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Utilization of Nephron-Sparing Surgery and Impact on Patient Survival in Pediatric Wilms Tumor — a SEER Analysis

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Abstract

Purpose—Nephron-Sparing Surgery (NSS) is the standard of care for many adults with renal tumors and has been described in some children with Wilms tumor (WT). Beyond case series, however, data concerning NSS utilization and outcomes in WT are scarce. Using a large cancer data registry, we examined NSS outcomes and factors associated with NSS use in WT.

Materials and Methods—We retrospectively reviewed the 1998–2010 Surveillance, Epidemiology, and End Results (SEER) database. We identified WT patients aged 18 years. Clinical, demographic and socioeconomic data were abstracted, and statistical analysis was performed using multivariate logistic regression (predicting use of NSS) and Cox regression (predicting Overall Survival, OS) models.

Results—We identified 876 boys and 956 girls with WT (mean age 3.3 ± 2.9 years). Of these, 114 (6.2%) underwent NSS (74 unilateral, 37 bilateral WT). Median follow up was 7.1 years. Regarding procedure choice, NSS was associated with unknown lymph node status (NX vs N0, $p < 0.001$) and smaller tumor size ($p < 0.001$). Regarding survival, only age (HR=1.09, $p = 0.002$), race (HR=2.48, $p = 0.002$), stage (HR=2.99, $p < 0.001$), and LN status (HR=2.17, $p = 0.001$) predicted reduced OS. Survival was not significantly different for children undergoing NSS vs. RN (HR=0.79, $p = 0.58$).

Conclusions—Among children with WT included in the SEER database, NSS is infrequently performed. NSS use is associated with smaller, bilateral tumors and with omission of lymphadenectomy; however, there are no evident differences in NSS use by demographic or socioeconomic factors. Despite lymph node under-staging, overall survival after NSS remains similar to radical nephrectomy.

Keywords

Nephron-Sparing Surgery; Nephrectomy; Wilms tumor; Pediatrics; Urologic Surgical Procedures; Survival Analysis

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INTRODUCTION

Wilms tumor (WT) is the most common solid renal malignancy in children, occurring in approximately 500 children per year in the US.¹ Historically, WT was a near-universally lethal disease despite aggressive surgical and chemotherapeutic interventions. However, over the last several decades, cooperative multi-institutional trials such as the National Wilms Tumor Study Group (NWTSG), the Children's Oncology Group (COG), the United Kingdom Children's Cancer Study Group (UKCCSG), and the Société Internationale d'Oncologie Pédiatrique (SIOP) have coordinated the care and study of children with renal tumors. Although treatment protocols vary between the groups, the cooperative efforts have significantly improved outcomes. Today, studies report an overall survival exceeding 90% for WT patients.²

Traditionally, nephron-sparing surgery (NSS) was reserved for absolute indications: namely, bilateral WT or WT in children with a solitary kidney as a means to prevent the need for immediate postoperative renal failure.³ More recently, however, NSS has been reported for children with WT in the absence of absolute indications. There are several reported reasons for this: first, the search for methods to reduce the morbidity of WT treatments while preserving excellent survival rates; second, the increased successful use of NSS in adults; third, the increased familiarity with NSS of a larger number of urologists and surgeons; and fourth, refinements in NSS techniques over time which have further increased surgical success rates.⁴⁻⁶ Investigators have reported that NSS in the adult population provides a significant benefit in preservation of long-term renal and cardiovascular function in addition to overall survival benefits.^{5, 7} Therefore, the use of NSS in children appears to be a logical option. The COG trial AREN 0534 allows for NSS in children with bilateral WT or WT-predisposing syndromes (e.g., Beckwith-Wiedemann and WAGR) which are known to increase risk for postoperative renal failure or metachronous bilateral WT development.⁸ However, other than a few single institution case series of NSS for WT, data on NSS utilization and WT-specific outcomes remain scarce.

The purpose of this study was therefore to use a large, population-based cancer registry in order to: 1) analyze survival outcomes in WT, specifically comparing NSS with radical nephrectomy (RN); and 2) to investigate factors which may be predictive of NSS utilization, specifically whether socioeconomic status (SES) or demographic factors play a role in determining whether a child receives NSS or RN.

MATERIALS and METHODS

Data source

The National Cancer Institute's *Surveillance, Epidemiology, and End Result* (SEER) collects demographic data including age, gender, race, income, and disease specific information such as year of diagnosis, tumor diagnosis and site, stage at diagnosis, treatment, and survival information. The SEER 18 registry is a representative sample consisting of 28% of the US population and includes tumors diagnosed between 1973 and 2010.⁹

Inclusion criteria

We included patients less than or equal to 18 years of age with the *International Classification of Diseases for Oncology* (ICD-O-3) histological diagnostic code 8960 for WT treated with NSS or RN. Patients were excluded if treatment occurred prior to 1988 (n=597) or if surgery type (n=201) or SEER tumor stage (n=77) was unavailable. Duplicate records (n=1) were also removed from the cohort.

Covariates for analysis

Covariates analyzed included basic patient demographics: age at diagnosis, gender, race (white, black, other), as well as disease-specific factors: surgery type (NSS versus RN), surgery year, tumor laterality (unilateral versus bilateral), tumor size (cm), lymph node (LN) status (N0: negative LN involvement; NX: unknown LN involvement; or N1: positive LN involvement), SEER tumor stage (localized: invasive cancer confined to primary site; regional: extension beyond the original site to nearby tissue or LNs; or distant: spread to distant organs or LNs),¹⁰ follow-up time, and vital status at last follow-up (alive versus dead).

SEER*Stat software version 8.1.2 was used to generate county-level SES factors as previously described.¹¹ We merged these data with the standard SEER file based on census data (2007–2011, 2000, and 1990 county attributes); these county-level SES factors included: indices of local population age (% population age <18, % age >65), housing crowding, education (% <9th grade education, % < high school education, % Bachelor's degree or higher), income (median family income, median household income), poverty (% of families below poverty level, % of population below poverty level, % of population <150% of poverty level, % of population <200% of poverty level), employment (% of population unemployed, % white collar), language barriers, foreign born, and migration (% moved within the same county, % moved to different county within the same State, % of population moved to different State, % moved abroad).

Statistical Analysis

Bivariate analyses were completed to compare patient characteristics between patients who received NSS or RN using Chi-Square tests, t-tests, or Wilcoxon rank-sum tests as appropriate based on data characteristics and distribution. Kaplan-Meier curves were generated, and the log-rank test was used for bivariate survival analyses.

Multivariate logistic regression models were fitted to examine factors that predicted the utilization of NSS. Because bilateral tumors and overwhelming large tumors are highly likely to receive NSS and RN respectively, we limited our multivariate analysis to unilateral WT and tumors less than 15cm in greatest dimension to generate more meaningful inferences. Cox proportional hazards models were constructed to investigate associations between surgery type (NSS versus RN) and overall survival (OS) after adjusting for possible confounding effects. Model covariates were chosen based on biologic plausibility and/or a bivariate p-value of 0.2 or less; the covariates entered into each final model were age, gender, race, laterality, SEER tumor stage, LN status, tumor size, surgery year, and income.

All tests were two-sided, and an alpha of 0.05 and/or 95% confidence intervals (CI) were used as criteria for statistical significance. All database linkages and analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). Model diagnostics revealed no significant violations of regression assumptions, including the proportional hazard assumption for the Cox models.

This study was deemed exempt from human studies research review by our Institutional Review Board.

RESULTS

Patient characteristics

In total, 1,834 patients (48% males) with WT were identified. Mean patient age at the time of diagnosis was 3.3 ± 2.9 years. Median tumor diameter was 10.7 cm (interquartile range 5.0 cm). Of 1,365 patients with regional LN sampling, 265 were positive confirmed by pathologists in 265 patients (19%). Median follow up was 7.1 years.

Of the 1,834 included patients, 114 (6%) patients underwent NSS and 1,720 (94%) patients received RN. Of those patients diagnosed with unilateral WT, 74 (4%) had a NSS while 1,648 (96%) of underwent RN. Importantly, patients undergoing NSS were significantly less likely to undergo regional lymphadenectomy than patients treated with RN (56% versus 16%, $p < 0.001$). Therefore, patients undergoing NSS were more likely to be under-staged than those treated with RN.

Procedure type: NSS versus RN

Patient characteristics by surgery type are detailed in Table 1. On bivariate analysis, NSS use was more common in patients with bilateral tumors ($p < 0.001$), advanced SEER stage ($p = 0.03$), unknown LN status ($p < 0.001$), smaller tumor size ($p < 0.001$), and more recent surgery year ($p = 0.01$). A total of 1,557 patients with unilateral WT and tumor less or equal to 15cm were included in the stratified analysis. In the stratified analysis of unilateral WT patients, unknown LN status ($p < 0.001$), smaller tumor size ($p < 0.001$), and more recent surgery year ($p = 0.04$) remained significantly associated with NSS. Other clinical factors such as age, gender, race, or tumor stage were not found to be significantly associated with the use of NSS in bivariate analysis. Importantly, only one of the 20 SES factors ("migration to different county but same state in quartiles", $p = 0.006$) was significantly associated with the use of NSS.

The multivariate logistic regression model predicting NSS use in unilateral WT is detailed in Table 2. NSS was found to be significantly associated with unknown LN status (NX versus N0, OR=4.55, $p < 0.001$) and smaller tumor size (OR=0.85 per 1 cm decrease in diameter, $p < 0.001$) after adjusting for age, SEER stage, surgery year, and SES ("migration to different county but same state in quartiles"). As a sensitivity analysis, all county-level SES factors were individually fitted in the multivariate logistic regression model, with no significant changes to the original result noted.

Survival analysis

Representative Kaplan-Meier curves for patient clinical and demographic/SES characteristics are shown in Figures 1 and 2. Older age at diagnosis ($p<0.001$), advanced SEER stage ($p<0.001$), positive regional LNs (N1 versus N0, $p<0.001$), and unknown regional LNs (NX versus N0, $p=0.01$) were associated with lower OS. No significant association between SES factors and overall survival of WT patients were noted in the analysis. The bivariate and multivariate survival analyses are listed in Table 3. After adjusting for gender, tumor laterality, tumor size, surgery year, and income, only age at diagnosis (HR=1.09, $p=0.002$), race (HR=2.48 for non-white-non-black versus white, $p=0.002$), tumor stage (HR=2.99 for distant disease versus localized, $p<0.001$), and LN status (HR=2.17 for N1 versus N0, $p=0.001$) significantly predicted reduced OS. By contrast, survival was not significantly different for children undergoing NSS versus RN (HR=0.79, $p=0.58$) after adjusting for potential confounders.

DISCUSSION

NSS for non-absolute indications in WT is one of the more controversial topics in pediatric urologic oncology. Historically, NSS was found to be associated with higher local recurrence rate compared with RN based on NWTs data.¹² Shamberger et al further linked local recurrence and tumor spillage to a significantly worsened prognosis.¹³ Due to appropriate concern for these worsened oncologic outcomes, NSS has thus been generally reserved for children in whom preservation of renal function is mandatory, such as bilateral WT or a tumor in a solitary kidney.³

However, given the dramatic recent gains in life expectancy in WT patients and the increasing successful use of NSS in adult tumors, the possibility of NSS assuming a larger role in WT management has become increasingly popular. NSS has garnered increasing attention from investigators by preserving renal function and better overall health.^{5, 7, 14} Although the technical feasibility of NSS in many WTs is still in question,^{15, 16} modern series have shown promising results with comparable oncologic outcomes of NSS in well-selected WT patients.^{17–24}

Our study is the largest cohort to date to address NSS in WT management with available long-term survival information. Interestingly, we found no apparent overall survival difference between patients undergoing NSS and those undergoing RN. This lack of survival benefit persisted even after adjusting for potential confounders such as age, gender, race, tumor laterality, tumor size, surgery year, income, tumor stage, and regional LN status. Since all SEER patients reside in the US, one may assume that most if not all of the patients were treated under COG protocols – which do not typically utilize neoadjuvant chemotherapy. It is encouraging that carefully selected WT patients may potentially benefit from NSS, as many previously reported series have exclusively utilized SIOP protocols – which typically do utilize neoadjuvant chemotherapy.

The decision to perform NSS was influenced by both tumor size (likely due to technical concerns) and treatment era (with more recent years showing a higher rate of NSS use). However, potential disparities such as gender, insurance payer, marital status, race, income,

education, and other SES factors, which have been shown to be factors in use of NSS in adults,^{4, 6, 25, 26} were not associated with NSS use in children. Rather, NSS use was associated with bilateral tumors, advanced SEER stage, smaller tumor size, and more recent surgery year. Neither demographic nor SES factors seemed to affect the use of NSS in WT patients in the current study.

We also found that NSS was significantly associated with unknown regional LN status (Nx) which is a critically important issue; this likely represents an omission of the recommended of regional LN sampling as recommended in current SIOP and COG protocols. This practice results in under-staging in NSS patients compared to RN patients. This practice is reflected to a lesser extent in the RN group as well, a significant number of whom did not undergo appropriate regional LN sampling (Nx rate of 56% in NSS versus 23% in RN). Similar findings have been previously reported,²⁷ and are cause for concern given that failure to sample region LNs results in sub-optimal WT management. Adequate LN sampling is beneficial in terms of recurrence and long-term survival for WT patients.^{13, 27, 28} In addition, adequate LN sampling plays a crucial role in correctly staging WT, ultimately leading to improved multi-disciplinary management.^{13, 29, 30} Based on these known advantages, regional LN sampling, including hilar and ipsilateral para-aortic or caval nodes, is mandated in COG protocols.

The findings of this study should be interpreted in light of its limitations. The SEER registry only covers around 28% of US population, and therefore our cohort may not be generalizable to the entire population. In order to avoid coding errors and to improve the generalizability of our findings, we excluded a significant fraction of patients with incomplete data, specifically those who were missing data on their surgery type, LN status, and SEER staging, including all patients in SEER treated before 1988, at the cost of reduced statistical power.

Additionally, there are likely to be unmeasured confounders influencing our results. In order to better assess this, we performed informal sensitivity analyses to estimate the influence of specific confounders, both measured and unmeasured. We are reassured by the lack of significant changes in the effect estimates after adjusting for other associated variables (Tables 2 and 3). This finding implies that although residual confounding may yet be present, it is unlikely to have a substantial effect on the reported results.

Due to the structure of SEER, we do not have access to important clinical information such as tumor location, clinical/COG stage, pathology reports (specifically favorable versus anaplastic histology), chemotherapy regimen, associated syndromes and comorbidities, or provider- and hospital-level information such as annual surgical volume. In particular, this limits our ability to make firm conclusions regarding the role of SES in influencing WT outcomes and procedure type, as county-level measures of SES may not be adequately granular markers as compared to individual-level data, or even census block or tract data. While all these factors clearly play a role in determining oncologic outcome and prognosis, there is unfortunately no way to conduct more detailed analysis with those covariates using this database. However, it is worth noting that short of examining COG or SIOP trial data, SEER is likely to be the most comprehensive population-based data source available.

CONCLUSION

In children with WT included in the SEER database, NSS is infrequently performed compared to RN. NSS is associated with smaller tumors, bilateral tumors and with failure to perform regional lymphadenectomy. Differences in RN and NSS utilization do not appear to be influenced by demographic or socioeconomic factors. Despite LN under-staging, overall survival after NSS remains similar to RN.

Key Abbreviations

WT	Wilms tumor
SEER	Surveillance, Epidemiology, and End Results
NSS	nephron-sparing surgery
RN	Radical nephrectomy
SES	socioeconomic status
OS	Overall Survival

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Figure 1.

Kaplan-Meier plots of overall survival, stratified by clinical characteristics: (A) Surgery type, (B) Tumor laterality, (C) Regional LN status (D) SEER stage

Figure 2.

Kaplan-Meier plots of overall survival, stratified by demographics and SES factors: (A) Gender, (B) Race, (C) Education (% < 9th Grade), (D) Income (median family income)

Table 1

Patient characteristics by surgery type

Characteristics	Total(n=1834)	PN (n=114)	RN (n=1720)	p value
Age at diagnosis in years (Mean, SD)	3.29 (2.87)	3.21 (2.96)	3.29 (2.87)	0.75
Gender				
Male	876	49(43%)	827(48%)	0.29
Female	956	65(57%)	893(52%)	
Race				
White	1436	94(83%)	1342(78%)	0.37
Black	288	13(11%)	275(16%)	
Others	101	5(4%)	96(6%)	
Laterality				
Unilateral	1722	74(65%)	1648(96%)	<0.001
Bilateral	104	37(33%)	67(4%)	
Tumor size (cm)				
Median (IQR)	10.7 (5.0)	9.0 (7.9)	11.0 (5.4)	<0.001
surgery year				
Median (IQR)	2002 (10)	2004 (7.0)	2002 (10)	0.003
SEER stage				
Localized	839	54(47%)	785(46%)	0.04
Regional	587	26(23%)	561(33%)	
Distant	408	34(30%)	374(22%)	
LN status				
N0	1098	42(37%)	1056(61%)	<0.001
Nx	471	64(56%)	407(24%)	
N1	265	8(7%)	257(15%)	
Vital Status				
Alive	1685	103(90%)	1582(92%)	0.54

Characteristics	Total(n=1834)	PN (n=114)	RN (n=1720)	p value
Dead	149	11(10%)	138(8%)	
Follow up time (months)				
Median (IQR)	85 (120)	64 (79)	87 (122)	0.006

Table 2

Multivariate analysis of NSS utilization in unilateral WT

Characteristics	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p value
Age at diagnosis (year)	1.01(0.94–1.08)	1.08(0.99–1.17)	0.07
SEER stage			
Localized	ref	ref	
Regional	0.66(0.40–1.08)	0.67(0.34–1.32)	0.26
Distant	1.51(0.96–2.38)	0.94(0.44–2.03)	0.70
LN status			
N0	ref	ref	
NX	4.42(2.92–6.70)	4.56(2.59–8.02)	<0.001
N1	0.78(0.34–1.76)	1.62(0.60–4.41)	0.57
Tumor size (cm)	0.87(0.82–0.92)	0.84(0.79–0.90)	<0.001
Surgery year	1.04(1.01–1.08)	1.02(0.96–1.09)	0.54
SES (Migration) ⁺	1.00(0.99–1.00)	1.00(1.00–1.00)	0.74

⁺ Percent in the same house without migration

* Adjusted for age at diagnosis, SEER stage, LN status, tumor size, surgery year, and SES

Table 3

Bivariate and multivariate analysis of patient characteristics on overall survival

Characteristics	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p value**
Age at diagnosis (year)	1.10(1.05–1.15)	1.09(1.03–1.14)	0.002
Gender			
Male	ref	ref	0.70
Female	1.17(0.85–1.62)	1.07(0.76–1.51)	
Race			
White	ref	ref	0.01
Black	1.04(0.66–1.62)	1.12(0.71–1.79)	
Others	1.97(1.13–3.44)	2.48(1.38–4.46)	
Laterality			
Unilateral	ref	ref	0.09
Bilateral	1.73(0.98–3.05)	1.78(0.92–3.44)	
SEER stage			
Localized	ref	ref	<0.001
Regional	1.52(0.97–2.37)	1.10(0.67–1.81)	
Distant	4.45(3.00–6.59)	2.99(1.89–4.73)	
LN status			
N0	ref	ref	0.003
NX	1.66(1.13–2.42)	1.19(0.77–1.82)	
N1	2.88(1.94–4.28)	2.17(1.38–3.40)	
Tumor size (cm)	1.01(0.99–1.03)	0.99(0.96–1.03)	0.77
Surgery year	0.99(0.97–1.03)	1.00(0.97–1.04)	0.89
Surgery			
PN	1.30(0.70–2.40)	0.79(0.35–1.80)	0.57
RN	ref	ref	
Income			
quartile 1	ref	ref	0.56
quartile 2	0.65(0.20–2.14)	1.03(0.45–2.37)	
quartile 3	0.78(0.32–1.94)	0.69(0.28–1.69)	
quartile 4 (highest)	1.07(0.47–2.43)	0.74(0.46–1.20)	

* Adjusted for age at diagnosis, race, tumor laterality, SEER stage, LN status, tumor size, surgery year, surgery type, and SES(income)

** Type 3 p-values