Special Article

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

Jane Lange,* Susan M. Peterson, Janice R. Takashima, Yevgeny Grigoriev, Michael L. Ritchey, Robert C. Shamberger, J. Bruce Beckwith, Elizabeth Perlman, Daniel M. Green and Norman E. Breslow

From the Department of Biostatistics, University of Washington (JL, NEB), and Department of Biostatistics and Bioinformatics, Fred Hutchinson Cancer Research Center (SMP, JRT, YG, NEB), Seattle, Washington; Department of Urology, Mayo Clinic, Scottsdale, Arizona (MLR); Department of Surgery, Children's Hospital Boston and Harvard Medical School, Boston, Massachusetts (RCS); Department of Pathology and Human Anatomy, Loma Linda School of Medicine, Loma Linda, California (JBB); Department of Pathology and Laboratory Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (EP); and Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, Tennessee (DMG)

Abbreviations and Acronyms

BWT = bilateral Wilms tumor
CRF = chronic renal failure
CRI = chronic renal insufficiency
DDS = Denys-Drash syndrome
DSD = disorder of sexual differentiation
ESRD = end stage renal disease
GU = genitourinary
ILNR = intralobar nephrogenic rests
NWTS = National Wilms Tumor Study
PBWT = progressive bilateral Wilms tumor
WAGR = Wilms tumor-aniridia
WT = Wilms tumor

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* Correspondence: Department of Biostatistics, University of Washington, Seattle, Washington 98112 (e-mail: janelange15@gmail.com).

Purpose: We assessed risk factors for end stage renal disease in patients with Wilms tumor 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 end stage renal disease due to chronic renal failure. We predicted a high risk of end stage renal disease due to progressive bilateral Wilms tumor in patients with metachronous bilateral disease.

Materials and Methods: End stage renal disease was ascertained in 100 of 7,950 nonsyndromic patients enrolled in a National Wilms Tumor Study during 1969 to 2002. Risk factors were evaluated with cumulative incidence curves and proportional hazard regressions.

Results: The cumulative incidence of end stage renal disease due to chronic renal failure 20 years after Wilms tumor diagnosis was 0.7%. For end stage renal disease due to progressive bilateral Wilms tumor the incidence was 4.0% at 3 years after diagnosis in patients with synchronous bilateral Wilms tumor and 19.3% in those with metachronous bilateral Wilms tumor. For end stage renal disease due to chronic renal failure stromal predominant histology had a HR of 6.4 relative to mixed (95% CI 3.4, 11.9; $p < 0.001$), intralobar rests had a HR of 5.9 relative to no rests (95% CI 2.0, 17.3; $p = 0.001$), and Wilms tumor diagnosis at less than 24 months had a HR of 1.7 relative to 24 to 48 months and 2.8 relative to greater than 48 months ($p = 0.003$ for trend).

Conclusions: Metachronous bilateral Wilms tumor is associated with high rates of end stage renal disease due to surgery for progressive Wilms tumor. Characteristics associated with a *WT1* etiology markedly increased the risk of end stage renal disease due to chronic renal failure despite the low risk in non-*WT1* syndromic cases overall.

Key Words: kidney failure, chronic; nephrectomy; Wilms tumor; genes, Wilms tumor

Treatment advances for Wilms tumor have greatly improved survival with cure rates now approaching 90%.[1] However, survivors of WT are at increased risk for additional health problems due to the direct effects of treatment and to genetic

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conditions associated with the disease. ESRD is a particularly serious outcome and identification of risk factors for ESRD in the WT population is a clinically important goal.

A prior National Wilms Tumor Study report estimated that patients with unilateral WT had a 20-year cumulative incidence of ESRD of 1.3% vs 15% for those with BWT.[2] High rates of ESRD were found among patients with the WAGR and DDS syndromes, and those with associated male GU anomalies all caused by germline *WT1* mutations.[3,4] Early onset ESRD developed by young adulthood in more than 70% of patients with DDS and in approximately 40% of those with WAGR.

In this study we investigated risk factors for ESRD in patients without *WT1* associated syndromes using an expanded NWTS cohort with longer followup. We considered ESRD separately due to progressive BWT and chronic renal failure, 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 1 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 cells responsible for synchronous bilateral disease.[5] Therefore, we hypothesized 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 nonmalignant 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 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] 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 2 anomalies were used here as a basis for exclusion from analysis 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 DSDs, 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 in 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 (69), DDS (37) or male GU anomalies (217) were excluded from the non-*WT1*-syndromic cohort. Additional exclusion factors, in order, included WT in an extrarenal site (22), a missing histology record (276), or a histological type recorded as rhabdoid tumor of the kidney, clear cell sarcoma of the kidney, or as another rare, indeterminant or non-WT type (665). The final non-*WT1*-syndromic cohort consisted of 7,950 subjects. Results are reported separately for the syndromic patients and those with rare histological types.

Definition of End Point

Patients with WT 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 (7, of which 5 had WAGR and 1 had DDS). ESRD was categorized as caused by PBWT if the patient required surgical removal of all kidney tissue as a consequence of PBWT. ESRD 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 to 23, 24 to 47 and 48+ months. Favorable histology tumors were classified as blastemal, epithelial or stromal predominant if a corresponding histological pattern comprised more than two-thirds of the available tumor sections, and otherwise were classified 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, and patients with both types were assigned to the intralobar group. This factor was available only for patients in NWTS 3 to 5 who had normal kidney tissue available for pathological 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 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 followup, termination of the study or development of ERSD of the other type. The risk factor analyses for ESRD due to CRF were stratified by unilateral WT vs BWT, and 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. 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 $p < 0.10$. Instantaneous hazards were estimated from cumulative hazards by kernel