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ORIGINAL ARTICLE

Predictive factors of long-term follow-up attendance in very long-term childhood cancer survivors

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Abstract

Background: Long-term follow-up (LTFU) clinics have been developed but only some childhood cancer survivors (CCS) attend long-term follow-up (LTFU).

Objective: To identify factors that influence LTFU attendance.

Methods: Five-year CCS treated for a solid tumor or lymphoma in Gustave Roussy before 2000, included in the FCCSS cohort (French Childhood Cancer Survivor Study), aged >18 years and alive at the date of the LTFU Clinic opening (January 2012) were invited to a LTFU visit. Factors associated with attendance at the LTFU clinic between 2012 and 2020 were estimated using logistic regression analyses. Analyses included different types of factors: clinical (tumor characteristics, cancer treatments, late effects), medical (medical expenses were used as a proxy of survivor's health status), social (deprivation index based on census-tract data relating

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to income, educational level, proportion of blue-collar workers, and unemployed people living in the area of residence), and spatial (distance to the LTFU clinic).

Results: Among 2341 CCS contacted (55% males, mean age at study, 45 years; SD \pm 10 years; mean age at diagnosis, 6 years; SD \pm 5 years), 779 (33%) attended at least one LTFU visit. Initial cancer-related factors associated with LTFU visit attendance were: treatment with both radiotherapy and chemotherapy (odds ratio [OR], 4.02; 95% CI, 2.11–7.70), bone sarcoma (OR, 2.43; 95% CI, 1.56–3.78), central nervous system primitive tumor (OR, 1.65; 95% CI, 1.02–2.67), and autologous hematopoietic cell transplant (OR, 2.07; 95% CI, 1.34–3.20). Late effects (OR, 1.70; 95% CI, 1.31–2.20), highest medical expenses (OR, 1.65; 95% CI, 1.22–2.22), living in the most advantaged area (OR vs. the most deprived area = 1.60; 95% CI, 1.15–2.22), and shorter distance from LTFU care center (<12 miles) also increased attendance.

Conclusions: Patients who are apparently healthy as well as socially disadvantaged and living far away from the center are less likely to attend LTFU care.

Plain Language Summary

- Among 2341 adult childhood cancer survivors contacted between 2012 and 2020, 33% attended at least one long-term follow-up visit.
- Clinical factors related to attendance were multimodal treatment of first cancer (combining chemotherapy and radiotherapy), stem cell transplant, type of diagnosis (bone tumor and central nervous system primitive tumor), late effects (at least one disease among second malignancy, heart disease, or stroke), and highest medical expenses.
- In addition, the study identified social and spatial inequalities related to attendance, with independent negative effects of distance and social deprivation on attendance, even though the medical costs related to the long-term follow-up examinations are covered by the French social security system.

KEYWORDS

cancer survivors, childhood cancer, follow-up study, health care utilization, tertiary prevention

INTRODUCTION

Therapeutic advances in pediatric oncology increased 5-year survival rates of children with cancer by more than 80%.^{1,2} However, pediatric treatments are mainly intensive and multimodal, combining surgery, chemotherapy, and radiation therapy, resulting in a high risk of sequelae and late complications.³ As many as 80% of childhood cancer survivors (CCS) are diagnosed with a serious or life-threatening condition in adulthood following clinical ascertainment⁴ and 42% of survivors report a severe or life-threatening condition 30 years after diagnosis.⁵ It is therefore recommended that survivors attend long-term follow-up (LTFU) care for prevention, early detection, and treatment of late effects.^{6,7} Personalized survivorship care plans, based on patient characteristics, history of cancer, and treatments, comorbidities, and familial history have to be established, considering individual global health needs.^{8–11} In addition to

personalized screening programs, LTFU visits provide an opportunity to promote information and education of patients regarding the preventable risk factors, healthy lifestyle, and self-care implications to improve survival and quality of life.

LTFU has to be a multicomponent health program that must be anticipated and integrated into life course risk-based health care.^{12–14} Although the current standard of care in pediatric oncology integrates education of patients and families about potential risks and about the need to comply with LTFU care, older cohorts of survivors were not informed about the risks nor the existence of LTFU clinics.¹⁵ The question of attendance to LTFU programs for these older cohorts of survivors is crucial because they have been treated with aggressive treatments and may experience late effects that most health care providers outside of pediatric oncology are not aware of.

Demographic, clinical, and socioeconomic barriers have been described as predictors of LTFU nonattendance, especially

socioeconomic disadvantage, older age, a longer interval from completion of treatment, and absence of health issues.^{16–20} However, these studies were mainly conducted on young adult survivors (mean age <25 years or follow-up <20 years) with limited possibilities of results generalization because of small sample sizes, low participation rate, only self-reported data, or few available information concerning nonattenders.^{16–20} Consequently, a better understanding of factors that could influence attendance to LTFU clinics in older patients is necessary to develop alternative strategies to target nonattending CCS.

The current study explored the factors associated with LTFU attendance in long-term CCS treated in a French specialized center, using clinical, epidemiological, and administrative data.

METHODS

Study population

Gustave Roussy's pediatric department was established in 1950. It is the oldest pediatric cancer center in France and has been a reference center since then. The survivorship program was established in 2012 and has a multidisciplinary team including specialists in pediatric oncology, psychologists, and nurses. Patients were invited through a postal mail with two reminders to attend a visit lasting approximately half a day. No incentive was used.

For this study, patients treated at Gustave Roussy from 1945 to 2000 for solid cancer or lymphoma before the age of 20 years and alive at the date of the LTFU clinic opening (January 1, 2012), were identified through the French Childhood Cancer Survivor Study (FCCSS) cohort. Of 4750 patients, 1858 (40%) had no available contact address in the National Health Data System (SNDS) and were not contacted. Overall, 2712 subjects were considered as eligible to be contacted for an LTFU visit. For this study, subjects for whom medico-economic data were missing (14%) were excluded so that the final population of analysis includes 2341 subjects (Figure 1).

The FCCSS cohort is a French multicenter cohort that aims to investigate any aspect of long-term childhood cancer survivorship. To date, the FCCSS includes 7670 5-year CCS (<20 years at diagnosis) treated for any malignancy except leukemia from 1950 to 2001 in five cancer treatment centers in France. Therapeutic and clinical information related to the first malignancy were collected for all patients from medical charts in the cancer centers. Because patients with leukemia were not included in this analysis, none of them received an allogenic stem cell transplant. Vital status was obtained from the national registry of death and follow-up information from self-administered questionnaires and, since 2006, from a linkage with the SNDS. The SNDS is the medico-economic health care claims database of the French national health insurance information system and covers approximately 98% of the French population.²¹ Eligible contacted patients between 2012 and 2020

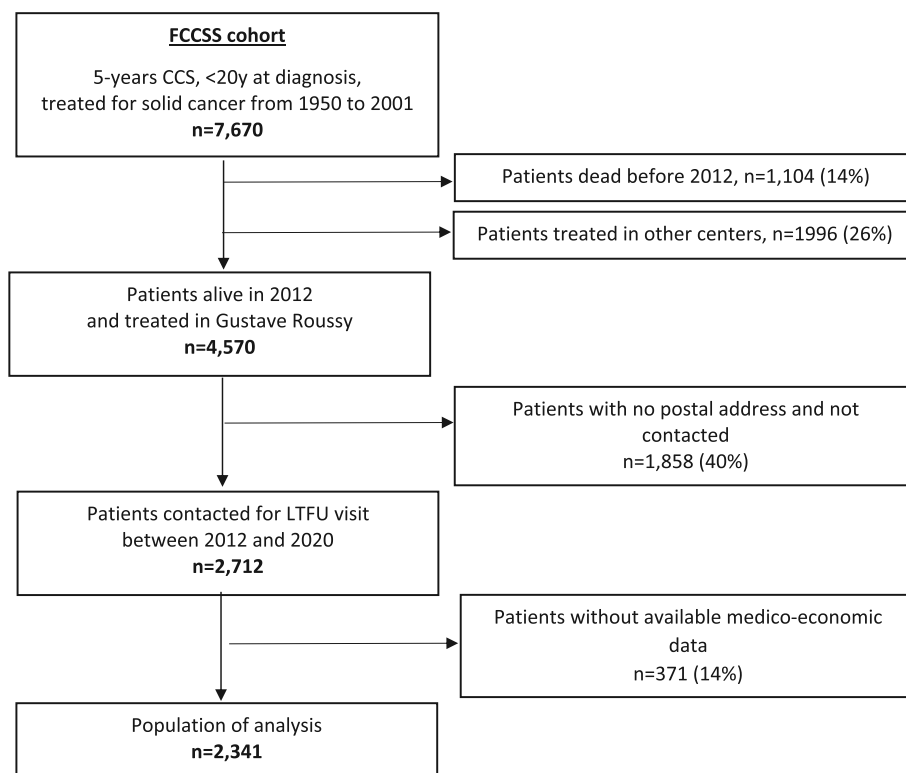


FIGURE 1 Flow chart of patients included in the FCCSS (French Childhood Cancer Survivor Study) cohort and contacted for a long-term follow-up (LTFU) visit in Gustave Roussy.

with available medico-economic data constituted the population of analysis.

The FCCSS protocol has been approved by the INSERM national ethics committee and the French National Agency regulating Data Protection. Informed consent was obtained from patients, parents, or guardians, according to national research ethics requirements.

Collected data and measurements

Outcome measure

Patients were classified according to LTFU clinic attendance during the study period (2012–2020). Those who came to at least one LTFU scheduled appointment were defined as “attenders” as opposed to “nonattenders.”

Demographic and clinical factors

Demographic information, tumor characteristics (classified according to the International Classification of Childhood Cancer), and cancer treatments, including cumulative chemotherapy doses, were extracted from medical charts. Serious and life-threatening late effects validated using medical charts or medico-economic data extracted from the SNDS were used: second malignant neoplasm (SMN), excluding basal cell carcinomas²²; cardiac diseases (myocardial infarction, angina, heart failure, valvular diseases, cardiac arrhythmia, conduction disorder, and pericardial disease, all coded according to the 9th and 10th revisions of the International Classification of Diseases),²³ and strokes.²⁴

Medical factors

We used health care expenditures extracted from the SNDS as a proxy of survivors' health status during follow up. The SNDS contains exhaustive medical information as well as cost data of the beneficiaries' inpatient and outpatient consultations including dispensed medication and cash payments made in the public or the private sectors related to sickness and disability.²⁵

We considered all the reimbursements made between January 2011 and December 2018 (the last date for which the overall reimbursement database was available at the time of study) or the date of death, and summed them to estimate the individual annual mean of medical expenses for each subject. These expenses include 14 categories: general practitioner visits, other specialists' visits, physiotherapy visits, nursing visits, other health professionals' visits, pharmacy, medical device, laboratory tests, technical medical procedures, transport, hospitalizations, disability benefits, sick leaves, and others. The annual mean was then categorized into three classes corresponding to its terciles.

Social and spatial factors

Socioeconomic status was approximated using the 2009 French Deprivation index.²⁶ This index was created in France to study social health inequalities at the most detailed census administrative level (French census tract IRIS, covering at least 2000 inhabitants) using the following socioeconomic indicators: median household income, percentage of high school graduates in the population aged ≥ 15 years old, percentage of blue-collar workers, and unemployment rate.²⁵ The deprivation index generated was divided into five categories, ranging from 1 (the least deprived) to 5 (the most deprived).

The last known address of patients extracted from the SNDS was transformed into latitude/longitude coordinates and plotted on a map of mainland France. We calculated the Euclidian distance in miles between the last known address and Gustave Roussy, divided into four categories corresponding to distance quartiles for patients living in mainland France, plus one category for patients living in overseas territories.

Statistical analysis

A descriptive analysis based on demographic, clinical, medical social, and spatial characteristics of CCS included in this analysis was performed. The decade of first primary childhood cancer diagnosis was categorized into four groups (<1970, 1970–1979, 1980–1989, and ≥ 1990), as well as age at first cancer diagnosis (0–4 years, 5–9 years, 10–14 years, and 15–19 years) and year of birth into five groups (before 1960, 1960–1970, 1970–1979, 1980–1989, and after 1989). Cancer type was classified according to the International Classification of Childhood Cancer.²⁷ Treatments were coded as radiotherapy alone, chemotherapy alone, both radiotherapy and chemotherapy, and/or either. Anthracyclines and alkylating agents cumulative doses were classified into three groups: $0 < 250 \leq 250$ mg/m² and $0 < 6000 \leq 6000$ mg/m², respectively, and censored at the date of the first LTFU visit for attenders or the date of last news of nonattenders.

Characteristics of patients included in the population of analysis were compared, using χ^2 tests, with those of the subset of the FCCSS population treated in Gustave Roussy, alive in 2012 but not contacted for LTFU visit, or those contacted but without available medico-economic data. Then, the characteristics of attenders and nonattenders to the LTFU clinic were compared.

To investigate the association between patients' characteristics (demographic, clinical, medical social, and spatial factors) and LTFU clinic attendance, multivariable logistic regression analyses was performed to estimate odds ratios (OR) with their 95% CIs. Predictors were entered based on significance in exploratory correlations. The performance of different models was compared using classical estimates. In the final model, late effects were considered as a unique binary variable defined by at least one disease among SMN, cardiac diseases, or stroke versus none. We compared the different types of medical expenses between attenders and nonattenders and ran sensitivity analyses to test the effect of inpatient hospitalization

TABLE 1 Demographic, clinical, social, and spatial factors of patients followed in Gustave Roussy depending on whether they were contacted or not to attend a long-term follow-up visit ($n = 4570$).

	All patients (N = 4570)		Contacted (N = 2712)				Lost to follow-up, noncontacted (N = 1858)		p*
			Total N = 2712		With national health data N = 2341		n	%	
			N	%	n	%			
Demographic factors									
Gender									
Female	2074	45.4	1216	44.8	1054	45.0	858	46.2	.4
Male	2496	54.6	1496	55.2	1287	55.0	1000	53.8	
Year of diagnosis									
Before 1970	418	9.2	337	12.4	277	11.8	81	4.4	<.0001
1970–1979	1015	22.2	735	27.1	639	27.3	280	15.1	
1980–1989	1542	33.7	1021	37.7	884	37.8	521	28.0	
After 1990	1595	34.9	619	22.8	541	23.1	976	52.5	
Year of birth									
Before 1960	237	5.2	185	6.8	149	6.4	52	2.8	<.0001
1960–1969	753	16.5	576	21.2	495	21.1	177	9.5	
1970–1979	1583	34.6	1002	37.0	870	37.2	581	31.3	
1980–1989	1408	30.8	769	28.4	673	28.7	639	34.4	
After 1989	589	12.9	180	6.6	154	6.6	409	22.0	
Clinical factors									
Age at diagnosis									
<5 years	2122	46.4	1312	48.4	1128	48.2	810	43.6	<.0001
5–9 years	1008	22.1	639	23.6	555	23.7	369	19.9	
10–14 years	988	21.6	582	21.5	509	21.7	406	21.8	
≥15 years	452	9.9	179	6.6	149	6.4	273	14.7	
Diagnosis									
Nephroblastoma	774	16.9	530	19.5	452	19.3	244	13.1	<.0001
Neuroblastoma	685	15.0	403	14.9	345	14.7	282	15.2	
Lymphoma	805	17.6	537	19.8	452	19.3	268	14.4	
Soft tissue sarcoma	532	11.6	330	12.2	291	12.4	202	10.9	
Malignant bone tumor	431	9.4	264	9.7	231	9.9	167	9.0	
CNS	598	13.1	319	11.8	286	12.2	279	15.0	
Others	744	16.3	329	12.1	284	12.1	415	22.3	
Systemic treatment (first malignancy)									
No radiotherapy, no chemotherapy	567	12.4	180	6.6	158	6.8	387	20.8	<.0001
Radiotherapy alone	577	12.6	342	12.6	300	12.8	235	12.6	
Chemotherapy alone	1656	36.3	988	36.4	862	36.8	668	36.0	
Both radiotherapy and chemotherapy	1770	38.7	1202	44.3	1021	43.6	568	30.6	

TABLE 1 (Continued)

	All patients (N = 4570)		Contacted (N = 2712)				Lost to follow-up, noncontacted (N = 1858)		p*
			Total N = 2712		With national health data N = 2341		n	%	
			N	%	n	%			
Anthracycline cumulative dose									<.0001
0	2832	62.0	1547	57.0	1339	57.2	1285	69.2	
<250 mg/m ²	864	18.9	498	18.3	435	18.6	366	19.7	
≥250 mg/m ²	871	19.1	665	24.5	565	24.2	206	11.1	
Alkylating agents' cumulative dose									<.0001
0	2120	46.4	1107	40.8	962	41.1	1013	54.5	
<6000 mg/m ²	1095	24.0	670	24.7	578	24.7	425	22.9	
≥6000 mg/m ²	1354	29.6	934	34.4	800	34.2	420	22.6	
Autologous hematopoietic cell transplant									.02
Yes	219	4.8	147	5.4	125	5.3	72	3.9	
No	4351	95.2	2565	94.6	2216	94.7	1786	96.1	
SMN ^a									<.0001
Yes	364	8.0	269	9.9	231	9.9	95	5.1	
No	4206	92.0	2443	90.1	2110	90.1	1763	94.9	
Cardiac disease ^b									<.0001
Yes	307	6.7	246	9.1	210	9.0	61	3.3	
No	4263	93.3	2466	90.9	2131	91.0	1797	96.7	
Stroke									<.0001
Yes	64	1.4	54	2.0	49	2.1	10	0.5	
No	4506	98.6	2658	98.0	2292	97.9	1848	99.5	
Cardiovascular disease and/or SMN ^c									<.0001
Yes	653	14.3	507	18.7	436	18.6	146	7.9	
No	3917	85.7	2205	81.3	1905	81.4	1712	92.1	
Social and spatial factors									
Deprivation index									.3
1 Least deprived area	861	20.7	503	20.0	417	19.1	358	21.8	
2	822	19.7	487	19.3	421	19.2	335	20.4	
3	836	20.1	526	20.9	468	21.4	310	18.9	
4	856	20.6	518	20.6	456	20.9	338	20.6	
5 Most deprived area	790	19.0	487	19.3	424	19.4	303	18.4	
Distance from center									<.0001
<11 miles	1058	23.2	636	23.5	535	19.7	422	22.7	
11-48 miles	1092	23.9	684	25.2	604	22.2	408	22.0	
49-211 miles	1081	23.7	691	25.5	606	22.3	390	22.1	
>211 miles	1080	23.6	623	23.0	536	19.7	457	24.6	
Overseas territories	259	5.7	73	2.7	60	22.1	181	9.7	

(Continues)

TABLE 1 (Continued)

	All patients (N = 4570)		Contacted (N = 2712)				Lost to follow-up, noncontacted (N = 1858)		p*
			Total N = 2712		With national health data N = 2341		n	%	
			N	%	n	%			
Living near Paris (Ile-de-France)									.07
Yes	1720	37.6	1050	38.7	909	38.8	670	36.1	
No	2850	62.4	1662	61.3	1432	61.2	1188	63.9	

Abbreviations: CNS, central nervous system; LTFU, long-term follow up; SMN, second malignant neoplasm.

^aExcept for carcinoma basocellular.

^bCardiovascular disease ascertained from a physician or a medical record: myocardial infarction, angina, heart failure, valvular disease, cardiac arrhythmia, conduction disorder, pericardial disease.

^cAt least one disease among SMN, cardiac disease, or stroke ascertained from a physician or a medical record or none.

*Prevalence of patients contacted for LTFU visit compared with those not contacted for LTFU visit and those contacted but without available national health data, χ^2 test.

care on the outcome variable. A *p* value threshold of .05 was considered statistically significant. All statistical tests were two-sided. Analyses were performed with SAS 9.4 software (SAS Institute, Cary, North Carolina) and QGIS 3.20.

RESULTS

Among 4570 CCS treated in Gustave Roussy and alive in 2012, 2712 had a valid address and could be contacted between 2012 and 2020 to propose an LTFU appointment (sex ratio M/F = 1.2; median age at diagnosis, 5 years; range, 0–19 years; median age at contact, 35 years; range, 13–70 years). Contacted patients compared with noncontacted patients had different distributions in age at diagnosis, year of diagnosis, primary cancer site, treatment of primary cancer, and late effects, whereas gender ratio and socioeconomic status were similar. CCS younger than aged 10 years at diagnosis, born before 1990, treated with both radiotherapy and chemotherapy or autologous hematopoietic cell transplant, who received higher cumulative doses of anthracyclines or alkylating agents, and who suffered from late effects (SMN, cardiac diseases, or strokes) were significantly more contacted to propose an LTFU appointment (Table 1). Subsequent analyses were restricted to the 2341 attenders and nonattenders who had available medico-economic data extracted from the SNDS (Figure 1).

Descriptive analysis of LTFU visit attenders

Among the 2341 CCS contacted to propose an LTFU appointment and with available medico-economic data, 779 (33.3%) attended at least one LTFU visit (Table 2). Sex ratio of attenders was 1.1 (M/F), with a median age at diagnosis of 5 years (range, 0–18 years) and a

median age at LTFU visit of 37 years (range, 18–70 years). Most attenders were diagnosed before 1980 (60.6%) and were treated for lymphoma, neuroblastoma, or Wilms tumor (20.1%, 15.7%, and 15.0%, respectively). Sixty-one percent of attenders had been exposed to radiation therapy and 88% to chemotherapy, with a median cumulative dose of alkylating agents of 4835 mg/m² (range, 0–87,900) and anthracyclines of 85 mg/m² (range, 0–763). Autologous hematopoietic cell transplant was performed in 9.4% of patients. Overall, 23.0% of patients suffered from at least one severe late effect among SMN (11%), cardiac disease (13%), or stroke (2%). The individual annual mean of medical expenses of attenders CCS was 1890 euros (range, 5–86,554). More than half of attenders lived at a distance <48 miles from Gustave Roussy, but many attenders were also living very far from it (Figure 2).

A comparative description of the clinical characteristics of attenders with those of the nonattenders is detailed in Table 2. Sex and age at diagnosis were similar between attenders and nonattenders, whereas survivors of bone sarcoma or brain tumor, or those exposed to both radiotherapy and chemotherapy, to high cumulative doses of anthracyclines or alkylating agents or to autologous hematopoietic cell transplant, or who suffered from late effects were more likely to attend an LTFU clinic. Moreover, the least deprived CCS, those born after 1990, living less than 12 miles from the center, or with an annual mean of medical expense higher than 500 euros were also more likely to be attenders.

Factors associated with LTFU visit attendance

In multivariable analyses, when all variables were included in the model (Table 3), systemic treatment of first malignancy with both radiotherapy and chemotherapy was the strongest predictor associated with attendance (OR, 4.02; 95% CI, 2.11–7.70). Other clinical

TABLE 2 Demographic, clinical, medical, social, and spatial factors of patients depending on whether they attended a long-term follow-up visit in Gustave Roussy or not ($n = 2341$).

	All patients (N = 2341)		Attenders (N = 779)		Nonattenders (N = 1562)		p*
	n	%	n	%	n	%	
Demographic factors							
Gender							.09
Female	1054	45.0	370	47.5	684	43.8	
Male	1287	55.0	409	52.5	878	56.2	
Age at diagnosis							.17
<5 years	1128	48.2	374	48.0	754	48.3	
5–9 year	555	23.7	172	22.1	383	24.5	
10–14 years	509	21.7	188	24.1	321	20.5	
≥15 years	149	6.4	45	5.8	104	6.7	
Year of birth							.0004
Before 1960	149	6.4	34	4.4	115	7.3	
1960–1969	495	21.1	161	20.7	334	21.4	
1970–1979	870	37.2	277	35.5	593	38.0	
1980–1989	673	28.7	236	30.3	437	28.0	
After 1989	154	6.6	71	9.1	83	5.3	
Clinical factors							
Year of diagnosis							<.0001
Before 1970	277	11.8	81	10.4	196	12.6	
1970–1979	639	27.3	187	24.0	452	28.9	
1980–1989	884	37.8	287	36.8	597	38.2	
After 1990	541	23.1	224	28.8	317	20.3	
Diagnosis							<.0001
Nephroblastoma	452	19.3	117	15.0	335	21.4	
Neuroblastoma	345	14.7	122	15.7	223	14.3	
Lymphoma	452	19.3	157	20.1	295	18.9	
Soft tissue sarcoma	291	12.4	87	11.2	204	13.1	
Malignant bone tumor	231	9.9	116	14.9	115	7.4	
CNS	286	12.2	106	13.6	180	11.5	
Others	284	12.1	74	9.5	210	13.4	
Systemic treatment (first malignancy)							<.0001
No radiotherapy, no chemotherapy	158	6.8	16	2.1	142	9.1	
Radiotherapy	300	12.8	78	10.0	222	14.2	
Chemotherapy	862	36.8	286	36.7	576	36.9	
Both radiotherapy and chemotherapy	1021	43.6	399	51.2	622	39.8	
Anthracycline cumulative dose							<.0001
0	1339	57.2	372	47.7	967	62.0	
<250 mg/m ²	435	18.6	179	23.0	256	16.4	
≥250 mg/m ²	565	24.2	228	29.3	337	21.6	

(Continues)

TABLE 2 (Continued)

	All patients (N = 2341)		Attenders (N = 779)		Nonattenders (N = 1562)		p*
	n	%	n	%	n	%	
Alkylating agents' cumulative dose							<.0001
0	962	41.1	237	30.4	725	46.4	
<6000 mg/m ²	578	24.7	227	29.1	351	22.5	
≥6000 mg/m ²	800	34.2	315	40.5	484	31.1	
Autologous hematopoietic cell transplant							<.0001
Yes	125	5.3	73	9.4	52	3.3	
No	2216	94.7	706	90.6	1510	96.7	
SMN ^a							.004
Yes	192	8.2	82	10.5	110	7.0	
No	2149	91.8	697	89.5	1452	93.0	
Cardiac disease ^b							<.0001
Yes	200	8.5	100	12.8	100	6.4	
No	2141	91.6	679	87.2	1462	93.6	
Stroke							.5
Yes	45	1.9	17	2.2	28	1.8	
No	2296	98.1	762	97.8	1534	98.2	
Cardiovascular disease and/or SMN ^c							<.001
Yes	394	16.8	179	23.0	215	13.8	
No	1947	83.2	600	77.0	1347	86.2	
Medical factors							
Individual annual mean of medical expenses							<.0001
<500 euros	622	26.6	145	18.6	477	30.5	
500–4500 euros	1133	48.4	416	53.5	717	45.9	
≥4500 euros	586	25.0	218	28.0	368	23.6	
Social and spatial factors							
Deprivation index							<.0001
1 Least deprived area	417	19.1	181	24.8	236	16.2	
2	421	19.2	142	19.5	279	19.2	
3	468	21.4	150	20.5	318	21.8	
4	456	20.9	137	18.8	319	21.9	
5 Most deprived area	424	19.4	120	16.4	304	20.9	
Distance from center							<.0001
<12 miles	569	24.3	243	31.2	326	20.9	
12–48 miles	575	24.6	193	24.8	382	24.5	
49–207 miles	569	24.3	181	23.2	388	24.8	
>207 miles	573	24.5	145	18.6	428	27.4	
Overseas territories	55	2.3	17	2.2	38	2.4	
Living near Paris (Ile-de-France)							<.0001

TABLE 2 (Continued)

	All patients (N = 2341)		Attenders (N = 779)		Nonattenders (N = 1562)		p*
	n	%	n	%	n	%	
Yes	909	38.8	366	47.0	543	34.8	
No	1432	61.2	413	53.0	1019	65.2	

Abbreviations: CNS, central nervous system; SMN, second malignant neoplasm.

^aExcept for carcinoma basocellular.

^bCardiovascular disease ascertained from a physician or a medical record: myocardial infarction, angina, heart failure, valvular disease, cardiac arrhythmia, conduction disorder, pericardial disease.

^cAt least one disease among SMN, cardiac disease, or stroke ascertained from a physician or a medical record or none.

*Prevalence of attenders compared with nonattenders, χ^2 test.

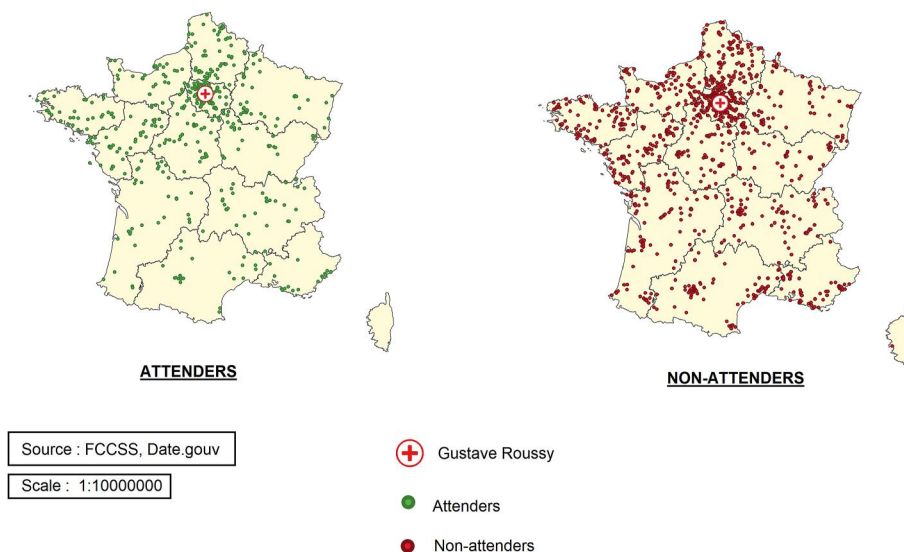


FIGURE 2 Mapping of attenders and nonattenders to the LTFU program in Gustave Roussy, France, 2012–2018 (N = 2286).

and medical factors significantly associated with an LTFU visit were the type of tumor, especially bone sarcoma and brain tumors (OR, 2.43; 95% CI, 1.56–3.78; and OR, 1.65; 95% CI, 1.02–2.67, respectively), autologous hematopoietic cell transplant (OR, 2.07; 95% CI, 1.34–3.20), late effects (OR, 1.70; 95% CI, 1.31–2.20), and the average annual rate of medical expenses (between 500 and 4500 euros: OR, 1.89; 95% CI, 1.47–2.42; higher than 4500 euros: OR, 1.65; 95% CI, 1.22–2.22). Independent of clinical and medical factors, living in the least deprived area increased the likelihood of attending an LTFU visit compared with the most deprived area (OR, 1.60; 95% CI, 1.15–2.22); whereas distance, especially the longest distance from the center (>207 miles) decreased the likelihood of attendance (OR, 0.47; 95% CI, 0.35–0.63) (Table 3).

DISCUSSION

Based on data from the LTFU clinic of a large, specialized center dedicated to childhood or adolescent cancer survivors, this study is the first to explore the attendance of very long-term survivors and its determinants. Overall, 33% of adult survivors attended at least one LTFU visit. Factors associated with attendance included clinical

factors (childhood cancer diagnosis and treatment, occurrence of late effects), high medical expenses, living in a privileged area, and shorter distance from the LTFU clinic.

In the literature, LTFU attendance may reach 88%.^{6,16,17,19,20,28} This discrepancy may be explained by the younger age of CCS in these studies because younger patients were treated more recently and may be more aware of late effects and more informed about LTFU care. Patients treated more recently were indeed more likely to attend LTFU. Another difference with other studies might be the national recruitment of patients (61% of patients lived outside of the Parisian area, implying several hours of transportation to come to the center).

Clinical and health care use outcomes

Adult survivors who are most at risk of late effects, especially patients who have received both radiotherapy and chemotherapy, were most likely to attend LTFU, which is consistent with previous studies.⁶ However, receiving high cumulative doses of alkylating agents or anthracyclines was not significantly associated with LTFU attendance despite the risks associated with these drugs. This result emphasizes

TABLE 3 Predictors of long-term follow-up visit attendance in a specialized center dedicated to childhood cancer survivors (France, Gustave Roussy, $n = 2183$)^a.

Variables	Long-term follow-up visit attendance	
	Odds ratio	95% CI
Gender		
Female	Reference	
Male	0.97	0.80–1.19
Year of diagnosis		
Before 1970	Reference	
1970–1979	0.76	0.53–1.08
1980–1989	0.84	0.59–1.21
After 1990	1.13	0.75–1.68
First malignancy		
Nephroblastoma	Reference	
Neuroblastoma	1.56	1.01–2.42
Lymphoma	1.13	0.75–1.71
Soft tissue sarcoma	1.21	0.78–1.89
Malignant bone tumor	2.43	1.56–3.78
CNS ^b	1.65	1.02–2.67
Others	1.13	0.71–1.81
Systemic treatment (first malignancy)		
No radiotherapy, no chemotherapy	Reference	
Radiotherapy alone	2.56	1.35–4.86
Chemotherapy alone	3.09	1.62–5.92
Both radiotherapy and chemotherapy	4.02	2.11–7.70
Anthracycline cumulative dose		
0	Reference	
<250 mg/m ²	1.32	0.97–1.80
≥250 mg/m ²	1.25	0.33–1.68
Alkylating agents' cumulative dose		
0	Reference	
<6000 mg/m ²	1.26	0.86–1.84
≥6000 mg/m ²	1.10	0.75–1.61
Autologous hematopoietic cell transplant		
No	Reference	
Yes	2.07	1.34–3.20
Cardiovascular disease and/or SMN ^a		
No	Reference	
Yes	1.70	1.31–2.20
Individual annual mean of medical expenses		
<500 euros	Reference	

TABLE 3 (Continued)

Variables	Long-term follow-up visit attendance	
	Odds ratio	95% CI
500–4500 euros	1.89	1.47–2.42
≥4500 euros	1.65	1.22–2.22
Deprivation index		
5 Most deprived area	Reference	
4	1.05	0.77–1.43
3	1.13	0.83–1.54
2	1.19	0.87–1.63
1 Least deprived area	1.60	1.15–2.22
Distance from center		
<12 miles	Reference	
12–48 miles	0.77	0.59–1.00
49–207 miles	0.72	0.54–0.97
>207 miles	0.47	0.35–0.63

Abbreviations: CNS, central nervous system; SMN, second malignant neoplasm.

^aThe model is adjusted on all the variables included in the table.

^bAt least one of the diseases among: SMN, cardiac disease, or stroke.

the need for personalized LTFU invitations and reminders based on the risk of late effects.²⁹ The clinical predictive variable most associated with attendance was the type of initial tumor, such as bone and brain tumors. The bone tumor-related association can be explained by the local and interdisciplinary follow-up care of bone tumors in Gustave Roussy, where an appointment for LTFU is systematically offered to these patients when they attend a consultation related to orthopedic follow up. Concerning brain tumors, the association is probably related to motor sequelae, which are more frequent in these patients and make them more attentive to their health status. Then, late effects (SMN and cardiovascular disease) were less strongly associated with attendance than systemic treatment.⁶ To better understand the health status of adult CCS in this study, we integrated the SNDS data that represents an up-to-date health care resource utilization relevant to evaluate the impact of first malignancy and treatment. Adults with higher individual mean of medical expenses, evoking more late effects and comorbidities, were more likely to come to the LTFU first visit. Conversely, nonattenders had a lower mean of medical expenses, suggesting that they are not followed up elsewhere and/or have not developed late effects.

Social and spatial outcomes

We observed a socioeconomic gradient in the adherence to LTFU, CCS living in the least deprived areas being significantly more likely

to attend LTFU than CCS living in the most deprived ones. Social inequalities for access to health care were already established in the general population³⁰ and CCS.^{7,16,18,28} They may result from unequal access to information on the disease and prevention messages, but also to socioeconomic constraints.

Indeed, patients with low occupational attainment have been described to be less likely to attend LTFU because of difficulties in taking a day off work and financial resources difficulties.³¹ The French health insurance system provides universal coverage for all citizens, regardless of age or socioeconomic status, but it does not ensure nonemergency medical transportation coverage, and the cost of travel may have hampered attendance. When controlling for clinical and socioeconomic variables, distance from the center was negatively associated with attendance with a gradual effect, showing that distance is, in itself, an important logistic barrier for attendance, consistent with previous studies.²⁰ Distance from the center associated with lower attendance may likely reflect financial hardship and difficulties to pay for costly travel. Yet, controlling for distance, we found that socioeconomic differences associated with attendance persist, suggesting that other factors, such as difficulty taking a day off, are involved.

Centralized and specialized clinical centers for follow-up care among survivors are needed to better prevent and inform cancer survivors about late effects and the many aspects of follow-up care, including services such as information regarding insurance and employment.³² However, regarding social and spatial possible barriers, centralization must be balanced. First, reimbursement of transport costs should enhance adherence to follow-up programs. Second, the skills of referral centers should be shared to offer access to follow-up care throughout the country and include primary care physicians.^{33–36}

Inequalities exist in terms of access to prevention messages. Identifying survivors most at risk of late effects and health risk behaviors should be useful for more targeted interventions and more efficient LTFU attendance. To reach the most vulnerable patients, prevention tools must be adapted and be based on local care, but also on new tools such as teleconsultation, which was not yet in place during the study.³⁷

Strengths and limitations

The study offered data on a large population and on a very long follow-up time of 30 years. Another strength is the accurate and up-to-date data on a large set of health conditions in adulthood based on the French administrative data, with severe conditions such as second cancer and cardiac diseases ascertained by physicians' reports. However, leukemia survivors are not included in the study because leukemia was not treated in Gustave Roussy during the study period, although it is the largest diagnosis group in childhood cancer patients. In addition, we cannot know if nonattenders are followed up in other LTFU clinics than Gustave Roussy because there is no specific code to identify an LTFU visit compared with another oncology appointment

(the LTFU visit is coded as a consultation in an oncology department). Yet, LTFU of older survivors is usually made in the center where childhood cancer was treated because paper-based medical files are difficult to transfer. Socioeconomic factors were calculated at the aggregated level (deprivation index), which is less accurate than economic factors at the individual level. Access to transportation, which is an important factor, could not be studied considering the large geographical coverage of the study.

Nevertheless, with accurate clinical, social, and spatial factors, the results gain knowledge of predictive factors of LTFU attendance and contribute to improving it for further survivors.³⁸

CONCLUSIONS

Among very long-term CCS contacted for LTFU, one-third attended one or more visits. This study helped to better identify those most in need of specific additional interventions to help them access LTFU. Specifically, socially disadvantaged patients and those living far from the specialized center were less likely to attend specialized LTFU. LTFU should be integrated into standard care to increase the participation of each patient in risk-based and adaptive programs over time. Local health resources including primary care services could be involved to equally give access to LTFU care to the CCS population.

AUTHOR CONTRIBUTION

Agnes Dumas: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing – original draft, and writing – review and editing. Karen Milcent: Data curation, formal analysis, investigation, methodology, software, validation, visualization, writing – original draft, and writing – review and editing. Nicolas Bougas: Data curation, formal analysis, investigation, methodology, software, validation, visualization, writing – original draft, and writing – review and editing. Daniel Bejarano-Quisoboni: data curation, formal analysis, investigation, methodology, software, validation, visualization, writing – original draft, and writing – review and editing. Chiraz El Fayech: Investigation, resources, and writing – review and editing. H el ene Charreire: Formal analysis, methodology, resources, and writing – review and editing. Odile Oberlin: Investigation, resources, and writing – review and editing. Catherine Patte: Investigation, resources, and writing – review and editing. Julie Allard: Investigation, resources, and writing – review and editing. Eric Thebault: Investigation, resources, and writing – review and editing. Amel Boumaraf: Writing – review and editing. Amel Belhout: Writing – review and editing. Vu-Bezin Giao: Data curation, software, and writing – review and editing. Vincent Souchard: Data curation, software, and writing – review and editing. Angela Jackson: Data curation, software, and writing – review and editing. Rodrigue Allodji: Writing – review and editing. Dominique Valteau-Couanet: Funding acquisition, resources, and writing – review and editing. Christelle Dufour: Funding acquisition, resources, and writing – review and

editing. Gilles Vassal: Funding acquisition, resources, and writing – review and editing. Nadia Haddy: Funding acquisition, resources, and writing – review and editing. Florent De Vathaire: Data curation, funding acquisition, resources, and writing – review and editing. Brice Fresneau: Conceptualization, data curation, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft, and writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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