Risk of Renal or Urinary Related Hospitalization in Survivors of Childhood Cancer: Results from the French Childhood Cancer Survivor Study

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ABSTRACT

Background: Hospitalization rates can be used as an indirect indicator of the burden and severity of adverse health outcomes in childhood cancer survivors (CCS). We aimed to determine the long-term risks of hospitalization related to renal and urinary diseases among 5-year CCS.

Methods: The French Childhood Cancer Survivor Study cohort was linked with data from the French National Healthcare System database, which enabled the identification of hospitalizations related to renal or urinary diseases. Clinical and detailed treatment data were collected from medical records. Dose-volume histograms were estimated for all patients treated with radiotherapy. Standardized Hospitalization Ratios and absolute excess risks (AER) were calculated. Relative risks were estimated using Poisson regression.

Results: A total of 5,498 survivors were followed for 42,118 person-years (PY). Survivors experience 2.9 times more renal hospitalizations than expected in the general population, with an AER of 21.2/10,000 PY. Exposing more than 10% of the kidneys' volume to at least 20 Gray increases the risk of being hospitalized for renal causes by 2.2 (95% confidence interval, 1.3–3.6). Nephrectomized survivors treated with high doses of ifosfamide (>60 g/m^2) have an extremely high risk of hospitalization for renal causes. Patients with comorbidities have about a 3-fold higher risk, and nephrectomized patients a 2-fold higher risk of being hospitalized for renal causes compared with other subjects. In the case of hospitalization for urinary causes, treatment by anthracycline administration was found to be associated with an almost 2-fold higher risk of hospitalization compared with the general population.

Conclusions: These results support the need for careful monitoring of long-term renal diseases in survivors who have undergone nephrectomy, those treated with high doses of radiation (≥20 Gy) even to small volumes of the kidneys, and those with predisposing risk factors.

Impact: This study provides new evidence with potential impact on surveillance guidelines related to dose-volume indicators associated with renal toxicity.

Introduction

In pediatric oncology, diagnostic and therapeutic advances have significantly improved 5-year survival after treatment, which is currently over 80% (1). Consequently, the numbers of those alive after successful treatment for childhood cancer have significantly increased. However, chronic health conditions related to cancer therapies have become major concerns. More than 60% of adults who have survived for 30 years after a diagnosis of cancer in childhood suffer from late effects such as secondary cancers, cardiovascular conditions, diabetes, renal and urinary (RU) disease etc. (2–5).

Survivors of childhood cancer also have significantly increased hospitalization rates when compared with the general population, including for RU diseases, indicating a higher rate of serious health conditions (6–8). This implies a potential deterioration in survival and quality of life among this population. The most common risk factors related to long-term kidney disease in childhood cancer survivors (CCS) are treatments with ifosfamide, cisplatin administration, and radiotherapy involving the kidneys (2, 9–11). To date, no study has evaluated the relationship between hospitalization due to RU conditions and treatment-related risk factors. Moreover, there are limited data on the urotoxicity of cancer treatments in CCS, although a recent study has highlighted an association between exposure to anthracyclines and higher risk of urinary tract dysfunction (12).

Hospitalization related to RU diseases can be analyzed as an indirect indicator of the burden and severity of these adverse health outcomes. It may also imply worse inpatient outcomes and increased morbidity, in addition to significantly higher healthcare costs. New evidence on dosages and nephrotoxicity is needed to guide both updates of RU surveillance strategies and designs of treatment regimes.

The aims of our study were: (i) to determine the long-term risks of hospitalization due to renal or urinary diseases among 5-year survivors of childhood cancer, through linkage of the French Childhood Cancer Survivor Study (FCCSS) with the French nationwide healthcare data system (French acronym: SNDS) database; and (ii) to identify risk

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factors related to RU hospitalizations, to better identify patients who may benefit from long-term follow-up both to reduce the risk of unfavorable outcomes and to monitor for complications.

Materials and Methods

Data sources

The FCCSS (https://fccss.fr/) includes 7,670 5-year cancer survivors treated before the age of 21 for a solid tumor or a lymphoma, between 1945 and 2000, in five French cancer centers: Gustave Roussy, Curie and Jean Godinot Institutes, Antoine Lacassagne, and Claudius Régaud centers. It was established between 1985 and 1995, and patients have been followed up prospectively thereafter. The main purpose of this cohort study is to investigate the long-term effects of cancer treatments.

The FCCSS cohort was linked to the SNDS database which includes around 99% of the French population (13). Linkage was provided by the national health insurance fund (French acronym: CNAM) by a probabilistic matching using subject's full name, sex, date and place of birth, and residence postal code. The SNDS database includes information from: (i) the national hospital discharge database (PMSI: Medicalized Information System) which contains data on all hospital admissions, and (ii) the national health insurance claims database (Données de consommation inter-régimes) which includes individual information on outpatient medical care, laboratory tests, and reimbursed drugs. The claims database is linked to the national hospital information database using the beneficiary's encrypted unique identifier.

The FCCSS (14–16) has been approved by the French national agency regulating data protection (agreements no. 902287. Patient informed consent was not required for this study because we obtained a specific act in law from the French "Conseil d'Etat", the highest court in France (Order 2014–96 of 2014 February 3), that approved the cession of the SNDS data for all patients included in the FCCSS (Supplementary Methods).

Study population

To study the FCCSS RU hospitalization records, we selected survivors who were alive in January 2011 living in France, and who were linked to the SNDS.

As hospitalization data for the general population were available from 1 January 2011 to 31 December 2018, only hospitalizations in this period were considered.

Follow-up of our study population started from January 1, 2011 and ended at the study end date December 31, 2018. Patients were censored at: death; loss to follow-up; hospitalization for RU causes; or the study end date, whichever came first. In this study, patients who were deceased before the start date, i.e., 1st of January 2011 were excluded as well as those with unavailable SNDS data. Dates and causes of death were identified through the French national exhaustive database for the medical causes of death. The final cohort included 5,498 patients (83% of survivors alive in 2011; **Fig. 1**).

Identification of RU hospitalizations

The identification of hospitalization related to RU disease was based on both the main and related causes of hospitalization coded in ICD-10. Specific ICD-10 codes used to identify RU disease are detailed in Supplementary Material (Supplementary Table S1). ICD-10 codes for renal related hospitalizations were: N00-N06, N08, N10-N19, R31, R33, R34, T861, Z992, Z490-Z492, and Z940. Codes for urinary related hospitalizations were: N20-N23, N31, N32, N35, and N36.

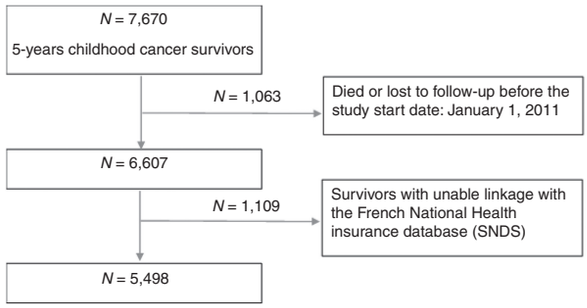

Figure 1.
Study flowchart of patients selection. The flowchart shows the process (i.e., exclusion criteria) used to select the 5,498 patients from the original population. *N*, number of patients.

Covariates

Cancer treatments data were exhaustively collected and are described in e-methods (Supplementary Methods). The doses of chemotherapeutic agents were extracted from the patient's medical records, including copies of medical prescriptions, pharmacy medicine delivery lists, and nurses' daily records. Doses of each cytotoxic drug were calculated as grams per square meter of body surface (g/m^2).

With dosimetry (ref. 17; Supplementary Method), estimated RT dose and dose-volume histogram indicators were calculated. In addition, dose-volume variables were created by calculating the percentage of kidney or pelvic volume that received at least 5 (V_{5Gy}), 10 (V_{10Gy}), 15 (V_{15Gy}), 20 (V_{20Gy}), or 30 (V_{30Gy}) Gy.

For each individual, we aggregated radiation doses for both kidneys and calculated an average, minimal and maximal kidney radiation dose. For patients with unilateral nephrectomy, the dose for the remaining kidney only was considered. For patients with bilateral nephrectomy, no dose was accounted for.

To avoid potential outliers, the maximum radiation doses to the kidneys and pelvic area were defined as the dose received by 5% or less of the organ/area volume ($D_{05\%}$). In the same way, the minimum radiation dose was defined as the dose received by at least 95% of the organ's or area's volume ($D_{95\%}$). In addition, the percentage of kidney/pelvic area volume that received at least 20 Gy (V_{20Gy}) was considered.

Cardiac disease, and diabetes diagnosed before the primary endpoint were considered as comorbidities.

Subsequent malignant neoplasms occurring 5 years or more after first cancer diagnosis, classified as "renal," "urinary," or "others", were also included.

Data availability

FCCSS (https://fccss.fr) welcomes requests from academic and commercial collaborators who have a valid health research request. Regulatory procedures to access the resources of the cohort for conducting specific research projects are outlined in a charter that we will make available upon request to project leaders. Researchers may request access to de-identified data by contacting the corresponding author.

Statistical analysis

Combined with demographic data, hospitalization rates were calculated. Expected numbers were estimated by combining person-years (PY) at risk within sex, age and calendar-year-specific strata and multiplied by the corresponding rates in the general population. To compare the observed number of hospitalizations by RU causes with

the number expected in the general population, Standardized Hospitalization Ratios (SHR) were calculated as the ratio of observed to expected number of hospitalizations by RU cause. Absolute excess risks (AER) were calculated as the observed minus the expected number of RU hospitalizations, divided by the PY at risk and multiplied by 10,000. SHRs can be interpreted as multiplicative factors of hospitalization for RU causes compared with the general population, as AERs can be interpreted as additive factors. Heterogeneity and trend tests were based on likelihood ratio tests.

Relative risks (RR) of being hospitalized for RU causes were estimated using univariable and multivariable Poisson regression. Multivariable models were adjusted on demographic, clinical and treatment related risk factors. Four models were used in analyses, according to the radiation dose: model 1 used mean kidney/pelvic area dose, model 2 used minimum dose, model 3 used maximum dose, model 4 used V_{20Gy}. We included different dose-volume indicators in separate models to avoid over-adjustment. Comorbidities were included as time-dependent variables. The multivariable models included variables on the basis of the clinical knowledge and literature (2–12), and also those significantly associated in bivariate analysis. To take into account the potential recurrence of hospitalizations, the mean cumulative count (MCC, also called cumulative mean function) of hospitalizations for RU causes was calculated (18), per survivor. Results can be interpreted as the average number of hospitalizations for RU causes per survivor, at time *t*. MCC was calculated with all RU causes included, then dialysis was excluded as it is a recurrent cause of hospitalization that repeats indefinitely, and can artificially inflate the results. Finally, we accounted for multiple hypothesis testing by using the Benjamini–Hochberg FDR method (19).

All statistical analyses were conducted in SAS 9.4 version software. A two-sided *P* value less than 0.05 was considered statistically significant.

Results

Cohort characteristics

A total of 5,498 survivors totaling 42,118 PY were included in the analysis (**Table 1**). The median age at childhood cancer diagnosis was 5.0 years [interquartile range (IQR), 1.6–11.0], and the median delay from childhood cancer to 2011 was 22.9 years (IQR, 16.0–30.5).

From 2011 to 2018, 2019 RU hospitalizations were identified corresponding to 230 patients (Supplementary Table S1). A total of 139 patients were hospitalized for renal causes at their first hospitalization, and 91 for urinary causes, and median age at first hospitalization was 37 (IQR, 28–46) and 35 (IQR, 29–43) for RU causes respectively.

The most common renal hospitalization cause was need for dialysis (64.5%). The most common urinary hospitalization causes were urolithiasis (73.2%) followed by diseases of the bladder (15.7%).

Overall RU hospitalizations

At 55 years of age, the average number of RU hospitalizations per survivor was 1.9 [MCC = 1.9; 95% confidence interval (CI), = 1.2–3.0] and 0.6 (MCC = 0.6; 95% CI, 0.5–0.7), with and without dialysis respectively (**Fig. 2A** and **B**).

The global AER for being hospitalized for RU causes was 26.2/10,000 PY (95% CI, 19.4–33.7). CCS were hospitalized for RU causes almost twice as often as the general population (SHR = 1.9; 95% CI, 1.7–2.2). SHR for RU hospitalizations were 2.9 (95% CI, 2.4–3.4) and 1.3 (95% CI, 1.0–1.6), respectively (**Table 2**).

Renal hospitalizations

Survivors experienced 2.9 times (95% CI, 2.4–3.4) the number of renal hospitalizations expected in the general population and 21.4 additional hospitalizations (95% CI, 16.2–27.4) per 10,000 PY (**Table 2**).

Demographic and clinical data

SHR was higher for men (SHR = 3.5; 95% CI, 2.7–4.5) than women (SHR = 2.5; 95% CI, 1.9–3.1; **Table 2**). The association remained significant in multivariable models, and female survivors were 30% less likely to be hospitalized for renal diseases compared with male survivors (RR = 0.72; 95% CI, 0.51–1.0; **Table 3**).

Patients who were younger at childhood cancer diagnosis had the highest risk of subsequent renal hospitalization compared with the general French population, with SHR = 3.7 (95% CI, 2.9–4.7) for survivors diagnosed before 3 years-old and 2.9 (95% CI, 2.0–4.1) for those diagnosed between 4 and 8 years old. There was no excess hospitalization risk for those diagnosed with their primary malignancy at 9 years old and above (**Table 2**).

Survivors of nephroblastoma had the highest risk of hospitalization for renal disease, reaching 6-fold higher (95% CI, 4.4–8.0) than the general French population, with an AER/10,000 PY of 60.2 (95% CI, 40.7–84.7; **Table 2**).

Role of treatment factors

Patients treated either by radiotherapy, whatever the site, by chemotherapy, or by both, had a significantly higher renal hospitalization rate than those treated by surgery only. The highest rate was recorded for those treated with chemotherapy and radiotherapy combined (SHR = 4.0; 95% CI, 3.2–5.0; AER = 35.2/10,000 PY; 95% CI, 25.1–47.1; **Table 2**). Patients treated with nephrectomy had the highest SHR of almost 6.5 (95% CI, 4.3–9.4) and AER which reached 60 cases/10,000 PY (95% CI, 37.4–94.6). Furthermore, in multivariable analyses, nephrectomized patients had a RR of 2.4 (95% CI, 1.5–3.7) compared with other subjects. No chemotherapy doses were associated with the risk of renal hospitalization in multivariable models (Supplementary Table S2). We explored a potential effect of ifosfamide use in nephrectomized patients, considering ifosfamide use as binary variable or continuous/categorical dose variable (Supplementary Table S3). We observed a significant effect when ifosfamide dose was greater than 60 g/m^2 in nephrectomized patients (RR = 23.7; 95% CI, 5.1–110.0). However, with lower dose thresholds, and continuous or binary variables, this effect was no longer significant.

In multivariable analyses, patients who received a mean kidney dose (M1) greater than 30Gy had a RR of being hospitalized for renal disease 4.2 times higher (95% CI, 1.6–10.8) than patients who did not receive any radiation (**Table 3**). Those who received a maximum dose higher than 15 Gy to the kidneys (M3) had a RR of 1.9 (95% CI, 1.2–3.1).

When considering dose-volume histograms, after adjusting for clinical data, cardiac diseases, diabetes and chemotherapeutic agents, exposing more than 10% of kidneys volume to at least 20 Gy (i.e., V_{20Gy} >10%) increased significantly the risk of being hospitalized, by 2.2 (95% CI, 1.3–3.6; **Table 3**).

Comorbidities

Cardiac disease and diabetes prior to hospitalization were both significantly associated with renal hospitalization. Patients with cardiac disease had hospitalization rates 8-fold higher than the general population (95% CI, 5.0–12.3) and the AER was 92.1/10,000 PY (95% CI, 52.1–147.7). The risk for patients with mellitus diabetes was almost 9 times higher than for the general population (SHR = 8.9; 95% CI,

Table 1. Characteristics of the FCCSS and hospitalizations from 2011 to 2018.

Factor	Level			RU hospitalizations				Renal hospitalizations				Urinary hospitalizations			
		N (%)		Cases (%)		Stays (%)		Cases (%)		Stays (%)		Cases (%)		Stays (%)	
Overall		5498	(100)	230	(100)	2019	(100)	139	(100)	1765	(100)	91	(100)	254	(100)
Sex	Men	2999	(54.5)	120	(52.2)	1039	(51.5)	65	(46.8)	879	(49.8)	55	(60.4)	160	(63.0)
	Women	2499	(45.5)	110	(47.8)	980	(48.5)	74	(53.2)	886	(50.2)	36	(39.6)	94	(37.0)
Childhood cancer	Nephroblastoma	834	(15.2)	57	(24.8)	660	(32.7)	45	(32.4)	617	(35.0)	12	(13.2)	43	(16.9)
	Lymphoma	943	(17.2)	36	(15.7)	189	(9.4)	16	(11.5)	282	(16.0)	18	(19.8)	39	(15.4)
	Neuroblastoma	767	(14.0)	34	(14.8)	321	(15.9)	16	(11.5)	139	(7.9)	20	(22.0)	50	(19.7)
	Soft tissue sarcoma	598	(10.9)	29	(12.6)	314	(15.6)	20	(14.4)	271	(15.4)	9	(9.9)	43	(16.9)
	Osteosarcoma	485	(8.8)	22	(9.6)	69	(3.4)	9	(6.5)	38	(2.2)	13	(14.3)	31	(12.2)
	CNS tumor	687	(12.5)	15	(6.5)	47	(2.3)	9	(6.5)	25	(1.4)	6	(6.6)	22	(8.7)
	Gonadal tumor	340	(6.2)	17	(7.4)	190	(9.4)	8	(5.8)	169	(9.6)	9	(9.9)	21	(8.3)
	Retinoblastoma	477	(8.7)	11	(4.8)	101	(5.0)	9	(6.5)	99	(5.6)	2	(2.2)	2	(0.8)
	Thyroid tumor	49	(0.9)	1	(0.4)	2	(0.1)	1	(0.7)	2	(0.1)	0	(0)	0	(0)
	Others	318	(5.8)	8	(3.5)	126	(6.2)	6	(4.3)	123	(7.0)	2	(2.2)	3	(1.2)
Age at diagnosis, in year	0–3	2442	(44.4)	116	(50.4)	1093	(54.1)	77	(55.4)	981	(55.6)	39	(42.9)	112	(44.1)
	4–8	1283	(23.3)	54	(23.5)	594	(29.4)	33	(23.7)	527	(29.9)	21	(23.1)	67	(26.4)
	9–11	638	(11.6)	23	(10.0)	71	(3.5)	11	(7.9)	41	(2.3)	12	(13.2)	30	(11.8)
	12–14	681	(12.4)	26	(11.3)	100	(5.0)	12	(8.6)	70	(4.0)	14	(15.4)	30	(11.8)
	15 and more	454	(8.3)	11	(4.8)	161	(8.0)	6	(4.3)	146	(2.3)	5	(5.5)	15	(5.9)
	Median (IQR)	5.0	(1.6–11.0)	3.8	(1.5–9.5)	2.5	(1.8–8.4)	3.4	(1.5–8.4)	2.3	(1.8–8.4)	5.4	(1.2–11.4)	5.3	(1.3–9.8)
Treatment era	<1970	339	(6.2)	24	(10.4)	270	(13.4)	20	(14.4)	262	(14.8)	4	(4.4)	8	(3.2)
	1970–1979	967	(17.6)	61	(26.5)	473	(23.4)	38	(27.3)	415	(23.5)	23	(25.3)	58	(22.8)
	1980–1989	1828	(33.2)	77	(33.5)	814	(40.3)	41	(29.5)	692	(39.2)	36	(39.6)	122	(48.0)
	1990–1999	2126	(38.7)	63	(27.4)	446	(22.1)	36	(25.9)	381	(21.6)	27	(29.7)	65	(25.6)
	2000 and more	238	(4.3)	5	(2.2)	16	(0.8)	4	(2.9)	15	(0.9)	1	(1.1)	1	(0.4)
	Median (IQR)	1988	(1980–1995)	1984	(1977–1991)	1982	(1978–1989)	1983	(1975–1991)	1982	(1977–1989)	1984	(1978–1991)	1982	(1979–1991)
Follow-up, in year	<20	613	(11.1)	36	(15.7)	136	(6.7)	24	(17.3)	108	(6.1)	12	(13.2)	28	(11.0)
	20–29	2129	(38.7)	76	(33.0)	631	(31.3)	38	(27.3)	533	(30.2)	38	(41.8)	98	(38.6)
	30–39	1728	(31.4)	79	(34.3)	918	(45.5)	46	(33.1)	812	(46.0)	33	(36.3)	106	(41.7)
	40–49	768	(14.0)	29	(12.6)	203	(10.1)	21	(15.1)	181	(10.3)	8	(8.8)	22	(8.7)
	50 and more	260	(4.7)	10	(4.4)	131	(6.5)	10	(7.2)	131	(7.4)	0	(0)	0	(0)
	Median (IQR)	30	(23–37)	30	(23–38)	29	(22–35)	32	(24–39)	29	(22–35)	29	(22–36)	30	(24–35)
Attained age, in year	<20	120	(2.2)	9	(3.9)	42	(2.1)	8	(5.8)	41	(2.3)	1	(1.1)	1	(0.4)
	20–29	1282	(23.3)	62	(27.0)	425	(21.1)	35	(25.2)	355	(20.1)	27	(29.7)	70	(27.6)
	30–39	1864	(33.9)	70	(30.4)	784	(38.8)	38	(27.3)	682	(38.6)	32	(35.2)	102	(40.2)
	40–49	1550	(28.2)	64	(27.8)	471	(23.3)	37	(26.6)	405	(23.0)	27	(29.7)	66	(26.0)
	50 and more	682	(12.4)	25	(10.9)	297	(14.7)	21	(15.1)	282	(16.0)	4	(4.4)	15	(5.9)
	Median (IQR)	37.4	(29.8–44.9)	35.4	(28.5–44.3)	34.9	(28.9–43.6)	36.6	(27.7–46.2)	35.6	(29.2–45.3)	34.9	(28.9–43.1)	34.9	(28.8–42.8)

Abbreviations: *N*, number of patients; CNS, central nervous system.

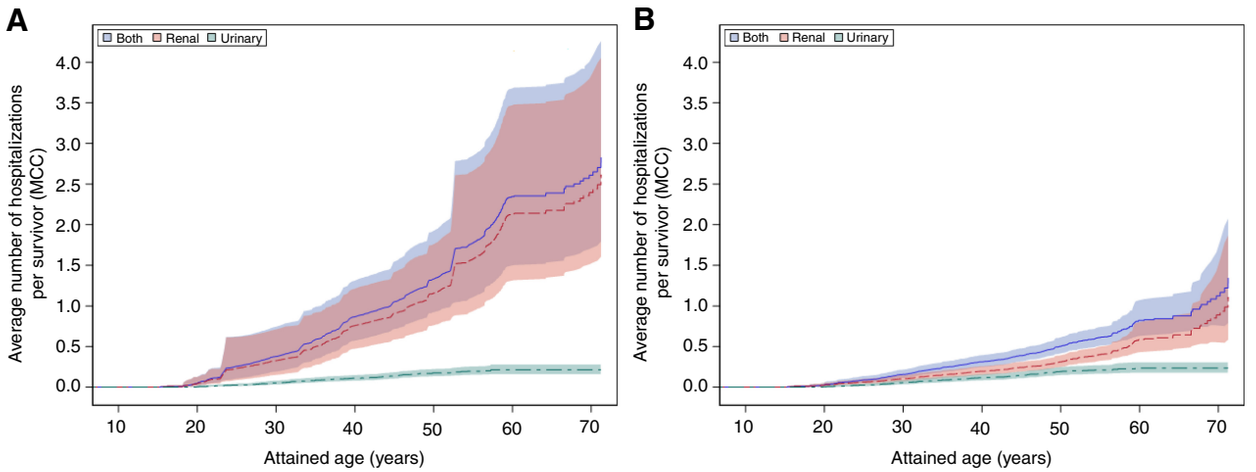

Figure 2.

A, MCC (lines and dotted lines) and corresponding 95% CIs (shades) of developing renal or urinary disease leading to hospitalization, including dialysis, among survivors of the FCCSS cohort from 2011 to 2018 as a function of attained age. **B,** MCC (lines and dotted lines) and corresponding 95% CIs (shades) of developing renal or urinary disease leading to hospitalization, excluding dialysis, among survivors of the FCCSS cohort from 2011 to 2018 as a function of attained age.

5.9–12.8) and AER was more than 110 cases/10,000 PY (AER = 113.2; 95% CI, 70.4–170.0; **Table 2**). In multivariable analyses, RRs of renal hospitalization for patients with comorbidities were almost 3 compared with patients without comorbidities (RR diabetes = 3.1; 95% CI, 2.0–4.9; RR cardiac disease = 2.8; 95% CI, 1.7–4.6; **Table 3**).

Urinary hospitalizations

For urinary diseases, survivors had 1.3 times (95% CI, 1.0–1.6) the number of hospitalizations expected in the general population and 4.8 excess hospitalizations (95% CI, 0.58–9.7) per 10,000 PY (Supplementary Table S4).

Demographic and clinical data

There was no difference between men and women concerning urinary hospitalization risk (Supplementary Table S4). Similarly, no difference was evidenced according to age at childhood cancer diagnosis or treatment area. Survivors after neuroblastoma had a 2-fold higher risk compared with the general population (SHR = 2.1; 95% CI, 1.3–3.3) and an AER of 15.8/10,000 PY (95% CI, 3.5–33.4). No other childhood cancer type was associated with a risk of urinary hospitalization (**Table 2**).

Role of treatment data

Primary treatment type (chemotherapy, radiotherapy, or both) was not associated with urinary hospitalization compared with the general hospitalization. Only patients treated by chemotherapy but no radiotherapy had a higher risk than the general French population (SHR = 1.6; 95% CI, 1.1–2.1; AER = 8.6/10,000 PY; 95% CI, 5.9–23.6; **Table 2**).

Among chemotherapy drugs tested, only anthracyclines administration was associated with an almost 2-fold higher risk of urinary hospitalization compared with the general population (SHR = 1.8; 95% CI, 1.4–2.4; AER = 13.8/10,000 PY; 95% CI, 18.0–32.8; adjusted RR = 1.7; 95% CI, 1.0–3.0). No association was found when considering chemotherapy drug doses.

Radiation dose to pelvic area was not significantly associated with an increase in urinary hospitalization risk, whatever the dose taken into account (i.e., mean, minimum, maximum dose or V_{20Gy}). However, the minimum dose to pelvic area ($D_{05\%}$) associated risk was barely close to significant (*P* value = 0.084), with a higher risk corresponding to a higher dose, i.e., more than 5Gy (SHR = 3.0; 95% CI, 0.8–7.6; AER = 37.6/10,000 PY; 95% CI, 3.7–126.0).

Comorbidities

Urinary hospitalization was not associated with comorbidities prior to hospitalization; neither cardiac disease, nor diabetes.

Discussion

Using the French national hospital discharge database cross-linked with the FCCSS, we found that survivors of childhood malignancies are at higher risk of being hospitalized for RU disease, particularly renal disease. Diabetes and cardiac disease are predisposing risk factors associated with a higher risk of renal hospitalization. These real-world results also provide supportive evidence that patients treated with nephrectomy or radiation to the kidneys are among the groups at highest risk. More specifically, we found that exposing small volumes of the kidney to high doses (V_{20Gy} >10%) leads to a significantly higher risk of renal hospitalization. Moreover, nephrectomized survivors treated with high ifosfamide doses (>60 mg/m^2) have an extremely high risk of hospitalization for renal causes. We also identified anthracyclines as a risk factor for hospitalization for urinary causes. Other chemotherapeutic agents and pelvic radiation were not found to be linked to urinary hospitalization.

Although treatment of pediatric solid tumors has changed considerably in recent decades, the availability of very long-term follow-up data in our cohort, and the linkage with the hospitalization database, provided an excellent opportunity to investigate the relationship between RU hospitalization and both kidney/pelvic-area radiation doses and chemotherapy.

Overall, survivors included in the FCCSS experienced 26.2 additional RU hospitalizations per 10,000 PY compared with the general population, which is consistent with previous results (ref. 6; AER = 22.9/10,000 PY). Nevertheless, treatment exposure was not accounted for in the before mentioned study. Similarly, other studies have investigated urinary or renal hospitalizations; however, these also

Table 2. Observed and expected numbers of any renal hospitalizations, SHRs and AERs, from the FCCSS cohort from 2011 to 2018.

Factor	Level	*N*	PY	Obs	Exp	SHR	95% CI		AER	95% CI	
Overall		5,498	42,118	139	48.8	2.9	2.4	3.4	21.4	16.2	27.4
Sex	Men	2,999	23,016	65	18.6	3.5	2.7	4.5	20.2	13.7	27.9
	Women	2,499	19,103	74	30.2	2.5	1.9	3.1	22.9	14.6	32.8
	$P_{heterogeneity}$					*0.037*			*0.219*		
Age at diagnosis, in year	0–3	2,442	18,728	77	20.7	3.7	2.9	4.7	30.1	21.4	40.3
	4–8	1,283	9,767	33	11.3	2.9	2.0	4.1	22.3	11.7	35.9
	9–11	638	4,887	11	5.9	1.9	0.94	3.4	10.5	−0.76	28.3
	12–14	681	5,203	12	6.7	1.8	0.93	3.1	10.2	−0.91	27.5
	15 and more	454	3,534	6	4.3	1.4	0.51	3.0	4.7	−6.0	24.7
	$P_{heterogeneity}$					*0.013*			*0.666*		
	P_{trend}					*0.001*			*<0.001*		
Treatment era	<1970	339	2,488	20	5.4	3.7	2.3	5.7	58.7	27.4	102.5
	1970–1979	2,364	18,519	40	19.5	2.1	1.5	2.8	11.1	4.9	18.9
	1980–1989	967	7,163	38	9.2	4.2	2.9	5.7	40.3	24.7	60.0
	1990 and more	1,828	13,949	41	14.7	2.8	2.0	3.8	18.9	10.6	29.3
	$P_{heterogeneity}$					*0.013*			*0.488*		
	P_{trend}					*0.003*			*<0.001*		
Years from childhood cancer treatment	<20	613	4,673	24	4.6	5.2	3.3	7.7	41.5	23.0	66.5
	20–29	2,129	16,400	38	17.6	2.2	1.5	3.0	12.4	5.7	21.1
	30–39	1,728	13,205	46	14.1	3.3	2.4	4.4	24.2	14.8	35.8
	40–49	768	5,863	21	7.9	2.7	1.7	4.1	22.4	8.7	41.3
	50 and more	260	1,977	10	4.6	2.2	1.1	4.0	27.5	1.1	69.9
	$P_{heterogeneity}$					*0.011*			*0.013*		
	P_{trend}					*0.194*			*0.910*		
Attained age, in year	<20	120	919	8	0.69	11.5	5.0	22.7	79.6	30.1	164.1
	20–29	1,282	9,834	35	10.7	3.3	2.3	4.5	24.7	13.9	38.6
	30–39	1,864	14,316	38	14.7	2.6	1.8	3.6	16.3	8.5	26.2
	40–49	1,550	11,841	37	13.0	2.9	2.0	3.9	20.3	11.0	32.1
	50 and more	682	5,209	21	9.7	2.2	1.3	3.3	21.7	6.3	43.0
	$P_{heterogeneity}$					*0.001*			*<0.001*		
	P_{trend}					*0.019*			*0.121*		
Childhood primary malignancy	Nephroblastoma	834	6,229	45	7.5	6.0	4.4	8.0	60.2	40.7	84.7
	Soft tissue sarcoma	598	4,610	20	5.5	3.7	2.2	5.7	31.5	14.6	55.1
	Gonadal tumor	340	2,617	8	3.3	2.5	1.1	4.8	18.1	0.72	47.8
	Neuroblastoma	767	5,955	16	6.7	2.4	1.4	3.9	15.7	4.0	32.5
	Lymphoma	943	7,285	16	8.0	2.0	1.1	3.3	11.0	1.6	24.7
	Retinoblastoma	477	3,732	9	4.0	2.3	1.0	4.3	13.5	0.4	35.1
	Osteosarcoma	485	3,701	9	4.6	2.0	0.90	3.7	12.0	−1.2	33.8
	CNS tumor	687	5,165	9	5.8	1.6	0.71	2.9	6.2	−3.3	21.8
	Thyroid tumor	49	385	1	0.60	1.7	0.04	9.3	10.3	−15.0	129.2
	Other	318	2,438	6	3.0	2.0	0.75	4.4	12.5	−3.1	41.5
	$P_{heterogeneity}$					*<0.001*			*0.154*		
Childhood cancer treatment	Surgery only	715	5,623	10	6.4	1.6	0.75	2.9	6.4	−2.9	21.3
	RT no CT	659	4,978	19	7.3	2.6	1.6	4.1	23.6	8.4	45.1
	CT no RT	2,022	15,724	36	16.7	2.2	1.5	3.0	12.3	5.4	21.1
	CT and RT	2,102	15,794	74	18.5	4.0	3.2	5.0	35.2	25.1	47.1
	$P_{heterogeneity}$					*0.002*			*0.228*		
Nephrectomy (partial or complete)	No	4,993	38,297	111	44.5	2.5	2.1	3.0	17.4	12.2	23.3
	Yes	505	3,821	28	4.3	6.5	4.3	9.4	62.0	37.4	94.6
	$P_{heterogeneity}$					*<0.001*			*0.683*		
Chemotherapy treatment	*No*	1,374	10,601	29	13.7	2.1	1.4	3.1	14.5	5.4	26.4
	Yes	4,124	31,518	110	35.1	3.1	2.6	3.8	23.8	17.5	30.9
	$P_{heterogeneity}$					*0.062*			*0.077*		
Anthracyclines administration	*No*	3,370	25,831	82	31.2	2.6	2.1	3.3	19.7	13.2	27.3
	Yes	2,128	16,287	57	17.6	3.2	2.5	4.2	24.2	15.7	34.6
	$P_{heterogeneity}$					*0.220*			*0.326*		
Ifosfamide administration	*No*	4,834	37,040	119	43.3	2.8	2.3	3.3	20.4	14.9	26.8
	Yes	664	5,079	20	5.5	3.6	2.2	5.6	28.5	13.2	50.0
	$P_{heterogeneity}$					*0.253*			*0.246*		
Cisplatin administration	*No*	4,804	36,769	123	43.0	2.9	2.4	3.4	21.8	16.1	28.2
	Yes	694	5,349	16	5.8	2.8	1.6	4.5	19.1	6.3	37.7
	$P_{heterogeneity}$					*0.890*			*0.691*		

(Continued on the following page)

Table 2. Observed and expected numbers of any renal hospitalizations, SHRs and AERs, from the FCCSS cohort from 2011 to 2018. (Cont'd)

Factor	Level	*N*	PY	Obs	Exp	SHR	95% CI		AER	95% CI	
Topoisomerase inhibitors administration	*No*	2,037	15,571	44	19.7	2.2	1.6	3.0	15.6	7.9	25.3
	Yes	3,461	26,547	95	29.1	3.3	2.6	4.0	24.8	18.0	32.8
	$P_{heterogeneity}$					*0.036*			*0.050*		
Cardiac pathology[a]	*No*	5,202	40,122	118	46.2	2.6	2.1	3.1	17.9	12.8	23.7
	Yes	296	1,997	21	2.6	8.1	5.0	12.3	92.1	52.1	147.7
	$P_{heterogeneity}$					*<0.001*			*<0.001*		
Diabetes[a]	*No*	5,191	39,924	111	45.6	2.4	2.0	2.9	16.4	11.4	22.1
	Yes	307	2,194	28	3.2	8.9	5.9	12.8	113.2	70.4	170.0
	$P_{heterogeneity}$					*<0.001*			*<0.001*		
Mean radiation dose to kidney, in Gy	*No RT*	2,737	21,347	46	23.1	2.0	1.5	2.7	10.7	5.0	17.9
	0	600	4,583	17	5.2	3.3	1.9	5.2	25.7	10.2	48.0
	]0;5]	1,279	9,667	36	12.2	2.9	2.1	4.1	24.6	13.4	38.9
	]5;15]	441	3,283	18	4.1	4.4	2.6	6.9	42.3	19.9	74.1
	]15;30]	376	2,768	17	3.5	4.8	2.8	7.7	48.7	23.0	85.6
	>30	65	471	5	0.56	9.0	2.9	20.9	94.4	22.6	236.1
	$P_{heterogeneity}$					*0.001*			*<0.001*		
	P_{trend}					*0.004*			*<0.001*		
Minimum radiation dose to kidney[b]***, in Gy***	*No RT*	2,737	21,347	46	23.1	2.0	1.5	2.7	10.7	5.0	17.9
	0	621	4,740	17	5.4	3.1	1.8	5.0	24.4	9.5	46.0
	]0;5]	1,651	12,406	54	15.7	3.4	2.6	4.5	30.9	20.1	44.2
	>5	489	3,626	22	4.6	4.8	3.0	7.3	48.0	25.4	79.2
	$P_{heterogeneity}$					*0.004*			*<0.001*		
	P_{trend}					*0.022*			*<0.001*		
Maximum radiation dose to kidney[c]***, in Gy***	*No RT*	2,737	21,347	46	23.1	2.0	1.5	2.7	10.7	5.0	17.9
	0	604	4,615	17	5.3	3.2	1.9	5.2	25.4	10.1	47.6
	]0;15]	1,368	10,350	36	13.2	2.7	1.9	3.8	22.0	11.6	35.4
	>15	789	5,807	40	7.2	5.5	4.0	7.5	56.4	36.8	81.4
	$P_{heterogeneity}$					*<0.001*			*<0.001*		
	P_{trend}					*0.001*			*<0.001*		
% of kidney volume that received at least 20 Gy	*No RT*	2,737	21,347	46	23.1	2.0	1.5	2.7	10.7	5.0	17.9
	0%	1,923	14,606	51	18.1	2.8	2.1	3.7	22.5	13.6	33.5
	]0;10%]	197	1,442	8	1.7	4.6	2.0	9.2	43.5	12.0	97.4
	]10;50%]	341	2,524	20	3.2	6.3	3.8	9.7	66.6	35.8	109.7
	]50%;100%]	300	2,200	14	2.7	5.2	2.9	8.7	51.4	22.6	94.6
	$P_{heterogeneity}$					*<0.001*			*<0.001*		
	P_{trend}					*0.016*			*<0.001*		

Abbreviations: *N*, number of patients; Obs, observed number; Exp, expected number; AER, absolute excess risk per 10,000 PY; RT, radiotherapy; Gy, Gray; CNS, central nervous system.

[a]Comorbidities prior to hospitalization.

[b]Minimum dose = D95. i.e. dose received by 95% of the kidney volume.

[c]Maximum dose = D05. i.e. dose received by 5% of the kidney volume.

included genital hospitalizations. The results were in accordance with ours, but not directly comparable (8, 20).

In this study, despite the relatively small sample size compared with other CCS cohorts, we used a large and very detailed data set on cancer treatments, particularly for radiotherapy doses including dose-volumes histograms focusing on specific organs, to shed light on the relationship between radiation dose distributions to the kidneys or pelvic area and hospitalization for RU disease. Previous studies found that doses higher than 15Gy were for late onset kidney disease (9). A monitoring for kidney toxicity after exposure to an abdominal dose of 10 Gy or 15 Gy to the kidneys has also been previously recommended (21, 22). Our findings suggest a significant risk of hospitalization for renal disease when the dose received by 5% of the kidneys volume ($D_{05\%}$) is higher than 15 Gy (RR = 1.9; 95% CI, 1.2–3.1). Another important result is that exposing small volumes of the kidney to at least 20 Gy leads to a significant risk of hospitalization for kidney disease.

The association between nephrectomy and kidney disease has previously been highlighted in several studies and is also confirmed in our findings, i.e., a SHR of 6.5 (95% CI, 4.3–9.4), an AER of 62/10,000 PY (95% CI, 37.4–94.6) and an adjusted RR of 2.4 (95% CI, 1.5–3.7; refs. 23, 24). Our findings suggest a potential role of high-dosage ifosfamide in long-term renal adverse outcomes in CCS. We found that high ifosfamide doses (> 60 g/m^2) in nephrectomized patients are associated with a very high risk of hospitalization for renal causes. Ifosfamide causes dose-dependent acute and chronic glomerular and tubular damage, and its effect on long-term kidney disease has been highlighted in several other studies (9–11). Ifosfamide nephrotoxicity is believed to be due to a toxic metabolite produced in significant amounts in the kidney by the breakdown of ifosfamide, resulting in cellular oxidative stress leading to mitochondrial damage and energy depletion (25).

The DNA damage caused by radiation can induce immediate cell death in the kidney. As well as cell death, oxidative stress, vascular dysfunction, cellular senescence, inflammation, release of profbrotic agents, and Renin–angiotensin–aldosterone system (RAAS)-activation have recently been discussed as pathomechanisms in radiation nephropathy (26, 27).

Table 3. Multivariable Analyses for Renal hospitalizations, From the FCCSS Cohort From 2011 to 2018.

Model	Factor	Level	*N*	Cases	RR (95% CI)	FDR adjusted *P*[d]
Model1	*Sex*	*Men*	2,879	65	ref.	0.077
		Women	2,389	74	0.72 (0.51–1.0)	
	Age at diagnosis, in year	*15 and more*	454	6	ref.	0.213
		0–1	1,623	49	2.5 (0.90–7.0)	
		2–3	819	28	2.3 (0.82–6.4)	
		4–8	1,283	33	1.7 (0.67–4.5)	
		9–11	638	11	1.2 (0.42–3.3)	
		12–15	681	12	1.1 (0.41–3.0)	
	Treatment era	*1990 and more*	2,364	40	ref.	0.324
		<1970	339	20	0.90 (0.24–3.3)	
		1970–1979	967	38	1.3 (0.51–3.3)	
		1980–1989	1,828	41	1.2 (0.61–2.2)	
	Attained age in 2011, in year	*<20*	998	20	ref.	0.317
		20–29	1,727	37	1.1 (0.57–2.3)	
		30–39	1,734	36	0.87 (0.34–2.3)	
		40–49	802	34	1.2 (0.35–4.1)	
		50 and more	237	12	0.92 (0.19–4.5)	
	Chemotherapy treatment	*No*	1,374	29	ref.	0.368
		Yes	4,124	110	1.1 (0.71–1.7)	
	Nephrectomy (partial or complete)	*No*	4,993	111	ref.	<0.001
		Yes	505	28	2.4 (1.5–3.7)	
	Diabetes[a]	*No*	5,191	111	ref.	<0.001
		Yes	307	28	3.1 (2.0–4.9)	
	Cardiac pathology[a]	*No*	5,202	118	ref.	<0.001
		Yes	296	21	2.8 (1.7–4.6)	
Model 1	*Mean radiation dose to kidney (Gy)*	*No RT*	2,737	46	ref.	0.075
		0	600	17	1.7 (0.94–2.9)	
		]0;5]	1,279	36	1.5 (0.92–2.3)	
		]5;15]	441	18	1.4 (0.76–2.5)	
		]15;30]	376	17	1.6 (0.89–3.0)	
		>30	65	5	4.2 (1.6–10.8)	
Model 2	*Minimum radiation dose to kidney (Gy)*[b]	*No RT*	2,737	46	ref.	0.147
		0	621	17	1.6 (0.90–2.8)	
		]0;5]	1,651	54	1.5 (1.0–2.4)	
		>5	489	22	1.6 (0.90–2.8)	
Model 3	*Maximum radiation dose to kidney (Gy)*[c]	*No RT*	2,737	46	ref.	0.099
		0	604	17	1.6 (0.93–2.9)	
		]0;15]	1,368	36	1.3 (0.82–2.1)	
		>15	789	40	1.9 (1.2–3.1)	
Model 4	*% of kidney volume that received at least 20 Gy*	*No RT*	2,737	46	ref.	0.049
		0%	1,923	51	1.4 (0.89–2.1)	
		]0;10%]	197	8	1.7 (0.76–3.7)	
		>10%	641	34	2.2 (1.3–3.6)	

Abbreviations: N, number of patients; ref., reference; RT, radiotherapy; Gy, Gray.
[a]Comorbidities prior to hospitalization.
[b]Minimum dose = D95. i. e. dose received by 95% of the kidney volume.
[c]Maximum dose = D05. i. e. dose received by 5% of the kidney volume.Multivariable models adjusted on sex, age at diagnosis, treatment area, attained age, nephrectomy status, comorbidities prior to hospitalization, chemotherapy treatment and radiation dose according to the model (only one way to account for radiation dose in each model).
[d]Adjusted *P* values for multiple tests.

We could not investigate the role of partial versus complete nephrectomy as the information was unavailable. We did not observe any association between cisplatin and the risk of hospitalization for renal disease, even at high doses. Although platinum-based agents have been associated with kidney injury (21), a recent study did not find an association between late onset severe renal disease and exposure to cisplatin (10). However, the association between platinum-based agents and long-term nephrotoxicity requires further investigations.

Our findings are also consistent with other studies that have reported diabetes and other cardiovascular disease as predisposing to severe renal disease and ESKD in CCS (9, 10). Indeed, diabetes and cardiac diseases are known to be common diseases after pediatric cancer treatments and are major risk factors for long-term renal disease (4, 28, 29).

In CCS, severe impairment of the bladder function and genitourinary malformations may be related to pelvic radiotherapy, or alkylating agents (30). In the current study, anthracyclines were the

only treatment-related risk factor associated with urinary hospitalization. A recent study has identified for the first time an association between anthracyclines and lower urinary tract dysfunction, suggesting a possible myotoxic effect of anthracyclines which may affect the bladder's physiology (12).

Surveillance for late adverse effects is an important part of the long-term care of CCS. Several national pediatric oncology societies and the International Late Effects of Childhood Cancer Guideline Harmonization Group have published long-term follow-up surveillance clinical practice guidelines (31). However, guidelines for late RU toxicities are still lacking. Due to lack of these guidelines, a targeted surveillance approach for prioritizing higher-risk survivors treated with higher-dose ifosfamide, radiation to the kidneys or nephrectomy can be envisaged. In addition, patients treated with anthracyclines may also benefit from long-term urologic follow-up strategies.

Strengths and limitations

We used the national hospitalization database to provide a real-life picture of the risks of RU disease in survivors of childhood malignancies in a large cohort with highly detailed treatment exposure data. We were able to identify clinically relevant predictors for RU hospitalizations using dose-volume histograms. These predictors can be used in current clinical practice and long-term follow-up recommendations.

Our study also has some limitations. We focused on hospitalizations and were not able to identify less severe morbidity related to RU disease which may nevertheless be important in this population. We also inevitably missed some hospitalizations before 2011, especially for patients treated in earlier years. We were able to link only 83% of survivors alive in 2011 with the French national health database. However, the characteristics of linked and non-linked patients were roughly similar (Supplementary Table S5).

Finally, stratification of hospitalization status (renal or urinary related) and doses of chemotherapy may have resulted in a lack of statistical power.

Conclusion

Our results support the need for careful monitoring of long-term renal disease in survivors who have exposures to nephrectomy, and especially for those treated with high radiation doses (≥ 20 Gy) even to small volumes of the kidneys. This new result may greatly impact clinical practice and needs to be supported by other studies. Patients with predisposing factors, more specifically cardiac disease or diabetes, may benefit from long-term renal follow-up. Further investigations of the role of high dosage ifosfamide in nephrectomized patients are required. Survivors treated with anthracyclines may be at risk of urinary disease outcomes. This supports the case for more investigation into the possible mechanisms implicated in the effect of anthracyclines on long-term urinary tract toxicity.

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Authors' Contributions

I. Mansouri: Data curation, formal analysis, validation, investigation, methodology, writing–original draft, writing–review and editing. **B. Schwartz:** Data curation, formal analysis, validation, investigation, methodology, writing–original draft, writing–review and editing. **G. Vu-Bezin:** Data curation, validation, writing–review and editing. **D. Bejarano-Quisoboni:** Validation, methodology, writing–review and editing. **B. Fresneau:** Validation, investigation, writing–review and editing. **C. El-Fayech:** Validation, investigation, writing–review and editing. **C. Dufour:** Validation, investigation, writing–review and editing. **S. Bolle:** Validation, investigation, writing–review and editing. **A. Surun:** Validation, investigation, writing–review and editing. **D. Orbach:** Validation, investigation, writing–review and editing. **R.S. Allodji:** Validation, methodology, writing–review and editing. **I. Diallo:** Validation, investigation, methodology, writing–review and editing. **C. Demoor-Goldschmidt:** Supervision, validation, writing–review and editing. **F. de Vathaire:** Conceptualization, supervision, validation, investigation, project administration, writing–review and editing. **N. Haddy:** Supervision, validation, investigation, methodology, writing–original draft, project administration, writing–review and editing.

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Note

Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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