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## Second Malignant Neoplasms in Patients Treated on SIOP Wilms Tumour Studies and Trials 1, 2, 5, and 6

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The incidence of second malignant neoplasms (SMNs) was investigated among 1,988 patients with complete data, enrolled in the SIOP Wilms tumor trials and studies 1, 2, 5, and 6, treated between September 1971 and October 1987. By the end of 1992, eight SMNs were documented, whereas only 1.3 were expected (standardized incidence ratio [SIR] = 4.15; 95% CI = 1.79, 8.17). The risk increases in the first 10 years from diagnosis, while no apparent excess of risk is observed in the subsequent periods. This finding however is difficult to interpret due to the low statistical power. The cu

mulative incidence of a second cancer observed at 15 years after Wilms tumor diagnosis was 0.65%. Six SMNs were registered in the cohort of patients treated in the SIOP studies 1, 2 and 5 (999 cases) compared to the two cases observed in the SIOP6 cohort (989 cases). If the suggested reduced incidence of second cancers between SIOP1-5 and SIOP6 patient cohorts is confirmed by longer follow-up, it might reflect changes in the treatment protocols. *Med. Pediatr. Oncol.* 29:239–244, 1997.

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**Key words:** Wilms tumor; second malignancy

### INTRODUCTION

Wilms tumor provides one of the most impressive examples of success in the treatment of childhood cancers. This success has been made possible through a stepwise process of refinements of a multidisciplinary approach including surgery, radiotherapy, and chemotherapy.

In Europe, the improvement achieved in the cure rate of children with Wilms tumor is well documented by the results reported by the International Society of Pediatric Oncology (SIOP) Wilms tumor studies in the last few decades. Before 1970 the 5-year survival rate of a large series of patients treated in a single institution from 1952 to 1967 [1] was 55%. The 5-year overall survival rate of children enrolled since 1971 in five consecutive SIOP studies increased from 64% for children treated in the early seventies (1971–1974; SIOP1) [2]; to 76% for those treated between 1974–1976 (SIOP2) [3]; 83% for those treated between 1976–1980 (SIOP5) [4]; and 84% for those treated during 1980–1987 (SIOP6) [5]. The 5-year overall survival for patients registered during 1987–1991 in the SIOP9 is 87% [6].

However, successfully treated patients are at risk of developing a second cancer later in life [7–11]. This report examines the risk of second malignant neoplasms (SMNs) among 1,988 children enrolled in the SIOP Wilms tumor trials and studies 1, 2, 5, and 6, treated between 1971–1987.

### PATIENTS AND METHODS

Between September 1971 and October 1987, 2,067 patients with Wilms tumors were entered in one of four SIOP trials and studies (SIOP 1, 2, 5, and 6). Of those, 1,988 were eligible for this report: 79 were excluded because of incomplete data. Of the 1,988, 995 were classified as “study” patients and 993 as “trial” patients. The clinical characteristics of this population of Wilms tumor patients are summarized in Table I. The treatments adopted in the different SIOP studies have already been reported [2–6]. “Study” patients were not included in the “trial” category because of one of the following reasons: age less than 6 months, or more than 15 years, stage IV, bilateral disease, inability to apply preoperative therapy, registration after surgery, parents refusal of the trial, or other reasons. Treatment recommendations for “study” patients were to follow the protocol regimens. Children less than 6 months were operated first and if

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**TABLE I. SIOP Wilms Tumor Trials and Studies 1, 2, 5, 6 Study Population (1,988 Cases)**

Characteristics	No. of patients	%
Sex		
Male	965	48.5
Female	1,023	51.5
Age at W.T. diagnosis (yr)		
<1	219	11.0
1-4	1,257	63.2
5-9	440	22.1
10-14	55	2.8
15+	17	0.9
Stage		
I	732	36.8
II	523	26.3
III	361	18.2
IV	259	13.0
V	85	4.3
MD	28	1.4

they were stage I, no postoperative treatment was given. Detailed treatment information were recorded only for trial patients.

Follow-up status was ascertained by the treating institutions using specific forms reporting any events which occurred during follow-up. No major difference between institutions was detectable in term of efficiency of follow-up. The statistical analysis used all data obtained through December 31, 1992. For every second tumor, relevant clinical data and the histopathological report were obtained, but only the slides of the primary lesions were centrally reviewed by the pathology panel of the SIOP Wilms tumour study.

Data processing and quality control analyses were performed at the Venetian Cancer Registry using common statistical packages [12]. The cohort analysis was performed using the date of diagnosis as the date of entry in the observation period. The date of death (for those who died), or the date of the last contact for those lost to follow-up or the date of the end of the study for those still on follow-up, have been used as the date of exit from the observation period. We report in Table II the distribution of subjects alive, dead, or lost to follow-up by time since Wilms tumour diagnosis.

An effort was made to use national incidence rates for each of the countries included in the study. Only a few European countries, however, had a nationwide cancer registry, and most of the collaborating centres were located in areas not covered by cancer registries. It was therefore decided to use the age, sex, and calendar specific cancer incidence rates of the Danish Cancer Registry because of their known high quality and long standing. Other similar studies carried out in Europe have used the Danish Cancer Registry as the reference [20].

Expected number of cancers (excluding skin cancers) [12] were obtained by multiplying the accumulated per-

**TABLE II. Fatal Events and Patients Lost to Follow-Up by Time Since Wilms Tumor Diagnosis**

Time since Wilms tumor diagnosis (yr)	No. of patients	Dead	Lost
0-4	1,988	396	405
5-9	1,187	27	611
10-14	549	3	389
15-19	157	0	157
Total	1,988	426	1,562

son-years in each stratum by the reference rates of the Danish Cancer Registry across age, sex, and calendar period.

Ratios (Standardized Incidence Ratio, SIR) between observed cancer cases and expected and 95% confidence intervals for SIRs were computed assuming a Poisson distribution.

The cumulative incidence of second cancers was estimated by the Kaplan-Meier method [13].

## RESULTS

Table III reports results by time since diagnosis. Among all 1,988 patients, eight new cancers were observed during 13979.85 PY of follow-up, whereas only 1.93 were expected (SIR = 4.15; 95% CI = 1.79, 8.17). The average contribution per patient was 7.03 person-years. The risk increases in the first 10 years from diagnosis (eight SMNs observed vs. 1.61 expected; SIR = 4.97 95% CI = 2.15, 9.79) reaching statistical significance ( $P < 0.05$ ) while no apparent excess of risk is observed in the subsequent periods.

The eight SMNs registered occurred in three females and five males during the surveillance period that ranged from 6 to 21 years.

Table IV lists the main clinical data of SIOP patients with SMNs. They include two acute myeloid leukemias, three bone tumors (two osteosarcomas and one chondrosarcoma), two CNS primitive neuroectodermal tumors (PNET), and one histiocytic lymphoma. All patients had received vincristine and dactinomycin associated with doxorubicin (three patients) and ifosfamide (one patient). Radiotherapy in the range of 2000-4000 cGy, was given to six out of eight children. The three bone tumors observed occurred within the field of prior radiation therapy. The two patients who did not receive radiotherapy developed a lymphoma and a CNS tumor respectively. The time interval between first malignancy and SMN ranged between 15 and 101 months (median 53 months); it was shorter for CNS tumors (15 and 29 months) and longer for bone tumors (74, 100, and 101 months respectively).

The cumulative probability of developing an SMN after 5 and 10 years from diagnosis of Wilms tumor was

**TABLE III. Standardized Incidence Ratio of Second Malignant Neoplasm by Time Since Diagnosis of Wilms Tumor**

Time since Wilms tumor diagnosis (yr)	No. of patients	Person-yr	Observed	Expected	SIR (95% C.I.)
0-4	1,988	7776.51	4	1.11	3.62 (0.98-9.23)
5-9	1,187	4269.40	4	0.50	7.99 (2.18-20.48)
10-14	549	1650.77	0	0.25	0.00
15-19	157	283.17	0	0.07	0.00
Total	1,988	13979.85	8	1.93	4.15 (1.79-8.17)

**TABLE IV. SIOP Patients With SMNs\***

No.	Sex	Associated anomalies	Histology		Age at Wilms tumor diagnosis (yr)	Stage	Irradiation (cGy)	Chemotherapy	Latency between neoplasms (mos.)	SMN (site)	Status
			NWTS [14]	SIOP [15]							
1	F	—	UH	HR/A	0.11	III	2500	ACT-D/VCR	74	Osteosarcoma (iliac bone)	Dead
2	M	Double pelvis	CC	HR/CC	1.6	II	3000	ACT-D VCR/DOXO	101	Osteosarcoma (rib)	Dead
3	M	—	FH	IR	3.3	IV	3000	ACT-D VCR/DOXO	40	AML	Dead
4	M	Microcephaly	FH	IR	3.4	IV	4000	ACT-D/VCR	43	AML	Dead
5	F	—	FH	IR	9.11	III	3000	ACT-D/VCR	100	Chondrosarcoma (rib)	Alive
6	M	—	FH	LR	1.6	II	2710	ACT-D/VCR	29	PNET (CNS)	Dead
7	F	—	FH	IR	2.11	I	—	ACT-D/VCR	63	Histiocytic Lymphoma	Alive
8	M	—	CC	HR/CC	1	1	—	ACT-D/ VCR/EPI/IFO	15	PNET (CNS)	Dead

\*M = male, F = female, FH = favorable histology, UH = unfavorable histology, CC = clear cell sarcoma, A = nephroblastoma with anaplasia, HR = high risk, IR = intermediate risk, LR = low risk, ACTD = Dactinomycin, VCR = Vincristine, DOXO = Doxorubicin, EPI = Epirubicin, IFO = Ifosfamide.

0.25% (95% C.I. = 0.004-0.5) and 0.65% (95% C.I. = 0.18-1.1) respectively. No second neoplasm was reported after 10 years (Fig. 1).

Six SMNs were registered in the cohort of patients treated in the SIOP studies 1, 2, and 5 (999 cases) compared to the two cases observed in the SIOP6 cohort (989 cases). Taking into account the first 10 years since diagnosis, which is the period of occurrence of all the cases of SMN registered and with practically the same total number of PY for the two cohorts, the SIRs were 7.32 (95% CI = 2.69, 15.93) and 2.56 (95% CI = 0.31, 9.26) in the SIOP1-5 and SIOP6 patient's cohort respectively (Table V).

Although the point estimates of the relative risk appear to differ, the difference is not statistically significant as it is evident from the overlapping confidence intervals.

Stratification by gender shows no difference in the SIR between two sexes (SIR = 4.71 vs. 3.46), as well as the analysis by age at diagnosis. In fact before the age of 5 the SIR was 3.42 (95% CI = 0.42, 12.46), while among the children aged 5 or more the SIR was 4.44 (95% CI = 1.63, 9.67).

**DISCUSSION**

We examined the risk of SMNs among 1,988 Wilms tumor patients treated between September 1971 and October 1987 on one of four consecutive SIOP trials and studies.

The cumulative incidence of second cancers observed at 15 years after diagnosis in our study population was 0.65%. Eight new cancers developed as compared with 1.93 expected on the basis of cancer incidence rates in the general population of the Danish Cancer Registry (SIR = 4.15). In our series the risk increased in the first 10 years, from diagnosis, (SIR = 4.97) reaching practically the same proportion of patients with second cancer (1%) observed in other similar studies [8,9,16]. No SMNs, have been observed in patients followed for more than 10 years from diagnosis.

Other similar hospital-based cohort studies have demonstrated that the incidence of SMN continues to rise even after the first decade from diagnosis with cumulative risk of SMNs of 1.6% [10], 2.95% [17], 5.6% [18], 6% [8], 8.5% [19], and 9.6% [20] between 15-30 years

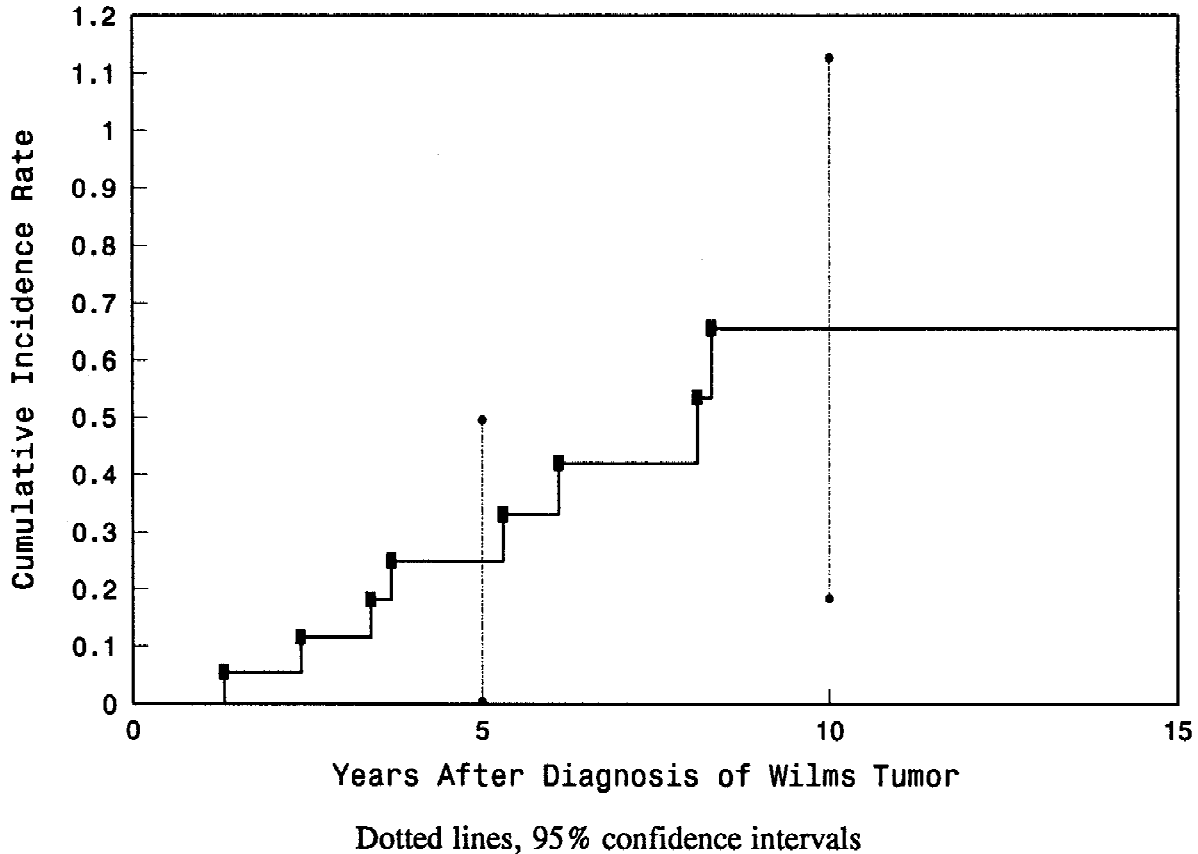


Fig. 1. Cumulative incidence of SMN after diagnosis of Wilms tumor.

TABLE V. Incidence Rates and Standardized Incidence Ratio of Second Malignant Neoplasm Within 10 Years From Wilms Tumor Diagnosis SIOP 1-2-5 vs. SIOP6

	No. of patients	Person-yr	Rates per 10 <sup>5</sup>	Observed	SIR (95% C.I.)
SIOP 1-2-5	999	6891.84	87.1	6	7.32 (2.69–15.93)
SIOP 6	989	5154.08	38.8	2	2.56 (0.31–9.26)
Total	1,988	12045.92	66.4	8	4.97 (2.15–9.79)

after treatment for the first cancer. Comparison with these studies is difficult because of incomplete ascertainment of our patients population after 10 years from diagnosis.

Should the suggested reduced incidence of second tumors between SIOP1–5 and SIOP6 patient cohorts be confirmed by longer follow-up, it might well reflect changes in the treatment protocols. The indications for radiation therapy and the doses delivered both have in fact been reduced. Breslow et al., in their recent update of SMNs in Wilms tumor survivors, found irradiation to be a factor, and a clear correlation between the dose of radiation given and the risk of SMN [10]. We cannot

perform this type of analysis because we have detailed treatment information only for trial patients. However according to the guidelines of the protocols, 80% of the patients in the SIOP1–5 studies were irradiated as compared to 40% in the SIOP6 study.

Furthermore, chemotherapy has been reduced in the SIOP series. The number of stage I Wilms' tumor patients who did not receive radiation therapy and who were treated with minimal chemotherapy increased through the studies. However, it should be emphasized that the two groups have different follow-up time and this might influence the results.

Among the eight cases of SMN, a clear relationship with radiotherapy is evident for the three cases of bone sarcomas occurred in the field of radiation. The two cases of leukemias were also associated with radiotherapy, but the interaction of chemotherapy cannot be excluded. Both cases in fact, were treated with intercalating topoisomerases II inhibitors such as doxorubicin and/or dactinomycin, which in combination with radiotherapy appeared to be leukemogenic [10,20,21].

Two children developed a CNS PNET. The association of Wilms tumor and cerebral neoplasms does not fit with any known cancer predisposing syndromes or con-

ditions. However it is quite interesting to point out that a cerebral PNET has been documented in the cohort of 43 SMNs occurring in long term survivors of Wilms tumor reported by Breslow et al. [10] and that three cases of brain tumors in the absence of brain radiotherapy and use of alkylating agents were reported by Meadows et al. [23] among 36 SMNs observed in Wilms tumor patients. Similarly neither one of our two cases were treated with CNS radiotherapy. It is worthwhile noticing that both children were very young at diagnosis (i.e., 1 and 1.6 years) and the latency period for SMN was the shortest observed in our series. This could suggest that an unknown genetic predisposition could be at the base of this rare tumor combination [24]. It is worthwhile mentioning that the diagnosis of both cases of cerebral PNET have been reviewed by members of the pathology panel of the SIOP Wilms tumor study.

Genetic predisposition has been associated with increased risk of SMNs [25]. Only the 999 patients enrolled in the SIOP1–5 studies have been the object of accurate epidemiologic investigation. Among these, about 20% had a multicentric or bilateral disease or a family member affected by Wilms tumor or characteristic congenital anomalies [26]. Out of the six cases of SMNs documented in this cohort (patients 1–6), two occurred in children having congenital anomalies (patients 2 and 4) which may be interpreted as signs of an underlying genetic defect predisposing to tumor development. Because of small numbers, however, an excess of SMNs among those patients with putative “hereditary conditions,” similarly to Breslow et al. [9,10], cannot be either confirmed or excluded.

In accordance with De Vathaire et al. [20] and with Breslow et al. [10], our results indicate no statistically different risk of SMN for children aged 5 years or more at diagnosis.

Our study cannot contribute to the evaluation of the possible protective or carcinogenic effect of dactinomycin as reported in other studies [27,28] because all our irradiated patients also received dactinomycin.

In conclusion, compared to the general population, SIOP Wilms tumor patients have a five-fold increased the risk of developing a second cancer within 10 years from diagnosis. However, our study tends to confirm the limited risk excess of SMNs in Wilms tumor children as compared to other childhood cancer patients [18,20]. In order to verify whether the risk of SMN in our European cohort of Wilms tumor patients have decreased, a longer follow-up is warranted.

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