Risk of a Second Kidney Carcinoma Following Childhood Cancer: Role of Chemotherapy and Radiation Dose to Kidneys

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Purpose: Kidney carcinoma is a rare second malignancy following childhood cancer.

Materials and Methods: We sought to quantify risk and assess risk factors for kidney carcinoma following treatment for childhood cancer. We evaluated a cohort of 4,350 patients who were 5-year cancer survivors and had been treated for cancer as children in France and the United Kingdom. Patients were treated between 1943 and 1985, and were followed for an average of 27 years. Radiation dose to the kidneys during treatment was estimated with dedicated software, regardless of the site of childhood cancer.

Results: Kidney carcinoma developed in 13 patients. The cumulative incidence of kidney carcinoma was 0.62% (95% CI 0.27%−1.45%) at 40 years after diagnosis, which was 13.3-fold higher (95% CI 7.1−22.3) than in the general population. The absolute excess risk strongly increased with longer duration of followup (p <0.0001). Compared to the general population, the incidence of kidney carcinoma was 5.7-fold higher (95% CI 1.4−14.7) if radiotherapy was not performed or less than 1 Gy had been absorbed by the kidney but 66.3-fold higher (95% CI 23.8−142.5) if the radiation dose to the kidneys was 10 to 19 Gy and 14.5-fold higher (95% CI 0.8−63.9) for larger radiation doses to the kidney. Treatment with chemotherapy increased the risk of kidney carcinoma (RR 5.1, 95% CI 1.1−22.7) but we were unable to identify a specific drug or drug category responsible for this effect.

Conclusions: Moderate radiation dose to the kidneys during childhood cancer treatment increases the risk of a second kidney carcinoma. This incidence will be further increased when childhood cancer survivors reach old age.

Key Words: drug therapy; kidney neoplasms; neoplasms, second primary; radiation dosage; radiotherapy

SURVIVAL after childhood cancer has improved markedly since the 1970s, with 5-year survival rates now approaching 80%. Second primary cancers are among the most serious late effects of chemotherapy and radiotherapy, and are an increasing concern regarding childhood cancer survivors.

Although genitourinary cancers as a whole have been addressed in some large cohort studies,[1−4] few series to date have investigated kidney carcinoma as a specific issue after

childhood cancer.[5−7] The main explanation is that KC as a second malignancy following childhood cancer is still rare, because most childhood cancer survivors are younger than 50 years and KC is rare overall in the younger population.[8]

A recent report on CCSS concluded that a radiation dose to the kidney of 5 Gy or greater increases the risk of KC by 3.8 (95% CI 1.6−9.3), and that administration of platinum based chemotherapy increases the risk by 3.5 (95% CI 1.0−11.2).[5] Since that is the only known study focusing on KC as a second malignancy following childhood cancer, the results need to be confirmed. We evaluated the role of first cancer type, type of treatment and radiation dose absorbed by the kidney in the risk of a second KC following childhood cancer treatment.

MATERIALS AND METHODS

Patients
We retrospectively studied children treated for cancer at 8 centers in France and the United Kingdom between 1985 and 1995. The study population consisted of patients with a first solid cancer diagnosed before age 16 years and before 1986 who were alive 2 years (in France) or 3 years (in United Kingdom) later. Inclusion criteria for the cohort were first described in 1995.[9] The original cohort included 4,567 patients. However, between 1995 and 2009 some French patients were excluded because of diagnostic errors and duplicate entries. Others were added who were initially missed because some medical records were unavailable at establishment of the initial cohort but were subsequently discovered during a systematic investigation of the Gustave Roussy Institute archives. The final database includes 4,649 patients, of whom 4,389 are 5-year survivors. Of these patients 39 who underwent bilateral nephrectomy were excluded from the analysis. The 4,350 remaining patients (3,133 treated in France) are included in the present study (table 1).

Followup of the 3,133 French patients was initially assessed using the medical records from the treatment centers, and later via a self-completed questionnaire sent

beginning in September 2005. This questionnaire, which is based on the CCSS survey,[10] provided information on health outcomes. A total of 2,455 patients were still alive, and, therefore, considered eligible to complete the questionnaire. This survey was sent by regular mail to the 2,105 patients for whom the most recent address was obtained and who had returned a signed consent form. A total of 1,920 patients (74%) returned the completed questionnaire by December 31, 2012. The 1,217 UK patients were monitored for the occurrence of KC and death using the National Health Service Central Registers.[11,12]

Radiation Dosimetry
Radiation dose was estimated for each kidney in patients who had undergone radiotherapy. Doses to most of the other anatomical sites, including the spleen and gonads, were also estimated. The software package Dos_EG was developed at Institut Gustave Roussy for these calculations.[13,14] Mean radiation dose absorbed by the kidney was 8.6 Gy (median 1.5, range 0 to 66.2, fig. 1).

Chemotherapy
Drugs were pooled into 6 classes according to the known mechanisms of action within the cell, ie anthracyclines, alkylating agents, epipodophyllotoxins, antimetabolites, vinca alkaloids and other. The cumulative dose of each cytotoxic drug was recorded. For alkylating agents we computed the cyclophosphamide dose equivalent score for toxicity proposed by Green et al.[15]

Statistical Methods
We used estimates of the UK national cancer incidence rates as reference rates for patients treated at UK centers,[11] and the French national cancer incidence rates for those treated at French centers.[16] The SIR, calculated as the ratio of the observed number of KCs to the expected number, was assessed statistically by considering that the observed number follows a Poisson distribution.[16] The absolute excess risk was calculated as the difference between the observed and expected number of KCs divided by the number of person-years of followup.

As the 2 kidneys of a given child may have received markedly different radiation doses during radiotherapy, we performed analyses of the relationship between the radiation dose absorbed by the kidney and the risk of KC using the kidney as the statistical unit. Thus, in these analyses each patient accounts for 2 kidneys, except the 877 patients who underwent unilateral nephrectomy, who only account for the remaining kidney.

An internal analysis was conducted using the clustered Cox proportional hazard regression model for aggregated data, to allow for the lack of independence between the 2 kidneys of the same subject.[17] To evaluate the dose-effect relationship between the kidney radiation dose and the risk of KC, we tested linear and linear exponential models by comparing nested models.[18] The linear model is expressed as, relative risk = Cst [1 + α dose], and the linear exponential model is expressed as, relative risk = Cst [1 + α dose × exp(β dose)], where Cst is constant, α and β are coefficients, and dose is kidney radiation dose. The DATAB and AMFIT modules of the Epicure statistical software package (Risk Sciences International, Ottawa, Ontario, Canada) were used for analyses.[19]

Table 1. *General characteristics of 5-year survivors of childhood cancer*

	Secondary Kidney Ca		No Secondary Kidney Ca	
Median treatment yr (range)	1970	(1951−1984)	1974	(1942−1986)
No. country of treatment:				
France	12		3,121	
UK	1		1,216	
Mean yrs age at diagnosis (range)	6	(0−13)	6	(0−16)
No. gender:				
Male	7		2,405	
Female	6		1,932	
No. first Ca treatment:				
No chemotherapy or radiotherapy	-		432	
Radiotherapy only	2		966	
Chemotherapy only	2		927	
Radiotherapy + chemotherapy	9		2,012	
Mean yrs followup (range)	27	(5−64)	27	(5−64)