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Long-Term Kidney and Cardiac Disease Following Childhood Cancer Treatment

Imène Mansouri

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Imène Mansouri. Long-Term Kidney and Cardiac Disease Following Childhood Cancer Treatment. Cancer. Université Paris Saclay (COMUE), 2019. English. NNT : 2019SACLS579 . tel-03091996

HAL Id: tel-03091996

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Long-term kidney and cardiac disease following childhood cancer treatment

Thèse de doctorat de l'Université Paris-Saclay
préparée à l'Université de Paris Sud

École doctorale n°570 EDSP Santé Publique
Spécialité de doctorat: Epidémiologie

Thèse présentée et soutenue à Villejuif, le 16 décembre 2019, par

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Publications during the thesis

▪ *Publications in the thesis frame work*

Published

Mansouri I, Allodji RS, Hill C, El-Fayech C et al. The role of irradiated heart and left ventricular volumes in heart failure occurrence after childhood cancer. European journal of heart failure. 2019 Apr;21(4):509-18.

Under revision

Imène Mansouri, Natalia Alencar de Pinho, Renaud Snanoudj, PhD, Christian Jacquelinet, Mathilde Lassalle, Clémence Bechade, Cécile Vigneau, Florent Devathaire, Nadia Haddy¹, Bénédicte Stengel Trends and outcomes with kidney failure from anti-neoplastic treatments and urinary tract cancer in France.

In preparation

Trends in long term cause mortality among 5-year survivors of childhood malignancies diagnosed between 1946 and 2000

Insight into long term chronic kidney disease in childhood cancer survivors: the experience of the French Childhood Cancer Survivors Study

▪ *Other publications*

- Journy, N., **Mansouri, I.**, Allodji, R. S., Demoor-Goldschmidt, C., Ghazi, D., Haddy, N., Rubino, C., Veres, C., Zrafi, W. S., Rivera, S., Diallo, I. & De Vathaire, F. 2019. Volume effects of radiotherapy on the risk of second primary cancers: A systematic review of clinical and epidemiological studies. Radiother Oncol, 131, 150-159.
- Allodji, R. S., Haddy, N., Vu-Bezin, G., Dumas, A., Fresneau, B., **MansourI, I.**, Demoor-Goldschmidt, C., El-Fayech, C., PacquemenT, H., Munzer, M., Bondiau, P. Y., Berchery, D., Oberlin, O., Rubino, C.,

Diallo, I. & De Vathaire, F. 2019. Risk of subsequent colorectal cancers after a solid tumor in childhood: Effects of radiation therapy and chemotherapy. *Pediatr Blood Cancer*, 66, e27495.

- Allodji, RS., Hawkins, MM., Bright, CJ., Fidler-benaoudia, MM., Winter, DL., Alessi, D., Fresneau, B., Journy, N., Morsellino, V., Bardi, E., Bautz, A., Byrne, J., Feijen, ELA., teepen, JC., Vu-bezin, G., Rubino, C., Garwicz, S., Grabow, D., Gudmundsdottir, T., Guha, J., Hau, EM., Jankovic, M., Kaatsch, P., Kaiser, M., Linge, H., Muraca, M., Llanas, D., Veres, C., Ofstaas, H., Diallo, I., **Mansouri, I.**, Ronckers, C. M., Skinner, R., Terenziani, M., Wesenberg, F., Wiebe, T., Sacerdote, C., Jakab, Z., Haupt, R., Lahteenmaki, P., Zaletel, LZ., Kuehni, CE., Winther, JF., Michel, G., Kremer, LCM., Hjorth, L., Haddy, N., Devathaire, F. Reulen, R. c. 2019. Risk of subsequent primary leukaemias among 69,460 five-year survivors of childhood cancer diagnosed from 1940 to 2008 in Europe: A cohort study within PanCareSurFup. *Eur J Cancer*, 117, 71-83.

Oral and poster presentations

Séminaire CESP « Santé des enfants et des adolescents ».

June, 2018, Villejuif France

Oral Presentation: Cardiac and renal diseases among childhood cancer survivors.

Conference on Radiation And Health & Radiation Research Society RADRES

September, 2018, Chicago, USA

Oral presentation: The role of irradiated heart and left ventricle volumes in heart failure occurrence after childhood cancer”.

Poster presentation: The role of irradiated heart and left ventricle volumes in heart failure occurrence after childhood cancer”.

Journées des coordinations régionales REIN

Mai, 2019, Saint Denis, France

Oral presentation: Incidence and outcomes of patients with cancer-related end stage renal disease: a national registry study.

North American Symposium on Late Complications After Childhood Cancer

June, 2019, Atlanta USA

Poster presentation: Insight into chronic kidney disease after childhood cancer treatment: the experience of the French Childhood Cancer Survivor Study

51st Congress the international society of pediatric oncology SIOP

October, 2019, Lyon, France

Poster presentation: Temporal trends in late mortality in 5-year survivors of childhood malignancy: the experience of the French Childhood Cancer Survivor Study.

51st Congress the international society of pediatric oncology SIOP

October, 2019, Lyon, France

Oral presentation: Insight into chronic kidney disease after childhood cancer treatment in the French Childhood Cancer Survivor Study.

Conference on Radiation And Health & Radiation Research Society RADRES

November, 2019, San Diego, USA

Oral presentation: Insight into chronic kidney disease after childhood cancer treatment: the experience of the French Childhood Cancer Survivor Study”.

Journée du CESP

December, 2019, Université Paris Sud, Le Kremlin-Bicêtre, France

Oral presentation: Effets des traitements du cancer à long terme sur le rein

Réunion du Comité de suivi à long terme : Société Française de lutte contre les Cancers et les leucémies de l'Enfant et de l'adolescent

December, 2019, Gustave Roussy, Villejuif, France

Oral presentation: Complications cardiaques à long terme, résultats de l'étude FCCSS

Oral presentation: Complications rénales après un cancer de l'enfant : une étude de cohort

Awards

- Early Stage Radiation Investigator Travel award on September 24th, 2018, Chicago, USA
- Radiation Research society Scholar-In-Training travel award on November 3rd, 2019, San Diego, USA

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Abbreviations list

CNS	Central nervous system
AER	Absolute Excess Risk
AIC	Akaike Information Criterion
BCCSS	British Childhood Cancer Survivor Study
BMI	Body Mass Index
CCS	Childhood Cancer Survivors
CCSS	Childhood Cancer Survivor Study
CKD	Chronic Kidney Disease
EMR	Excess Mortality Ratio
ERR	Excess Relative Risk
ESKD	End Stage Kidney Disease
FCCSS	French Childhood Cancer survivor Study
GFR	Glomerular Filtration Rate
Gy	Gray
HR	Hazard Ratio
HT	Heart Transplant
ICCC	International Childhood Cancer Classification
ICD-10	International Classification of Disease 10th revision
IQR	Interquartile Range
LRD	Living related donation
LV	Left Ventricle
MHD	Mean Heart Dose
MLVD	Mean Left Ventricle Dose
OR	Odds Ratios
PD	Peritoneal dialysis
pmi	per million inhabitants
PMSI	Medicalisation Program of the Information Systems
REIN	The renal epidemiology and information network
RT	Radiation
SAZ	Spike at zero
SHR	Standardized Hazard Ratio
SMR	Standardized Mortality Ratio
SPN	Secondary primary neoplasms
V10	Volume receiving at least 10Gy
V20	Volume receiving at least 20Gy
V30	Volume receiving at least 30 Gray
V40	Volume receiving at least 40 Gray

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Chapter I. General introduction

1. Descriptive epidemiology of childhood cancer

1.1 Incidence

In France, an average of 1,780 new cases of cancer are diagnosed every year among patients aged less than 15 (1). Between 2000 to 2004, incidence rates of childhood malignancies in France was 156.6 cases per million children per year (1) and remained stable, reaching 156.2 from 2004 to 2010. Said incidence rates were highly similar to those observed in both the USA (150.9 cases per million) and Germany (147 cases per million) in the same periods.

Overall, the most frequent paediatric cancers in France were leukaemia (29%) followed by central nervous system (CNS) tumours (23%) (Figure 1). However, types of childhood cancer vary by age: Among patients less than 10 years old, the most frequent type of paediatric malignancies were leukaemia, followed by CNS tumours. In the 10-14 age group, CNS tumours were the most common type of malignancy (23%), followed by lymphomas (22.3%). Germ-cell tumours, epithelial neoplasms, and malignant melanomas were also more frequent in patients aged more than 10 years (1). Incidence rates were also slightly higher among boys with an overall sex ratio of 1.2, which was also true in other developed countries with a sex ratio typically between 1.1 and 1.4 (2); suggesting that sex could be a biological risk factor for childhood cancer (3-5).

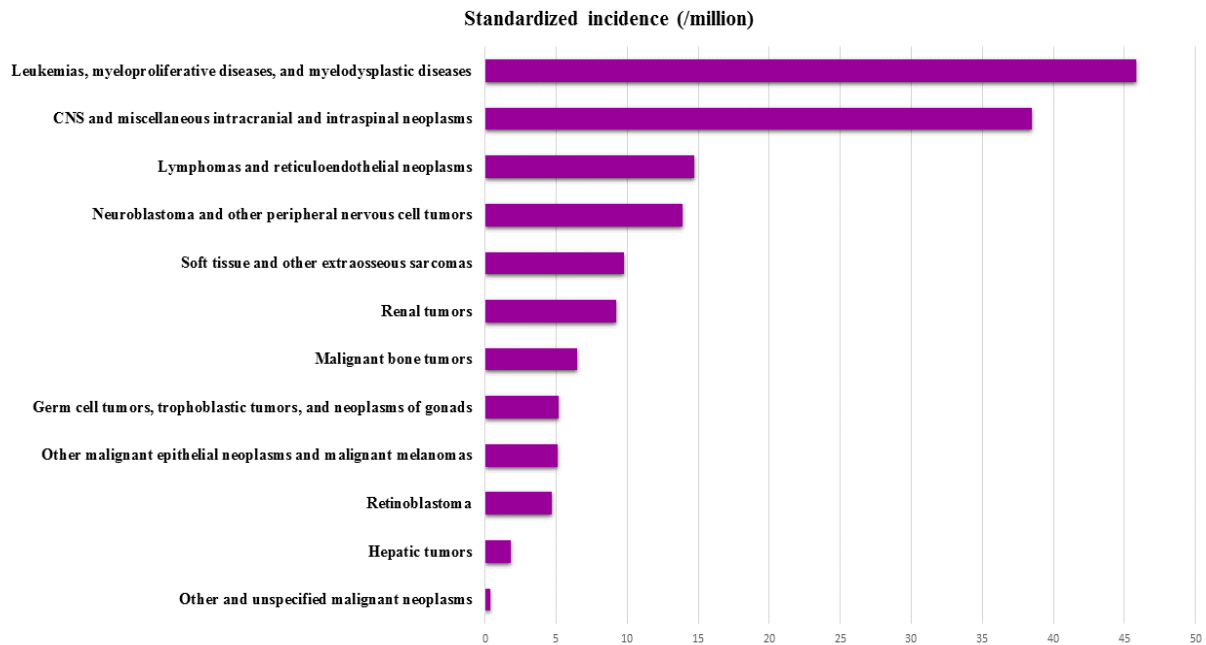


Figure 1. Incidence of cancer in children between 2010 and 2014 in France based on National Registry of Childhood Haematopoietic Malignancies (NRCH) and the French National Registry of Childhood Solid Tumours (NRCST)

1.2 Survival of childhood cancer

Survival rates for childhood cancer in the developed countries have improved considerably over recent decades (6). In France, the percentage of patients surviving at least 5 years was 75.2% during the period 1990–1999 (7). These five-year survival rates increased significantly to 81.6% between 2000–2008 (8) and reached 83.1% for the period of 2007 to 2014(9). The French five-year survival rates were similar to those reported in developed countries in the 2000s (10). These improved prognoses were observed to a various extent for all major types of childhood tumours and were attributed to improved treatment protocols and diagnostic procedures (Figure 2) (11).

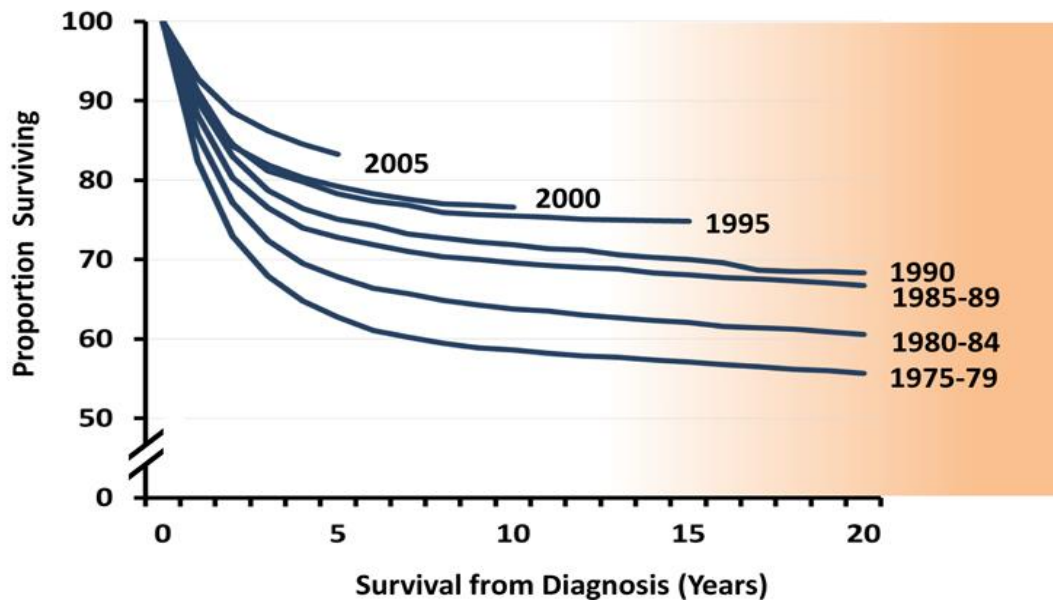


Figure 2. Improvements in overall survival among cancer patients diagnosed before the age of 20 years by year of cancer diagnosis, Robison et al. 2014 (12).

2. Treatment of childhood cancer

Treatment protocols are determined based on the type of cancer and the age of the patients. Childhood cancer treatment has gone through various changes over the past few decades and generally includes surgery, radiation therapy, and/or chemotherapy (13-15).

While surgery and radiotherapy dominated the field of childhood cancer therapy into the 1960s, the introduction of chemotherapy in the same decade has since allowed for the use of the multi-modality approach, i.e., the use of surgery and radiation in the treatment of cancer (14).

2.1 Radiotherapy

The use of radiotherapy has historically been one of the great successes in the treatment of paediatric cancers, particularly in acute lymphoblastic leukaemias, Hodgkin lymphomas, neuroblastomas, and sarcomas (16).

Historically, radiotherapy fields were designed on two-dimensional plain radiographs based on anatomic landmarks. To account for localization uncertainties, larger margins around the tumour site that may include healthy organs were used in treatment planning (17, 18). Damage

of healthy cells surrounding the malignant tumour was the major limitation of radiotherapy (19).

Two factors play a major role in the decreased healthy-tissue effect (1) the fractionation for external beam radiotherapy, typical external beam radiotherapy schedules consist of daily fractions delivered over weeks or months, with each fraction consisting of a relatively small dose (generally 1.2–3 Gy) (20) (2) improving radiotherapy technologies and techniques that increased dose-delivery precision and reduced the volume of irradiated healthy tissues (18). Intensity-modulated radiation therapy (IMRT) represents one of the most significant technical advances in radiation therapy, allowing for the clinical implementation of highly conformal dose distributions (21).

However, radiation fields are chosen to provide the maximum radiation dose to the tumour while minimizing that of healthy tissue and surrounding organs. Therefore, if the tumour exists in close proximity to critical normal structures, irradiation of these normal structures is sometimes unavoidable (18). The use of radiation therapy to treat childhood cancers has generally declined in more recent treatment eras (16).

2.2 Chemotherapy

Surgery and radiotherapy dominated the field of cancer therapy into the 1960s until it became clear that cure rates were not improving after ever more radical local treatments due to the presence of micro metastases; new data showed that combination chemotherapy could cure patients with various advanced cancers (22). Combining treatment modalities and adjuvant chemotherapy treatment became standard clinical practice (23-26). As a result, survival from childhood cancers, many of which were fatal in the pre-chemotherapy era, has increased dramatically from 20-30% in the 1960s to 62% in the 1970s (14). During that period, Vincristine, asparaginase, cyclophosphamide, daunomycin, and cytarabine were all introduced into clinical practice in addition to combinations of chemotherapy mechlorethamine, vincristine

(Oncovin), procarbazine, and prednisone (MOPP regimen) were also introduced to treat Lymphomas (24). The identification of additional chemotherapeutic agents also facilitated the development of combination chemotherapy regimens. Notably, vincristine, methotrexate, and cyclophosphamide, which continue to be the backbone of contemporary therapy (25, 27) (Table 1).

In the 1990s, modulation of treatment intensity based on risk was evaluated to improve treatment outcome and reduce late effects (28). Important late effects that are often not clinically evident for many years include cardiac dysfunction and coronary artery disease, cognitive impairment, renal disease, infertility, and secondary malignant neoplasms (19, 29-31).

Technological advances during the past decade in the area of genome and transcriptome analysis accelerated identification of potential targets and resulted in the identification of multiple potential specific targets to treat multiple types of malignancies (33). The identification of targets on the cell surface made it possible to treat tumour cells with specifically tailored antibodies and hence to pursue new therapeutic options. Many current molecular profiling programs for patients with relapsed or high-risk tumours aim to sequence tumour genomes to identify genetic alterations and switch off related genes with targeted therapies (34). Immunotherapies have also shown increasing promise in the treatment of adult cancer and a small but increasing body of evidence suggests that immunotherapy could improve outcomes for childhood cancers as well (35).

While novel biological and molecularly targeted agents are the subjects of ongoing research, cytotoxic chemotherapy, and irradiation continue to be used for the treatment of the majority of children diagnosed with cancer (14).

Table 1. List antineoplastic chemotherapies included in the World Health Organization's essential Medicines list for Children (32).

Cytotoxic agent	Class	Indication
Bleomycin	Antitumor Antibiotic	Hodgkin Lymphoma Testicular Germ Cell Tumours Ovarian Germ Cell Tumours
Carboplatin	Alkylating Agent	Osteosarcoma Retinoblastoma
Cisplatin	Alkylating Agent	Osteosarcoma Testicular Germ Cell Tumours Ovarian Germ Cell Tumours
Cyclophosphamide	Alkylating Agent	Rhabdomyosarcoma Ewing Sarcoma Acute Lymphoblastic Leukemia Burkitt Lymphoma Hodgkin Lymphoma
Cytarabine	Antitumor Antibiotic	Acute Lymphoblastic Leukemia Burkitt Lymphoma
Dacarbazine	Alkylating Agent	Hodgkin Lymphoma
Dactinomycin	Antitumor Antibiotic	Rhabdomyosarcoma Wilms Tumour
Daunorubicin	Anthracycline	Acute Lymphoblastic Leukaemia
Doxorubicin	Anthracycline	Osteosarcoma Ewing Sarcoma Acute Lymphoblastic Leukemia Wilms Tumour Burkitt Lymphoma Hodgkin Lymphoma
Etoposide	Epipodophyllotoxins	Retinoblastoma Ewing Sarcoma Acute Lymphoblastic Leukemia Burkitt Lymphoma Hodgkin Lymphoma Testicular Germ Cell Tumours Ovarian Germ Cell Tumours
Ifosfamide	Alkylating Agent	Osteosarcoma Rhabdomyosarcoma Ewing Sarcoma Testicular Germ Cell Tumours Ovarian Germ Cell Tumours
Methotrexate	Antitumor Antibiotic	Osteosarcoma Acute Lymphoblastic Leukemia
Paclitaxel	Taxane	Ovarian Germ Cell Tumour Testicular Germ Cell Tumours
Vinblastine	Vinca-Alkaloids	Ovarian Germ Cell Tumours Hodgkin Lymphoma
Vincristine	Vinca-Alkaloids	Retinoblastoma Rhabdomyosarcoma Ewing Sarcoma Acute Lymphoblastic Leukemia Wilms Tumour Burkitt Lymphoma. Hodgkin Lymphoma

3. Long term adverse effects after childhood cancer

As a consequence of the increased survival, it is estimated that there are between 300,000 and 500,000 survivors in Europe (36). More CCS are confronted to late effects of the cancer treatment and these cancer-related adverse effects don't become apparent until many years after cancer treatment, during adulthood (37).

Following cancer treatment, CCS have at least a 62.3% chance of developing at least one chronic health condition, and at least 20.5% have a severe or life-threatening chronic condition (38). The etiology and the associated morbidity of many adverse outcomes are generally multifactorial, involving combinations of treatment-related risk factors, patient's age at diagnosis, gender, pre-morbid conditions, genetic factors and health-related behaviours. Nevertheless, with the exception of specific genetic conditions with mutations in relevant genes, it is typically treatment-related factors that determine the risk of these adverse late effects (Figure 3) (12). Treatment-related adverse effects include cardiac diseases, renal impairment, secondary malignant neoplasms, diabetes, cognitive dysfunction, infertility, and lower quality of life (28, 38-40). Given the fact that survivors of paediatric cancers live longer, it is crucial to understand the long-term risks associated with these adverse effects.

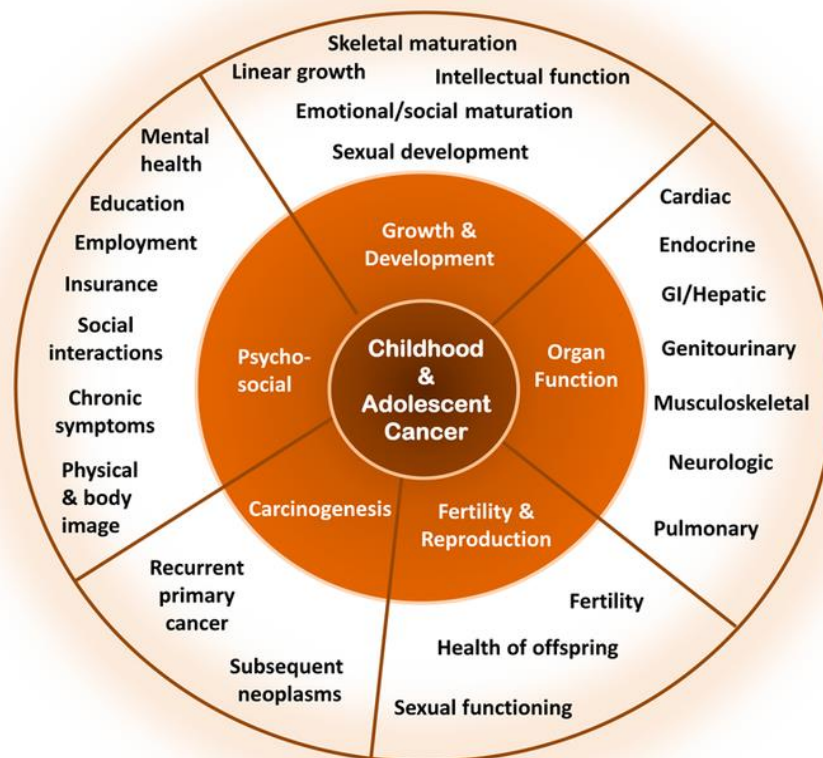


Figure 3. Spectrum of adverse effects among long-term survivors of childhood malignancies, Robison et al. 2014 (12).

3.1 Long term mortality

Five-year survival has been the primary benchmark of therapeutic success for childhood cancer. However, the risk of cancer and cancer therapy-related death extends well beyond this arbitrary 5-year point (41). Studies have found that long-term mortality of CCS remained higher than the general population beyond 25 years after diagnosis (41-44). According to large cohort studies, survivors experienced 8.4 to 11 times the number of expected deaths from the general population (41, 44-46). This significant long-term morbidity and mortality is associated with treatments of childhood cancer (47, 48).

Death by recurrence or progression of the primary malignancy was the leading cause of death in all of these studies followed by subsequent primary neoplasms (45, 46, 49). Cardiovascular

disease was also the leading non-malignant cause of death among CCS, responsible for up to sevenfold higher risk of death compared to the general population (41, 47). Furthermore, the proportion of extra deaths related to secondary neoplasms, cardiovascular diseases, respiratory diseases, and other chronic diseases kept increasing steadily over time from the first malignancy diagnosis (44).

Higher rates of death due to SPNs were seen in patients diagnosed with their primary malignancy at a younger age, those who received radiotherapy and those who were treated with alkylating agents and epipodophyllotoxins (41, 46, 50). Cardiac radiation, alkylating agents and higher doses of anthracycline exposure were also associated with cardiac related death (47, 51). The overall pattern of late mortality among childhood-cancer survivors has been studied in few cohorts. These studies have found evidence that late mortality is decreasing for patients treated in the more recent treatment eras (42, 43, 48). Said reduction in late mortality among these patients could be attributed to temporal reduction of exposure to anthracycline, cranial irradiation, and generally decreasing the dose and/or volume of radiation therapy (48, 52-55).

3.2 Secondary malignant neoplasms

The risks of subsequent primary neoplasms (SPNs) has been investigated in different cohorts of childhood cancer survivors, including the Childhood Cancer Survivor Study (CCSS) (56, 57) and British CSS (BCCSS) (49) and the Nordic countries (58). The risk was found to be between 3.9 and 12.5-fold and increased steadily with age, compared to the general population (49, 56, 59-61).

Studies have found that the burden of SMNs remained increased even beyond 30 years from cancer diagnosis and did not reach a plateau (60). Hereditary retinoblastoma, soft-tissue sarcomas, and Hodgkin's disease are the most common first cancers associated with the development of second cancers, and are considerably over-represented among patients with second cancers relative to their incidence in the general population (62).

SMNs are known side effects of childhood cancer treatments and the major treatment-related risk factors include chemotherapy, radiotherapy and hematopoietic stem cell transplantation (HSCT). The role of ionizing radiation as a carcinogen and the subsequent risk of SMN development have been well-reported in the literature (63, 64). In data reported by the CCSS, ionizing radiation exposure was the strongest independent risk factor SMN development (57, 60). Chemotherapies are also associated with increased risk of SMNs, with treatment-related acute myeloid leukaemia and myelodysplastic syndrome being linked to alkylating agents (60, 65). Chemotherapy use also increases the risk of solid malignancies, which typically occur >10 years after exposure. Exposure to alkylating agents increase the risk of lung, thyroid, gastrointestinal, and bladder cancer as well as sarcoma (64, 65). Association of bladder cancer with the exposure of cyclophosphamide is one of the examples that a specific alkylating agent has a carcinogenic potential for a specific site, which is due to direct exposure of bladder epithelium to cyclophosphamide metabolites (66). Risk of gastrointestinal malignancies after procarbazine exposure is also an example of direct exposure (67) in addition to exposure to epipodophyllotoxins, which were also proven to be associated with secondary acute myeloid leukaemia (60).

3.3 Cardiovascular diseases

Thirty years after a diagnosis of cancer, almost three fourths of survivors have a chronic health condition, more than 40% have a serious health problem, and one third have multiple conditions (38). The leading non-cancer-related cause of morbidity and mortality in long-term survivors is cardiovascular disease (41, 44, 45, 47). CCS have a high risk of experiencing symptomatic cardiac events at an early age and this risk remains high for at least 30 years, wherein almost one in eight will experience severe heart disease (68). Long term cardiotoxicity can manifest as myocardial ischemia, left ventricular dysfunction, heart failure, valvular disease, pericardial disease, or arrhythmias (69-75). Recent studies showed that the risk of cardiac disease increased with age, which is alarming given the young age of CCS (69).

Anthracyclines (doxorubicin, daunorubicin, mitoxantrone, epirubicin, and idarubicin), which are widely used as anticancer agents, and radiation therapy involving the heart are major treatment-related risk factors for cardiac disease among these patients (47, 70, 76-79). More than 50% of survivors who were treated with anthracyclines showed progressive cardiotoxicity (75, 80). Anthracycline principally damages cardiomyocytes directly, resulting ultimately in diffuse myocardial fibrosis (Figure 4). Anthracycline-induced cardiotoxicity ranges from subclinical ventricular dysfunction to severe cardiomyopathy and heart failure (72, 73). Risk factors for anthracycline cardiotoxicity in survivors include a younger age at treatment, increased time since primary cancer diagnosis, female sex, and higher cumulative doses(68). CCS can develop restrictive cardiomyopathy and left ventricular diastolic dysfunction, which could lead to heart failure.

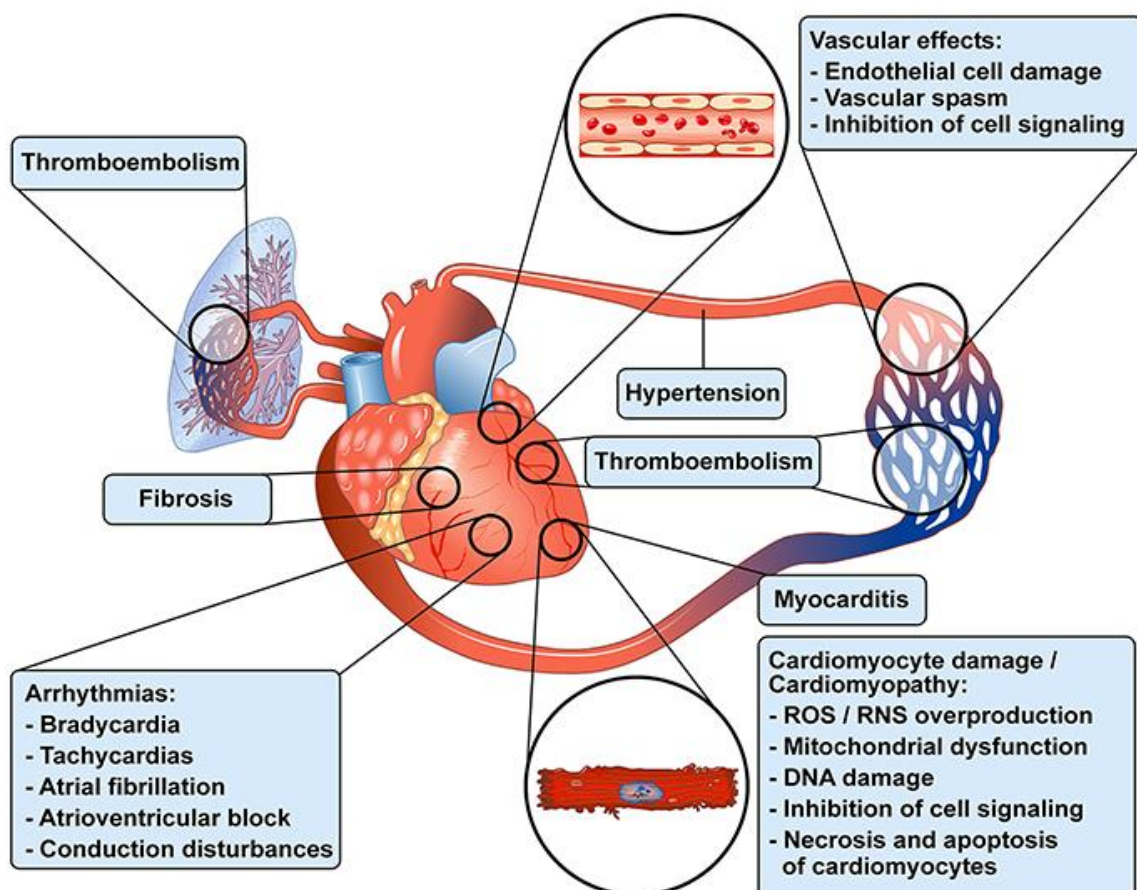


Figure 4. Schematic representation of some of the cardiovascular toxicities associated with antineoplastic drugs Varricchi et al. 2018 (81).

Furthermore, Survivors treated with radiation involving the heart were also found to have increased risks of heart failure, myocardial infarction, valvular dysfunction and pericardial diseases (69, 75). The major common mechanism of radiation-induced heart diseases is the formation of fibrosis and damaging the endothelium of myocardial capillaries leading to ischemia and ultimately myocardial fibrosis (82). Studies have shown that valves of patients exposed to mediastinal radiotherapy exhibit diffuse or focal leaflet fibrosis and thickening together with calcification (

Figure 5). The development of radiation-induced heart disease is slow and progressive, which would result in a long latency period between irradiation and the diagnosis of cardiac disease (82). Younger age at diagnosis is also a known risk factor for long-term radiation induced cardiac diseases (82).

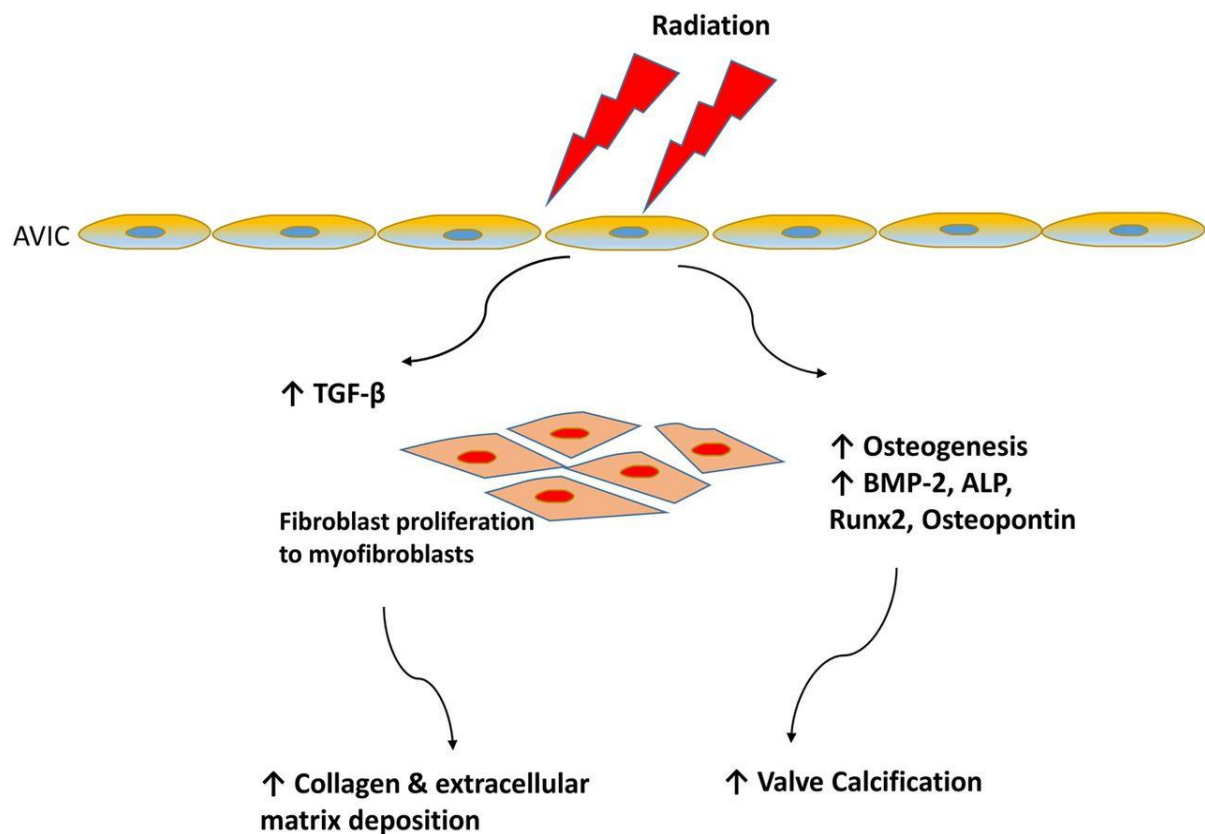


Figure 5. Pathophysiology of radiation-induced valve disease Gujral et al. 2015 (83)**3.4 Renal diseases and chronic kidney disease**

Long term renal disease in CCS is not well-documented as cardiac diseases and most of the studies only focused on survivors of nephroblastoma (84-90). According to a recent review study, the prevalence of chronic kidney disease (CKD) in CCS ranged between 2.4% and 32% (91). The St. Jude Lifetime Cohort Study also reported kidney dysfunction in 5% of adult cancer survivors (31). CCS were also found to have 3.3 fold higher risk of being hospitalized for CKD compared to the general population (92). Nephrotoxic chemotherapy, abdominal irradiation, and nephrectomy contribute to renal injury which can result CKD and eventually end stage kidney disease (ESKD). CKD is defined as kidney damage or Glomerular Filtration Rate (GFR) below 60 mL/min/1.73 m² for at least 3 months (94). GFR can be estimated from calibrated serum creatinine and estimating equations, such as the Modification of Diet in Renal Disease (MDRD) Study equation or the Cockcroft-Gault formula. Kidney disease severity is classified into five stages according to the level of GFR (95). Potentially nephrotoxic antineoplastic agents include ifosfamide and the platinum compounds cisplatin and carboplatin (93). These cancer treatments can cause acute kidney injury and/or carry the risk of irreversible damage and long-term CKD. Risk factors such as cumulative chemotherapy and radiotherapy doses, age at diagnosis of primary malignancy, duration of follow-up could also be related to the risk of long term renal disease in CCS (91, 94). Cisplatin, which is a platinum compound, is the most well-known nephrotoxic chemotherapy agent, and is cleared by the kidney by both glomerular filtration and tubular secretion. Multiple mechanisms are involved in renal dysfunction following exposure to cisplatin. These include tubular epithelial cell death in the form of necrosis or apoptosis, vasoconstriction in the renal microvasculature, and pro-inflammatory effects (31, 95). Ifosfamide which is an alkylating agent and could also cause tubulopathies

such as proximal tubular injury or Fanconi syndrome and nephrogenic diabetes (96). Studies have shown that ifosfamide and platinum toxicities persist during follow-up, even up to 10 years after treatment (30, 97). Other chemotherapies like cyclophosphamide and methotrexate could also cause renal diseases (30). Unilateral nephrectomy is also a risk factor for long-term CKD, causing hyper-filtration in unilateral nephrectomized survivors, which may ultimately lead to hypertension and glomerular impairment (91, 98). Radiotherapy is also a major risk factor for renal disease in CCS, however the long latency of radiation induced kidney disease and the presence of other confounding factors (ie nephrotoxic chemotherapy, cardiovascular comorbidities etc. have hindered the ability to understand the role of kidney radiation in the occurrence of long-term renal impairment (99). In CCS there are currently no studies that derived a dose response relationship based on irradiation dose to the kidneys. In a study on adult patients treated with radiotherapy, irradiation of the entire kidney with 20 Gy results in a marked reduction in size, associated with a significant reduction in renal function (100). Renal impairment is also a common adverse effect of hematopoietic cell transplantation (HCT) and the incidence of CKD among patients who received HCT ranged between 3% and 89% (101-103) and was approximately 16% in CCS (101). However, total body radiation (TBI) is the principal risk factor for post-HCT renal dysfunction (104, 105). Furthermore, comorbidities (ie heart failure, liver disease etc.) in CCS could also influence the development of renal dysfunction and CKD. Studies in the general population have found that decreased GFR was associated with a higher risk of CVDs such as heart failure and ischemic cardiac disease (106-108). However, both CKD and heart failure could coexist on the basis of shared risk factors or systemic disorders, and determining the distinction of which disease is primary and which is secondary may be challenging (109).

3.5 Long term follow-up for CCS

Because of the young age of these patients, and thus their potential long-life expectancy, CCS

require ongoing comprehensive care and long-term follow-up to monitor and treat the late effects that may occur as a result of their previous cancer therapies. Raising awareness about the adverse effects of childhood cancer treatments is crucial for both medical practitioners and survivors themselves to optimize their long-term outcome. Long-term follow-up of CCS and screening strategies should be individualized on the basis of previous therapeutic exposures, age at diagnosis, and specific therapeutic modality (110-112) and interdisciplinary , focusing on both preventing or managing late effects and educating survivors on these treatment-related adverse effects if to encourage healthy lifestyle behaviours. There are currently no randomized clinical trials on which recommendations for periodic screening in this population are based on. Therefore, recommended screening guidelines are generally based on the collective clinical experience and prospective studies that describe the late effects and identify demographic and treatment related risk factors. CCS cohorts provide opportunities to study lifetime risks, and shed light on all types of late effects and filling out the gaps in knowledge on very late disease outcomes that emerge in late adulthood. Moreover, as this growing population ages, only with ongoing observation of these survivors will we be able to characterize and describe the emerging long-term consequences of cancer therapies (111). Dose-response evaluations based on reconstructed radiation doses received by different organs and administrated chemotherapeutic regimes retrieved from medical records would allow for a better understanding of the long-term effects of these cancer treatments, and a better identifying of patients that are at an increased risk for late adverse effects, which is crucial for the concurrent development of screening and long-term follow-up recommendations.

Risk stratification is also essential to insure effective follow-up strategies and define the required level of care (113). The National Cancer Survivorship initiative (NCSI) suggested a system of risk stratification mainly based on the type of childhood malignancy and treatment received and ranges from level 1 to level 3 (114).

Level 1 and 2 patients could be discharged to a primary care physicians who should be aware of their treatment modalities. Level 3 patients with higher prevalence and grades late effects will need on-going specialist long term follow-up.

Table 2. Possible levels of follow-up more than five years from completion of treatment (114).

Level	Treatment	Method of follow-up	Frequency	Examples of childhood malignancies
1	<ul style="list-style-type: none"> • Surgery alone • Low risk chemotherapy 	Postal or telephone	1-2 years	Wilms Stage (stages <3) Gem cell tumours Langerhans cell histiocytosis (single system disease)
2	<ul style="list-style-type: none"> • Chemotherapy • Low dose cranial irradiation (<24Gy) 	Nurse (with late effects experience) or primary care-led	1-2 years	Majority of patients (e.g. All in first remission)
3	<ul style="list-style-type: none"> • Radiotherapy, except low dose cranial irradiation • Megatherapy 	Medically supervised late effects clinic	Annual	Brain tumours Post bone marrow transplantation Stage 4 patients (any tumour types)

4. Research hypothesis and objective

Knowledge of these adverse effects and their treatment related risk factors has resulted in modification of contemporary therapeutic strategies that will likely reduce the occurrence of late effects (115). Ongoing clinical evaluation of well-characterized cohorts is important if to advance knowledge about the influence of aging on morbidity and mortality in CCS, and to guide the development of health screening and risk-reducing interventions (116).

Long-term, follow-up studies have found that the risk of very late mortality among CCS was still higher than the general population even 45 years after diagnosis (45, 49). Recently, cause-specific late mortality in CCS has been investigated in many European countries (45, 46, 49, 117, 118) and in the USA (41-43). However, only one study in France has explored long term mortality in this population, and only focused on cardiovascular deaths (47). This study also didn't include survivors treated in more recent eras, who may have benefited from new treatment regimens and strategies. Patients included in that study were also five-fold more likely

to die of cardiovascular diseases and 5.8-fold more likely to die of cardiac diseases (47). The risk of cardiotoxicity after childhood cancer treatment has already been known for several decades (38); heart failure remains one of the most frequent late effects in CCS, contributing to significant morbidity and mortality (69, 75). Nevertheless, few studies have addressed the effect of the interaction between radiation and cardiotoxic chemotherapy (ie anthracycline) on the risk of heart failure in CCS. In addition, the radiation dose–volume effects in the heart and cardiac substructures have been explored only in a few studies on adult survivors of Hodgkin’s lymphoma. Therefore, the role of irradiated heart volumes in heart failure remains unclear, and the consequences of irradiating large parts of the heart with a lower dose vs. irradiating smaller parts of the heart with a higher dose need to be further investigated. Studies on the general population have found that decreased kidney function is an independent risk factor of cardiovascular disease, including heart failure (119), myocardial infarction, and stroke (120, 121) which is a major cause of premature mortality in patients with CKD (122). Early identification of CKD is crucial to prevent disease progression to end stage renal failure and reduce the risk of cardiovascular morbidity and mortality. Little is known on long-term renal disease in CCS. Several treatment-related risk factors linked to the development of late renal effects have been described in the literature, but these effects were often examined in small, selected study populations. Although larger cohort studies have recently investigated late kidney disease in CCS, very long-term follow-up studies are still lacking (91). Furthermore, studies inspecting the evolution of renal impairment to ESKD among CCS focused mainly on survivors of Wilm’s tumours (85, 90, 123) and found that ESKD was rare with a cumulative incidence less than 1%. Nonetheless, the outcome of CCS with ESKD related to cancer treatment remains unknown. Because these patients have a high risk of recurrence and secondary malignancies, CCS with ESKD they could be exposed a delay in enrolment in wait-lists and thus limited access to kidney transplant.

The present work aims at further understanding adverse cardiac and renal outcomes with particular focus on long-term, circulatory mortality, heart failure, and CKD in this population.

This thesis aims to address and examine the following:

- 1) Long-term cause-specific mortality, including mortality from cardiovascular diseases among 5-year survivors of childhood malignancies, and trends in excess mortality by causes and by treatment eras in the FCCSS cohort.
- 2) The effects of cardiotoxic chemotherapy and radiation dose volume of the heart and the left ventricle on the risk of heart failure in CCS.
- 3) The risk factors of long-term CKD in CCS and the role of nephrotoxic chemotherapy, irradiation dose and irradiated volume of the kidneys.
- 4) The incidence and outcome of ESKD related to nephrotoxic cancer treatment and radiation in the national population of France based on the renal epidemiology and information network REIN

Long term follow-up studies have found that the risk of very late mortality among CCS was still higher than the general population even 45 years after diagnosis (45, 49). Recently, cause specific late mortality in CCS have been investigated in many European countries (45, 46, 49, 117, 118) and in the USA (41-43). However only one study in France have explored long term mortality in this population and only focused on cardiovascular deaths (47). This study also didn't include survivors treated in more recent eras who may have benefited from new treatment regimens and strategies. Patients included in that study were also five-fold more likely to die of cardiovascular diseases and 5.8-fold more likely to die of cardiac diseases (47). The risk of cardiotoxicity after childhood cancer treatment has already been known for several decades (38), heart failure remains one of the most frequent late effects in CCS, contributing to significant morbidity and mortality (69, 75). Nevertheless, few studies have addressed the effect of the interaction between radiation and cardiotoxic chemotherapy (ie anthracycline) on the risk of heart failure in CCS. In addition, the radiation dose–volume effects in the heart and cardiac

substructures have been explored only in a few studies on adult survivors of Hodgkin's lymphoma. Therefore, the role of irradiated heart volumes in heart failure remains unclear, and the consequences of irradiating large parts of the heart with a lower dose vs. irradiating smaller parts of the heart with a high dose need to be further investigated. Studies in the general population have recognized that decreased kidney function is an independent risk factor cardiovascular disease including heart failure (119), myocardial infarction and stroke (120, 121) which is a major cause of premature mortality in patients with CKD (122). Early identification of CKD is crucial to prevent disease progression to end stage renal failure and reduce the risk of cardiovascular morbidity and mortality. Little is known on long term renal disease in CCS. Several treatment-related risk factors linked to the development of late renal effects have been described in the literature, but these effects were often examined in small, selected study populations. Although larger cohort studies have recently investigated late kidney disease in CCS, very long-term follow-up studies are still lacking (91). Furthermore, studies inspecting the evolution of renal impairment to ESKD among CCS focused mainly on survivors of Wilm's tumours (85, 90, 123) and found that ESKD was rare with a cumulative incidence less than 1%. Nonetheless, the outcome of CCS with ESKD related to cancer treatment remains unknown. Because these patients have a high risk of recurrence and secondary malignancies, CCS with ESKD they could be exposed a delay in enrolment in wait-lists and thus limited access to kidney transplant.

The present work aimed at further understanding of adverse cardiac and renal outcomes after focusing particularly on long term circulatory mortality, heart failure and CKD in this population. This thesis aims to address the following:

- 1) To investigate long-term cause-specific mortality including mortality from cardiovascular diseases among 5-year survivors of childhood malignancies and to assess trends in excess mortality by causes and by treatment eras in the FCCSS cohort.

- 2) To examine the effects of cardiotoxic chemotherapy and radiation dose volume of the heart and the left ventricle on the risk of heart failure in CCS.
- 3) To study the risk factors of long-term CKD in CCS and the role of nephrotoxic chemotherapy, irradiation dose and irradiated volume of the kidneys.
- 4) To study the incidence and outcome of ESKD related to nephrotoxic cancer treatment and radiation in the national population of France based on the renal epidemiology and information network REIN

5. Thesis Framework

This thesis comprises a total of seven chapters. In chapter II it describes the two data used for this study: the FCCSS cohort and the REIN registry. Chapter III of the thesis explores long-term mortality among CCS. This includes studying cause-specific mortality in this population along with deaths by cardiovascular causes and the trends of cause-specific mortality by treatment era. In chapter IV, we investigate the risks of heart failure in CCS and explore the role of the interaction between cardiac radiation and anthracycline. Chapter V focuses on the long-term risk of CKD in CCS and its related risk factors in CCS, exploring the role of nephrotoxic chemotherapy, radiation involving the kidneys, and nephrectomy. Chapter VI studies the incidence and outcome of patients with ESKD related to nephrotoxic chemotherapy and radiation in the national registry REIN.

Chapter II. Data sources

Data from two sources were used for the analysis of this thesis, the French Childhood Cancer Survivor Study (FCCSS) and the national French Renal Epidemiology and Information Network (REIN).

1. The French Childhood Cancer Survivor Study (FCCSS)

1.1 Cohort definition

Data from the FCCSS cohort was used for investigations into (i) cause specific mortality among 5-year survivors of childhood malignancies in France (ii) the role of anthracycline and cardiac radiation in the occurrence of heart failure in CCS (iii) the risk of CKD among CCS studying the impact of radiation involving the kidneys and chemotherapy.

The FCCSS cohort includes 5-year childhood cancer survivors (CCS) treated from 1942 to 2000 for solid cancer or lymphoma before the age of 20 years (Figure 6). The FCCSS combines data from Euro2K cohort (i.e. patients diagnosed between 1942 and 1985 in 5 cancer centers in France: Gustave Roussy, Curie Institut, Jean Godinot Institut, Antoine Lacassagne cancer center and Claudius Régaud center) and its extension (i.e. patients treated between 1986 and 2000 in 2 cancers centers in France: Gustave Roussy and Curie Institute)

The FCCSS protocol has been approved by the INSERM national ethics committee and the French National Agency regulating Data Protection (CNIL). Consent was obtained from patients, parents or guardians according to national research ethics requirements. Since 2005, a self-report questionnaire covering a range of adverse health events was sent to living patients who had returned a written informed consent form, and whose addresses were available through the national health insurance system. By 2019, a total of 3293 had responded. The FCCSS data was also linked to the French nationwide healthcare data system (SNDS) providing data for a decade of follow-up from 2006 until 2016. Data from SNDS contains outpatient data: date of reimbursed drugs dispensation, medical and paramedical acts and attribution and type of long-

term diseases coded according to the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) linked with hospitalization data from “medicalized information system program” (PMSI) which include information regarding the admission date, duration and the main and related associated coded ICD-10. Information on universal complementary health insurance (CMUC) for people with low income are also available. A total of 1092 (14.2%) of patients included in the FCCSS cohort attended the long-term follow-up clinic for patients treated at Gustave Roussy which started in 2012. Causes of death for deceased patients, coded according to the ICD 9th and 10th revisions were obtained from the epidemiological Center on the Medical Causes of death (CépiDc).

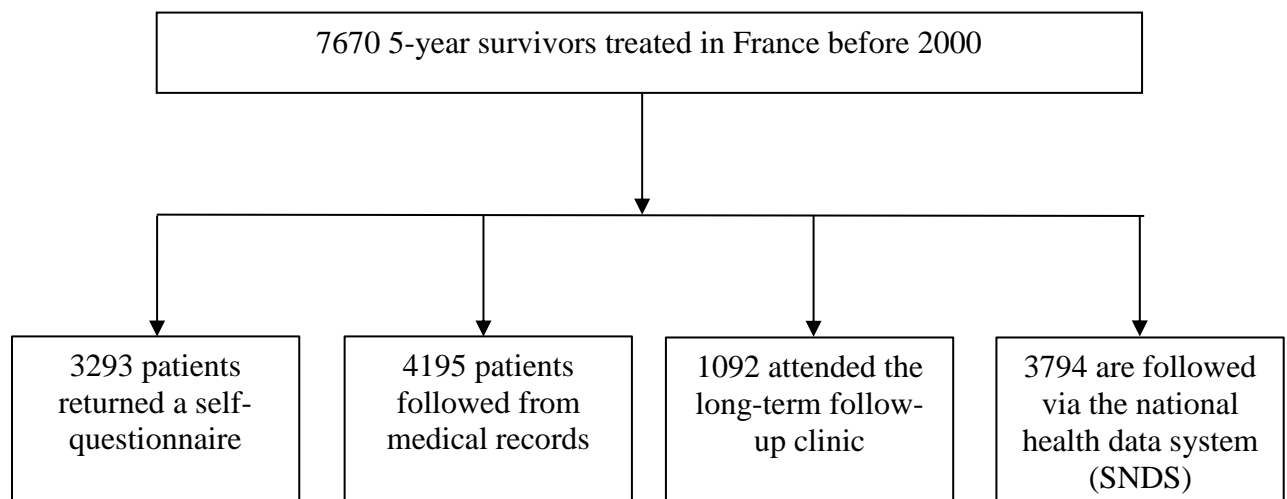


Figure 6. Diagram of the FCCSS cohort.

Table 3. Demographic characteristics of the patients included in the FCCSS cohort.

Characteristics	N=7670	(%)
Sex		
Male	4201	(54.8)
Female	3469	(45.2)
Centers		
Gustave Roussy, Villejuif	5504	(71.8)
Curie Institut, Paris	1917	(25.0)
Centre Antoine Godinot, Nice	15	(0.2)
Jean Godinot Institut, Reims	75	(1.0)
Centre Claudius Regaud, Toulouse	159	(2.0)
Type of primary childhood malignancy		
Hodgkin lymphoma	490	(6.4)
Non-Hodgkin lymphomas	790	(10.3)
CNS tumours	1140	(14.9)
Neuroblastoma and other peripheral nervous cell tumours	1036	(13.5)
Retinoblastoma	619	(8.1)
Renal tumours	1138	(14.8)
Malignant bone tumours	710	(9.3)
Soft tissue and other extrasosseous sarcomas	837	(10.9)
Germ cell tumours	469	(6.1)
Other	441	(5.7)
Age at primary cancer diagnosis, years		
Median (Range)	5.2 (0-20.6)	
Age at primary cancer diagnosis, years		
<1	1241	(16.2)
1-4	2485	(32.4)
5-9	1679	(22.0)
10-14	1624	(21.0)
≥15	641	(8.4)
Year of primary cancer diagnosis, year		
Median (Range)	1986 (1946-2000)	
Follow-up		
Median (Range)	24.4 (5.0-67.8)	
Vital status		
Alive	6471	(84.4)
Dead	1199	(15.6)

1.2 Data collection

Demographic data, clinical and histopathologic characteristics of the childhood cancer and detailed information on treatments, were extracted from medical charts. Tumours are classified according to the International Classification of Childhood Cancer (ICCC), 3rd edition (124).

1.3 Treatment characteristics

1.3.1 Chemotherapy

Antineoplastic drugs were classified according to their known mechanisms of action in the cell: antimetabolites, alkylating agents, Topoisomerase II inhibitors, Spindle poison, vinca alkaloids, cytotoxic enzyme, topoisomerase I inhibitors, tyrosine kinase inhibitors and other.

Description of chemotherapy drugs in the FCCSS cohort is presented in Table 4, data on was extracted from medical charts (type of drugs, dose, body surface area, routes of administration etc.).

Table 4. Description of chemotherapy drugs in the FCCSS cohort.

Type of chemotherapy	Drug name	Total Cohort (n=7670) N (%)
Antimetabolites	Methotrexate	1135 (14.8)
	Cytarabine	757 (9.9)
	Thioguanine	191 (2.5)
	Hydroxyurea	230 (3.0)
	Mercaptopurine	95 (1.2)
	Fluorouracil	54 (0.7)
	Methylguanine	27 (0.4)
	Fufol	8 (0.1)
Alkylating agents	Cyclophosphamide	2813 (36.7)
	Cisplatine	1052 (13.7)
	Carboplatine	1108 (14.4)
	Ifosfamide	945 (12.3)
	Melphalan	351 (4.6)
	Lomustine-CCNU	298 (3.9)
	Procarbazine	715 (9.3)
Busulfan	228 (3.0)	

Type of chemotherapy	Drug name	Total Cohort (n=7670) N (%)
	Carmustine-BCNU	245 (3.2)
	Dacarbazine	172 (2.2)
	ThioTepa	118 (1.5)
	Caryolisine	287 (3.7)
	Temodal	57 (0.7)
	Chlorambucil	19 (0.2)
	Degranol	4 (0.1)
	Oxaliplatine	10 (0.1)
	Fotemustine	6 (0.1)
Topoisomerase II inhibitors	Actinomycine	2162 (28.2)
	Etoposide	1585 (20.7)
	Rubidomycine	141 (1.8)
	Teniposide	163 (2.1)
Anthracyclines	Adriamycine	2485 (32.4)
	Epiadriamycine	231 (3.0)
	Epirubicine	140 (1.8)
	Mitoxantrone C	14 (0.2)
Vinca Alakloids	Vincristine	4098 (53.4)
	Vinblastine	487 (6.3)
	Vindesine	113 (1.5)
	Navelbine	43 (0.6)
	Paclitaxel	10 (0.1)
Cytotoxic enzyme	Asparaginase	315 (4.1)
Topoisomerase I inhibitors	Irinotecan	29 (0.4)
Tyrosine kinase inhibitors	Imatinib	11 (0.1)
Other and unspecified	Bleomycine	550 (7.2)
	Interleukine	16 (0.2)
	Interféron alpha	10 (0.1)
	Rufomycine	7 (0.1)
	Vaccin	5 (0.1)

1.3.2 Radiotherapy

Radiation dose estimation was based on the use of a voxel-based anthropomorphic phantom to generate for each subject a surrogate whole-body radiotherapy planning computed tomography according to gender, age, weight and height. As a result, a specific phantom anatomy is generated as a surrogate for each individual patient depending on gender, age, and treatment position (125) (Figure 7).

Reconstitutions of the radiotherapy plans were made with the Isogray (Dosisoft, Cachan, France) treatment planning system which enabled computations of doses and dose-volume histograms to different organs in the body (

Figure 8). Because dose estimates were based on individual treatment parameters, the accuracy of the dose reconstructions may depend on medical charts. Complete documentation, including some imaging data, was available for $\approx 93\%$ of patients. Information on radiation therapy techniques and their combination with other modalities was also available (Figure 9) (Table 6).

Table 5. Temporal changes in radiotherapy techniques used for treatment of the primary childhood malignancy.

Radiotherapy technique	<1970 n=565 N (%)	1970-1979 n=1181 N (%)	1980-1989 n=1260 N (%)	1990-2000 n=1232 N (%)	Overall n=4238 N (%)	<i>P</i>
Kilovoltage (kV)	248 (44.0)	13 (1.1)	1 (0.1)	2 (0.2)	264 (6.2)	<.0001
Cobalt	180 (31.8)	875 (74.1)	543 (43.1)	65 (5.3)	1663 (39.2)	
Linear accelerator photon beam	85 (15.0)	132 (11.2)	465 (36.9)	869 (70.5)	1551 (36.6)	
Linear accelerator electron beam	29 (5.1)	108 (9.1)	84 (6.7)	61 (4.9)	282 (6.6)	
Other	23 (4.1)	53 (4.5)	167 (13.2)	235 (19.1)	478 (11.3)	

Other radiotherapy techniques include brachytherapy, iodine nanoparticle radiotherapy

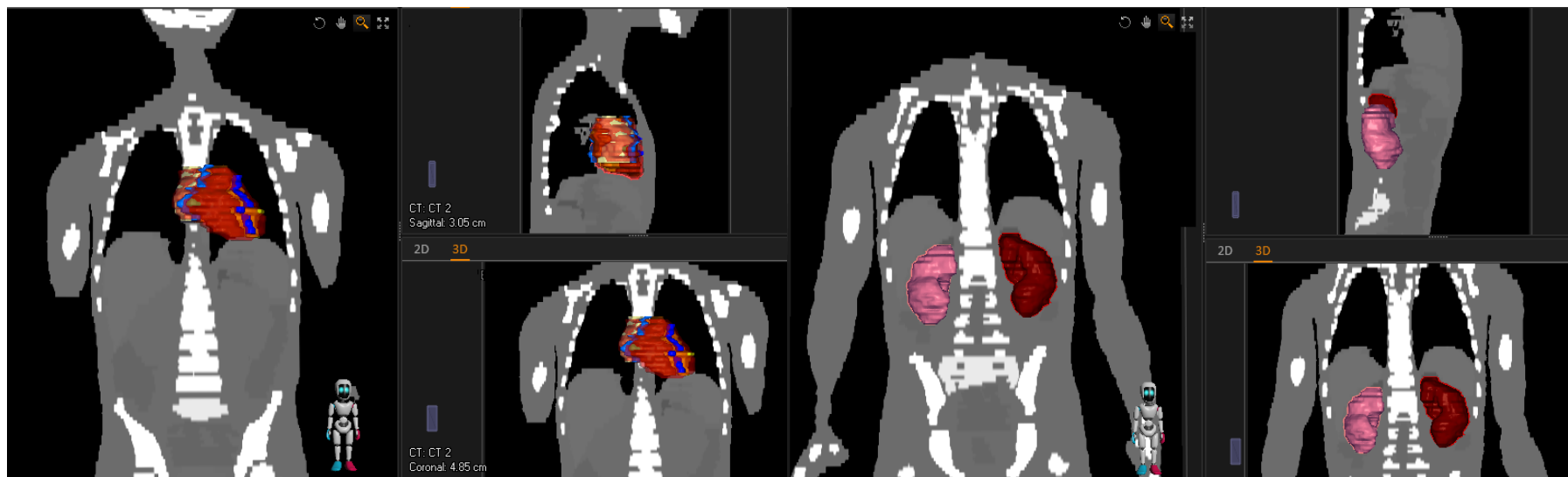


Figure 7. 3D representation of the heart and kidneys in patient's phantom.

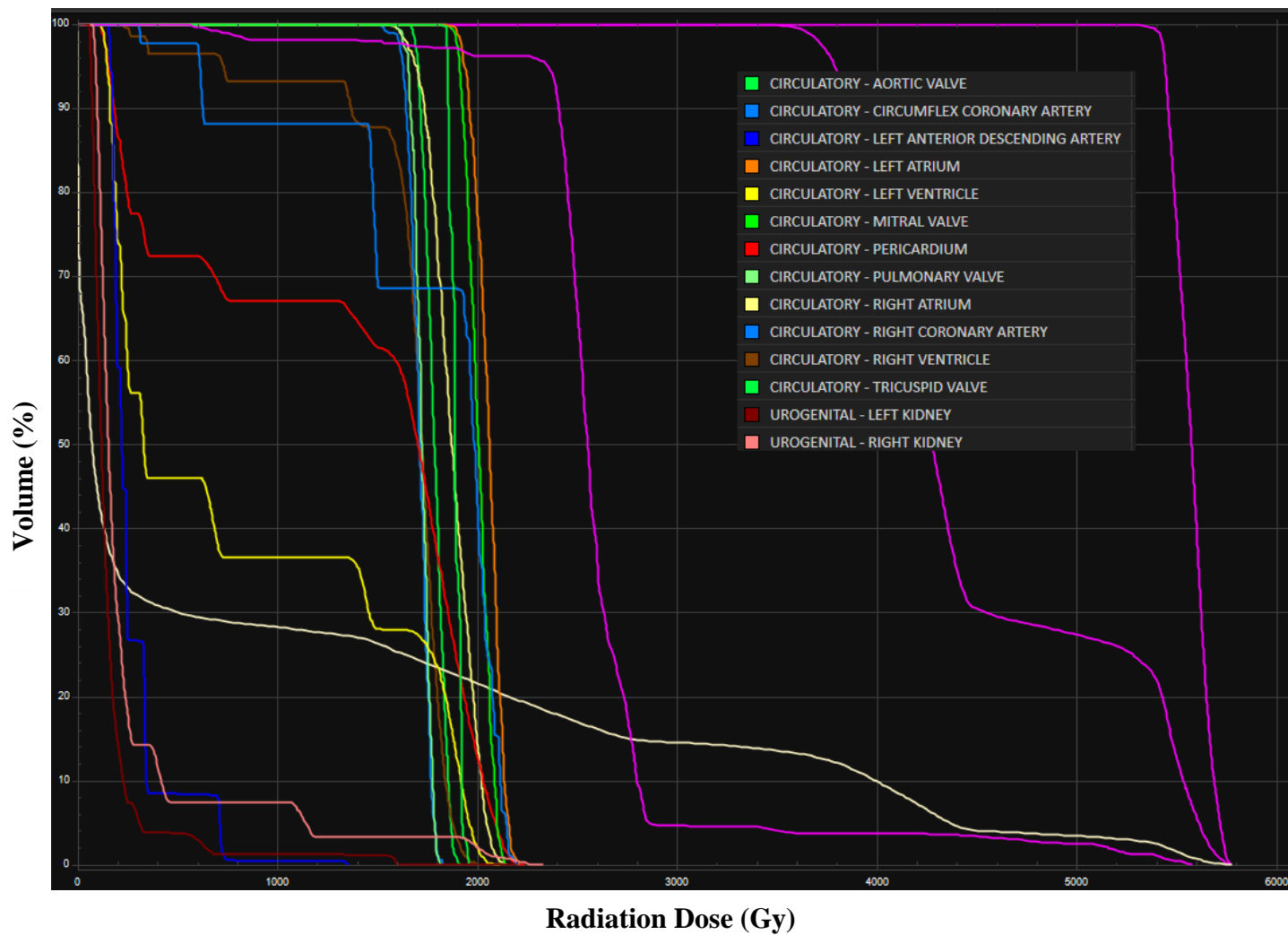


Figure 8. Dose volume histograms for the heart, cardiac substructures and the kidneys.

Table 6. Evolution of types of childhood malignancies and treatments by period in the FCCSS cohort.

Characteristics	<1970		1970-1979		1980-1989		1990-2000		Overall	
	n=658	N (%)	n=1549	N (%)	n=2483	N (%)	n=2980	N (%)	N=7670	N (%)
Type of primary childhood malignancy										
Hodgkin lymphoma	44	(6.7)	117	(7.6)	151	(6.0)	178	(6.0)	490	(6.4)
Non-Hodgkin lymphomas	39	(5.9)	151	(9.7)	345	(13.9)	255	(8.6)	790	(10.3)
CNS tumors	92	(14.0)	242	(15.6)	373	(15.0)	433	(14.5)	1140	(14.9)
Neuroblastoma and other peripheral nervous cell tumors	97	(14.7)	203	(13.1)	344	(13.9)	392	(13.2)	1036	(13.5)
Retinoblastoma	21	(3.2)	58	(3.7)	149	(6.0)	391	(13.1)	619	(8.1)
Renal tumors	180	(27.3)	325	(21.0)	330	(13.3)	303	(10.2)	1138	(14.8)
Malignant bone tumors	42	(6.4)	106	(6.8)	233	(9.4)	329	(11.0)	710	(9.3)
Soft tissue and other extraosseous sarcomas	75	(11.4)	190	(12.3)	278	(11.2)	294	(9.9)	837	(10.9)
Germ cell tumors	34	(5.2)	89	(5.7)	156	(6.3)	190	(6.4)	469	(6.1)
Other	34	(5.2)	68	(4.4)	124	(5.0)	215	(7.1)	441	(5.7)
Surgery only, N(%)										
Yes	44	(6.7)	124	(8.0)	226	(9.1)	477	(16.0)	871	(11.4)
Chemotherapy only, N(%)										
Yes	3	(0.4)	30	(1.9)	159	(6.4)	188	(6.3)	380	(5.0)
Radiotherapy only, N(%)										
Yes	25	(3.8)	55	(3.6)	69	(2.8)	37	(1.2)	186	(2.4)
Chemotherapy + radiotherapy, N(%)										
Yes	323	(49.1)	920	(59.4)	951	(38.3)	1040	(34.9)	3234	(42.2)
Chemotherapy + surgery, N (%)										
Yes	350	(53.2)	974	(62.9)	1605	(64.6)	1890	(63.4)	4819	(62.8)
Radiotherapy + surgery, N (%)										
Yes	521	(79.2)	968	(62.5)	1020	(41.1)	982	(33.0)	3491	(45.5)
Radiotherapy + chemotherapy+ surgery, N (%)										
Yes	304	(46.2)	762	(49.2)	780	(31.4)	827	(27.8)	2673	(34.9)
Any surgery, N(%)										
Yes	611	(92.9)	1304	(84.2)	2071	(83.4)	2522	(84.6)	6508	(84.9)
Any chemotherapy, N(%)										
Yes	372	(56.5)	1162	(75.0)	1935	(77.9)	2291	(76.9)	5760	(75.1)
Any radiotherapy, N(%)										
Yes	565	(85.9)	1181	(76.2)	1260	(50.7)	1232	(41.3)	4238	(55.3)

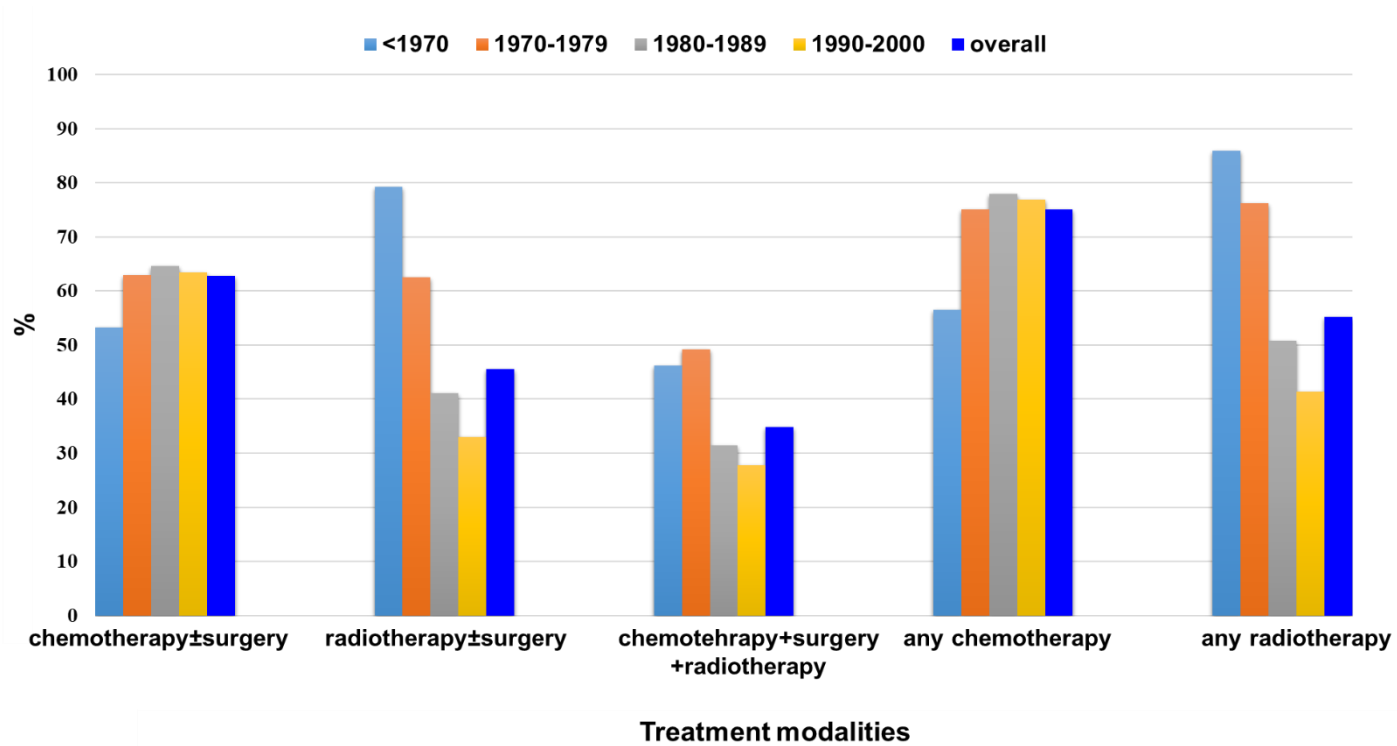


Figure 9. Temporal changes in treatment modalities, overall and by treatment era, described in the FCCSS study.

2. The National French Renal Epidemiology and Information Network (REIN)

2.1 Population

Data from the national REIN registry was used to investigate the incidence and outcomes of patients with ESKD related to nephrotoxic chemotherapy, radiation and urinary tract cancers.

The REIN registry was founded in 2001 with the aim of providing tools to evaluate renal replacement therapy practices and outcomes, and to support public health decisions related to ESKD (126). The registry relies mainly on a network of nephrologists, epidemiologists, patients and public health representatives, coordinated regionally and nationally.

The REIN registry covers all dialyzed and transplanted patients in France and incident patients are reported since the first day of dialysis or kidney transplantation, patients with acute renal failure are not included. Causes of ESKD are coded according to the thesaurus of the French-language Society of Nephrology based upon the ICD-10.

In 2012, in France, 9 710 patients started a treatment by dialysis (incidence of dialysis: 149 per million inhabitants and 338 patients with a pre-emptive graft without previous dialysis (incidence of pre-emptive graft: 5 pmp), with an overall incidence of 154 pmp increasing 0.5% annually (

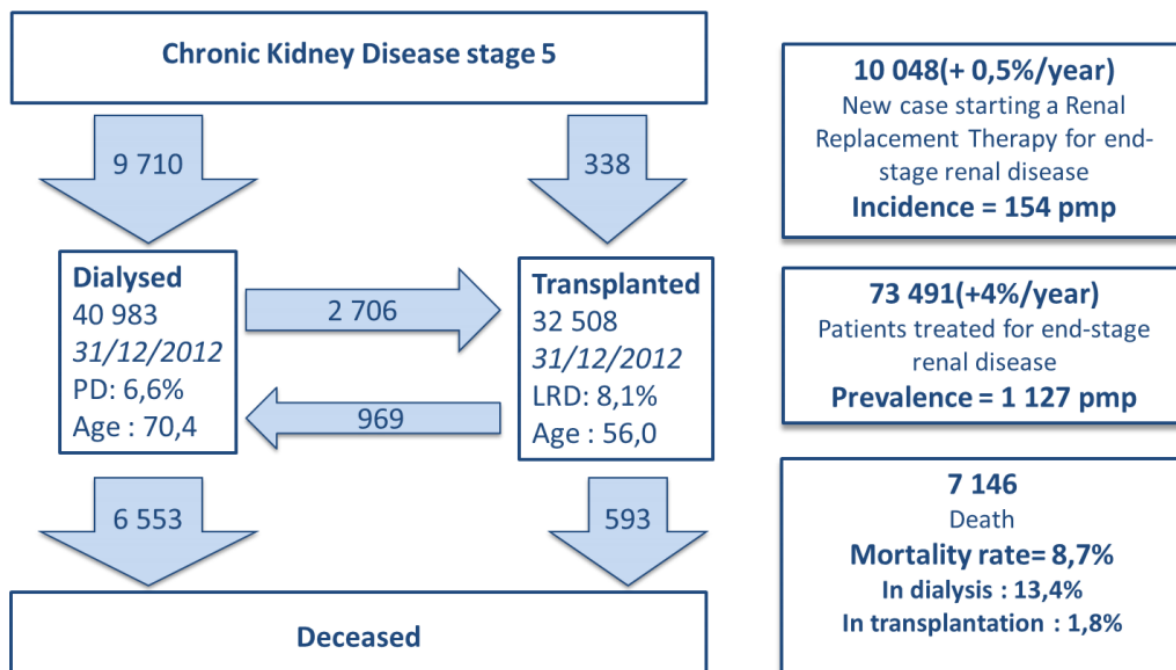
Figure 10).

Since 2005 the number of new patients with ESKD treated with dialysis or transplant has been steadily growing by 2.2% per year (128).

2.2 Clinical and demographic data

REIN contains demographics and clinical data including type and duration of dialysis (ie hemodialysis, peritoneal dialysis etc.), placement on the French national renal transplant waiting list and contradiction of wait listing, access to kidney transplant with a living or deceased donor and kidney transplant failure leading to return to dialysis. Patients are placed on the list by a nephrologist after assessment of their medical status.

Information on comorbidities are also available in the registry and included diabetes, chronic respiratory disease, cardiovascular coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure, and dysrhythmia.



LRD, living related donation

PD, peritoneal dialysis

In 2012, in France, 9 710 patients started a treatment by dialysis and 338 patients with a pre-emptive graft without previous dialysis, with an overall incidence of 154 pmi

Figure 10. Summary of REIN annual report in 2012 in France according to REIN registry data (127).

Chapter III. Cause specific mortality in childhood cancer survivors

1. Context

Although 5-year survival rate for childhood malignancies has significantly increased (129), survivors of childhood cancer are still at risk of late and mortality. In previous studies, CCS were found to be 8.4 to 10.8 times more at risk of dying than expected in the general population even after 25 years from the primary cancer diagnosis (41, 42, 44, 45, 48, 55). These studies also identified a higher risk of mortality related to recurrence or progression, subsequent primary neoplasms and circulatory disease which persisted up to beyond 30 years from diagnosis of childhood malignancy (42-45, 130). This continuous increased excess mortality due to causes other than the recurrence of primary cancer, are recognized as late effects of treatment and it is suggested that more intensive treatment regimens may lead to increased mortality later in life from causes other than the primary cancer (48). The overall pattern of late mortality among childhood cancer survivors has been investigated in studies in Europe and in the USA (43, 45, 48). These studies have found a generally a decrease in long term mortality for patients treated in recent treatment periods. However there are some conflicting data, overall mortality and all cause specific mortality decreased in the CCSS (41) while mortality from subsequent primary neoplasms wasn't found to be decreasing in the BCCSS (45). Only one study explored long term mortality among CCS in France and didn't study mortality trends or include those treated in recent treatment eras (47). The aims of the present research were to complete the gaps of that previous study within the extended FCCSS cohort, which now includes 7670 patients treated up to 2000, by investigating long-term cause-specific mortality among 5-year survivors of childhood malignancies in France and assessing trends in excess mortality by causes and by treatment eras.

2. Methods

2.1 Study population

The FCCSS cohort (<https://fccss.fr>) includes 7670 5-year survivors of childhood cancers who were treated before the age of 21 years, between 1942 and 2000 for any type of childhood malignancy, except leukemia in different centers in France (Table 3).

Patients were followed via self-questionnaire, access to medical records, cohort linkage with the French National Health Data System (SNDS) database and, long term follow-up clinic for patients treated in Gustave Roussy (Figure 6). Demographic information, tumor characteristics and information on cancer treatments data were extracted from medical charts (Table 4) (Table 6).

2.2 Ascertaining causes of death

Data on vital statistics were obtained by matching FCCSS patients to the National Identification Repertory. Causes of death among CCS were ascertained by linking the FCCSS cohort with The French National Mortality Database (INSERM CepiDC) (<https://www.cepidc.inserm.fr/>) for patients who were living and died in France. The CepiDC provided underlying and associated causes of death for all deceased patients but 125 (10.4%). Causes of death were coded according to the 9th and 10th revisions of the International Classification of Diseases (ICD-9 and ICD-10).

Causes of death were classified as per the Causes of Death, European Shortlist of May 2012 (131), into the following subgroups: infectious and parasitic diseases (A00-B99), neoplasms (C00-D48), diseases of the blood and blood forming organs (D50-D89), , endocrine disorders (E00-E89), circulatory diseases (I00-I99); respiratory diseases (J00-J99), digestive system diseases (K00-K92), skin diseases (L00-L9), mental disorders (F01-F99), diseases of the musculoskeletal system and connective tissue (M00-M99), diseases of genitourinary system

(N00-N99), symptoms, complications of pregnancy, childbirth and puerperium (O00-O99), congenital malformations (Q00-Q99), ill-defined causes (R00-R99), and external causes of morbidity and mortality (V01-Y89). Whenever the underlying cause of death was neoplastic, medical records were examined to decide whether the death was related to recurrence or progression of the primary cancer, or to a secondary primary neoplasm.

Follow-up of cohort members started at the date of 5-year after the initial childhood cancer diagnosis. The cohort exist date for this study was December 31, 2013, with earlier exits at death or loss to follow-up. In accordance with French regulations, the protocol of the study has been approved by the National Commission on Informatics and Liberty.

3. Statistical analysis

Cumulative Mortality was estimated for different causes of death and stratified according to treatment era using attained age as time scale. Causes of death other than the ones under study were treated as competing risks according to the Aalen-Johansen method (132). Gray's test was used to compare the cumulative incidence functions (133).

Standardized mortality ratios (SMRs) were calculated as the ratio observed to the expected numbers of different causes of death. Absolute Excess Risks (AERs) per 10 000 per year were calculated as the observed minus the expected number of deaths over the total number of person years, multiplied by 10 000. To derive the expected number of deaths used in the calculation of the SMR and AER, person-years for each sex-specific, age specific (5-year period), and calendar year-specific (1-year bands) stratum were multiplied by the corresponding mortality rate for the population of France and then summed across the strata. Derivation of SMRs for deaths related to recurrence or progression of the primary malignancy was not possible because there was no corresponding death in the general population.

Excess Mortality Ratio (EMR) related to treatment era among the study participants was estimated using a modified Poisson regression model as suggested by Dickman et al. (134).

Data from individual records were aggregated by stratum to yield a count of deaths by year, sex and age and then included in the model by calendar year and then a generalized linear model with a Poisson error structure based on aggregated data using exact survival time (person-years) was fitted for each treatment era.

A stratum j represents then a combination between the year of death and the previously mentioned variables. The number of observed events o_j , are the realizations of the random variable O_j which follows a poisson distribution with a mean $\mu_j = PA_j \lambda_j$.

$O_j \sim \text{Poisson}$ with PA_j as the number of person-years (sum of the observations for each individual in the stratum) and λ_j as the death rate.

This model quantifies the extent to which the excess risk of death in a given period differs from the excess risk of death in the reference period (<1970) after controlling for sex, type of primary malignancy, age at diagnosis and attained age. The EMR in the period <1970 was set to a value of 1.0. An EMR less than 1 in another period indicates that the excess risk of death in that period was less than that in the reference period, and vice versa, 95% CIs for the EMRs were calculated using the estimated coefficients and standard errors from the Poisson models. To test for heterogeneity or trend, likelihood ratio tests within Poisson regression models were used.

A $P \leq 0.05$ was statistically significant and all analyses were performed using SAS[®] version 9.4.

4. Results

4.1 Study patients

This study included 7670 patients who were diagnosed of their primary malignancies between 1946 and 2000 and were followed for a median of 24.4 years (IQR 17.2-33.0) (Table 7). These patients provided a total of 195 822 person-years of observation. A total of 1199 patients (15.6%) were deceased by the end of follow-up. A total of 460 deaths (38.4%) were related to

the primary malignancy, 309 to subsequent primary neoplasms (25.8%) and 73 (6.1%) to circulatory diseases.

Among deceased patients the most common type of primary malignancy was central nervous system tumours (CNS) (32.4%). Overall, 38.9% of the FCCSS patients were treated for their primary cancer in the 90s era and only 8.6% were treated before 1970 (Table 7).

Table 7. Characteristics of patients in the FCCSS study.

Characteristics	Dead	Alive	Total
	N=1199 N (%)	N=6471 N (%)	N=7670 N (%)
Sex			
Male	674 (56.2)	3527 (54.5)	4201 (54.8)
Female	525 (43.8)	2944 (45.5)	3469 (45.2)
Type of primary cancer			
Hodgkin lymphoma	101 (8.4)	389 (6.0)	490 (6.4)
Non-Hodgkin lymphomas	61 (5.1)	729 (11.3)	790 (10.3)
CNS tumours	388 (32.4)	752 (11.6)	1140 (14.9)
Neuroblastoma and other peripheral nervous cell tumours	108 (9.0)	928 (14.3)	1036 (13.5)
Retinoblastoma	51 (4.3)	568 (8.8)	619 (8.1)
Renal tumours	139 (11.6)	999 (15.4)	1138 (14.8)
Malignant bone tumours	120 (10.0)	590 (9.1)	710 (9.3)
Soft tissue and other extraosseous sarcomas	127 (10.6)	710 (11.0)	837 (10.9)
Germ cell tumour	40 (3.3)	429 (6.6)	469 (6.1)
Other	64 (5.3)	377 (5.8)	441 (5.7)
Age at diagnosis, years			
<5	484 (40.4)	3242 (50.1)	3726 (48.6)
5-9	316 (26.4)	1363 (21.1)	1679 (21.9)
10-14	308 (25.7)	1316 (20.3)	1624 (21.2)
≥15	91 (7.6)	550 (8.5)	641 (8.4)
Years from cancer diagnosis, years			
5-9	376 (31.4)	97 (1.5)	473 (6.2)
10-19	303 (25.3)	1933 (29.9)	2236 (29.2)
20-29	246 (20.5)	2192 (33.9)	2438 (31.8)
30-39	185 (15.4)	1582 (24.4)	1767 (23.0)
≥40	89 (7.4)	667 (10.3)	756 (9.9)
Attained age, years			
5-19	401 (33.4)	802 (12.4)	1203 (15.7)
20-29	346 (28.9)	1814 (28.0)	2160 (28.2)
30-39	228 (19.0)	2185 (33.8)	2413 (31.5)
40-49	164 (13.7)	1243 (19.2)	1407 (18.3)
≥50	60 (5.0)	427 (6.6)	487 (6.3)
Treatment period			

Characteristics	Dead	Alive	Total
	N=1199 N (%)	N=6471 N (%)	N=7670 N (%)
<1970	251 (20.9)	407 (6.3)	658 (8.6)
1970-1979	396 (33.0)	1153 (17.8)	1549 (20.2)
1980-1989	340 (28.4)	2143 (33.1)	2483 (32.4)
1990-2000	212 (17.7)	2768 (42.8)	2980 (38.9)
Chemotherapy			
No	297 (28.8)	1613 (24.9)	1910 (24.9)
Yes	902 (75.2)	4858 (74.1)	5760 (75.1)
Anthracycline			
No	800 (66.8)	3953 (61.1)	4753 (62.0)
Yes	399 (33.2)	2518 (38.9)	2917 (38.0)
Radiotherapy			
No	182 (15.2)	3250 (50.2)	3432 (44.7)
Yes	1017 (84.8)	3221 (49.8)	4238 (55.3)
Cranial radiation			
No	732 (61.0)	5311 (82.1)	6043 (78.8)
Yes	467 (39.0)	1160 (17.9)	1627 (21.2)

4.2 Overall mortality

Survivors experienced 8.2 times (95% CI, 7.7-8.6) more deaths than that expected from the general population, which corresponded to 53.7 (95% CI, 50.6-57.1) excess deaths per 10 000 person years (Table 8).

The CM of death by any cause after 10 years from cancer diagnosis was 2.7% among patients treated before 1970, 6.0% among those treated in the 70s, 5.3% for patients treated in the 80s and 4.6% among those treated in the 90s. Although the cumulative incidence of all causes at 10years from cancer diagnosis didn't seem to be decreasing in more recent treatment eras, the decrease in long term global mortality was obvious at 20 years from cancer diagnosis as the CM went from 10.4% for patients treated in the 70s to only 7.8% for CCS treated in the 90s.

4.2.1 Cause specific mortality in the FCCS study cohort

AERs were significantly increased for all causes of death, except for death related to blood disorders, skin disease, musculoskeletal disease and pregnancy and childbirth (Table 8). In terms of AERs, survivors were most at risk of dying from subsequent primary neoplasm (AER, 23.5; 95% CI, 21.4-25.7) followed by recurrence or progression of primary neoplasm (AER, 14.3; 95% CI, 12.7-16.0). Among non-neoplastic causes the highest AER was attributed to circulatory diseases (AER, 3.1; 95% CI, 2.4-4.0) (Table 8).

4.2.2 Mortality from recurrence or progression

A total of 460 deaths were attributed to recurrence or progression of the primary malignancy which translated to 14.3 extra deaths per 10 000 person-year (Table 8). Mortality from recurrence or progression was the highest among patients with CNS and brain tumours presenting 73.2 excess deaths per 10 000 person years followed by malignant bone tumours with a total of 40.2 excess deaths per 10 000 person years. Furthermore, mortality related to recurrence of the primary malignancy decreased significantly by attained age (P trend <0.0001), the AERs for went from 23.8 (95% CI 21.0-27.1) for patients aged under 20 years to 26.0 (95% CI 12.4-54.6) for those aged ≥ 50 years.

However, the AERs of death related to mortality from the primary neoplasm didn't seem to decrease for patients treated in recent eras. (P trend 0.17). At 20 years after cancer diagnosis the CM of mortality from the primary malignancy was 4.2%, 6.6%, 4.0% and 4.8% across the 4 different treatment eras respectively (Table 9) (Figure 11).

4.2.3 Mortality from subsequent primary neoplasms

Survivors of childhood cancer were 10.3 times (95% CI 9.2 to 11.5) more at risk of death from subsequent primary neoplasm than expected in the general population (Table 8). Survivors of

CNS and brain tumours had the highest AER of mortality by subsequent primary neoplasms (AER=25.6 95% CI 20.1-32.5) followed by Hodgkin lymphoma (AER=20.0 95% CI 13.5-29.7) (Table 10).

The number of excess deaths related to subsequent primary neoplasms increased significantly with increased follow-up reaching 56.9 excess deaths per 10,000 person years for patients followed for ≥ 40 years in comparison to only 7.6 excess deaths per 10,000 person years for those followed for less than 10 years. Conversely AERs for deaths by subsequent primary neoplasms seemed to decrease for patients treated in recent eras going from 26.1 (95% CI 20.7-32.9) for those treated before 1970 to 4.0 (95% CI 11.5-17.3) for patients treated between 1990 and 2000 (Table 10). CM of deaths by subsequent primary neoplasm was also declining among those treated in recent periods (

Figure 11). At 20 years of follow-up, the cumulative mortality was 2.6% in patients treated before 1970, 1.3% in patients treated in the 70s, 1.4% in CCS treated in the 80s and only 0.4% in those treated in the 90s (

Figure 11).

4.2.4 Mortality from Circulatory diseases

Survivors of childhood malignancy were 6.4 (95% CI 5.0-8.0) times more likely to die from circulatory diseases than expected from the general population. Male CSS also had significantly higher AER of death by circulatory diseases compared to females ($P = 0.004$) (Table 11). Patients with Hodgkin Lymphoma had the highest number of excess deaths related to circulatory diseases experiencing 14.6 excess deaths per 10 000 person-year.

With regards to treatment era, there were no registered deaths among patients treated between 1990 and 2000, however, AERs seemed to decrease significantly by treatment period ($P < 0.0001$). Survivors treated before 1970 experienced 6.7 (95% CI 4.2-10.5) excess deaths per

10,000 person year, those treated in the 70s experienced 4.9 excess deaths (95% CI 3.3-7.3) and those treated in the 80s had only 2.8 excess deaths (95% CI 1.8-4.5) (Table 11).

Table 8. Cause-Specific standardized mortality ratio, and absolute excess risk among 5-year survivors the FCCSS cohort.

Causes of Death	Obs/Exp	SMR (95% CI)	AER (95 % CI)
All causes	1199/147.1	8.2 (7.7-8.6)	53.7 (50.6-57.1)
Unknown	125	(NA)	(NA)
Recurrence or progression	460/0	(NA)	14.3 (12.7-16.0)
Subsequent primary neoplasm	309/30	10.3 (9.2-11.5)	23.5 (21.4-25.7)
Infection	18/4.6	4.0 (2.3-6.2)	0.7 (0.4- 1.2)
Blood	1/0.7	1.4 (0-7.9)	0.0 (NA)
Endocrine	14/2.3	6.2 (3.4-10.4)	0.6 (0.3- 1.1)
Mental	8/3.8	2.1 (0.9-4.2)	0.2 (0.1- 0.6)
Nervous	17/5.1	3.3 (1.9-5.3)	0.6 (0.3- 1.1)
Circulatory	73/11.5	6.4 (5.0-8.0)	3.1 (2.4- 4.0)
Respiratory	21/2.9	7.3 (4.5-11.2)	0.9 (0.6- 1.5)
Digestive	7/5	1.4 (0.6-2.9)	0.1 (0.0- 0.4)
Skin and subcutaneous tissue	1/0	21.2 (0.5-118.0)	0.0 (NA)
Musculoskeletal	1/0.4	2.7 (0.1-15.3)	0.0 (NA)
Genitourinary	5/0.4	11.7 (3.8-27.2)	0.2 (0.1- 0.6)
Pregnancy and childbirth	1/0.3	3.6 (0.1-20.1)	0.0 (NA)
Congenital Diseases	11/1.9	5.8 (2.9-10.4)	0.5 (0.2- 0.9)
External	84/65.3	1.3 (1.0-1.6)	1.0 (0.6- 1.5)
Other	43/2.3	18.3 (13.2-24.7)	2.1 (1.5- 2.8)

Abbreviations: AER, absolute excess risk; CI, confidence interval; NA, not applicable; SMR, standardized mortality ratio
 SMRs were calculated a per 100 000 person-years
 AERs were calculated a per 10 000 person-years

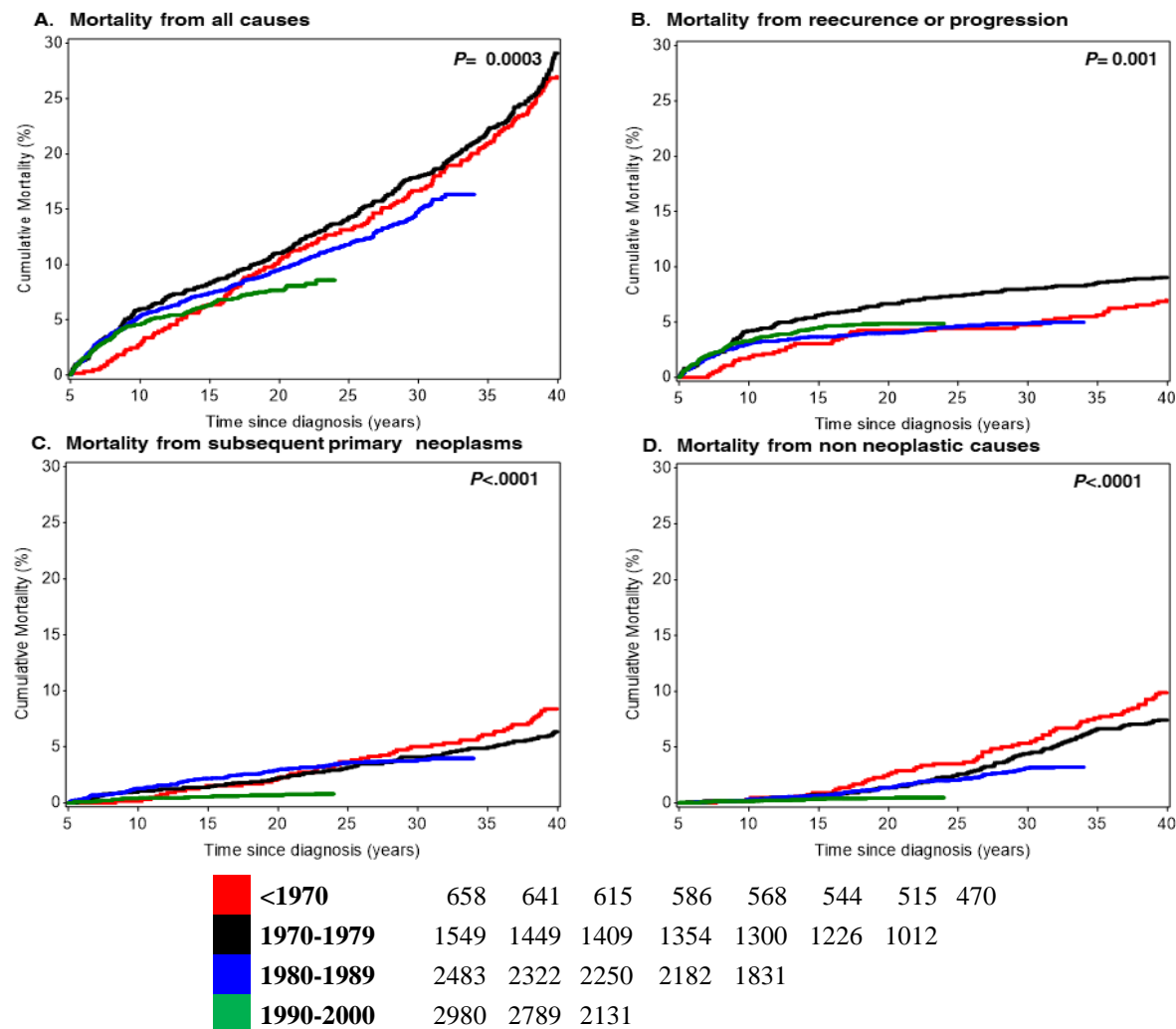


Figure 11. Cumulative mortality from all causes, recurrence or progression, subsequent primary neoplasms and non-neoplastic causes among 5-Year Survivors of Childhood Cancer in the FCCSS cohort

Table 9. Cumulative Incidence of death at 10, 15 and 20 years after primary cancer diagnosis among 5-year survivors.

Treatment era	Mortality from all causes (%)			Mortality from recurrence or progression (%)			Mortality from subsequent primary malignancies (%)			Mortality from non-neoplastic causes (%)		
	10 years	15 years	20 years	10 years	15 years	20 years	10 years	15 years	20 years	10 years	15 years	20 years
<1970	2.7	6.4	10.4	1.7	3.0	4.2	0.1	1.5	2.1	0.3	0.9	2.6
1970-1979	6.0	8.3	11.0	4.2	5.6	6.6	1.0	1.3	2.2	0.2	0.7	1.3
1980-1989	5.3	7.4	9.5	3.0	3.6	4.0	1.3	2.2	3.0	0.3	0.7	1.4
1990-2000	4.6	6.3	7.8	3.3	4.5	4.8	0.4	0.5	0.7	0.2	0.3	0.4

Table 10. Standardized mortality ratios and absolute excess risks for deaths related to all causes, recurrence or progression and subsequent primary neoplasms by potential explanatory factors among 5-year survivors the FCCSS cohort.

Factors	Overall mortality					Recurrence or progression			Subsequent primary neoplasms				
	Obs /Exp	SMR (95% CI)	AER (95% CI)	Obs	AER (95% CI)	Obs	AER (95% CI)	Obs/Exp	SMR (95% CI)	AER (95% CI)	Obs	SMR (95% CI)	AER (95% CI)
Sex													
Male	674/ 107	6.3 (5.8- 6.8)	53.0 (48.8-57.5)	246	23.0 (20.3-26.0)	168/17.6	9.5 (8.2-11.1)	14.0 (12.0-16.5)					
Female	525/40.4	13.0 (11.9-14.2)	54.6 (50.0-59.7)	214	24.1 (21.1-27.6)	141/12.4	11.4 (9.6-13.5)	14.5 (12.2-17.2)					
<i>P</i> for heterogeneity		<.0001	0.61		0.60		<.0001	0.78					
Type of primary cancer													
Hodgkin lymphoma	101/10.1	10.0 (8.2-12.2)	72.1 (58.5-88.7)	30	24.3 (17.0-34.8)	27/ 2.3	11.8 (7.8-17.2)	20.0 (13.5-29.7)					
Non-Hodgkin lymphomas	61/10.8	5.6 (4.3- 7.3)	20.0 (14.8-27.1)	13	6.2 (3.6-10.6)	18/ 3.2	5.6 (3.3- 8.9)	6.9 (4.1-11.5)					
CNS and other brain tumors	388/13.4	29.0 (26.1-32.0)	141.0 (127.0- 156)	192	73.2 (63.6-84.4)	71/ 3.7	19.4 (15.2-24.5)	25.6 (20.1-32.5)					
Neuroblastoma and other peripheral nervous cell tumors	108/ 9.2	11.8 (9.6-14.2)	34.2 (27.9- 41.9)	37	13.5 (9.8-18.6)	23/ 2.4	9.6 (6.1-14.4)	7.4 (4.8-11.5)					
Retinoblastoma	51/ 3.5	14.7 (10.9-19.3)	34.0 (25.4-45.4)	12	8.9 (5.1-15.7)	25/ 0.8	31.8 (20.6-46.9)	17.9 (12.0-26.7)					
Renal tumors	139/16.0	8.7 (7.3-10.2)	33.8 (28.2-40.6)	28	8.3 (5.7-12.0)	49/ 4.7	10.4 (7.7-13.8)	12.9 (9.6-17.4)					
Malignant bone tumours	120/15.3	7.9 (6.5- 9.4)	63.3 (52.2-76.7)	66	40.2 (31.5-51.1)	23/ 3.3	6.9 (4.4-10.3)	12.0 (7.7-18.6)					
Soft tissue sarcomas	127/11.9	10.7 (8.9-12.7)	48.9 (40.5-59.0)	49	22.1 (16.7-29.3)	41/ 3.5	11.9 (8.5-16.1)	16.7 (12.1-23.1)					
Germ cell tumour	40/ 7.9	5.1 (3.6- 6.9)	24.9 (17.5-35.5)	7	5.7 (2.7-11.9)	17/ 2.0	8.7 (5.0-13.9)	12.1 (7.3-20.2)					
Other	64/ 8.0	8.0 (6.1-10.2)	52.3 (40.2-68.0)	26	24.5 (16.7-36.0)	15/ 2.0	7.4 (4.2-12.3)	12.2 (7.0-21.0)					
<i>P</i> for heterogeneity		<.0001	<.0001		0.04		<.0001	0.02					
Age at diagnosis, years													
<5	484/33.4	14.5 (13.2-15.9)	43.1 (39.2-47.4)	156	15.7 (13.4-18.4)	144/ 9.1	15.8 (13.3-18.6)	13.4 (11.3-15.9)					
5-9	316/19.4	16.3 (14.6-18.2)	65.6 (58.4-73.8)	129	30.0 (25.3-35.7)	81/ 5.8	14.1 (11.2-17.5)	17.3 (13.8-21.7)					
10-14	308/26.2	11.8 (10.5-13.2)	66.5 (58.9-74.9)	124	31.0 (26.0-37.0)	75/ 8.5	8.8 (6.9-11.0)	16.4 (12.9-20.9)					

Factors	Overall mortality					Recurrence or progression			Subsequent primary neoplasms				
	Obs /Exp	SMR (95% CI)	AER (95% CI)	Obs	AER (95% CI)	Obs/Exp	SMR (95% CI)	AER (95% CI)	Obs/Exp	SMR (95% CI)	AER (95% CI)		
≥15	91/ 8.3	11.0 (8.9-13.5)	56.1 (44.8-70.2)	51	37.5 (28.5-49.3)	9/ 2.6	3.4 (1.6- 6.5)	4.4 (2.0- 9.8)					
<i>P</i> for trend		<.0001	<.0001		<.0001			0.50					
Years from cancer diagnosis, years													
<10	376/17.0	22.2 (20.0-24.5)	46.3 (41.7-51.4)	248	32.9 (29.1-37.3)	61/ 2.9	20.9 (16.0-26.9)	7.6 (5.9- 9.9)					
10-19	303/20.8	14.6 (13.0-16.3)	41.7 (37.0-47.1)	126	20.0 (16.8-23.8)	80/ 3.7	21.8 (17.3-27.2)	12.0 (9.6-15.0)					
20-29	246/20.1	12.2 (10.8-13.9)	56.5 (49.3-64.6)	46	12.4 (9.3-16.5)	71/ 6.0	11.9 (9.3-15.0)	17.4 (13.6-22.2)					
29-39	185/16.3	11.3 (9.8-13.1)	104 (88.6- 121)	33	21.5 (15.3-30.2)	62/ 7.0	8.8 (6.8-11.3)	35.2 (26.9-45.9)					
≥40	89/12.0	7.4 (6.0- 9.1)	149 (118- 189)	7	14.8 (7.1-31.1)	35/ 6.1	5.7 (4.0- 7.9)	56.9 (39.0-83.1)					
<i>P</i> for trend		<.0001	<.0001		<.0001		<.0001	<.0001					
Attained age, years													
<20	401/21.8	18.4 (16.6-20.2)	37.3 (33.7-41.4)	233	23.8 (21.0-27.1)	84/ 3.6	23.1 (18.4-28.6)	8.1 (6.5-10.1)					
20-29	346/20.6	16.8 (15.1-18.7)	56.6 (50.6-63.3)	144	26.6 (22.6-31.4)	83/ 3.7	22.2 (17.7-27.6)	14.6 (11.7-18.2)					
30-39	228/19.7	11.6 (10.1-13.2)	63.8 (55.5-73.5)	55	18.1 (13.9-23.5)	68/ 6.6	10.3 (8.0-13.0)	20.1 (15.7-25.8)					
40-49	164/15.2	10.8 (9.2-12.6)	130 (110.0- 153)	21	19.4 (12.6-29.8)	48/ 7.0	6.8 (5.0- 9.1)	36.7 (26.9-50.1)					
≥50	60/ 9.0	6.7 (5.1- 8.6)	173 (129.0- 230)	7	26.0 (12.4-54.6)	26/ 4.7	5.5 (3.6- 8.1)	72.9 (46.8- 114)					
<i>P</i> for trend		<.0001	<.0001		0.20		<.0001	<.0001					
Treatment period													
<1970	251/26.1	9.6 (8.5-10.9)	75.6 (66.0-86.6)	52	18.8 (14.3-24.7)	85/10.1	8.4 (6.7-10.4)	26.1 (20.7-32.9)					
1970-1979	396/27.3	14.5 (13.1-16.0)	67.8 (61.0-75.3)	141	27.4 (23.2-32.3)	103/ 8.2	12.6 (10.3-15.3)	18.2 (14.9-22.3)					
1980-1989	340/22.1	15.4 (13.8-17.1)	46.0 (41.1-51.5)	123	18.8 (15.8-22.5)	98/ 5.3	18.4 (15.0-22.4)	14.1 (11.5-17.3)					
1990-2000	212/10.5	20.2 (17.6-23.1)	37.7 (32.7-43.4)	144	28.0 (23.8-33.0)	23/ 2.1	10.8 (6.8-16.2)	4.0 (2.6- 6.2)					
<i>P</i> for trend		<.0001	<.0001		0.17		<.0001	<.0001					

AER, absolute excess risk; CI, confidence interval; NA, not applicable; SMR, standardized mortality ratio; Obs, observed; Exp, expected
SMRs were calculated per 100 000 person year and AERs were calculated per 10 000 person year

Table 11. Standardized mortality ratios and absolute excess risks for deaths related to circulatory diseases by potential explanatory factors.

Factors	Circulatory diseases				
	Obs /Exp	SMR (95% CI)	AER (95% CI)		
Sex					
Male	45/ 8.2	5.5	(4.0- 7.3)	3.4	(2.5- 4.7)
Female	28/ 3.3	8.6	(5.7-12.4)	2.8	(1.9- 4.1)
<i>P</i> for heterogeneity			<.0001		0.42
Type of primary cancer					
Hodgkin lymphoma	19/ 0.8	23.7	(14.3-37.0)	14.6	(9.2-23.2)
Non-Hodgkin lymphomas	6/ 1.0	6.3	(2.3-13.7)	2.2	(0.9- 5.4)
CNS and other brain tumours	11/ 1.2	9.3	(4.7-16.7)	3.6	(1.9- 6.8)
Neuroblastoma and other peripheral nervous cell tumours	11/ 0.7	15.9	(7.9-28.4)	3.7	(2.0- 6.8)
Retinoblastoma	0/ 0.2		NA		NA
Renal tumours	9/ 1.3	6.7	(3.1-12.7)	2.1	(1.0- 4.4)
Malignant bone tumours	3/ 1.3	2.3	(0.5- 6.7)	1.0	(0.2- 4.6)
Soft tissue sarcomas	6/ 1.0	6.0	(2.2-13.0)	2.0	(0.8- 5.1)
Germ cell tumour	5/ 0.6	7.8	(2.5-18.1)	3.5	(1.3- 8.9)
Other	3/ 0.7	4.2	(0.9-12.2)	2.1	(0.6- 7.8)
<i>P</i> for heterogeneity			0.05		<.0001
Age at diagnosis, years					
<5	27 / 2.4	11.2	(7.4-16.3)	2.3	(1.5- 3.5)
5-9	18 / 1.5	11.9	(7.0-18.8)	3.6	(2.2- 5.9)
10-14	21 / 2.4	8.8	(5.4-13.4)	4.3	(2.7- 6.9)
≥15	7 / 0.7	9.9	(4.0-20.3)	4.2	(1.9- 9.6)
<i>P</i> for heterogeneity			<.0001		0.20
<i>P</i> for trend			<.0001		0.04
Years from cancer diagnosis, years					
5-9	3 / 0.8	3.6	(0.8-10.7)	0.3	(0.1- 1.1)
10-19	9 / 1.3	7.0	(3.2-13.3)	1.1	(0.5- 2.4)
20-29	28 / 1.7	16.4	(10.9-23.8)	6.7	(4.6-10.0)
29-39	24 / 1.6	14.7	(9.4-21.9)	13.6	(8.9-20.9)
≥40	9 / 1.4	6.4	(2.9-12.2)	13.5	(6.2-29.3)
<i>P</i> for heterogeneity			<.0001		0.03
<i>P</i> for trend			<.0001		0.008
Attained age, years					
<20	6 / 1.1	5.7	(2.1-12.3)	0.5	(0.2- 1.2)
20-29	9 / 1.4	6.6	(3.0-12.6)	1.3	(0.6- 2.7)
30-39	24/ 1.8	13.4	(8.6-20.0)	6.8	(4.5-10.5)
40-49	28/ 1.6	18.0	(11.9-25.9)	23.1	(15.6-34.2)
≥50	6/ 1.1	5.4	(2.0-11.8)	14.8	(5.6-39.6)
<i>P</i> for heterogeneity			<.0001		<.0001
<i>P</i> for trend			<.0001		<.0001
Treatment period					
<1970	23/ 2.5	9.2	(5.8-13.8)	6.7	(4.2-10.5)
1970-1979	29/ 2.1	13.6	(9.1-19.6)	4.9	(3.3- 7.3)
1980-1989	21/ 1.5	13.6	(8.4-20.8)	2.8	(1.8- 4.5)
1990-2000	0 / 0.6		NA		NA
<i>P</i> for heterogeneity			<.0001		0.03
<i>P</i> for trend			<.0001		0.008

Abbreviations: AER, absolute excess risk; CI, confidence interval; NA, not applicable; SMR, standardized mortality ratio; Obs, observed; Exp, expected
SMRs were calculated per 100 000 person year and AERs were calculated per 10 000 person year

4.3 The evolution of treatment modalities by treatment era

For patients treated before 1970 and in the 70s the most common type of childhood malignancy were renal tumours 27.4% and 21% respectively. Conversely the most common type of childhood malignancy among those treated in the 80s and 90s was CNS tumours (Table 12).

In the FCCSS cohort, the use of chemotherapy increased significantly since 1970. Similarly, the proportion of patients treated with anthracycline also increased from 5.5% among those treated before 1970 to 41.2% for those treated between 1990 and 2000. However, patients treated in the most recent treatment era seemed to receive significantly lower doses with only 13.9% of patients receiving a dose of anthracycline higher than 250mg/m² compared to 21.8% and 25.6 for those treated in the 70s and 80s respectively (Table 12).

Conversely, the use of radiotherapy decreased in the more recent treatment eras, going from 85.9% in patients treated before 1970 to 41.3% for patients treated between 1990 and 2000. The use of cranial radiation also decreased from 29.1% for patients treated in the 70s to 16.4% for those treated in the 90s (Table 12). CCS treated in the 70s were also exposed to the highest doses of radiation as the maximum dose to the brain among CNS patients treated in the 70s reached 61.0 Gy (IQR 56.0-69.) and the maximum dose to the heart among Hodgkin lymphoma patients also reached 40.7 Gy (37.0-44.5). Contrarily, patients treated in the 90s seemed to receive less radiation doses with the maximum cardiac radiation dose decreasing to 21.4 Gy and the maximum dose to the kidneys among nephroblastoma patients also decreasing from 32.0Gy for those treated in the 70s to 20.0 Gy for those treated in the 90s (Table 12).

Table 12. Cancer and treatment related characteristics by treatment era.

Characteristics	<1970		1970-1979		1980-1989		1990-2000		P
	n=658		n=1549		n=2483		n=2980		
	N	(%)	N	(%)	N	(%)	N	(%)	
Type of primary childhood malignancy									<.0001
Hodgkin lymphoma	44	(6.7)	117	(7.6)	151	(6.0)	178	(6.0)	
Non-Hodgkin lymphomas	39	(5.9)	151	(9.7)	345	(13.9)	255	(8.6)	
CNS tumours	92	(14.0)	242	(15.6)	373	(15.0)	433	(14.5)	
Neuroblastoma and other peripheral nervous cell tumours	97	(14.7)	203	(13.1)	344	(13.9)	392	(13.2)	
Retinoblastoma	21	(3.2)	58	(3.7)	149	(6.0)	391	(13.1)	
Renal tumours	180	(27.3)	325	(21.0)	330	(13.3)	303	(10.2)	
Malignant bone tumours	42	(6.4)	106	(6.8)	233	(9.4)	329	(11.0)	
Soft tissue and other extraosseous sarcomas	75	(11.4)	190	(12.3)	278	(11.2)	294	(9.9)	
Germ cell tumours	34	(5.2)	89	(5.7)	156	(6.3)	190	(6.4)	
Other	34	(5.2)	68	(4.4)	124	(5.0)	215	(7.1)	
Chemotherapy									<.0001
No	286	(43.5)	387	(25.0)	548	(22.1)	689	(23.1)	
Yes	372	(56.5)	1162	(75.0)	1935	(77.9)	2291	(76.9)	
Anthracycline									<.0001
No	622	(94.5)	1060	(68.4)	1318	(53.1)	1753	(58.8)	
Yes	36	(5.5)	489	(31.6)	1165	(46.9)	1227	(41.2)	
Anthracycline mg/m²									<.0001
None	622	(94.5)	1060	(68.4)	1318	(53.1)	1753	(58.8)	
<250	17	(2.6)	142	(9.2)	512	(20.6)	792	(26.6)	
≥250	17	(2.6)	338	(21.8)	636	(25.6)	414	(13.9)	
Missing	2	(0.3)	9	(0.6)	17	(0.7)	21	(0.7)	
Alkylating agents									<.0001
No	489	(74.3)	760	(49.1)	959	(38.6)	1150	(38.6)	
Yes	169	(25.7)	789	(50.9)	1524	(61.4)	1830	(61.4)	

Characteristics	<1970		1970-1979		1980-1989		1990-2000		P
	n=658		n=1549		n=2483		n=2980		
	N	(%)	N	(%)	N	(%)	N	(%)	
Alkylating agents g/m²									
None	489	(74.3)	760	(49.1)	959	(38.6)	1150	(38.6)	<.0001
<4	91	(13.8)	204	(13.2)	363	(14.6)	602	(20.2)	
4-7.9	34	(5.2)	205	(13.2)	441	(17.8)	406	(13.6)	
≥8	39	(5.9)	366	(23.6)	690	(27.8)	799	(26.8)	
Radiotherapy									<.0001
No	93	(14.1)	368	(23.8)	1223	(49.3)	1748	(58.7)	
Yes	565	(85.9)	1181	(76.2)	1260	(50.7)	1232	(41.3)	
Cranial radiation									<.0001
No	499	(75.8)	1099	(70.9)	1953	(78.7)	2492	(83.6)	
Yes	159	(24.2)	450	(29.1)	530	(21.3)	488	(16.4)	
Mean dose to the brain (Gy)*									<.0001
Median (IQR)	13.7	(6.9-23.4)	27.4	(16.6-37.3)	25.1	(14.4-37.4)	22.5	(12.5-36.0)	
Maximum dose to the brain (Gy)*									<.0001
Median (IQR)	56.4	(42.7-65.7)	61.0	(56.0-69.0)	58.4	(53.0-66.0)	58.0	(41.7-65.1)	
Mean dose to the heart (Gy)[†]									<.0001
Median (IQR)	29.1	(17.1-34.4)	32.4	(23.0-37.6)	18.3	(3.5-36.5)	18.0	(12.7-20.0)	
Maximum dose to the heart (Gy)[†]									<.0001
Median (IQR)	41.8	(30.1-48.7)	40.7	(37.0-44.5)	22.0	(18.0-40.7)	21.4	(20.2-26.1)	
Mean dose to the kidneys (Gy)[‡]									0.0002
Median (IQR)	7.2	(4.1-12.9)	8.6	(4.2-16.6)	7.1	(3.0-17.1)	8.8	(4.8-14.8) [°]	
Maximum dose to the kidneys (Gy)[‡]									<.0001
Median (IQR)	31.0	(20.6-38.0)	32.0	(22.9-38.0)	29.5	(21.5-32.3)	20.0	(15.5-29.6)	

* mean cranial dose among patients with CNS and other brain tumours

[†] mean dose to the heart among Hodgkin Lymphoma patients

[‡] mean dose to the kidneys among patients with renal tumours

4.4 Excess mortality by treatment era

Overall, the number of excess deaths from all causes among survivors declined in more recent treatment periods (P for trend<0.0001). However, after adjusting for sex, type of first primary neoplasm, age at diagnosis, and attained age; survivors diagnosed in the 80s and 90s both experienced exactly the same number of excess deaths (EMRs 0.6, 95% CI 0.5 to 0.7) (Table 13). For deaths related to recurrence or progression, the number of excess deaths didn't seem to decrease for patients treated in the more recent treatment eras compared to patients treated before 1970 (adjusted P trend 0.37).

The decrease in excess mortality by treatment era was much obvious for deaths related to subsequent primary neoplasms with EMRs going from 0.7 (95% CI 0.5-1.0) for those treated in the 70s to 0.4 (95% CI 0.2-0.6) for those treated in the most recent treatment era. This decline persisted after adjusting for sex, type of first primary neoplasm, age at diagnosis, and attained age. Mortality from circulatory diseases also decreased by treatment era, CCS treated in the 80s experienced 60% excess number deaths (adjusted EMR 0.8, 95% CI 0.2 to 1.7) compared to those treated before 1970. While patients treated in the 70s experienced 80% excess deaths (adjusted EMR 0.8, 95% CI 0.3 to 1.7) compared to those treated before 1970 (Table 14).

Table 13. Excess mortality ratios for deaths related to all causes, recurrence or progression and subsequent primary neoplasms by treatment era.

Treatment era	All Causes			Recurrence or progression			Subsequent primary neoplasms		
	Obs/Exp	Univariable model	Multivariable model*	Obs	Univariable model	Multivariable model*	Obs/Exp	Univariable model	Multivariable model*
		EMR (95% CI)	EMR (95% CI)		EMR (95% CI)	EMR (95% CI)		EMR (95% CI)	EMR (95% CI)
<1970†	251/26.1	1.0	1.0	52	1.0		85/10.1	1.0	1.0
1970-1979	396/27.3	0.9 (0.8-1.1)	0.8 (0.7-1.0)	141	1.5 (1.1-2.0)	1.3 (0.9-1.8)	103/ 8.2	0.7 (0.5-0.9)	0.7 (0.5-1.0)
1980-1989	340/22.1	0.6 (0.5-0.7)	0.6 (0.5-0.7)	123	1.0 (0.7-1.4)	0.8 (0.6-1.2)	98/ 5.3	0.5 (0.4-0.7)	0.6 (0.4-0.9)
1990-2000	212/10.5	0.5 (0.4-0.6)	0.6 (0.5-0.7)	144	1.5 (1.1-2.0)	1.1 (0.8-1.5)	23/ 2.1	0.2 (0.1-0.3)	0.4 (0.2-0.6)
<i>P</i> trend‡		<.0001	<.0001		0.17	0.37		<.0001	0.0004

Abbreviations: CI, confidence interval; EMR=excess mortality ratios; Obs, observed; Exp, expected

*Adjusted for sex, type of primary malignancy, age at diagnosis and attained age

†reference category

EMRs were calculated using likelihood ratio tests to assess the effect of treatment period

Table 14. Mortality from circulatory diseases by treatment era.

Treatment era	Circulatory Disease		
	Obs/Exp	Univariable model	Multivariable model*
		EMR (95% CI)	EMR (95% CI)
<1970†	23.0/ 2.5	Ref	Ref
1970-1979	29.0/ 2.1	0.7 (0.4-1.3)	0.8 (0.3-1.7)
1980-1989	21.0/ 1.5	0.4 (0.2-0.8)	0.6 (0.2-1.7)
1990-2000	0.0/ 0.6	NA	NA
<i>P</i> trend‡		0.008	0.33

Abbreviations: CI, confidence interval; EMR=excess mortality ratios; Obs, observed; Exp, expected

*Adjusted for sex, type of primary malignancy, age at diagnosis and attained age

†reference category

‡ Calculated using likelihood ratio tests to assess the effect of treatment period.

Table 15. Excess mortality ratios for deaths related to all causes, recurrence or progression and subsequent primary neoplasms by treatment era between 1970 and 2000

Treatment era	All Causes				Recurrence or progression				Subsequent primary neoplasms						
	Obs/Exp P	Univariable model		Multivariable model*		Obs	Univariable model		Multivariable model*		Obs/Exp	Univariable model		Multivariable model*	
		EMR		EMR			EMR		EMR			EMR		EMR	
		(95% CI)		(95% CI)			(95% CI)		(95% CI)			(95% CI)		(95% CI)	
1970-1979†	396/27.3	Ref		Ref		141	Ref		Ref		103/ 8.2	Ref		Ref	
1980-1989	340/22.1	0.7	(0.6-0.8)	0.7	(0.6-0.9)	123	0.7	(0.5-0.9)	0.6	(0.5-0.8)	98/ 5.3	0.8	(0.6-1.0)	0.9	(0.6-1.2)
1990-2000	212/10.5	0.6	(0.5-0.7)	0.7	(0.6-0.9)	144	1.0	(0.8-1.3)	0.8	(0.6-1.0)	23/ 2.1	0.2	(0.1-0.4)	0.5	(0.3-0.9)
<i>P</i> trend†		<.0001		0.0006			0.83		0.09			<.0001		0.03	

Abbreviations: CI, confidence interval; EMR=excess mortality ratios; Obs, observed; Exp, expected

*Adjusted for sex, type of primary malignancy, age at diagnosis and attained age

†reference category

EMRs were calculated using likelihood ratio tests to assess the effect of treatment period

4.5 Mortality and treatment related risk factors

Patients treated with chemotherapy had significantly more excess deaths related to all causes, recurrence or progression and subsequent primary neoplasms. Furthermore, CCS treated with radiotherapy had 220% excess related to all causes globally to those who didn't receive any radiotherapy (adjusted EMR 2.2 95% CI 1.8-2.7). Contrarily, patients treated with surgery had 70% excess deaths globally (adjusted EMR 0.7 95% CI 0.6-0.9) compared to patients who received other treatments (Table 16). Patients treated with radiotherapy didn't have any significant excess deaths related to subsequent primary neoplasms compared to those who didn't receive any radiotherapy. Also, CCS treated by surgery had 50% excess deaths compared to those treated with no surgery (adjusted EMR 0.5 95% CI 0.3-0.8) (Table 16). We also found that even a dose of anthracycline below 250mg/m² was associated with higher excess mortality compared to patients who didn't receive any anthracycline even after adjusting for sex, type of primary malignancy, age at diagnosis, attained age and the mean dose to the heart. The number of excess deaths by circulatory diseases increased among CCS who received ≥ 250 mg/m² of anthracycline reaching 510% excess deaths (adjusted EMR 5.1 95% CI 1.4- 18.0). EMRs of death by circulatory diseases was much higher among patients who received ≥ 15 Gy to the heart reaching 870% of excess deaths (adjusted EMR 8.7 95% CI 2.9- 26.0) (Table 17).

Table 16. Excess mortality ratios for deaths related to all causes, recurrence or progression and subsequent primary neoplasms by treatment factors.

Treatment factors	Obs/Exp	All Causes		Recurrence or progression				Subsequent primary neoplasms					
		Univariable model		Multivariable model*		Univariable model		Multivariable model*		Univariable model		Multivariable model*	
		EMR (95% CI)	EMR (95% CI)	Obs	EMR (95% CI)	EMR (95% CI)	Obs/Exp	EMR (95% CI)	EMR (95% CI)	Obs/Exp	EMR (95% CI)	EMR (95% CI)	
Chemotherapy													
No†	297/29.1	1.0		106	1.0		51/9.8	1.0					
Yes	902/56.9	1.2 (1.0-1.4)	1.5 (1.3-1.8)	354	1.2 (1.0-1.5)	2.0 (1.6-2.5)	258/15.8	2.2 (1.6-3.2)	1.6 (1.1-2.2)				
<i>P</i> for heterogeneity		<.0001	<.0001		<.0001	<.0001		<.0001	0.01				
Radiotherapy													
No†	182/26.9	1.0		76	1.0		34/7.1	1.0					
Yes	1017/59.5	4.7 (3.9-5.6)	2.2 (1.8-2.7)	384	3.5 (2.7-4.5)	2.6 (2.0-3.4)	275/18.7	6.7 (4.5-10)	1.1 (0.7-1.7)				
<i>P</i> for heterogeneity		<.0001	<.0001		<.0001	<.0001		<.0001	NS				
Surgery													
No†	146/13.1	1.0		46	1.0		35.0/3.8	1.0					
Yes	1053/73.5	1.3 (1.1-1.6)	0.7 (0.6-0.9)	414	1.6 (1.2-2.1)	1.7 (1.2-2.3)	274/22.1	1.4 (1.0-2.0)	0.5 (0.3-0.8)				
<i>P</i> for heterogeneity		<.0001	0.002		<.0001	0.001		<.0001	0.001				

Abbreviations: CI, confidence interval; EMR=excess mortality ratios; Obs, observed; Exp, expected

*Adjusted for sex, type of primary malignancy, age at diagnosis, attained age, chemotherapy (yes/no), radiotherapy (yes/no) and surgery (yes/no)

†reference category

EMRs were calculated using likelihood ratio tests to assess the effect of treatment factors

Table 17. Excess mortality ratios of circulatory diseases by cardiotoxic treatment factors.

Treatment factors	Circulatory Disease				
	Obs/Exp	Univariable model		Multivariable model*	
		EMR	(95% CI)	EMR	(95% CI)
Anthracycline mg/m²					
0	49/8.7	Ref		Ref	
]0-250[4/1.1	0.3	(0.1-0.9)	4.7	(1.3- 18.0)
≥250	20/1.7	1.7	(1.0-2.9)	5.1	(1.4- 18.0)
<i>P</i> trend†			0.01		0.007
Cardiac radiation mean dose (Gy)					
0	11/3.6	Ref		Ref	
<15	30/6.5	3.5	(1.5-8.0)	1.1	(0.4-2.8)
≥15	32/1.4	19.0	(8.3- 42)	8.7	(2.9- 26.0)
<i>P</i> trend†			<.0001		<.0001

Abbreviations: CI, confidence interval; EMR=excess mortality ratios; Obs, observed; Exp, expected

*Adjusted for sex, type of primary malignancy, age at diagnosis, attained age, anthracycline dose and the mean dose to the heart

† Calculated using likelihood ratio tests to assess the effect of treatment factors.

5. Discussion

This study was the first to investigate the effect of treatment era on late cause specific mortality in 5-year CCS in France. We previously reported long term mortality in survivors of childhood malignancies in France (47), nevertheless, this updated analysis included an additional 4572 patients and extended to patients treated up to 2000.

We confirmed previously reported results showing a continuous increasing risk of death among CCs even up to 40 years from the primary cancer diagnosis. Despite the differences in composition between the FCCSS and the CCCS cohort, we found very similar SMRs for overall mortality, SMR in the CCS 8.4 (95% CI 8.0-8.7) compared to an SMR of 8.2 (95% CI 7.7-8.6) in our study. However, SMRs were slightly higher in the BCCSS (44, 45), Swiss Childhood Cancer Registry (SCCR) (46) and the Nordic countries (48). The AERs in the CCSS for mortality from all cause were also higher compared to our study (AER 73.6 per 10 000 person years compared to 53.7 in our study). However, the AERs related to circulatory diseases found in our study (AER=6.4) were much higher than those observed in the BCCSS and in the Nordic countries where AREs only ranged between 2.9 and 3.6.

When we examined the trends of long-term mortality by treatment period, we found that overall long-term mortality decreased in recent treatment eras but was identical for CCS treated in the 80s and 90s after accounting for sex, type of primary malignancy, age at diagnosis and attained age.

In our study, we also found that mortality related the primary malignancy did not decrease among those treated recently, which were not consistent with results found in other cohorts (42-45). This could be explained by the fact that we included 5-year survivors treated before 1970 who are most probably patients with good prognosis who can maintain durable remission because they had low risk tumours treatable with radiotherapy and surgery. Contrarily more patients with less durable remission and aggressive high-risk tumours treated in recent years

would make the 5-year survival mark. Mortality patterns related to the primary malignancy could also be impacted by the misclassifications of the underlying cause of deaths among CCS and cancer survivors in general for whom deaths related to causes other than malignancies are probably underestimated (135, 136).

On the other hand, our results showed significant improvement in long term mortality related to causes which are likely caused by late effects as deaths related to subsequent primary neoplasms and circulatory diseases among patients treated with modern therapy.

This improvement could be related to the significant improvement of surveillance and management for late effects among CCS diagnosed more recently (137, 138). In addition, the more recent decades, focus has been on maintaining the improved outcome of patients with pediatric malignancies and at the same time adjusting the intensity of therapeutic regimens with the prognosis and severity of the primary cancer to reduce late treatment effects. This approach resulted in less use of cranial radiation (52, 139), reduction of radiation doses for patients with Hodgkin's lymphoma (116), and lower cumulative doses of anthracycline to reduce cardiac toxicity (140). This was also underlined in this study, we found significant decrease in the intensity of therapeutic regimens in recent treatment periods and a significant decline in the use of radiotherapy. This adjustment of childhood cancer treatments would explain the reductions of the deaths related to secondary neoplasms, non-neoplastic causes and circulatory in the FCCS cohort among those treated more recently. More specifically the reduction of the doses of radiation to the heart received by Hodgkin lymphoma patients along with the significant decrease of anthracycline doses the cumulative doses of anthracycline would explain the significant decrease in long term mortality from circulatory diseases among CCS treated more recently. Regardless, in line with other studies we found that there is no safe dose for anthracyclines (141), as even patients exposed to cumulative doses of anthracycline less than

250 mg/m² had significantly higher number of excess deaths by circulatory diseases compared to those who didn't receive any anthracycline.

To conclude, this study completed the findings of the previous study by Tukenova et al (47) and shed the light on the patterns of mortality in the FCCSS cohort. One of the most important findings was that mortality related to adverse effects of cancer treatments decreased significantly in recent treatment periods while mortality from the primary malignancy was similar between patients treated in the 90s and the 80s. Also, one of the major strengths of this study was that treatment related factors were available for all cohort members, which allowed to attribute the decrease of mortality related to subsequent primary neoplasms and circulatory diseases to the decrease in the intensity of therapeutic regimens in recent years. However, patients treated in the recent treatment era would require longer follow-up to account for the very late effects including cardiovascular causes that may appear only later in patients treated with modern therapy. Although reduction in mortality related to cardiovascular causes was also highlighted in other studies on CCS (45, 141). Recent study found that although mortality related to cardiovascular disease decreased, the incidence of severe heart failure increased with more recent treatment periods (141).

Chapter IV. The risk of heart failure after childhood cancer treatment

1. Context

Cardiovascular disease is the most frequent non-neoplastic cause of death in CCS and mortality from cardiac causes remain higher in these patients compared to the general population (42, 44, 45, 47). Heart failure was found to be one of the most frequent cardiac diseases in CCS (38, 69). Both anthracycline exposure and thorax irradiation increase the risks of these conditions, but with different effects on the frequency and type of cardiac disease. Anthracycline is associated with cardiac toxicity in the form of left ventricular (LV) dysfunction (systolic or diastolic), while long term radiation is associated with cardiac disease, often manifest as congestive heart failure, ischemia, coronary artery disease or myocardial infarction (142). The role of irradiated heart volume remains unclear. The consequences of irradiating a large part of the heart with a lower dose versus irradiating a smaller part of the heart with a high dose should be further studied (144).

Other studies have examined the radiation dose response for heart failure in CCS (69, 75, 130) and in adult Hodgkin lymphoma patients (145). However, the radiation dose-volume effects on the risk of heart failure were not explored in these CCS studies. Additional studies are needed to analyse the relationship between radiation doses to sub-volumes of the heart and the risk of heart failure.

Our aim was to study the consequences of exposure to anthracyclines and cardiac radiation in terms of risk of heart failure, investigating the effects on the risk of cardiac failure of radiation dose-volume metrics for the entire heart and the LV.

2. Methods

2.1 Study description

A case control study was nested in FCCSS cohort, which includes 5-year survivors of a solid cancer diagnosed before age 20 and treated before 2000. This cohort currently includes 7670 patients: 3172 from the Euro2k cohort treated between 1945 and 1985 in several centers in France, and 4498 patients treated between the years 1985 and 2000 at the Gustave Roussy center.

Heart failure cases were individually and randomly matched to controls on gender, age at first primary cancer diagnosis (+/- 3years), year of first primary cancer diagnosis (+/- 3years), and follow-up duration: the follow-up of each control patient had to be at least as long as the follow-up of their matched case. To avoid overmatching, study participants were not matched on type of childhood cancer. Each case was matched to at least two and at most five controls. A total of 1 281 cancer survivors were included in this study: 239 cases matched to 1 042 controls.

2.2 Identification and validation of heart failure

Heart failure cases were identified through self-questionnaire, medical records, long-term follow-up consultation reports, causes of death, and the French nationwide healthcare data system (SNDS) cross linked with the French hospital discharge database (PMSI). The PMSI database provides medical information on all patients admitted to a hospital in France, including discharge diagnoses coded using the International Classification of Disease 10th revision.

The general practitioner or the cardiologist of a patient with an identified heart failure was invited to complete a form confirming the diagnosis and specifying the date of onset (Appendix 1). The validation of each diagnosis was based on the criteria of the European Society of Cardiology and from the Framingham and PRIME studies (69, 146).

If the medical doctor was not aware of a recent cardiac complication or did not reply, the validation of heart failure was based on the database information. Specifically, a heart failure case was validated only if it satisfied at least two of the three following criteria: (1) the mention of heart failure as a chronic disease inducing full coverage of its treatment under the long term affectation scheme, (2) a diagnosis of heart failure in the hospital database associated with hospitalization or surgery (3) a heart failure medication in the reimbursement database.

All heart failures caused by sepsis, renal disease, or congenital disorders were excluded. Validated heart failure patients were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. A patient's disease is grade I if the patient is asymptomatic but with laboratory or cardiac imaging abnormalities, grade II if there are symptoms in case of mild to moderate activity or exertion, grade III if there are symptoms at rest or at minimal activity that require medical treatment, grade IV when the disease has life-threatening consequences and indicates urgent intervention and grade V if the patient died of heart failure (Table 18).

In accordance with French regulations, the protocol of the study was approved by a regional committee on ethics and by the national committee for data protection (Commission Nationale de l'Informatique et des Libertés).

Table 18. Grades of heart failure according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (147).

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Heart failure	Asymptomatic with Laboratory (e.g., BNP [BNatriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with moderate activity or exertion	Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death

2.3 Chemotherapy

Information on all chemotherapeutic agents administered for the primary cancer, for recurrences and for any subsequent primary cancer was collected up to the date of diagnosis of heart failure for case patients and during the corresponding follow-up period for their matched controls. The information included the type and dose of the drug in mg or g, the start and end date of each chemotherapy treatment, and height and weight for body surface area estimation. For each participant, doses of chemotherapy were summed across cycles to obtain cumulative doses of each drug received per m² (Table 4).

The chemotherapy treatments were summarized in three categories based on their molecular mechanisms of action: anthracyclines, alkylating agents and vinca-alkaloids.

3. Radiation Dosimetry

A highly individualized dose reconstructions as closely as possible to patient actual treatment conditions was achieved for each subject, taking into account the patient sex, age, height, weight, target-volume location, prescribed dose, number of fields, field configuration(s), field size(s), type of treatment machine, beam energies, and other parameters.

Because the patients under study were treated by RT decades ago, setting up an appropriate strategy for data collection and quality control was an essential part of the efforts of the dosimetry team. RT plans reconstructions were based on the technical and clinical information from individual patient's records. The RT institutions where the patients were treated have excellent medical archives policies and that complete RT field set-up characteristics and complete RT description, imaging data, simulation films, location and shape of each treatment field was obtained for about 90 % of the patients. When some information was missing for a patient, data from another patient of same age, gender, treated for the same disease in the same institution in the same period was imputed (148). The dosimetry system can produce, for any site of interest defined as a labelled contour within the voxel phantom, dose-volume metrics comparable to those used for modern computed tomographic-based 3-dimensional radiotherapy planning (125, 149). A set of contours representing the entire heart and the LV was defined in the phantoms (Figure 7).

Mean radiation doses and the volumes of the heart and the LV receiving at least 20Gy, 30Gy and 40Gy (V20, V30, V40, respectively) were then estimated (Figure 8).

These dose-volume parameters were chosen because they were considered as clinically important endpoints or predictors for acute and late heart disease (142, 150, 151).

Because complete medical documentation was crucial for the reconstruction of the heart radiation dosimetry, dose estimation could not be performed for five participants with incomplete medical records.

4. Statistical analysis

Chemotherapy dose classes were calculated according to tertiles for alkylating agents and vinca alkaloids. The anthracycline dose categories were selected according to other published studies (69, 72, 130). The cumulative incidence of heart failure was estimated using the nonparametric

Aalen-Johansen estimator. The attained age was used as time scale and death from other causes than heart failure was considered a competing event.

Conditional logistic regression was conducted for matched sets to estimate the risk of heart failure. Multivariable models were adjusted to the type of primary childhood malignancy, treatment characteristics and the presence or absence of splenectomy.

Models that included the V5, V20, V25, V30 and the V40 for the whole heart and for the LV were tested and then ranked according to the Akaike Information Criterion (AIC). The models selected based on the AIC were the models containing the mean dose and the V30 for the heart and LV.

The risk of heart failure due to radiation was studied as a function of the mean radiation dose and of the fraction of the volume receiving ≥ 30 Gy, both for the entire heart and for the LV. The interaction between anthracycline use and radiation doses to the heart and LV was studied using conditional regression models that included radiation dose as the categorical factor and anthracycline exposure as the binary variable (yes/no). These models provide odds ratios (ORs) associated with each level of cumulative radiation to the heart or LV, as compared to the reference level corresponding to no radiation or anthracycline exposure. Results were reported as ORs with 95% confidence intervals.

The dose–response relationship was evaluated by testing a linear model using the formula $OR = \alpha_s (1 + \beta d)$, and a quadratic model using the formula $OR = \alpha_s [1 + \beta d^2]$, where α_s is a constant specific to each stratum, β is the excess relative risk (ERR) of heart failure per unit increase in dose and d is the mean heart dose (MHD) or the mean left ventricle dose (MLVD). Nonlinearity was evaluated by including an exponential term using the formula $OR = \alpha_s [1 + \beta d \exp(\gamma d)]$. The radiation dose is modelled as a continuous variable estimate the ERR/Gy. The role of each potential dose–response modifier was tested by comparing models based on the dose received in each of the two categories with nested models based on the total dose alone.

Goodness of fit was assessed by likelihood ratio tests, and interactions were evaluated using interaction terms and likelihood ratio tests.

Sensitivity analysis was performed on a subset of 117 cases and 353 controls who returned the self-reported questionnaire and adjusted for the effects of tobacco consumption, physical activity and body mass index. A total of 16 patients had missing BMI. The ORs were first estimated separately for each risk factor with a missing category created for the missing BMI data. Then multiple imputation was performed to provide missing BMI data and 20 imputed datasets were created. The 20 imputed data sets were analysed with all risk factors included in one multivariable model, results were then combined using Rubin et al.'s rules (152).

Statistical inference was based on two-sided tests, and $P \leq 0.05$ was considered to be statistically significant. Analyses were performed using SAS[®] version 9.3 and Epiwin[®] software version 1.81.

5. Results

5.1 Patients

A total of 239 cases of heart failure were identified after a median follow-up of 19.7 years (IQR: 13.7-26.9) and matched to two to five controls. The characteristics of the 1281 patient cases and controls are listed in

Table 19. The median age at diagnosis of the first malignancy was 5 years for both cases and controls (IQR: 2.4-9.8 and 2.3-9.6 for cases and controls respectively (

Table 19). Of the 239 cases, 85.4% had symptomatic heart failure, of which 46.4% had grade three heart failure, 21.4% had grade four heart failure and 17.6% had died from it. The median age of heart failure diagnosis was 25.1 years (

Table 20). A total of 25 cases received a cardiac transplantation at a median age of 20.3 years

(IQR=15.3-28.1).

Table 19. General and treatment characteristics of the cases of heart failure and their matched controls.

Characteristics	Cases (n=239)		Controls (n=1042)		P
	n or median	(% or range)	n or median	(% or range)	
Gender*					*
Female, n (%)	114	(47.7)	499	(47.9)	
Male, n (%)	125	(52.3)	543	(52.1)	
Follow-up* (years)					*
Median (IQR)	19.7	(13.7-26.9)	33.0	(27.2-39.0)	
Age at diagnosis of cancer* (years)					*
Median (IQR)	5.0	(2.4-9.8)	5.0	(2.3 -9.6)	
Status at the end of follow-up					<.0001
Alive	143	(59.8)	917	(88.0)	
Deceased	96	(40.2)	125	(12.0)	
Year of cancer diagnosis*					*
Median (range)	1979	(1942-2000)	1979	(1942-2000)	
Type of first malignancy					<.0001
Nephroblastoma, n (%)	81	(33.9)	321	(30.8)	
Sarcoma, n (%)	61	(25.5)	191	(18.3)	
Hodgkin's disease, n (%)	35	(14.6)	79	(7.6)	
Non-Hodgkin lymphoma, n (%)	34	(14.2)	125	(12.0)	
Other, n (%)	21	(8.8)	170	(16.3)	
Central Nervous System, n (%)	4	(1.7)	140	(13.4)	
Neuroblastoma, n (%)	3	(1.3)	16	(1.5)	
Chemotherapy, n (%)	229	(95.8)	798	(76.6)	<.0001
Anthracyclines, n (%)	172	(72.0)	362	(34.7)	<.0001
Dose in mg/m ² , median (range)	357.3	(2.1-998.1)	292.4	(6.1-1021.8)	
Doxorubicin, n(%)	157	(65.7)	322	(30.9)	<.0001
Dose in mg/m ² , median (range)	352.7	(2.1-860.6)	284.6	(6.1-619.2)	
Daunorubicin, n(%)	25	(2.4)	10	(4.2)	<.0001
Dose in mg/m ² , median (range)	508.2	(279.3-998.1)	316.2	(81.9-998.1)	
Alkylating agents n (%)	182	(76.2)	530	(50.9)	<.0001
Dose in g/m ² , median (range)	10.4	(0.2-367.1)	7.3	(0.02-140.2)	
Cisplatin n (%)	33	(13.8)	91	(8.7)	0.8
Dose in mg/m ² , median (range)	455.4	(97.1-1154.7)	431.3	(74.3-4128.2)	
Vinca Alkaloids n (%)	197	(82.4)	655	(62.9)	<.0001
Dose in mg/m ² , median (range)	25	(1.65-10611.6)	19.6	(1-2556)	
Radiotherapy, n (%)	174	(72.8)	648	(62.2)	0.0001
Radiation to the heart					
Mean dose in Gy, median (range)	12.3	(0.004-49.1)	2.1	(0.005-45.3)	<.0001
Volume (%) receiving 30+ Gy, median (range)	61.1	(0.1-100)	16.9	(0.03-100)	<.0001
Radiation to the left ventricle					
Mean dose in Gy, median (range)	11.9	(0.003-47.4)	2.1	(0.005-39.5)	<.0001
Volume (%) receiving 30+ Gy, median (range)	37.3	(0.01-100)	23.8	(0.06-100)	<.0001

Table 20. Characteristics of heart failure patients.

Characteristics	Men n=125		Women n=114		Total patients n=239	
	n or median	(% or range)	n or median	(% or range)	n or median	(% or range)
CTCAE grade of heart failure*						
I, n (%)	10	(8.0)	8	(7.0)	18	(7.5)
II, n (%)	9	(7.2)	8	(7.0)	17	(7.1)
III, n (%)	57	(45.6)	54	(47.4)	111	(46.4)
IV, n (%)	25	(20.0)	26	(22.8)	51	(21.4)
V, n (%)	24	(19.2)	18	(15.8)	42	(17.6)
Heart failure secondary to:						
Valvular disease, n (%)	2	(1.6)	4	(3.5)	6	(2.5)
Arrhythmia, n (%)	1	(0.8)	0	0	1	(0.4)
Ischemic cardiac disease, n (%)	1	(0.8)	2	(1.8)	3	(1.25)
Heart transplant						
No, n (%)	113	(90.4)	101	(88.6)	214	(89.5)
Yes, n (%)	12	(9.6)	13	(11.4)	25	(10.5)
Age at diagnosis of heart failure in years						
Median (IQR)	27.5	(19.4-34.5)	24.2	(17.2-33.7)	25.1	(18.3-34.2)
Status at end of follow-up						
Alive, n (%)	73	(58.4)	70	(61.4)	143	(59.8)
Died of heart failure, n (%)	24	(19.2)	18	(15.8)	42	(17.6)
Died of other cause, n (%)	28	(22.4)	26	(22.8)	54	(22.6)

*CTCAE: common terminology criteria for adverse event (version5)

A total of 72% of heart failure patients and 34.7% of controls received anthracycline, and 91.3% of cases and 88.9% of controls who received anthracycline received doxorubicin (

Table 19). Case patients received a median anthracycline dose of 357.3 mg/m²; however, controls received 292.4 mg/m²

A total, of 72.8% of case patients and 62.2% of controls were treated with radiotherapy. Among cases treated with radiotherapy, the mean doses to the heart and LV were 12.3 Gy (range: 0.004–49.1) and 11.9 Gy (range: 0.003–47.4), respectively (

Table 19). Control patients received a mean dose of 2.1 Gy (range: 0.005–45.3) to the heart and 2.1 Gy (range: 0.005–39.5) to the LV. The median volume of the heart that received ≥ 30 Gy was 61.1% (range: 0.1%–100%) in cases and 16.9% (range: 0.03%–100%) in controls. The median volume of the LV that received ≥ 30 Gy was 37.3% (range: 0.01%–100%) in cases and 23.8% (range: 0.06%–100%) in controls. The MHD was highly correlated with the mean left ventricle dose (MLVD) ($R^2=0.89$) (Table 21).

Table 21. Pearson’s correlation coefficients between radiation exposure measures.

DVH parameter	Mean dose heart	Mean dose LV	V20 Gy Heart	V20 Gy LV	V30 Gy heart	V30 Gy LV	V40 Gy heart	V40 Gy LV
Mean dose heart	1.00							
Mean dose LV	0.89	1.00						
V20 Gy heart	0.79	0.79	1.00					
V20 Gy LV	0.76	0.97	0.97	1.00				
V30 Gy heart	0.72	0.71	0.91	0.91	1.00			
V30 Gy LV	0.69	0.69	0.86	0.88	0.94	1.00		
V40 Gy heart	0.53	0.51	0.63	0.63	0.70	0.73	1.00	
V40 Gy LV	0.50	0.49	0.59	0.60	0.65	0.69	0.93	1.00

LV left ventricle

V(x) Gy Volume (%) of the heart or left ventricle receiving at least x Gy

5.2 Chemotherapy and splenectomy

The risk of heart failure increased with the cumulative dose of anthracycline ($P_{\text{trend}} < 0.0001$); compared to survivors who did not receive anthracycline, the risk of heart failure was multiplied by 3.4 (CI 95% 1.5-7.6) for patients who received doses below 250mg/m², by 11.4 (CI 95% 5.0-25.9) for those who received doses between 250mg/m² and 360 mg/m², and by 15.0 (CI 95% 7.1-31.7) for patients who received a dose higher than 360 mg/m² (Table 22). Alkylating agents were associated with a significantly increased risk of heart failure only at a cumulative dose of 10.7 mg/m² or higher, and vinca-alkaloids were not associated with heart failure even at higher doses (Table 22).

A total of 16 cases (6.7%) had undergone a splenectomy; these patients had a risk of heart failure multiplied by 3.5 (CI 95% 1.5-9.2) compared to those who had not received a splenectomy (Table 22).

Table 22. Heart failure risks by exposure to chemotherapy agents and splenectomy.

Treatment	Cases n=239		Controls n=1042		Odds ratio* (95% CI)	P-value
	n	(%)	N	(%)		
Anthracycline						<.0001
No†	67	(28.0)	680	(65.2)	1.0	
Yes	172	(72.0)	362	(34.8)	11.5	(6.6-20.1)
Alkylating agents						0.03
No†	57	(23.8)	512	(49.1)	1.0	
Yes	182	(76.2)	530	(50.9)	2.0	(1.2-3.4)
Vinca alkaloids						0.45
No†	42	(17.6)	387	(37.1)	1.0	
Yes	197	(82.4)	655	(62.9)	0.7	(0.4-1.4)
Cisplatin						0.76
No†	206	(86.2)	951	(91.3)	1.0	
Yes	33	(13.8)	91	(8.7)	1.1	(0.6-1.9)
Anthracycline mg/m²						<.0001
None†	67	(28.0)	680	(65.2)	1.0	
]0-250[34	(14.2)	144	(13.8)	3.4	(1.5-7.6)
[250-360[54	(22.6)	99	(9.5)	11.4	(5.0-25.9)
≥ 360	84	(35.2)	119	(11.5)	15.0	(7.1-31.7)
Doxorubicin mg/m²						<.0001
None‡	82	(34.3)	720	(69.1)	1.0	
]0-250[36	(15.0)	132	(12.7)	4.2	(2.4-7.9)
[250-360[50	(21.0)	86	(8.2)	14.8	(7.8-27.9)
≥ 360	71	(29.7)	104	(10.0)	19.6	(10.5-36.3)
Alkylating agents g/m²						0.03
None†	57	(23.8)	512	(49.1)	1.0	
]0-4.75[39	(16.3)	177	(17.0)	1.5	(0.7-3.3)
[4.75-10.7[54	(22.6)	176	(16.9)	1.2	(0.6-2.6)
≥10.7	89	(37.3)	177	(17.0)	2.4	(1.2-4.7)
Cisplatin mg/m²						0.23
None†	206	(86.2)	951	(91.3)	1.0	
]0-320[5	(2.2)	31	(3.0)	0.8	(0.2-2.6)
[320-500[14	(5.8)	28	(2.7)	2.2	(0.9-5.1)
≥500	14	(5.8)	32	(3.0)	1.5	(0.6-3.5)
Vinca alkaloids mg/m²						0.45
None†	42	(17.6)	387	(37.2)	1.0	
]0-14[54	(22.6)	221	(21.2)	1.5	(0.6-3.8)
[14-25[53	(22.1)	221	(21.2)	1.6	(0.6-4.0)

≥25	90 (37.7)	213 (20.4)	1.8	(0.7-4.3)	
Splenectomy					0.006
No†	223 (93.3)	1026 (98.5)	1.0		
Yes	16 (6.7)	16 (1.5)	3.5	(1.5-9.2)	

† Reference category

CI, confidence interval

*The odds ratio of developing heart failure were calculated using a logistic regression model conditional on matched sets adjusted for splenectomy, type of first childhood malignancy, chemotherapy agents, splenectomy and the mean radiation heart dose

5.3 Anthracycline and radiation dose–volume indicators

The relative risks of heart failure for patients receiving less than 250 mg/m² without and with cardiac radiation compared to patients unexposed to anthracycline and radiation were 3.3 and 7.2 respectively (Table 23). The interactions between anthracycline administration and the MHD (P = 0.007) and the MLVD (P < 0.004) were significant. In comparison to patients who did not receive either anthracycline or cardiac radiation, a mean radiation dose to the heart or LV below 15 Gy was associated with a non-significant risk of heart failure in patients unexposed to anthracycline (Table 24).

Table 23. Risks of heart failure among patients exposed to doses of anthracycline <250 mg/m² or ≥250 mg/m² and cardiac radiation.

Anthracycline	Cardiac radiotherapy	Cases		Controls		Odds ratio* (95% CI)
		N=238	(%)	N=1038	(%)	
None †	No	10	(4.2)	252	(24.3)	1.0
[0-250[No	10	(4.2)	65	(6.2)	3.3 (1.1-9.6)
≥ 250	No	49	(20.6)	108	(10.4)	13.9 (6.0-32.6)
None	Yes	57	(23.9)	425	(41.0)	2.6 (1.2-5.9)
[0-250[Yes	23	(9.7)	78	(7.5)	7.2 (3.0-18.0)
≥ 250	Yes	89	(37.4)	110	(10.6)	29.7 (12.9-68.6)

† Reference category

CI, confidence interval

*The odds ratio of developing heart failure were calculated using a logistic regression model conditional on matched sets adjusted for splenectomy, type of first childhood malignancy, vinca alkaloids, alkylating agents and other chemotherapies

Radiation doses were missing for 1 case and 4 controls

The risk of heart failure increased as increasing volumes of the heart and LV received ≥ 30 Gy. Among patients who had not received anthracycline, the risk of heart failure increased 3.6-fold (95% CI: 1.3–10.1) when $< 10\%$ of the LV received at least 30 Gy, compared to patients who were not exposed to any cardiac radiation and anthracycline. When $\geq 50\%$ of the volume of the LV received ≥ 30 Gy, the risk ratio reached 24.6 (95% CI: 10.3–58.7) (Table 24). CCS unexposed to anthracycline who received ≥ 30 Gy to 10%–50% and $\geq 50\%$ of the heart volume had ORs of 5.5 (95% CI: 2.1–14.1) and 17.0 (95% CI: 7.6–38.0), respectively. These risks were much higher among patients treated with anthracycline and were increased 28.3-fold (CI 95% 9.4–85.2) in patients receiving at least 30 Gy to $\geq 50\%$ of the heart volume (Table 24).

5.4 ERR and dose response relationship

The ERR/Gy for the MHD was 0.09/Gy (95% CI: 0.02–0.22) for patients exposed to anthracycline and 0.44/Gy (95% CI: 0.18–1.12) for patients unexposed to anthracycline. This lower slope for the effect of MHD in anthracycline-treated patients was associated with a higher baseline risk at a cardiac radiation dose of 0, leading to similar risks at higher MHD with and without anthracycline. Similar results were observed for the MLVD.

The potential ERR-modifying effects of other factors were evaluated. Apart from anthracycline treatment, no other factors significantly modified the effect of radiation. However, heart failure risk increased with each category of age, with ERR/Gy values for the MHD of 0.06, 0.33, 0.38 and 0.48 in those aged < 15 , [15–25[, [25–35[, and ≥ 35 years old, respectively.

Table 24. The risk of heart failure by the MHD, MLVD, V30 and anthracycline.

Radiation exposure measure	Treated without anthracycline					Treated with anthracycline					P-value	
	Cases N=67 (%)		Controls N=677 (%)		Odds Ratio (95% CI)*	Cases N=171 (%)		Controls N=361 (%)		Odds Ratio (95% CI)*		
Mean heart dose (Gy)												<.0001
0†	10	(4.2)	252	(24.3)	1.0	59	(24.8)	173	(16.7)	11.3	(4.7-27.0)	
]0 -5[8	(3.4)	251	(24.2)	0.7 (0.2-2.0)	61	(25.6)	127	(12.2)	21.5	(8.8-52.6)	
[5-15[6	(2.5)	64	(6.1)	2.0 (0.6-6.3)	12	(5.0)	18	(1.7)	23.8	(7.6-75.0)	
[15-30[16	(6.7)	83	(8.0)	5.2 (1.9-13.8)	33	(13.9)	34	(3.3)	54.4	(19.3-153)	
≥30	27	(11.4)	27	(2.6)	20.6 (7.6-55.3)	6	(2.5)	9	(0.9)	24.6	(7.2-84.1)	
Mean left ventricle dose (Gy)												<.0001
0†	10	(4.2)	252	(24.3)	1.0	58	(24.4)	174	(16.8)	11.7	(4.8-28.2)	
]0 -5[8	(3.4)	258	(24.8)	0.6 (0.2-1.8)	63	(26.4)	126	(12.1)	23.4	(9.3-56.7)	
[5-15[8	(3.4)	68	(6.6)	2.1 (0.7-6.5)	16	(6.7)	21	(2.0)	31.8	(10.6-95.0)	
[15-30[15	(6.3)	70	(6.7)	4.5 (1.7-12.0)	28	(11.8)	26	(2.5)	39.8	(14.4-110)	
≥30	26	(10.9)	29	(2.8)	42.1 (14.1-126)	6	(2.5)	14	(1.4)	35.8	(8.2-157)	
Volume of the heart (%) receiving 30+ Gy												<.0001
0†	24	(10.1)	559	(53.8)	1.0	142	(59.6)	324	(31.2)	16.5	(8.5-32.1)	
]0-10[6	(2.5)	49	(4.7)	1.9 (0.7-5.5)	9	(3.8)	13	(1.2)	22.2	(7.4-66.3)	
[10-50[9	(3.8)	36	(3.5)	5.5 (2.1-14.1)	10	(4.2)	12	(1.2)	26.4	(8.7-80.0)	
≥50	28	(11.8)	33	(3.2)	17 (7.6-38.0)	10	(4.2)	12	(1.2)	28.3	(9.4-85.2)	
Volume of the left ventricle (%) receiving 30+ Gy												<.0001
0†	27	(11.3)	580	(55.9)	1.0	143	(60.1)	329	(31.7)	14.7	(7.7-28.0)	
]0-10[6	(2.6)	32	(3.1)	3.6 (1.3-10.1)	11	(4.6)	9	(0.9)	37.9	(12.5-115)	
[10-50[13	(5.5)	42	(4.0)	6.6 (2.8-15.4)	11	(4.6)	12	(1.2)	26.5	(8.9-78.6)	
≥50	21	(8.8)	23	(2.2)	24.6 (10.3-58.7)	6	(2.5)	11	(1.0)	16.9	(4.9-58.4)	

† Reference category, MHD mean heart dose, MLVD mean left ventricle dose, V30 Gy volume of the heart receiving at least

*The odds ratio of developing heart failure were calculated using a logistic regression model conditional on matched sets, adjusted for splenectomy, type of first childhood malignancy, vinca alkaloids, alkylating agents and other chemotherapies

Radiation doses were missing for 1 case and 4 controls

5.5 Conventional cardiac disease risk factors.

Conventional cardiac disease risk factors were studied in the subpopulation of patients, who returned the lifestyle self-questionnaire, and this subpopulation included 117 cases and 353 matched controls. Diagnosis of diabetes mellitus before heart failure diagnosis was not associated with an increased risk of heart failure (OR = 0.7, 95% CI: 0.1–3.6), nor was smoking at the time of heart failure diagnosis or obesity (BMI ≥ 30) at the cut-off date. Patients who engaged in regular physical activity for ≥ 3 hours/week did not exhibit a reduced risk of heart failure compared to sedentary survivors (Table 25).

Table 25. Risk of heart failure according to cardiovascular disease risk factors.

Cardiovascular disease risk factors‡	Cases n=117		Controls n=353		Crude Odds ratio (95%CI)		Model ¹ Odds ratio (95%CI)		Model ² Odds ratio (95%CI)	
	n	(%)	n	(%)						
Smoker at diagnosis of heart failure										
Yes	20	(16.9)	93	(25.9)	0.6	(0.3-1.1)	0.8	(0.4-1.5)	0.6	(0.3-1.1)
Diabetes mellitus										
Yes	3	(2.5)	12	(3.3)	0.6	(0.2-2.5)	0.7	(0.1-3.6)	0.9	(0.4-2.0)
Obesity before the diagnosis of heart failure										
Yes	7	(5.9)	25	(7.0)	0.8	(0.3-1.9)	1.1	(0.4-3.1)	1.1	(0.6-2.0)
Regular physical activity										
< 1 hour weekly†	76	(64.4)	255	(71.0)	1.0		1.0		1.0	
1-3 hours weekly	18	(15.3)	38	(10.6)	1.4	(0.7-2.7)	0.9	(0.3-2.1)	1.0	(0.5-1.9)
≥ 3 hours weekly	24	(20.3)	66	(18.4)	1.2	(0.7-2.1)	0.9	(0.5-1.8)	1.1	(0.6-1.8)

† Reference group

‡ Patients were classified as having the risk factor if it was mentioned in their patient's medical record or by their cardiologist and/or general practitioner. Information on obesity was missing for 12 controls and 4 cases.

*The odds ratio of developing heart failure were calculated using a logistic regression model conditional on matched sets, all multivariable models were adjusted on anthracycline, vinca alkaloids, alkylating agents, other chemotherapies, mean dose of radiation to the heart, type of first childhood malignancy and splenectomy.

Model ¹: Each cardiovascular risk factor was studied in a separate multivariable model.Model ²: Cardiovascular risk factors were all included in the one multivariable model after multiple imputation for the missing values of BMI

6. Discussion

An important novel finding of this study was that there was a significantly elevated risk of heart failure in CCS, even when <10% of the LV volume received ≥ 30 Gy. The findings of this case–control study also confirmed that CCS who have been exposed to anthracycline and cardiac radiation are at higher risk of developing heart failure at a relatively young age.

To the best of the author’s knowledge, this is the first study to report a dose–response relationship based on dose–volume indicators in CCS. This study found that the risk of cardiac failure was related to both dose and irradiated volume. There are currently no published data concerning the dose–volume recommendations for radiation-induced heart failure in CCS. According to Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) reviews, which summarise the dose–volume and outcome information for many organs (153), patients who receive at least 25 Gy to >10% of the total heart volume are at increased risk of cardiac death (154). However, the QUANTEC reviews only provide dose–volume outcome information for adult cancer survivors.

It has been reported elsewhere that ventricular dysfunction can also occur, particularly in the context of anthracycline chemotherapy and radiation doses higher than 30 Gy to large volumes of the heart (155). Nevertheless, in our study, exposing small volumes of the heart or LV to at least 30 Gy led to a significant risk of cardiac failure.

The radiation dose–volume effects in the heart and cardiac substructures have been explored only in a few studies on adult survivors of Hodgkin Lymphoma (29, 145). The results support the findings of the current study. The mean dose to the heart provides an incomplete picture of the risk of heart failure as small volumes of the heart could receive highly inhomogeneous doses. The evaluation of the radiation dose received by the cardiac substructures (eg. heart valves, pericardium) is also crucial for understanding the specific types of cardiac toxicity. A recent study investigated the dose–response relationship based on dose–volume metrics among

adult survivors of Hodgkin lymphoma and found no significant interaction between anthracycline treatment and MHD or MLVD. The risk of heart failure in patients unexposed to anthracycline and with large volumes of the heart or LV exposed to at least 30 Gy was found to be moderate (145). The differences in heart failure risks between the previous study and the study reported in this paper may be explained by the differences in study populations, as the participants of the previous study were adults at the time of Hodgkin's lymphoma diagnosis. It could also be due to the fact that that study compared heart failure risk among patients who received at least 30 Gy to 25%–100% of the heart and LV volume to the heart failure risk in those who received 30 Gy to 0%–25% of the heart and LV volume.

Our study showed that, without anthracycline exposure, the risk of heart failure increased substantially with increasing doses to the heart or LV. Conversely, patients who received anthracycline had a higher baseline risk of heart failure which increased only moderately with increasing radiation doses to the heart. More precisely, CCS who did not receive anthracycline had an ERR/Gy for the MHD of 0.44 (95% CI: 0.18–1.12), while those treated with anthracycline and cardiac radiation had an ERR/Gy of 0.09 (95% CI: 0.02–0.22). In a study on self-reported CDs among CCS, the risk of heart failure was increased 1.6, 3.1 and 10.5-fold for MHD of 5–14, 15–34 and ≥ 34 Gy, respectively (130). The results from this previous study could not be compared to the results reported here as it did not include the interaction between anthracycline and cardiac radiation and did not provide ERRs.

The cumulative anthracycline dose is also a major factor for cardiotoxicity. Although a dose of anthracycline < 250 mg/m² was considered to be reasonably safe (80), our study shows that patients who received a dose of < 250 mg/m² without any cardiac radiation, had a heart failure risk that was 3.3-fold higher than those who did not receive either anthracycline nor any cardiac radiation. Similar results were also found in a study of 14 358 5-year CCS, where use of < 250 mg/m² of anthracycline was associated with a 2.4-fold higher risk of developing congestive

heart failure compared to patients who did not receive anthracycline (75). These results suggest that CCS exposed to low cumulative doses of anthracycline may also require long-term cardiac follow-up.

Splenectomy was the only other treatment factor, apart from anthracycline and radiation exposure, that was associated with an increased heart failure risk in this study. Similarly, another study found that splenectomy was also related to the risk of valvular disease in Hodgkin's lymphoma survivors (144). The mechanisms underlying splenectomy-related CDs in CCS are not yet understood and further studies need to be conducted.

In our study, 25 patients (10%) underwent heart transplantation (HT). This represents 49% of the patients with heart failure of grade 4, the population for whom HT is indicated. This is very similar to the 48% proportion of heart transplants in France reported in a study by Dorent R, et al. (156).

Diabetes mellitus, smoking, obesity and physical activity were tested for association with the risk of heart failure and were not significant. Patients were diagnosed with cardiac failure in their twenties, which may explain why these risk factors had no effect on their risk of heart failure. In a study by Nathan et al., the frequency of smoking initiation was lower among CCS compared with the general population; however, smoking was still considered as the most important risky health behaviour in CCS as it can potentiate organ damage associated with exposure to chemotherapy and radiation (157). Diet and physical activity can also affect the risk of long-term complications in CCS (158). Studies have reported that CCS are less physically active than the general population and that adult survivors are more likely to report a sedentary lifestyle than their siblings (159). Further studies are needed to identify and characterise the type and intensity of physical exercise recommended to reduce the cardiovascular disease burden in CCS (160).

There were some limitations to this study; for example, there were some uncertainties in the radiation-dose estimation due to the limitations of the computational phantoms three-

dimensional radiotherapy planning and due to the radiation-dose reconstruction being based on data from treatment planning charts. Hence, the estimation of the heart and LV volumes could have uncertainties as the calculation were derived from the phantoms and not based on actual volume measurement. Also, it was not possible to compare different anthracycline analogues in terms of heart failure risk, as most of the study participants received doxorubicin.

Another limitation to this study is the lack of data on renal function. Studies estimate that heart failure prevalence and incidence increases with the severity of CKD (161). Accordingly, the relation between CKD and CDs in CCS needs to be investigated in further studies.

Finally, in this study, we could not find a significant association between cardiovascular risk factors and the risk of heart failure in CCS. This could be related to the small number of responders included in the sensitivity analysis which may have lowered the statistical power and therefore reduced chances of detecting the true effect of these risk factors. However our results are not unanticipated as case patients were diagnosed with heart failure at a young age and were probably strongly affected by the burden of their childhood cancer treatments.

Chapter V The risk of chronic kidney disease among childhood cancer survivors

1. Context

Impaired renal function is one of the known potential late-effects after childhood cancer treatment which could manifest as acute irreversible renal failure, slowly progressive renal dysfunction or as specific defects in renal tubule cell function (162, 163). Renal dysfunction is currently defined as a spectrum known as CKD, which ranges from 1 to 5 based on age-adjusted GFR (164, 165).

Platinum based chemotherapies, ifosfamide, cyclophosphamide, radiotherapy involving the kidneys, and/or unilateral nephrectomy are risk factors for chronic renal impairment in CCS (30, 91). Furthermore, malignant disease itself may cause chronic renal impairment through several mechanisms like tumour infiltration, urinary tract obstruction or tumour lysis syndrome (30, 98).

Early CKD often has no sign or symptoms, patients can lose up to 90% of their kidney function before experiencing any signs (166). Furthermore, CKD is an independent potent risk factor for cardiovascular diseases (167) leading to serious cardiovascular events, cardiomyopathy, heart failure and ischemic heart disease (167). There is conflicting evidence on the risks of CKD in CCS and many studies have produced conflicting results, according to a review of the literature, the prevalence of decreased GFR ranged between 0% and 50% in CCS (168). Recently, larger studies have investigated long term renal impairment in CCS (92, 98, 169, 170). However, very long-term follow-up studies are still lacking (91). Therefore, we sought to investigate the risk factors of CKD after very long-term follow-up in the 5-year survivors of childhood malignancies included in the FCCSS cohort.

2. Methods

2.1 Patients

The FCCSS cohort comprises 7670 5-year survivors of childhood cancer treated between 1942 and 2000 for a solid cancer or a lymphoma before the age of 20 years (Table 1).

Clinical and histopathologic characteristics of the childhood cancer, detailed information on treatments, and follow-up data were abstracted from medical records. Childhood cancers were classified according to the International Childhood Cancer Classification (ICCC) (124).

A total of 87 patients with bilateral nephroblastoma were eliminated because they were mainly treated with bilateral nephrectomy. The analysis was therefore performed on a total of 7583 5-year CCS.

2.2 Outcome definition

CKD defined was defined according to the recommendations proposed by the Kidney Disease Quality Outcome Initiative (K/DOQI) (171) as kidney damage or GFR <60 mL/min/1.73 m² for at least 3 months disease (172) (Table 26). Kidney damage in many kidney diseases can be ascertained by the presence of albuminuria, defined as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens. GFR can be estimated from calibrated serum creatinine and estimating equations, such as the Modification of Diet in Renal Disease (MDRD) Study equation or the Cockcroft-Gault formula. Kidney disease severity is classified into five stages according to the level of GFR (172)

MDRD equation GFR (mL/min/1.73 m²) = 175 × (Scr)^{-1.154} × (Age)^{-0.203} × (0.742 if female) × (1.212 if African American)

The equation does not require weight or height variables because the results are reported normalized to 1.73 m² body surface area, which is an accepted average adult surface area.

Table 26. Classification of chronic kidney disease (CKD).

Stage	Description	Classification by severity		ICD-10 coding
		GFR mL/min/1.73 m ²	Related terms	
1	Kidney damage with normal or ↑ GFR	≥90	Albuminuria, proteinuria, haematuria	N18.1
2	Kidney damage with mild ↓GFR	60–89	Albuminuria, proteinuria, haematuria	N18.2
3	Moderate ↓ GFR	30–59	Chronic renal insufficiency, early renal insufficiency	N18.3
4	Severe ↓ GFR	15–29	Chronic renal insufficiency, late renal insufficiency, pre-ESKD	N18.4
5	Kidney failure	<15 (or dialysis)	Renal failure, uraemia, ESKD	N18.5

GFR, glomerular filtration rate; ESKD, end-stage kidney disease, Related terms for CKD stages 3 to 5 do not have specific definitions, except ESKD

Table 27. Classification of CKD according to the Common Terminology Criteria for Adverse Events (CTCAE) (147).

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) 0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m ²	eGFR or CrCl 29 - 15 ml/min/1.73 m ²	eGFR or CrCl <15 ml/min/1.73 m ² ; dialysis or renal transplant indicated	Death

2.3 Identification and validation of chronic kidney disease patients

CKD patients were identified from multiple sources: auto-reported in self-questionnaires, medical records, long-term follow-up consultation CCS, the French national healthcare data system and from the causes of death (Figure 6).

Patients were identified as having a CKD from the French national healthcare data system if they were hospitalized at least once for a CKD coded in ICD-10 in the main or associated causes (Table 26), if they had severe chronic nephropathy as a long term illness referred to as (Affection de Longue Durée ALD) associated with a CKD diagnosis coded in ICD-10, and if they were dialyzed for at least 3 months or were kidney transplanted.

The nephrologists or general practitioners of patients who provided a written consent and returned self-questionnaires reporting a kidney dysfunction and those identified as having a CKD in the National Health Data System were contacted to fill a detailed medical form containing information on the date of the onset of the CKD, GFR, serum creatinine levels and comorbidities (Appendix 2). Kidney imaging and clinical laboratory tests (ie blood urea nitrogen, creatinine, and GFR) were also extracted for patients who attended the long-term follow-up clinic for CCS in Gustave Roussy. For deceased patients all causes listed on the death certificate were extracted to identify those who died from a CKD. Overall a total of 275 patients with CKD were validated and included in this study.

2.4 Treatment factors

Data on childhood cancer diagnosis and treatment were extracted from the medical records for all patients (Table 4). For reconstruction of the radiation doses, each patient's clinical parameters, including sex, age, height, weight, and any available data on external measurements that could be obtained were collected from treatment planning charts (Figure 7). Each patient's radiotherapy parameters, including target-volume locations, prescribed dose, and number of fields, field configuration, field size, and type of treatment machine, beam energies, and other

parameters were abstracted. This enabled us highly individualized reconstruction of radiation doses to the kidneys as close as possible to actual treatment conditions of each patient (Figure 8). The maximum dose and mean dose to the kidneys were tested in addition to the volume of both kidneys or the remaining kidney among nephrectomized patients that received at least 10Gy (V10Gy) and 20Gy (V20Gy).

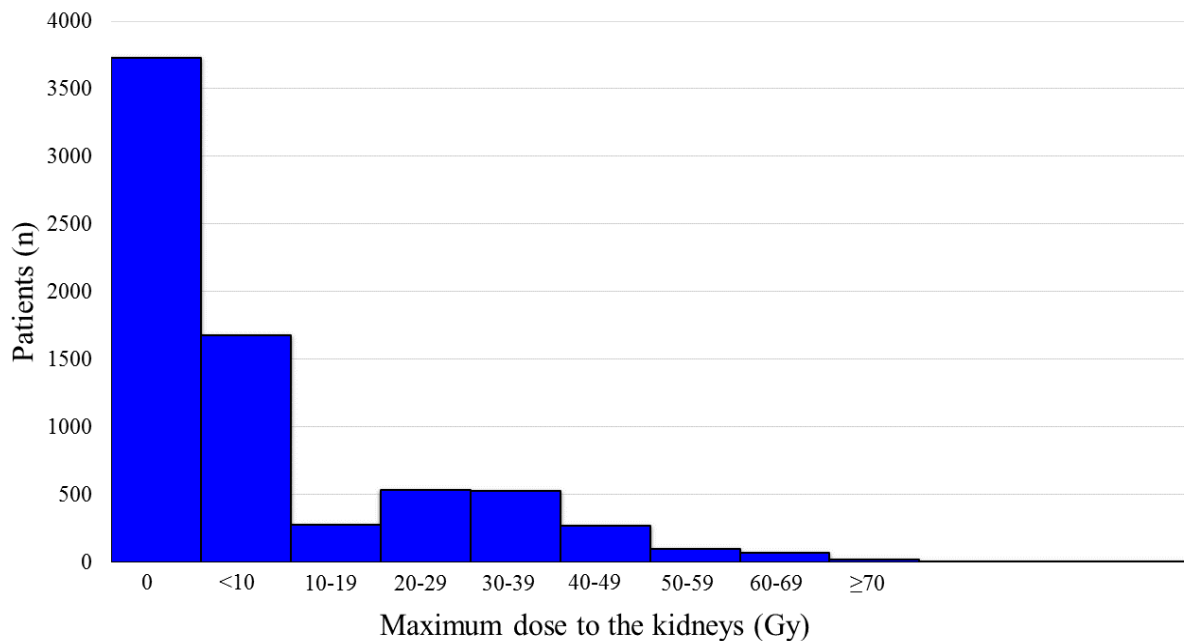


Figure 12. Distribution of the maximum radiation dose to the kidneys.

3. Statistical analysis

Follow-up started 5-years after childhood cancer diagnosis and ended at the date of death for deceased patients, the date of last medical contact or the date of onset of the CKD for case patients. Values of continuous variables were expressed as median and IQR. Pearson chi-square test and Wilcoxon-Mann-Whitney were used to compare differences in categorical and continuous variables.

We estimated the cumulative incidence of CKD with attained age as time scale using the nonparametric Aalen-Johansen estimator and death from causes other than CKD was

considered competing events (132). Gray's test was used to compare cumulative incidence functions between two groups (133).

We assessed risk factors for CKD using a multivariable cox proportional hazards model with follow-up as the time scale. Cox proportional-hazards models were tested and verified for proportionality of hazards by visual inspection of the Schoenfeld residuals. The final multivariable model included known potential risk factors for CKD and all characteristics with P-values <0.05. This final model was used to compute Hazard Ratios (HRs) along with their 95% confidence intervals. For covariates that were missing more than 2% of values, a missing category was created. Cardiac diseases in general, heart failure, cerebrovascular diseases and diabetes was included in Cox models as time-dependent variable during follow-up. Interactions between the radiation dose to the kidneys and other covariates was tested by adding an interaction term to a Cox proportional hazards model and testing its significance with the Wald test.

To modelize dose-response relationship of radiation doses we used two methods. We first we used the method described by Robertson et al (173) and more recently by Lorenz et al (174) for Spike At Zero (SAZ) variables. This method is suitable for variable that include a high proportion of unexposed patients which corresponds to radiation exposure to the kidneys in our study (Figure 12). Using SAZ models, we included a binary variable (z) for individuals who were unexposed to any radiation involving the kidneys. The SAZ model included the continuous maximum radiation dose to the kidneys in addition to the binary SAZ variable z . We then analysed the maximum radiation dose to the kidneys with classical Cox proportional hazard models. All models were then ranked according to the Akaike Information Criterion (AIC).

A sensitivity analysis on a subset of 3145 patients who returned self-reported questionnaire was used to evaluate the role of treated hypertension, alcohol consumption, obesity and smoking. Smoking status was classified as never-smokers (smoked <100 cigarettes in their lifetime and

not currently smoking), former smokers (smoked ≥ 100 cigarettes in their lifetime and currently a nonsmoker), and current-smokers (smoked ≥ 100 cigarettes in their lifetime and currently a smoker).

Two-sided *P*-values were reported, and those of less than 0.05 were considered statistically significant. Analyses were performed using SAS 9.4.

4. Results

4.1 Patients

A total of 7583 5-year childhood cancer survivors were included in this study including 275 with CKD. The median year of diagnosis of childhood malignancy was 1987 (IQR, 1979-1994). These patients were followed for a median of 24.7 years (IQR, 17.3-33.2) and 16.7% were deceased by the end of follow-up (Table 28).

4.2 Characteristics of CKD patients

The median age at diagnosis of CKD was 39.3 (6.1-65.5). Among CKD patients, 39.3% had severely decreased GFR or ESKD, 17.1% were treated with dialysis and 16.4% received a kidney transplant (Table 29).

CKD patients were also treated significantly more with unilateral nephrectomy compared to other CCS which is mostly related to the fact that they had more renal tumours and neuroblastomas than the rest of the FCCSS cohort. Overall, 38% for CCS without CKD were treated with anthracycline compared to only 28.4% among CKD patients and only 8.7% of CKD patients received cisplatin compared to 14% in the FCCSS cohort (Table 30). Patients with renal malignancies in the FCCSS cohort were rarely treated with cisplatin which explained the smaller number of CKD patients who were treated with Cisplatin compared to the rest of the cohort.

In most cases, CKD patients were treated mainly with radiotherapy (85.1%) and the maximum dose received by the kidneys was also much higher in patients with renal impairment 19.0 Gy

(IQR 1.1-35.0) compared to 10.3 Gy (IQR 0.3-31.3) for the rest of CCS (Table 30). Among patients treated with radiation involving the kidneys, the median volume that received at least 10Gy was 1.1% (IQR 0-48%) in patients with CKD compared to a median of 0% (IQR 0-45%) in other cohort members. The median volume that received at least 20Gy was also very low among both CKD and the remaining cohort patients.

Table 28. Characteristics of survivors of childhood cancer with and without chronic kidney disease (CKD).

Patient characteristics	CCS with CKD (n=275)		Patients without CKD (n= 7308)		P
Sex, n (%)					0.23
Male	141	(51.3)	4014	(54.9)	
Female	134	(48.7)	3294	(45.1)	
Type of primary childhood malignancy, n (%)					<.0001
Hodgkin lymphoma	11	(4.0)	479	(6.6)	
Non-Hodgkin lymphomas	17	(6.2)	772	(10.6)	
CNS and brain tumours	22	(8.0)	1123	(15.4)	
Neuroblastoma	29	(10.5)	1005	(13.8)	
Retinoblastoma	20	(7.3)	706	(9.7)	
Renal tumours	86	(31.3)	971	(13.3)	
Malignant bone tumours	27	(9.8)	682	(9.3)	
Soft tissue and other extraosseous sarcomas	39	(14.2)	798	(10.9)	
Germ cell tumours	17	(6.2)	452	(6.2)	
Other	7	(2.5)	320	(4.4)	
Year of primary cancer diagnosis, median (IQR)	1967 (1957-1980)		1987 (1979-1994)		<.0001
<1970	145	(52.7)	503	(6.9)	
1970-1979	58	(21.1)	1462	(20.0)	
1980-1989	52	(18.9)	2401	(32.9)	
1990-2000	20	(7.3)	2942	(40.3)	
Age at diagnosis (years),					0.01
Median (IQR)	4.2 (1.6-9.5)		5.4 (1.7-11.3)		
Follow-up, (years)					<.0001
Median (IQR)	39.3 (31.6-51.7)		24.7 (17.3-33.2)		
Vital status at the end of follow-up, n (%)					<.0001
Alive	156	(56.7)	6088	(83.3)	
Deceased	119	(43.3)	1220	(16.7)	
Any cardiovascular disease, n (%)					<.0001
Yes	53	(19.3)	417	(5.7)	
Heart failure, n (%)					<.0001
Yes	27	(9.8)	193	(2.6)	
Cerebrovascular disease, n (%)					<.0001
Yes	14	(5.1)	112	(1.5)	

CNS= Central Nervous system

Cardiovascular disease included heart failure, valvular disease, ischemic heart disease, angina, dysrhythmia, cerebrovascular disease

Table 29. Characteristics of chronic kidney disease patients by unilateral nephrectomy.

Characteristics	Non-nephrectomized patients n=157		Nephrectomized patients n=118		Total n=275	
Stages of CKD						
Mildly or moderately decreased GFR 60-30 mL/min/1.73m ²	126	(80.3)	87	(73.7)	167	(60.7)
Severely decreased GFR or ESKD <30 mL/min/1.73m ²	31	(19.7)	31	(26.3)	108	(39.3)
Dialysis						
Yes (%)	28	(17.8)	19	(16.1)	47	(17.1)
Kidney transplantation						
Yes (%)	21	(13.4)	24	(20.3)	45	(16.4)
Vital status at the end of follow-up						
Alive	91	(58.0)	65	(55.1)	156	(56.7)
Dead related to renal disease*	1	(0.6)	0	(0)	1	(0.4)
Death related to cardiovascular disease*	6	(3.8)	4	(3.4)	10	(3.6)
Age at diagnosis of CKD						
Median (range)	37.4 (6.1-63.8)		42.6 (16.8-65.5)		39.3 (6.1-65.5)	

GFR, Glomerular Filtration Rate

*based on the underlying cause of death

Table 30. Treatment characteristics of survivors of childhood cancer with and without chronic kidney disease (CKD).

Patient characteristics	CCS with CKD (n=275)		Patients without CKD (n= 7308)		P
	N	(%)	N	(%)	
Chemotherapy					<.0001
Yes n (%)	165	(60.0)	5510	(75.4)	
Anthracycline					
Yes n (%)	78	(28.4)	2805	(38.4)	0.0008
Dose mg/m ² , median (IQR)	313.2 (202.4-391.3)		241.7 (150.4-357.7)		0.13
Missing	5	(1.8)	44	(0.6)	
Doxorubicin					
Yes n (%)	63	(22.9)	2397	(32.8)	0.0006
Dose mg/m ² , median (IQR)	324.0 (224.7-391.3)		228.9 (134.9-350.0)		0.14
Missing	4	(1.4)	39	(0.5)	
Vinca Alkaloids					
Yes n (%)	104	(37.8)	4267	(58.4)	<.0001
Dose mg/m ² , median (IQR)	21.4 (12.5-32.0)		16.5 (8.2-27.8)		0.002
Missing	1	(0.4)	128	(1.8)	
Alkylating agents					
Yes, n (%)	98	35.6	4202	(57.5)	<.0001
Dose g/m ² , median (IQR)	9.7 (4.5-22.2)		6.6 (3.2-15.3)		<.0001
Missing	3	(1.1)	70	(1.0)	
Cyclophosphamide					
Yes, n (%)	56	20.4	2747	(37.6)	<.0001
Dose g/m ² , median (IQR)	5.7 (3.7-11.6)		5.4 (3.0-8.9)		<.0001
Missing	0	(0)	49	(0.7)	
Ifosfamide					
Yes, n (%)	27	(9.8)	913	(12.5)	0.18
Dose g/m ² , median (IQR)	54.0 (27.4-59.2)		34.7 (18.0-54.0)		0.06
Missing	2	(0.7)	25	(0.3)	
Cisplatin					
Yes, n (%)	24	(8.7)	1022	(14.0)	0.01
Dose mg/m ² , median (IQR)	503.0 (297.0-604.0)		368.1 (239.3-505.0)		0.06
Missing	2	(0.7)	25	(0.3)	
Radiotherapy					
Yes, n (%)	234	(85.1)	3961	(54.2)	<.0001
Radiation to the kidneys[†]					
Max dose (Gy), median (IQR)	19.0 (1.1-35.0)		10.3 (0.3-31.3)		<.0001
V10 Gy, (%) *, (IQR)	1.1 (0-48.0)		0 (0-45.0)		
V20 Gy, (%) *, (IQR)	0 (0-46.0)		0 (0-27.0)		
Unilateral nephrectomy					
Yes, n (%)	118	(42.9)	1074	(14.7)	<.0001

[†] if patients were unilaterally nephrectomized the maximum dose was estimated for the remaining kidney

*among patients treated with radiotherapy involving the kidney

V10, volume of the two kidneys receiving at least 10Gy

V20, volume of the kidneys receiving at least 20Gy

4.3 Cumulative incidence of CKD

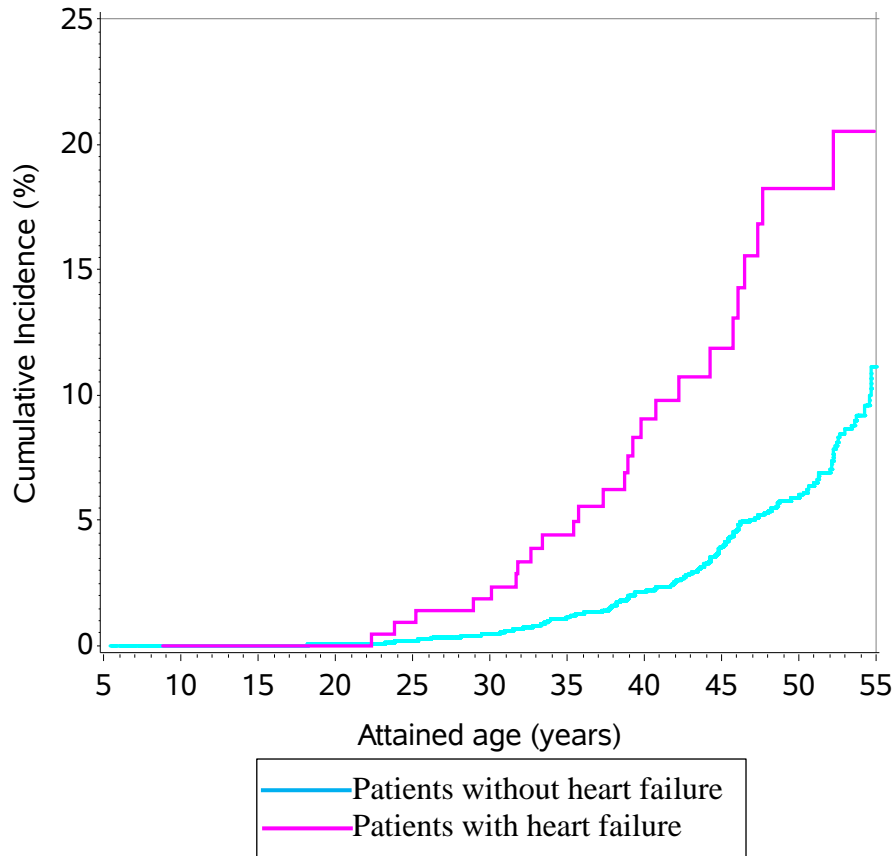
The cumulative incidence of CKD at 40 years old was 2.4%, severe or ESKD was very rare in CCS with a cumulative incidence of only 0.9% (Table 31).

The cumulative incidence of CKD was significantly higher among nephrectomized patients (P Gray test <0.0001), at 40 years the cumulative incidence of CKD among CCS treated with unilateral nephrectomy was 5.9% compared to only 1.4% in other CCS (Figure 13).

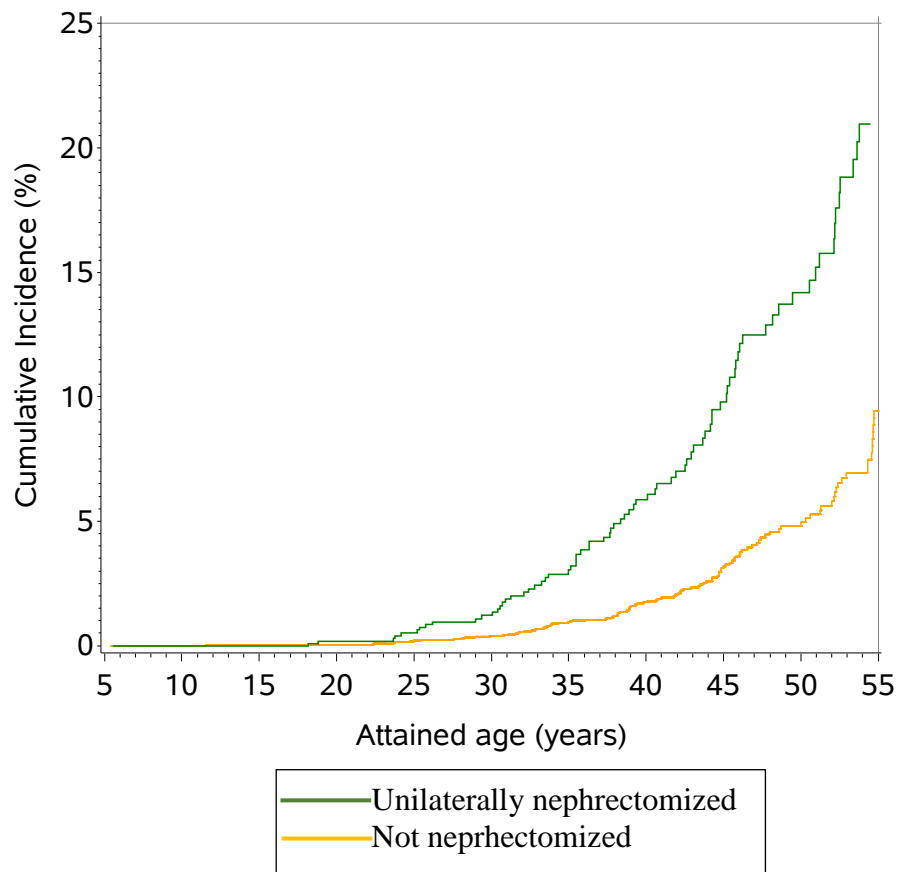
The cumulative incidence of CKD at 40 years of age was also 6.1% and 5.5% among nephrectomized patients who received less than 20Gy and ≥ 20 Gy respectively. Among patients with both kidneys the cumulative incidence was much lower, with only 1.6% among those who received less than 20Gy and 2.0% among those who received a maximum dose higher than 20Gy (Figure 13).

CCS with heart failure had also a significantly higher cumulative incidence of CKD, at 40 years 9.0% of heart failure patients had CKD compared to 2.1% in those without heart failure.

A- Cumulative incidence of CKD by heart failure



B- Cumulative incidence of CKD by unilateral nephrectomy



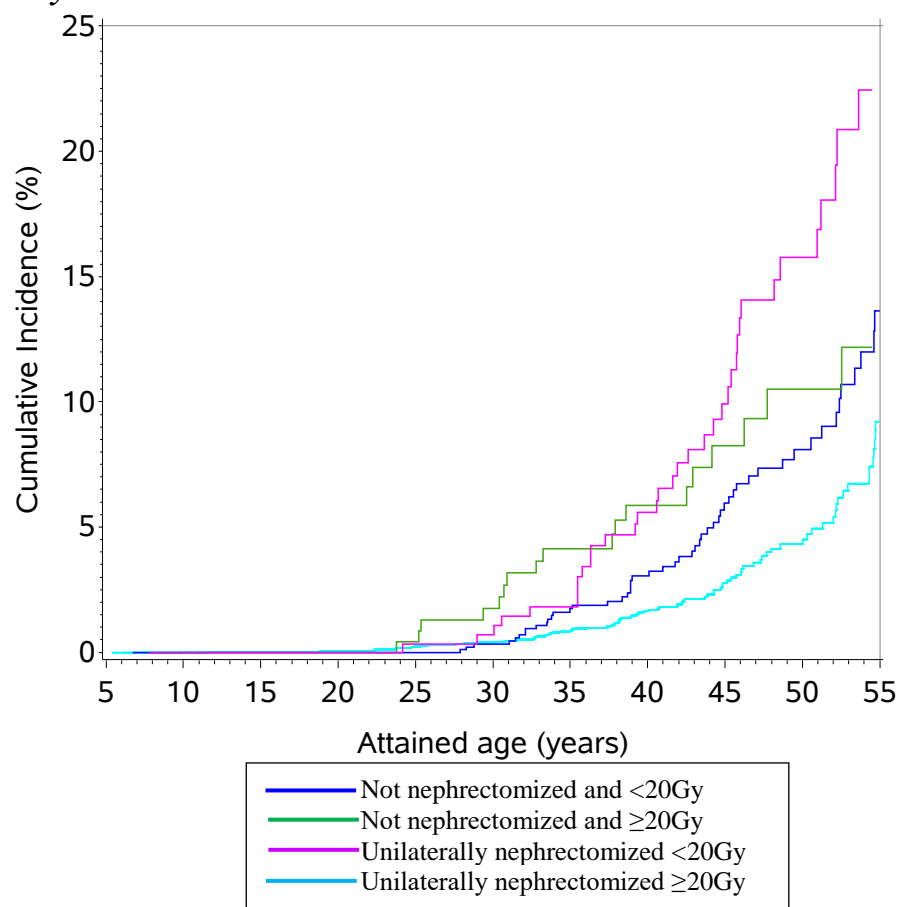
C- Cumulative incidence of CKD by exposure to radiation and unilateral nephrectomy**Figure 13. Cumulative incidence of chronic kidney disease (CKD) in the FCCSS cohort.**

Table 31. Cumulative incidence of chronic kidney disease (CKD) and severe or life-threatening chronic kidney disease by types of childhood malignancies.

Type of primary childhood malignancy	All grades n=275			Severe or life-threatening chronic kidney disease* n=108		
	Cases	Cumulative incidence at age 40 (95% CI)		Cases	Cumulative incidence at age 40 (95% CI)	
Overall	275	2.4	(2.0-3.0)	108	0.9	(0.6-1.0)
Hodgkin lymphoma	11	0.9	(0.2-2.6)	1	0	NA
Non-Hodgkin lymphomas	17	0.7	(0.2-1.9)	10	0.3	(0.07-1.2)
CNS and brain tumours	22	1.0	(0.4-2.0)	10	0.2	(0.05-0.9)
Neuroblastoma	29	4.9	(2.9-7.7)	13	2.6	(1.2-4.89)
Retinoblastoma	20	2.2	(0.6-5.7)	8	1.6	(0.3-5.2)
Renal tumours	86	5.1	(3.5-7.2)	31	1.7	(0.9-3.1)
Malignant bone tumours	27	2.2	(1.1-3.8)	8	0.2	(0.02-1.3)
Soft tissue and other extraosseous sarcomas	39	2.3	(1.2-4.0)	14	0.5	(0.1-1.6)
Germ cell tumours	17	2.7	(1.2-5.4)	11	2.5	(0.1-5.1)
Other	7	1.3	(0.2-4.3)	2	0.5	(0.05-2.8)

*according to the Common Terminology Criteria for Adverse Events (CTCAE)

4.4 The effect of cardiovascular risk factors on the risks of CKD

In this study patients with at least one cardiovascular disease had 2.8-fold higher risk of developing CKD compared to those without any cardiovascular disease. Heart failure, which was the most frequent cardiovascular comorbidity in all CCS was also associated with a very high risk of CKD (HR=4.8 95% CI 3.0-7.6). Diabetes was rare in CCS with CKD (4%) and was not associated with any higher risk of CKD (Table 32).

The results remained the same when we restricted the analysis to severe CKD or ESKD except for cerebrovascular disease which was not associated with the severe form of CKD in this study (Table 32).

Table 32. The link between cardiovascular disease, diabetes and chronic kidney disease among 5-year survivors of childhood malignancies.

Cardiovascular disease and diabetes	N/n	Any chronic kidney disease n=275		Severe or life-threatening chronic kidney disease* n=108		
		HR	95% CI	N/n	HR	95% CI
Any cardiovascular disease						
No	6892/222	Ref		7020/94	Ref	
Yes	417/53	2.8	(2.0-3.9)	456/14	2.0	(1.1-3.6)
Heart failure						
No	7116/248	Ref		7263/101	Ref	
Yes	193/27	4.8	(3.0-7.6)	213/7	5.5	(2.3-13.4)
Cerebrovascular disease						
No	7197/261	Ref		7353/105	Ref	
Yes	112/14	2.2	(1.1-4.2)	123/3	1.0	(0.5-2.3)
Diabetes mellitus						
No	7165/264	Ref		7329/100	Ref	
Yes	144/11	0.6	(0.3-1.1)	147/8	0.8	(0.2-3.4)

N; number of patients without CKD, n; number of patients with CKD, Ref; reference, HR; Hazard ratio, CI; confidence interval

Cardiovascular disease included heart failure, valvular disease, ischemic heart disease, angina, dysrhythmia, cerebrovascular disease

*according to CTCAE grades

4.5 The role of chemotherapy and unilateral nephrectomy

In this study we found that an older age at diagnosis of primary malignancy was associated with a higher risk of CKD HR=2.0 (95% CI 1.1-3.5). Patients with renal tumours and other renal malignancies didn't have a significantly higher risk of CKD compared to patients with other childhood malignancies after adjustment for treatment related risk factors. Nevertheless, patients treated with unilateral nephrectomy had 2.9-fold-increased risk of CKD compared CCS with both kidneys. Because of the small number of CKD patients who received Cisplatin we couldn't establish a dose response relationship, however those who received cisplatin had 1.6-fold higher risk of CKD compared to those who didn't (Table 33).

Ifosfamide was also a major risk factor for CKD, risks were 2.2-fold-higher (95% CI 1.0-4.3) in CCS who received a cumulative doses less than 40g/m² and 5.0 fold-higher (95% 2.7-9.1) in those treated with ≥ 40 g/m² (Table 33).

Anthracycline was also associated with a higher risk of CKD, however, after adjusting for heart failure only doses higher than 350 mg/m² remained associated with a significant risk of CKD HR=1.7 (95% CI 1.0-2.7) (Table 33).

Table 33. Risk factors of all and severe or life-threatening chronic kidney disease among 5-year survivors in the FCCSS cohort

Characteristic	All CKD			Severe or life-threatening CKD	
	N/n	HR	95% CI	HR	95% CI
Sex					
Male [†]	4014/141	Ref		Reference	
Female	3294/134	1.1	(0.9-1.4)	1.1	(0.8-1.4)
Age at cancer diagnosis, years					
<5 [†]	3499/153	Ref		Reference	
5-9	1611/58	1.1	(1.1-1.4)	1.1	(0.8-1.5)
10-14	1574/49	1.0	(1.0-1.4)	1.0	(0.7-1.4)
≥15	624/15	1.9	(1.9-3.3)	2.0	(1.1-3.5)
Type of childhood malignancy					
Renal malignancies [†]	971/86	Ref		Reference	
Other malignancies	6337/189	1.0	(0.6-1.6)	0.9	(0.6-1.6)
Anthracycline, mg/m²					
0 [†]	4503/197	Ref		Reference	
<350	2009/43	1.3	(0.9-2.0)	1.1	(0.7-1.6)
≥350	752/30	2.2	(1.4-3.5)	1.7	(1.0-2.7)
Ifosfamide, g/m²					
0 [†]	6395/248	Ref		Reference	
<40	533/10	2.2	(1.1-4.5)	2.1	(1.0-4.3)
≥40	355/15	5.2	(2.9-9.6)	5.0	(2.7-9.1)
Cisplatin					
No [†]	6286/251	Ref		Reference	
Yes	1022/24	1.6	(1.0-2.6)	1.6	(1.0-2.6)
Unilateral nephrectomy					
No [†]	6234/157	Ref		Reference	
Yes	1074/118	2.9	(1.9-4.4)	2.8	(1.9-4.3)

N, number of patients without CKD; n, number of patients with CKD; Ref, reference category; HR, Hazard Ratios; CI, confidence intervals; Multivariable models were adjusted on sex, type of childhood malignancy, year of diagnosis of childhood cancer malignancy, anthracycline, ifosfamide, cisplatin, unilateral nephrectomy and maximum radiation dose to the kidneys

4.6 The role of the radiation dose and dose-volume of the kidneys

Multivariable SAZ model (model 1), was adjusted on sex, type of childhood malignancy, year of diagnosis of childhood cancer malignancy, anthracycline, ifosfamide, cisplatin, unilateral nephrectomy and an additional to the z which stands for radiotherapy involving the kidneys (yes/no). Model 2 was also adjusted on the same variables without z. When studying the effect of the radiation therapy to the kidneys, multivariable SAZ model and Model 2 were similar in

terms of AIC. (Table 34) and the HR per Gy was 1.01 (CI 95% 1.0-1.02) for both models. Because SAZ performed like Model 1, multivariable analysis for dose volume and radiation dose categories were only based on model 1.

The interaction between the maximum radiation dose and unilateral nephrectomy was statistically significant (P interaction =0.01) therefore risks for CKD were stratified by nephrectomy status.

In non-nephrectomized patients, a maximum radiation dose less than 20Gy were not associated with a significant risk of CKD and patients exposed to a maximum radiation dose to both kidneys higher than 20Gy had a 2-fold higher risk of developing CKD compared to those who didn't receive any radiation to the kidneys. In contrast, even very small radiation doses to the kidneys (<1Gy) were associated with a significant risk of CKD in patients with one functional kidney. HRs started at 4.8 (95% CI 1.6-14.3) among nephrectomized patients who received a maximum dose less than 1Gy and remained in the same range for much higher doses (Table 35). Results remained similar when analysis was restricted to patients who returned self-reported questionnaire (Table 37).

4.7 The role of hypertension and lifestyle risk factors

In a sensitivity analysis, we evaluated the role of treated hypertension declared by patients who returned the self-questionnaire, a total of 148 CKD patients and 2 997 CCS without CKD were included in the analysis (Table 36). A total of 23% of CKD patients received treatment for hypertension and there was significant association between hypertension and the risk of CKD. Obesity, smoking and alcohol consumption were also not associated with an increased risk of CKD in 5-year CCS who returned the self-questionnaire (Table 36).

Table 34. Adjusted and unadjusted risks of chronic kidney disease (CKD) by 1Gy of maximum radiation dose to the kidneys using Spike At Zero (SAZ) and classical Cox models.

Model	Chronic kidney disease all stages n=275					
	Unadjusted HR/Gy (95%CI)		AIC	Adjusted HR/Gy (95%CI)		AIC
Maximum dose to the kidneys						
Model 1 SAZ linear dose+z	1.0	(1.0-1.01)	3397	1.01	(1.0-1.02)	3271
Model 2 linear dose	1.01	(1.01-1.02)	3400	1.01	(1.0-1.02)	3274

N= number of patients without CKD; n=number of patients with CKD, HR= Hazard Ratios, CI= confidence intervals, AIC=Akaike information criterion

Model 1 included z: radiation involving the kidneys (yes/no)

Model 1 and model 2 were adjusted on sex, type of childhood malignancy, year of diagnosis of childhood cancer malignancy, anthracycline, ifosfamide, cisplatin and unilateral nephrectomy

Table 35. The risks of CKD by the maximum dose to the kidneys, V5, V20 and V30

	All CKD					
	Non nephrectomized patients			Unilaterally nephrectomized patients		
	N/n	HR	95% CI	N/n	HR	95% CI
Maximum dose to the kidneys						
0	2990/37	Ref		500/7	Ref	
<5	1564/61	1.3	(0.8-2.0)	57/22	3.4	(1.3-9.0)
5-14	147/10	1.6	(0.8-3.4)	128/29	3.0	(1.2-7.4)
15-29	433/15	1.4	(0.8-2.7)	248/33	3.1	(1.3-7.4)
≥30	644/30	2.3	(1.4-3.9)	119/23	4.0	(1.5-9.7)
V5 Gy kidneys (%)						
No Rt	2990/37	Ref		500/7	Ref	
0	1564/61	1.3	(0.8-2.0)	57/22	3.3	(1.3-8.9)
<50	439/19	1.7	(0.9-3.0)	193/30	3.0	(1.2-7.3)
≥50	785/36	2.0	(1.2-3.3)	302/55	3.4	(1.4-8.1)
V20 Gy kidneys (%)						
No Rt	2990/37	Ref		500/7	Ref	
0	1814/75	1.4	(0.8-2.1)	271/60	2.9	(1.2-7.0)
<50	671/29	1.8	(1.1-3.1)	200/39	3.9	(1.6-9.4)
≥50	303/12	2.3	(1.2-4.6)	81/8	2.8	(1.0-8.1)
V30 Gy kidneys (%)						
No Rt	2990/37	Ref		500/7	Ref	
0	2144/86	1.4	(0.8-2.1)	433/84	3.1	(1.3-7.2)
<25	358/20	2.4	(1.3-4.2)	85/17	3.9	(1.5-10.0)
≥25	286/10	2.2	(1.1-4.5)	34/6	3.9	(1.2-12.5)

N, number of patients without CKD; n, number of patients with CKD; Ref, reference category; HR, Hazard Ratios; CI, confidence intervals; V5 Gy, volume of the kidneys that received at least 5 Gy; V20 Gy, volume of the kidneys that received at least 20 Gy; V30 Gy, volume of the kidneys that received at least 30 Gy

Multivariable models were adjusted on sex, type of childhood malignancy, year of diagnosis of childhood malignancy, age at diagnosis of primary malignancy, anthracycline, ifosfamide, cisplatin, heart failure, diabetes and cerebrovascular disease

Table 36. Hazard ratios of CKD according to treated hypertension, obesity, smoking status and alcoholic consumption among patients who returned self-questionnaire

	All CKD n=148			Severe or life-threatening CKD n=53		
	n/N	HR	95% CI	n/N	HR	95% CI
Treated hypertension						
No	2755/114	Ref		2835/34		
Yes	242/34	0.8	(0.5-1.3)	257/19	1.3	(0.7-2.6)
Body mass index						
<18.5	536/25	0.6	(0.4-1.0)	552/9	0.6	(0.2-1.3)
18.5-24.9	1825/95	Ref		1890/30	Ref	
25.0-29.9	233/7	0.7	(0.3-1.5)	238/2	0.5	(0.1-2.3)
≥30	61/3	1.0	(0.3-3.2)	62/2	1.0	(0.2-4.7)
Smoking						
Never smoker	1737/85	Ref		1783/39		
Former somker	539/31	0.9	(0.5-1.4)	561/9	0.5	(0.2-1.3)
Current smoker	721/32	1.2	(0.7-1.8)	748/5	0.4	(0.1-1.3)
Alcoholic drinks/day						
<1	2817/135	Ref		2906/45	Ref	
1-2	158/11	1.0	(0.5-2.1)	163/6	1.4	(0.4-4.4)
≥3	22/2	0.6	(0.1-2.7)	23/1	0.7	(0.1-6.8)

N, number of patients without CKD; n, number of patients with CKD, Ref; reference, HR, Hazard Ratios, CI, confidence intervals,

Multivariable models were adjusted on sex, type of childhood malignancy (Wilms yes/no), year of diagnosis of childhood cancer malignancy, anthracycline, ifosfamide, cisplatin, unilateral nephrectomy, maximum radiation dose to the kidneys, treated hypertension, body mass index, smoking status and alcoholic consumption

Table 37. The risks of CKD by the maximum dose to the kidneys, V5, V20 and V30 among patients who returned self-questionnaire

	All CKD					
	Non nephrectomized patients			Unilaterally nephrectomized patients		
	N/n	HR	95% CI	N/n	HR	95% CI
Maximum dose to the kidneys						
0	1135/21	Ref		230/2	Ref	
<5	665/32	1.2	(0.6-2.1)	4/8	20.5	(3.0-139.6)
5-14	70/8	2.3	(0.9-5.4)	12/4	14.6	(2.3-92.2)
15-29	47/2	1.2	(0.3-5.2)	37/8	8.7	(1.7-45.7)
≥30	427/5	2.1	(1.1-3.8)	281/36	5.2	(1.1-24.4)
V5 Gy kidneys (%)						
No Rt	1135/21	Ref		230/2	Ref	
0	665/32	1.1	(0.6-2.1)	34/9	7.0	(1.3-37.5)
<50	196/13	1.8	(0.8-3.7)	122/18	7.0	(1.5-33.0)
≥50	348/22	2.2	(1.1-4.1)	178/29	6.3	(1.3-29.2)
V20 Gy kidneys (%)						
No Rt	1135/21	Ref		230/2	Ref	
0	782/42	1.3	(0.7-2.3)	53/20	11.3	(2.3-55.0)
<50	283/18	2.1	(1.1-4.0)	167/20	4.3	(1.0-20.6)
≥50	144/7	2.0	(1.0-5.0)	114/16	7.0	(1.4-33.6)
V30 Gy kidneys (%)						
No Rt	1135/21	Ref		230/2	Ref	
0	931/50	1.4	(0.8-2.4)	268/45	6.7	(1.5-30.3)
<25	143/12	2.6	(1.2-5.5)	52/7	6.5	(1.2-34.6)
≥25	135/5	1.6	(1.0-4.3)	14/4	6.8	(1.1-42.5)

N, number of patients without CKD; n, number of patients with CKD; Ref, reference category; HR, Hazard Ratios; CI, confidence intervals; V5 Gy, volume of the kidneys that received at least 5 Gy; V20 Gy, volume of the kidneys that received at least 20 Gy; V30 Gy, volume of the kidneys that received at least 30 Gy

Multivariable models were adjusted on sex, type of childhood malignancy, year of diagnosis of childhood malignancy, age at diagnosis of primary malignancy, anthracycline, ifosfamide, cisplatin, heart failure, diabetes and cerebrovascular disease

A total of 91 patients had missing radiation doses

5. Discussion

This study was the first to derive a dose response relationship for CKD in survivors of childhood malignancies based on radiation dose to the kidneys and dose-volume metrics. Our study shows that patients with renal tumours were not at increased risk of CKD compared to other types of childhood malignancies after accounting for treatment factors. In contrast, patients treated with nephron-ablative surgery had a significantly higher risk of CKD. These patients may be at risk for long-term consequences of glomerular hyper-filtration characterized by compensatory changes that increase GFR and tubule function of remaining nephrons as well as progressive renal injury that can progress in the most severe manifestation to stage 5 CKD or ESKD (175, 176). Previous studies suggest that the risk of ESKD is remarkably low for patients with Wilms tumour (91, 177). However, ESKD is only the tip of the ice berg and there could be a significant number of patients who underwent unilateral nephrectomy and had further exposure to other nephrotoxic treatments with undiagnosed CKD (178). In our study we also found that radiation to the remaining kidney in case of a 50% reduction in renal mass affected significantly renal function. In fact, patients who received less than 1 Gy to the remaining kidney had a significantly high risk of CKD compared to patients who didn't receive any radiation involving the kidneys. Other studies have also found that radiation therapy negatively affected the ability of the remaining kidney to adjust its function (179). One of the early studies on renal function following unilateral nephrectomy for malignant disease in children was published by Mitus et al. and found that the incidence of renal dysfunction in patients who received low radiation doses to the kidneys ranging from 1.2 to 2.4 Gy was 33% (180).

There are currently no studies in CCS that derived dose-response relationships based on radiation dose to the kidneys after long term follow-up. Studies indicated that doses less than 18 Gy to the whole kidney appear to rarely cause severe or long-lasting renal injury while doses greater than 20 Gy result in significant nephropathy (100, 163, 181). Although, these studies

didn't have longer follow-up and only included adult cancer patients, their results seem to be consistent with our findings for patients with two healthy kidneys.

In this study we also found that irradiation less than 50% of both kidneys with at least 10Gy was associated with a significant risk of CKD. There are currently no studies that derived a dose response relationship for CKD based on dose-volume parameters in CCS. In adult patients, a study found a volume-dependent decrease in kidney function after at least 26 Gy to $\geq 50\%$ of one kidney (99, 182). The differences observed between our results and studies on adult survivors of malignancies could be related to the fact that children are more sensitive to radiation than adults (183).

We also found that ifosfamide was also related to a significant risk of CKD even at doses less than 40 g/m², this risk was dose-dependent and was much higher in patients who received higher cumulative doses. Oberlin et al found that almost 92% of patients treated with a median dose of 54 g/m² of ifosfamide had normal tubular function after 10 years of follow-up (97). This could mean that the nephrotoxicity of ifosfamide may only appear only after longer follow-up (30). Additionally, we also found that cisplatin was associated with an increased risk of CKD, but we couldn't investigate dose response relationship mainly because of the very small number of patients treated with cisplatin in the FCCSS cohort.

Another major finding in this study was that heart failure was a major risk factor for CKD in CCS. In fact, heart failure may cause progressive CKD and deterioration of renal function and conversely CKD is a major contributor to severe cardiac damage (161, 184). The relationship between CKD and heart failure could be a vicious circle as heart failure may cause renal impairment and renal impairment would worsen cardiac failure even further (161). In this study, 219/220 of heart failures were primitive and diagnosed before CKD. Nevertheless, because CKD is generally asymptomatic diagnosis dates may be imprecise it is therefore challenging to be certain about which disease is primary and which is secondary.

In sum, because renal impairment is a multifactorial disease (15) there is a need to develop risk stratification for renal dysfunction for CCS and more specifically unilaterally nephrectomized patients (178). It is crucial to enrol CCS into long-term follow-up programs to monitor their renal function and blood pressure. Patients with heart failure and those treated with unilateral nephrectomy, radiation involving the kidneys and those who received nephrotoxic chemotherapy are high-risk groups that could benefit from targeted interventions and long-term follow-up monitoring.

Chapter VI. End Stage Kidney Disease related to nephrotoxic cancer treatment: a national registry study

1. Context

CKD and cancer are associated in several ways as CKD may be associated with cancer and cancer could also lead to the development of CKD and eventually ESKD (185).

Therapeutic interventions including the use of medications targeting the renin-angiotensin-aldosterone system like Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs) has demonstrated success in slowing the progression of CKD (186-188). However, because CKD doesn't often present symptoms in the early stages, many patients would eventually evolve to the ESKD stage. There is limited information available on the outcome of patients with cancer ESKD related to chemotherapy and/or radiation. The outcomes of patients with cancer related ESKD have been mainly studied in patients with kidney cancer (189-191). One study on patients with ESKD secondary to renal malignancy reported poor outcomes of patients with ESKD with a median survival of 3.4 years and a 5-year survival of 38.4% (191).

Although renal transplantation is the optimal treatment for ESKD with the best outcomes among those who receive a transplant early in the course of renal replacement therapy; patients with cancer related ESKD could be denied listing for kidney transplantation and be exposed a delay in enrolment in wait-lists (192). The waiting periods are employed due to a higher risk of cancer recurrence post-transplantation (193). Clinical guidelines for kidney transplant in recipients with a previous malignancy is often deferred 2 to 5 years after cancer treatment due to fear of cancer, a 2-year duration has been proposed for those with a history of renal cell carcinoma (RCC) or other renal malignancies We used data from REIN registry to (1) describe recent trends in the incidence of ESKD related to chemotherapy and/or radiation and (2)

compare mortality and access to kidney transplantation between these patients and those with ESKD from other causes, while taking malignancy status (active or not) at dialysis initiation into account.

2. Materials and Methods

2.1 Patients

This study includes all incident patients for whom the attending nephrologist reported chemotherapy or radiotherapy as the cause of ESKD in the years 2002–2015 and excludes who underwent pre-emptive transplantation. Among nephrotoxic chemotherapies cited as the cause of ESKD in the REIN registry were: methotrexate, mitomycin C, vincristine, cisplatin, carboplatin, cyclophosphamide and Ifosfamide.

Patients were individually matched to 2 to 10 patients with other causes of ESKD for sex, age (± 5 years), year of dialysis initiation (± 5 years), and diabetes status. Controls with active malignancy reported as a comorbidity at dialysis initiation were excluded to avoid any misclassification due to errors in assigning the cause of ESKD. The French data protection authority approved the data collection conducted by the REIN registry, and the REIN scientific committee approved the study.

2.2 Information

Baseline information included demographics, body mass index, comorbidities, mobility status (autonomous, partially or totally dependent) used as a surrogate for frailty, and dialysis start condition (planned or unplanned, i.e., started on an emergency basis). Comorbidities included diabetes, chronic respiratory disease, the number of cardiovascular diseases (0, 1, 2, ≥ 3) among coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure, and dysrhythmia, and active malignancy. REIN coding instructions call for patients to be classified as having an active malignancy at the initiation of renal replacement therapy if they then had

any type of cancer not in remission or if they had been treated for cancer or had metastases in the two years before renal replacement therapy.

2.3 Outcomes

We studied mortality on chronic dialysis in the overall population, as well as access to the national transplant waiting list and to kidney transplantation in patients younger than 75 years, through December 31, 2015. For the first two outcomes, time to event was calculated from dialysis initiation. Time to kidney transplantation was calculated from wait-listing date, either before or after dialysis start, to avoid immortal time bias.

3. Statistical Analysis

We calculated mean incidence rates of cancer-related per million inhabitants (pmi), overall, by sex and by age group (<44, 45-64, 65-74, ≥ 75 years) for the overall 2006-2015 period. We also calculated age- and sex-adjusted annual incidence rates and their 95% CI from 2006 to 2015, standardized according to the French population as of June 30, 2015. Time trends in incidence rates over the 10-year period were tested with JoinPoint software.(194)

We then used Chi-square or Mann-Whitney tests, as appropriate, to describe baseline patient characteristics and compared cases with their matched controls. Missing data for some variables led to the performance of multiple imputations of 20 datasets with the fully conditional specification method. Analyses of the 20 complete datasets were combined according to Rubin's rules.(152). We used cumulative incidence functions and Fine and Gray's competing-risk regression models to estimate and compare mortality rates of all cases and matched controls. Similarly, we estimated and compared transplant wait-listing and kidney transplantation rates for cases aged less than 75 years and their matched controls. Cumulative incidence rates were estimated separately for cases with and without active malignancy at baseline, given this condition's strong influence on prognosis and kidney transplant indication. The competing event in the mortality analysis was kidney transplantation; for the analyses of

waiting-list and kidney transplantation access, the competing event was death. Finally, for each subtype of cancer-related ESKD, we estimated sub-distribution hazard ratios (SHRs) of death and their 95% confidence intervals (95% CI) before and after adjustment for age, sex, diabetes status, cardiovascular comorbidities, liver disease, respiratory disease, and dialysis start condition. Similarly, we estimated SHRs of wait-listing and kidney transplantation before and after adjustment for age, sex, diabetes status, cardiovascular comorbidities, and temporary contraindication for transplantation. *P*-values <0.05 were considered statistically significant.

4. Results

4.1 Patient characteristics at baseline

We identified 287 patients with ESKD due to chemotherapy and radiation including 203 patients with ESKD related to nephrotoxic chemotherapy and 86 due to radiation treatment. Among the 287 patients, 59% were attributed to platinum-based chemotherapies, 3 patients had ESKD caused by at least two nephrotoxic chemotherapy agents (Table 38).

At dialysis initiation, around 60% of the patients in both subgroups had an active malignancy. (Table 39) Compared with their matched controls, case patients had cardiovascular and liver disease significantly less often, were more likely to be treated with haemodialysis than peritoneal dialysis, and less likely to be wait-listed for kidney transplantation.

Table 38. Studied causes of end-stage kidney disease by subtype, coded according to the International Classification of Disease 10th revision (ICD10).

Cancer related end stage kidney disease	ICD 10 code	Cause of end-stage kidney disease	N*
Adverse effects of antineoplastic drugs	T45.1	Antimetabolites: methotrexate	8
		Anti-tumour antibiotic : mitomycin C	3
		Vinca alkaloid : vincristine	1
		Platinum derivatives: cisplatin, carboplatin	169
		Alkylating agents: cyclophosphamide	11
		Ifosfamide	14
Radiation effects, unspecified	T66	Radiotherapy	86

Table 39. Baseline characteristics of patients with ESKD related to nephrotoxic cancer treatment and matched controls at dialysis initiation.

Characteristics	Case patients n=287	Matched controls n=2368	P-value	Missing (%)
Men* (%)	61.0	61.3	-	0
Median age, years (range)*	65.2 (20.9-92.7)	65.1 (20.9-92.9)	-	0
Age, years*				
<44	30 (10.4)	259 (11.0)		
45-64	109 (38.0)	914 (38.6)		
65-74	95 (33.1)	738 (31.1)		
≥75	53 (18.5)	457 (19.3)		
Year at dialysis start*			-	0
<2009	27.2	33.2		
2009-2012	36.9	36.5		
2013-2015	35.9	30.3		
Diabetes*(%)	14.3	15.6	-	0
Body mass index, kg/m² (%)			<.0001	21.5
<18.5	14.5	6.2		
18.5-24.9	52.6	44.7		
25-29.9	26.5	32.3		
≥30	6.4	16.8		
Active malignancy‡ (%)	60.6	-	-	-
Respiratory disease (%)	11.7	10.1	NS	0.8
Cardiovascular disease ‡ (%)			0.02	8.0
0	61.9	56.7		
1	24.1	21.4		
2	9.3	12.8		
≥3	4.7	9.2		
Liver disease (%)	0.7	3.2	0.02	0.5
Treatment modality (%)			0.001	0
Hemodialysis	95.4	88.3		
Peritoneal dialysis	4.6	11.7		
Started emergency dialysis (%)	34.2	28.0	0.03	6.4
Wait-listed for kidney transplantation at dialysis start (%)	14.3	39	<.0001	
Reasons for not being wait-listed (%)			<.0001	25.1
Medical contraindication	80.6	45.0		
Assessment in progress	11.8	40.5		
Patient refusal	0.5	2.0		
Other	7.1	12.5		

ESKD, end-stage kidney disease, *Matching criteria

¶IQR, interquartile range,

‡ Active malignancy was an exclusion criteria among controls

‡ Cardiovascular diseases included coronary heart disease, cerebrovascular disease, peripheral artery disease, heart failure, and dysrhythmia

4.2 Incidence of cancer-related end-stage kidney disease

The mean incidence of ESKD related to chemotherapy and radiation was 0.43 pmi (95% CI, 0.38–0.49) with a significant annual increase of 5.2% (95% CI, 0.1%–10.7%). Incidence was almost twice as high in men as women and increased only slightly with age up to 65-74 years, but not afterwards (Table 40).

Table 40. Standardized incidence rates of ESKD related to nephrotoxic cancer treatment per million inhabitants, overall and by age, and sex, 2006-2015.

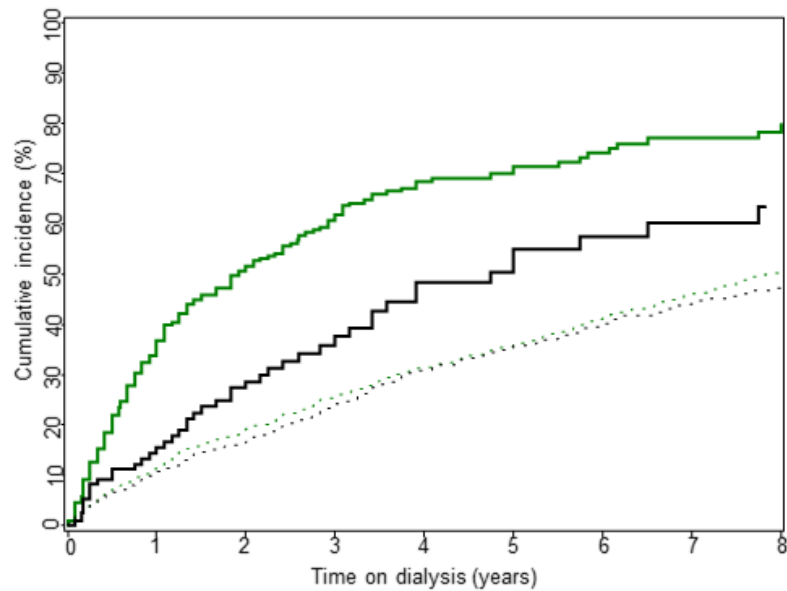
	N	Incidence	(95% CI)
Overall	264	0.43	(0.38-0.49)
Sex			
Men	163	0.58	(0.49-0.66)
Women	101	0.33	(0.27-0.40)
Age (years)			
<44	26	0.07	(0.05-0.10)
45-64	103	0.66	(0.53-0.79)
65-74	85	1.65	(1.30-2.01)
≥75	50	0.91	(5.27-6.60)
Year at dialysis start			
2006	16	0.34	(0.17-0.50)
2007	17	0.32	(0.17-0.48)
2008	19	0.34	(0.19-0.50)
2009	24	0.40	(0.24-0.57)
2010	27	0.42	(0.26-0.58)
2011	22	0.34	(0.20-0.48)
2012	35	0.53	(0.35-0.71)
2013	31	0.47	(0.30-0.63)
2014	24	0.36	(0.22-0.50)
2015	49	0.73	(0.53-0.94)

4.3 Mortality on dialysis

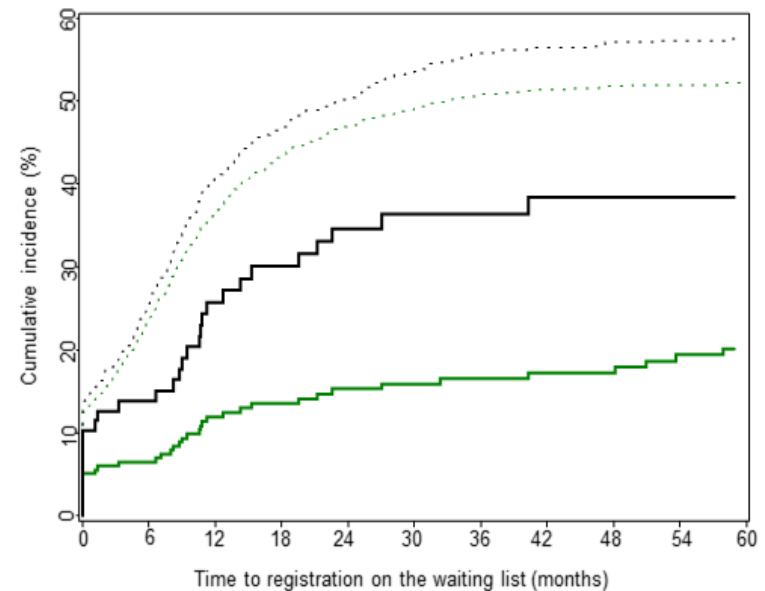
In patients without active malignancy at dialysis initiation, two-year mortality was 29% versus 16% in controls, and for those with active malignancy, 65% versus 21%. (

Figure 14) Adjusting for covariates did not substantially modify the SHRs for mortality estimated by the Fine and Gray models in any subgroup (Table 41).

A- Cumulative incidence of death on dialysis among patients with nephrotoxin related ESKD **B- Cumulative incidence of registration on the kidney transplant waiting-list among patients with nephrotoxin related ESKD**



Number at risk	0	1	2	3	4	5	6	7	8
Controls ^a	1433	1024	707	479	341	235	158	96	51
Nephrotoxin related-ESKD with active malignancy	174	75	42	28	19	13	8	3	3
Controls ^b	935	689	486	333	218	138	87	57	38
Nephrotoxin related-ESKD without active malignancy	113	75	51	29	20	14	11	9	5



Number at risk	0	6	12	18	24	30	36	42	48	54	60
Controls ^a	1188	795	570	438	361	310	257	226	194		
Nephrotoxin related-ESKD with active malignancy	146	91	52	37	30	27	20	17	15		
Controls ^b	723	475	337	272	222	186	153	131	115		
Nephrotoxin related-ESKD without active malignancy	88	64	43	35	25	21	17	15	12		

Nephrotoxin related ESKD patients with active malignancy ———
^aControls for nephrotoxin-related ESKD patients ———
 Nephrotoxin related ESKD patients without active malignancy ———
^bControls for nephrotoxin-related ESKD patients without active malignancy ———

Figure 14. Cumulative incidence of mortality and wait-listing for kidney transplantation.

4.4 Registration on the waiting list for kidney transplantation

In all, 41 patients (18%) were wait-listed for kidney transplantation during the study period. Time to wait-listing was significantly longer for patients with ESKD related to nephrotoxic cancer treatment compared with their matched controls (

Figure 14). Patients without active malignancy at dialysis initiation waited for a median time of 8.7 months (IQR: 0-12.7) versus 6.7 months (IQR: 0–12.9) in controls (*P*-value 0.05), and those with active malignancy, 40.3 months (3.6–55.7) versus 6.3 months (0–12.9) (*P*-value 0.01).

A total of 34% of those without an active malignancy were wait-listed within two years, 50% of their controls, 4% of those with active malignancy, and 45% of their controls (Figure 14). Adjusting for covariates did not substantially modify SHRs for wait-listing (Table 41).

4.5 Access to kidney transplantation

Once on the waiting list, the probability or timing of kidney transplantation differed significantly between ESKD patients due to nephrotoxic cancer treatment compared with their matched controls, but the number of events was small. A total of, 21% without and 55% with active malignancy at dialysis start were transplanted in the 12 months after being wait-listed, compared with 32% in both control groups. In the multivariable models, the probability of transplantation did not differ significantly between cases and controls (Table 41).

Table 41. Number of events, crude and adjusted sub-distribution hazard ratios for mortality on dialysis, wait-listing and kidney transplantation.

Outcome	Controls	ESKD patients	
		Patients with active malignancy	Patients without active malignancy
Mortality on dialysis			
Number of patients	2368	174	113
Number of deaths	802	124	47
Crude SHR (95% CI)	Reference	3.7 (3.0-4.7)	1.3 (1.0-1.8)
Adjusted SHR (95% CI) ¹	Reference	4.2 (3.2-5.5)	1.4 (1.0-2.0)
Wait-listing			
Number of patients	1911	146	88
Number of events	919	12	29
Crude SHR (95% CI)	Reference	0.20 (0.11-0.34)	0.67 (0.5-0.90)
Adjusted SHR (95% CI) ²	Reference	0.19 (0.11-0.32)	0.62 (0.43-0.88)
Kidney transplantation			
Number of patients	919	12	29
Number of events	597	8	14
Crude SHR (95% CI)	Reference	1.2 (0.44-3.1)	0.67 (0.40-1.2)
Adjusted SHR (95% CI) ²	Reference	1.1 (0.40-3.2)	0.65 (0.40-1.4)

ESKD, end-stage kidney disease; SHR (95%CI), subdistribution hazard ratios (95% confidence interval); 1 SHR adjusted for sex, age at dialysis initiation, diabetes status, cardiovascular comorbidities, liver disease, respiratory disease, and emergency dialysis Patients and cases aged < 75 years

SHR adjusted for sex, age at dialysis initiation, diabetes status, cardiovascular comorbidities, and temporary transplantation contraindication

Patients and cases aged < 75 years wait-listed for kidney transplantation

5. Discussion

This registry-based study shows that ESKD related to nephrotoxic cancer treatment has been slowly but steadily increasing over the past decade in the French population. As expected, survival among patients with active malignancy at dialysis initiation was very poor and their access to kidney transplantation limited. More unexpectedly, patients whose cancer had not been active in the two years before starting dialysis also experienced a much lower rate of wait-listing than matched controls with other causes of ESKD, despite similar survival on dialysis.

Our study has several strengths including the availability of ESKD causes from the most commonly used nephrotoxic chemotherapies over a 10-year period and the unselected nature of the REIN registry population, which enables our findings to be generalized to all patients on dialysis in France. Most importantly, patients' malignancy status was known at dialysis initiation, whether it was active before then or not. This allowed assessment of both mortality and transplantation access by subgroup according to this critical determinant of both outcomes, involving 60% of all cases.

The incidence of renal replacement therapy for ESKD continues to rise in most countries including France, mainly as a result of population aging, increasing diabetes prevalence, and extended dialysis access criteria (195). However, the annual increases of 5.2% far exceeded the 0.8% annual increase estimated for the overall French ESKD population over this period (196). These findings highlight the growing importance of cancer-related ESKD, which we may nonetheless have underestimated, due to the lack of coding for ESKD causes related to more novel anti-cancer agents such as vascular endothelial growth factor or epidermal growth factor receptor pathway inhibitors (93, 197). Patient characteristics at dialysis initiation were similar to those from other studies, with a lower prevalence of comorbidities among those with cancer-related causes than among other ESKD patients, and their preference for haemodialysis rather than peritoneal dialysis (189, 198). The lower prevalence of comorbidities in these patients may

reflect some selection process resulting from the evaluation of overall prognosis and treatment options for each patient and then by shared decision-making about starting dialysis (189).

Our findings about mortality in patients with ESKD caused by nephrotoxic cancer treatment difficult to compare to other studies where malignancy status at dialysis initiation was not available. Nevertheless, like others we found that these patients had worse survival than patients with other ESKD causes when they were reported to have had active malignancy at dialysis start (189, 191). When they did not, their survival was similar, consistent with the better survival observed for patients with renal cell cancer undergoing nephrectomy (189).

Kidney transplantation is the gold-standard renal replacement therapy in ESKD, for both survival and quality of life (199). Among the patients who begin haemodialysis, early transplantation improves long-term outcomes (191). In this study, patients whose cancer was not active at dialysis start had a lower rate of access to the transplant waiting list than their matched controls. However, once on the waiting list, their probability of transplantation was similar to that of their controls. Several factors may partly explain this limited access for cancer-related ESKD patients. Pelvic radiation for urinary tract, gynecologic, or colorectal cancers can cause tissue injury that leads to radiation-induced atherosclerosis, atrophy, tissue ischemia, and fibrosis (200). Hence, kidney transplantation in these patients may be very complex and in some cases impossible due to extreme tissue frailty, with a high risk of bleeding or leakage during dissection of iliac vessels, ureters, and the bladder (201). Consequently, transplantation may be definitively contraindicated for patients who have previously been treated with pelvic radiotherapy. Complex urologic, gynecologic, and gastrointestinal oncologic surgery with local tissue impairment may also prevent surgeons from performing transplantation because of the high risk of early graft failures (202).

Kidney transplant candidates with a history of malignancy usually face waiting times even longer than most because of the challenging nature of decision-making related to their high risk of cancer recurrence and mortality (193, 203). Clinical practice guidelines on the evaluation

and management of candidates for kidney transplantation recommend excluding those with active malignancy and waiting from 2 to 5 years after completion of potentially curative cancer treatment, depending on the cancer type and stage.(192, 204-206) These waiting times, however, often relied on high recurrence rates based on old retrospective studies.(207, 208) It is therefore difficult to make recommendations of specific waiting times according to cancer location, although a 5-year waiting time remains recommended for cancers with a high risk of recurrence, such as invasive melanoma, or advanced-stage breast, colorectal, and uterine cancers (205). In these situations, it is thus recommended that an in-depth pretransplant evaluation be performed for any signs of recurrence at the time of wait-listing and that these wait-listed patients then be evaluated regularly. To prevent compromising their chances of transplantation, ESKD patients with cancer in remission may, however, be registered on the waiting list with a temporary medical contraindication as early as possible (209). Nephrologists and oncologists must work closely together to improve decision-making about kidney transplantation in these patients (210). It is worth noting that a study in Norway, where the transplantation rate is very high, showed that this country's policy of a short one-year waiting period between cancer treatment and kidney transplantation yielded similar overall survival for kidney transplant recipients with and without a cancer history (211). This study also reported that deaths related to cancer recurrence seemed to occur regardless of the waiting period with no fatal recurrences occurring among patients with kidney cancer (211).

This study has several limitations. The type and grade of underlying cancer for patients was unknown, which prevented us from assessing mortality by malignancy type and limits information about the causes of delay in wait-listing. Likewise, CKD status at cancer onset was unavailable, so that we could not estimate the role of pre-existing CKD on the onset of ESKD. Finally, our definition of "active" malignancy at baseline did not provide the exact duration of cancer remission for those without reported active malignancy. Notably, lack of knowledge of

the number of patients in remission for more than 5 years prevented us from estimating the wait-listing rate in this patient subgroup.

Improvement in cancer survival appears to be associated with an increase in kidney replacement therapy for ESKD related to antineoplastic treatments. Our study indicates that survival among patients starting dialysis with cancer-related ESKD, but whose cancer had not been active in the previous two years is similar to that of other ESKD patients of similar age, sex, and diabetes status. Nonetheless, and despite their lower prevalence of comorbidities than patients with other ESKD causes, these patients were less likely to be wait-listed for transplantation. Uncertainties regarding the optimal waiting time before transplantation for many cancers and fear of cancer recurrence remain major obstacles to wait-listing patients in remission. Further studies are needed to evaluate the best timing for kidney transplantation in patients with ESKD after cancer treatment. Close collaboration between nephrologists and oncologists is needed to improve decision-making about kidney transplantation in this rapidly growing patient population, to further improve their quality of life and outcomes.

VII Discussion and conclusion

1. Summary of main findings

In this thesis we first examined the burden of adverse effects in CCS, focusing mainly on long-term mortality, cardiovascular disease, and renal impairment using data from the FCCSS cohort. In the four studies that we have presented in this thesis, we first conducted analyses to examine mortality among CCS and studied the trends in overall deaths, death by recurrence of the primary malignancy, and mortality attributed to adverse effects of childhood cancer treatment focusing on deaths by secondary malignancies and cardiovascular causes. We then studied the risks of heart failure in survivors of childhood malignancies and highlighted the role of irradiated heart and cardiac substructures and interaction between cardiac radiation and cardiotoxic chemotherapy. We then aimed to identify risk factors for the development of CKD in an effort to specify high-risk groups in need to receive long term follow-up and evaluation of their kidney function. Finally, we investigated the incidence and outcomes of ESKD related to nephrotoxic chemotherapy and radiation in the national population of France using data from the REIN registry.

In the FCCSS cohort, we found that CCS died mostly of causes related to recurrence or progression of the primary, secondary primary neoplasms and circulatory diseases. We also demonstrated that mortality among CCS remained higher than the general population even after more than 40 years of the primary cancer diagnosis. This study was the first in France to investigate the trends in long-term mortality of CCS by treatment period. Overall mortality declined in more recent treatment periods. However, the number of excess deaths for survivors diagnosed in both the 80s and 90s was identical. Furthermore, the decrease in long-term mortality related to the primary neoplasm was not distinct especially for those treated in the more recent treatment era compared to those treated before 1970. This could be explained by the fact that we included 5-year survivors treated before 1970 who are most probably patients

with good prognoses who can maintain durable remission because they had low-risk tumors treatable with radiotherapy and surgery. Contrarily, owing to the higher survival rates of childhood cancer observed in recent years, more patients with highly recurrent and less durable remission would make the 5-year survival mark. Nevertheless, mortality attributed to adverse effects and, more specifically, mortality from secondary primary neoplasms and circulatory diseases declined significantly for patients treated in more recent years. This decline in mortality was more likely attributed to the reduction of the intensity of therapeutic regimens more specifically the declining use of radiotherapy, cranial radiation, and reduction of radiation doses to the heart received by Hodgkin lymphoma patients along with the decrease of cumulative doses of anthracycline doses in addition to the improvement of long-term follow-up strategies for these patients.

When we focused on heart failure in CCS, we conducted a case-control study nested in the FCCSS cohort. We demonstrated that there was a significantly elevated risk of heart failure in CCS, even when <10% of the LV volume received ≥ 30 Gy. We also confirmed that CCS who have been exposed to anthracycline and cardiac radiation are at higher risk of developing heart failure at a relatively young age. Our study also showed that, without anthracycline exposure, the risk of heart failure increased substantially with increasing doses to the heart or LV. However, in patients treated with anthracycline, risks of heart failure only increased moderately with increasing radiation doses to the heart because they already had a higher baseline risk of heart failure. In addition, we found that there is no safe dose for anthracycline and even patients who received relatively moderated doses, given their significantly increased risk of developing heart failure.

We then studied kidney function in CCS and we found that patients with renal malignancies were not at increased risk of CKD compared to other types of childhood malignancies after accounting for treatment factors. In contrast, unilateral nephrectomy was associated with a high risk of CKD. The effect of radiation dose to the kidneys was also different among

nephrectomized patients for whom any exposure to radiation was associated with an elevated risk of CKD even at doses less than 1Gy. In contrast, patients with both kidneys were at higher risk of CKD only at very high doses ≥ 20 Gy. For non-nephrectomized patients CKD risk was increased if less than 50% of both kidneys received at least 10Gy. We also found that ifosfamide was also related to a significant risk of CKD even at doses less than 40 g/m², this risk was dose-dependent and was much higher in patients who received higher cumulative doses. Another major finding in this study was that cardiac diseases was a major risk factor for CKD in CCS especially heart failure, patients with heart failure had 6-fold higher risk of getting CKD. The findings of this chapter suggest that systematic ongoing follow-up should be considered for nephrectomized patients who received low radiation doses or no nephrotoxic chemotherapy. Data from the REIN registry gave us the opportunity to investigate ESKD related to nephrotoxic chemotherapy and/or radiation. Our registry-based study shows that ESKD related to nephrotoxic cancer treatment has been steadily increasing over the past decade in the French population. This increase of 5.2% was much higher than the general increase of 0.8% in the general population. As expected, survival among patients with active malignancy at dialysis initiation was very poor and their access to kidney transplantation limited. More unexpectedly, patients whose cancer had not been active in the two years before starting dialysis also experienced a much lower rate of wait-listing than matched controls with other causes of ESKD, despite similar survival on dialysis. .

2. Research strengths and limitations

2.1 Research strengths

The general objective of this thesis was to advance knowledge on the very long morbidity associated with childhood cancer, the ultimate goal being to improve both the long-term outcome and quality of life of survivors. The FCCSS was designed as a multicentre retrospective cohort study with a median follow-up that exceeded 25 years. A strength of all

four studies presented in this thesis is that we aimed to study clinically relevant outcomes. Long-term mortality is the ultimate endpoint to monitor the health status of these patients and identify the leading causes of premature death. We also focused on heart failure, which is one of the most frequent and devastating cardiac disease in CCS, in addition to renal impairment, which have only been studied in small cohorts of carefully selected participants.

An important strength of our research was also the very exhaustive patient, cancer, and treatment data available. The completeness of treatment information, which ranged between 93% and 100%, also allowed for minimal information bias. Detailed treatment-exposure data in addition to lifestyle related risk factors have also allowed us to adjust for several important confounders, taking multiple exposures into account.

Another strength of this study is the validation of all self-reported medical outcomes included in our analysis. The validation process has allowed for the identifying of false-positive self-reported outcomes. In addition, we also had access to the national-health, insurance-scheme data, which was linked to the FCCSS cohort. This data contains information on all reimbursements issued by the French national health insurance scheme for every patient (laboratory tests, medications, ambulances, health care professionals consulted etc.) in addition to detailed hospitalization data, with causes coded in ICD-10. This reliable data allowed us to account for false-negative outcome events that were not reported by patients.

2.2 Study imitations

A significant challenge we faced in our cohort study was the fact that, like with any cohort study of the sort, patients may fail to follow-up in later years, leading to the risk of attrition bias. Data obtained from the national health insurance scheme data was also only available for a 10-year period, between 2006 and 2016. However, the follow-up in the FCCSS was achieved using several methods: Self-administrated questionnaires, record linkage with the national health insurance scheme data (SNDS), long term follow-up clinic in Gustave Roussy, medical

records, and the medical causes of death that would allow for the substantial decrease of the number of lost-to-follow-up patients.

There is, however, potential selection bias regarding survival, particularly among the group of older 5-year survivors treated before 1970, although said bias did not affect our results by virtue of the fact that when restricting our analysis to survivors treated after 1970, we found similar results. Another limitation to this study was that the FCCSS cohort doesn't include survivors of leukaemia. This could affect the comparability of our results to other CCS studies, although our results remained similar to those observed in other cohorts of childhood cancer survivors such as the CCS, the BCCSS, and Nordic countries.

Finally, the analysis in the REIN registry could not be restricted to CCS only because the registry does not include oncological data related to the primary malignancy. To focus only on the outcome of CCS with ESKD, a linkage between the FCCSS and the REIN registry would be necessary.

3. Clinical implications

The studies presented in this thesis are related to survivors treated with radiotherapy and chemotherapy many decades ago, of which a large proportion had received radiotherapy and chemotherapy as part of their initial treatment. Although childhood cancer therapies have evolved over the years, the use of chemotherapy and radiation is still a major part of the therapeutic arsenal of childhood malignancies. Previous studies have demonstrated that by the second decade of life, more than 60% of CCS will suffer from at least one chronic disease related to the treatment they have received (37).

Because of the higher 5-year survival rates of childhood malignancies and hopefully their long-life expectancy, it has become crucial to reduce both short and long-term treatment-related complications. This is best achieved by a risk-adapted therapeutic approach, which have been made possible through identifying clinical and biologic prognostic factors, stratifying patients using these risk factors, and modifying therapy according to risk group assignment.

The studies presented in this thesis provide a reliable basis for long term follow-up guidelines and recommendations for survivors of childhood malignancies. Our findings are useful because they provide evidence for risk stratification and information on high risk patient groups in need for long-term follow-up interventions.

4. Future research

Risk factors influencing the onset of CKD in CCS are complex and heterogeneous, future research assessing dose-response relationships between radiation doses, chemotherapy, and adverse late effects is necessary in order to provide a stronger evidence base applicable in clinical practice. A study on long-term mortality related to renal causes in the PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup) cohort is ongoing, seeking to determine the risk of long-term mortality from renal adverse effects. This study will include 83,333 five-year survivors of childhood cancer in 12 European countries and can allow for the inclusion of a higher number of case patients. Furthermore, a pooled analysis assessing hospitalization related to renal diseases is also ongoing. This study will include survivors from the BCCSS and the FCCSS cohorts.

The interrelationship between CKD and cardiac disease and, more specifically, heart failure, needs to be further investigated. Causal mediation analysis could be employed to understand the association and possible causal inference between these two outcomes.

Finally, linkage between the FCCSS cohort and the REIN registry would provide a great and unique opportunity to access the detailed data available in REIN registry and complete the picture with the detailed oncological data from the FCCSS cohort and thus study the evolution of CKD to ESKD in addition to the outcome and treatment options of CCS with ESKD.

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Appendix 2. Validation form for chronic kidney diseases in the FCCSS cohort sent to general practitioners and/or nephrologists.



Fiche de validation des maladies rénales chroniques

Date du remplissage de la fiche ____/____/____ Numéro anonyme.....

Cochez les cases correspondantes et remplissez la date et les résultats des examens si nécessaire

DIAGNOSTIC DE LA MALADIE RENALE CHRONIQUE*

Le patient a-t-il été diagnostiqué avec une maladie rénale chronique ? Non Oui

- Quelle est la cause(s) de la MRC ?
 - Néphropathie diabétique
 - Néphropathie hypertensive ou vasculaire
 - Glomérulonéphrite chronique
 - Néphropathie tubulointerstitielle due à une chimiothérapie anticancéreuse
 - Néphropathie tubulointerstitielle due à une radiothérapie
 - Polykystose rénale
 - Inconnue
 - Autre, précisez
- Quand la maladie rénale chronique a-t-elle été reconnue pour la première fois ? ____/____/____
MM AAAA
- Diagnostic confirmé par une biopsie rénale? Non Oui
- Le patient a-t-il eu une imagerie rénale (échographie, scanner, IRM) ? Non Oui
Si Oui
Longueur du rein droit _____ cm ou Rein absent
Longueur du rein gauche _____ cm ou Rein absent

- Le patient a-t-il subi une néphrectomie ?
 - Non Oui, totale Oui, partielle côté gauche
 - Oui, partielle côté droit Oui, partielle côté inconnu inconnue

Si Oui, quelle était la date de la néphrectomie ? ____/____/____
JJ MM AAAA

Si Oui, raison de la néphrectomie Cancer/tumeur Traumatisme Autre inconnue

- Antécédents et facteurs de risque
 - HTA
 - Diabète
 - Insuffisance cardiaque
 - Maladie coronarienne
 - AVC
 - Autres maladies cardiovasculaires
 - Précisez.....

TRAITEMENT DE LA MALADIE RENALE CHRONIQUE

- Le patient est-il traité par dialyse ? Non Oui, Hémodialyse Oui, Dialyse péritonéale
- Le patient a-t-il eu une greffe rénale ? Non Oui
Si Oui, quelle était la date de la transplantation rénale? ____/____/____
JJ MM AAAA
Si Non, est-il inscrit sur la liste d'attente de greffe rénale? Non Oui inconnue

* La maladie rénale chronique est définie par la présence d'anomalies biologiques (protéinurie, albuminurie ou hématurie), histologiques ou morphologiques, et/ou par la baisse de la fonction rénale (débit de filtration glomérulaire < 60 ml/min/1,73 m²) pendant plus de 3 mois. Ne pas inclure les calculs rénaux, les infections et autres affectations rénales aiguës, ou l'incontinence urinaire.



Fiche de validation des maladies rénales chroniques

EXAMENS CLINIQUES ET BIOLOGIQUES		
Saisir la valeur des mesures cliniques et biologiques à l'examen le plus récent (colonne 1) et au moment du diagnostic (colonne 2), en précisant la date de chaque examen.		
	A la date de l'examen le plus récent	A la date du diagnostic de la maladie rénale
Date des examens	____/____/____ JJ MM AAAA	____/____/____ JJ MM AAAA
EXAMENS CLINIQUES		
9. Pression artérielle (mm Hg)	____/____ Systolique / Diastolique	____/____ Systolique / Diastolique
10. Poids (kg)
11. Taille (cm)
BIOLOGIE SANG		
12. Créatinine sérique <input type="checkbox"/> micromol/L <input type="checkbox"/> mg/L <input type="checkbox"/> micromol/L <input type="checkbox"/> mg/L
13. Débit de filtration glomérulaire (DFG) Spécifier l'équation mL/min/1,73 m ² <input type="checkbox"/> MDRD <input type="checkbox"/> Cockcroft-Gault <input type="checkbox"/> CKD-EPI <input type="checkbox"/> non précisée mL/min/1,73 m ² <input type="checkbox"/> MDRD <input type="checkbox"/> Cockcroft-Gault <input type="checkbox"/> CKD-EPI <input type="checkbox"/> non précisée
14. Hémoglobine (g/dl) g/dl g/dl
ECHANTILLON D'URINE		
15. Protéine <input type="checkbox"/> g/L <input type="checkbox"/> mg/L <input type="checkbox"/> g/L <input type="checkbox"/> mg/L
16. Albumine mg/L mg/L
17. Créatinine <input type="checkbox"/> mmol/L <input type="checkbox"/> g/L <input type="checkbox"/> mmol/L <input type="checkbox"/> g/L
18. Protéine <input type="checkbox"/> g/24h <input type="checkbox"/> mg/24h <input type="checkbox"/> g/24h <input type="checkbox"/> mg/24h
19. Albumine mg/24h mg/24h
20. Hématurie	<input type="checkbox"/> Non <input type="checkbox"/> Oui	<input type="checkbox"/> Non <input type="checkbox"/> Oui
BANDELETTE URINAIRE (à compléter en cas d'absence d'examen d'urine au laboratoire)		
21. Protéine	<input type="checkbox"/> : aucune ou traces <input type="checkbox"/> :1+ <input type="checkbox"/> :2+ <input type="checkbox"/> :3+	<input type="checkbox"/> : aucune ou traces <input type="checkbox"/> :1+ <input type="checkbox"/> :2+ <input type="checkbox"/> :3+

DECES

22. Le patient est-il décédé ? Non Oui

23. **Si Oui**, précisez la date du décès ____/____/____
JJ MM AAAA

24. Causes du décès :

.....
.....

Appendix 3. Résumé substantiel

De nos jours, la survie à 5 ans des enfants atteints d'un cancer dépasse les 80% en France. Ces progrès dans le traitement des cancers pédiatriques font qu'il existe un nombre croissant d'enfants survivants à long terme, ce qui correspond à plus de 50 000 adultes guéris d'un cancer pédiatrique.

Plusieurs études s'intéressent maintenant au devenir des enfants guéris d'un cancer pédiatrique du fait de l'apparition possible de séquelles consécutives aux traitements, parfois graves conduisant au décès prématuré. En effet la prévalence des complications à long terme dépasse chez les survivants de cancers pédiatriques 60% après un suivi de 30 ans. L'objectif général de cette thèse était de faire avancer les connaissances actuelles sur la mortalité et la morbidité à long terme liées aux cancers pédiatriques.

Plusieurs études ont montré que le risque de mortalité tardive des survivants, était supérieur à celui attendu dans la population générale pour toutes causes confondues. Ce sur-risque induit par les traitements reçus augmente avec le temps.

La cohorte FCCSS (French Childhood Cancer Survivor Study) inclut des patients guéris d'un cancer pédiatrique solide ayant survécu au moins 5 ans et traités entre 1946 et 2000. Nous avons réalisé une étude sur les causes spécifiques et les tendances de mortalité par période de traitement chez les patients de cette cohorte. Nous avons pu démontrer que le risque de mortalité chez ses patients demeure plus élevé que la population générale même à plus de 40 ans après le diagnostic de leur premier cancer. Les causes de décès majeures dans cette population étaient : les récurrences ou rechute du premier cancer, les seconds cancers et les maladies circulatoires. Dans cette étude, nous avons aussi trouvé que la mortalité liée aux séquelles de traitements de cancer, plus spécifiquement les seconds cancers et maladies circulatoires a significativement baissé parmi les sujets traités entre 1990 et 2000 comparés aux patients traités avant 1970. Cette amélioration est probablement liée à l'évolution des attitudes thérapeutiques qui ne cessent de

s'améliorer, notamment la réduction des indications de la radiothérapie et doses cumulées d'anthracycline.

Après les seconds cancers, les maladies cardiovasculaires représentent la deuxième complication à long terme la plus fréquente et la plus sévère des traitements des cancers pédiatriques. On compte parmi les facteurs de risque majeurs de complications cardiaques à long terme : les anthracyclines et l'irradiation de l'aire cardiaque. Les maladies cardiaques les plus souvent rencontrées sont les insuffisances cardiaques, les coronaropathies, les valvulopathies, les arythmies et les péricardites.

Nous avons réalisé une étude cas témoins nichée dans la cohorte FCCSS pour étudier le risque d'insuffisance cardiaque chez les patients guéris de cancer pédiatrique et le rôle de la chimiothérapie cardiotoxique ainsi que la dose moyenne au cœur et le volume du cœur et des sous-structures cardiaques irradiés dans la survenue de l'insuffisance cardiaque. Nous avons confirmé que les anthracyclines sont liés à un risque significativement élevé d'insuffisance cardiaque même à des doses cumulées <250 mg/m². Nous avons aussi trouvé que l'irradiation de faibles volumes du cœur ($<10\%$ du ventricule gauche) à une dose ≥ 30 Gy est associée à un risque significatif de cette pathologie. Nous avons aussi trouvé une interaction significative entre la prise d'anthracycline et la dose d'irradiation cardiaque et démontré que chez les patients non-exposés aux anthracyclines, le risque d'insuffisance cardiaque augmentait fortement avec la dose d'irradiation absorbée par le cœur. Par contre chez ceux ayant été traités par anthracycline le risque augmentait de façon modérée du fait de leur risque de base particulièrement élevé. Chez ses patients, l'obésité, le tabac, l'activité physique et le diabète n'étaient pas significativement associés à un risque accru d'insuffisance cardiaque.

Les maladies rénales font partie des conséquences à très long terme des traitements des cancers de l'enfant et contribuent en partie à l'augmentation de la mortalité des survivants d'un cancer. Elle constitue un élément de mauvais pronostic et un vrai problème de santé chez ces patients. La maladie rénale chez les survivants d'un cancer pédiatrique est une maladie multifactorielle

associant la néphrotoxicité due à la radiothérapie et aussi à la chimiothérapie en particulier, le cisplatine, la carboplatine et l'ifosfamide. Les pathologies rénales radio-induites ne sont encore pas assez documentées tel que les seconds cancers et les maladies cardiovasculaires et constituent une question de santé majeure surtout qu'elles sont-elles mêmes liées aux maladies cardiovasculaires. Peu d'études ont évalué les facteurs de risque à long terme de la toxicité rénale après traitement d'un cancer dans l'enfance. Ces études ont été réalisées seulement dans des petits groupes de patients avec un suivi maximal de 10 ans.

Dans la cohorte FCCSS, nous avons investigué les facteurs de risques de la maladie rénale chronique à long terme chez les patients guéris d'un cancer pédiatrique. Nous avons trouvé que les patients ayant subi une néphrectomie unilatérale étaient à plus de risque de développer cette maladie. L'effet de la dose de l'irradiation aux reins différait aussi significativement entre les patients ayant subi une néphrectomie et ceux avec deux reins. Chez les patients ayant deux reins, les fortes doses plus spécifiquement une dose maximale ≥ 20 Gy aux deux reins était associée à un risque significatif de maladie rénale chronique. Cependant chez les sujets ayant subi une néphrectomie même une dose maximale < 1 Gy était associée un risque élevé de dysfonctionnement rénal. Nous avons aussi trouvé que la prise d'ifosfamide, cisplatine et des fortes doses d'anthracycline étaient liées à un risque accru d'atteinte rénale. Les maladies cardiaques et plus spécifiquement l'insuffisance cardiaque étaient aussi un facteur risque majeur de dysfonctionnement rénal chez ces patients.

La maladie rénale chronique peut évoluer vers le stade terminal nécessitant la dialyse ou une greffe rénale. Peu d'études ont examiné le devenir thérapeutique des patients avec une insuffisance rénale terminale liée aux traitements anticancéreux et notamment leurs accès à la greffe. La plupart de ces études ont été réalisées chez les patients diagnostiqués par un cancer rénal. Le registre REIN (Réseau Epidémiologie et Information en Néphrologie) est un registre national qui a comme objectif général de décrire l'incidence et la prévalence de l'insuffisance rénale chronique terminale traitée par dialyse. Il permet également de mieux connaître les

caractéristiques de ces patients, leurs modalités de traitements par dialyse et leur évolution dans le temps.

Grâce aux données du registre REIN, nous avons aussi pu montrer que l'incidence de l'insuffisance rénale terminale traitée liée à la chimiothérapie néphrotoxique et/ou à la radiothérapie est en train d'augmenter au fil des années. Les patients dialysés et ayant un cancer évolutif avaient un très mauvais pronostic. Cependant les patients en rémission et dialysés pour une insuffisance rénale terminales liée aux traitements anticancéreux étaient moins inscrits en liste d'attente comparé à d'autres malades rénaux et avaient par conséquent un accès très limité à la transplantation rénale.

En conclusion, c'est avec l'amélioration de la survie et l'augmentation du nombre de patients guéris d'un cancer pédiatrique que l'on a pris conscience des nombreuses séquelles des traitements pouvant menacer la vie ou entraîner une morbidité importante. Ces séquelles peuvent apparaître de nombreuses années après la guérison et augmentent avec l'âge. Ainsi l'organisation d'un suivi à long terme pour ces patients est nécessaire. Ce suivi doit avant tout être personnalisé et adapté aux risques. Le travail effectué courant cette thèse pourrait aider à identifier les patients à risque accru de complications tardives majeures liées aux traitements anticancéreux. Nos résultats pourraient être utilisés dans la pratique clinique courante pour l'adaptation de la prise en charge thérapeutique des enfants atteints de cancer et pour les recommandations de leurs suivi à long terme.

Submitted and published papers

1 **Trends and outcomes with kidney failure from anti-neoplastic**

2 **treatments and urinary tract cancer in France**

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25 *Word count: Abstract 300/Text 3018*

26

27 Key words: End-stage kidney disease, cancer, radiation, nephrotoxicity, urinary tract cancer, survival,
28 kidney transplantation

29 Abstract**30 Background and objectives**

31 Cancer survival is improving along with the potential for adverse kidney effects from antineoplastic
32 treatments or nephrectomy. We sought to describe recent trends in the incidence of kidney failure
33 related to antineoplastic treatments and urinary tract cancers and evaluate patient survival and
34 kidney transplantation access.

35 Design, setting, participants, and measurements

36 Searching the French Renal Epidemiology and Information Network registry in 2003–2015 identified
37 287 kidney failure cases related to nephrotoxin - chemotherapy or radiation - and 1157 to urinary
38 tract cancer. After matching them to 2-10 controls (N=11,678) with other kidney failure causes for
39 age, sex, year of dialysis initiation, and diabetes status, we estimated subdistribution hazard ratios
40 (SHR) of mortality and transplantation separately for patients with and without active malignancy.

41 Results

42 The mean age- and sex-adjusted incidence of nephrotoxin-related kidney failure was 0.43 (95%
43 confidence interval [95%CI], 0.38–0.49) per million inhabitants and , 1.80 (95%CI, 1.68-1.90) for
44 urinary tract cancer-related kidney failure; they increased significantly, by 5.2% and 1.9% annually,
45 respectively, during 2006-2015. Age-, sex-, and comorbidity-adjusted SHRs for mortality in patients
46 with nephrotoxin-related kidney failure were 4.2 (95% CI, 3.2-5.5) and 1.4 (95% CI, 1.0-2.0) for those
47 with and without active malignancy, respectively, compared with matched controls and for those
48 with urinary tract cancer, 2.0 (95% CI, 1.7-2.2) and 1.1 (95% CI, 0.9-1.2); the corresponding SHRs for
49 transplant wait-listing were 0.19 (95% CI, 0.11-0.32) and 0.62 (95% CI, 0.43-0.88) for nephrotoxin-
50 related kidney failure cases and 0.28 (95% CI, 0.21-0.37) and 0.47 (95% CI, 0.36-0.60) for urinary tract
51 cancer cases. Once on the waiting list, access to transplantation did not differ significantly between

52 cases and controls.

53 **Conclusions**

54 Cancer-related kidney failure is slowly but steadily increasing. Mortality does not appear to have

55 increased among patients without active malignancy at dialysis start, but their access to kidney

56 transplant remains limited.

57

58 Introduction

59 Improvement in diagnosis and more effective treatments have resulted in substantially better cancer
60 survival for all ages worldwide.^(1, 2) In France, cancer incidence increased from 321 per 100 000
61 person-years in 1990 to 402 in 2005, but recent trends (2010-2018) indicate this rate dropped by
62 1.4% per year. In contrast, mortality has been steadily declining by 1.8% per year on average over the
63 last 20 years.^(3, 4) Cancer survivors are, however, at risk of developing adverse effects caused by their
64 oncologic treatments or surgery, which may affect the kidneys.⁽⁵⁻⁷⁾ Nephrotoxicity is a known side
65 effect of radiotherapy and of several commonly used antineoplastic drug classes, which can cause
66 glomerular or tubular dysfunction and impair kidney functions.^(8, 9) The importance of overall
67 nephrotoxin-related end-stage kidney disease (ESKD) is currently unknown. Nephrectomy for urinary
68 tract cancer, whether radical or partial, has also been associated with the onset of chronic kidney
69 disease (CKD)⁽¹⁰⁾ and ESKD.⁽¹¹⁻¹³⁾

70 Mortality associated with cancer-related ESKD has mainly been studied in patients with kidney
71 cancer.^(11, 13, 14) Overall, survival of these patients on kidney replacement therapy is reported to be
72 worse than that of those with other known ESKD causes.^(11, 13) Furthermore, patients with cancer-
73 related ESKD have tended to wait longer to be registered on the transplant waiting-list — from two
74 to five years longer, depending on the cancer type and stage.⁽¹⁴⁻¹⁷⁾ An evaluation of cancer-related
75 ESKD trends and outcomes in the context of improved cancer survival and broader access to dialysis
76 and transplantation is needed.

77 We used data from the French Renal Epidemiology and Information Network (REIN) registry to
78 describe trends in the incidence of cancer-related ESKD, whether due to nephrotoxins or to urinary
79 tract cancer, and compare mortality and access to kidney transplantation between these patients
80 and those with ESKD from other causes, while taking malignancy status (active or not) at dialysis

81 initiation into account.

82 **Materials and Methods**

83 ***Patients***

84 The French REIN registry includes all patients on kidney replacement therapy for ESKD either dialysis
85 or transplantation. The registry started in 2002 and expanded progressively to achieve nationwide
86 coverage in 2012. Details of its methods and quality control have been reported elsewhere.⁽¹⁸⁾ This
87 study includes all incident patients for whom the attending nephrologist reported chemotherapy,
88 radiotherapy, or urinary tract cancers as the main or contributing cause of ESKD in the years 2002–
89 2015 (Supplemental Table 1) and excludes those with ESKD related to hematological malignancies or
90 who underwent preemptive transplantation.

91 In all, 1435 cases were identified, including 287 patients with nephrotoxin-related ESKD due to
92 chemotherapy or radiation treatment, and 1157 with urinary tract cancer-related ESKD (Figure 1).
93 ESKD for nine of these patients was attributed to both causes. Patients with cancer-related ESKD
94 were individually matched to 2 to 10 patients with other causes of ESKD for sex, age (± 5 years), year
95 of dialysis initiation (± 5 years), and diabetes status. Controls with active malignancy reported as a
96 comorbidity at dialysis initiation were excluded to avoid any misclassification due to errors in
97 assigning the cause of ESKD. A total of 11 748 control ESKD patients were selected. The French data
98 protection authority approved the data collection conducted by the REIN registry, and the REIN
99 scientific committee approved the study.

100 ***Information***

101 Baseline data were collected from patients' medical records by nephrologists or clinical research
102 assistants. Three ESKD causes could be reported and were coded using the 10th revision of the
103 International Classification of Disease (ICD-10) ⁽¹⁸⁾. Biopsy-proven diagnoses were specifically

104 reported. Other information included demographics, body mass index, comorbidities, mobility status
105 (autonomous, partially or totally dependent), and dialysis start condition (planned or unplanned, i.e.,
106 started on an emergency basis). Comorbidities included diabetes, chronic respiratory disease, the
107 number of cardiovascular diseases (0, 1, 2, ≥ 3) among coronary artery disease, cerebrovascular
108 disease, peripheral artery disease, heart failure, and dysrhythmia, and active malignancy. REIN coding
109 instructions call for patients to be classified as having an active malignancy at the initiation of kidney
110 replacement therapy if they then had any type of cancer not in remission or if they had been treated
111 for cancer or had metastases in the two years before kidney replacement therapy.

112 **Outcomes**

113 We studied mortality on maintenance dialysis in the overall population, as well as access to the
114 national transplant waiting list and to kidney transplantation in patients younger than 75 years,
115 through December 31, 2015. For the first two outcomes, time to event was calculated from dialysis
116 initiation. Time to kidney transplantation was calculated from wait-listing date, either before or after
117 dialysis start, to avoid immortal time bias.

118 **Statistical Analysis**

119 We calculated mean incidence rates of cancer-related ESKD, nephrotoxin-related ESKD, and urinary
120 tract cancer-related ESKD per million inhabitants (pmi), overall, by sex and by age group (<44, 45-64,
121 65-74, ≥ 75 years) for the overall 2006-2015 period. We also calculated age- and sex-adjusted annual
122 incidence rates of cancer-related ESKD and their 95% confidence intervals (CI), overall and by
123 subtype, from 2006 to 2015, standardized according to the French population as of June 30, 2015.
124 Time trends in incidence rates over the 10-year period were tested for overall cancer-related ESKD
125 and by subtype with JoinPoint software.⁽²⁰⁾

126 We then used Chi-square or Mann-Whitney tests, as appropriate, to describe baseline patient
127 characteristics and compared cases with nephrotoxin- and urinary tract cancer-related ESKD with
128 their matched controls. Missing data for some variables led to the performance of multiple
129 imputations of 20 datasets with the fully conditional specification method. Analyses of the 20
130 complete datasets were combined according to Rubin's rules.(21) We used cumulative incidence
131 functions and Fine and Gray's competing-risk regression models to estimate and compare all-cause
132 mortality as well as cancer and non-cancer mortality of all cases and matched controls.

133 Similarly, we estimated and compared transplant wait-listing and kidney transplantation rates for
134 cases aged less than 75 years and their matched controls. Cumulative incidence rates were estimated
135 separately for cases with and without active malignancy at baseline, given this condition's strong
136 influence on prognosis and kidney transplant indication. The competing event in the mortality
137 analysis was kidney transplantation; for the analyses of waiting-list and kidney transplantation
138 access, the competing event was death. Finally, for each subtype of cancer-related ESKD, we
139 estimated subdistribution hazard ratios (SHRs) of death and their 95% confidence intervals (95% CI)
140 before and after adjustment for age, sex, diabetes status, cardiovascular comorbidities, liver disease,
141 respiratory disease, and dialysis start condition. Similarly, we estimated SHRs of wait-listing and
142 kidney transplantation before and after adjustment for age, sex, diabetes status, cardiovascular
143 comorbidities, and temporary contraindication for transplantation. *P*-values <0.05 were considered
144 statistically significant, and all analyses were performed with SAS 9.4.

145

146 **Results**

147 ***Incidence of cancer-related end-stage kidney disease***

148 The mean incidence for overall cancer-related ESKD over the study period was 2.22 pmi (95%
149 CI, 2.11–2.34). It significantly increased by 2.6% (95% CI, 0.6%–4.7%) annually from 2006 to
150 2015. (Figure 2) The mean incidence of nephrotoxin-related ESKD was 0.43 pmi (95% CI, 0.38–
151 0.49) with a significant annual increase of 5.2% for urinary tract cancer-related ESKD, it was
152 1.80 pmi (95% CI, 1.68–1.90) with an annual increase of 1.9%. The incidence of urinary tract
153 cancer-related ESKD was more than three times higher in men than women and increased
154 strongly with age. (Supplemental Table 2). Nephrotoxin-related ESKD incidence was almost
155 twice as high in men as in women and increased only slightly with age up to 65-74 years, but
156 not afterwards.

157 ***Patient characteristics at baseline***

158 Among the 287 patients with nephrotoxin-related ESKD it was attributed to platinum-based
159 chemotherapies for 59%. Among the 1157 patients with urinary tract cancer-related ESKD,
160 58% of these cases were related to renal cell carcinoma (Supplemental Table 1). Nephrectomy
161 was reported as a contributing cause of ESKD in 50% of urinary tract cancer cases and only in
162 4.5% of nephrotoxin-related ESKD, and nonneoplastic disease in 34.4% and 27.5%,
163 respectively. The percentage of biopsy-proven diagnosis, however, was very low in both
164 groups (Table 1).

165 At dialysis initiation, around 60% of the patients in both subgroups had an active malignancy
166 (Table1). Compared with their matched controls, patients with nephrotoxin- and urinary tract
167 cancer-related ESKD had cardiovascular and liver disease significantly less often, were more
168 likely to be treated with hemodialysis than peritoneal dialysis, and were less likely to be wait-
169 listed for kidney transplantation.

170 Mortality on dialysis

171 Median follow-up was 2.4 years (range 0-13.9) and 3.6 years (range 1.7-13.7) for nephrotoxin-
172 and urinary tract cancer-related ESKD, respectively. In patients with nephrotoxin-related
173 ESKD and without active malignancy at dialysis initiation, two-year mortality was 29% versus
174 16% in controls, and for those with active malignancy, 65% versus 21% (Figure 3A). The
175 corresponding rates in patients with urinary tract cancer-related ESKD and active malignancy
176 were 48% versus 26% in their controls, but were similar for patients without active
177 malignancy and their controls (Figure 3B). The cumulative incidence of cancer versus
178 noncancer mortality was higher in patients with active malignancy at baseline, regardless of
179 the type of cancer-related ESKD (Table 2). In those without active malignancy at baseline, the
180 cumulative incidence of cancer compared with noncancer mortality was much lower. It
181 although still higher than in matched controls.

182 Adjusting for covariates did not substantially modify the SHRs for all-cause mortality
183 estimated by the Fine and Gray models in any subgroup (Table 3).

184 Registration on the waiting list for kidney transplantation

185 In all, 41 patients with nephrotoxin-related ESKD(18%) and 100 urinary tract cancer-related
186 ESKD (16%) were wait-listed for kidney transplantation during the study period, together with
187 2855 controls (41%). Nephrotoxin-related ESKD patients without active malignancy at dialysis
188 initiation waited for a median time of 8.7 months (interquartile range [IQR]: 0-12.7) *versus*
189 6.7 months (IQR: 0-12.9) in controls (*P*-value 0.05), and those with active malignancy, 40.3
190 months (3.6-55.7) *versus* 6.3 months (0-12.9) (*P*-value 0.01). Urinary tract cancer-related
191 ESKD patients without active malignancy waited a median of 12.8 (IQR 4.5-31.0) *versus* 7.3

192 months (IQR 0.7-15.1) for their controls (P -value 0.01), and those with active malignancy, 14.8
193 (6.3–33.0) versus 6.8 months (0.5–14.8) ($P < 0.001$).

194 Of those with nephrotoxin-related ESKD patients, the 34% without an active malignancy were
195 wait-listed within two years, 50% of their controls, 4% of those with active malignancy, and
196 45% of their controls. (Figure 3C) Corresponding figures for patients with urinary tract cancer-
197 related ESKD were 19% of those without active malignancy, 36% of their controls, 7% of those
198 with active malignancy, and 37% of their matched controls. (Figure 3D) Adjusting for
199 covariates did not substantially modify SHRs for wait-listing (Table 3).

200 **Access to kidney transplantation**

201 Once on the waiting list, neither the probability nor the timing of kidney transplantation
202 differed significantly between nephrotoxin- or urinary tract cancer-related ESKD patients
203 compared with their matched controls, but the number of events was small. Of the
204 nephrotoxin-related ESKD patients, 55% with and 21% without active malignancy at dialysis
205 start were transplanted within 12 months after being wait-listed, compared with 32% in both
206 control groups. Among the urinary tract cancer-related ESKD patients, these percentages
207 were 36% and 41% for patients with and without active malignancy, and 32% and 38% for
208 their respective controls (Figure S1). In the multivariable models, the probability of
209 transplantation did not differ significantly between cases and controls (Table 4).

210

211

212 Discussion

213 This registry-based study shows that cancer-related ESKD has been slowly but steadily
214 increasing over the past decade in the French population, notably nephrotoxin-related ESKD.
215 As expected, survival among patients with active malignancy at dialysis initiation was very
216 poor and their access to kidney transplantation limited. More unexpectedly, patients whose
217 cancer had not been active in the two years before starting dialysis also experienced a much
218 lower rate of wait-listing than matched controls with other causes of ESKD, despite similar
219 survival on dialysis.

220 The incidence of kidney replacement therapy for ESKD continues to rise in most countries
221 including France, mainly as a result of population aging, increasing diabetes prevalence, and
222 extended dialysis access criteria.⁽²²⁾ However, the annual increases of 5.2% for nephrotoxin-
223 related ESKD and 1.9% for urinary tract cancer-related ESKD far exceeded the 0.8% annual
224 increase estimated for the overall French ESKD population over this period.⁽²³⁾ These findings
225 highlight the growing importance of cancer-related ESKD, which we may nonetheless have
226 underestimated, due to the lack of coding for ESKD causes related to more novel anti-cancer
227 agents such as vascular endothelial growth factor, epidermal growth factor receptor pathway
228 inhibitors, targeted therapies and immunotherapy.^(6,9)

229 Although we cannot ascertain whether this increase is due to higher use of nephrotoxic anti-
230 cancer drugs or increase of cancer incidence before 2005, improved cancer survival in France
231 in the most recent period may be a key contributor to cancer-related ESKD increase.^(3,4) Of
232 note, the sex ratio for nephrotoxin-related ESKD was similar to that reported for the overall
233 French dialysis population,⁽²³⁾ while it was much higher for urinary tract cancer, as expected
234 from well-documented sex disparities in this cancer incidence.⁽²⁴⁾

235 Patient characteristics at dialysis initiation were similar to those from other studies, with a
236 lower prevalence of comorbidities among those with cancer-related causes than among other
237 ESKD patients, and their preference for hemodialysis rather than peritoneal dialysis.^(13, 25) The
238 lower prevalence of comorbidities in these patients may reflect some selection process
239 resulting from the evaluation of overall prognosis and treatment options for each patient and
240 then by shared decision-making about starting dialysis.⁽¹³⁾

241 Our findings about mortality in patients with ESKD related to nephrotoxins or urinary tract
242 cancer are difficult to compare to other studies where malignancy status at dialysis initiation
243 was not available. Like others we found that these patients had worse survival than patients
244 with other ESKD causes when they were reported to have had active malignancy at dialysis
245 start.^(11, 13) When they did not, adjusted SHR for all-cause mortality was similar, consistent
246 with the better survival observed for patients with renal cell cancer undergoing
247 nephrectomy.⁽¹³⁾ Nevertheless, in these patients without active malignancy, cancer mortality
248 remained higher than in controls.

249 Kidney transplantation is the gold-standard kidney replacement therapy in ESKD, for both
250 survival and quality of life.⁽²⁶⁾ Among the patients who begin hemodialysis, early
251 transplantation improves long-term outcomes.⁽¹¹⁾ In this study, both urinary tract cancer- and
252 nephrotoxin-related ESKD patients whose cancer was not active at dialysis start had a lower
253 rate of access to the transplant waiting list than their matched controls. However, once on
254 the waiting list, their probability of transplantation was similar to that of their controls.

255 Several factors may partly explain this limited access for cancer-related ESKD patients. Pelvic
256 radiation for urinary tract, gynecologic, or colorectal cancers can cause tissue injury that leads
257 to radiation-induced atherosclerosis, atrophy, tissue ischemia, and fibrosis.⁽²⁷⁾ Hence, kidney
258 transplantation in these patients may be impossible due to extreme tissue frailty, and

259 consequently, be definitively contraindicated.⁽²⁸⁾ Complex urologic, gynecologic, and
260 gastrointestinal oncologic surgery with local tissue impairment may also prevent surgeons
261 from performing transplantation because of the high risk of early graft failures.⁽²⁹⁾
262 Kidney transplant candidates with a history of malignancy usually face waiting times even
263 longer than most because of the challenging nature of decision-making related to their high
264 risk of cancer recurrence and mortality.^(30, 31) Clinical practice guidelines on the evaluation and
265 management of candidates for kidney transplantation recommend excluding those with
266 active malignancy and waiting from 2 to 5 years after completion of potentially curative
267 cancer treatment, depending on the cancer type and stage.^(16, 32-34) These waiting times often
268 relied on high recurrence rates based on old retrospective studies.^(35, 36) It is worth noting,
269 however, that a study in Norway, where the transplantation rate is very high, showed that
270 this country's policy of a short one-year waiting period between cancer treatment and kidney
271 transplantation yielded similar overall survival for kidney transplant recipients with and
272 without a cancer history.⁽³⁸⁾ Such difference in clinical practice between France and Norway
273 may lead to recommend more studies on whether the wait time to listing should be shorten.
274 Our study has several strengths including the availability of ESKD causes from the most
275 commonly used nephrotoxins over a 10-year period and the unselected nature of the REIN
276 registry population, which enables our findings to be generalized to all patients on dialysis in
277 France. Most importantly, patients' malignancy status was known at dialysis initiation,
278 whether it was active before then or not. This allowed assessment of both mortality and
279 transplantation access by subgroup according to this critical determinant of both outcomes,
280 involving 60% of all cases.

281 This study also has limitations. The type and grade of underlying cancer for patients with
282 nephrotoxin-related ESKD was unknown, which prevented us from assessing mortality by

283 malignancy type. Likewise, the type of nephrectomy, whether radical or partial was not
284 recorded, so that we could not estimate the percentage of patients with ESKD after surgery.
285 Similarly, CKD status at cancer onset was unavailable. In some cases, non-neoplastic diseases
286 were also reported at dialysis start, but the low percentage of biopsy-proven diagnosis makes
287 it difficult to determine the relative contribution of each presumed cause in the onset of ESKD.
288 We cannot rule out, however, that it may have been multifactorial in some cases. Finally, the
289 duration of cancer remission for those without reported active malignancy at baseline was
290 not recorded which prevented us from estimating the wait-listing rate in patients in remission
291 for more than 5 years. The number of kidney transplant was also too low to draw meaningful
292 conclusions about this outcome.

293 **Conclusion**

294 Improvement in cancer survival appears to be associated with an increase in kidney
295 replacement therapy for ESKD related to antineoplastic treatments. Our study indicates that
296 survival among patients starting dialysis with cancer-related ESKD, but whose cancer had not
297 been active in the previous two years is similar to that of other ESKD patients of similar age,
298 sex, and diabetes status. Nonetheless, and despite their lower prevalence of comorbidities
299 than patients with other ESKD causes, these patients were less likely to be wait-listed for
300 transplantation. Uncertainties regarding the optimal waiting time before transplantation for
301 many cancers and fear of cancer recurrence remain major obstacles to wait-listing patients in
302 remission. Further studies are needed to evaluate the best timing for kidney transplantation
303 in patients with ESKD after cancer treatment. Close collaboration between nephrologists and
304 oncologists is needed to improve decision-making about kidney transplantation in this rapidly
305 growing patient population, to further improve their quality of life and outcomes.

306 **Disclosure**

307 The authors of this manuscript have no conflicts of interest to disclose

308 **Acknowledgments**

309 We thank all the registry participants, especially the nephrologists and professionals who

310 collected the data and conducted the quality control. The dialysis units participating in the

311 registry are listed in its annual report: <http://www.agence->

312 [biomedecine.fr/IMG/pdf/rapport_rein2016.pdf](http://www.biomedecine.fr/IMG/pdf/rapport_rein2016.pdf).

313 We also thank Jo-Ann Cahn for revising and editing this manuscript.

314 **Funding**

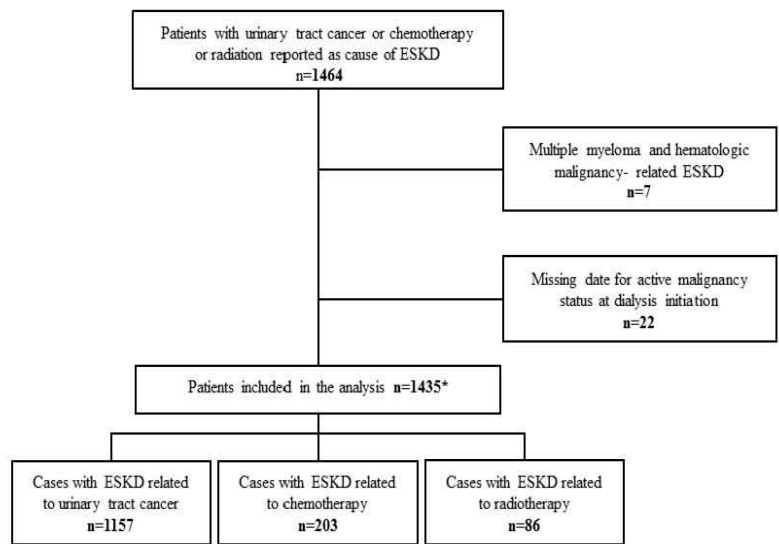
315 Imene Mansouri was supported by a PhD grant from the Ministry of Research for this work.

316 **Availability of data and materials**

317 Data are available upon request to the REIN registry, coordinator: Dr. Christian Jacquelinet

318 Email: christian.jacquelinet@biomedecine.fr.

319



* 9 cases had ESKD related to more than one cause

Figure 1: Study flow chart

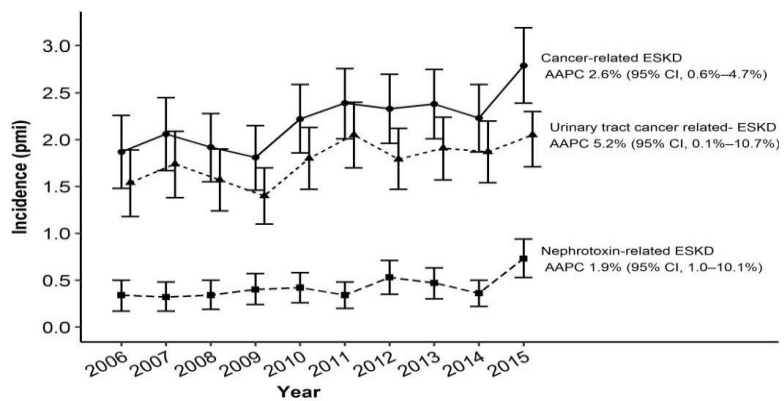


Figure 2. Standardized incidence rates of cancer-related ESKD per million inhabitants between 2006 and 2015

Table 1. Baseline characteristics of patients with nephrotoxin- or urinary tract cancer-related ESKD and matched controls at dialysis initiation

Characteristics	Nephrotoxin-related ESKD		Urinary tract cancer-related ESKD	
	Case patients n=287	Matched controls n=2368	Case patients n=1157	Matched controls n=9380
Men* (%)	61	61	76	75
Median age, years (range)*	65 (21-93)	65 (21-93)	73 (1- 100)	73 (0-100)
Age, years*				
<44	10	11	3	3
45-64	38	39	22	23
65-74	33	31	29	29
≥75	19	19	46	45
Year at dialysis start*	23			
<2009	27	33	33	33
2009-2012	37	37	37	37
2013-2015	36	30	30	30
Kidney biopsy (%)	15	23	10	16
Diabetes*(%)	14	16	23	24
Body mass index, kg/m² (%)				
<18.5	15	6	5	5
18.5-24.9	53	45	43	45
25-29.9	26	32	34	33
≥30	6	17	18	17
Active malignancy‡ (%)	61	-	59	-
Respiratory disease (%)	12	10	13	14
Cardiovascular disease ‡ (%)				
0	62	57	53	42
1	24	21	22	26
2	9	13	16	18
≥3	5	9	9	14
Liver disease (%)	1	3	1	2
Treatment modality (%)				
Hemodialysis	95	88	96	88
Peritoneal dialysis	5	12	4	12
Started emergency dialysis (%)	34	28	32	29
Wait-listed for kidney transplantation at dialysis start (%)	14	39	9	21
Reasons for not being wait-listed (%)				
Medical contraindication	81	45	88	53
Assessment in progress	12	41	7	32
Patient refusal	0	2	0	2

Other	7	12	5	13
ESKD, end-stage kidney disease				
*Matching criteria				
‡ Active malignancy was an exclusion criteria among controls				
‡Cardiovascular diseases included coronary heart disease, cerebrovascular disease, peripheral artery disease, heart failure, and dysrhythmia				

Table 2. Cumulative incidence of mortality from malignancy and other causes in nephrotoxin and urinary tract cancer-related ESKD patients and their matched controls.

	Mortality from malignancy (%)		Mortality from other causes (%)	
	1 year	2 years	1 year	2 years
Nephrotoxin-related ESKD				
Patients with active malignancy	28.2	39.7	21.8	29.5
Patients without active malignancy	6.0	10.8	10.3	18.5
Controls	0.5	1.2	11.3	17.8
Urinary tract cancer-related ESKD				
Patients with active malignancy	17.7	26.1	15.4	21.9
Patients without active malignancy	2.4	6.0	14.0	24.5
Controls	0.8	1.6	16.2	25.8

Table 3. Number of events, crude and adjusted subdistribution hazard ratios for mortality on dialysis, wait-listing and kidney transplantation

Outcome	Nephrotoxin-related ESKD					Urinary tract cancer-related ESKD				
	Controls	Patients with active malignancy	<i>P</i>	Patients without active malignancy	<i>P</i>	Controls	Patients with active malignancy	<i>P</i>	Patients without active malignancy	<i>P</i>
Mortality on dialysis										
Number of patients	2368	174		113		9380	683		474	
Number of deaths	802	124		47		4335	420		247	
Crude SHR (95% CI)	Ref	3.7 (3.0-4.7)	<.001	1.3 (1.0-1.8)	0.05	Ref	1.7 (1.5-1.9)	<.001	1.1 (0.9-1.2)	0.7
Adjusted SHR (95% CI) ¹	Ref	4.2 (3.2-5.5)	<.001	1.4 (0.9-2.0)	0.3	Ref	2.0 (1.7-2.2)	<.001	1.1 (0.9-1.2)	0.9
Wait-listing*										
Number of patients	1911	146		88		5113	404		225	
Number of events	919	12		29		1936	45		55	
Crude SHR (95% CI)	Ref	0.20 (0.11-0.34)	<.001	0.67 (0.5-0.90)	<.001	Ref	0.33 (0.25-0.45)	<.001	0.51 (0.40-0.67)	<.001
Adjusted SHR (95% CI) ²	Ref	0.19 (0.11-0.32)	0.03	0.62 (0.43-0.88)	0.01	Ref	0.28 (0.21-0.37)	<.001	0.47 (0.36-0.60)	<.001
Kidney transplantation†										
Number of patients	919	12		29		1935	45		55	
Number of events	597	8		14		1277	24		32	
Crude SHR (95% CI)	Ref	1.2 (0.44-3.1)	0.7	0.67 (0.40-1.2)	0.2	Ref	0.91 (0.60-1.4)	0.6	1.0 (0.7-1.5)	0.9
Adjusted SHR (95% CI) ²	Ref	1.1 (0.40-3.2)	0.6	0.65 (0.40-1.4)	0.6	Ref	0.90 (0.60-1.2)	0.6	1.0 (0.8-1.6)	0.5

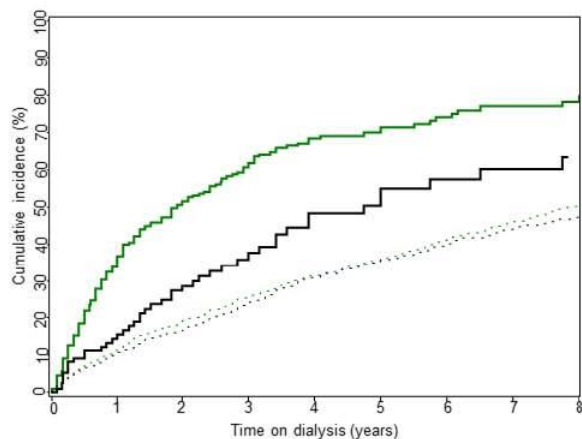
ESKD, end-stage kidney disease; SHR (95%CI), subdistribution hazard ratios (95% confidence interval); Ref, reference

*Among patients aged < 75 years; † Among patients aged < 75 years wait-listed for kidney transplantation

¹ SHR adjusted for sex, age at dialysis initiation, diabetes status, cardiovascular comorbidities, liver disease, respiratory disease, and emergency dialysis

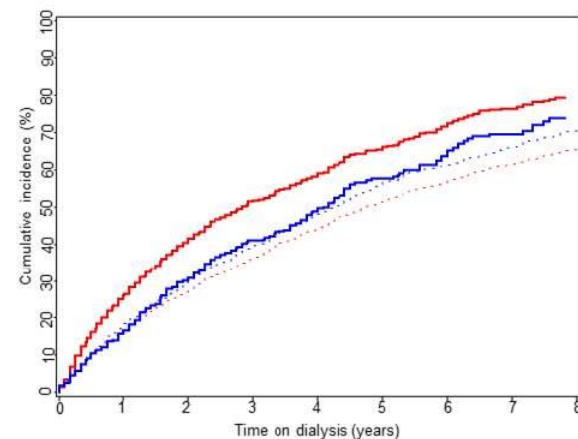
² SHR adjusted for sex, age at dialysis initiation, diabetes status, cardiovascular comorbidities, and temporary transplantation contraindication

A- Mortality on dialysis among nephrotoxin-related ESKD patients



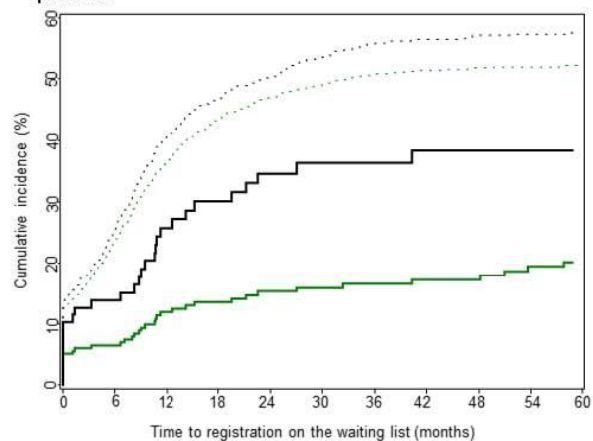
Number at risk									
Controls ^a	1433	1024	707	479	341	235	158	96	51
Nephrotoxin related-ESKD with active malignancy	174	75	42	28	19	13	8	3	3
Controls ^b	935	689	486	333	218	138	87	57	38
Nephrotoxin related-ESKD without active malignancy	113	75	51	29	20	14	11	9	5

B- Mortality on dialysis among urinary tract cancer-related ESKD patients



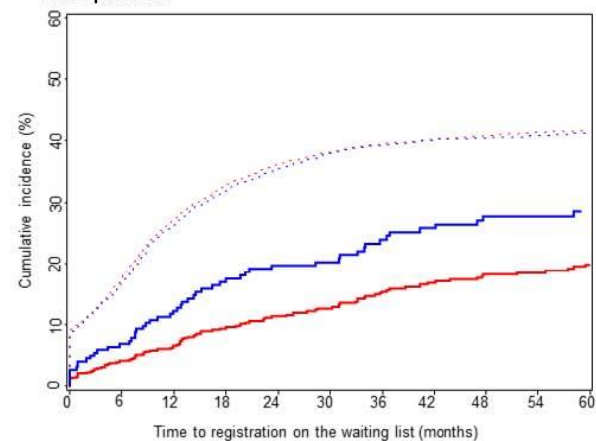
Number at risk									
Controls ^c	5558	3959	2792	1984	1386	936	611	383	225
Urinary tract cancer-ESKD with active malignancy	683	392	263	167	116	61	34	23	17
Controls ^d	3822	2664	1852	1269	848	522	329	204	114
Urinary tract cancer-ESKD without active malignancy	474	359	249	179	128	83	48	31	15

C- Kidney transplant wait-listing among nephrotoxin-related ESKD patients



Number at risk									
Controls ^a	1188	795	570	438	361	310	257	226	194
Nephrotoxin related-ESKD with active malignancy	146	91	52	37	30	27	20	17	15
Controls ^b	723	475	337	272	222	186	153	131	115
Nephrotoxin related-ESKD without active malignancy	88	64	43	35	25	21	17	15	12

D- Kidney transplant wait-listing among urinary tract cancer-related ESKD patients



Number at risk										
Controls ^c	3305	2359	1816	1503	1230	1064	906	782	687	
Urinary tract cancer-ESKD with active malignancy	404	304	241	196	156	128	99	81	64	
Controls ^d	1808	1322	1002	825	680	559	476	399	348	
Urinary tract cancer-ESKD without active malignancy	225	191	161	127	111	97	79	72	58	

Nephrotoxin related ESKD patients with active malignancy ———
Controls for nephrotoxin-related ESKD patients - - - - -
Nephrotoxin related ESKD patients without active malignancy ———
Controls for nephrotoxin-related ESKD patients without active malignancy - - - - -
Urinary tract cancer-related patients with active malignancy ———
Controls for urinary tract cancer-related patients with active malignancy - - - - -
Urinary tract cancer-related patients without active malignancy ———
Controls for urinary tract cancer-related patients without active malignancy - - - - -

Figure 3. Cumulative incidence of all-cause mortality and wait-listing for kidney transplantati

Figure Legend

Figure 2. Standardized incidence rates of cancer-related ESKD per million inhabitants between 2006 and 2015

AAPC, average annual percent change; 95% CI, 95% confidence interval; ESKD, end-stage kidney disease

Figure 3. Cumulative incidence of all-cause mortality and wait-listing for kidney transplantation

Supplemental material

Supplemental Table 1. Studied causes of end-stage kidney disease by subtype, coded according to the International Classification of Disease (ICD10).

Supplemental Table 2. Standardized incidence rates of cancer-related ESKD per million inhabitants, overall and by subtype, age, and sex, 2006-2015.

Supplemental Figure. Access to kidney transplantation among wait-listed patients with cancer-related ESKD and matched controls

Supplemental Table 1. Studied causes of end-stage kidney disease by subtype, coded according to the International Classification of Disease 10th revision (ICD10)

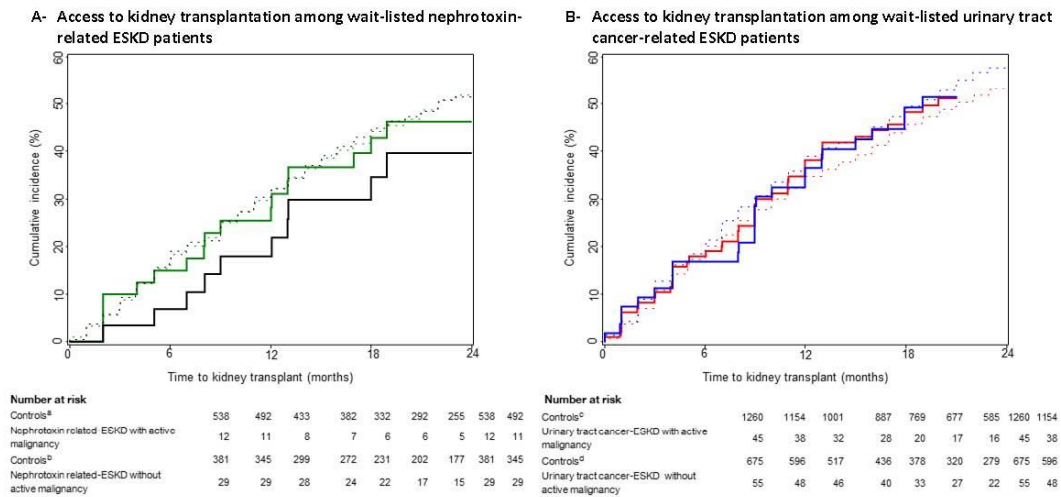
Cancer related end stage kidney disease	ICD 10 code	Cause of end-stage kidney disease	N*
Kidney and urinary tract cancer			
Benign neoplasm of kidney and the urinary tract	D30.0	Benign neoplasm of kidney	72
Malignant neoplasm of kidney	C64	Nephroblastoma, Wilm's tumor	19
		Renal cell carcinoma	547
		Tubulopapillary carcinoma	16
		Other renal cell carcinoma including human chromophobe cell renal carcinoma	126
		Renal sarcoma	14
Malignant neoplasm of urinary tract	C65	Malignant neoplasm of renal pelvis	63
	C66	Malignant neoplasm of ureter	44
	C67.9	Malignant neoplasm of bladder	107
	Z85.5	Personal history of malignant neoplasm of urinary tract	128
Nephrotoxins			
Adverse effects of antineoplastic drugs	T45.1	Antimetabolites: methotrexate	8
		Anti-tumor antibiotic : mitomycin C	3
		Vinca alkaloid : vincristine	1
		Platinum derivatives: cisplatin, carboplatin	169
		Alkylating agents: cyclophosphamide	11
		ifosfamide	14
Radiation effects, unspecified	T66	Radiotherapy	86

*Cases could have multiple causes of ESKD

Supplemental Table 2. Standardized incidence rates of cancer-related ESKD per million inhabitants, overall and by subtype, age, and sex, 2006-2015.

	Cancer-related ESKD			nephrotoxin-related end-stage kidney disease			urinary tract cancer-related end-stage kidney disease		
	N	Incidence	(95% CI)	N	Incidence	(95% CI)	N	Incidence	(95% CI)
Overall	1351	2.22	(2.10-2.34)	264	0.43	(0.38-0.49)	1087	1.80	(1.68-1.90)
Sex									
Men	995	3.38	(3.17-3.59)	163	0.58	(0.49-0.66)	832	2.96	(2.76-3.16)
Women	356	1.02	(1.25-1.17)	101	0.33	(0.27-0.40)	255	0.83	(0.73-0.94)
Age (years)									
<44	61	0.17	(0.13-0.22)	26	0.07	(0.05-0.10)	35	0.10	(0.07-0.13)
45-64	333	2.14	(1.91-2.37)	103	0.66	(0.53-0.79)	230	1.48	(1.29-1.67)
65-74	393	7.59	(6.84-8.35)	85	1.65	(1.30-2.01)	308	5.94	(5.27-6.60)
≥75	564	10.38	(9.52-11.24)	50	0.91	(0.66-1.17)	514	9.46	(8.64-10.28)
Year at dialysis start									
2006	89	1.87	(1.48-2.26)	16	0.34	(0.17-0.50)	73	1.54	(1.18-1.89)
2007	108	2.06	(1.67-2.45)	17	0.32	(0.17-0.48)	91	1.74	(1.38-2.09)
2008	106	1.92	(1.55-2.28)	19	0.34	(0.19-0.50)	87	1.57	(1.24-1.90)
2009	107	1.81	(1.46-2.15)	24	0.40	(0.24-0.57)	83	1.40	(1.10-1.70)
2010	142	2.22	(1.86-2.59)	27	0.42	(0.26-0.58)	115	1.80	(1.47-2.13)
2011	155	2.39	(2.01-2.76)	22	0.34	(0.20-0.48)	133	2.05	(1.70-2.40)
2012	153	2.33	(1.96-2.70)	35	0.53	(0.35-0.71)	118	1.79	(1.47-2.12)
2013	157	2.38	(2.01-2.75)	31	0.47	(0.30-0.63)	126	1.91	(1.57-2.24)
2014	148	2.23	(1.87-2.59)	24	0.36	(0.22-0.50)	124	1.87	(1.54-2.20)
2015	186	2.79	(2.39-3.19)	49	0.73	(0.53-0.94)	137	2.05	(1.71-2.30)

CI, confidence interval; Incidence was estimated per million population and adjusted for age and sex, with the 2015 French population as the reference



Nephrotoxin related ESKD patients with active malignancy ———
Controls for nephrotoxin-related ESKD patients ———
Nephrotoxin related ESKD patients without active malignancy ———
Controls for nephrotoxin-related ESKD patients without active malignancy ———
Urinary tract cancer-related patients with active malignancy ———
Controls for urinary tract cancer-related patients with active malignancy ———
Urinary tract cancer-related patients without active malignancy ———
Controls for urinary tract cancer-related patients without active malignancy ———

Supplemental Figure. Access to kidney transplantation among wait-listed patients with cancer-related ESKD and matched controls

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The role of irradiated heart and left ventricular volumes in heart failure occurrence after childhood cancer

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Received 21 February 2018; revised 1 October 2018; accepted 6 November 2018

Background

Paediatric cancer survivors have a high risk of developing cardiac diseases, and the most frequent cardiac disease is heart failure (HF). The radiation dose–volume effects in the heart and cardiac substructures have not been explored in childhood cancer survivors (CCS). Therefore, the role of irradiated heart volume in the occurrence of HF among this population remains unclear. The aims of this study were to determine the doses and irradiated volumes of the heart and left ventricle (LV) related to the risk of HF in CCS and to investigate the impact of anthracycline exposure on this risk.

Methods and results

A case-control study nested in the French Childhood Cancer Survivors Study cohort. The mean heart and left ventricular doses and volumes indicators were estimated by reconstruction of individual treatments. A total of 239 HF cases and 1042 matched controls were included. The median age of HF diagnosis was 25.1 years. The median volume of the heart that received ≥ 30 Gy was 61.1% for cases and 16.9% for controls. In patients who did not receive anthracycline, the risk of HF was increased 3.6-fold when less than 10% of the LV received ≥ 30 Gy when compared to patients who were not exposed to any cardiac radiation and anthracycline.

Conclusions

Small irradiated volumes of the heart or LV were significantly associated with HF risk. To the author's knowledge, this is the first study to report a dose–response relationship based on dose–volume indicators in CCS, which can be translated efficiently into current clinical practice.

Keywords

Heart failure • Heart radiation dose • Left ventricle • Volume histograms • Dose response

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Introduction

There has been a significant improvement in survival rates among children with cancer, with 5-year survival rates now over 80%, which is largely due to improved therapeutic strategies. Increased numbers of childhood cancer survivors (CCS)¹ has given rise to an increased need to focus on the long-term outcomes of cancer treatment, including quality of life, functional status, morbidity, and mortality. CCS suffer late effects and complications due to cancer treatment; for example, 40% of patients report a chronic health condition within 5 years of their diagnosis and this proportion reaches 73% within 30 years of diagnosis.² CCS have a high risk of developing cardiac diseases (CDs), the most frequent of which is heart failure (HF).^{3,4} Previous studies have shown that the cumulative incidence of HF among CCS, 30 years after diagnosis, ranges between 2.7% and 7%.^{3–6}

Anthracycline and cardiac radiation increase the risk of cardiac failure in CCS.⁷ Studies have examined the radiation dose response for HF in CCS^{4,6,8} and in adults with Hodgkin's lymphoma.^{9,10} Nevertheless, few studies have addressed the effect of the interaction between radiation and cardiotoxic chemotherapy on the risk of HF. In addition, the radiation dose–volume effects in the heart and cardiac substructures have been explored only in a few studies on adult survivors of Hodgkin's lymphoma.^{9,10} Therefore, the role of irradiated heart volumes in HF remains unclear, and the consequences of irradiating large parts of the heart with a lower dose vs. irradiating smaller parts of the heart with a high dose need to be further investigated.¹¹ Additional studies should also analyse the relationship between radiation doses to sub-volumes of the heart and the risk of HF.

Therefore, the aims of this study were to determine the doses and irradiated volumes of the heart and left ventricle (LV) in relation to the risk of HF in CCS and to investigate the impact of anthracycline exposure on this risk.

Methods

Study population

The French Childhood Cancer Survivors Study (FCCSS) is a cohort that included a total of 7032 5-year survivors of solid cancers diagnosed before age 20 between 1945 and 2000 in France and is the extension of the Euro2K cohort. The French Euro2K cohort included 3172 5-year survivors treated in several centres in France between 1942 and 1985 for any type of malignant neoplasm except leukaemia.⁴ The FCCSS combines to date the 3172 patients from the Euro2K and 3860 patients treated between 1985 and 2000 at the Gustave Roussy Centre.

A total of 1281 CCS were included in this case-control study. This case-control study was nested in the FCCSS cohort and the inclusion of cancer patients occurred before the diagnosis of HF or before any death. Overall, 239 HF cases were individually matched to 1042 controls. Each case was matched to between two and five controls on the basis of gender, age at first primary cancer diagnosis (± 3 years), year of first primary cancer diagnosis (± 3 years), and follow-up duration (the follow-up of each control patient was at least as long as the follow-up of their matched case). If more than five matching controls were found, five were randomly selected. To avoid

overmatching, study participants were not matched based on the type of childhood cancer. Controls had to be free of any CD at the cut-off date.

In accordance with the French regulations, the protocol of the study was approved by a regional committee on ethics and by the national committee protecting the confidentiality of the data (Commission Nationale de l'Informatique et des Libertés).

Follow-up

Data on patient outcomes, including cause of death for deceased patients, were obtained from the Centre d'Epidémiologie sur les Causes Médicales de Décès (<https://www.cepdc.inserm.fr/>). Causes of death for all deceased patients, coded according to the 9th and 10th versions of the International Classification of Diseases (ICD-9¹² and ICD-10¹³), were obtained from the French Death Registry. Follow-up ran from the time of diagnosis of childhood cancer until the occurrence of HF or death from HF for case patients and until response to the self-administered questionnaire, last medical contact reporting no CD or death from causes other than CD for controls.

Identification and validation of heart failure

Heart failure cases were identified using self-questionnaires, medical records, long-term follow-up consultation reports, the causes of death, and the French national health insurance reimbursement database (SNIRAM) which provides medical information on all patients admitted to hospital in France, including discharge diagnoses coded using the ICD-10.

Medical doctors and/or cardiologists of patients who were alive were invited to complete a questionnaire confirming the HF diagnosis, including B-type natriuretic peptide (N-terminal proBNP) and echo data and specifying the date of onset and which drug and/or interventional treatment was given. The validation of each diagnosis was based on criteria from the European Society of Cardiology and the Framingham studies.¹⁴ For deceased patients with HF as a cause of death, a physician reviewed the available medical charts and the causes of death. HF was then graded according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.03)¹⁵ (online supplementary Methods S7).

Chemotherapy

Information on all chemotherapeutic agents administered during primary cancer, recurrences and any subsequent primary cancer was collected up to the date of HF diagnosis for cases and during the corresponding follow-up period for their matched controls. The information included the type and dose (mg or g) of the drug, the start and end date of each chemotherapy treatment, and height and weight for body surface area estimation. For each participant, chemotherapy doses were summed across cycles to obtain cumulative doses of each drug received per m². The doses of chemotherapy were calculated from the time of diagnosis of childhood malignancy till the end of follow-up. Chemotherapy treatments were classified into three categories based on their molecular mechanisms of action: anthracyclines, alkylating agents, and vinca alkaloids.

Radiation dosimetry

Reconstitutions of the radiotherapy plans were made with the Isogray (Dosisoft, Cachan, France) treatment planning system which enabled computations of dose–volume metrics. The basic characteristics of the dosimetry software package have already been published.¹⁶ The software package involves the use of a voxel-based anthropomorphic phantom to generate for each subject a surrogate whole-body radiotherapy planning computed tomography according to gender, age, weight and height. As a result, a specific phantom anatomy is generated as a surrogate for each individual patient depending on gender, age, and treatment position.^{17,18}

A set of contours representing the entire heart and LV was defined in the phantoms. Mean radiation doses to the heart and LV and the volumes receiving at least 20, 30 and 40 Gy (V20, V30 and V40, respectively) were then estimated. These dose–volume parameters were chosen because they were considered as clinically important endpoints or predictors of acute and late heart disease.^{11,19,20} The radiation doses and volumes of the heart and LV were estimated at the time of the childhood cancer and before the onset of HF.

Complete medical documentation was crucial for the reconstruction of heart radiation dosimetry (online supplementary *Methods S1*). Therefore, dose estimation could not be performed for five participants with incomplete medical records.

Statistical analysis

Chemotherapy dose classes were calculated according to tertiles for alkylating agents and vinca alkaloids. The anthracycline dose categories were selected according to other published studies.^{4,8,21} The cumulative incidence of HF was estimated using the non-parametric Aalen–Johansen estimator. The attained age was used as time scale and death from other causes than HF was considered a competing event.

Conditional logistic regression was conducted for matched sets to estimate the risk of HF. Multivariable models were adjusted to the type of primary childhood malignancy, treatment characteristics, and the presence or absence of splenectomy.

Models that included the V5, V20, V25, V30 and V40 for the whole heart and LV were tested and then ranked according to the Akaike Information Criterion (AIC). The models selected based on the AIC were the models containing the mean dose and the V30 for the heart and LV.

The risk of HF due to radiation was studied as a function of the mean radiation dose and of the fraction of the volume receiving ≥ 30 Gy, both for the entire heart and LV. The interaction between anthracycline use and radiation doses to the heart and LV was studied using conditional regression models that included radiation dose as the categorical factor and anthracycline exposure as the binary variable (yes/no). These models provide odds ratios (ORs) associated with each level of cumulative radiation to the heart or LV, as compared to the reference level corresponding to no radiation or anthracycline exposure. Results were reported as ORs with 95% confidence intervals (CIs).

The dose–response relationship was evaluated by testing a linear model using the formula $OR = \alpha_s (1 + \beta d)$, and a quadratic model using the formula $OR = \alpha_s [1 + \beta d^2]$, where α_s is a constant specific to each stratum, β is the excess relative risk (ERR) of HF per unit increase in dose and d is the mean heart dose (MHD) or the mean left ventricular dose (MLVD). Non-linearity was evaluated by including an exponential term using the formula $OR = \alpha_s [1 + \beta d \exp(\gamma d)]$. The radiation dose is modelled as a continuous variable estimate of the ERR/Gy. The role

of each potential dose–response modifier was tested by comparing models based on the dose received in each of the two categories with nested models based on the total dose alone. Goodness of fit was assessed by likelihood ratio tests, and interactions were evaluated using interaction terms and likelihood ratio tests.

Sensitivity analysis was performed on a subset of 117 cases and 353 controls who returned the self-reported questionnaire and adjusted for the effects of smoking status, physical activity, and body mass index (BMI). A total of 16 patients had missing BMI. The ORs were first estimated separately for each risk factor with a missing category created for the missing BMI data. Then multiple imputation was performed to provide missing BMI data, and 20 imputed datasets were created. The 20 imputed data sets were analysed with all risk factors included in one multivariable model, results were then combined using Rubin and Schenker's rules.²²

Statistical inference was based on two-sided tests, and a P -value ≤ 0.05 was considered statistically significant. Analyses were performed using SAS[®] version 9.3 and Epiwin[®] software version 1.81.

Results

Study population

A total of 239 cases of HF were identified after a median follow-up of 19.7 years [interquartile range (IQR) 13.7–26.9] and matched to two to five controls. The characteristics of the 1281 patient cases and controls are listed in *Table 1*. The median age at diagnosis of the first malignancy was 5 years for both cases and controls (IQR 2.4–9.8 and 2.3–9.6 for cases and controls, respectively).

Of the 239 cases, 85.4% had symptomatic HF, of which 46.4% had grade three HF, 21.4% had grade four HF, and 17.6% had died from HF. The median age of HF diagnosis was 25.1 years (*Table 2*). A total of 25 cases received a cardiac transplantation at a median age of 20.3 years (IQR 15.3–28.1).

A total of 72% of HF patients and 34.7% of controls received anthracycline, and 91.3% of cases and 88.9% of controls who received anthracycline received doxorubicin (*Table 1*). Case patients received a median anthracycline dose of 357.3 mg/m²; however, controls received 292.4 mg/m² (*Table 1*).

A total of 72.8% of case patients and 62.2% of controls were treated with radiotherapy. Among cases treated with radiotherapy, the mean doses to the heart and LV were 12.3 Gy (range: 0.004–49.1) and 11.9 Gy (range: 0.003–47.4), respectively (*Table 1*). Control patients received a mean dose of 2.1 Gy (range: 0.005–45.3) to the heart and 2.1 Gy (range: 0.005–39.5) to the LV. The median volume of the heart that received ≥ 30 Gy was 61.1% (range: 0.1–100%) in cases and 16.9% (range: 0.03–100%) in controls. The median volume of the LV that received ≥ 30 Gy was 37.3% (range: 0.01–100%) in cases and 23.8% (range: 0.06–100%) in controls (*Table 1*).

Cumulative incidence

The cumulative incidence of HF was 2.5% (95% CI 2.1–2.9%) at 30 years and 5.7% (95% CI 5.0–6.6%) at 50 years (*Figure 1* and online supplementary *Table S1*).

Table 1 General and treatment characteristics of the cases of heart failure and their matched controls

Characteristics	Cases (n = 239)	Controls (n = 1042)	P-value
Gender ^a , n (%)			*
Female	114 (47.7)	499 (47.9)	
Male	125 (52.3)	543 (52.1)	
Follow-up ^a , years, median (IQR)	19.7 (13.7–26.9)	33.0 (27.2–39.0)	*
Age at diagnosis of cancer ^a , years, median (IQR)	5.0 (2.4–9.8)	5.0 (2.3–9.6)	*
Status at the end of follow-up			< 0.0001
Alive	143 (59.8)	917 (88.0)	
Deceased	96 (40.2)	125 (12.0)	
Year of cancer diagnosis ^a , median (range)	1979 (1942–2000)	1979 (1942–2000)	*
Type of first malignancy, n (%)			< 0.0001
Nephroblastoma	81 (33.9)	321 (30.8)	
Sarcoma	61 (25.5)	191 (18.3)	
Hodgkin's disease	35 (14.6)	79 (7.6)	
Non-Hodgkin's lymphoma	34 (14.2)	125 (12.0)	
Other	21 (8.8)	170 (16.3)	
Central nervous system	4 (1.7)	140 (13.4)	
Neuroblastoma	3 (1.3)	16 (1.5)	
Chemotherapy, n (%)	229 (95.8)	798 (76.6)	< 0.0001
Anthracyclines, n (%)	172 (72.0)	362 (34.7)	< 0.0001
Dose, mg/m ² , median (range)	357.3 (2.1–998.1)	292.4 (6.1–1021.8)	
Doxorubicin, n (%)	157 (65.7)	322 (30.9)	< 0.0001
Dose, mg/m ² , median (range)	352.7 (2.1–860.6)	284.6 (6.1–619.2)	
Daunorubicin, n (%)	25 (2.4)	10 (4.2)	< 0.0001
Dose, mg/m ² , median (range)	508.2 (279.3–998.1)	316.2 (81.9–998.1)	
Alkylating agents, n (%)	182 (76.2)	530 (50.9)	< 0.0001
Dose, g/m ² , median (range)	10.4 (0.2–367.1)	7.3 (0.02–140.2)	
Cisplatin, n (%)	33 (13.8)	91 (8.7)	0.8
Dose, mg/m ² , median (range)	455.4 (97.1–1154.7)	431.3 (74.3–4128.2)	
Vinca alkaloids, n (%)	197 (82.4)	655 (62.9)	< 0.0001
Dose, mg/m ² , median (range)	25 (1.65–10611.6)	19.6 (1–2556)	
Radiotherapy, n (%)	174 (72.8)	648 (62.2)	0.0001
Radiation to the heart			
Mean dose, Gy, median (range)	12.3 (0.004–49.1)	2.1 (0.005–45.3)	< 0.0001
Volume (%) receiving ≥ 30 Gy, median (range)	61.1 (0.1–100)	16.9 (0.03–100)	< 0.0001
Radiation to the left ventricle			
Mean dose, Gy, median (range)	11.9 (0.003–47.4)	2.1 (0.005–39.5)	< 0.0001
Volume (%) receiving ≥ 30 Gy, median (range)	37.3 (0.01–100)	23.8 (0.06–100)	< 0.0001

IQR, interquartile range.

*Matching variables.

Treatment-related factors and radiation dose–volume indicators

The risk of HF increased with the cumulative dose of anthracycline ($P_{\text{trend}} < 0.0001$); compared to CCS who did not receive anthracycline, the risk of HF increased 3.4-fold (95% CI 1.5–7.6) in CCS who received doses < 250 mg/m², 11.4-fold (95% CI 5.0–25.9) in those who received doses of 250–360 mg/m², and 15-fold (95% CI 7.1–31.7) in those who received doses ≥ 360 mg/m² (Table 3). The risks remained similar when restricting the study to grade ≥ 3 HF (online supplementary Table S2).

The relative risks of HF for patients receiving < 250 mg/m² without and with cardiac radiation compared to patients unexposed

to anthracycline and radiation were 3.3 and 7.2, respectively (Table 4).

The interactions between anthracycline administration and the MHD ($P = 0.007$) and the MLVD ($P < 0.004$) were significant. In comparison to patients who did not receive either anthracycline or cardiac radiation, a mean radiation dose to the heart or LV < 15 Gy was associated with a non-significant risk of HF in patients unexposed to anthracycline (Table 5).

The risk of HF increased as increasing volumes of the heart and LV received ≥ 30 Gy. Among patients who had not received anthracycline, the risk of HF increased 3.6-fold (95% CI 1.3–10.1) when < 10% of the LV received ≥ 30 Gy, compared to patients who were not exposed to any cardiac radiation and anthracycline.

Table 2 Characteristics of heart failure patients

Characteristics	Men (n = 125)	Women (n = 114)	Total patients (n = 239)
CTCAE grade of HF, n (%)			
I	10 (8.0)	8 (7.0)	18 (7.5)
II	9 (7.2)	8 (7.0)	17 (7.1)
III	57 (45.6)	54 (47.4)	111 (46.4)
IV	25 (20.0)	26 (22.8)	51 (21.4)
V	24 (19.2)	18 (15.8)	42 (17.6)
HF secondary to, n (%)			
Valvular disease	2 (1.6)	4 (3.5)	6 (2.5)
Arrhythmia	1 (0.8)	0 (0)	1 (0.4)
Ischaemic heart disease, n (%)	1 (0.8)	2 (1.8)	3 (1.25)
Heart transplant, n (%)			
No	113 (90.4)	101 (88.6)	214 (89.5)
Yes	12 (9.6)	13 (11.4)	25 (10.5)
Age at diagnosis of HF, years, median (IQR)	27.5 (19.4–34.5)	24.2 (17.2–33.7)	25.1 (18.3–34.2)
Status at end of follow-up, n (%)			
Alive	73 (58.4)	70 (61.4)	143 (59.8)
Died of HF	24 (19.2)	18 (15.8)	42 (17.6)
Died of other cause	28 (22.4)	26 (22.8)	54 (22.6)

CTCAE, Common Terminology Criteria for Adverse Events; HF heart failure; IQR, interquartile range.

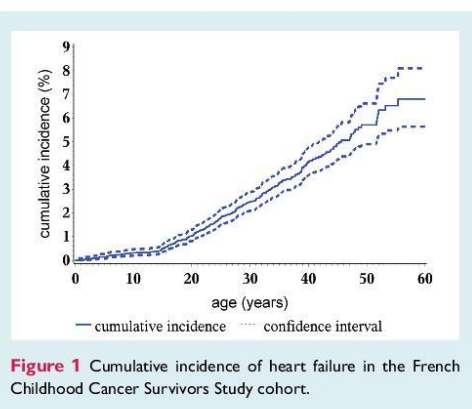


Figure 1 Cumulative incidence of heart failure in the French Childhood Cancer Survivors Study cohort.

When $\geq 50\%$ of the volume of the LV received ≥ 30 Gy, the risk ratio reached 24.6 (95% CI 10.3–58.7) (Table 5). CCS unexposed to anthracycline who received ≥ 30 Gy to 10–50% and $\geq 50\%$ of the heart volume had ORs of 5.5 (95% CI 2.1–14.1) and 17.0 (95% CI 7.6–38.0), respectively. These risks were much higher among patients treated with anthracycline and were increased 28.3-fold (95% CI 9.4–85.2) in patients receiving ≥ 30 Gy to $\geq 50\%$ of the heart volume (Table 5). Similar results were observed for the V20 Gy and V40 Gy (online supplementary Table S3).

The ERR/Gy for the MHD was 0.09/Gy (95% CI 0.02–0.22) for patients exposed to anthracycline and 0.44/Gy (95% CI 0.18–1.12) for patients unexposed to anthracycline. This lower slope for the effect of MHD in anthracycline-treated patients was associated

with a higher baseline risk at a cardiac radiation dose of 0, leading to similar risks at higher MHD with and without anthracycline. Similar results were observed for the MLVD (online supplementary Figure S1).

The potential ERR-modifying effects of other factors were evaluated (online supplementary Figure S1). Apart from anthracycline treatment, no other factors significantly modified the effect of radiation. However, HF risk increased with each category of age, with ERR/Gy values for the MHD of 0.06, 0.33, 0.38 and 0.48 in those aged < 15 , 15–25, 25–35, and ≥ 35 years, respectively (online supplementary Figure S1).

Other treatment factors

Alkylating agents were associated with a significantly increased risk of HF but only at a cumulative dose of ≥ 10.7 g/m² (Table 3). Exposure to cisplatin and to vinca alkaloids was not associated with an increased risk of HF, even at higher doses (Table 3).

A total of 16 cases (6.7%) underwent a splenectomy, and the risk of HF in these patients was increased 3.5-fold (95% CI 1.5–9.2) compared to those who did not have a splenectomy (Table 3).

Conventional cardiac disease risk factors

Conventional CD risk factors were studied in the subpopulation of patients who returned the lifestyle self-questionnaire, and this subpopulation included 117 cases and 353 matched controls. Diagnosis of diabetes mellitus before HF diagnosis was not associated with an increased risk of HF (OR 0.7, 95% CI 0.1–3.6), nor was smoking at the time of HF diagnosis, or obesity (BMI ≥ 30 kg/m²) at

Table 3 Heart failure risks by exposure to chemotherapy agents and splenectomy

Treatment	Cases (n = 239)	Controls (n = 1042)	Odds ratio* (95% CI)	P-value
Anthracycline				< 0.0001
No [†]	67 (28.0)	680 (65.2)	1.0	
Yes	172 (72.0)	362 (34.8)	11.5 (6.6–20.1)	
Alkylating agents				0.03
No [†]	57 (23.8)	512 (49.1)	1.0	
Yes	182 (76.2)	530 (50.9)	2.0 (1.2–3.4)	
Vinca alkaloids				0.45
No [†]	42 (17.6)	387 (37.1)	1.0	
Yes	197 (82.4)	655 (62.9)	0.7 (0.4–1.4)	
Cisplatin				0.76
No [†]	206 (86.2)	951 (91.3)	1.0	
Yes	33 (13.8)	91 (8.7)	1.1 (0.6–1.9)	
Anthracycline, mg/m ²				< 0.0001
None [†]	67 (28.0)	680 (65.2)	1.0	
0–250	34 (14.2)	144 (13.8)	3.4 (1.5–7.6)	
250–360	54 (22.6)	99 (9.5)	11.4 (5.0–25.9)	
≥ 360	84 (35.2)	119 (11.5)	15.0 (7.1–31.7)	
Doxorubicin, mg/m ²				< 0.0001
None [†]	82 (34.3)	720 (69.1)	1.0	
0–250	36 (15.0)	132 (12.7)	4.2 (2.4–7.9)	
250–360	50 (21.0)	86 (8.2)	14.8 (7.8–27.9)	
≥ 360	71 (29.7)	104 (10.0)	19.6 (10.5–36.3)	
Alkylating agents, g/m ²				0.03
None [†]	57 (23.8)	512 (49.1)	1.0	
0–4.75	39 (16.3)	177 (17.0)	1.5 (0.7–3.3)	
4.75–10.7	54 (22.6)	176 (16.9)	1.2 (0.6–2.6)	
≥ 10.7	89 (37.3)	177 (17.0)	2.4 (1.2–4.7)	
Cisplatin, mg/m ²				0.23
None [†]	206 (86.2)	951 (91.3)	1.0	
0–320	5 (2.2)	31 (3.0)	0.8 (0.2–2.6)	
320–500	14 (5.8)	28 (2.7)	2.2 (0.9–5.1)	
≥ 500	14 (5.8)	32 (3.0)	1.5 (0.6–3.5)	
Vinca alkaloids, mg/m ²				0.45
None [†]	42 (17.6)	387 (37.2)	1.0	
0–14	54 (22.6)	221 (21.2)	1.5 (0.6–3.8)	
14–25	53 (22.1)	221 (21.2)	1.6 (0.6–4.0)	
≥ 25	90 (37.7)	213 (20.4)	1.8 (0.7–4.3)	
Splenectomy				0.006
No [†]	223 (93.3)	1026 (98.5)	1.0	
Yes	16 (6.7)	16 (1.5)	3.5 (1.5–9.2)	

CI, confidence interval.

*The odds ratio of developing heart failure were calculated using a logistic regression model conditional on matched sets.

†Reference category.

the cut-off date. Patients who engaged in regular physical activity for ≥ 3 h/week did not exhibit a reduced risk of HF compared to sedentary survivors (online supplementary Table S4).

Discussion

An important novel finding of this study was that there was a significantly elevated risk of HF in CCS, even when < 10% of the LV volume received ≥ 30 Gy. The findings of this case-control study also confirmed that CCS who have been exposed to anthracycline and cardiac radiation are at higher risk of developing HF at a relatively young age.

To the best of the authors' knowledge, this is the first study to report a dose–response relationship based on dose–volume indicators in CCS. This study found that the risk of cardiac failure was related to both dose and irradiated volume. There are currently no published data concerning the dose–volume recommendations for radiation-induced HF in CCS. According to Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) reviews, which summarise the dose–volume and outcome information for many organs,¹⁹ patients who receive ≥ 25 Gy to > 10% of the total heart volume are at increased risk of cardiac death.²⁰ However, the QUANTEC reviews only provide dose–volume outcome information for adult cancer survivors.

Table 4 Risks of heart failure among patients exposed to doses of anthracycline < 250 mg/m² or ≥ 250 mg/m² and cardiac radiation

Anthracycline	Cardiac radiotherapy	Cases (n = 238)	Controls (n = 1038)	Odds ratio* (95% CI)
None [‡]	No	10 (4.2)	252 (24.3)	1.0
0–250	No	10 (4.2)	65 (6.2)	3.3 (1.1–9.6)
≥ 250	No	49 (20.6)	108 (10.4)	13.9 (6.0–32.6)
None	Yes	57 (23.9)	425 (41)	2.6 (1.2–5.9)
0–250	Yes	23 (9.7)	78 (7.5)	7.2 (3.0–18.0)
≥ 250	Yes	89 (37.4)	110 (10.6)	29.7 (12.9–68.6)

Values are given as n (%).

CI, confidence interval.

Radiation doses were missing for one case and four controls.

*The odds ratio of developing heart failure were calculated using a logistic regression model conditional on matched sets adjusted for splenectomy, type of first childhood malignancy, vinca alkaloids, alkylating agents, and other chemotherapies.

[‡]Reference category.

It has been reported elsewhere that ventricular dysfunction can also occur, particularly in the context of anthracycline chemotherapy and radiation doses higher than 30 Gy to large volumes of the heart.²³ Nevertheless, in our study, exposing small volumes of the heart or LV to ≥ 30 Gy led to a significant risk of cardiac failure.

The radiation dose–volume effects in the heart and cardiac substructures have been explored only in a few studies on adult survivors of Hodgkin's lymphoma.^{9,10} The results support the findings of the current study. The mean dose to the heart provides an incomplete picture of the risk of HF as small volumes of the heart could receive highly inhomogeneous doses. The evaluation of the radiation dose received by the cardiac substructures (e.g. heart valves, pericardium) is also crucial for understanding the specific types of cardiac toxicity. A recent study investigated the dose–response relationship based on dose–volume metrics among adult survivors of Hodgkin's lymphoma and found no significant interaction between anthracycline treatment and MHD or MLVD. The risk of HF in patients unexposed to anthracycline and with large volumes of the heart or LV exposed to ≥ 30 Gy was found to be moderate.⁹ The differences in HF risks between the previous study and the study reported in this paper may be explained by the differences in the study populations, as the participants of the previous study were adults at the time of Hodgkin's lymphoma diagnosis. It could also be due to the fact that that study compared HF risk among patients who received ≥ 30 Gy to 25–100% of the heart and LV volume to the HF risk in those who received 30 Gy to 0–25% of the heart and LV volume.

Our study showed that, without anthracycline exposure, the risk of HF increased substantially with increasing doses to the heart or LV. Conversely, patients who received anthracycline had a higher baseline risk of HF, which increased only moderately with increasing radiation doses to the heart. More precisely, CCS who did not receive anthracycline had an ERR/Gy for the MHD of 0.44 (95% CI 0.18–1.12), while those treated with anthracycline and cardiac radiation had an ERR/Gy of 0.09 (95% CI 0.02–0.22). In a study on self-reported CDs among CCS, the risk of HF was

increased 1.6, 3.1 and 10.5-fold for MHD of 5–14, 15–34 and ≥ 34 Gy, respectively.⁸ The results from this previous study could not be compared to the results reported here as it did not include the interaction between anthracycline and cardiac radiation and did not provide ERRs.

The cumulative anthracycline dose is also a major factor for cardiotoxicity. Although a dose of anthracycline < 250 mg/m² was considered to be reasonably safe,²⁴ our study showed that patients who received a dose of < 250 mg/m² without any cardiac radiation, had a HF risk that was 3.3-fold higher than those who did not receive either anthracycline nor any cardiac radiation. Similar results were also found in a study of 14 358 5-year CCS, where use of < 250 mg/m² of anthracycline was associated with a 2.4-fold higher risk of developing congestive HF compared to patients who did not receive anthracycline.⁶ These results suggest that CCS exposed to low cumulative doses of anthracycline may also require long-term cardiac follow-up.

Splenectomy was the only other treatment factor, apart from anthracycline and radiation exposure, that was associated with an increased HF risk in this study. Similarly, another study found that splenectomy was also related to the risk of valvular disease in Hodgkin's lymphoma survivors.²⁵ The mechanisms underlying splenectomy-related CDs in CCS are not yet understood, and further studies need to be conducted.

In our study, 25 patients (10%) underwent heart transplantation. This represents 49% of the patients with HF of grade 4, the population for whom heart transplantation is indicated. This is very similar to the 48% proportion of heart transplants in France reported in a study by Dorent *et al.*²⁶

Diabetes mellitus, smoking, obesity and physical activity were tested for association with the risk of HF and were not significant. Patients were diagnosed with cardiac failure in their twenties, which may explain why these risk factors had no effect on their risk of HF. In a study by Nathan *et al.*,²⁷ the frequency of smoking initiation was lower among CCS compared with the general population; however, smoking was still considered as the most important risky health behaviour in CCS as it can potentiate organ damage associated with exposure to chemotherapy and radiation. Diet and physical

Table 5 The risk of heart failure by mean heart dose, mean left ventricular dose, volume of the heart receiving ≥ 30 Gy and anthracycline

Radiation exposure measure	Treated without anthracycline			Treated with anthracycline			P-value
	Cases (n = 67)	Controls (n = 677)	Odds ratio (95% CI)*	Cases (n = 171)	Controls (n = 361)	Odds ratio (95% CI)*	
Mean heart dose, Gy							<0.0001
0 [†]	10 (4.2)	252 (24.3)	1.0	59 (24.8)	173 (16.7)	11.3 (4.7–27.0)	
0–5	8 (3.4)	251 (24.2)	0.7 (0.2–2.0)	61 (25.6)	127 (12.2)	21.5 (8.8–52.6)	
5–15	6 (2.5)	64 (6.1)	2.0 (0.6–6.3)	12 (5.0)	18 (1.7)	23.8 (7.6–75.0)	
15–30	16 (6.7)	83 (8.0)	5.2 (1.9–13.8)	33 (13.9)	34 (3.3)	54.4 (19.3–153)	
≥ 30	27 (11.4)	27 (2.6)	20.6 (7.6–55.3)	6 (2.5)	9 (0.9)	24.6 (7.2–84.1)	
Mean left ventricular dose, Gy							<0.0001
0 [†]	10 (4.2)	252 (24.3)	1.0	58 (24.4)	174 (16.8)	11.7 (4.8–28.2)	
0–5	8 (3.4)	258 (24.8)	0.6 (0.2–1.8)	63 (26.4)	126 (12.1)	23.4 (9.3–56.7)	
5–15	8 (3.4)	68 (6.6)	2.1 (0.7–6.5)	16 (6.7)	21 (2.0)	31.8 (10.6–95.0)	
15–30	15 (6.3)	70 (6.7)	4.5 (1.7–12.0)	28 (11.8)	26 (2.5)	39.8 (14.4–110)	
≥ 30	26 (10.9)	29 (2.8)	42.1 (14.1–126)	6 (2.5)	14 (1.4)	35.8 (8.2–157)	
Volume of the heart (%) receiving ≥ 30 Gy							<0.0001
0 [†]	24 (10.1)	559 (53.8)	1.0	142 (59.6)	324 (31.2)	16.5 (8.5–32.1)	
0–10	6 (2.5)	49 (4.7)	1.9 (0.7–5.5)	9 (3.8)	13 (1.2)	22.2 (7.4–66.3)	
10–50	9 (3.8)	36 (3.5)	5.5 (2.1–14.1)	10 (4.2)	12 (1.2)	26.4 (8.7–80.0)	
≥ 50	28 (11.8)	33 (3.2)	17 (7.6–38.0)	10 (4.2)	12 (1.2)	28.3 (9.4–85.2)	
Volume of the left ventricle (%) receiving ≥ 30 Gy							<0.0001
0 [†]	27 (11.3)	580 (55.9)	1.0	143 (60.1)	329 (31.7)	14.7 (7.7–28.0)	
0–10	6 (2.6)	32 (3.1)	3.6 (1.3–10.1)	11 (4.6)	9 (0.9)	37.9 (12.5–115)	
10–50	13 (5.5)	42 (4.0)	6.6 (2.8–15.4)	11 (4.6)	12 (1.2)	26.5 (8.9–78.6)	
≥ 50	21 (8.8)	23 (2.2)	24.6 (10.3–58.7)	6 (2.5)	11 (1.0)	16.9 (4.9–58.4)	

Values are given as n (%).

CI, confidence interval.

Radiation doses were missing for one case and four controls.

*The odds ratio of developing heart failure were calculated using a logistic regression model conditional on matched sets, adjusted for splenectomy, type of first childhood malignancy, vinca alkaloids, alkylating agents, and other chemotherapies.

[†]Reference category.

activity can also affect the risk of long-term complications in CCS.²⁸ Studies have reported that CCS are less physically active than the general population and that adult survivors are more likely to report a sedentary lifestyle than their siblings.²⁹ Further studies are needed to identify and characterise the type and intensity of physical exercise recommended to reduce the cardiovascular disease burden in CCS.³⁰

There were some limitations to this study; for example, there were some uncertainties in the radiation dose estimation due to the limitations of the computational phantoms three-dimensional radiotherapy planning and due to the radiation dose reconstruction being based on data from treatment planning charts. Hence, the estimation of the heart and LV volumes could have uncertainties as the calculation were derived from the phantoms and not based on actual volume measurement. Also, it was not possible to compare different anthracycline analogues in terms of HF risk, as most of the study participants received doxorubicin.

Another limitation to this study is the lack of data on renal function. Studies estimate that HF prevalence and incidence increase with the severity of chronic kidney disease.³¹ Accordingly, the

relation between chronic kidney disease and CDs in CCS needs to be investigated in further studies.

Finally, in this study, we could not find a significant association between cardiovascular risk factors and the risk of HF in CCS. This could be related to the small number of responders included in the sensitivity analysis, which may have lowered the statistical power and therefore reduced chances of detecting the true effect of these risk factors. However, our results are not unanticipated as case patients were diagnosed with HF at a young age and were probably strongly affected by the burden of their childhood cancer treatments.

Conclusion

This study confirmed that CCS are at risk of developing HF at a relatively young age. The results showed that HF is related to both dose and irradiated volume, with small irradiated volumes of the heart or LV being associated with a significant risk of HF.

It is important that both oncologists and clinical cardiologists recognize the potential cardiovascular side effects of childhood cancer treatments and their risk factors to reduce the burden

of HF among this population. Currently, published studies on the long-term risk of CDs including HF do not provide clinical data that could be applied to current clinical practice since the dose–response relationships were derived using only the mean radiation doses to the heart, rather than dose volume parameters. Consequently, guidelines do not provide specific recommendations regarding radiation-induced HF or CDs in CCS.

Our study has significant implications for planning and new radiotherapy treatments, setting treatment recommendations and for long cardiologic follow-up of adults who have survived paediatric cancer.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Methods S1. Supplementary methods.

Table S1. Risk of developing heart failure by type of first childhood cancer.

Table S2. Risk of heart failure of grade CTCAE ≥ 3 by exposure to chemotherapy and splenectomy.

Table S3. Risks of heart failure by V20, V40 and anthracycline.

Table S4. Risk of heart failure according to cardiovascular disease risk factors.

Figure S1. Evaluation of potential effect modifiers of the dose–response relationship for the mean heart dose and the mean left ventricle dose.

Funding

This work was supported by Electricité de France (EDF), the Pfizer Foundation for childhood and adolescent health, the Ligue Nationale Contre le Cancer (LNCC), the Institut de Recherche en Santé Publique (IRESP), the Programme Hospitalier de Recherche Clinique (PHRC), the Agence Française de Sécurité Sanitaire et Produit de Santé (AFSSAPS), and the French Agence Nationale Pour la Recherche Scientifique (Hope-Epi Project). The funding agencies had no role in the design or conduct of the study; in the collection, management, analysis or interpretation of the data; or in the preparation, review or approval of the manuscript.

Conflict of interest: none declared.

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Appendix

Appendix 1. Validation form for cardiovascular diseases in the French Childhood Cancer survivor Study

Fiche de validation :

Numéro d'anonymat du patient :

► **INFARCTUS DU MYOCARDE**

Oui **Date de diagnostic :**/...../.....
 Non
 Je ne sais pas

Si oui, s'agit-il :

. d'un infarctus aigu ? Oui Non
 .d'un infarctus ancien passé inaperçu ? Oui Non

Pouvez-vous s'il vous plaît nous indiquer quels étaient les signes présentés par le patient? (nous vous remercions de joindre ou de nous transmettre par fax une copie des résultats de ces examens):

Elévation des enzymes
 Troponine. Valeur :
 Fraction MB des Creatine Kinase (CKMB). Valeur :
 Autres. Lesquelles ?

Signes cliniques
 Douleurs retrosternales constrictives aux irradiations classiques (cou, mâchoires, bras, poignets) . Durée :minutes
 Autres. Lesquels ?

ECG anormal
 Onde T ample en regard du territoire de l'infarctus
 Sus décalage du segment ST supérieur à 2 mm en précordiales, à 1 mm en standard au moins au niveau de deux dérivations –
 Onde Q de nécrose
 Autres. Lesquelles ?

Imagerie
 Echocardiographie
 Scintigraphie cardiaque
 IRM
 Autres. Lesquels ?

S'agit-il d'une récurrence? Oui Non
 Si oui, quelle est la date du premier événement ?/...../.....

Dans quel établissement le patient a-t-il été hospitalisé?

Classification topographique de cet infarctus

Y a-t-il eu des complications aiguës ?

Oui Lesquelles ?

Non
 Je ne sais pas

Quel a été le traitement de la crise ?

Médicamenteux :

Interventionnel :

Quel est le traitement au long court ?

Médicamenteux :

Interventionnel :

► ANGOR INSTABLE

Oui **Date de diagnostic** :/...../.....

Non

Je ne sais pas

Si oui, pouvez-vous s'il vous plaît nous indiquer quels sont les signes présentés par le patient ? (nous vous remercions de joindre ou de nous transmettre par fax une copie des résultats de ces examens):

Elévation des enzymes

Troponine. Valeur :

Fraction MB des Creatine Kinase (CKMB). Valeur :

Autres. Lesquelles ?

Signes cliniques

Douleurs retrosternales constrictives aux irradiations classiques (cou, mâchoires, bras, poignets) . Si oui, quelle était sa durée ?min

Autres. Lesquels ?

ECG anormal. Si oui : quelles étaient les anomalies observées ?

Imagerie

Echocardiographie

Coronarographie

Autres. Lesquels ?

Epreuve d'effort. Si oui, quelles étaient les anomalies observées ?

Dans quel établissement le patient a-t-il été hospitalisé?

S'agit-il d'une récurrence? Oui Non

Si oui, quelle est la date du premier événement ?/...../.....

Y a-t-il eu des complications aiguës ?

Oui **Les quelles ?**

.....

.....

Non

Je ne sais pas

Quel a été le traitement de la crise ?

Médicamenteux :

Interventionnel :

Quel est le traitement au long court ?

- Médicamenteux :
- Interventionnel :

► **ANGOR STABLE:**

- Oui **Date de diagnostic :**/...../.....
- Non
- Je ne sais pas

Si oui, pouvez-vous s'il vous plaît nous indiquer le type d'angor et quels sont les signes cliniques et les examens complémentaires ayant permis le diagnostic de cette pathologie ? (nous vous remercions de joindre ou de nous transmettre par fax une copie des résultats de ces examens)

- Douleur thoracique
- déclenchée par l'effort durée <10 min cédant à l'arrêt de l'effort cédant à la trinitrine
- ECG au repos
- Epreuve d'effort
- Coronarographie
- Autres. Précisez.....

Quel est le traitement au long court ?

- Médicamenteux :
- Interventionnel :

► **INSUFFISANCE CARDIAQUE :**

- Oui **Date de diagnostic :**/...../.....
- Non
- Je ne sais pas

Si oui, pouvez-vous s'il vous plaît nous indiquer :

1) **Quel est le traitement ?**

- Aucun
- Médicamenteux. Lequel ?
- Interventionnel. Lequel ?

2) **Quels sont les paramètres altérés (joindre un compte rendu d'échographie) ?**

- Fraction de raccourcissement :%...
- Fraction d'éjection :%
- Autres paramètres modifiés. Précisez

3) **Selon la classification de la NYHA, quelle est la classe de cette Insuffisance cardiaque ?**

.....

4) **Quels étaient les signes présentés par le patient parmi les critères de Framingham ?**

1- **Critères majeurs**

- | | |
|--|--|
| <input type="checkbox"/> Dyspnée paroxystique nocturne | <input type="checkbox"/> Turgescence jugulaire |
| <input type="checkbox"/> Râles crépitants | <input type="checkbox"/> Cardiomégalie radiologique |
| <input type="checkbox"/> Œdème aigu pulmonaire | <input type="checkbox"/> B3 (galop à l'auscultation) |
| <input type="checkbox"/> Temps de circulation > 25 s | <input type="checkbox"/> Reflux hépatojugulaire |
- Augmentation de la pression veineuse centrale (> 16 cm d'eau dans l'oreillette droite)
- Œdème pulmonaire, aspect de congestion viscérale ou cardiomégalie à l'autopsie

2 - Critères mineurs

- Œdèmes des chevilles bilatéraux Dyspnée d'effort pour des efforts de la vie courante
- Hépatomégalie Epanchement pleural
- Toux nocturne
- Diminution de la capacité vitale > un tiers par rapport à la valeur
- Tachycardie > 120/min maximale enregistrée

3 - Critères mineurs ou majeurs

- Perte de poids > 4,5 kg en 5 jours en réponse à un traitement de l'insuffisance cardiaque

4) L'étiologie de l'insuffisance cardiaque est-elle connue ?

- Etiologie inconnue
- Infarctus du myocarde ou angor
- Hypertension artérielle
- Valvulopathie
- Cardiomyopathie non obstructive
- Autre
- Laquelle ?

► TRANSPLANTATION CARDIAQUE :

- Oui **Date :**/...../.....
- Dans** **quel** **établissement ?**
-
-
- Non
- Je ne sais pas

► PERICARDITE AIGUE:

- Oui **Date de diagnostic :**/...../.....
- Non
- Je ne sais pas

Si oui, pouvez-vous s'il vous plaît nous indiquer quels sont les signes cliniques et les examens complémentaires ayant permis le diagnostic de cette pathologie ? (nous vous remercions de joindre ou de nous transmettre par fax une copie des résultats de ces examens)

- Douleur thoracique
- Caractéristiques de cette douleur ? (durée, augmentation à la toux, en position allongée...)
-
-

- Frottement péricardique à l'auscultation cardiaque
- ECG : anomalie de repolarisation
- Echographie cardiaque : épanchement péricardite
- IRM cardiaque
- Biopsie péricardique
- Autre. Précisez
-
-

► VALVULOPATHIE :

- Oui **Date de diagnostic :**/...../.....
- Non

Je ne sais pas

Si oui, pouvez-vous s'il vous plaît nous indiquer :

1) La nature de cette valvulopathie et le territoire atteint :

2) Quels étaient les signes cliniques présentés par le patient :

- Souffle détecté à l'auscultation
- Troisième bruit à l'auscultation
- Essoufflement à l'effort
- Angine de poitrine
- Etourdissements
- Syncope
- Œdème pulmonaire
- Patient asymptomatique

3) Quels examens complémentaires ont permis de confirmer le diagnostic (**nous vous remercions de joindre ou de nous transmettre par fax une copie des résultats de ces examens**) :

- Echocardiographie
- Electrocardiogramme
- Radiographie pulmonaire

► **ACCIDENT VASCULAIRE CEREBRAL :**

- Oui **Date de diagnostic :**/...../.....
 Non
 Je ne sais pas

Si oui, pouvez-vous s'il vous plaît nous indiquer

Dans quel établissement le patient a-t-il été hospitalisé?

1) Le territoire atteint :

2) Le type d'AVC : Hémorragique Ischémique Non précisé

3) S'il s'agit d'une récurrence : Oui Non
 Si oui, quelle est la date du premier événement ?/...../.....

4) S'il le patient a gardé des séquelles : Oui Non

5) Quels étaient les signes cliniques présentés par le patient :
 Déficit sensitif
 Déficit moteur

6) Combien de temps ont duré ces signes cliniques ?
 moins de 24h Plus de 24h Non précisé

7) S'agit-il d'un AVC transitoire ? : Oui Non

8) Quels examens complémentaires ont permis de confirmer le diagnostic (**nous vous remercions de joindre ou de nous transmettre par fax une copie des résultats de ces examens**) :

- Tomodensitométrie
- IRM
- Artériographie

9) Quel a été le traitement ?

- Antivitamine K Aspirine Anti-aggrégants plaquettaires
 Autre. Précisez.....

► **TROUBLE DU RYTHME OU DE LA CONDUCTION:**

- Oui **Date de diagnostic :**/...../.....
 Non
 Je ne sais pas

Si oui pouvez-vous s'il vous plaît nous indiquer les examens ayant permis le diagnostic (**nous vous remercions de joindre ou de nous transmettre par fax une copie des résultats de ces examens**) :

- Electrocardiogramme
 Holter

Nature de l'anomalie :

Le patient a-t-il présenté des signes cliniques attribués à cette anomalie ? Oui Non
 Si oui les quels ?.....

► **AUTRE PATHOLOGIE CARDIOVASCULAIRE**

- Angor **Date de diagnostic :**/...../.....
 Infarctus du myocarde **Date de diagnostic :**/...../.....
 Péricardite **Date de diagnostic :**/...../.....
 Insuffisance cardiaque **Date de diagnostic :**/...../.....
 Transplantation cardiaque **Date de diagnostic :**/...../.....
 Accident vasculaire cérébral **Date de diagnostic :**/...../.....
 Phlébite **Date de diagnostic :**/...../.....
 Embolie pulmonaire **Date de diagnostic :**/...../.....
 Valvulopathie **Date de diagnostic :**/...../.....
 Troubles du rythme **Date de diagnostic :**/...../.....
 Troubles de la conduction **Date de diagnostic :**/...../.....
 Hypertension artérielle **Date de diagnostic :**/...../.....
 Artérite des membres inférieurs **Date de diagnostic :**/...../.....
 Autre Précisez.....

 Aucune
 Je ne sais pas

► **DECES:**

- Date de décès :**/...../.....
Lieu de décès :
Cause principale de décès :
 Premier cancer

- Second cancer
- Autre
- Inconnu
- Cardiaque
- Pulmonaire

Code CIM attribué aux causes du décès :

1^{re} cause :

2^e cause :

3^e cause :

4^e cause :

5^e cause :

6^e cause :

DATE :/...../.....

SIGNATURE ET CACHET DU MEDECIN :

Appendix 1. Validation form for chronic kidney diseases in the French Childhood Cancer survivor Study



Fiche de validation des maladies rénales chroniques

Date du remplissage de la fiche ____/____/____ Numéro anonyme.....

Cochez les cases correspondantes et remplissez la date et les résultats des examens si nécessaire

DIAGNOSTIC DE LA MALADIE RENALE CHRONIQUE*

Le patient a-t-il été diagnostiqué avec une maladie rénale chronique ? Non Oui

1. Quelle est la cause(s) de la MRC ?

- Néphropathie diabétique
 Néphropathie hypertensive ou vasculaire
 Glomérulonéphrite chronique
 Néphropathie tubulointerstitielle due à une chimiothérapie anticancéreuse
 Néphropathie tubulointerstitielle due à une radiothérapie
 Polykystose rénale
 Inconnue
 Autre, précisez

2. Quand la maladie rénale chronique a-t-elle été reconnue pour la première fois ? ____/____/____
MM AAAA

3. Diagnostic confirmé par une biopsie rénale? Non Oui

4. Le patient a-t-il eu une imagerie rénale (échographie, scanner, IRM) ? Non Oui

Si Oui

Longueur du rein droit _____ cm ou Rein absent
 Longueur du rein gauche _____ cm ou Rein absent

5. Le patient a-t-il subi une néphrectomie ?

- Non Oui, totale Oui, partielle côté gauche
 Oui, partielle côté droit Oui, partielle côté inconnu inconnu

Si Oui, quelle était la date de la néphrectomie ? ____/____/____
JJ MM AAAA

Si Oui, raison de la néphrectomie Cancer/tumeur Traumatisme Autre inconnue

6. Antécédents et facteurs de risque

- HTA
 Diabète
 Insuffisance cardiaque
 Maladie coronarienne
 AVC
 Autres maladies cardiovasculaires

Précisez.....

TRAITEMENT DE LA MALADIE RENALE CHRONIQUE

7. Le patient est-il traité par dialyse ? Non Oui, Hémodialyse Oui, Dialyse péritonéale

8. Le patient a-t-il eu une greffe rénale ? Non Oui

Si Oui, quelle était la date de la transplantation rénale? ____/____/____
JJ MM AAAA

Si Non, est-il inscrit sur la liste d'attente de greffe rénale? Non Oui inconnue

* La maladie rénale chronique est définie par la présence d'anomalies biologiques (protéinurie, albuminurie ou hématurie), histologiques ou morphologiques, et/ou par la baisse de la fonction rénale (débit de filtration glomérulaire < 60 ml/min/1,73 m²) pendant plus de 3 mois. Ne pas inclure les calculs rénaux, les infections et autres affectations rénales aiguës, ou l'incontinence urinaire.



Fiche de validation des maladies rénales chroniques

EXAMENS CLINIQUES ET BIOLOGIQUES		
Saisir la valeur des mesures cliniques et biologiques à l'examen le plus récent (colonne 1) et au moment du diagnostic (colonne 2), en précisant la date de chaque examen.		
	A la date de l'examen le plus récent	A la date du diagnostic de la maladie rénale
Date des examens	____/____/____ JJ MM AAAA	____/____/____ JJ MM AAAA
EXAMENS CLINIQUES		
9. Pression artérielle (mm Hg)	____/____ Systolique / Diastolique	____/____ Systolique / Diastolique
10. Poids (kg)
11. Taille (cm)
BIOLOGIE SANG		
12. Créatinine sérique <input type="checkbox"/> micromol/L <input type="checkbox"/> mg/L <input type="checkbox"/> micromol/L <input type="checkbox"/> mg/L
13. Débit de filtration glomérulaire (DFG) Spécifier l'équation mL/min/1,73 m ² <input type="checkbox"/> MDRD <input type="checkbox"/> Cockcroft-Gault <input type="checkbox"/> CKD-EPI <input type="checkbox"/> non précisée mL/min/1,73 m ² <input type="checkbox"/> MDRD <input type="checkbox"/> Cockcroft- Gault <input type="checkbox"/> CKD-EPI <input type="checkbox"/> non précisée
14. Hémoglobine (g/dl) g/dl g/dl
ECHANTILLON D'URINE		
15. Protéine <input type="checkbox"/> g/L <input type="checkbox"/> mg/L <input type="checkbox"/> g/L <input type="checkbox"/> mg/L
16. Albumine mg/L mg/L
17. Créatinine <input type="checkbox"/> mmol/L <input type="checkbox"/> g/L <input type="checkbox"/> mmol/L <input type="checkbox"/> g/L
18. Protéine <input type="checkbox"/> g/24h <input type="checkbox"/> mg/24h <input type="checkbox"/> g/24h <input type="checkbox"/> mg/24h
19. Albumine mg/24h mg/24h
20. Hématurie	<input type="checkbox"/> Non <input type="checkbox"/> Oui	<input type="checkbox"/> Non <input type="checkbox"/> Oui
BANDELETTE URINAIRE (à compléter en cas d'absence d'examen d'urine au laboratoire)		
21. Protéine	<input type="checkbox"/> : aucune ou traces <input type="checkbox"/> :1+ <input type="checkbox"/> :2+ <input type="checkbox"/> :3+	<input type="checkbox"/> : aucune ou traces <input type="checkbox"/> :1+ <input type="checkbox"/> :2+ <input type="checkbox"/> :3+

DECES

22. Le patient est-il décédé ? Non Oui

23. **Si Oui**, précisez la date du décès ____/____/____
JJ MM AAAA

24. Causes du décès :

.....
.....

Appendix 3. Résumé substantiel

De nos jours, la survie à 5 ans des enfants atteints d'un cancer dépasse les 80% en France. Ces progrès dans le traitement des cancers pédiatriques font qu'il existe un nombre croissant d'enfants survivants à long terme, ce qui correspond à plus de 50 000 adultes guéris d'un cancer pédiatrique.

Plusieurs études s'intéressent maintenant au devenir des enfants guéris d'un cancer pédiatrique du fait de l'apparition possible de séquelles consécutives aux traitements, parfois graves conduisant au décès prématuré. En effet la prévalence des complications à long terme dépasse chez les survivants de cancers pédiatriques 60% après un suivi de 30 ans. L'objectif général de cette thèse était de faire avancer les connaissances actuelles sur la mortalité et la morbidité à long terme liées aux cancers pédiatriques.

Plusieurs études ont montré que le risque de mortalité tardive des survivants, était supérieur à celui attendu dans la population générale pour toutes causes confondues. Ce sur-risque induit par les traitements reçus augmente avec le temps.

La cohorte FCCSS (French Childhood Cancer Survivor Study) inclut des patients guéris d'un cancer pédiatrique solide ayant survécu au moins 5 ans et traités entre 1946 et 2000. Nous avons réalisé une étude sur les causes spécifiques et les tendances de mortalité par période de traitement chez les patients de cette cohorte. Nous avons pu démontrer que le risque de mortalité chez ses patients demeure plus élevé que la population générale même à plus de 40 ans après le diagnostic de leur premier cancer. Les causes de décès majeures dans cette population étaient : les récurrences ou rechute du premier cancer, les seconds cancers et les maladies circulatoires. Dans cette étude, nous avons aussi trouvé que la mortalité liée aux séquelles de traitements de cancer, plus spécifiquement les seconds cancers et maladies circulatoires a significativement baissé parmi les sujets traités entre 1990 et 2000 comparés aux patients traités avant 1970. Cette amélioration est probablement liée à l'évolution des attitudes thérapeutiques qui ne cessent de

s'améliorer, notamment la réduction des indications de la radiothérapie et doses cumulées d'anthracycline.

Après les seconds cancers, les maladies cardiovasculaires représentent la deuxième complication à long terme la plus fréquente et la plus sévère des traitements des cancers pédiatriques. On compte parmi les facteurs de risque majeurs de complications cardiaques à long terme : les anthracyclines et l'irradiation de l'aire cardiaque. Les maladies cardiaques les plus souvent rencontrées sont les insuffisances cardiaques, les coronaropathies, les valvulopathies, les arythmies et les péricardites.

Nous avons réalisé une étude cas témoins nichée dans la cohorte FCCSS pour étudier le risque d'insuffisance cardiaque chez les patients guéris de cancer pédiatrique et le rôle de la chimiothérapie cardiotoxique ainsi que la dose moyenne au cœur et le volume du cœur et des sous-structures cardiaques irradiés dans la survenue de l'insuffisance cardiaque. Nous avons confirmé que les anthracyclines sont liés à un risque significativement élevé d'insuffisance cardiaque même à des doses cumulées <250 mg/m². Nous avons aussi trouvé que l'irradiation de faibles volumes du cœur ($<10\%$ du ventricule gauche) à une dose ≥ 30 Gy est associée à un risque significatif de cette pathologie. Nous avons aussi trouvé une interaction significative entre la prise d'anthracycline et la dose d'irradiation cardiaque et démontré que chez les patients non-exposés aux anthracyclines, le risque d'insuffisance cardiaque augmentait fortement avec la dose d'irradiation absorbée par le cœur. Par contre chez ceux ayant été traités par anthracycline le risque augmentait de façon modérée du fait de leur risque de base particulièrement élevé. Chez ses patients, l'obésité, le tabac, l'activité physique et le diabète n'étaient pas significativement associés à un risque accru d'insuffisance cardiaque.

Les maladies rénales font partie des conséquences à très long terme des traitements des cancers de l'enfant et contribuent en partie à l'augmentation de la mortalité des survivants d'un cancer. Elle constitue un élément de mauvais pronostic et un vrai problème de santé chez ces patients.

La maladie rénale chez les survivants d'un cancer pédiatrique est une maladie multifactorielle associant la néphrotoxicité due à la radiothérapie et aussi à la chimiothérapie en particulier, le cisplatine, la carboplatine et l'ifosfamide. Les pathologies rénales radio-induites ne sont encore pas assez documentées tel que les seconds cancers et les maladies cardiovasculaires et constituent une question de santé majeure surtout qu'elles sont-elles mêmes liées aux maladies cardiovasculaires. Peu d'études ont évalué les facteurs de risque à long terme de la toxicité rénale après traitement d'un cancer dans l'enfance. Ces études ont été réalisées seulement dans des petits groupes de patients avec un suivi maximal de 10 ans.

Dans la cohorte FCCSS, nous avons investigué les facteurs de risques de la maladie rénale chronique à long terme chez les patients guéris d'un cancer pédiatrique. Nous avons trouvé que les patients ayant subi une néphrectomie unilatérale étaient à plus de risque de développer cette maladie. L'effet de la dose de l'irradiation aux reins différait aussi significativement entre les patients ayant subi une néphrectomie et ceux avec deux reins. Chez les patients ayant deux reins, les fortes doses plus spécifiquement une dose maximale ≥ 20 Gy aux deux reins était associée à un risque significatif de maladie rénale chronique. Cependant chez les sujets ayant subi une néphrectomie même une dose maximale < 1 Gy était associée un risque élevé de dysfonctionnement rénal. Nous avons aussi trouvé que la prise d'ifosfamide, cisplatine et des fortes doses d'anthracycline étaient liées à un risque accru d'atteinte rénale. Les maladies cardiaques et plus spécifiquement l'insuffisance cardiaque étaient aussi un facteur risque majeur de dysfonctionnement rénal chez ces patients.

La maladie rénale chronique peut évoluer vers le stade terminal nécessitant la dialyse ou une greffe rénale. Peu d'études ont examiné le devenir thérapeutique des patients avec une insuffisance rénale terminale liée aux traitements anticancéreux et notamment leurs accès à la greffe. La plupart de ces études ont été réalisées chez les patients diagnostiqués par un cancer rénal. Le registre REIN (Réseau Epidémiologie et Information en Néphrologie) est un registre

national qui a comme objectif général de décrire l'incidence et la prévalence de l'insuffisance rénale chronique terminale traitée par dialyse. Il permet également de mieux connaître les caractéristiques de ces patients, leurs modalités de traitements par dialyse et leur évolution dans le temps.

Grâce aux données du registre REIN, nous avons aussi pu montrer que l'incidence de l'insuffisance rénale terminale traitée liée à la chimiothérapie néphrotoxique et/ou à la radiothérapie est en train d'augmenter au fil des années. Les patients dialysés et ayant un cancer évolutif avaient un très mauvais pronostic. Cependant les patients en rémission et dialysés pour une insuffisance rénale terminales liée aux traitements anticancéreux étaient moins inscrits en liste d'attente comparé à d'autres malades rénaux et avaient par conséquent un accès très limité à la transplantation rénale.

En conclusion, c'est avec l'amélioration de la survie et l'augmentation du nombre de patients guéris d'un cancer pédiatrique que l'on a pris conscience des nombreuses séquelles des traitements pouvant menacer la vie ou entraîner une morbidité importante. Ces séquelles peuvent apparaître de nombreuses années après la guérison et augmentent avec l'âge. Ainsi l'organisation d'un suivi à long terme pour ces patients est nécessaire. Ce suivi doit avant tout être personnalisé et adapté aux risques. Le travail effectué courant cette thèse pourrait aider à identifier les patients à risque accru de complications tardives majeures liées aux traitements anticancéreux. Nos résultats pourraient être utilisés dans la pratique clinique courante pour l'adaptation de la prise en charge thérapeutique des enfants atteints de cancer et pour les recommandations de leurs suivi à long terme.

Titre: Complications rénales et cardiaques à long terme après traitement d'un cancer dans l'enfance

Mots clés: cancer pédiatrique, maladies cardiaques, maladies rénales, radiothérapie, chimiothérapie, suivi à long terme

Résumé :

Les progrès thérapeutiques ont conduit à une augmentation de la survie à 5 ans des enfants traités pour un cancer et qui dépasse actuellement 80%. En France il a été estimé que 50 000 adultes guéris d'un cancer pédiatrique, mais la prévalence des complications à long terme causées par la maladie et par ses traitements dépasse 60% après un suivi de 30 ans. L'objectif général de cette thèse était de faire avancer les connaissances actuelles sur la mortalité et la morbidité à long terme liées aux cancers pédiatriques.

Avec les données de la cohorte FCCSS (French Childhood Cancer Survivor Study) qui inclut des sujets ayant été traités pour entre 1946 et 2000 pour un cancer pédiatrique solide, nous avons observé que le risque de mortalité chez ces patients demeure plus élevé que la population générale même à plus de 40 ans après le diagnostic de leur premier cancer. D'autre part, la mortalité liée plus aux effets à long terme des traitements anticancéreux, plus spécifiquement les seconds cancers et maladies circulatoires, a significativement baissé parmi les sujets traités plus récemment.

Par ailleurs, nous avons aussi confirmé le rôle des anthracyclines dans la survenue de l'insuffisance cardiaque et montré que la fraction du volume médian du cœur ayant reçu 30 Gray était beaucoup plus élevés chez les sujets ayant développé une insuffisance cardiaque par rapport aux autres.

Nous avons aussi observé que des faibles volumes du cœur (10% du volume du ventricule gauche) ayant reçus au moins 30 Gy

sont associés à un risque élevé de développer une insuffisance cardiaque.

Cette étude est la première à rapporter une relation dose-effet basée sur des indicateurs dose-volume et ces résultats peuvent être utilisés dans la pratique clinique courante

Nos travaux ont aussi montré que les patients ayant subi une néphrectomie unilatérale étaient à risque de développer une maladie rénale chronique à très long terme. L'effet de la dose de radiation reçue aux reins différait selon si les patients ayant subi une néphrectomie unilatérale ou non. En effet, une dose au seul rein même <5Gy était associée à un risque élevé de dysfonctionnement rénal. Par ailleurs, grâce aux données du registre REIN (Réseau Epidémiologie et Information en Néphrologie), nous avons pu montrer que l'incidence de l'insuffisance rénale terminale liée aux traitements anticancéreux était en train d'augmenter au fil des années. Cependant ces patients étaient moins inscrits en liste d'attente comparés à d'autres malades rénaux et avaient par conséquent un accès très limité à la transplantation rénale.

En conclusion, le travail effectué courant cette thèse pourrait aider à identifier les patients à risque accru de complications tardives majeures liées aux traitements anticancéreux. Nos résultats pourraient être utilisés dans la pratique clinique courante pour l'adaptation de la prise en charge thérapeutique des enfants atteints de cancer et pour les recommandations de leurs suivi à long terme.

Title: Long-term kidney and cardiac disease following childhood cancer treatment

Key words: childhood cancer, cardiac disease, renal disease, radiotherapy, chemotherapy, long term follow-up

Abstract:

Advances in treatment have increased the overall 5-year survival rate for childhood cancers to approximately 80%. In France, it estimated that about 50,000 adults have survived childhood cancer. However, previous studies have demonstrated that by the second decade of life, more than 60% of survivor of childhood malignancies (CCS) will suffer from at least one chronic disease related to the treatment they have received.

The general objective of this thesis was to advance knowledge about the very long morbidity associated with childhood cancer, with the ultimate target to improve both the long term outcome and quality of life of survivors.

Using data from the French Childhood Cancer Survivor Study (FCCSS) cohort, which includes patients treated for a solid pediatric malignancy between 1942 and 2000, we found that that mortality among CCS remained higher than the general population even after more than 40 years of the primary cancer diagnosis. A major finding of this study was that mortality attributed to adverse effects of cancer treatments (secondary primary neoplasm and circulatory disease) declined among patients treated in more recent treatment periods. We also conducted a case control study nested in the FCCSS cohort and further affirmed the role of anthracycline in the occurrence of heart failure. We demonstrated that the median heart volume that received at least 30Gy was higher among heart failure cases and that exposing small volumes of the heart (10% of the volume of

the left ventricle) to at least 30Gy was associated with an elevated risk of cardiac failure. This study was the first to derive a dose response relationship based on dose-volume metrics which can be used in current clinical practice.

Our results also showed that unilateral nephrectomy was associated with a high risk of renal impairment. The effect of radiation dose to the kidneys was also different among nephrectomized patients for whom any exposure to radiation was associated with an elevated risk of chronic kidney disease even at doses less than 5 Gy.

Furthermore, data from the renal epidemiology and information network (REIN) registry allowed us to investigated ESKD (end stage kidney disease) related to nephrotoxic chemotherapy and/or radiation. Our registry-based study showed that ESKD related to nephrotoxic cancer treatment has been steadily increasing over the past decade in the French population. These patients experienced a much lower rate of wait-listing than matched controls with other causes of ESKD, despite similar survival on dialysis.

To conclude the results of this thesis are useful to identify survivors of childhood malignancies who are at risk of developing severe long term adverse effects related to the treatment of their primary cancer. Our results could be applied in current clinical practice to help adapt current treatment strategies and improve the long-term follow-up recommendations of childhood cancer survivors.