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► To cite this version:

Thibaud Charrier, Nadia Haddy, Brice Fresneau, Boris Schwartz, Neige Journy, et al.. Life years lost by childhood cancer treatment and health related late effects among childhood cancer survivors. *Cancer Epidemiology*, 2024, 93, 10.1016/j.canep.2024.102692 . hal-04781953

HAL Id: hal-04781953

<https://hal.science/hal-04781953v1>

Submitted on 14 Nov 2024

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Life years lost by childhood cancer treatment and health related late effects among childhood cancer survivors

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ARTICLE INFO

Keywords:

Childhood cancer survivors
Late mortality
Iatrogenic effect
Life years lost
Years of life lost
Pseudo observations
Landmark

ABSTRACT

Background: Identifying risk factors contributing the most to mortality of childhood cancer survivors is essential to guide harm reduction efforts in childhood cancer treatments, and long-term follow-up of childhood cancer survivors.

Methods: We assessed Life Years Lost from childhood cancer treatments and their health-related late effects among the French Childhood Cancer Survivors Study, a cohort of 7670 5-year childhood cancer survivors. Using a landmark strategy, we also assessed time-varying effects of risk factors, and how the multi-morbidity affects life years lost.

Results: We found subsequent malignant neoplasm (9.0 years [95 %CI: 4.3–13.7]), severe cardiac disease (8.0 years [95 %CI: 1.2–14.9]), and the use of radiotherapy (6.0 years [95 %CI: 4.7–7.3]) to be the highest contributors to Life Years Lost among childhood cancer survivors. We found no interaction impact on life years lost between health related late effects considered.

Conclusions: Those findings suggest that radiotherapy is the root cause of early mortality among childhood cancer survivors. Moreover patients experiencing a subsequent malignant neoplasm or a cardiac disease should be monitored closely after the event, as comorbidity is common and causes premature deaths.

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<https://doi.org/10.1016/j.canep.2024.102692>

Received 5 August 2024; Received in revised form 17 October 2024; Accepted 25 October 2024

Available online 7 November 2024

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1. Introduction

Clinical progress has greatly improved 5-year survival of childhood cancer, reaching $\sim 82\%$ in Western Europe and the USA nowadays [1]. Most 5-year survivors become very long-term survivors, but they are at increased risk for a wide range of treatment-related health-related late effects, up to and including death [1–3]. We defined mortality 5 years after childhood cancer diagnosis as late mortality, a time point at which patients are rarely at direct risk of death due to the childhood cancer itself. Previous works have summarized the magnitude, causes, and temporal patterns of childhood cancer late mortality using Standardized Mortality Ratios (SMR), Absolute Excess Risk (AER), Poisson models, and Cox models [4]. They showed three important facets of mortality: (i) excess mortality magnitude varies by cancer type and childhood cancer treatment [5], (ii) excess mortality is important at all ages and does not seem to waver at later ages [6], (iii) death by cancer recurrence/progression is the leading cause of death during the first years after diagnosis while death by Subsequent Malignant Neoplasm (SMN), Cardiac disease (CD), and Pulmonary disease is the leading cause of death starting 15–25 years after diagnosis [5].

Other studies have investigated Life Years Lost (LYL) among childhood cancer survivors, giving valuable insight into survivors' life expectancy. Yeh et al. provided LYL estimates using hazard-based models for stratified treatment effects, and cause-specific LYL [7]. Because those estimates are model-based they are susceptible to give results different than a direct regression on LYL, which avoids unnecessary uncertainties in intermediate estimates [8]. Chang et al. have studied LYL due to health-related late effects at various ages among children, teenagers, and young adult cancer survivors, but didn't link them to cancer treatments, however a necessary step to accurately guide harm reduction of childhood cancer treatments [9]. Furthermore, previous works showed that multi-morbidity is important among Childhood Cancer Survivors, with over a third of survivors who experience multiple health conditions; and is likely to be associated with both poor quality of life and premature death [10].

We aimed to build upon those previous studies and investigate concomitantly the association of LYL with childhood cancer treatments and cancer treatment-related late effects. Furthermore, we also investigated the time-varying effects of those factors. To achieve those goals, we used regression models directly on life years lost. To investigate the time-varying effects of covariates on LYL, we fitted those models across a sequence of landmark times, using age as a time scale. Finally, we investigated the presence of a two-way interaction between health-related late effects on LYL, to better the understanding of multi-morbidity consequences among childhood cancer survivors.

2. Material and methods

2.1. Data

2.1.1. Population

The French Childhood Cancer Survivors Study (FCCSS [11]) cohort follows 7670 5-year survivors treated between 1945 and 2000 for solid cancer in five cancer centers in France. Included survivors aren't representative of the general french childhood cancer survivors population, as they were treated for more severe and complex cases due to the centers used for recruitment. The FCCSS received approval from a National committee on ethics and the French national agency regulating data protection (Commission Nationale Informatique et Liberté, agreements no. 902287 and no. 12038829). Written informed consent was obtained from all patients, parents, or guardians, following national research ethics requirements. The present analysis included all 7670 survivors.

2.1.2. Cancer treatments exposures

Chemotherapy and radiotherapy information for childhood cancer

treatment were abstracted from medical records. For this study, chemotherapy exposures were defined as receipt (or not) of any chemotherapy agent, anthracyclines, alkylating agents, or platinum compounds.

2.1.3. Outcome definitions: identification and validation of deaths and late effects

The vital status of all patients were obtained from CépiDC, which registers deaths in France [12]. Causes of deaths from CépiDC were available only for the most recent deaths, and were therefore not used in this analysis. Clinical and epidemiological follow-up, including self-administered questionnaires and cohort linkage with the French Hospital Database and Health Insurance Information System (SNDS [13]), were performed to identify the occurrence of iatrogenic effects. Long-term clinic follow-up was also performed for patients treated at Gustave Roussy Institute. SMNs and CDs were identified through these different sources and subsequently validated by a clinical research associate. Validation was based on medical, pathology, or radiological reports from the treating centers or referring doctors, regardless of the data source used for first identification. All events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.03) (Fig. 1).

We included late effects occurring within the first five years after childhood cancer diagnosis. For all results including time since late effect occurrence, we defined it as the time since the last occurrence of the late effect.

2.2. Statistical analysis

For each subject $i = 1, \dots, n$, let $T_i, C_i, \tilde{T}_i := \min(T_i, C_i)$ respectively denote the time of death by any cause, the right censoring time which is the time of last follow-up or death, Let \mathbf{X} be a time-fixed covariate, and $\mathbf{Z}(t)$ be a time-dependent covariate at time t . We used attained age as the time scale.

2.2.1. Life years lost

LYL up to a pre-specified time horizon τ is defined as τ - the area under the survival curve [14]. With S the Kaplan-Meier estimator, $LYL(\tau) = \tau - \int_0^\tau S(t)dt$. We have to use a pre-specified time horizon τ , because few patients are observed at later times due to right censoring, therefore it would be difficult to correctly estimate LYL without τ . Here, we set $\tau = 60$ years old. In the following sections, whenever we talk about LYL, we're actually talking about LYL up to τ .

LYL by a binary covariate \tilde{X} is the difference of LYL for population $\tilde{X} = 1$ and $\tilde{X} = 0$, $LYL(\tau, X) = LYL(\tau|\tilde{X} = 1) - LYL(\tau|\tilde{X} = 0)$. In a more general case we used a regression model using pseudo observations [14, 15].

2.2.2. Pseudo observations for LYL

Let $\hat{\theta} := \tau - \int_0^\tau \hat{S}(t)dt$ be a non parametric estimator of LYL, where S is the Kaplan-Meier estimator. Then for each patient i , we define the pseudo observation

$$\hat{\theta}_i = n\hat{\theta} - (n-1)\hat{\theta}^{(-i)} \quad (1)$$

where $\hat{\theta}$ is the estimate based on the entire data set, and $\hat{\theta}^{(-i)}$ is the estimate where subject i was discarded. Using a linear model on $\hat{\theta}_i$, we can estimate a linear model on LYL [15].

For more details see Appendix A.

2.2.3. Regression with left truncation and right censoring

Patients were included conditionally on their survival 5 years after their childhood cancer diagnosis. Therefore failure times are subject to left truncation and right censoring. We modeled the occurrence of

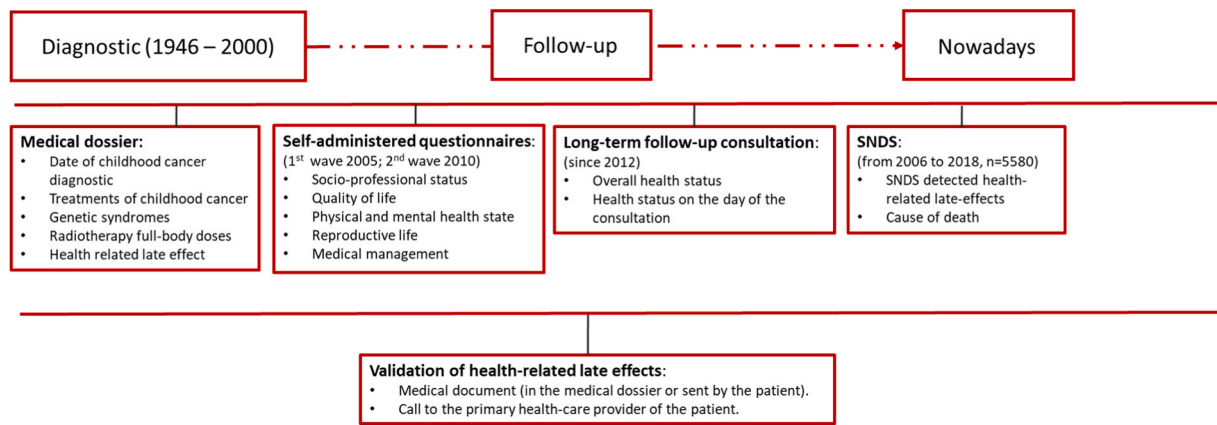


Fig. 1. Flowchart of data acquisition process in the FCCSS.

health-related late effects (e.g. second cancer) by time dependent covariate $Z(\cdot)$. Following [16,17] we used the landmark method to account for left truncation and time-dependent covariates. That is, we chose K landmark time points $(l_k)_{k \in \{1, \dots, K\}}$ and performed the analysis at each $l_k \in (l_k)_k$ using only patients at risk at l_k and substituting the time dependent covariate $Z(\cdot)$ for its time fixed equivalent $Z(l_k)$. Our new pseudo observations are the *strict* pseudo observations of Grand [16].

We chose $(l_k) = (16, 32, 48)$, corresponding to various stages of aging while being close to the quartiles of times of death and l_1 being late enough for late effects of interest to have occurred. We did not use a consensus on biologically meaningful times [18] because it did not exist, and chose equidistant time points because the use of the Aalen additive model for all-cause hazards [19] showed an overall linear trend. We also fitted our models at $(l_k) = (6, \dots, 50)$ to verify that our choice of landmark time points didn't condition our results. To choose τ , we considered the number of patients at risk, the number of events during at-risk windows, and the clinical relevance of this time. We chose $\tau = 60$ for the first analysis and $\tau' = l_k + 10$ to investigate time-varying coefficients.

2.2.4. Covariates

We are interested in the effect of both multiple childhood cancer treatments and of those treatments' late effects (SMN, CD, diabetes, and chronic renal failure). LYL being positive and bound by tau, it's natural to considered a linear model to study the effect of the exposure (health-related late effects) on LYL, while adjusting for confounders (childhood cancer treatments):

$$\text{LYL}(\tau|X, Z(\cdot), l_k) = \tau - \mathbb{E}[\min(T, \tau)|X] = \beta_0 + \beta_1 X + \beta_2 Z_{l_k} \quad (2)$$

The covariates (childhood cancer treatment and late effects) were chosen using literature [9,20–22]. We retained the following childhood cancer treatment covariates for the analysis: use of radiotherapy, chemotherapy, or both radiotherapy and chemotherapy, sex, and age at childhood cancer diagnosis.

We dichotomized exposure to radiotherapy and chemotherapy because it is unclear how to adjust using doses for a population with a wide range of childhood cancer diagnoses and, therefore, treatment regimens and body areas treated.

We estimated univariable and multivariable models adjusted for all childhood cancer treatment covariates and zero or one late effect. We also estimated multivariable models adjusted for all childhood cancer treatment covariates, two late effects, and the two-way interaction of those late effects.

2.2.5. Life years lost by cardiac death

We defined cardiac death as death after a CD of grade 5 (corresponding to death). We used cause-specific life years lost to perform a side analysis on cardiac death [14]. All other methodological details of

the cardiac-death analysis are the same as the main analysis performed on all-cause death.

2.3. Reproducibility

The code used for the analyses is given in Appendix B. All analysis were performed using R 4.2.0. This study adhered to STROBE guidelines for observational studies [23]

3. Results

3.1. Description of the FCCSS cohort

The demographic and treatment characteristics of the 7670 5-year childhood cancer survivors of the FCCSS cohort are presented in Table 1. The cohort includes 3469 women and 4200 men. A total of 1088 patients were treated with radiotherapy and without chemotherapy, 2574 with chemotherapy and without radiotherapy, and 3105 with both radiotherapy and chemotherapy. With a median follow-up of 30 years [Inter Quartile Range: 22.8 years, 38.7 years], we observed 1496 deaths, 828 SMN, and 380 CD of grade ≥ 3 . We have respectively 5371, 5110, and 1488 patients included for analysis at landmark times 16, 32, and 48 years of attained age. Cumulative incidences of death, SMN, and CD are shown in Appendix C.1.

3.2. Life years lost

LYL up to 60 years by childhood cancer treatment and health-related late effects are summarized in Fig. 2 and Fig. 3. Complete results are shown in Appendix C.2.1.

Results are to be interpreted as “conditional on survival at time points 16, 32, and 48 years, exposition to *covariate* is associated with a reduction of restricted life expectancy of X years.” Restricted life expectancy is the life expectancy up to time τ (here $\tau = 60$ years old).

When adjusting for childhood cancer treatment only, we found that treating patients with radiotherapy and no chemotherapy was the treatment regimen contributing the most to LYL, with 6.0 [95 %CI: 4.7–7.4], 3.5 [95 %CI: 2.5–4.5], 1.2 [95 %CI: 0.6–1.7] LYL at landmark times 16 years old, 32 years old, and 48 years old, respectively. Use of both radiotherapy and chemotherapy was also associated with LYL, with 5.1 [95 %CI: 4.2–6.0], 2.6 [95 %CI: 1.9–3.3], 1.3 [95 %CI: 0.8–1.7] LYL at landmark times 16 years old, 32 years old, and 48 years old, respectively. Use of chemotherapy and no radiotherapy was associated with LYL, but contributed a lot less to LYL than other treatment regimen, with 0.7 [95 %CI: –0.0–1.4], 0.7 [95 %CI: 0.1–1.3], 0.6 [95 %CI: 0.1–1.0] LYL at landmark times 16 years old, 32 years old, and 48 years old, respectively.

We found no effect of sex, and only a small effect of age at diagnosis,

Table 1
Description of the FCCSS cohort.

	n in FCCSS (deaths) % (% deaths)	n at 16 (deaths) % at 16 (% deaths)	n at 32 (deaths) % at 32 (% deaths)	n at 48 (deaths) % at 48 (% deaths)
Overall	7669 (1496) 100 % (19.5 %)	5371 (824) 100 % (15.3 %)	5110 (651) 100 % (12.7 %)	1488 (206) 100 % (13.8 %)
Sex				
Men	4200 (838) 54.8 % (20.0 %)	2982 (472) 55.5 % (15.9 %)	2828 (362) 55.3 % (12.8 %)	785 (105) 52.8 % (13.4 %)
Women	3469 (658) 45.2 % (19.0 %)	2389 (352) 44.5 % (14.7 %)	2282 (289) 44.7 % (12.7 %)	703 (101) 47.2 % (14.4 %)
Decade of CC diagnosis				
1945–1969	756 (356) 9.9 % (47.1 %)	605 (264) 11.3 % (43.6 %)	649 (252) 12.7 % (38.8 %)	531 (134) 35.7 % (25.2 %)
1970s	1676 (487) 21.9 % (29.1 %)	1275 (287) 23.7 % (22.5 %)	1433 (259) 28.0 % (18.1 %)	655 (68) 44.0 % (10.4 %)
1980s	2497 (409) 32.6 % (16.4 %)	1721 (198) 32.0 % (11.5 %)	2024 (119) 39.6 % (5.9 %)	302 (4) 20.3 % (1.3 %)
1990s	2740 (409) 35.7 % (8.9 %)	1770 (75) 33.0 % (4.2 %)	1004 (21) 19.6 % (2.1 %)	0 (0) NaN% (NaN%)
Age at CC diagnosis				
< 1 years old	1244 (135) 16.2 % (10.9 %)	1186 (97) 22.1 % (8.2 %)	598 (42) 11.7 % (7.0 %)	139 (13) 9.3 % (9.4 %)
1–4 years old	2482 (474) 32.4 % (19.1 %)	2322 (355) 43.2 % (15.3 %)	1410 (190) 27.6 % (13.5 %)	317 (48) 21.3 % (15.1 %)
5 – 9 years old	1677 (396) 21.9 % (23.7 %)	1584 (314) 29.5 % (19.9 %)	1159 (167) 22.7 % (14.4 %)	332 (43) 22.3 % (13.0 %)
10 – 14 years old	1623 (374) 21.2 % (23.0 %)	279 (58) 5.2 % (20.8 %)	1374 (199) 26.9 % (14.5 %)	516 (84) 34.7 % (16.3 %)
15+ years old	643 (117) 8.4 % (18.2 %)	0 (0) NaN% (NaN%)	569 (53) 11.1 % (9.3 %)	184 (18) 12.4 % (9.8 %)
Treatment combination				
Nor radiotherapy nor chemotherapy	902 (54) 11.8 % (6.0 %)	631 (27) 11.7 % (4.3 %)	535 (20) 10.5 % (3.7 %)	126 (5) 8.5 % (4.0 %)
Radiotherapy alone	1088 (369) 14.2 % (33.9 %)	739 (240) 13.8 % (32.5 %)	827 (222) 16.2 % (26.8 %)	371 (91) 24.9 % (24.5 %)
Chemotherapy alone	2574 (197) 33.6 % (7.7 %)	1874 (91) 34.9 % (4.9 %)	1630 (62) 31.9 % (3.8 %)	253 (8) 17.0 % (3.2 %)
Radiotherapy and chemotherapy	3105 (876) 40.5 % (28.2 %)	2127 (466) 39.6 % (21.9 %)	2118 (347) 41.4 % (16.4 %)	738 (102) 49.6 % (13.8 %)
Anthracycline dose				
< 100 mg/m2	5268 (1149) 68.7 % (21.8 %)	3790 (663) 70.6 % (17.5 %)	3444 (541) 67.4 % (15.7 %)	1133 (184) 76.1 % (16.2 %)
[100–250] mg/m2	1257 (129) 16.4 % (10.3 %)	863 (57) 16.1 % (6.6 %)	773 (48) 15.1 % (6.2 %)	101 (8) 6.8 % (7.9 %)
> 250 mg/m2	1144 (218) 14.9 % (19.1 %)	718 (104) 13.4 % (14.5 %)	893 (62) 17.5 % (6.9 %)	254 (14) 17.1 % (5.5 %)
Radiotherapy dose at the heart				
< 5 Gy	5971 (968)	4301 (546)	3955 (403)	1078 (135)

Table 1 (continued)

	n in FCCSS (deaths) % (% deaths)	n at 16 (deaths) % at 16 (% deaths)	n at 32 (deaths) % at 32 (% deaths)	n at 48 (deaths) % at 48 (% deaths)
	77.8 % (16.2 %)	80.1 % (12.7 %)	77.4 % (10.2 %)	72.4 % (12.5 %)
[5,20] Gy	912 (249) 11.9 % (27.4 %)	617 (155) 11.5 % (25.2 %)	676 (121) 13.2 % (17.9 %)	255 (39) 17.1 % (15.3 %)
> 20 Gy	395 (186) 5.1 % (47.1 %)	196 (83) 3.6 % (42.3 %)	300 (111) 5.9 % (37.0 %)	119 (28) 8.0 % (23.5 %)
Missing data	391 (93) 5.1 % (23.8 %)	257 (40) 4.8 % (15.6 %)	179 (16) 3.5 % (8.9 %)	36 (4) 2.4 % (11.1 %)
Type of childhood cancer				
Unknown	10 (0) 0.1 % (0.0 %)	7 (0) 0.1 % (0.0 %)	9 (0) 0.2 % (0.0 %)	3 (0) 0.2 % (0.0 %)
02 -Lymphomas	1278 (219) 16.7 % (17.1 %)	724 (108) 13.5 % (14.9 %)	1054 (143) 20.6 % (13.6 %)	325 (45) 21.8 % (13.8 %)
03 -CNS tumor	1140 (469) 14.9 % (41.1 %)	790 (264) 14.7 % (33.4 %)	641 (171) 12.5 % (26.7 %)	153 (39) 10.3 % (25.5 %)
04 -Peripheral nervous tumors	1034 (131) 13.5 % (12.7 %)	950 (82) 17.7 % (8.6 %)	576 (44) 11.3 % (7.6 %)	129 (17) 8.7 % (13.2 %)
05 - Retinoblastomas	619 (68) 8.1 % (11.0 %)	583 (52) 10.9 % (8.9 %)	177 (16) 3.5 % (9.0 %)	23 (6) 1.5 % (26.1 %)
06 -Renal tumors	1140 (196) 14.9 % (17.2 %)	1052 (157) 19.6 % (14.9 %)	798 (121) 15.6 % (15.2 %)	267 (42) 17.9 % (15.7 %)
07 -Hepatic tumors	79 (9) 1.0 % (11.4 %)	71 (5) 1.3 % (7.0 %)	45 (3) 0.9 % (6.7 %)	5 (0) 0.3 % (0.0 %)
08 -Bone sarcomas	686 (144) 8.9 % (21.0 %)	236 (39) 4.4 % (16.5 %)	528 (42) 10.3 % (8.0 %)	178 (18) 12.0 % (10.1 %)
09 -Soft-tissue sarcomas	859 (147) 11.2 % (17.1 %)	586 (72) 10.9 % (12.3 %)	613 (52) 12.0 % (8.5 %)	204 (20) 13.7 % (9.8 %)
10 -Germ cells and gonadal tumors	469 (50) 6.1 % (10.7 %)	244 (22) 4.5 % (9.0 %)	388 (26) 7.6 % (6.7 %)	115 (9) 7.7 % (7.8 %)
11 -Other carcinomas	344 (60) 4.5 % (17.4 %)	122 (22) 2.3 % (18.0 %)	275 (33) 5.4 % (12.0 %)	84 (10) 5.6 % (11.9 %)
12 -Other or unspecified tumors	11 (3) 0.1 % (27.3 %)	6 (1) 0.1 % (16.7 %)	6 (0) 0.1 % (0.0 %)	2 (0) 0.1 % (0.0 %)
Cardiac Disease (grade > = 3)				
No	7289 (1332) 95.0 % (18.3 %)	5327 (810) 99.2 % (15.2 %)	4988 (616) 97.6 % (12.3 %)	1400 (186) 94.1 % (13.3 %)
Yes	380 (164) 5.0 % (43.2 %)	44 (14) 0.8 % (31.8 %)	122 (35) 2.4 % (28.7 %)	88 (20) 5.9 % (22.7 %)
Second Malignant Neoplasm				
No	6841 (1119) 89.2 % (16.4 %)	5285 (785) 98.4 % (14.9 %)	4866 (584) 95.2 % (12.0 %)	1273 (149) 85.6 % (11.7 %)
Yes	828 (377) 10.8 % (45.5 %)	86 (39) 1.6 % (45.3 %)	244 (67) 4.8 % (27.5 %)	215 (57) 14.4 % (26.5 %)
Diabetes				

(continued on next page)

Table 1 (continued)

	n in FCCSS (deaths) % (% deaths)	n at 16 (deaths) % at 16 (% deaths)	n at 32 (deaths) % at 32 (% deaths)	n at 48 (deaths) % at 48 (% deaths)
No	7530 (1476) 98.2 % (19.6 %)	5361 (824) 99.8 % (15.4 %)	5064 (645) 99.1 % (12.7 %)	1426 (196) 95.8 % (13.7 %)
Yes	139 (20) 1.8 % (14.4 %)	10 (0) 0.2 % (0.0 %)	46 (6) 0.9 % (13.0 %)	62 (10) 4.2 % (16.1 %)
Chronic Renal Failure				
No	7557 (1460) 98.5 % (19.3 %)	5352 (818) 99.6 % (15.3 %)	5070 (643) 99.2 % (12.7 %)	1462 (203) 98.3 % (13.9 %)
Yes	112 (36) 1.5 % (32.1 %)	19 (6) 0.4 % (31.6 %)	40 (8) 0.8 % (20.0 %)	26 (3) 1.7 % (11.5 %)

Note: Column “n in FCCSS” includes details of all patients included in the FCCSS. Columns “n at 16”, “n at 32”, and “n at 48” includes patients included for analysis at each respective landmark time. Format is “number of patient (number of those patients who died)”, and the line below corresponds to “% of patients of this column who have this level (% of patients with this level who died)”.

with patients diagnosed at 1–4 years old faring the worst, with 1.2 [95 % CI: 0.4–2.0], 1.5 [95 % CI: 0.7–2.3], 0.6 [95 % CI: –0.0–1.3] LYL at landmark times 16 years old, 32 years old, and 48 years old respectively, using patients diagnosed at < 1 year old as reference.

SMN and CD were both associated with LYL. When adjusting for childhood cancer treatment, SMN point estimates were higher than CD point estimates, which is consistent with the usual hierarchy of SMN contributing more to mortality than CD. SMN diagnosed less than 5 years before landmark time point was associated with 9.0 [95 % CI: 4.3–13.7], 3.1 [95 % CI: 1.2–5.1], 1.6 [95 % CI: 0.7–2.4] LYL at

landmark times 16 years old, 32 years old, and 48 years old respectively. CD diagnosed less than 5 years before landmark time point was associated with 8.0 [95 % CI: 1.2–14.9], 5.3 [95 % CI: 1.2–9.3], 2.3 [95 % CI: 0.3–4.3] LYL at landmark times 16 years old, 32 years old, and 48 years old respectively.

Using univariable models, we found an association between LYL and SMN (11.0 [95 % CI: 5.9–16.2] at 16 years, 3.8 [95 % CI: 0.9–6.7] at 32 years, and 2.2 [95 % CI: 0.6–3.9] at 48 years) and CD (7.7.0 [95 % CI: 0.5–14.8] at 16 years, 5.9 [95 % CI: 1.6–10.0] at 32 years, and 2.5 [95 % CI: 0.5–4.6] at 48 years), but not between LYL and diabetes and chronic renal failure. We found no two-way interaction for either combination of SMN, CD, diabetes, and chronic renal failure.

3.3. Time varying effects

Results across all three at-risk time periods after landmark time points (τ) showed similar trends of small time-varying effects. Results of LYL for $\tau = 10$ are displayed in Fig. 4 and Fig. 5 while complete results are shown in Appendix C.2.2. A recent SMN diagnosis has a strong association with 10-LYL at all ages (1.1 [95 % CI: 0.4–1.9] at 16 years, 0.4 [95 % CI: 0.1–0.8] at 32 years, 1.3 [95 % CI: 0.6–1.9] at 48 years). A recent CD diagnosis has a stronger association with 10-LYL at older ages, and no clear association at early ages (0.4 [95 % CI: –0.5 – 1.3] at 16 years, 1.2 [95 % CI: 0.2–2.3] at 32 years, 1.8 [95 % CI: 0.2–3.3] at 48 years). 10-LYL by radiotherapy appears to increase as patients age (0.2 [95 % CI: 0.1–0.3] at 16 years, 0.4 [95 % CI: 0.3–0.6] at 32 years, 0.8 [95 % CI: 0.4–1.2] at 48 years). We observe the same trend for use of radiotherapy with chemotherapy, and for use of chemotherapy alone.

3.4. Cardiac death

LYL by cardiac death up to 60 years are shown in Appendix D. Our analysis of the cohort observations yielded an average of 0.3 LYL by cardiac death, out of the average 8 LYL by all-cause death.

When adjusting for average radiotherapy dose at the heart and brain, cumulative dose of anthracyclines, sex, and age at diagnosis, we found

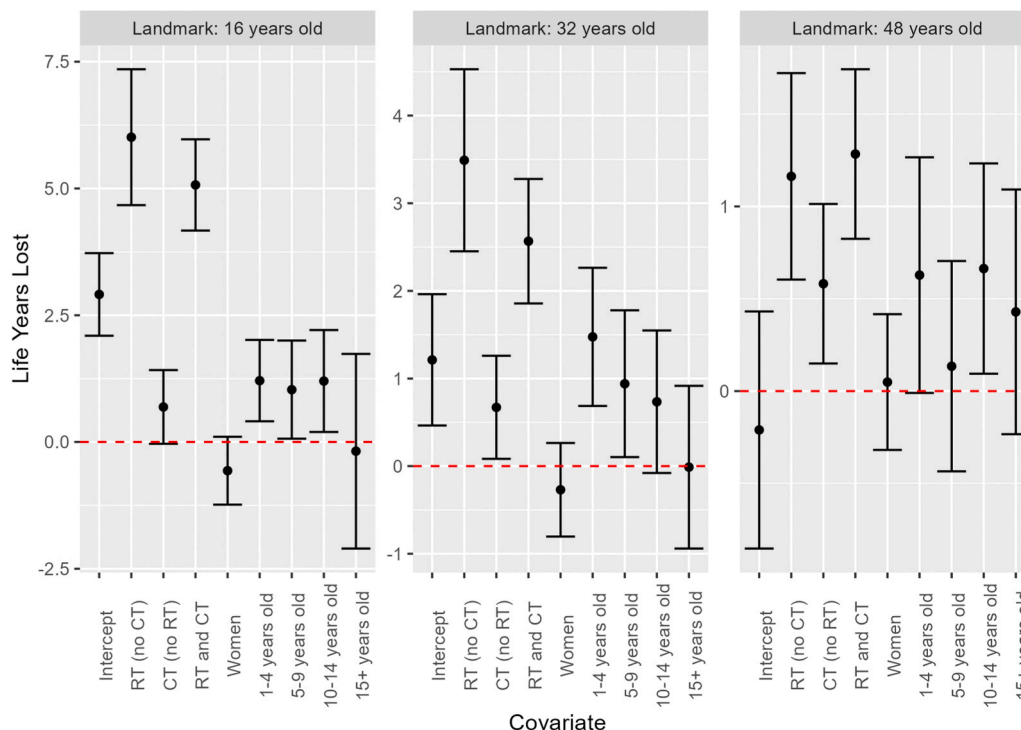


Fig. 2. Life Years Lost by all cause death up to 60 years old, conditional on survival at each landmark time. Errorbars represent 95 % confidence interval. All estimates correspond to a model adjusted on intercept, radiotherapy and chemotherapy, Sex, and age at diagnosis. CT = Chemotherapy, RT = Radiotherapy.

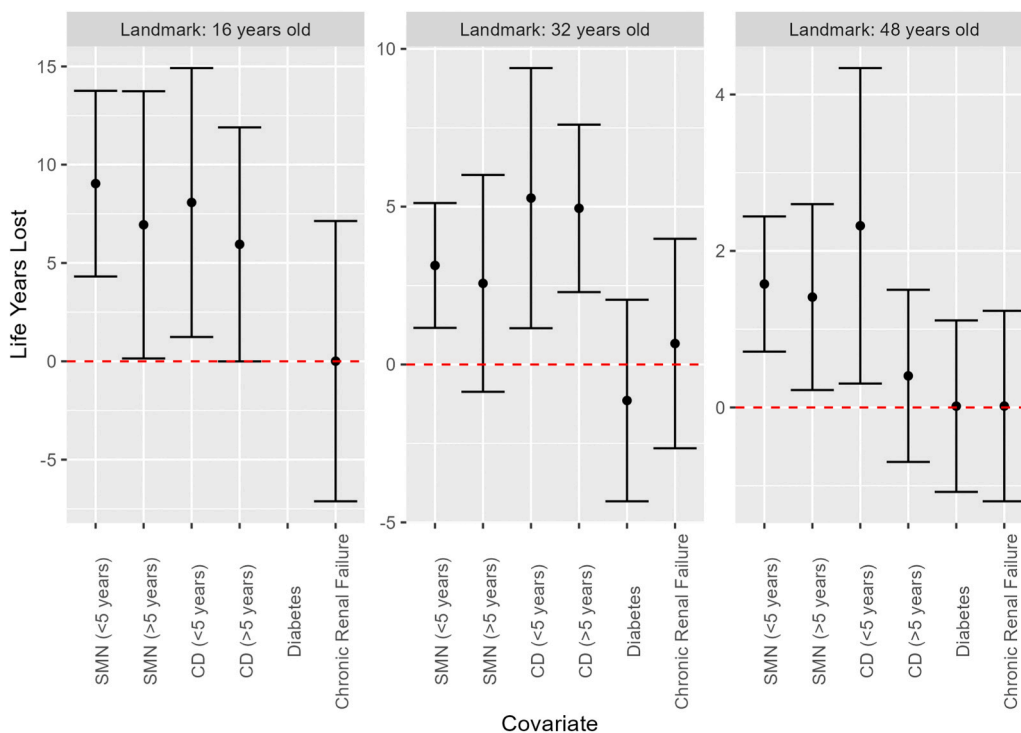


Fig. 3. Life Years Lost by all cause death up to 60 years old, conditional on survival at each landmark time. Errorbars represent 95 % confidence interval. All estimates correspond to a model adjusted on intercept, radiotherapy and chemotherapy, Sex, and age at diagnosis, and one of either Subsequent Malignant Neoplasm, Cardiac Disease, Diabetes, or Chronic Renal Failure. Subsequent Malignant Neoplasm and Cardiac Disease are separated conditional on occurring within the 5 years prior to landmark time. CD = Cardiac Disease, SMN = Subsequent Malignant Neoplasm.

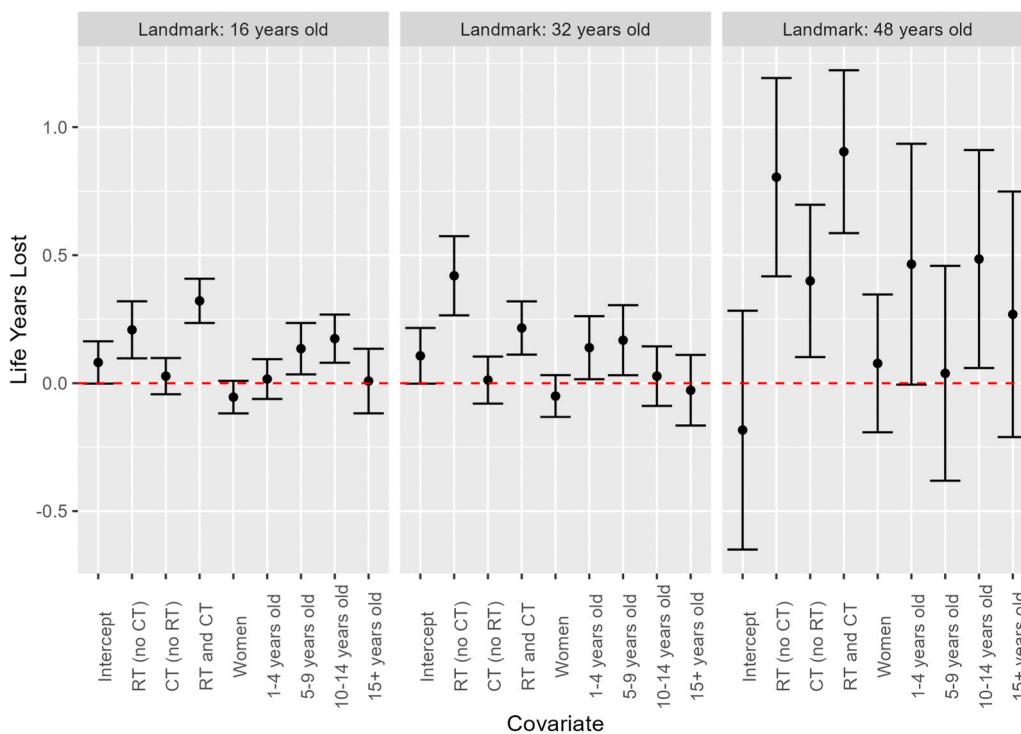


Fig. 4. Life Years Lost by all cause death within 10 years of landmark time, conditional on survival at each landmark time. Errorbars represent 95 % confidence interval. All estimates correspond to a model adjusted on intercept, radiotherapy and chemotherapy, Sex, and age at diagnosis. CT = Chemotherapy, RT = Radiotherapy.

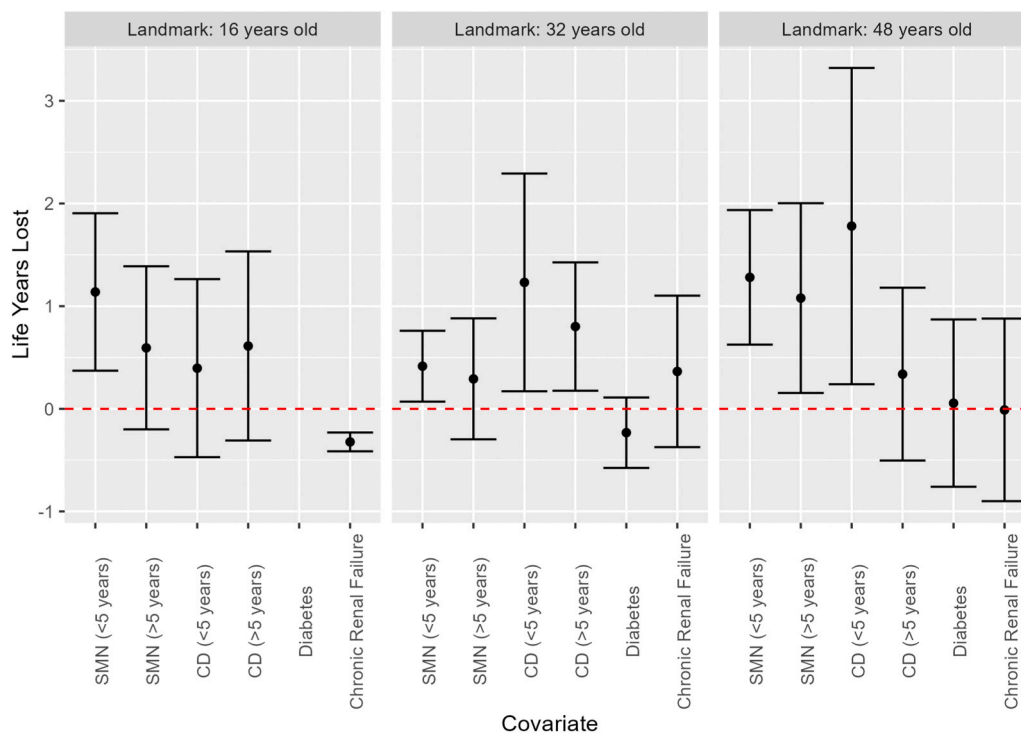


Fig. 5. Life Years Lost by all cause death within 10 years of landmark time, conditional on survival at each landmark time. Errorbars represent 95 % confidence interval. All estimates correspond to a model adjusted on intercept, radiotherapy and chemotherapy, Sex, and age at diagnosis, and one of either Subsequent Malignant Neoplasm, Cardiac Disease, Diabetes, or Chronic Renal Failure. Subsequent Malignant Neoplasm and Cardiac Disease are separated conditional on occurring within the 5 years prior to landmark time. CD = Cardiac Disease, SMN = Subsequent Malignant Neoplasm.

LYL up to 60 years old by cardiac death to be associated with average radiotherapy dose at the heart higher than 20 Gy to an important extent (2.6 [95 %CI: 1.5–3.6] at 16 years, 1.8 [95 %CI: 1.0–2.6] at 32 years, 0.0 [95 %CI: – 0.1 – 0.3] at 48 years), but found no association with other variables, including cumulative dose of anthracyclines higher than 250 mg/m².

4. Discussion

In this retrospective with a prospective follow-up cohort study of childhood cancer survivors, we examined: 1) the associations between childhood cancer treatments and Life Years Lost, 2) the associations between health-related late effects of childhood cancer treatments and LYL, 3) trends across survivors' life span of those associations. We found that radiotherapy was the childhood cancer treatment most strongly associated with LYL and that other childhood cancer treatments' associations with LYL were very small in comparison. We also showed that both SMN and CD were important contributors to the LYL by childhood cancer survivors. We found no two-way interaction between two health related effects and LYL. A supplementary analysis showed some small difference of life years lost by radiotherapy and chemotherapy when stratifying on decade of childhood cancer diagnosis, without a clear trend (Appendix C). Those findings suggest that radiotherapy is the principal root cause of early mortality among CCS, supporting the need of long-term follow-up of all patients treated with RT in childhood. Personalized long-term follow-up care plan should be established for all survivors, especially those exposed to RT, with prevention and screening procedures according to published guidelines. Moreover patients experiencing a SMN or a CD should be monitored closely after the event, as comorbidity is common and causes premature deaths.

Previous works on this population focused on epidemiological measures such as Standardized Mortality Ratios, Absolute Excessive Risk, and Proportional Hazard Ratios (PHR). These are useful for clinicians and public health decision-makers, but require extra work and care

to be interpreted and communicated to patients who may lack the knowledge to interpret relative metrics. Moskalewicz et al. summarized SMR and AER results of previous studies on Childhood Cancer Survivors, with SMR ranging from 5.6 to 17.2 and AER ranging from 34.1 to 70.1 excess deaths per 10,000 person years [4].

Although SMR, AER, and PHR are the most common metrics to study childhood cancer survivors, previous studies did analyze the LYL by childhood cancer survivors. Chang et al studied LYL by health conditions among children, teenagers, and young adult cancer survivors [9]. Similarly to us, they assessed health-related late effects associations with Life Years Lost depending on the age at the health condition onset. They did not adjust for childhood cancer treatment, or use a τ , but found results coherent with ours regarding Life Years Lost by SMN and CDs at 32 and 48 years old. They found CD to be associated with 10.13 (95 %CI: [7.13–14.30]) LYL at 32.5 years old, and –0.29 (95 %CI: [– 0.29 – 0.29]) LYL at 45 years old. They also found Subsequent Malignant Neoplasm to be associated with 11.67 (95 %CI: [9.29–15.27]) LYL at 32.5 years old, and 1.06 (95 %CI: [0.00–2.98]) LYL at 45 years old. The differences with our results can be attributed to differences in population included (solid tumors and lymphomas survivors vs all childhood cancer survivors), in at-risk periods (1950–2024 vs 1998–2020), in control populations (healthy childhood cancer survivors vs community control), methodology used regarding LYL computation, time since health related late effect onset, and inclusion of additional covariates.

LYL are often combined with causes of death and studied as Cause Specific LYL. This allows for a simple visualization ranking causes of death by the magnitude of LYL. This also enables the study of risk factors associated with each cause of death, such as investigating if anthracyclines contribute to non-cardiac death. Causes of death were not usable in our case; therefore, we studied all-cause death. Nonetheless, we still provided valuable results on all-cause mortality and did a side analysis on cardiac death.

A limitation of the study is the lack of access to alcohol consumption, smoking status, and socio-economic data. Those factors are known to be

associated with mortality, and previous works have shown an association between those and childhood cancer type (and therefore treatment regimen and health-related late effects) [24–26]. This may bias the results towards a higher association of health-related late effects and death. Nonetheless, we believe the marginal associations of secondary cancer and cardiac disease with LYL to be of interest. The FCCSS population was treated prior to 2000, and treatment regimen have evolved with time. Therefore, our results may not be translatable to patients being treated for childhood cancer nowadays. We also suggest that using a landmark strategy and looking at the effect of SMN/CD already diagnosed at that time provide estimates less susceptible to those biases than Cause Specific LYL. The design of the study (analysis at various landmark time points) shifts away from survival bias to results conditional on survival. The interpretation of results still must be made by keeping in mind that patients surviving up to a landmark time point are survivors of survivors, and therefore a special case of initial survivors. This is especially true regarding health-related late effects, which often occurred months before each landmark time point.

Further work is needed to investigate with more significant details how radiotherapy doses are linked to disparities of mortality by childhood cancer type, especially to determine which combination of radiotherapy doses and organ exposure contributes the most to late mortality.

5. Conclusions

Using Life Years Lost, we provided a new perspective on the mortality of Childhood Cancer Survivors, detailing the significant impact of radiotherapy use during childhood cancer, Subsequent Malignant Neoplasms, and Cardiac Diseases on the life expectancy of patients at various stages of their life.

List of abbreviations

AER: Absolute Excessive Risk
 CD: Cardiac Disease
 CI: Confidence Interval
 LYL: Life Years Lost
 PHR: Proportional Hazard Ratio
 SMN: Subsequent Malignant Neoplasm
 SMR: Standardized Mortality Rate

Ethics approval

The FCCSS received approval from a National committee on ethics and the French national agency regulating data protection (Commission Nationale Informatique et Liberté, agreements no. 902287 and no. 12038829).

Consent to participate

Written informed consent was obtained from all patients, parents, or guardians, following national research ethics requirements

Consent to publish

Not applicable.

Funding

This work was supported and funded by the Gustave Roussy Foundation (Pediatric Program “Guérir le Cancer de l’Enfant”), the ITMO (Instituts thématiques multiorganismes) Cancer d’Aviesan Program (RadioPrediTool project no. 20CM112–00), the INCa/ARC (Institut national du cancer) foundation (CHART project), the Foundation ARC for Cancer Research (grant no. Pop-HaRC 201401208), the ‘START’ PAIR Research Program (grant no. INCa-Fondation ARC-LNCC 11902), and

the “Ligue Nationale Contre le Cancer” association. These funding agencies had no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the manuscript’s preparation, review, and approval.

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Declaration of Competing Interest

None

Data Availability

The datasets generated and/or analysed during the current study are not publicly available due to patients confidentiality, but are available from the corresponding author on reasonable request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.canep.2024.102692](https://doi.org/10.1016/j.canep.2024.102692).

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