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Impact of nephrectomy on long-term renal function in non-syndromic children treated for unifocal Wilms tumor

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Abstract *Objective:* The present study is designed to assess the long-term renal function of children who underwent radical nephrectomy for unifocal Wilms tumor.
Methods: A single institution retrospective cohort study of non-syndromic children treated with radical nephrectomy for unifocal Wilms tumor between 1995 and 2011 was performed to identify risk factors for decreased glomerular filtration rate (GFR). The primary endpoint was decrease in age-adjusted GFR below normal published ranges. The secondary endpoint was progression to chronic renal insufficiency (CRI).
Results: A total of 55 patients were identified in the cohort. Eight (15%) patients exhibited decreased age-adjusted GFR during the follow-up period, with 2 (4%) progressing to CRI. Increasing time between surgery and the last known GFR follow-up was associated with decreased GFR, with the normal GFR group having median follow-up of 7.32 years versus 11.47 years ($p = 0.019$) in the decreased GFR group.
Conclusions: A trend toward decline in GFR was detected with longer follow-up. Longer follow-up may reveal that clinically significant decline in renal function occurs years following nephrectomy among a subset of Wilms tumor survivors, even among those who do not progress to end stage renal disease.

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Introduction

Wilms tumor (WT) survival rates have risen dramatically in the modern era. Using contemporary approaches to surgical technique and adjuvant therapy, present-day overall cure rates approach 90% [1]. Yet, survivors carry the burden of side effects from therapy, and these children may accrue future health problems as they age into adulthood. Of particular note is the potential for loss of renal function, given both renal parenchymal loss and exposure to adjuvant chemotherapy and/or radiation early in life. These concerns have motivated recent efforts to utilize nephron-sparing surgery (NSS) in WT patients.

Pediatric WT may present either in the context of a clinical syndrome (such as WT-1 germline mutation, Beckwith—Wiedemann syndrome, WAGR, or Denys—Drash syndrome), or as an isolated spontaneous event. Syndromic children are significantly more likely to present with bilateral synchronous tumors, and are also at elevated risk for subsequently developing ipsilateral or contralateral metachronous recurrence [2]. The risk of end-stage renal disease (ESRD) in syndromic children rises commensurately as total loss of renal mass increases. In contrast, non-syndromic children with an isolated occurrence of WT have a lower risk of metachronous recurrence. Classic dogma highlights the importance of complete resection of WT in achieving the best overall cure rates; however, more centers are now performing NSS for syndromic patients given the imperative of renal preservation.

The National Wilms Tumor Survey (NWTS) has reported an overall 20-year cumulative incidence of ESRD of 0.7% among unilateral WT survivors [3]. This rate rises to 4% at 3 years among children with bilateral synchronous WT. Children with bilateral metachronous WT in the NWTS cohort had a 19.3% incidence of ESRD [1]. Published data also identifies that syndromic children are much more likely to suffer ESRD compared to non-syndromic children. For example, at 20 years of follow up in NWTS, 74% of Denys—Drash patients had ESRD, as did 36% of WAGR patients, 7% of hypospadias or cryptorchidism patients, compared with only 0.6% of non-syndromic children having ESRD.

While previously reported NWTS data are highly informative, these studies uniformly stratify outcomes in a binary fashion based on development of stage V chronic kidney disease (i.e., ESRD), which usually takes place as WT survivors mature into adulthood. Yet, recent literature has shown that even small gradations in diminished GFR among adults may portend negative health outcomes. For example, in one large cohort of adult patients, an independent, graduated association was noted between reduced estimated GFR and the risk of death, cardiovascular events and hospitalization during a follow-up period of only slightly less than 3 years [4]. These effects were noted at reduced GFR values much higher than those meeting ESRD criteria.

A general consensus exists that syndromic children are candidates for NSS, particularly if they present with multiple tumor foci. In contrast, non-syndromic children have a remarkably low ESRD rate at 20 years of follow-up despite the widespread historic employment of radical unilateral nephrectomy for optimal oncologic control. The authors hypothesize that, although rates of chronic renal insufficiency (CRI) and ESRD are low among non-syndromic WT survivors, non-syndromic patients may nonetheless suffer incremental decreases in GFR that portend adverse health outcomes later in life. Although partial nephrectomy for WT has not been historically utilized at our institution, the authors sought to identify long-term GFR outcomes following radical nephrectomy in a WT population with a goal of identifying selection criteria for NSS versus radical nephrectomy.

Table 1 Age-adjusted glomerular filtration rate (GFR) reference ranges.

Age (yr)	GFR (mL/min/1.73 m^2)(mean ± SD)
3—4	111.2 ± 18.5
5—6	114.1 ± 18.6
7—8	111.3 ± 18.3
9—10	110.0 ± 21.6
11—12	116.4 ± 18.9
13—15	117.2 ± 16.1
2.7—11.6	127.1 ± 13.5
9—12	116.6 ± 18.1
16.2—34	112 ± 13

Methods

Our departmental institute review board-approved database of renal surgeries was queried for cases performed between 1995 and 2011 involving children <18 years of age who carried a diagnosis of WT. Patient medical records were retrospectively reviewed and relevant clinical, pathological, and laboratory values were collected. Patients were excluded from the study cohort because of syndromic presentation, lack of GFR data, having undergone partial nephrectomy, and multifocal tumor presentation.

The primary study endpoint was decrease in age-adjusted GFR (calculated using the Schwartz formula) [5]: 1 standard deviation below age-adjusted published GFR norms (Table 1). The secondary endpoint was progression to chronic renal insufficiency (CRI) defined as age-adjusted GFR < 60 mL/min/1.73 m^2.

Statistical analysis was performed using SPSS, version 16 (IBM Corporation, Armonk, NY, USA). Categorical variables were compared using the chi-squared and Fisher's exact tests and continuous variables were compared with the Mann—Whitney *U* test and the Student *t*-test as appropriate. In addition, logistic regression analysis was applied for select analyses. Data are expressed as mean standard deviation. A p-value < 0.05 was considered statistically significant.

Results

During the study period, 55 patients (22 males and 33 females) underwent nephrectomy for WT (Table 2). Median follow-up time between surgery and last GFR calculation was 6.3 years. Eight (15%) patients exhibited decreased