## Title

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# Second Malignant Neoplasms among Children, Adolescents and Young Adults with Wilms Tumor

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## Abstract

**Background—**The goal of this study was to describe the incidence, characteristics, and outcomes of secondary malignant neoplasms (SMN) in survivors of Wilms tumor.

**Procedures—**Patients who were 0-20 years of age at time of primary diagnosis with Wilms tumor and reported to the Surveillance, Epidemiology, and End Results [SEER] program between 1973 and 2011 were eligible for inclusion in the cohort. We used competing risks methods to estimate the cumulative incidence of SMNs and assess contributing factors for developing SMN. We estimated standardized incidence ratios (SIR), absolute excess risk and overall survival after SMN using standard methods.

**Results—**Within the SEER database, 2,851 patients were diagnosed with Wilms tumor as their first malignancy. Of these, 34 patients were reported to have a SMN. Cumulative incidence of for a secondary malignancy was 0.6% (95% confidence interval [95% CI] 0.3-1.0%) at 10 years, 1.6% (95% CI 1.0-2.3%) at 20 years, and 3.8% (95% CI 2.4-5.9%) at 30 years. Median time from primary diagnosis to SMN diagnosis was 12.5 years. SIR for SMN for survivors of Wilms tumor was 3.4 (95% CI 2.2-4.9) with an absolute excess risk of 7.6 per 10,000 persons per year. Exposure to radiation did not significantly increase risk for development of second malignancy. Overall survival for patients with SMN was 64.5% at 5 years.

**Conclusion—**Survivors of Wilms tumor are at an increased risk of SMN compared to the general population, but the added risk is relatively small compared to other pediatric cancers.

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Conflict of Interest: None

## Introduction

Wilms tumor is the most common renal malignancy of childhood with an incidence of about 500 new cases per year in the United States. About 5% of pediatric cancers are Wilms tumors.[1] The treatment paradigm has evolved over time. Surgery, first described as early as the 19th century, remains an essential aspect of care. Radiation therapy was first used for treatment in the early 20th century and continues to play an important role in advanced disease. Chemotherapy was first introduced in the 1960s and now most patients receive chemotherapy as part of their risk based regimen as determined by their stage and histology.[2,3] With current multi-modal therapy, more than 90% of children diagnosed with Wilms tumor are expected to be long-term survivors.[4]

Cancer survivors are monitored long term for the development of a secondary malignant neoplasm (SMN). A series of reports of survivors of Wilms tumor estimate the 10-year cumulative incidence of SMN between 0-1%.[5-8] About 4% to 17% of Wilms tumors are reported to be associated with other abnormalities or with a predisposition syndrome which may make them more susceptible to second malignancy.[9] Patients are also exposed to cytotoxic therapy and, potentially, to radiation as a part of their treatment regimen. In addition, the high cure rates for Wilms tumor result in the majority of patients surviving for many decades after diagnosis during which they carry a risk of second malignancy.

We utilized the Surveillance, Epidemiology, and End Results (SEER) Program database, a large public registry, to evaluate the risk of SMN after treatment of primary Wilms tumor. The aims of this study were to estimate the incidence of SMN, to describe the clinical features and potential risk factors, and to determine the outcomes after development of SMN in survivors of Wilms tumor.

## Methods

### Patients and Case Definition

Patient information was obtained from the SEER database of the United States National Cancer Institute, which included data from 1973 to 2011.[10] The SEER system includes 18 registries from around the US, representing ~28% of the US population. The SEER registries include data from 11 states and 2 additional metropolitan areas. The SEER program routinely collects data on patient demographics, primary tumor site, tumor morphology, tumor size, tumor extension and metastasis, stage at diagnosis, limited treatment data such as radiation and surgical intervention, and survival data.

Patients, between 0 and 20 years of age, diagnosed with Wilms tumor as a first primary tumor and reported to SEER between 1973 and 2011 were eligible for inclusion in our cohort. The limits of age were chosen to capture cases of Wilms tumor in children and adolescents, while excluding adults who may have a biologically different type of nephroblastoma. The cohort included 2,861 patients. Of these patients, 7 patients without secondary malignancy had unknown survival data, so were excluded from the analyses, leaving a cohort of 2,854.

Classification as a primary Wilms tumor was determined using the sequence number field in SEER. Wilms tumor was identified in the SEER database by searching for histology labeled as “Nephroblastoma, NOS”. Of the 2,854 patients with Wilms tumor, 37 patients had a potential SMN. To include only patients with a clear SMN, patients diagnosed with a malignancy concurrent to their Wilms tumor or who developed a malignancy within 6 months of their Wilms tumor diagnosis (n = 2) were excluded from the cohort. Any patients with primary nephroblastoma reported to have a second nephroblastoma at a later time (n = 1) were not considered to have a SMN as it was not possible to determine if the second nephroblastoma was a recurrence or an independent second malignancy. These 3 patients were excluded from all analyses. After these exclusions, our cohort included 2,851 patients with Wilms tumor of whom 34 patients were considered to have SMN.

## Analytic Variables

Evaluated risk variables included age, sex, year/era of diagnosis, race, exposure to radiation therapy, surgical intervention, stage, location of Wilms tumor, and tumor size. Stage was extrapolated from available information relating to extension, lymph nodes and metastasis. For staging purposes, patients were given a stage based on the Children’s Oncology Group Staging System.[11] In order to assign a stage, it was assumed that the tumor was completely resected without tumor spillage, as these surgical variables are not specifically recorded in the SEER database. Primary outcomes included cumulative incidence of SMN and overall survival after SMN.

## Analytic Approach

Cumulative incidence of SMNs was calculated using the competing risks method of Coviello and Boggess in which death prior to SMN was a competing risk.[12] Subhazard ratio of each patient characteristic was calculated using a competing risks method of Fine and Gray in which death prior to SMN was a competing risk.[13] Overall survival from the time of diagnosis of SMN was estimated using Kaplan Meier methods, with surviving patients censored at the time of last follow-up.

Standardized incidence ratios (SIR) and excess risk were calculated within the SEER database. SIR calculations utilize data from only 9 of the 18 available SEER registries, as only 9 SEER registries have data extending back to 1973.[14] These 9 registries include a subset of the patients with second malignancies in our cohort (n = 26). SIR calculations are adjusted for gender, race, age, and calendar year. Absolute excess risk within SEER is displayed as the excess cancers per 10,000 persons per year which is calculated as follows ((Observed count - Expected count) x 10,000) / Person years at risk.

The SEER database was accessed using SEER*Stat version 8.1.5. Statistical analyses were performed using STATA, version 13.0 and SEER*Stat version 8.1.5.[10,14,15]

## Results

### Demographics

The 2,851 patients with Wilms tumor had a median age at diagnosis of 3.0 years (range, 0-20 years). Median length of follow-up was 7.9 years (range, 0-39 years). Within the cohort, 608 patients were Stage 1, 723 patients were Stage 2, 388 patients were Stage 3, 513 were stage 4, and 182 patients were Stage 5 (bilateral Wilms tumor). There were 437 patients that did not have sufficient data available to assign a stage. Within the cohort, 1,294 patients received radiation therapy and 1,525 received no radiation therapy. There were 32 patients that did not have available radiation data.

### Survival

Among the 2,851 patients with Wilms tumor, overall survival at 10, 20, 30 years from Wilms tumor diagnosis was 87.9% (95% CI 86.6-89.2%), 86.0% (95% CI 84.4-87.5%), and 84.0% (95% CI 81.9-85.8%), respectively. Of the 2,851 patients, 2,485 patients were alive at last follow-up without development of SMN and 332 patients died prior to the development of SMN. Of these patients, 276 died from their Wilms tumor or associated complications. Overall survival at 10 years for patients with Wilms tumor classified as Stage 1, Stage 2, Stage 3, Stage 4, Stage 5 was 95.5% (95% CI 93.0-97.2%), 93.2% (95% CI 90.8-95.0%), 85.0% (95% CI 80.6-88.4%), 75.3% (95% CI 70.8-79.1%), 80.8% (95% CI 73.4-86.4%), respectively.

### Incidence of Second Malignancies after Wilms tumor

The cumulative incidence of SMN was 0.6% (95% CI 0.3-1.0%) at 10 years, 1.6% (95% CI 1.0-2.3%) at 20 years, and 3.8% (95% CI 2.4-5.9%) at 30 years after initial diagnosis of Wilms tumor (Figure 1). Compared to the general population, patients with Wilms tumor were at a 3.4 fold increased risk of developing a secondary malignancy of any type (SIR 3.4, 95% CI 2.2-4.9) from 1973-2011 (Table I). The absolute excess risk was 7.6 per 10,000 persons per year. These patients were at significantly higher risk of developing a soft tissue (SIR 11.4, 95% CI 2.4-33.4), colon (SIR 14.1, 95% CI 1.7-51.1), liver (SIR 34.7, 95% CI 4.2-125.5), and thyroid malignancy (SIR 4.4, 95% CI 1.2-11.3) than the general population. Interestingly, they were not more likely to develop a breast cancer or leukemia than the general population. Though there was not a significant increased risk of developing a hematologic malignancy when all types of hematologic malignancies were taken together, patients were at significantly higher risk of developing acute myeloid leukemia (SIR 10.9, 95% CI 1.3-39.3).

### Features of Second Malignancies after Wilms Tumor

The median latency from diagnosis of Wilms tumor to diagnosis of the SMN was 12.5 years (range 1-35). Median time from primary diagnosis to SMN by type of secondary malignancy can be seen in Table II. The median age of diagnosis of a SMN was 18 years (range 3-42).

The SMNs included thirty solid SMNs and four hematologic malignancies. The types of SMN can be broken down as follows: connective tissue/bone (29%), thyroid carcinoma

(15%), nervous system (15%), leukemias (12%), gastrointestinal system (12%), carcinoma of the breast (9%), renal system (6%), genitourinary system (3%) (Table II).

Among the 34 patients with SMN, 4 patients had multiple subsequent neoplasms. The types of third malignancies included lymphoblastic leukemia (n=1), malignant peripheral nerve sheath tumor (n=2), spindle cell sarcoma (n=1) and mesothelioma (n=1). One patient developed a fourth malignancy, papillary carcinoma of the bladder. The following combinations of multiple subsequent neoplasms were seen: myxoid liposarcoma and precursor cell lymphoblastic leukemia; pilocytic astrocytoma and malignant peripheral nerve sheath tumor; fibrous histiocytoma and mesothelioma of the peritoneum; renal cell carcinoma, malignant peripheral nerve sheath tumor and papillary carcinoma of the bladder

### Predictors of Second Malignancy Following Wilms Tumor Diagnosis

To identify potential risk factors for developing a SMN, we compared the clinical features of patients with Wilms tumor with SMN to patients with Wilms tumor without SMN (Table III). Patients who were diagnosed with Wilms when they are older (i.e., 11-20 years old) were more likely to develop SMN. The development of SMN did not differ based on sex, year/era of diagnosis, race, exposure to radiation therapy, stage, Wilms primary site, and Wilms maximum dimension. Of note, bilateral Wilms disease was not associated with an increased rate of SMN. In addition, we investigated whether radiation exposure increased the risk of SMN and observed no difference for patients treated with or without radiation (Figure 2; p-value = 0.11). The cumulative incidence of SMN for patients with radiation was 0.7% (95% CI 0.3-1.5%) at 10 years, 2.0% (95% CI 1.1-3.4%) at 20 years, and 4.4% (95% CI 2.5-7.1%) at 30 years after initial diagnosis of Wilms tumor, and for patients who did not receive radiation was 0.3% (95% CI 0.1-0.9%) at 10 years, 0.8% (95% CI 0.3-1.6%) at 20 years, and 3.1% (95% CI 1.1-6.7%) at 30 years (Figure 2). However, the small numbers preclude any definitive conclusion regarding the risk of these potential factors.

### Survival after Second Malignancy

The estimated 5-year overall survival rate of the patients with Wilms tumor after diagnosis of the SMN was 64.5% (95% CI 43.4-79.5%) (Figure 3). Median length of follow-up was 2.6 years (range 0-24.6 years).

## Discussion

The treatment for Wilms tumors has evolved over time, improving the prognosis for children with Wilms tumor. The 10-year cumulative incidence of SMN of 0.6% (95% CI 0.3-1.0%) at 10 years was similar to several previous reports. In 1987, the National Wilms Tumor Study (NWTS) published a SMN cumulative incidence of 1% at 10 years with SIR of 8.5.[5] The International Society of Pediatric Oncology (SIOP) published a SMN cumulative incidence of 0.65% at 10 years and SIR of 4.15, with no SMN reported after 10 years.[6] St Jude Children's Research Hospital Childhood Cancer Survivor Study reported a 0.3% cumulative incidence of SMN at 10 years for all kidney tumors, the large majority being Wilms tumor. SMN cumulative incidence continued to increase at 20 and 30 years to 1.5% and 3.9% respectively.[8] A subsequent study from St Jude Children's Research

Hospital looking specifically at Wilms tumor reported a 3.0% cumulative incidence of SMN at 25 years and SIR of 3.4.[16] The British Childhood Cancer Survivor Study followed patients diagnosed from 1940-1991 and showed a cumulative incidence for solid SMN of 0% at 10 and 20 years, 2.3% at 30 years and 6.8% at 40 years. The SIR for solid malignancies was 6.7 for all patients, with a specific SIR for solid second malignancy in the 1970s-1990s ranging from 8.3-8.8.[7] Breslow et al published data of the largest cohort of patients with Wilms tumor, which included patients from North America, the UK and the Nordic countries totaling over 13,000 patients. They found that among patients who survived to age 15 with no SMN, the cumulative incidence of solid SMN by age 40 was 6.7%. In contrast, the incidence of leukemia was greatest during the first 5 years after treatment. SIR was 5.1 for solid tumors and 5.0 for leukemias. [17] Within our database, we found that leukemias similarly occurred within 5 years of initial Wilms diagnosis, with a median time of 3 years. Solid malignancies occurred a median of 9 years after diagnosis of the primary tumor.

Many previous papers noted that many of the SMN developed within the irradiation field, such as breast cancer. Moreover, radiation exposure is shown to cause thyroid cancers, the most common SMN in patients with Wilms tumor. In our cohort, of the patients who developed breast cancer, all 3 patients received beam radiation. Of the patients who developed thyroid cancer, 4 of them had received beam radiation and 1 did not receive any radiation. See Table II for further details about radiation exposure by type of SMN. However, our analysis did not find that radiation exposure was associated with the development of SMN. It is possible that the lower doses of radiation that are now used for treatment decreases the risk of SMN for more recently treated patients. In the 1970s and 1980s, the National Wilms Tumor Study (NWTS) trials found that Stage I and II with favorable histology did not need post-operative radiation therapy, and the dose utilized for Stage III Wilms Tumor was decreased from 20 Gy to 10 Gy.[3,18] However, our analysis did not find any significant difference in treatment era. Alternatively, the risk of radiation related SMN may become more apparent with longer follow-up.

Though we were unable to determine the presence of specific genetic syndromes (i.e., Beckwith–Wiedemann syndrome, WAGR syndrome), some patients with SMN exhibited malignancies commonly associated with these syndromes: gonadoblastoma (3 patients), hepatoblastoma (2 patients). WT1 gene alterations seen in Wilms tumor can be associated with increased risk of SMN.[17] The prevalence of bilateral Wilms is higher in individuals with genetic predisposition syndromes than those individuals without.[19] However, as noted above, our data did not show a significant increase in SMN for patients with bilateral Wilms.

Data analysis using the SEER registry has several advantages. First, the SEER registry provides a heterogeneous group of patients with Wilms tumor from across the United States and is not limited to patients enrolled in clinical trials. Also, the database includes a large number of patients with Wilms tumor allowing statistical analyses to potentially identify risk factors for developing SMN. The SEER registry spans over 4 decades permitting longitudinal evaluation of SMN risk. Finally, our study included SMNs of all types.

However, data analysis using the SEER registry has some inherent limitations. The SEER database lacks specific surgical information regarding completeness of resection and tumor spillage, factors that directly affect local staging and treatment. Furthermore, SEER does not include information about whether a patient received chemotherapy as part of their treatment nor what type of chemotherapy received. The SEER database also does not indicate if patients were treated on NWTS or SIOP protocols. Also, the SEER database only indicates if the patient received radiation, without specifying the dose or location, thus we are unable to correlate it with the location of SMN. The de-identified nature of the SEER database does not allow us to contact patients to determine exact details of their treatment course. This de-identified nature also prevents us from gathering family history data, which may indicate whether or not some of the patients we captured had a genetic predisposition to a SMN, such as Beckwith-Weidemann or WAGR syndrome. Large databases can have a variable amount of follow-up, which can be seen in our cohort where the median follow-up is shorter than the median latency. Thus, it is possible that SMNs are underrepresented in our database. Also, the patient population used to calculate the SIR was a subset of the total available population, as only 9 registries had data that spanned the entire 4 decades. However, this smaller subset was still able to capture 76% of the patients with Wilms tumor and SMNs identified in our analysis.

The overall incidence of SMN in Wilms is less than that of other pediatric cancers. In comparison, a recent paper about SMN in neuroblastoma from St Jude Children's Research Hospital reported a cumulative incidence of 2.6% at 20 years and 4.6% at 30 years.[20] However, our results indicate that survivors of Wilms tumor are still at risk of SMN. Survivors of Wilms tumor should continue to be screened for SMN throughout life, with an emphasis on connective tissue/bone, thyroid, nervous system, GI and blood malignancies. Early identification of secondary malignancies may lead to better long-term survival.

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## References

1. Friedman AD. Wilms tumor. Pediatrics in review / American Academy of Pediatrics. 2013; 34(7): 328–330. discussion 330. [PubMed: 23818087]
2. Pietras W. Advances and changes in the treatment of children with nephroblastoma. Advances in clinical and experimental medicine : official organ Wroclaw Medical University. 2012; 21(6):809–820. [PubMed: 23457141]
3. Green DM. The evolution of treatment for Wilms tumor. Journal of pediatric surgery. 2013; 48(1): 14–19. [PubMed: 23331787]
4. Cotton CA, Peterson S, Norkool PA, Takashima J, Grigoriev Y, Green DM, Breslow NE. Early and late mortality after diagnosis of wilms tumor. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009; 27(8):1304–1309. [PubMed: 19139431]
5. Breslow NE, Norkool PA, Olshan A, Evans A, D'Angio GJ. Second malignant neoplasms in survivors of Wilms' tumor: a report from the National Wilms' Tumor Study. Journal of the National Cancer Institute. 1988; 80(8):592–595. [PubMed: 2836600]

6. Carli M, Frascella E, Tournade MF, de Kraker J, Rey A, Guzzinati S, Burgers JM, Delemarre JF, Masiero L, Simonato L. Second malignant neoplasms in patients treated on SIOP Wilms tumour studies and trials 1, 2, 5, and 6. Medical and pediatric oncology. 1997; 29(4):239–244. [PubMed: 9251727]
7. Taylor AJ, Winter DL, Pritchard-Jones K, Stiller CA, Frobisher C, Lancashire ER, Reulen RC, Hawkins MM. British Childhood Cancer Survivor S. Second primary neoplasms in survivors of Wilms' tumour--a population-based cohort study from the British Childhood Cancer Survivor Study. International journal of cancer Journal international du cancer. 2008; 122(9):2085–2093. [PubMed: 18196579]
8. St. Jude Children's Research Hospital. The Childhood Cancer Survivor Study: Baseline Data.
9. Gleason JM, Lorenzo AJ, Bowlin PR, Koyle MA. Innovations in the management of Wilms' tumor. Therapeutic advances in urology. 2014; 6(4):165–176. [PubMed: 25083165]
10. Surveillance, E.; End Results (SEER) Program. SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2013 Sub (1973-2011 varying) - Linked To County Attributes - Total U.S., 1969-2012 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014 (updated 5/7/2014), based on the November 2013 submission.
11. Metzger ML, Dome JS. Current therapy for Wilms' tumor. The oncologist. 2005; 10(10):815–826. [PubMed: 16314292]
12. Coviello V, Boggess MM. Cumulative incidence estimation in the presence of competing risks. Stata Journal. 2004; 4(2):103–112.
13. Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association. 1999; 94:496–509.
14. Surveillance, E.; End Results (SEER) Program. SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2013 Sub (1973-2011) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2012 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014, based on the November 2013 submission.
15. StataCorp. Stata Statistical Software: Release 13. StataCorp LP; College Station, TX: 2013.
16. Termuhlen AM, Tersak JM, Liu Q, Yasui Y, Stovall M, Weathers R, Deutsch M, Sklar CA, Oeffinger KC, Armstrong G, Robison LL, Green DM. Twenty-five year follow-up of childhood Wilms tumor: a report from the Childhood Cancer Survivor Study. Pediatric blood & cancer. 2011; 57(7):1210–1216. [PubMed: 21384541]
17. Breslow NE, Lange JM, Friedman DL, Green DM, Hawkins MM, Murphy MF, Neglia JP, Olsen JH, Peterson SM, Stiller CA, Robison LL. Secondary malignant neoplasms after Wilms tumor: an international collaborative study. International journal of cancer Journal international du cancer. 2010; 127(3):657–666. [PubMed: 19950224]
18. Jairam V, Roberts KB, Yu JB. Historical trends in the use of radiation therapy for pediatric cancers: 1973-2008. International journal of radiation oncology, biology, physics. 2013; 85(3):e151–155.
19. Dome, JSHV. Wilms Tumor Overview. Pagon, RA.; Adam, MP.; Ardinger, HH., et al., editors. University of Washington, Seattle; Seattle (WA): 1993-2014. 2003 Dec 19 [Updated 2013 Sep 19]GeneReviews® [Internet]
20. Federico SM, Allewelt HB, Spunt SL, Hudson MM, Wu J, Billups CA, Jenkins J, Santana VM, Furman WL, McGregor LM. Subsequent malignant neoplasms in pediatric patients initially diagnosed with neuroblastoma. Journal of pediatric hematology/oncology. 2015; 37(1):e6–e12. [PubMed: 24633303]

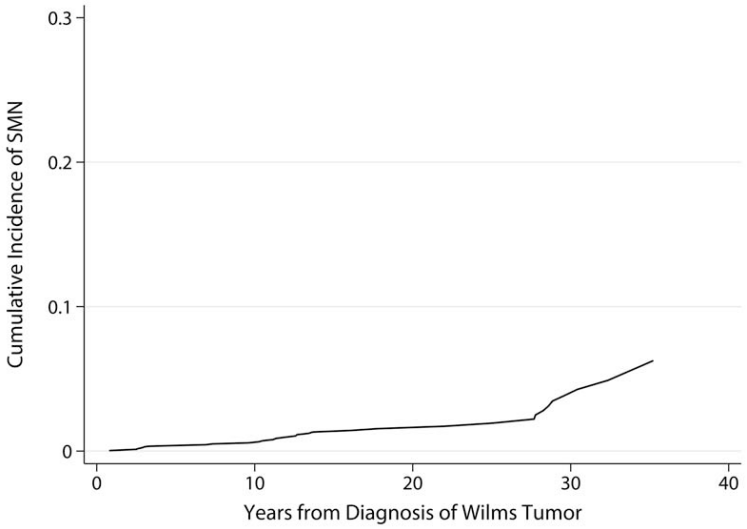


**Figure 1.**

Cumulative incidence of any second malignant neoplasms among all patients with Wilms tumor

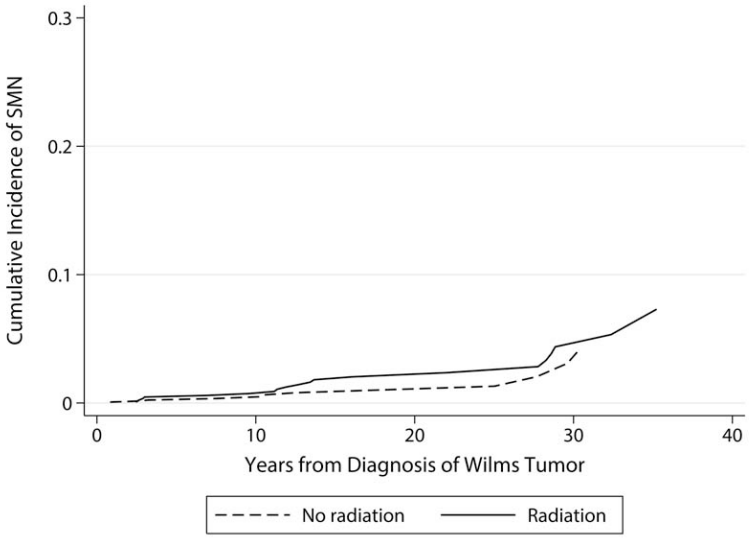


**Figure 2.**

Cumulative incidence of any second malignant neoplasms among patients with Wilms tumor who did and did not receive radiation treatment

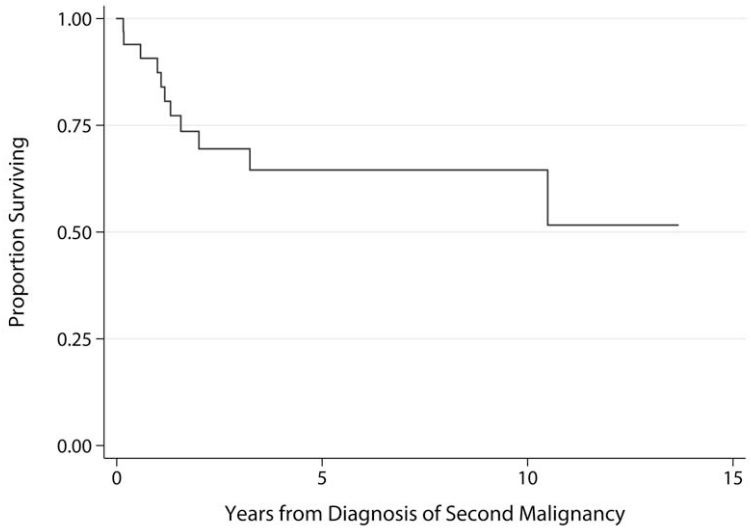


**Figure 3.**
Overall survival for patients with Wilms tumor with second malignant neoplasm

## Table I

Standardized Incidence Ratioof Secondary Neoplasms in Patients with Primary WilmsTumor (1973-2011)

| | n | 1973-2011 | | |
|---|---|---|---|---|
| | | SIR | CI Lower | CI Upper |
| All Sites | 26 | 3.4# | 2.2 | 4.9 |
| Digestive System | 4 | 9.4# | 2.6 | 23.9 |
| Bones and Joints | 1 | 4.6 | 0.1 | 25.6 |
| Soft Tissue | 3 | 11.4# | 2.4 | 33.4 |
| Skin excluding Basal and Squamous | 3 | 3.5 | 0.7 | 10.2 |
| Breast | 3 | 4.5 | 0.9 | 13.0 |
| Female Genital System | 2 | 3.9 | 0.5 | 13.9 |
| Urinary System | 2 | 8.0 | 1.0 | 28.7 |
| Brain and Other Nervous System | 2 | 2.8 | 0.3 | 10.1 |
| Endocrine System | 4 | 4.4# | 1.2 | 11.3 |
| Leukemia | 2 | 2.5 | 0.3 | 9.2 |

#P<0.05CI Confidence Interval, SIR Standardized Incidence Ratio

## Table II

Breakdown of Type of Second Malignant Neoplasm and Median Number of Years until Occurrence of Second Malignant Neoplasm

| Type of SMN | % of Patients who Received Radiation for Treatment of their Primary Tumor* | Median Number of Years Until SMN Occurrence (Range) |
|---|---|---|
| Connective tissue/Bone (n=10) | 50% | 10.5 (3-30) |
| Thyroid (n=5) | 80% | 16 (12-30) |
| Nervous system (n=5) | 40% | 9 (1-13) |
| Gastrointestinal system (n=4) | 100% | 30.5 (13-35) |
| Leukemias (n=4) | 50% | 3 (3-5) |
| Breast (n=3) | 100% | 28 (28-29) |
| Renal system (n=2) | 50% | 10 (2-18) |
| Genitourinary system (n=1) | 0% | 25 |

* Patients who had unknown radiation status were assumed not to have received radiation SMN Second Malignant Neoplasm

## Table III

Characteristics of Patients with Wilms Tumor with and without Secondary Malignant Neoplasms

| Characteristics of Patients with Wilms tumor[1] | Patients with Wilms Tumor, no. of pts (%) | | |
|---|---|---|---|
| | Without SMN | With SMN | |
| | N = 2,817 | N = 34 | |
| Gender | | | |
| Male | 1,315 46.7% | 11 32.4% | p=0.12 |
| Female | 1,502 53.3% | 23 67.6% | |
| Age at Wilms tumor diagnosis (in years) | | | |
| Median, years | 3.0 | 4.5 | |
| 0-1 | 840 29.8% | 5 14.7% | p=0.01 |
| 2-10 | 1883 66.8% | 25 73.5% | |
| 11-20 | 94 3.3% | 4 11.8% | |
| Race | | | |
| Caucasian | 2204 78.6% | 29 85.3% | |
| African-American/African | 453 16.2% | 3 8.8% | p=0.67 |
| Other | 147 5.2% | 2 5.9% | |
| Stage | | | |
| Stage I | 606 25.4% | 2 8.0% | |
| Stage II | 716 30.0% | 7 28.0% | |
| Stage III | 383 16.0% | 5 20.0% | p=0.11 |
| Stage IV | 502 21.0% | 11 44.0% | |
| Stage V | 182 7.6% | 0 0.0% | |
| Radiation | | | |
| Yes | 1273 45.7% | 21 65.6% | p=0.11 |
| No | 1514 54.3% | 11 34.4% | |
| Surgery | | | |
| Yes | 2695 96.4% | 34 100.0% | N/A |
| No | 101 4.6% | 0 0.0% | |
| Size (in mm) | | | |
| 0-100 | 996 45.2% | 5 23.8% | p=0.08 |
| 101+ | 1209 54.8% | 16 76.2% | |
| Laterality | | | |
| Left primary | 1299 46.5% | 14 42.4% | |
| Right primary | 1308 46.8% | 19 57.6% | p=0.07 |
| Bilateral | 187 8.5% | 0 0.0% | |
| Era of diagnosis | | | |
| 1973-1979 | 240 8.5% | 10 29.4% | |
| 1980-1989 | 417 14.8% | 7 20.6% | p=0.62 |
| 1990-1999 | 599 21.3% | 11 32.4% | |
| 2000-2011 | 1561 55.4% | 6 17.6% | |

[1]Patients who did not have data for a specified characteristic were not included in the evaluation for that characteristic. SMN Second Malignancy Neoplasm