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Risk Factors for End Stage Renal Disease in Non-*WT1*-Syndromic Wilms Tumor

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Abstract

Purpose—We assessed risk factors for end stage renal disease (ESRD) in Wilms Tumor (WT) patients without known *WT1*-related syndromes. We hypothesized that patients with characteristics suggestive of a *WT1* etiology (early onset, stromal predominant histology, intralobar nephrogenic rests) would have a higher risk of ESRD due to chronic renal failure (CRF). We predicted a high risk of ESRD due to progressive bilateral WT (PBWT) in patients with metachronous bilateral disease.

Methods—ESRD was ascertained in 100 of 7,950 non-syndromic patients enrolled on a National Wilms Tumor Study during 1969-2002. Risk factors were evaluated with cumulative incidence curves and proportional hazard regressions.

Results—The cumulative incidence of ESRD due to CRF 20 years after WT diagnosis was 0.7%. For ESRD due to PBWT, it was 4.0% at 3 years post-WT diagnosis in patients with synchronous BWT and 19.3% in patients with metachronous BWT. For ESRD due to CRF, stromal predominant histology had a hazard ratio (HR) of 6.4 relative to mixed (95% CI [3.4 11.9], $p < .001$); intralobar rests had a HR of 5.9 relative to no rests (95% CI [2.0, 17.3], $p = .001$); and WT diagnosis <24 months had a HR of 1.7 relative to 24-48 months and 2.8 relative to >48 months ($p = .003$ for trend).

Conclusions—Metachronous BWT is associated with high rates of ESRD due to surgery for progressive WT. Characteristics associated with a *WT1* etiology markedly increased the risk of ESRD due to CRF, despite a low risk in non-*WT1* syndromic patients overall.

Keywords

Kidney Failure, Chronic; Nephrectomy; Wilms Tumor; Genes, Wilms Tumor

Introduction

Treatment advances for Wilms tumor (WT) have greatly improved survival, with cure rates now approaching 90%.¹ Survivors of WT are at increased risk of additional health problems, however, due to direct effects of treatment and to genetic conditions associated with the disease. End-stage renal disease (ESRD) is a particularly serious outcome, and identification of risk factors for ESRD in the WT patient population is a clinically important goal.

A prior National Wilms Tumor Study (NWTs) report estimated that unilateral WT patients had a 20-year cumulative incidence of ESRD of 1.3%; it was 15% for bilateral WT (BWT).² High rates of ESRD were found among patients with the Wilms tumor-aniridia (WAGR) and Denys-Drash (DDS) syndromes and those with associated male genitourinary (GU) anomalies, all caused by germline *WT1* mutations.^{3,4} Over 70% of DDS patients developed early onset ESRD, while approximately 40% of WAGR patients developed ESRD by young adulthood.

The present study investigates risk factors for ESRD in patients without *WT1* associated syndromes, using an expanded NWTs cohort with longer follow-up. We consider separately ESRD due to (1) progressive BWT (PBWT) and (2) chronic renal failure (CRF), the latter encompassing ESRD attributable to other or unspecified etiologies. BWT may be synchronous or metachronous. There is a greater chance of saving part of one kidney and thus preventing renal failure in patients with synchronous disease, who have 2 kidneys when the BWT is diagnosed. Moreover, tumor cells that develop in the contralateral kidney while the patient is undergoing primary treatment may be less likely to respond to further treatment than those responsible for synchronous bilateral disease.⁵ We hypothesized, therefore, that patients with metachronous BWT would experience higher rates of treatment failure leading to ESRD from PBWT than those with synchronous BWT.

Host factors may predispose individuals to non-malignant kidney pathology, and thus to ESRD due to CRF, even if it is an apparent consequence of radiation or chemotherapy. Early age at diagnosis, stromal predominant histology and the presence of intralobar nephrogenic rests (ILNR) are strongly associated in the NWTs cohort.⁶ Since these 3 characteristics are also associated with germline *WT1* mutations,^{7,8} we suggested earlier that they could be markers for a *WT1* etiology.⁹ Here we further hypothesized that these factors were predictors of ESRD due to CRF among patients who did not have known *WT1* related syndromes. We also considered how clinical risk factors were related to ESRD due to PBWT.

Our earlier ESRD study limited the GU anomaly category to hypospadias and cryptorchidism.² These two anomalies were used here as a basis for exclusion due to the presence of a *WT1* associated syndrome. However, we also examined the association between ESRD due to CRF and other genital anomalies, specifically streak ovaries and disorders of sexual differentiation (DSD), that are associated with *WT1* mutations and may represent a forme fruste of DDS.¹⁰

Methods

Study and analysis cohort

The complete cohort consisted of 9,237 patients enrolled by North American institutions on 1 of 5 NWTs protocol studies between October, 1969 and April, 2002.¹¹ The closing date for data acquisition was December 31, 2008. Patients with WAGR syndrome ($n=69$), DDS ($n=37$) or male GU anomalies ($n=217$) were excluded from the non-*WT1*-syndromic cohort. Additional exclusion factors, in order, included WT in an extra-renal site ($n=22$), a missing histology record ($n=276$) or a histologic type recorded as rhabdoid tumor of the kidney, clear cell sarcoma of the kidney or as another rare, indeterminant or non-WT type ($n=665$). The final non-*WT1*-syndromic cohort consisted of 7,950 subjects. Brief results are reported separately for the syndromic patients and those with rare histologic types.

Definition of endpoint

WT patients were considered to have ESRD if they required long-term dialysis or kidney transplant, or if they died of renal failure before treatment for ESRD was initiated ($n=7$, of which 5 WAGR and 1 DDS). ESRD was categorized as due to PBWT if the patient required surgical removal of all kidney tissue as a consequence of PBWT. ESRD occurring in patients with unilateral WT, or in those with BWT who had been in complete remission for at least 1 year with no intervening relapse, was categorized as due to CRF.

Classification of risk factors

Age at WT diagnosis was categorized as 0-23, 24-47, and 48+ months. Favorable histology tumors were classified as blastemal, epithelial or stromal predominant if a corresponding histologic pattern comprised more than 2/3 of the available tumor sections, otherwise as mixed. The few tumors with anaplastic histology were classified as anaplastic regardless of the mixture of cell types. Nephrogenic rests were classified as intralobar, perilobar or none; patients with both types were assigned to intralobar. This factor was available only for patients on NWTs studies 3-5 who had normal kidney tissue available for pathology evaluation.

Statistical methods

Cumulative incidence of ESRD of specific type as a function of time since WT diagnosis was estimated for various patient subgroups, treating death and ESRD due to the other cause as competing events.^{12,13} Cox regression was used to examine relationships between risk factors and ESRD rates, with event times censored by death, loss to follow-up, termination of the study or development of ESRD of the other type. The risk factor analyses for ESRD due to CRF were stratified by unilateral WT vs. BWT; for metachronous BWT the stratification was time-dependent. Stratified regressions of ESRD due to PBWT were restricted to individuals with synchronous BWT or metachronous disease after contralateral relapse. Both single and multiple regressions were examined to determine marginal and adjusted relationships between risk factors and ESRD rates. Tests of proportionality of ESRD rates were reported as significant for $p < .10$. Instantaneous hazards were estimated from cumulative hazards by kernel smoothing with a 5 year bandwidth. All statistical analyses were conducted with R 2.11.14

Results

Patients with *WT1* syndromes

Table 1 shows estimates of cumulative incidence of ESRD at 20 years since WT onset in patient anomaly groups. Thirty of 37 subjects with DDS developed ESRD, 6 prior to or at

the same time as their diagnosis of WT. Among GU anomaly patients, those with both cryptorchidism and hypospadias had the highest cumulative incidence; however, a test for differences in hazard rates across the 3 GU anomaly subgroups was not significant ($p=.25$).

Subjects with unusual or missing histologic types

Eleven cases of ESRD occurred among 941 patients with rare or missing histologic types. Three cases of ESRD due to PBWT occurred in 9 of 45 patients with teratoid histology who had synchronous ($n=7$) or metachronous ($n=2$) BWT. Thirteen patients with intralobar rests, but only 2 with perilobar rests and none with both types, were identified among the 34 patients with teratoid histology who were evaluable for nephrogenic rests.

The non-WT1-syndromic cohort

The main analysis cohort consisted of 512 patients with synchronous BWT at diagnosis, 7,351 patients with unilateral WT, and 87 patients with metachronous BWT. One unilateral WT patient diagnosed with ESRD due to hemolytic uremic syndrome 197 days before WT was excluded from all further analyses, bringing the main cohort size to 7,949. We identified 100 cases of ESRD in the main cohort, 45 classified as due to PBWT and 55 to CRF. Table 2 tabulates patient ESRD outcomes by risk factors. Additional demographic information and putative causes of ESRD for patients with CRF is available as supplementary material.*

Median follow-up for surviving patients in the main cohort was 14.2 years; 4,537 patients were still under observation at 10 years from WT diagnosis, 2,082 at 20 years. The average annual loss-to-follow-up rate was 1.5% for the first 10 years and 1.8% for the next 10.

Cumulative incidence of ESRD

The 20-year cumulative incidence of ESRD of either type in non-syndromic patients was 1.7% (95% CI[1.3,2.1]). Figure 1 plots the cumulative incidence of ESRD due to PBWT for patients with synchronous and metachronous BWT. Twenty nine patients with synchronous BWT developed ESRD due to PBWT, as did 16 with metachronous disease. The percentages of patients who survived and developed ESRD due to PBWT within 3 years of bilateral diagnosis were 4.0% (95% CI[2.3, 5.7]) for synchronous and 19.3% (95% CI[10.7,27.9]) for metachronous BWT. Nine cases of ESRD due to PBWT occurred 3 or more years after synchronous BWT diagnosis. All but one of these late ESRD events coincided with the date of nephrectomy, either for persistent WT ($n=1$), or a first ($n=5$), second ($n=1$) or third ($n=1$) relapse in the residual kidney. One patient, who developed renal failure 9 years after partial bilateral nephrectomy and a subsequent relapse, was found to have WT regrowth in the remaining kidney prior to transplant, indicating PBWT as the cause of ESRD. The hazard ratio for patients with metachronous vs. synchronous BWT was 4.9 (95% CI[2.6, 9.0], $p<.001$).

Figure 2 plots the cumulative incidence of ESRD due to CRF for patients with unilateral vs. bilateral disease. Forty patients with unilateral WT developed ESRD due to CRF, as did 14 with synchronous and 1 with metachronous BWT. The cumulative incidence among patients with unilateral WT was 0.7 % (95% CI[0.4, 1.0]) at 20 years; it was 3.1 % (95% CI[0.9, 5.3]) for those with BWT. The estimated hazard ratio was 5.9 (95% CI[3.2,10.6], $p<.001$) for BWT vs. unilateral WT. In both groups the cumulative incidence rose steadily from diagnosis for 20 years and beyond.

Table 3 shows the results of fitting separate univariate regression models, each of which will be discussed in turn.

*Supplementary material found at <http://authors.fhcr.org/467/>.

Age at WT diagnosis

Diagnosis of WT prior to 24 months of age was more common in those with ESRD due to PBWT than in unaffected patients (Table 2) and was associated with a 2-fold increase in the rate of ESRD due to PBWT ($p=.05$ for trend with age category after stratification). In an analysis limited to the 28 cases of ESRD due to PBWT that occurred among 240 BWT patients diagnosed before 24 months, the hazard of ESRD due to PBWT decreased 10% with each additional month of age at WT diagnosis (per-month HR .90, 95% CI[0.84, .97], $p=.003$ after stratification), suggesting the highest rates occurred in the very young.

Over half of CRF patients were diagnosed with WT before 24 months (Table 2). Early WT diagnosis predicted a 70% increase in rate of ESRD due to CRF relative to those diagnosed between 24-47 months and a 2.8 fold increase relative to those diagnosed after 48 months ($p=.003$ for test of trend with age category after stratification). However, among those diagnosed before 24 months, the ESRD hazard did not decrease with increasing age at diagnosis (per-month HR 1.04, 95% CI[.99,1.10], $p=.09$).

Histologic type

Strikingly, 27% of patients with ESRD due to CRF had stromal predominant histology compared with 7% for ESRD due to PBWT and 3% for no ESRD (Table 2). Among patients who did not develop ESRD, blastemal and epithelial predominant histology were relatively frequent. Mixed histology was the most common type among all patients (48%, $n=3791$).

In a regression stratified on bilateral status, rates of ESRD due to CRF in those with stromal predominant histology were 6.4 times those for mixed histology ($p<.001$) and more than 10 times those for blastemal and epithelial predominant histology (Table 3). For ESRD due to PBWT, by contrast, the HR for ESRD among those with stromal predominant histology relative to mixed was under 1.0 and not statistically significant ($p=.82$).

Nephrogenic rests

The occurrence of ILNR, whether or not perilobar rests were also present, was 2-3 times more common among patients who later developed ESRD due to PBWT (50%, $n=15$) and CRF (64%, $n=14$) versus no ESRD (20%, $n=1087$) (Table 2). Associations between nephrogenic rests and ESRD due to PBWT, however, reflect the association between nephrogenic rests and bilaterality: patients with BWT were much more likely to have nephrogenic rests of either type [(52%, $n=208$) with perilobar only and 32% ($n=124$) with intralobar or both] compared to unilateral patients [(18%, $n=926$) with perilobar only and 20% ($n=992$) with intralobar or both]. For patients with BWT, stratified regressions indicated that neither perilobar nor intralobar rests were significantly predictive of a higher hazard of ESRD due to PBWT (Table 3).

By contrast, stratified regression indicated ILNR predicted 6-fold higher rates of ESRD due to CRF ($p=.001$). The hazard rate for patients with ILNR increased with time since unilateral WT diagnosis (Figure 3), although non-proportionality tests were not significant.

Other GU anomalies

In the non-syndromic cohort, 5 patients had potentially *WT1*-related genital anomalies, two children with DSD and three with streak ovaries not related to radiation treatment or other anomaly syndromes (e.g., Turner syndrome). Stromal histology was present in 2/5 patients; the rest had mixed histology. Three patients had nephrogenic rests; one had ILNR while 2 were diagnosed before nephrogenic rests were distinguished by type. All 5 patients had WT before 2 years of age.

Two of the 5 patients were diagnosed with ESRD due to CRF. The child with ovotesticular DSD had unilateral WT with stromal predominant histology and developed ESRD due to “chronic kidney disease, etiology unknown” 23 years after WT diagnosis. One girl with “streak gonads” had unilateral WT with mixed histology and developed ESRD due to focal-segmental glomerulosclerosis 24 years after WT diagnosis. Neither had evidence of nephrogenic rests. While the risk of ESRD was much higher in this small group than among other “non-syndromic” patients, precise estimates of the HR were not possible due to the small numbers.

The significant univariate associations between *WT1*-related predictors and ESRD due to CRF were not much changed if these patients were excluded: ILNR had a HR of 5.9 (95% CI [2.0,17.3], $p < .001$) and stromal predominant histology had a HR of 6.2 (95% CI [3.2,11.7], $p < .001$).

Other Predictors

Stratified univariate regressions did not suggest differences in rates of ESRD due to PBWT or CRF by study cohort (Table 3). Radiation of 15 Gy or more to the contralateral kidney was associated with an increased risk of ESRD, particularly of ESRD due to PBWT for which the HR was 4.2 ($p = .003$).

Multiple regressions for CRF and PBWT ESRD

Results of multiple Cox regression analyses are shown in Table 4. Although restricted to patients from NWTs 3-5 for whom nephrogenic rest status was evaluable, and with different reference categories for some factors as a result of having collapsed factor levels, the results are broadly consistent with those obtained from the separate univariate regressions. The exclusion resulted in a loss of 33 cases of ESRD due to CRF since the earlier studies had the longest follow-up and incidence rises sharply with increasing follow-up. Confidence limits widened accordingly. For ESRD due to CRF, the hazard ratios associated with stromal predominant histology and young age at diagnosis increased somewhat in the multiple regression analysis, while those associated with intralobar rests decreased. Nonetheless, both stromal histology and ILNR remained statistically significant. The multiple predictor model for ESRD due to PBWT was similar to the univariate regressions in that young age at diagnosis and high radiation dose predicted increased risk.

Discussion

The results in the present study confirm that patients with congenital anomaly syndromes associated with *WT1* mutations accounted for a large fraction of ESRD cases, especially in patients with unilateral WT. By 20 years from WT diagnosis, the cumulative incidence of ESRD was 83% in patients with DDS, 43% in those with WAGR syndrome and 9% in those with associated GU anomalies.

Our prior study² considered separately ESRD occurring in patients with unilateral vs. bilateral disease because of the obvious risk of ESRD due to PBWT. With increasing follow-up came the recognition that this dichotomy was no longer adequate. Several cases of ESRD occurred in patients who had long been cured of their BWT and had been functioning without even a single intact kidney. It seemed reasonable to suppose that the subsequent decline in their renal function might be influenced by the same factors as those operating in patients with unilateral WT. Consequently, all ESRD due to factors other than PBWT was grouped under the rubric “ESRD due to CRF”.

Since the high risk of ESRD in patients with *WT1* related syndromes and anomalies was becoming well known, our attention shifted to the much larger cohort of non-syndromic

patients, in whom an increasing fraction of the ESRD cases occurred as follow-up lengthened. Results of the statistical analyses confirmed the hypotheses specified *a priori*: once the risk of PBWT had passed, ESRD occurred preferentially in patients whose WT phenotype was consistent with a *WT1* etiology.

ESRD due to progressive bilateral Wilms tumor

The cumulative incidence curves for ESRD due to PBWT showed a rapid accumulation of cases shortly after the diagnosis of BWT, whether synchronous or metachronous. All of these cases became anephric following removal of their cancerous kidneys. The earliest cases occurred in patients who never achieved remission from their BWT. Later cases occurred in patients who had one or more periods of remission followed by relapse leading to ESRD.

Three years from the diagnosis of BWT, the cumulative incidence of ESRD due to PBWT was nearly 5 fold higher in patients with metachronous compared to synchronous BWT. This dramatic finding is consistent with our expectation that aggressive disease developing after initial treatment in a solitary remaining kidney may require surgical excision of all remaining kidney tissue to prevent further progression and metastasis.

Radiation doses to the contralateral kidney of 15 Gy and above predicted higher rates of ESRD due to PBWT, possibly reflecting more aggressive surgical and adjuvant treatments for patients with more severe disease. We found no association of NWTs study with ESRD due to PBWT. However, treatment for BWT was not specified by study protocols and varied substantially, from complete bilateral nephrectomy to treatment with chemotherapy and radiation only.¹⁵

A diagnosis of WT under the age of 2 years increased the risk of ESRD due to PBWT, and younger children in this age range had even higher risk. This effect persisted in multiple regressions that adjusted for histology and nephrogenic rests. It is possibly a chance finding, however, given lack of prior hypotheses or adjustment for multiple testing.

ESRD due to CRF

The cumulative incidence of ESRD due to CRF at 20 years from WT diagnosis was low: 3.1% for patients with BWT and under 1% for those with unilateral WT. Monitoring of renal function was not part of the original study design, and we are unable to report the stages of chronic kidney disease as defined by the National Kidney Foundation. It is likely, however, that the cumulative incidence of chronic renal insufficiency (CRI) may be considerably higher than that of ESRD in the non-syndromic WT patient population. Rates of CRI are elevated in adult cancer patients with unilateral and bilateral nephrectomies,^{16,17} CRI predicts serious health outcomes, and may eventually evolve into ESRD.¹⁸ With longer follow-up, we will likely see the cumulative incidence of ESRD due to CRF continue to steadily but gradually increase.

Our results provide circumstantial support for the hypothesis that germline *WT1* mutations leading to WT may predispose to renal failure and ESRD due to CRF, even in patients without the classic *WT1* syndromes. In univariate regression analyses a stromal predominant histology increased the incidence rates more than 6 fold compared to mixed favorable histology, even more so in comparison to blastemal or epithelial predominant histology, while the presence of ILNR increased them nearly 6 fold. Diagnosis of WT before 2 years of age predicted a 2-fold increase in rates of ESRD relative to those diagnosed between 2 and 4. Estimates of the frequency of germline *WT1* mutations among WT patients are generally on the order of 5% or less overall, and only 2% in the non-syndromic subgroup.^{19,20, 21}

Thus a large fraction of the cases of ESRD due to CRF may occur in a relatively small subset of the WT population.

Molecular analysis has revealed a variety of *WT1* mutations that are associated with a diversity of WT phenotypes.⁸ *WT1* mutations may be associated with kidney pathology in patients who lack all criteria for specific syndromes.²² *WT1* mutations with or without genital anomalies and WT may lead to steroid resistant nephrotic syndrome²³ and diffuse mesangial sclerosis characteristic of DDS.²⁴

We found two cases of ESRD due to CRF in patients with DSD who did not fall into the DDS or WAGR categories. In both cases ESRD occurred in young adulthood, which is characteristic of ESRD in patients with WAGR or Frasier syndromes rather than DDS.²⁵ Their clinico-pathologic characteristics were also consistent with a *WT1* mutation. These GU anomalies should likely be considered together with cryptorchidism and hypospadias as *WT1*-related risk factors of ESRD due to CRF in WT patients.

The putative causes of ESRD due to CRF mentioned on flow sheets and other clinical records were diverse, and may obscure a more direct relationship to *WT1* mutation. *WT1* expression plays a crucial role in normal kidney development as well as in maintenance of adult kidney function, where it continues to be expressed in the podocytes.²⁶ Studies in mice show that disruption of the activity of *WT1* may lead to fewer functional nephrons at birth,²⁷ and histologic studies of WAGR patients indicate a reduction in size of glomeruli that is presumably related to the *WT1* deletion.²⁸ Reductions in nephron and podocyte number and mass could increase an individual's susceptibility to renal failure, particular in those with unilateral or partial bilateral nephrectomies.^{29,30} Reduced expression of *WT1* in adult podocytes may reduce the glomerular filtration rate and eventually lead to glomerular sclerosis.³¹

Implications for Renal-sparing Surgery

Renal-sparing surgery has long been advocated for BWT. Tumor resections that leave the surrounding tissue intact aim to prevent or delay the onset of ESRD, thereby improving quality of life. On the other hand, radical nephrectomy is more successful at preventing relapse. A prior review of NWTs-4 BWT patients who had renal sparing procedures under modern surgical practices found that 8% had recurrence of WT, compared to 2% of those with radical bilateral nephrectomies.³²

Some have suggested performing renal sparing surgery for children with unilateral WT, with the primary motivation of preventing renal failure.^{33,34} However, only the occasional child with WT will present with a lesion small enough to allow partial nephrectomy at diagnosis, e.g., tumors detected due to screening studies. Most WT are too large at diagnosis to allow partial nephrectomy and therefore require preoperative chemotherapy. Moreover, as with BWT, there is increased risk for local recurrence after partial nephrectomy for unilateral disease,^{35,36} and patients that develop intra abdominal relapse have a markedly decreased survival.³⁷ Results of the present study will help identify unilateral patients most at risk of ESRD. Prospective studies can then clarify the role of renal sparing surgery in this select group of patients.

Conclusion

In summary, we hypothesize that in patients treated for WT, many, though not all, cases of ESRD due to CRF are related to underlying *WT1* mutations, even without other phenotypic characteristics of *WT1*-related syndromes. To ground our hypothesis in more than circumstantial evidence, one would ideally conduct a retrospective molecular analysis using

stored biological material to determine if patients who developed ESRD, especially ESRD due to CRF, were more likely to have *WT1* mutations than the WT patient population in general. Results of such a study would help to quantify the associations between *WT1* mutation and such phenotypic characteristics as stromal predominant histology and the presence of ILNR. Whether or not the hypothesis is borne out, we recommend that patients with these characteristics should undergo increased surveillance for chronic kidney disease and ESRD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key to Abbreviations

ESRD end stage renal disease

WT	Wilms Tumor
CRF	chronic renal failure
PBWT	progressive bilateral Wilms Tumor
BWT	bilateral Wilms Tumor
WAGR	Wilms tumor-aniridia
DDS	Denys-Drash syndrome
GU	genitourinary
DSD	disorder of sexual differentiation
NWTS	National Wilms Tumor Study

Figure 1. Cumulative incidence of ESRD due to PBWT by time since diagnosis of BWT for patients with synchronous vs. metachronous BWT.

Figure 2.
Cumulative incidence of ESRD due to CRF by time since WT diagnosis for patients with unilateral vs. bilateral disease.

Figure 3.
Smoothed hazard rates for ESRD due to CRF among patients with unilateral WT classified according to presence or absence of nephrogenic rests.

Table 1
Cumulative incidence of ESRD at 20 years since WT onset in *WT1* syndromic patients

	No. Patients	Cases of ESRD/PBWT	CRF	Total	Cumulative Incidence	95% CI
DDS	37	1	29	30	82.7	(60.5, 92.4)
WAGR	69	1	18	19	43.3	(20.8, 59.5)
GU Anomalies	217	6	14	20	9.4	(4.2, 14.4)
Cryptorchidism only	139	4	10	14	10.5	(3.5, 17.1)
Hypospadias only	46	0	1	1	0.0	(0.0, 0.0)
Both	32	2	3	5	16.6	(0.0, 31.1)

Table 2
ESRD outcomes by risk factors in the non-WT1 syndromic cohort

	ESRD Status		PBWT		CRF	
	None		N	%	N	%
Age at WT Diagnosis (months)	N	%	N	%	N	%
0-23	2171	27.7	28	62.2	29	52.7
24-47	2578	32.8	10	22.2	16	29.1
>48	3100	39.5	7	15.6	10	18.2
Histology						
Mixed	3734	47.6	29	64.4	28	50.9
Blastemal	2394	30.5	5	11.1	9	16.4
Epithelial	845	10.8	3	6.7	3	5.5
Stromal	208	2.7	3	6.7	15	27.3
Anaplastic	668	8.5	5	11.1	0	0
Nephrogenic Rests [*]						
No rests detected	3219	59.3	5	16.7	6	27.3
Perilobar	1121	20.7	10	33.3	2	9.1
Intralobar or both	1087	20.0	15	50.0	14	63.6
Radiation Dose to Contralateral Kidney (Gy)						
None	6904	88	34	75.6	44	80.0
0.1-14.9	723	9.2	5	11.1	5	9.1
15.0+	221	2.8	6	13.3	6	10.9

* Intralobar and perilobar nephrogenic rests were not evaluable in 2470 subjects.

Table 3
Single predictor Cox regression analyses of ESRD due to PBWT and CRF

	ESRD status					
	CRF			PBWT		
	HR	95% CI	p	HR	95% CI	p
Age at WT diagnosis (months)			0.003			0.05
>48 (ref)						
0-23	2.8	(1.4, 5.6)	0.004	2.1	(0.9, 4.9)	0.08
24-48	1.6	(0.7, 3.6)	0.24	1.1	(0.4, 2.8)	0.92
Histologic Type	HR	95% CI	p	HR	95% CI	p
Mixed (ref)			<.001			0.11
Blastenal	0.6	(0.3, 1.2)	0.12	0.3	(0.1, 0.9)	0.02
Epithelial	0.4	(0.1, 1.3)	0.14	0.3	(0.1, 1.1)	0.07
Stromal	6.4	(3.4, 11.9)	<.001	0.9	(0.3, 2.7)	0.82
Anaplastic				0.8	(0.3, 2.1)	0.68
Nephrogenic Rests *	HR	95% CI	p	HR	95% CI	p
No rests detected (ref)			<.001			0.10
Intralobar or both	5.9	(2, 17.3)	0.001	1.4	(0.6, 3.7)	0.45
Perilobar	0.5	(0.1, 2.8)	0.43	0.6	(0.2, 1.6)	0.31
NWTS Study Cohort	HR	95% CI	p	HR	95% CI	p
I (ref)			0.94			0.95
II	0.8	(0.3, 1.9)	0.57	0.7	(0.1, 4.1)	0.73
III	0.6	(0.3, 1.5)	0.28	1.0	(0.3, 3.5)	0.97
IV	1.0	(0.4, 2.5)	0.96	1.3	(0.4, 4.4)	0.63
V	0.9	(0.2, 3.8)	0.91	0.9	(0.2, 3.1)	0.83
Radiation Dose to Contralateral Kidney (Gy)	HR	95% CI	p	HR	95% CI	p
			0.18			0.06

ESRD status						
	CRF			PBWT		
	HR	95% CI	p	HR	95% CI	p
None (ref)						
0.1-14.9	0.9	(0.3, 2.2)	0.76	0.8	(0.3, 2)	0.59
15.0+	2.3	(0.9, 5.7)	0.08	4.2	(1.6, 10.7)	0.003

HR: hazard ratio; p: Wald p-value.

Overall p-values are from group tests for categorical variables and tests of the variable as a linear predictor for ordinal variables.

* Intralobar and perilobar nephrogenic rests were not evaluable in 2470 subjects.

Table 4
Multiple predictor Cox regression analyses of ESRD due to CRF and PBWT

	ESRD status					
	CRF			PBWT		
	No. Patients*	Cases	HR	95% CI	p	
Age at WT diagnosis (months)						
>24 (ref)	3999	7				
0-23	1480	15	2.0	(0.7, 5.9)	0.22	11 19 2.5 (1.0, 5.9) 0.04
Histologic type						
All others (ref)	5331	14				28
Stromal	148	8	7.8	(3.0, 20.6)	<.001	2 1.4 (0.4, 5.4) 0.62
Nephrogenic rests					0.04	0.56
None identified (ref)	3230	6				5
Intralobar or both	1133	2	3.8	(1.2, 11.8)	0.02	10 1.0 (0.4, 2.5) 0.92
Perilobar rests	1116	14	0.7	(0.1, 3.7)	0.67	15 0.6 (0.2, 1.8) 0.37
Radiation Dose to Contralateral Kidney (Gy)**			0.3	(.1, 1.7)	0.17	1.8 (0.9, 3.8) 0.12
None	4859	20				24
0.1-14.9	533	2				4
15.0+	87	0				2

HR: hazard ratio; p: Wald p-value.

* Patients limited to those with evaluable nephrogenic rests.

** Radiation Dose to contralateral kidney was treated as a grouped linear predictor in the regression.