

Long-term Mortality from Second Malignant Neoplasms in 5-Year Survivors of Solid Childhood Tumors: Temporal Pattern of Risk according to Type of Treatment

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Abstract

Background: The temporal pattern in mortality from late second malignant neoplasms in solid childhood cancer survivors, according to the type of treatment, has not been investigated in detail.

Methods: We studied 4,230 5-year survivors of solid childhood cancer diagnosed between 1942 and 1986 in France and the United Kingdom. Complete clinical, chemotherapy, and radiotherapy data were recorded and the integral radiation dose was estimated for 2,701 of the 2,948 patients who had received radiotherapy.

Results: After a median follow-up of 28 years, 134 fatal events were due to second malignancies, compared with the 13.3 expected from the general France-UK population rates. The standardized mortality ratio was of a similar magnitude after radiotherapy alone and chemotherapy alone and higher after both treatments. The standardized mortality ratio decreased with follow-up, whereas the absolute excess risk increased significantly over a period of at least 25 years after the first cancer. This temporal pattern was similar after chemotherapy alone, radiotherapy alone, or both treatments. We observed a similar long-term temporal pattern among survivors who had died of a second malignant neoplasm of the gastrointestinal tract and breast. Survivors who had received a higher integral radiation dose during radiotherapy were at a particularly high risk, as well as those who had received alkylating agents and epipodophyllotoxins.

Conclusions: Five-year survivors of childhood cancer run a high long-term mortality risk for all types of second malignant neoplasms whatever the treatment received and require careful long-term screening well beyond 25 years after the diagnosis. *Cancer Epidemiol Biomarkers Prev*; 19(3); 707–15.  2010 AACR.

Introduction

The occurrence of additional malignancies in long-term survivors of childhood cancer is a recognized late sequela of specific cancer therapy and genetic predisposition (1-7). The temporal pattern of mortality from a late second malignant neoplasm (SMN) after a first malignant neoplasm (FMN) in childhood is not well known. The existing survivor cohorts (Childhood Cancer Survivor Study and Nordic) have shown that the risk of death from SMN decreased with increasing follow-up and that certain aspects of anticancer treatment increase this risk (8, 9). However, the duration of follow-up was not long

enough to determine the temporal pattern of the late occurrence of SMN (9-12).

On the other hand, it is a known fact that children treated with radiation, alkylating agents, epipodophyllotoxins, and antimetabolite therapy for a primary malignancy run an increased risk of developing a SMN (8, 13-18), and few studies have estimated the radiation dose-response relationship (19, 20).

We evaluated long-term mortality from SMN in a multicentric French-UK cohort of 4,230 5-year survivors of childhood cancer, including detailed information on the drugs received and radiation dosimetry, to investigate temporal patterns and the role of radiotherapy and chemotherapy.

Patients and Methods

Study Population

An initial cohort including 4,590 2- to 5-y survivors of a childhood cancer treated in or before the end of 1985 in eight cancer centers in France and the United Kingdom for all types of FMN (with the exception of leukemia) was established between 1985 and 1995 (21). Of these patients, 4,230 5-y survivors of a FMN treated before the age of 17 y were included in the present analysis.

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The clinical and histopathologic characteristics of the FMN and SMN, detailed information on treatments, and follow-up data were recorded from hospital clinical records.

FMN were grouped according to the diagnostic group (22) classification scheme for childhood cancer, whereas SMN were coded according to histology using the International Classification of Diseases for Oncology (23). The vital status of 3,074 patients treated in France was obtained by matching the first name, last name, date and place of birth, as recorded in the hospital files, with the National Identification Registry. This identification process failed in the case of 80 patients whose vital status could not be obtained. Those subjects were included until the date of the last follow-up. The causes of death occurring before the end of 2005 were provided by the French Death Registry (24) for all but 28 deceased patients. The vital status and cause of death of 1,156 British patients were obtained by "flagging" individuals within the National Health Service Central Register which, among other things, is linked to national death registration (notifications include type/site of cancer and cause of death) and is described in detail elsewhere (25).

A SMN was defined as a malignant neoplasm of any site with a different histology from that of the primary tumor. A total of 690 patients had died. Cancer was registered as the main cause of death on 170 death certificates. We obtained a copy of the histologic examination and other institutional records to verify each case. Thirty-six were due to a relapse or a metastasis from the initial tumor. A total of 134 deaths were confirmed as due to a SMN.

Radiation Dosimetry

Direct individual radiotherapy reconstruction was done using the homemade Dos_EG software package (26, 27). For each patient, a simple mathematical phantom anatomy was generated according to patient dimensions (i.e., mainly sagittal and transversal contouring) and simulation films. To calculate the integral dose, beams were positioned on the phantom according to details in the patient's medical record, as well as information on equipment, common treatment techniques, and guidelines used at the time of the treatment. Radiotherapy parameters included beam size, shape and inclination, location, radiation energy, and the delivered dose. The dose calculation algorithm took into account primary radiation from the treatment machine and scattered radiation from the patient and from beam collimation, leakage radiation, and lung heterogeneity. The integral dose may be considered as the volume-weighted sum of the doses, the mean dose multiplied by the volume, or the total energy (joules) deposited (27-30).

Basically, an integral dose of 1 J corresponds to a dose of 1 Gy in a 1-liter water volume. When radiotherapy delivered to the same patient involved several beams, the resulting integral dose was the sum of the integral doses of different beams. With this approach, the integral dose

was estimated exclusively for the volumes within the geometric limits of the beams. The energy deposited outside this volume was not taken into account.

Chemotherapy Measurement

The doses of the drugs received for the initial treatment or for recurrences of the first cancer (local relapses or distant metastasis) during the follow-up period were summed per cycle and expressed in milligrams per square meter of the body surface area. We pooled the drugs into six categories according to their known mechanism of action in the cell: anthracyclines (the reference drug was doxorubicin), alkylating agents (the reference drug was cyclophosphamide), epipodophyllotoxins, anti-metabolites, *Vinca* alkaloids (the reference drug was vincristine), and other drugs. We converted the dose of each drug into the dose of a reference drug, based on either dose equivalence in terms of hematologic toxicity or substitution rules commonly used in clinical practice, a method we called "Equi-tox." A detailed description of the quantification of chemotherapy has already been published (20). We used a classic method of summing the dose (per square meter) for other drug categories.

Statistical Analysis

Person-years at risk were accumulated from entry into the study (at 5-y survivorship after the first cancer) until death (died of a SMN before January 1, 2006). The standardized mortality ratio (SMR) was calculated as the ratio of the observed number of deaths to the expected number. The expected number of deaths due to cancers in the general population was extracted by sex, age (5-y categories), and calendar period (5-y) from the French Death Registry (24) for patients treated in France and from the National Health Service Central Register for those treated in the United Kingdom. The absolute excess risk was defined as the difference between the observed and the expected numbers of cancer deaths, divided by the person-years at risk and multiplied by 1,000. SMR and absolute excess risk 95% confidence intervals (95% CI) were calculated with exact Poisson probability (31).

Patterns in the risk of death with time since the diagnosis were analyzed in the following periods: 5 to 14, 15 to 25, and 25 y or more of survivorship since the diagnosis.

Multivariate Poisson regression models were used to estimate the relative risk (RR) of dying of a SMN associated with radiotherapy, evaluating the integral dose and with each pharmacologic drug category. Analyses were adjusted for categorized variables: sex, country of treatment, type of FMN, time since diagnosis of FMN, age at diagnosis of FMN, and treatment period (<1969, 1970-1979, 1980>). We were unable to estimate the radiation dose in 248 survivors due to insufficient information, but we adjusted for the missing radiation doses in the multivariate analysis. A significant trend test ($P < 0.05$) implies that the risk increases with higher doses. Interaction

Table 1. Type of SMN among 5-y survivors of childhood cancer according to first cancer diagnosis

First cancer diagnosis	SMN sites												No. events	Integral dose (J), mean (min-max)
	Oral	Digest	Respi	Bone	Conn	Skin	Breast	CNS	Thyr	Lymph	Leuk	Other		
Nephroblastoma (<i>n</i> = 854)		8	1	1	3	1	4			1	2	3	24	75.6 (0.9-433.6)
Neuroblastoma (<i>n</i> = 561)		1	2	1	1		2	2	2		1		12	40.6 (0.6-725.3)
Hodgkin's disease (<i>n</i> = 363)		8	2	2	1	1	3	1					18	208.8 (0.1-1,075.3)
Non-Hodgkin's lymphoma (<i>n</i> = 444)	1	3		1	1			1		1	3		10	125.6 (0.4-1,247.9)
Soft tissue sarcoma (<i>n</i> = 530)	1	7	1	5		1	2	2			1	2	22	49.8 (0.6-441.8)
Bone tumors (<i>n</i> = 257)			2		2								4	177.4 (5.3-882.0)
CNS neoplasms (<i>n</i> = 683)	2	2			1	1	1		2			3	12	109.5 (3.2-567.9)
Germ-cell neoplasm's (<i>n</i> = 223)		2	1	2	1							2	8	145.9 (1.7-701.1)
Thyroid (<i>n</i> = 47)							1				1		2	37.7 (0.2-124.7)
Retinoblastoma (<i>n</i> = 144)	1		2	7	2					1		1	14	17.2 (0.4-702.1)
Other malignant neoplasm's (<i>n</i> = 124)		1		2	2		1			1			7	96.0 (2.0-499.4)
All (<i>n</i> = 4,230)	5	32	11	21	14	4	14	6	4	4	8	11	134	160.3 (0.1-1,247.9)

NOTE: Oral (ICD 140-149)—tumors in oral cavity and pharynx; Digest (ICD 150-159)—tumors in gastrointestinal tract; Respi (ICD 160-165)—tumors in respiratory system; Bone (ICD 170)—tumors in bones; Conn (ICD 171)—tumors in connective tissues; Skin (ICD 172-173)—tumors in skin; Breast (ICD 174-175)—tumors in breast; CNS (ICD 191-192)—brain and other nervous system tumors; Thyr (ICD 193)—thyroid carcinoma; Lymph (ICD 200-202)—lymphomas; Leuk (ICD 204-208)—leukemias; Others (ICD 179-190 194-195 199)—other sites; All (ICD 140-208)—malignant neoplasms.

Table 2. General characteristics and comparison of the SMN mortality in the French-UK cohort to that in the general population

SMN sites	Attained age (y), mean (range)	First cancer treatment, n (%)			No. of observed events (female %)	No. of expected events	SMR (95% CI)	Absolute excess risk/1,000 person-years (95% CI)
		Chemotherapy alone	Radiotherapy alone	Both				
Oral cavity and pharynx	22 (9-41)	0	2 (40)	3 (60)	5 (80)	0.5	9.5 (3.9-22.7)	0.05 (0.01-0.10)
Gastrointestinal tract	34 (9-59)	4 (12)	10 (31)	15 (46)	32 (31)	2.6	12.2 (8.4-16.9)	0.23 (0.14-0.34)
Respiratory system	37 (23-51)	2 (18)	3 (27)	5 (45)	11 (18)	4.5	2.5 (1.3-4.2)	0.03 (0.01-0.10)
Bone	19 (7-46)	2 (10)	2 (10)	16 (76)	21 (33)	0.5	40.2 (25.4-59.9)	0.19 (0.12-0.28)
Connective tissues	26 (12-37)	0	1 (7)	12 (86)	14 (21)	0.3	37.6 (21.2-60.9)	0.13 (0.07-0.21)
Skin	27 (17-46)	0	1 (25)	3 (75)	4 (100)	0.3	11.4 (3.5-26.5)	0.03 (0.01-0.08)
Breast	35 (18-50)	1 (7)	5 (36)	8 (57)	14 (100)	1.8	7.4 (4.2-12.0)	0.08 (0.03-0.16)
Brain and other nervous system	19 (11-37)	0	2 (33)	4 (67)	6 (33)	1.3	4.5 (1.8-9.1)	0.05 (0.01-0.10)
Thyroid	15 (10-19)	0	2 (50)	4 (50)	4 (25)	0.05	82.6 (25.7-191.9)	0.03 (0.01-0.08)
Lymphomas	17 (6-23)	0	0	3 (75)	4 (25)	0.9	4.4 (1.1-8.6)	0.03 (0.01-0.07)
Leukemias	13 (7-24)	2 (25)	0	5 (62)	8 (50)	1.9	4.2 (1.9-7.8)	0.06 (0.01-0.12)
Other	36 (21-61)	0	5 (46)	6 (54)	11 (54)	2.2	5.7 (2.8-8.8)	0.06 (0.01-0.13)
All SMN	28 (6-61)	12 (9)	34 (25)	80 (60)	134 (43)	16.8	8.0 (6.7-9.4)	1.14 (0.94-1.39)

between the integral dose and different drug categories (yes/no) was tested. Statistical tests were done by comparing the deviance of nested models (32). AMFIT software was used for these analyses (33). Estimation of 95% CIs for parameters was done using maximum likelihood (34).

Results

The median follow-up was 28 years (range, 5-63), and 2,392 (56%) survivors were followed up for 25 years or longer. A total of 690 (16%) patients had died, 134 (19%) due to a SMN. Tumors of the gastrointestinal tract accounted for 24% of all SMN, followed by bone (15%), connective tissue (10%), and breast (10%) cancers (Table 1). The highest risk of dying of a SMN was seen in survivors of retinoblastoma and Hodgkin's disease.

Compared with the general France-UK population, the risk for mortality from a SMN was almost 8-fold higher (SMR, 8.0; 95% CI, 6.7-9.7; Table 2); one additional patient in every 1,000 had died each year (absolute excess risk, 1.14; 95% CI, 0.94-1.39). Although the SMR decreased with follow-up, the absolute excess risk increased considerably ($P < 0.001$) over time following the first cancer, from 1.0 additional case annually per 1,000 persons from 5 to 14 years to 1.5 additional cases from 25 years or more thereafter (Fig. 1). We observed a tendency over time to develop second cancers particularly of the main sites af-

fected in adulthood: gastrointestinal tract, breast, and respiratory system. Interestingly, the absolute excess risk decreased over time for leukemia, and no significant trend was observed for second tumors involving bone, connective tissue, or the central nervous system (Fig. 1).

Gender did not influence the risk of death due to any type of SMN, except for breast cancer.

After controlling for follow-up, mortality due to second malignancies was similar among survivors treated with chemotherapy alone (SMR, 19.8; 95% CI, 10.4-37.7) and radiotherapy alone (SMR, 16.5; 95% CI, 9.2-29.6) and higher among subjects treated with combined therapy (SMR, 45.8; 95% CI, 30.7-68.4).

The time trend did not depend on the treatment modality and was similar in survivors treated with chemotherapy alone, radiotherapy alone, and combined therapy. They were all at an increasing absolute excess risk of death from a second cancer with increasing follow-up (Fig. 2). No interaction was observed between radiotherapy and follow-up ($P = 0.9$), nor between chemotherapy and follow-up ($P = 0.4$).

The highest integral radiation dose was observed among survivors of primary Hodgkin's disease, bone sarcoma, and non-Hodgkin's lymphoma (Table 1). Cumulative mortality from second cancers was higher among survivors who had received 150 J or more (Fig. 3).

In the multivariate analysis, the risk of death due to second malignancies increased with exposure to alkylating

agents ($P = 0.01$, test of trend) and epipodophyllotoxins ($P = 0.003$, test of trend) and mainly with a higher integral radiation dose ($P < 0.001$, test of trend; Table 3).

No significant interaction was found between drug categories (coded yes/no) and the integral radiation dose.

Discussion

The very long follow-up of 4,230 patients treated between 1942 and 1986 showed that 5-year survivors of childhood cancer face an increased risk of late mortality from all types of SMN. The absolute excess risk from 15 to 24 years and from 25 years and beyond doubled after the diagnosis of the first cancer. An increase was observed in the absolute excess risk of death due to SMN of the gastrointestinal tract, breast, and respiratory system. The magnitude of the risk of death was similar among survivors treated with chemotherapy alone and radiotherapy alone but higher among those who had received both modalities. The absolute excess risk of dying of a SMN increased with follow-up whatever the type of treatment and was particularly high after 25 years. Survivors who had received high doses of alkylating agents and of epipodophyllotoxins were at a higher risk. Due to the large number of patients who had received a high integral radiation dose during radiotherapy, this indicator accounts for the high number of second cancer-related deaths.

The length of follow-up, the very high percentage of information on the vital status (98%), the cause of death (95%), and the validated ascertainment of a SMN status in this cohort strengthen our results. In particular, we consulted the medical files of all deaths registered as due to cancer of the bone, liver, lung, or brain, which are frequent sites of metastasis, or to cancers that could have been a recurrence or a progression of the primary malignancy. Twenty-two percent of fatalities attributed to a SMN were in fact due to a recurrence or a metastasis from the FMN.

This cohort was established between 1985 and 1995, and medical and treatment data were collected diligently and exhaustively during this period from medical and radiological records. Although Dos_EG was last updated in 2006, new dosimetric estimations were generated for the whole cohort by running the software in batches using patient and technical data collected between 1992 and 1995 without manual intervention.

Another strong point in our study is that we registered the dose of each drug received by all patients in the cohort and summed this amount per drug category after taking into account their hematologic toxicity, a method commonly used in clinical practice.

Nevertheless, there are several limitations to our study. It could be criticized that therapy in the 1950s and 1980s does not reflect that of the present era. Our results on chemotherapy and radiotherapy are probably not extendable to modern practices. It should be noted that there

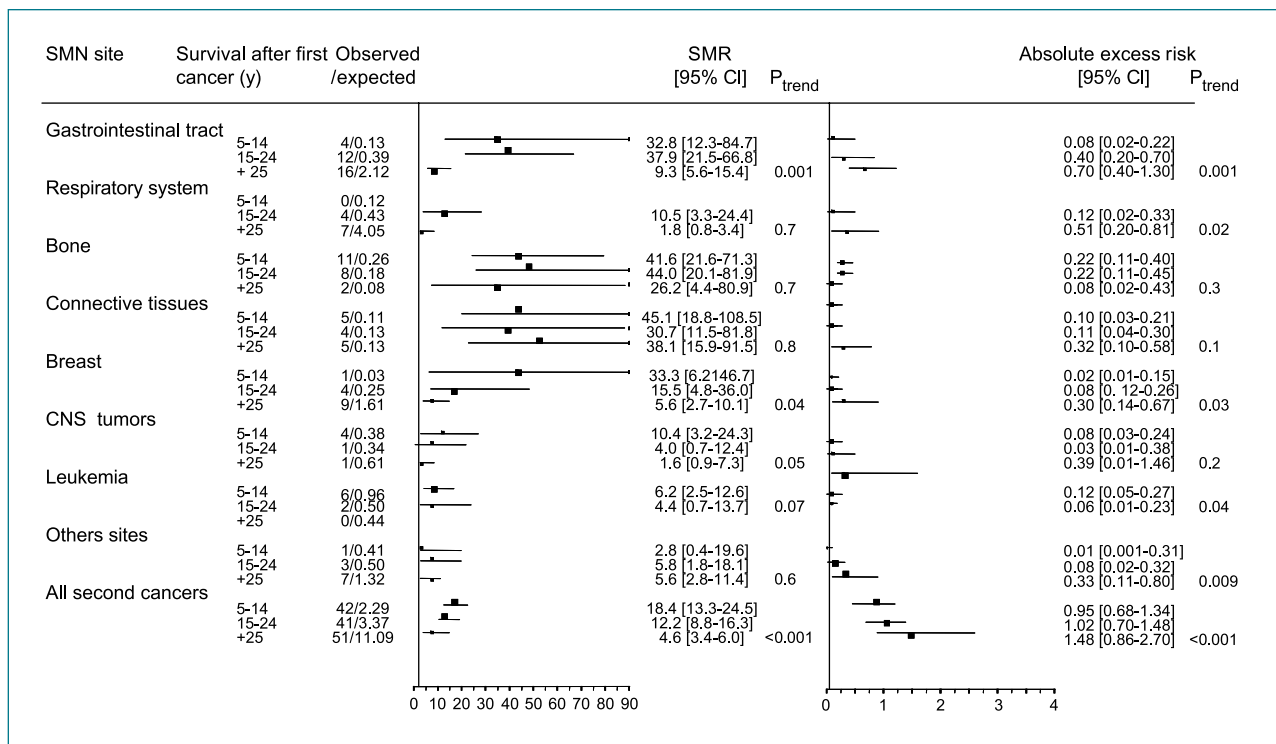


Figure 1. SMN according to time since first cancer.

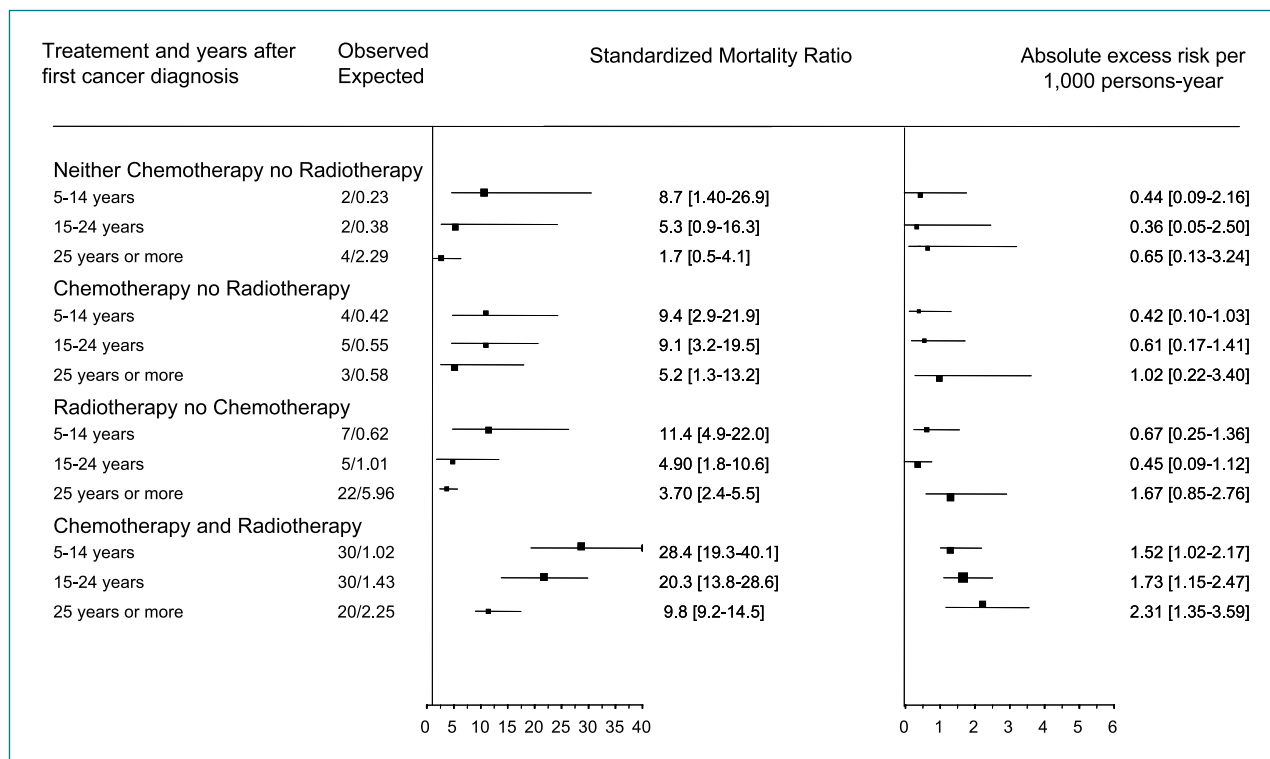


Figure 2. Risk of all SMN according to time since first cancer and type of first cancer treatment.

is an overlap between simple and intensive multiagent chemotherapies in our cohort, and therefore treatment practice is more heterogeneous than in the population-based Childhood Cancer Survivor Study (CCSS) or the Nordic countries cohort. In contrast, and particularly since the 1990s, both total cumulative doses and volumes of radiotherapy have been far more limited compared with those applied previously for many treatment indications. The calculated absorbed integral dose was limited to radiation fields. This can be used in routine practice by radiation therapists. Scattered radiation outside the fields is mainly produced by the patient himself/herself and the amount of this scattered radiation is directly proportional to the absorbed integral dose evaluated in this study. Therefore, the integral dose restricted to the fields is a good indicator of the true integral dose to the whole body when evaluating different radiotherapy regimens as predictors of second cancers (35, 36).

To our knowledge, no other large-scale population or hospital-based cohort of childhood cancer survivors has analyzed mortality from SMN with a median follow-up of more than 25 years. In our cohort, 66 deaths from a SMN occurred in survivors treated more than 20 years earlier, as compared with 3 among the Dutch childhood cancer survivors (37), 35 in the population-based study in the Nordic countries (9), and fewer than 40 in the CCSS (38).

Limitations, however, include the absence of patients with a primary diagnosis of leukemia and the inability

to draw conclusions about early second leukemias that occurred within the first 5 years of follow-up because our study focused on long-term excess mortality in 5-year survivors of childhood cancer. This approach was also used in most of the other studies devoted to long-term excess mortality (8, 9, 37).

As a general matter, our study confirms a trend toward the risk of a SMN with increasing follow-up as described in other studies and particularly among survivors of Hodgkin's disease (39, 40) and Wilms' tumor (41). This continued increase in the absolute excess risk is therefore of major clinical interest. The increasing absolute excess risk over the incremental long term observed in our study of the usual adult malignancies such as cancers of the breast, gastrointestinal tract, and respiratory system has already been described (12, 13, 42). The main new finding in our study is the extreme similarity in the average excess risk of SMN and in its temporal pattern, whatever the treatment received. Our results on the role of chemotherapy in the risk of death from a SMN remained similar after excluding second leukemias and restricting the analysis to second solid malignancies.

It is well known that chemotherapy with alkylating agents or epipodophyllotoxins is a risk factor for the development of second primary leukemia during the first 7 to 10 years after the initial diagnosis (13, 14, 43). Alkylating agents are a regularly mentioned risk factor for SMN (6, 13, 15, 16, 44). In the large-scale CCSS cohort, the risk of mortality from a SMN was related to exposure

to alkylating agents and epipodophyllotoxins (8, 38). We found a significant effect of these drug categories, which is in agreement with the CCSS study.

Radiotherapy has been shown to be associated with an increased risk for solid SMN 10 to 15 years after treatment and later (15, 17, 44-46). Few previous studies have investigated the roles of radiotherapy (yes/no; refs. 18, 38) or local radiation dose and chemotherapeutic drugs (20) as risk factors for mortality from SMN.

The aim of our study was to find an indicator of the overall risk of SMN, all types considered together, rather than the risk for a SMN of a specific anatomic site. The integral dose is the simplest among such indicators of the overall risk of SMN, and our results show that the integral dose is of interest for predicting the risk of SMN in clinical practice. Indeed, in our cohort, among the survivors who had received radiotherapy, 38% had in fact received an integral dose of less than 40 J and were therefore at a low risk of SMN (RR, 1.27; 95% CI, 0.72-2.26),

whereas 49% of them had received an integral dose exceeding 41 J and were at a high risk of death from an SMN [RR, 2.05 (95% CI, 1.12-3.75) for 41-149 J and 5.89 (95% CI, 3.07-11.31) for 150 J or more]. In clinical practice, 40 J is approximately the integral dose delivered by a 40-Gy field measuring 10 cm × 10 cm, whereas 150 J is the dose delivered by a 40-Gy field measuring 20 cm × 20 cm, whatever the age of the child.

In conclusion, the absolute excess risk of a SMN in adult survivors of solid pediatric cancer is of a similar magnitude and has a comparable time pattern after radiotherapy alone and chemotherapy alone, but the risk is higher after both treatments. This risk seems to be partially attributable to a high integral dose delivered by large radiotherapy fields, as well as to high doses of alkylating agents and epipodophyllotoxins.

Our results strongly suggest that a greater number of adult SMN affecting the gastrointestinal tract and breast are likely to occur hereafter as follow-up periods become

Figure 3. Cumulative observed SMN mortality (95% CI) according to integral dose.

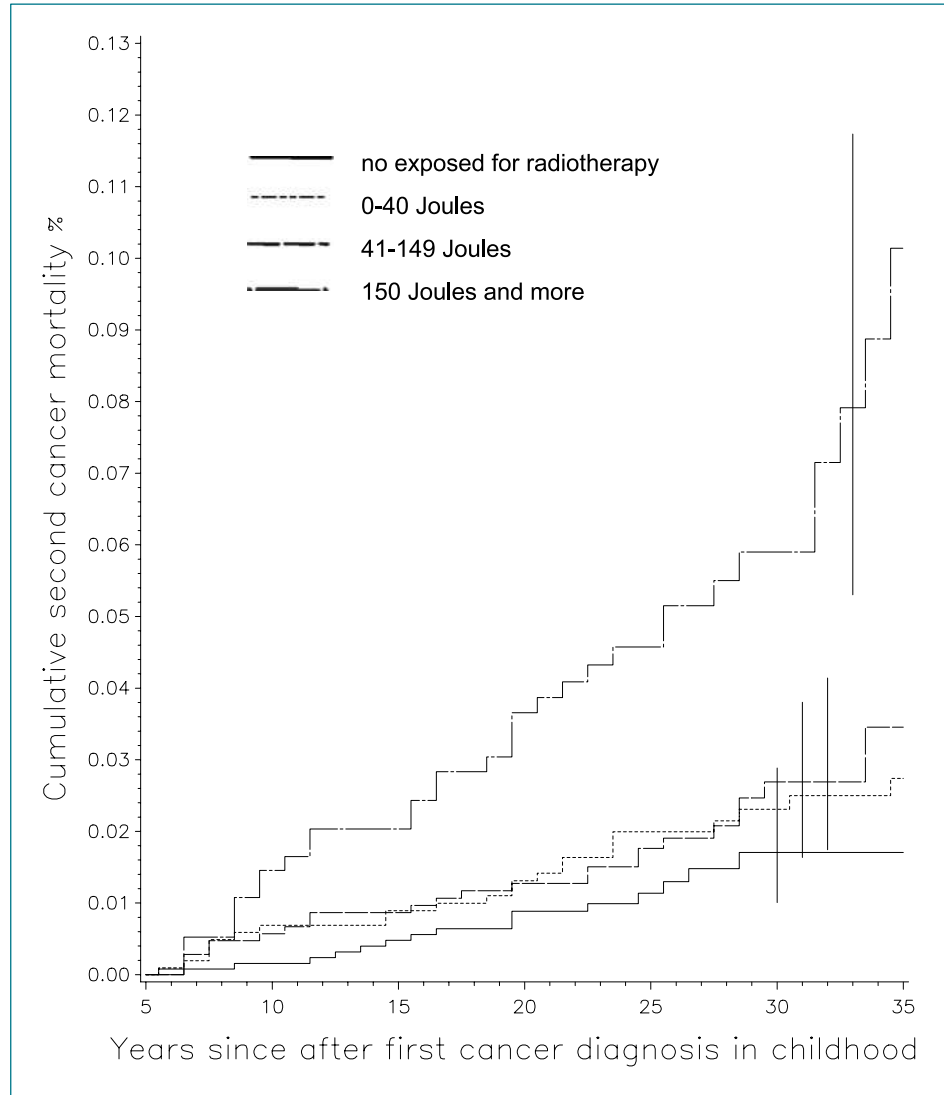


Table 3. Relative risk of SMN mortality among 5-y childhood cancer survivors according to radiotherapy exposure and chemotherapy

First cancer treatment	Survivors	Fatal events	Univariate		Multivariate*	
			RR (95% CI)	<i>P</i> _{trend}	RR (95% CI)	<i>P</i> _{trend}
Integral radiation dose (J)						
Not exposed	1,282	21	1		1	
0-40	1,030	37	1.49 (0.87-2.57)		1.27 (0.72-2.26)	
41-149	1,087	30	1.64 (0.93-2.89)		2.05 (1.12-3.75)	
≥150	585	33	3.93 (2.26-6.85)	<0.001	5.89 (3.07-11.31)	<0.001
Missing	247	13	1.80 (0.88-3.68)		1.77 (0.83-3.75)	
Alkylating agents (mg/m ²) [†]						
Not exposed	2,309	76	1		1	
0-9,000	894	19	1.68 (1.01-2.77)		1.13 (0.59-2.17)	
9,001-12,000	402	12	2.89 (1.57-5.32)		1.99 (0.89-4.48)	
≥12,001	625	27	3.56 (2.29-5.54)	<0.001	2.18 (1.08-4.40)	.01
Anthracycline (mg/m ²) [†]						
Not exposed	2,990	100	1		1	
0-240	352	9	2.36 (1.19-4.67)		1.52 (0.69-3.38)	
241-360	441	13	2.75 (1.54-4.90)		1.96 (0.98-3.95)	
≥361	447	12	2.49 (1.37-4.53)	0.001	1.37 (0.63-2.98)	0.21
Epipodophyllotoxins (mg/m ²)						
Not exposed	3,991	124	1		1	
0-981	119	3	2.84 (0.91-8.94)		1.87 (0.55-6.34)	
≥982	120	7	6.00 (2.80-12.85)	<0.001	3.48 (1.46-8.30)	0.003
Vinca alkaloids (mg/m ²) [†]						
Not exposed	1,867	71	1		1	
0-20	1,133	24	2.00 (1.24-3.13)		0.89 (0.45-1.78)	
21-50	1,071	29	2.67 (1.73-4.13)		1.12 (0.56-2.26)	
≥51	159	10	5.02 (2.59-9.74)	<0.001	1.80 (0.76-4.22)	0.21

*Multivariate Poisson regression model, stratified on the type of first cancer diagnosis, adjusted for all the other treatment variables in the table: sex, follow-up interval after diagnosis, age at diagnosis, and treatment period.

[†]Alkylating agent reference drug was cyclophosphamide; anthracycline reference drug was doxorubicin; *Vinca* alkaloid reference drug was vincristine.

longer. Careful long-term (well beyond 25 years after the diagnosis) screening programs such as colonoscopies and mammograms are required for the early detection and treatment of subsequent malignant neoplasms.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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