSS was 94% for carcinomas, 89% for germ-cell tumours, 85% for lymphomas, 67% for soft-tissue sarcomas, 64% for CNS tumours, 55% for malignant bone tumours, and 41% for leukaemia. Compared with paediatric series, poor results in acute lymphoblastic leukaemia, malignant bone tumours, and soft-tissue sarcomas have to be highlighted, and deserve further studies concerning the type of regimens used for these patients. Multidisciplinary management of adolescent cancer in paediatric, adult, or specialized units will improve cure rates and treatment outcomes for these patients.

1. Introduction

In France, Desandes and colleagues [1] estimated that annual incidence of adolescent cancer is about 173 per million. One in every 1100 adolescents develop cancer between 15 and 19 years of age and approximately 700 new cases are diagnosed annually. Although adolescent cancers account for less than 0.5% of all cancers diagnosed in France each year [2], they remain the leading cause of death due to disease. In 1997 in France, there were 4797 deaths per year in the 15–24 age

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doi:10.1016/j.ejca.2005.07.035

range. After road traffic accidents (1842 deaths) and suicides (771 deaths), cancers are the third most significant cause of mortality in young people with 395 deaths per year [3].

Cancer in adolescence differs from that in adults and children: embryonal tumours observed in children are rare in adolescents (1%) and one third of all cancers pooled in this age group are epithelial tumours that occur more frequently in adults [1]. The adolescent population is rarely included in survival analyses. Recently, Gatta [4] have studied 5-year survival rates in young European adults (15–24 years) diagnosed with cancer during 1990–1994. Only 294 young adults from three French Registries were included. However, specific data concerning cancer survival among French adolescents (15–19 years) have never been reported.

Our study has used follow-up data from nine French population-based registries of adolescent cancer to examine patterns of survival over a 10-year period (from 1988 to 1997).

2. Patients and methods

All cancers in adolescents from nine population-based cancer registries of several French administrative areas (Calvados, Doubs, Hérault, Isère, Manche, Bas-Rhin, Haut-Rhin, Somme and Tarn) were included (covering rate: 10% of French population). All these population-based cancer registries collected data using both active search procedures in hospital departments and mailing questionnaires to public and private hospitals, specialized practitioners (surgeons, medical oncologists, paediatricians, and neurologists) and pathologists. They are tumour-based and multiple primaries occurring in the same person are recorded separately. Eligibility criteria were as follows: diagnosis of cancer ("/3" of the behaviour code in morphology according to the ICD-O second edition [5] signifies the existence of a malignant neoplasm of a primary site); 15–19 years of age at diagnosis; and period of diagnosis between January 1st 1988 and December 31st 1997. Cutaneous basal cell carcinomas were excluded from our study because they were not homogeneously recorded by all French General Cancer Registries.

The data collected for each case were: gender, age at diagnosis, diagnostic information (morphology and topography code according to the ICD-O second edition [5]), and follow-up information. Case data were tabulated simultaneously by tumour type categorized into the 12 major diagnostic groups according to the International Classification of Childhood Cancer (ICCC) [6]. The ICCC structure provided a clearer view of common cancers in adolescents than did the International Classification of Adult Cancer (9th Revision of the International Classification of Diseases) [7,8].

Response criteria (complete response [CR], progressive disease [PD]) were evaluated at the end of treatment. According to the World Health Organization criteria, CR is defined as the complete disappearance of all lesions and PD as tumour growth exceeding 25% since treatment began.

Follow-up information (cancer recurrence or progression, death from treatment side-effects or from the cancer itself) became available after actively searching the medical records of each hospital in which patients have been treated. Overall survival (OS), disease-specific survival (DSS), and event-free survival (EFS) were calculated using Kaplan–Meier methods [9]. A survival analysis was performed on a dataset containing all cases diagnosed between January 1st 1988 and December 31st 1997 and followed-up until December 31st 2002. The endpoint of interest was death from any cause for OS, death from cancer or from treatment side-effects for DSS, death from cancer or from treatment side-effects and cancer recurrence for EFS, with the date of diagnosis acting as the time-origin. Differences between survival curves were tested by log-rank tests [10]. Relative risks were calculated as the ratio between rates of risk of dying for two groups (males vs. females, and cases diagnosed between 1988 and 1992 vs. those diagnosed between 1993 and 1997).

All statistic analyses were performed using SPSS Base 9.0 for Windows software.

3. Results

Table 1 describes the number of cases and deaths (whatever the cause) for the diagnostic groups and details those lost to follow-up at 5 years. Leukaemia cases had by far the largest proportion of deaths (almost 61% died). On the contrary, 15% or less of cases with carcinomas, germ-cell tumours, non-rhabdomyosarcomas, and Hodgkin's disease (HD) died. With 1.1% and 2.5% of patients lost to follow-up at 2 and 5 years, respectively, the length of follow-up ranged from 0 to 16 years, with a median of 6 years and 9 months. For survivors, median follow-up was 8 years.

Treatment response criteria were evaluated in 636 cases (8 missing data, and 4 deaths before starting treatment). Among the most common diagnoses, a complete response after treatment was achieved in 100.0% of thyroid carcinomas, 99.0% of HD, 98.4% of malignant melanomas, 92.1% of germ-cell tumours, 80.0% of acute non-lymphoblastic leukaemia (ANLL) and non-Hodgkin's lymphoma (NHL), 78.7% of soft-tissue sarcomas, 76.1% of acute lymphoblastic leukaemia (ALL), 70.1% of malignant bone tumours, and 67.7% of central nervous system (CNS) tumours. Tumour progression was mainly observed in 23.9% of malignant bone tumours, 19.1% of soft-tissue sarcomas, 12.3% of CNS tumours, and 6.7% of germ-cell tumours.

Among 539 complete responders, relapse rates (median time from the end of treatment) were 48.6% for ALL (5.4 months), 38.3% for malignant bone tumours (14.1 months), 25.7% for NHL (7.3 months), 25.0% for ANLL (4.3 months) and CNS tumours (13.4 months), 18.9% for soft-tissue sarcomas (7.0 months), 14.5% for malignant melanomas (23.6 months), 13.4% for germ-cell tumours (9.4 months), 10.3% for HD (13.9 months), and 0% for thyroid carcinomas.

Overall survival (OS) for all cancers pooled were, respectively, 80.5%, 74.0%, and 72.5% at 2 years (95% CI: 77.4–83.5), 5 years (95% CI: 70.7–77.4), and 7 years (95% CI: 69.0–75.9). All causes of death were attributed to primary cancer (treatment side-effects ($n = 22$) or the cancer itself ($n = 160$)), except for 5 adolescents (three died of a secondary cancer, one from a road traffic accident, and one of unknown cause).

Table 1 presents 5-year DSS and EFS rates by diagnostic group. DSS rates for all cancers combined were 81.0%, 74.5%, and 73.0% at 2 years (95% CI: 78.0–84.1), 5 years (95% CI: 71.2–77.9), and 7 years (95% CI: 69.5–76.4), respectively. Five-year DSS rates attained 80% or more for melanoma

Table 1 – Five-year survival for French adolescents (15–19 years) diagnosed with cancer during the period 1988–1997, by type of tumour

Diagnostic group	Number of cases	M/F ratio	Number of deaths	Lost to follow-up at 5 years (% of cases)	5-year DSS		5-year EFS	
					%	CI95%	%	CI95%
I. Leukaemia	75	1.9	46	0.0	41.3	[30.2–52.5]	36.0	[25.1–46.9]
Ia. Acute lymphoblastic leukaemia	47	2.1	29	0.0	42.6	[28.4–56.7]	34.0	[20.5–47.6]
Ib. Acute non-lymphoblastic leukaemia	20	1.5	11	0.0	45.0	[23.2–66.8]	45.0	[23.2–66.8]
II. Lymphomas	147	1.3	23	3.4	84.8	[79.0–90.7]	80.2	[73.7–86.6]
IIa. Hodgkin's disease	98	0.9	4	3.1	95.8	[91.8–99.8]	90.7	[85.0–96.5]
IIIb,c,e. Non Hodgkin's lymphoma	49	2.5	19	4.1	62.8	[49.2–76.5]	59.1	[45.3–72.9]
III. Central nervous system tumours	67	1.0	27	1.5	64.1	[52.7–75.6]	56.7	[44.8–68.6]
IIIb. Astrocytoma	43	1.2	18	0.0	58.1	[43.4–72.9]	51.2	[36.2–66.1]
IIIc. Medulloblastoma[a]	5	–	1	–	–	–	–	–
IV. Sympathetic nervous system tumours[a]	7	–	4	–	–	–	–	–
V. Retinoblastoma[a]	0	–	0	–	–	–	–	–
VI. Renal tumours	10	–	2	–	–	–	–	–
VII. Hepatic tumours[a]	5	–	4	–	–	–	–	–
VIII. Malignant bone tumours	68	1.8	35	1.5	55.4	[43.5–67.3]	47.9	[36.0–59.9]
VIIIa. Osteosarcoma	38	1.7	21	2.6	48.9	[32.7–65.0]	43.5	[27.5–59.5]
VIIIc. Ewing's sarcoma	19	1.7	12	0.0	52.6	[30.2–75.1]	36.8	[15.1–58.5]
IX. Soft-tissue sarcomas	49	1.7	18	4.1	67.0	[53.8–80.3]	65.2	[51.8–78.6]
IXa. Rhabdomyosarcoma	16	3.0	10	0.0	41.7	[16.8–66.6]	35.7	[11.5–59.9]
IXb,c,d,e. Non rhabdomyosarcoma	33	1.4	8	6.1	78.8	[64.8–92.8]	78.8	[64.8–92.8]
X. Germ-cell tumors	89	1.7	10	2.2	88.8	[82.2–95.3]	82.0	[74.0–90.0]
XI. Carcinomas	129	0.6	18	2.3	94.4	[90.4–98.5]	88.8	[83.3–94.3]
XIb. Thyroid carcinoma	35	0.3	0	0.0	100.0	–	100.0	–
XId. Melanoma	63	0.6	8	4.8	96.7	[92.2–100.0]	90.1	[82.6–97.6]
XII. Other neoplasms[a]	2	–	0	–	–	–	–	–
All tumors	648	1.2	187	2.5	74.5	[71.2–77.9]	69.0	[65.4–72.5]

a $n < 15$ cases (too small number of cases); DSS, disease-specific survival; EFS, event-free survival.

($n = 63$), HD ($n = 98$), thyroid carcinoma ($n = 35$), germ-cell tumours ($n = 89$), and non-rhabdomyosarcoma ($n = 33$). Five-year DSS rates attained 50% or less for rhabdomyosarcoma ($n = 16$), ALL ($n = 47$), and ANLL ($n = 20$). The 5-year DSS was 62.8% (95% CI: 49.2–76.5) for NHL, 64.1% (95% CI: 52.7–75.6) for CNS tumours, and 55.4% (95% CI: 43.5–67.3) for malignant bone tumours. EFS rates for all cancers combined were 74.3%, 69.0%, and 67.4% at 2 years (95% CI: 71.0–77.7), 5 years (95% CI: 65.4–72.5), and 7 years (95% CI: 63.7–71.1), respectively. Concerning the most common diagnoses, 5-year EFS rate was 100% thyroid carcinoma, 90.7% (95% CI: 85.0–96.5) for HD, 90.1% (95% CI: 82.6–97.6) for melanoma, 82.0% (95% CI: 74.0–90.0) for germ-cell tumours, 65.2% (95% CI: 51.8–78.6) for soft-tissue sarcoma, 59.1% (95% CI: 45.3–72.9) for NHL, 56.7% (95% CI: 44.8–68.6) for CNS tumours, 47.9% (95% CI: 36.0–59.9) for malignant bone tumours, 45.0% (95% CI: 23.2–66.8) for ANLL, and 34.0% (95% CI: 20.5–47.6) for ALL.

Kaplan–Meier DSS curves for the most common haematological and solid malignancies diagnosed between 1988 and 1997 are presented, respectively, in Figs. 1 and 2. A comparison of DSS rates in the 1993–1997 period with those in an earlier time period 1988–1992 indicated that substantial survival gains were achieved for all cancers pooled (Fig. 3), with, respectively, 78.4% (95% CI: 74.0–82.8) and 70.3% (95% CI: 65.2–75.5) at 5 years ($P = 0.02$). Adolescents with cancer diagnosed from 1993 to 1997 had a reduced risk of dying compared with those whose cancer had been diagnosed between 1988 and 1992 (relative risk = 0.71; 95% CI: 0.52–0.95). The diagnostic group and gender distribution were the same in the two 5-year periods.

Five-year DSS for all cancers was different between males and females, with, respectively, 67.9% (95% CI: 63.0–72.8) and 82.5% (95% CI: 78.2–86.9); $P < 0.001$. Males were 2-fold more likely to die than females (95% CI: 1.44–2.70). This pattern was correlated with the occurrence of cancers with a poorer likelihood of survival in males (male/female ratios by diagnosis are presented in Table 1).

4. Discussion

This is the first study to present data concerning cancer overall, disease-specific, and event-free survival rates in French adolescents (15–19 year olds) during the 1988–1997 period.

First, caution must be exercised when interpreting these results owing to possible biases due to a small number of patients for each tumour type (e.g. ANLL, Ewing tumour, rhabdomyosarcoma) for whom survival rates are associated with a large confidence interval. Second, this study includes all adolescents with cancer in geographic area defined by population-based registries. Event-free survival rates of this population are usually lower than those found in studies selecting samples within frameworks of therapeutic protocols. Comparing our results with clinical data for specific diagnostic groups in trials enrolling adolescents with cancer, 5-year

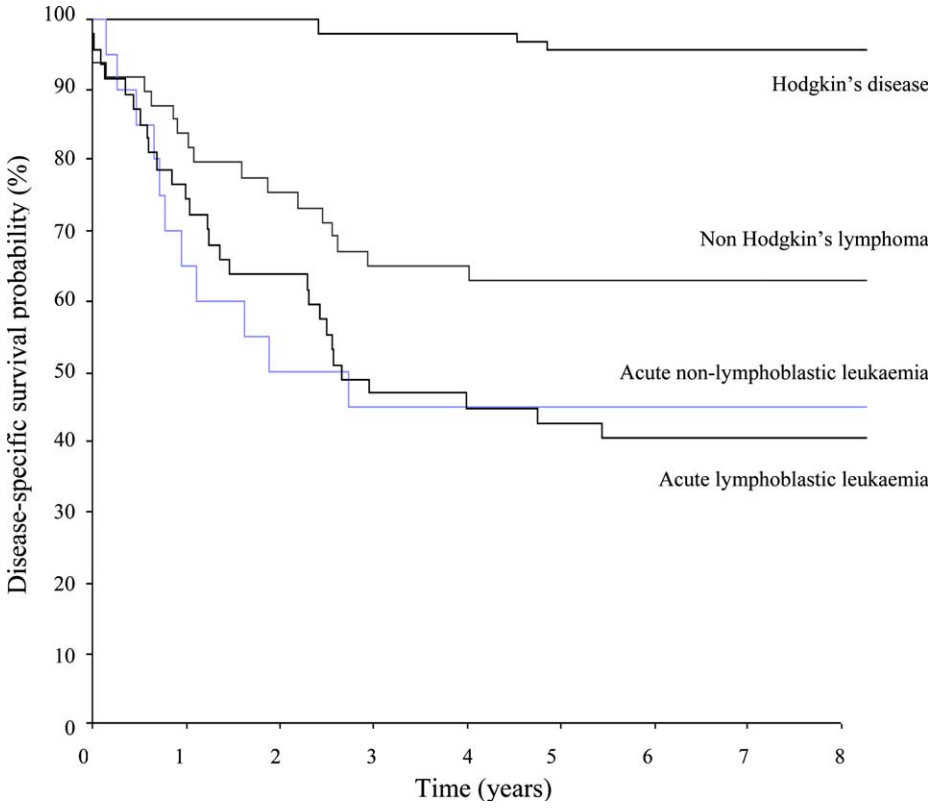

Fig. 1 – Kaplan–Meier disease-specific survival curves for haematological malignancies diagnosed from 1988 to 1997.

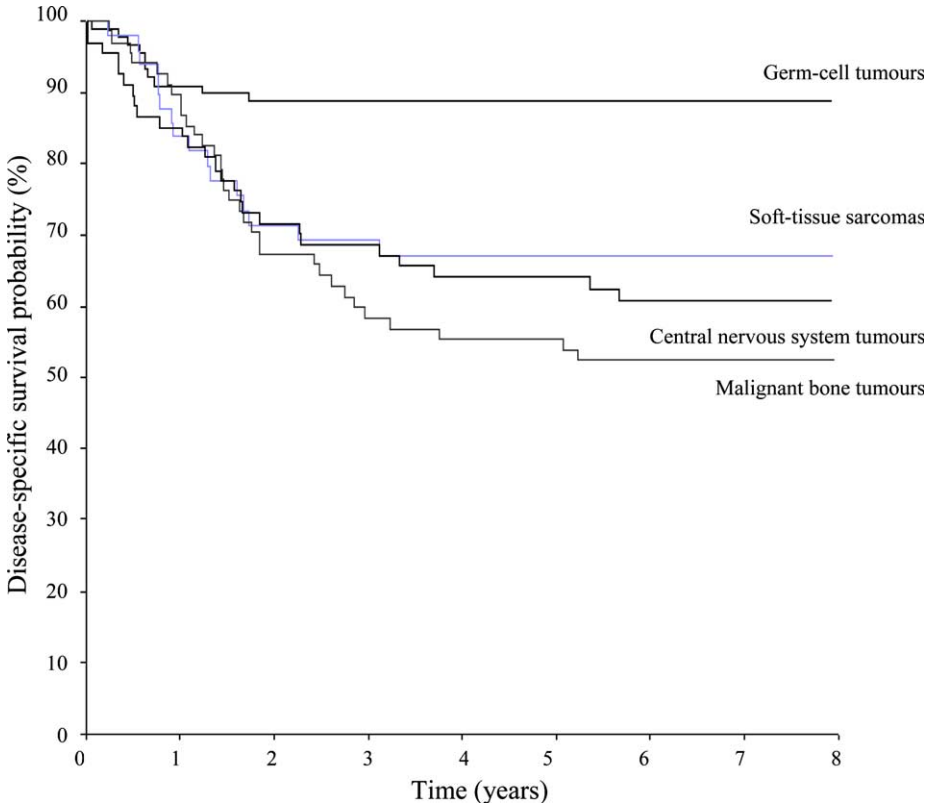

Fig. 2 – Kaplan–Meier disease-specific survival curves for solid malignancies diagnosed from 1988 to 1997.

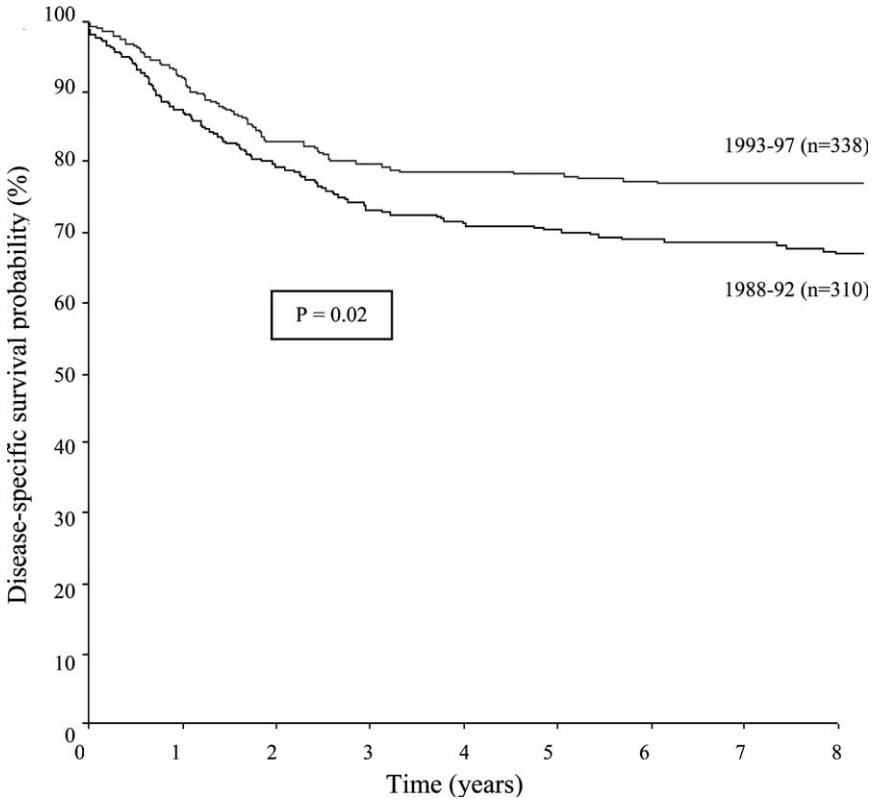

Fig. 3 – Kaplan–Meier disease-specific survival curves comparing the two 5-year periods (1988–1992 vs. 1993–1997).

EFS is 34% (95% CI: 20.5–47.6) vs. 52 ± 8% for ALL [11], 59.1% (95% CI: 45.3–72.9) vs. 65 ± 6.1% for NHL [12], 43.5% (95% CI: 27.5–59.5) vs. 64.8% for osteosarcomas [13], 36.8% (95% CI: 15.1–58.5) vs. 66% for Ewing's tumours of bone [14], 35.7% (95% CI: 11.5–59.9) vs. 51 ± 8% for rhabdomyosarcomas [15]. The inclusion in a clinical trial is probably a factor that increases the chances of cure.

For melanoma, NHL, and soft-tissue sarcomas, it is noteworthy that the percentage of cases lost to follow-up at 5 years is rather high in our series (from 4.1% to 4.8%). It might be due to the specific difficulty of managing adolescents, who as they grow older, move from sub-specialty paediatric wards to adult medicine departments. A disease-specific model based on a multidisciplinary approach, perhaps via an interim service for adolescents and young adults, could make transition easier [16,17].

Table 2 shows the comparison between our results for the 1988–1997 period and those of the surveillance, epidemiology, and end results (SEER) Program in the United States for the 1985–1999 period among children (0–14 years) and adolescents (15–19 years) [18].

Our results for adolescents are similar to those obtained by the SEER program with, respectively, 74.5% (95% CI: 71.2–77.9) in our study and 78.4% in SEER program (Table 2). The 5-year survival rates were similar per diagnostic group, except for ALL, NHL, CNS tumours, and osteosarcomas where our rates were lower (respectively, 42.6% vs. 54.9%, 62.8% vs. 71.3%, 64.1% vs. 76.3%, and 48.9% vs. 61.5%).

Our results are comparable to those published by Gatta [4] for young European adults (15–24 years) diagnosed with cancer during 1990–1994 including Registries of Northern Europe (NE: Denmark, Finland, Island, Norway, and Sweden), Southern and Central Europe (SCE: Austria, France, Germany, Italy, Malta, Portugal, the Netherlands, Spain, and Switzerland), United Kingdom (UK: England and Scotland), and Eastern Europe (EE: Czech, Estonia, Poland, Slovakia, and Slovenia). Five-year survival ranged from 55.5% (EE) to 75.6% (NE) for CNS tumours, from 50.0% (EE) to 63.3% for osteosarcoma, and from 33.3% (EE) to 52.7% (NE) for ALL. This study revealed a wide variation in survival across Europe, probably due to differences in cancer management [4,19]. These geographical differences were confirmed by Steliarova-Foucher [20] for adolescents (15–19 years) diagnosed with cancer in the 1990s: 63% (59–66%) in the East compared with 75% (74–77%) in the West ($P < 0.0001$) for all cancers combined and for most diagnostic groups too.

In this study, French male adolescents were found to have poorer survival than females. The same gender difference has also been described in Gatta's European study with 5-year survival attaining 74.0% vs. 79.5% in males and females, respectively, for all cancers combined [4]. This is probably easily explained by the higher incidence of malignancies with the worst outcomes (ALL, ANLL, osteosarcoma, and rhabdomyosarcoma with 5-year DSS below 50%) in males (sex-ratio greater than 1.5). Conversely, thyroid carcinoma, HD, and melanoma, the most common cancers in females (sex-ratio below 0.9) were associated with a better prognosis with 5-year DSS over 90%. In our study, it was difficult to compare gender adjusted on cancer type due to the small number of cases per diagnostic group.

Table 2 – Comparison of France and SEER[a] 5-year survival rates (%)

Diagnostic group	France Disease-specific survival (5-year)	SEER Relative survival (5-year)	
	1988–1997	1985–1999	1985–1999
	15–19 years	0–14 years	15–19 years
I. Leukaemia	41.3	74.4	48.3
Ia. Acute lymphoblastic leukaemia	42.6	81.8	54.9
Ib. Acute non-lymphoblastic leukaemia	45.0	41.1	40.5
II. Lymphomas	84.8	83.4	86.1
IIa. Hodgkin's disease	95.8	93.6	92.4
IIIb,c,e. Non Hodgkin's lymphoma	62.8	77.1	71.3
III. Central nervous system tumours	64.1	66.4	76.3
IIIb. Astrocytoma	58.1	78.2	75.8
IIIc. Medulloblastoma	–	56.6	75.9
IV. Sympathetic nervous system tumours	–	66.0	44.3
V. Retinoblastoma	–	94.7	–
VI. Renal tumours	78.8	90.4	75.6
VII. Hepatic tumours	–	55.8	16.3
VIII. Malignant bone tumours	55.4	67.5	62.4
VIIIa. Osteosarcoma	48.9	66.9	61.5
VIIIc. Ewing's sarcoma	52.6	64.7	54.8
IX. Soft-tissue sarcomas	67.0	73.1	65.8
IXa. Rhabdomyosarcoma	41.7	68.2	46.0
IXb,c,d,e. Non rhabdomyosarcoma	78.8		
X. Germ-cell tumours	88.8	86.7	91.0
XI. Carcinomas	94.4	89.2	89.7
XIb. Thyroid carcinoma	100.0	97.3	99.1
XId. Melanoma	96.7	88.0	93.3
All tumours	74.5	74.7	78.4

a Data from Ref. [18].

In France the improvement of survival over the two 5-year periods (1988–1992 vs. 1993–1997) was not a surprising finding and has been reported in previous studies [20–23] given the progress and breakthroughs in treatment over time, especially in acute leukaemia [11]. In Europe 5-year actuarial survival was 50% (48–51%) for adolescents (15–19 years) diagnosed in the 1970s, 63% (62–64%) for those diagnosed in the 1980s, and 74% (73–76%) [20]. For American adolescents, 5-year relative survival rates increased from 63.8% in 1974–1976 to 79.3% in 1992–1999. This improvement in survival rates was recently confirmed for adolescents and expanded to young adults (20–24 years) diagnosed with cancer in Southern Netherlands between 1973 and 1999 [21].

Most previous studies concerning survivorship in adolescent and young adult treated for cancer show that the results in this age group are not as good as in children [24].

Compared with the SEER program paediatric series (Table 2), the poor results in ALL, malignant bone tumours, and soft-tissue sarcomas in our 15–19 age-group series must be highlighted (42.2% vs. 81.8%, 56.4% vs. 67.5%, and 68.4% vs. 73.1%). In Europe similar survival rates have been published regarding children (0–14 years) over the 1990–1994 period (79.0% for ALL, 66.0% for osteosarcoma, and 67.0% for rhabdomyosarcoma). It is not quite clear why such differences exist but reasons could include a lack of defined protocols, lower enrolment in clinical trials, differences in the biological behaviour of the same cancer, or the lack of multidisciplinary approaches to cancer management for the 15–19 year age group [4].

In the United States, 21% of adolescents with cancer are registered with either the Children's Cancer Group or the Paediatric Oncology Group, and less than 3% of patients in this age group are entered in adult clinical trials [25]. In France the proportion of adolescents recorded in paediatric groups or entered in clinical trials is unknown.

The disparities in drug selection and dose intensity in treatment practices between paediatric and adult departments may exacerbate these differences [11]. Adolescents may be relatively under-dosed as compared to children [26]. That treatment with paediatric protocols is beneficial to adolescents has been demonstrated for ALL, ANLL, and osteosarcomas [11,27–29]. With the exception of these cancer types, the results of paediatric and adult treatments have not yet been compared. All these reasons justify an increasing need to compare adult or paediatric therapeutic practices for the most common cancers in adolescents.

In conclusion, the increasing complexity of management of the physical and psychological aspects of cancer in adolescents are clearly the over-riding reasons for the development of special care facilities [30]. The real challenge however, is to determine whether the multidisciplinary management of adolescent cancer in paediatric, adult, or specialized units will improve cure rates and treatment outcomes for these patients. It should serve to homogenize treatment practices, to

broaden clinician's knowledge of prognosis factors, and to achieve better follow-up of these individuals.

Even though survival of adolescents with cancer in France is rather good with five-year disease-specific survival exceeding 74%, there are still major differences in survival when the same malignancies in children are compared. Further studies are warranted in order to elucidate whether these differences are biological or due to patient care practices.

Conflict of interest statement

None declared.

Acknowledgements

The contribution of members of French General Cancer Registries, clinical departments, and pathology laboratories is acknowledged. The authors thank the French League against Cancer for financial support, Lorna Saint-Ange for editing, Mrs. Avon, Colle, Cotté, Duchenet, Ferré-Grevaz, Lemiègre, Louvat, Mouchel for technical assistance.

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