Risk of Adverse Health and Social Outcomes up to 50 years after Wilms' Tumour: The British Childhood Cancer Survivor Study.

Running Head: Adverse Outcomes in Survivors of Childhood Wilms' Tumour

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ABSTRACT

Purpose: Wilms' tumour (WT) survivors are at risk of adverse health and social outcomes but risks beyond 30 years from diagnosis remain uncertain. We investigated risks of adverse outcomes among 5-year survivors of WT, particularly between 30 and 50 years from diagnosis.

Patients and Methods: British Childhood Cancer Survivor Study includes 1,441 5-year survivors of WT. We investigated cause-specific mortality, risk of subsequent primary neoplasms (SPNs)—and for those who completed a questionnaire—extent of smoking and drinking, educational achievement, health-status and health service use compared to the general population.

Results: Cumulative risk of death, from all causes excluding recurrence, increased substantially from 5.4% by 30 years after WT diagnosis to 22.7% by 50 years—75% of excess deaths beyond 30 years from diagnosis were attributable to SPNs (50%) and cardiac diseases (25%). Digestive cancer (most frequently bowel) accounted for 41% of the excess cancers beyond 30 years.

Conclusion: Between 30 and 50 years from diagnosis, survivors of WT are at a substantially increased risk of premature mortality and 75% of the excess deaths were accounted for by SPNs and cardiac diseases. Radiotherapy exposure was a risk factor for both outcomes. The proportion of WT patients exposed to radiotherapy has reduced substantially in recent decades from initiatives like the SIOP WT 2001 clinical trial which sought to reduce late effects. However the majority of current survivors, at least 30 years from diagnosis, received radiotherapy. Surveillance of this group should focus on SPNs (particularly bowel and breast cancers) and cardiac conditions.

Introduction

Advances in anti-cancer therapy have led to five-year survival after WT improving to 90%[1]. Although WT is increasingly curable, survivors are at risk of a range of treatment related long-term adverse health and social outcomes. WT survivors have increased mortality compared to the general population[2,3], are at excess risk of developing second primary cancers[3-6], adverse pregnancy outcomes[7-9], cardiac disease and renal dysfunction[10].

Although a number of previous studies investigated the risks of adverse health and social outcomes among WT survivors[9,11-16], none had sufficient follow-up to investigate the risks beyond 30 years from WT diagnosis satisfactorily, hence there remains considerable uncertainty regarding the magnitude of these risks. The main advantage of the current study—in addition to being large-scale and population-based—is that 65% of the cohort survived for more than 30 years from WT diagnosis.

The objective of this study was to investigate risks of adverse health and social outcomes among 5-year survivors of WT up to 50 years from diagnosis. Specific objectives were to investigate: (i) cause-specific late mortality; (ii) risks of developing subsequent primary neoplasms (SPNs); (iii) risks of adverse pregnancy outcomes; (iv) health-status; (v) smoking and alcohol consumption, educational attainment and marriage status; (vi) health services use.

Methods

British Childhood Cancer Survivor Study (BCCSS)

The British Childhood Cancer Survivor Study (BCCSS) is a large-scale population-based cohort study established to investigate adverse health and social outcomes among such survivors. The BCCSS includes 1,441 survivors of WT—who were diagnosed before 15 years of age, between 1940 and 1991 in Great Britain, and who survived for at least five years[17]. The BCCSS cohort was ascertained through the population-based National Registry of Childhood Tumours. Limited treatment information was obtained from clinical records to the level of detail given in Table 1.

Ascertainment of deaths and subsequent primary neoplasms

Ascertainment of deaths (including underlying cause of death) and SPNs in the BCCSS was achieved through flagging of the entire cohort of childhood cancer survivors at the National Health Service Information Centre. Flagging informs the BCCSS when a survivor dies or develops a SPN by providing linkage between the population-based cohort and the national population-based death and cancer registration systems. Confirmation of all SPNs was undertaken by writing to relevant clinician(s) to obtain all diagnostic, particularly pathology reports[4]. Validation of causes of deaths was undertaken by two clinicians (co-authors ES and GL) by reviewing all available clinical records, in addition to the death certificates, to ascertain the underlying cause of death. Consequently, all SPNs and causes of death were validated.

BCCSS Questionnaire

Between 2001 and 2007, all survivors who were alive and aged over 16 years were sent a 40-page questionnaire by their primary care physician on behalf of the BCCSS[18]. In total, 947 (70.5%) of all eligible Wilms' survivors completed and returned the questionnaire[17].

The BCCSS questionnaire inquired about potential adverse health and social outcomes of childhood cancer and its treatment including questions regarding health-status (SF-36), health services use, medical conditions, medical procedures, marriage, adverse pregnancy outcomes (e.g. miscarriage, stillbirth, preterm birth), smoking and alcohol consumption and educational achievements.

Ethical approval for the BCCSS was obtained from the relevant Multi-Centre Research Ethics Committee and every Local Research Ethics Committee in Britain (212 in total).

Statistical Analysis

Cause-Specific Mortality

Numbers of observed deaths among WT survivors were compared with the number of expected deaths based on the population of England & Wales. The period at risk began 5 years following initial diagnosis of childhood WT until the first occurrence of emigration, death or exit (31st December 2010). Standardised mortality ratios (SMR) for specific causes of death were calculated as the ratio of observed over expected number of deaths. Absolute excess risks (AERs) were calculated from the observed minus expected number of deaths divided by the number of person-years at risk multiplied by 10,000. Cumulative mortality for specific causes of death was estimated by treating other causes of death as competing risks[19].

Subsequent Primary Neoplasms

The period at risk of developing a SPN began 5 years from diagnosis of WT and continued until the first occurrence of SPN, emigration, death or exit (31st December 2006). Multiple observed SPNs per survivor were permitted for comparisons with those expected from the general population to avoid bias, but only the first SPN was considered in measures of

cumulative risk. Standardised incidence ratios (SIRs), AERs and cumulative risk of developing an SPN were calculated as described above in relation to death.

Health-status – *"Short Form 36"*

Health-status was measured using the SF-36 questionnaire[20]. To compare SF-36 scale scores observed among WT survivors with the general population, normative data from the Oxford Healthy Life Survey (OHLS) were used[21]. For each SF-36 scale, the difference in mean scores between survivors of WT and OHLS was calculated using linear regression which adjusted for age and sex. Also, we examined responses to the individual questions (items) underlying the specific SF-36 scales by comparing the directly standardised percentage (for age and sex) of WT survivors that reported a limitation or other problem to that reported by the general population.

Adverse Pregnancy Outcomes

To investigate the risks of adverse pregnancy outcomes, logistic regression models were used to calculate odds ratios (ORs) to compare likelihood of low birth weight, preterm births and miscarriage between pregnancy outcomes among female WT survivors treated with abdominal radiotherapy and female survivors of non-WT childhood cancers who did not receive abdominal radiotherapy. Most female WT survivors, who reported being pregnant at least once, had been treated with abdominal irradiation (87%).

Smoking status, alcohol consumption and education level

Among those WT survivors who completed the BCCSS questionnaire, smoking and alcohol consumption and educational attainment were compared to the general population by using data from the nationwide General Household Survey (GHS)[22]. Adjustment for confounders and classification of current regular smokers, alcohol consumption and

educational attainment have been defined in previous BCCSS studies[23-25]. For each outcome, ORs comparing WT survivors to the GHS were calculated using multivariable logistic regression with a generalized estimating equation modification that took into account clustering within the GHS; these ORs were adjusted for attained age and sex.

Marital status

To investigate marital status among WT survivors, ORs of ever being married—stratified by sex and attained age—were calculated using data from the National Marriage Registry as the reference population[26]. Age-specific ORs were then pooled into one overall OR by using the Mantel-Haenszel method for combining ORs[27].

Health services use

Frequency of consultations with a doctor, hospital outpatient visits, day-patient hospitalisations and inpatient hospitalisations were evaluated by calculating ORs—comparing WT survivors with the GHS— using a multivariable logistic regression model. ORs were adjusted for attained age, sex, educational attainment and stratified by whether survivors were on regular long-term hospital follow-up in relation to their childhood cancer and its treatment[28].

Statistical significance for all analyses was defined as a 2-sided $P<0.05$. All analyses were carried out in Stata 12 (StataCorp, College Station, Texas).

Results

Cohort Characteristics

From the total of 1,441 WT survivors in the cohort, 10% (N=146) had died, 2% (N=31) emigrated and 88% (N=1264) were alive at the exit date (31st December 2010). Characteristics of WT survivors who completed the questionnaire were similar to all WT survivors in the BCCSS cohort (Table1). In relation to mortality there were 38,803 person-years subsequent to 5-year survival with mean and median follow-up of 26.9 and 26.0 years, respectively. Table 1 indicates that 82% (756/920) of the survivors were exposed to direct abdominal radiotherapy and only 164 were known to be unexposed. Consequently analysis of the entire cohort, used for analysis of deaths and SPNs, corresponds to a group overwhelmingly exposed to direct abdominal radiotherapy.

Causes-Specific Mortality

Survivors experienced over 5 times the number of deaths expected (SMR=5.4;95%CI:4.6,6.4) with 30.7 additional deaths (95%CI:24.6,36.8) per 10,000 person-years in excess of that expected (Table2). For specific causes of death with at least 20 observed deaths results are reported separately. In multiplicative terms, cause-specific mortality was highest for SPNs (SMR=7.3;95%CI:5.3,9.8) and cardiac disease (SMR=10.1;95%CI:6.5,14.9). In terms of the AER, the highest excess which accounted for 32% of all excess deaths related to SPNs, followed by deaths due to recurrence and cardiac causes which accounted for 21% and 19% of the excess deaths, respectively. Deaths due to recurrence mostly occurred relatively early with 22/25 such deaths between 5-14 years, 3/25 between 15-24 years and none from 25 years from diagnosis (not shown in tables). The AER due to all causes of death except recurrence was 14 excess deaths (per 10,000 person-years) between 5-29 years after WT diagnosis, but increased 8-fold to 108.4 excess deaths beyond 30 years – which is equivalent to 1 extra death per 100

survivors each year (Table3). From 30 years subsequent to WT diagnosis deaths from SPNs and cardiac disease accounted for 50% and 25% of the total number of excess deaths, respectively.

Cumulative mortality due to recurrence was 1.8% by 30 years after WT diagnosis, and remained the same by 50 years as there were no more deaths due to recurrence. Cumulative mortality due to all causes except recurrence was 5.4% by 30 years after WT diagnosis, but increased substantially to 22.7% by 50 years. By 50 years from WT diagnosis, the cumulative mortality from SPNs and cardiac diseases were 8.2% and 6.3%, respectively (Figure1).

There were 25 cardiac deaths according to the underlying cause of death on the death certificate and we summarise the results of a comprehensive review of these causes of death taking account of all hospital records and autopsy reports still available (Online Only Table1). This comprehensive review ascertained that 4 deaths were due to renal failure; 9 myocardial infarction (4 with chest irradiation and/or lung metastases); 7 cardiomyopathy/heart failure (6 with chest irradiation); 3 pulmonary embolism; 2 other causes.

Subsequent Primary Neoplasms

The cumulative risk of developing an SPN was 3.7% (95%CI:2.7,5.0) by 30 years after WT diagnosis increasing to 16.4% (95%CI:10.7,23.2) by 50 years (Figure2). The most common SPN were those of digestive sites, which occurred in 17 WT survivors, 7 were bowel cancers and the other affected sites are specified in Table4; all 17 had previously received abdominal radiotherapy. Over 40% of SPNs developed beyond 30 years from diagnosis of WT, for digestive SPNs 10 of 17 developed in this period and these accounted for 41% of the excess number of cancers in this period of follow-up. All WT

survivors who developed breast cancer had previously received either abdominal or chest radiotherapy.

Health-status (SF-36)

WT survivors scored significantly lower than the general population on two of the eight SF-36 scales: physical functioning (difference in means, D=-1.8;95%CI:-3.3,-0.9) and general health perception (D=-6.7;95%CI:-8.1,-5.2) (Online Only Table2). However, WT survivors reported significantly better role-emotional functioning (D=3.4;95%CI:1.2,5.6) than the general population. When examining the responses to individual questions which comprise the physical functioning scale, WT survivors reported significantly higher limitations on most items compared to the general population (Online Only Figure1). When examining responses to the individual questions which comprise the general health perception scale, WT survivors reported higher agreement that their health was worse in relation to each question compared to the general population (Online Only Figure2).

Pregnancy Outcomes

Of the 511 female WT survivors who completed the BCCSS questionnaire, 412 pregnancies were reported by 184 females of which 32% resulted in low birth weight, 35% in a preterm delivery and 22% in a miscarriage for those who responded to the relevant questions and had received abdominal irradiation. Female survivors of WT treated with abdominal radiotherapy were at higher risk of giving birth to a low birth weight baby (OR=3.3;95%CI:2.2,4.9) and giving birth preterm (OR=3.1;95%CI:2.1,4.7) compared to non-WT survivors of childhood cancer not treated with abdominal radiotherapy. Pregnancy analyses were stratified by eras of treatment (<1970 and ≥1970), however no statistical differences were found ($p \geq 0.386$).

Smoking, Alcohol, Education and Marriage

Compared to the general population, WT survivors were less likely to be a regular smoker (OR=0.7;95%CI:0.6,0.8), consume alcohol (OR=0.7;95%CI:0.6,0.9) or consume harmful amounts of alcohol (OR=0.5;95%CI:0.3,0.7). WT survivors did not significantly differ from the general population in achieving specific levels of education (all p-values>0.05). Male survivors were significantly less likely to be married (OR=0.7;95%CI:0.5,0.9) compared to the general population.

Health services use

Compared to the general population, survivors of WT were significantly more likely to attend hospital outpatients (OR=2.6;95%CI:2.2,3.1) at least once in the last 3 months, be hospitalised as a day patient (OR=1.7;95%CI:1.3,2.1) at least once in the last year and be hospitalised as an inpatient (OR=2.0;95%CI:1.6,2.6) at least once in the last year. When stratified by whether WT survivors were on long-term hospital follow-up in relation to their childhood cancer or its treatment, survivors not on long-term hospital follow-up (N=546) were still significantly more likely to be hospitalised as an outpatient (OR=2.1;95%CI:1.7,2.6), day patient (OR=1.5;95%CI:1.1,2.0) and inpatient (OR=1.9;95%CI:1.4,2.6) compared to the general population; whilst survivors on such long-term hospital follow-up (N=360) were even more likely to be hospitalised as an outpatient (OR=3.5;95%CI:2.7,4.6), day patient (OR=1.9;95%CI:1.3,2.7) and inpatient (OR=2.3;95%CI:1.6,3.5).

Discussion

New findings include the identification of a substantial increase in cumulative mortality due to causes of death other than recurrence in the period from 30 to 50 years after WT diagnosis increasing from 5.4% to 22.7%, corresponding to 1 extra death per 100 survivors per year. Consistent with our study, a previous US based large-scale study[3] found that cumulative mortality at 30 years from WT diagnosis was approximately 3%, but thus far—to our knowledge—no study has demonstrated the substantial increase in mortality from 30 to 50 years from WT diagnosis. The excess of deaths after 30 years was mainly attributable to SPNs (50%) and cardiac (25%) related deaths which together accounted for 75% of all excess deaths. The absolute excess risk for the first 30 years following diagnosis is consistent with that found in the National Wilms' Tumor Study[29]; but this study also did not have sufficient follow-up to demonstrate a substantial increase in the absolute excess risk beyond 30 years from diagnosis as observed in the present study.

The excess of SPNs during the initial 30 years from WT was comparable to that reported in previous studies[6,30]. Beyond 30 years from WT, previous studies had insufficient follow-up to satisfactorily assess evidence for an excess. Our cumulative risk increased from 3.7% by 30 years to 16.4% by 50 years. Beyond 30 years from WT there were 4.5 excess cancers observed per 1,000 per year, this excess was mainly attributable to digestive cancers (41%) and breast cancers (7%) – together accounting for 48% of the total excess of cancers. All WT survivors who developed a digestive SPN had received abdominal radiotherapy and all survivors who developed breast cancer received either abdominal or chest radiotherapy. We have previously reported the strong link between abdominopelvic irradiation and subsequent bowel cancer[31], specifically the risk of developing bowel cancer among childhood cancer survivors treated with direct abdominopelvic irradiation is at least that observed among individuals who have at least 2 first-degree relatives diagnosed with bowel cancer, and for whom colonoscopy is currently

recommended from ages 35 to 45[32] or from age 50[33]. This raises the serious question of whether irradiated Wilms' survivors, which comprise the majority of childhood cancer survivors treated with direct abdominopelvic irradiation, should be similarly recommended for colonoscopy.

Previous studies have shown that survivors of WT reported adverse health-status outcomes comparable to our study[3,34], that is, lower general health perception and physical function. In addition, WT survivors also reported lower overall health-status in previous studies[15,35-37]. WT survivors in our study reported that role-emotional was significantly higher than OHLS, however, this is likely due to ceiling effects as role-emotional were measured by 3 categories causing a clustering of scores at the maximum level[38].

Consistent with previous studies[7-9,14,39], completed pregnancies were more likely to be premature and result in low birth weight. The results of the current and previous studies suggest that female survivors treated with abdominal radiation should be carefully monitored during pregnancy.

With respect to social outcomes, and consistent with previous studies, WT survivors appear to have a healthier life style being less likely a regular smoker[40,41] and consuming lower amounts of alcohol than the general population. Similar to a previous study, male survivors were less likely to be married than the general population[42].

WT survivors were more likely to visit the hospital and also were more likely to be hospitalised irrespective of whether they were on regular long-term hospital follow-up in relation to their childhood cancer or its treatment, a finding that is similar to previous studies[3,43].

Study Limitations

A limitation of our study was the lack of detailed information on radiotherapy and chemotherapy exposures given for WT. It is also important to acknowledge that survivors included in the cohort were treated between 1940 and 1991 and hence our findings are unlikely to be generalisable to survivors treated in more recent years due to changes in exposure to different treatments. For example, the vast majority (82%) of the survivors presented here had received radiotherapy as part of initial treatment. In contrast, only 27% of non-anaplastic Wilms' tumour patients included within a relatively recent randomised clinical trial (UKW3)[44], which recruited between 1991 and 2001, received radiotherapy as part of initial treatment. Nevertheless there are still an entire cohort of survivors being seen in follow-up clinics, or discharged into the community, who were treated before 1991 and our evidence relates directly to them.

Conclusion

Between 30 and 50 years from diagnosis, survivors of WT are at a substantially increased risk of premature mortality and 75% of the excess deaths were accounted for by SPNs and cardiac diseases. Radiotherapy exposure was a risk factor for both outcomes. The proportion of WT patients exposed to radiotherapy has reduced substantially in recent decades, from initiatives like the SIOP WT 2001 clinical trial which sought to reduce late effects[44]. However the majority of current survivors, at least 30 years from diagnosis, received radiotherapy. Surveillance of this group should focus on SPNs (particularly bowel and breast cancers) and cardiac conditions as these account for 50% and 25% of the total excess deaths observed, respectively.

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Tables and Figures

Table 1. Characteristics of all 1,441 Wilms' tumour (WT) survivors in the British Childhood Cancer Survivor Study and of all those who completed a questionnaire.

		All WT Survivors (N = 1,441)	Completed Questionnaire Returned (N = 947)	No Completed Questionnaire Returned (N = 494)
Sex	Male	733 (51%)	436 (46%)	297 (60%)
	Female	708 (49%)	511 (54%)	197 (40%)
Age at Diagnosis (years)	Mean	3.3	3.3	3.3
	Median	2.8	2.9	2.7
	0 – 4	1156 (80.2%)	760 (80.3%)	396 (80.2%)
	5 – 9	252 (17.5%)	166 (17.5%)	86 (17.4%)
	10 – 14	33 (2.3%)	21 (2.2%)	12 (2.4%)
Age at Questionnaire Completion[1] (years)	Mean	n/a	28.3	n/a
	5 – 9	n/a	0 (0.0%)	n/a
	10 – 19	n/a	221 (23.3%)	n/a
	20 – 29	n/a	350 (37.0%)	n/a
	30 – 39	n/a	261 (27.6%)	n/a
	40 – 49	n/a	90 (9.5%)	n/a
	50 – 59	n/a	22 (2.3%)	n/a
	60+	n/a	3 (0.3%)	n/a
Years from WT diagnosis[2] (years)	5-9	30 (2.1%)	0 (0.0%)	30 (6.1%)
	10-19	94 (6.5%)	27 (2.9%)	67 (13.6%)
	20-29	349 (24.2%)	234 (24.7%)	115 (23.3%)
	30-39	652 (45.2%)	455 (48.0%)	197 (39.9%)
	40+	316 (21.9%)	231 (24.4%)	85 (17.2%)
On long-term hospital follow up[3]	Yes	n/a	360 (38.3%)	n/a
	No	n/a	546 (58.0%)	n/a
	Missing	n/a	35 (3.7%)	n/a
Treated with abdominal radiotherapy	Yes	756 (52.5%)	489 (51.7%)	267 (54.1%)
	No	164 (11.4%)	111 (11.7%)	53 (10.7%)
	Missing	521 (36.1%)	347 (36.6%)	174 (35.2%)
Treated with chemotherapy	Yes	701 (48.6%)	460 (48.6%)	241 (48.8%)
	No	203 (14.1%)	125 (13.2%)	78 (15.8%)
	Missing	537 (37.3%)	362 (38.2%)	175 (35.4%)
Surgery	Yes	921 (63.9%)	598 (63.2%)	323 (65.4%)
	No	13 (0.9%)	9 (0.9%)	4 (0.8%)
	Missing	507 (35.2%)	340 (35.9%)	167 (33.8%)

[1] The BCCSS questionnaire was sent out to survivors aged 16 or over.

[2] Years of follow-up after initial diagnosis; percentages correspond to the total number in cohort or completed questionnaire.

[3] Regular hospital follow-up appointments in relation to the childhood cancer or its treatment.

Table 2. Cause-specific standardised mortality ratios (SMRs) and absolute excess risks (AERs) for 1,441 survivors of Wilms tumour.

Cause of death	Obs/Exp	SMR (95%CI)	AER (95%CI)‡	% of Total AER
All Causes	146 / 26.8	5.4 (4.6 , 6.4)	30.7 (24.6, 36.8)	100%
OverallYears from diagnosis				
5 – 9 Years	25 / 1.6	15.7 (10.2, 23.2)	36.2 (21.0, 51.3)	
10 – 19 Years	29 / 6.1	4.8 (3.2, 6.9)	16.5 (8.9, 24.0)	
20 – 29 Years	37 / 6.8	5.5 (3.8, 7.5)	21.1 (11.1, 31.1)	
30 – 39 Years	27 / 5.9	4.6 (3.0, 6.6)	38.2 (19.8, 56.7)	
40+ Years	28 / 6.5	4.3 (2.9, 6.3)	92.7 (48.1, 137.4)	
Infection	5 / 0.6	8.7 (2.8 , 20.2)	1.1 (0.0, 2.3)	4%
Recurrence	25 / 0	-	6.4 (3.9, 9.0)	21%
SPN	44 / 6.0	7.3 (5.3 , 9.8)	9.8 (6.4 , 13.1)	32%
Blood	0 / 0.1	NA	0.0 (NA)	0%
Endocrine	0 / 0.6	NA	-0.1 (-0.1, -0.1)	0%
Mental	1 / 0.9	1.1 (0.0 , 6.2)	0.0 (-0.5, 0.5)	0%
Nervous	3 / 1.3	2.2 (0.5 , 6.6)	0.4 (-0.4, 1.3)	1%
Cardiac	25 / 2.5	10.1 (6.5 , 14.9)	5.8 (3.3, 8.3)	19%
Respiratory	6 / 1.2	4.9 (1.8 , 10.7)	1.2 (0.0, 2.5)	4%
Digestive	6 / 1.5	3.9 (1.4 , 8.5)	1.2 (-0.1, 2.4)	4%
Muscoskeletal	0 / 0.2	NA	0.0 (NA)	0%
Genitourinary	6 / 0.2	33.1 (12.2 , 72.1)	1.5 (0.3 , 2.7)	5%
Perinatal	2 / 0.7	3.0 (0.4 , 10.8)	0.3 (-0.4 , 1.1)	1%
External	19 / 9.6	2.0 (1.2 , 3.1)	2.1 (0.2 , 4.6)	7%
Other	4 / 1.4	2.9 (0.8 , 7.3)	0.7 (-0.3 , 1.8)	2%

Calculation of SMR for deaths due to recurrence of Wilms' tumour would not be appropriate since the expected mortality rate in the general population would be 0. AER for recurrence was calculated as the incidence rate per 10,000 person-years. Confidence intervals for SMR were calculated using the approximate method where the number of deaths≥100 and the Poisson exact method where number of deaths<100 [45]. Perinatal deaths refer to cause congenital abnormalities (2). External causes of death comprise accidents (7 motor accidents and 5 accidental poisoning), suicides (2) and other (one death could not be determined as accident or suicide and one death was due to a medical procedure). Other causes of death were either unknown or ill-defined (2) or due to general symptoms (1)and stroke (1). ‡ Overall AER for all causes of death was 30.7 per 10,000 person-years, but due to rounding, the specific causes of death sum to 30.4.

Table 3. AER of specific causes of death by years of follow-up as a proportion of total absolute excess risk.

Cause of Death	AER < 30 Years from diagnosis			AER ≥ 30 Years from diagnosis		
	Obs/Exp	AER (95%CI)	% of Total AER	Obs/Exp	AER (95%CI)	% of Total AER
Recurrence	25 / 0	7.2 (4.4-10.0)	34%	0 / 0	0.0 (NA)	0%
SPN	18 / 2.8	4.4 (2.0-6.8)	21%	26 / 3.2	53.8 (30.2-77.4)	50%
Cardiac	12 / 0.9	3.2 (1.2-5.2)	15%	13 / 1.5	27.0 (10.3-43.7)	25%
External	14 / 8.3	1.6 (-0.5-3.7)	7%	5 / 1.2	8.9 (-1.4-19.2)	8%
All Other Causes	22 / 5.5	5.0 (2.3-7.7)	23%	11 / 2.9	19.1 (3.8-34.4)	17%
All Deaths‡	91 / 17.8	21.2 (15.8-26.6)	100%	55 / 9.0	108.4 (74.1-142.7)	100%

Absolute Excess Risks presented per 10,000 person-years. ‡ AER for all causes of death was 21.2 per 10,000 person-years prior to 30 years from diagnosis and 108.4 per 10,000 person-years poster 30 years from diagnosis, but due to rounding the specific causes of death sum to 21.4 and 108.8 respectively.

Table 4. SIRs and AERs for developing specific SPNs after Wilms' tumour

Outcome	Obs/Exp	SIR (95%CI)	AER (95%CI)[1]	AER (95%CI)[1], (N) < 30 Years from diagnosis	AER (95%CI)[1], (N) ≥ 30 Years from diagnosis
All	71/15.1	4.7 (3.7-5.9)	16.6 (11.7-21.5)	11.8 (7.4-16.1) (41)	44.6 (23.0-66.3) (30)
Digestive[2]	17/1.3	13.0 (7.6-20.9)	4.7 (2.3-7.1)	2.3 (0.5-4.1) (7)	18.2 (5.7-30.7) (10)
Genitourinary	9/3.5	2.6 (1.2-4.9)	1.6 (-0.1-3.4)	1.8 (0.0-3.6) (7)	0.5 (-5.1-6.1) (2)
Breast	9/2.9	3.1 (1.4-5.8)	1.8 (0.1-3.5)	1.5 (-0.4-1.8) (5)	3.3 (-4.6-11.2) (4)
Bone	6/0.3	20.6 (7.5-44.8)	1.7 (0.3-3.1)	1.6 (0.1-3.2) (5)	2.0 (-2.0-5.9) (1)

[1] indicates that AER is shown per 10,000 person – years. 30 other SPNs include: soft tissue sarcoma (6), unknown primary site (5), glioma (3), leukaemia (3), NHL (3), thyroid (3), melanoma (2), adrenal (1), Hodgkin's lymphoma (1), mesothelioma (1), leiomyosarcoma (1) and oral (1). [2]The 17 digestive SPNs comprise: Bowel (7), Retroperitoneum/Peritoneum (4), Liver (2), Pancreas (1), Small Intestine (1), Pyloric Antrum (1) and Unknown Digestive Site (1).

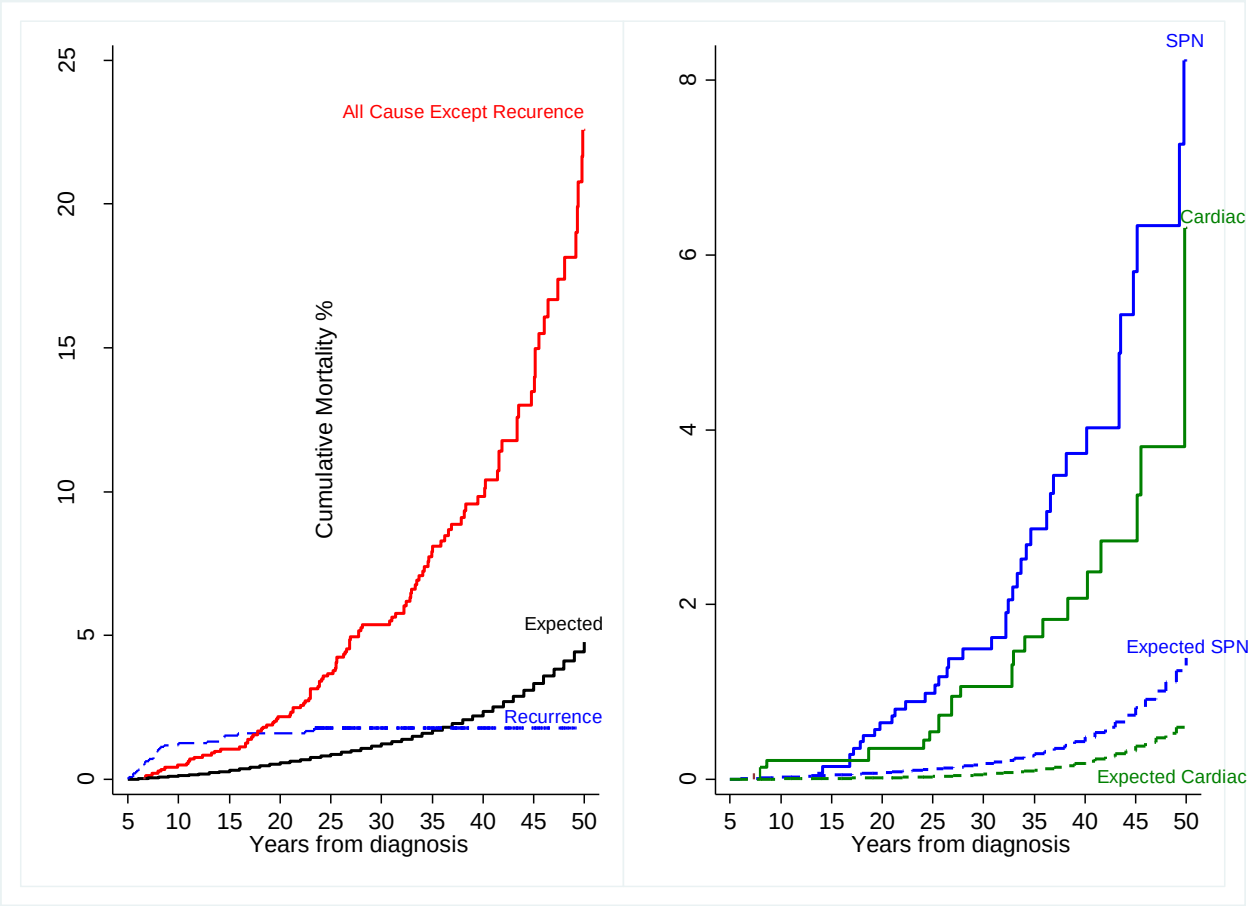

Figure 1. Observed and expected cumulative mortality among 1,441 survivors of Wilms' tumour.

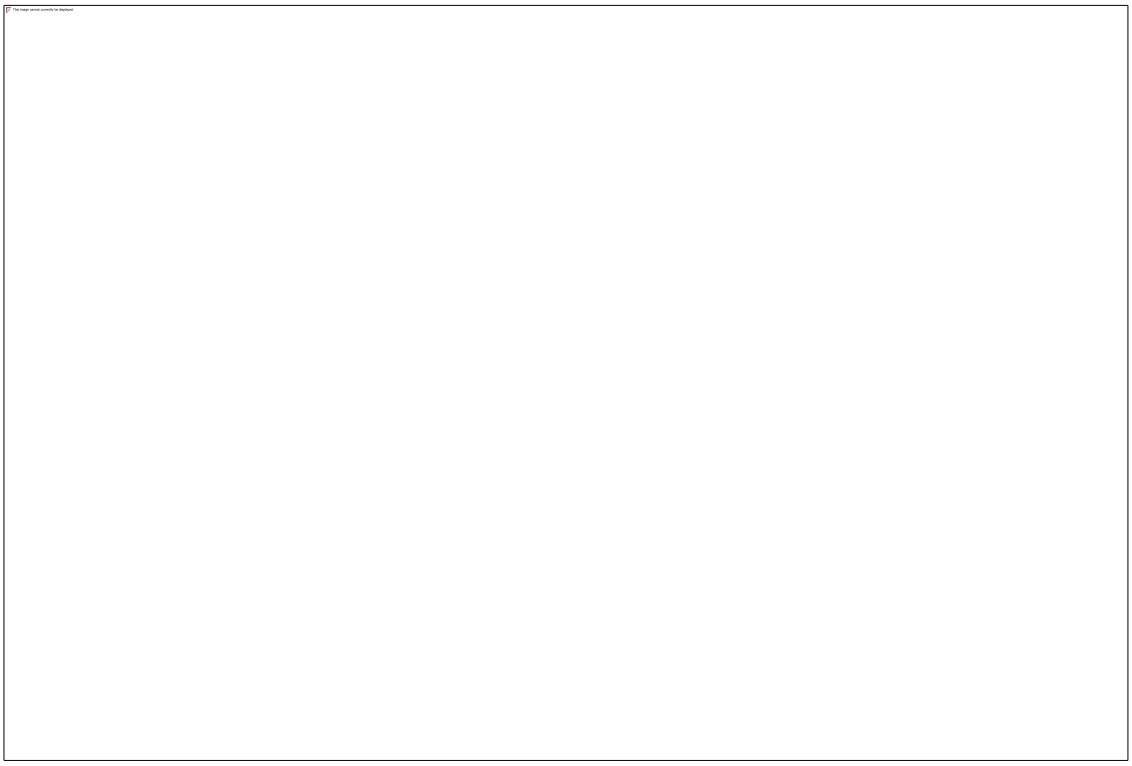

Figure 2. Observed and expected cumulative incidence of developing a SPN among 1,441 survivors of Wilms' tumour with 95% Confidence Intervals.