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Complications Following Nephron-Sparing Surgery for Wilms Tumor

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Abstract

Purpose: Because of the increasing use of nephron-sparing surgery (NSS) in bilateral Wilms tumor, we sought to review the early postoperative complications associated with NSS.

Methods: A retrospective review of patients who underwent NSS at our institution from 2000–2017 was performed. For comparison, a cohort of patients who underwent radical nephrectomy (RN) was also reviewed. Early (30-day) postoperative complications and oncologic outcomes were assessed.

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Results: Fifty-five patients underwent either bilateral (46) NSS or unilateral (9) NSS due to prior resection or congenital solitary kidney. Fifty-four patients who underwent unilateral RN were also evaluated. Twenty NSS patients (36.4%) experienced 21 postoperative complications, including prolonged urine leak (9), infection (8), transient renal insufficiency (1), and intussusception (3). Seven RN patients (13.0%) experienced surgical complications, including infection (4) and intussusception (3). Average intraoperative blood loss was significantly greater in NSS as compared to RN (483.51 ± 337.92 mL and $278.15 \text{ mL} \pm 390.25$, respectively, $p < 0.001$), as was the incidence of positive tumor resection margins (20 [36.4%] and 12 [22.2%], respectively, ($p = 0.037$)).

Conclusions: In our experience, prolonged urine leak, intraoperative blood loss, and positive margins were more frequent in patients undergoing NSS as compared to RN. However, the complications were successfully managed, suggesting that an aggressive approach to NSS in patients with bilateral Wilms tumor is safe and appropriate.

Keywords

Nephroblastoma; Wilms tumor; Nephron-sparing surgery; Bilateral Wilms tumor; Complications; Radical nephrectomy

Background:

Wilms tumors comprise 95% of malignant pediatric renal tumors. The vast majority of Wilms tumors occur in one kidney, with only about 5% of cases arising bilaterally [1]. In the United States, most unilateral tumors are treated with upfront radical nephrectomy followed by adjuvant chemotherapy. In distinction, patients with bilateral WT, WT predisposition syndromes, or WT arising in a solitary kidney are treated with neoadjuvant chemotherapy prior to surgical resection, followed by adjuvant chemotherapy +/- radiation therapy depending on tumor histology and local stage [2].

Another difference in the management of unilateral versus bilateral disease relates to the surgical procedure most commonly performed. Nephron-sparing surgery (NSS) is an attempt at retaining the greatest amount of normal kidney possible to maximize potential renal function while still ensuring complete removal of the tumor, and is currently recommended for patients with bilateral Wilms tumor (or unilateral Wilms tumor with a predisposition to metachronous disease), while radical nephrectomy is recommended for non-syndromic unilateral WT [3][4]. Historically, the surgical approach for treating BWT had been nephrectomy on the more involved side with contralateral partial nephrectomy on the less involved side, as described first by Rickham in 1957 [5]. Several studies within the National Wilms Tumor Study Group (NWTSG) subsequently modified the treatment approach using neoadjuvant chemotherapy and preservative surgical techniques, but still, few patients underwent bilateral nephron-sparing surgery [6][7]. While this greatly improved the overall survival and maintained low recurrence rates for patients with BWT, aggressive removal of nephrons resulted in 12% of patients developing renal failure through NWTSG 1-4 [8].

Aggressive surgical approaches to bilateral WT may leave patients dependent on potentially life-long renal replacement therapy. Preserving viable kidney in this population not only

maintains a better quality of life but also protects from the morbidity and mortality associated with dialysis and renal transplantation [9]. Thus, greater consideration should be given to a surgical approach that aims to leave the maximal amount of normal renal parenchyma for all patients at risk of impaired long-term renal function. A prospective trial was performed recently in the Children's Oncology Group wherein the use of NSS was encouraged for patients with BWT. In that trial, 87% of patients underwent NSS on at least one side but only 35% underwent bilateral NSS [4]. In our own experience, we have been able to perform bilateral NSS in over 90% of patients with BWT [9]. Additionally, neither study reported on the complications associated with this approach.

Given the increasing use of NSS for patients with bilateral Wilms tumor, the present study was performed to review the early (30-day) postoperative complications associated with NSS in Wilms tumor patients operated on at a single institution.

1. Methods

1.1 Setting and subjects

A retrospective review of Wilms tumor patients who underwent nephron-sparing surgery at St. Jude Children's Research Hospital between January 2000 and June 2017 was conducted. For comparison, a cohort of consecutive Wilms tumor patients with unilateral disease, who underwent unilateral radical nephrectomy since 2009 was also evaluated. Patients who underwent concurrent RN and NSS were excluded.

1.2 Study design

The comprehensive review consisted of evaluating surgery details, tumor pathology, and early (30-day) postoperative complications and oncologic outcome. Local tumor stage and histology were considered for each individual kidney in bilateral disease. Approval from the Institutional Review Board was obtained prior to beginning the study, and all data was utilized in accordance with the Health Insurance Portability and Accountability Act of 2013.

1.3 Statistical Analysis

Demographic and complication characteristics were summarized by descriptive statistics (mean, standard deviation, median, and range for continuous variables; counts and percentages for categorical variables). The differences of continuous variables between radical nephrectomy and partial nephrectomy patients were tested by Wilcoxon Rank Sum test (non-parametric). Chi-square tests and Fisher exact tests were used to compare categorical variables between RN and NSS. Fisher's exact test was used if any expected frequency number in the contingency table was smaller than five. Otherwise, a Chi-square test was used. The generalized linear model (GEE) was used to assess the significance of the association between tumor stage and RN/NSS and that between tumor histology and RN/NSS. Overall survival and recurrence for the RN and NSS patients were estimated with Kaplan-Meier estimator. The differences between the RN and NSS patients were assessed with the log-rank test. Statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). A two-sided significance level of $p < 0.05$ was used for all statistical tests.

2. Results

2.1 Patient categorization and demographics

Sixty Wilms tumor patients underwent NSS from January 2000 to June 2017. Five patients were excluded due to the performance of a concomitant contralateral radical nephrectomy. Of the 55 NSS cases, forty-six (83.6%) underwent bilateral NSS for synchronous bilateral Wilms tumors. The remaining nine (16.36%) had unilateral NSS due to prior contralateral RN (4), prior contralateral NSS (4), or congenital solitary kidney (1). For comparison, fifty-four Wilms tumor patients who underwent a unilateral radical nephrectomy since 2009 were also reviewed. The average age at diagnosis of the NSS (mean $\pm$ SD) (2.32 ± 1.58 years) cohort was significantly younger than the RN (4.73 ± 3.72 years) group ($p < 0.001$); the male to female ratio was not significantly different between NSS and RN groups (60% and 61.11% female, respectively) (Table 1).

2.2 Tumor and operation characteristics

Of the 101 kidneys (in 55 patients) that underwent NSS, 51 kidneys (55.4%) were local stage I tumors, 9 kidneys (9.8%) were local stage II tumors, and 32 kidneys (34.8%) were local stage III tumors at the time of resection. For those that underwent radical nephrectomies (54 kidneys), 15 kidneys (27.8%) had local stage I tumors, 12 kidneys (22.2%) had local stage II tumors, and 27 kidneys (50.0%) had local stage III tumors. There was a statistically significant difference in tumor stage between the cohorts ($p = 0.008$). Patients that underwent radical nephrectomy were less likely to have local stage I tumors than patients that had nephron-sparing surgery (OR: 0.35, CI: [0.15, 0.80], $p = 0.013$). Ten (11.1%) kidneys that underwent NSS had anaplastic disease, while 6 (11.3%) kidneys that underwent radical nephrectomy had anaplastic disease. There was no statistically significant difference in tumor histology between RN and NSS groups ($p = 0.971$). The average intraoperative blood loss was significantly higher ($p < 0.001$) during nephron-sparing surgery (483.51 ± 337.92 mL) as compared to radical nephrectomy (278.15 ± 390.25 mL). Finally, patients who underwent NSS were significantly more likely to have a positive tumor resection margin on at least one surgical specimen, as compared to RN (20 [36.4%] and 12 [22.2%], respectively, $p = 0.037$).

Twenty NSS patients (36.4%) experienced 21 postoperative complications (Table 2). These included: prolonged urine leak (9), infection (8), four of which were UTIs; transient renal insufficiency (1), and intussusception (3). The four other infections included a staphylococcal bloodstream infection, hospital-acquired pneumonia, and two *clostridium difficile* infections. Nine patients (16.4%) had a prolonged urine leak, defined as persisting greater than 5 days after surgery, with 7 requiring intervention, either via stent insertion (1) or manipulation of a stent that had been placed at the time of NSS (6). Internal stents have not been used in the last thirteen patients, despite sometimes complex closure of the collecting system, and no persistent urine leak has occurred in any of these patients. Transient renal insufficiency, defined as requiring temporary renal replacement therapy, occurred in one patient. This patient received continuous venovenous hemodialysis for 30 hours, at which point adequate endogenous renal function returned. Intussusception occurred in three patients (5.5%) on postoperative days 5, 6, and 7. These events were heralded by

feeding intolerance after initial tolerance of enteral feeds and were confirmed by ultrasonography. Each of these cases required open surgical reduction of an ileo-ileal intussusception; bowel resection was never required.

2.4 Postoperative complications for RN

Seven RN patients (13.0%) experienced surgical complications, which included infection (4), three of which were UTIs; and intussusception (3) (Table 2). The intussusceptions occurred on postoperative days 3, 4, and 6; all were treated with open surgical reduction as well. RN patients did not experience urine leak or renal insufficiency.

2.5 Recurrence and overall survival

With a median follow-up of 3.89 years (0.02–16.71) the recurrence rate for NSS patients (9) was similar to that of RN patients (8) at 16.36% and 14.82%, respectively. Eight of the nine recurrences in NSS cases occurred within the kidney that had previously undergone nephron-sparing surgery. One patient had a recurrence in the lumbar spine following NSS. As previously reported, all patients with recurrence in the kidney underwent successful redo nephron-sparing surgery, with 2 undergoing a third NSS procedure [10]. Of the eight patients who underwent RN and had recurrence, five patients had metastases to the lungs, two patients had liver metastases, and one patient had metastasis in the peritoneum. Overall survival at last follow-up was 87.3% in NSS cases and 90.7% in RN cases. Comparison of Kaplan-Meier survival curves between the two groups are shown in Figure 1. Overall survival ($p = 0.677$) and recurrence ($p = 0.811$) are not significantly different between the RN and NSS patients.

3. Discussion

Here we report the short-term, peri-operative complications and oncologic outcomes following nephron-sparing surgery for bilateral Wilms tumor (or WT in a solitary kidney) over a seventeen-year period. Patients who underwent NSS had a significantly earlier age at diagnosis than those with unilateral tumors, consistent with the earlier appearance of bilateral disease, likely due to “first-hit” germline mutations. As compared to patients who underwent radical nephrectomy, patients who underwent NSS experienced prolonged urine leaks, had an increased amount of intraoperative blood loss, and were more likely to have a positive tumor resection margin. These results are not surprising given the different surgical approaches. A urine leak, in particular, after radical nephrectomy would be a distinctly unusual complication. More recently, however, we have modified our surgical practice in the performance of NSS and no longer place internal stents at the time of NSS, even after complicated closures of the collecting system, only leaving flank Penrose drains in some of these circumstances. Interestingly, this seems to have reduced our incidence of prolonged postoperative urine leaks in our NSS patients.

Increased intra-operative blood loss and higher incidence of positive margins are also not unexpected for the cohort undergoing nephron-sparing surgery, in which the kidney parenchyma is cut across. This did not impact survival, although, patients in whom there was a positive margin on at least one of the surgical specimens did receive adjuvant radiation

therapy. There was a surprisingly high incidence of positive margins following radical nephrectomy in our experience, in part due to the nature of referrals received at tertiary care centers. Of the twelve RN resections with positive margins, six were attributed to vascular thrombus and three were due to preoperative tumor rupture. Other short-term complications including rates of intussusception and UTIs were comparable between the two cohorts. Additionally, recurrence rates and overall survival were not significantly different between surgical approaches.

Limitations of this study, including the limited sample size and retrospective study design, should be considered when extrapolating from these results. Nevertheless, our results suggest that an ardent approach to preserving nephrons in kidneys which both harbor Wilms tumor(s) can be safely pursued, with the short term complications being easily managed and the long term benefit being the preservation of more kidney parenchyma to support kidney function. However, the short term complications, especially the higher incidence of positive margins and local recurrence, should be carefully considered when contemplating performing NSS for patients with unilateral, non-syndromic Wilms tumor, as these patients have a lifetime incidence of renal failure of less than 0.25% [8].

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How this paper will improve care:

This single-institution, retrospective review of patients with bilateral Wilms tumor undergoing nephron-sparing surgery found although complications occurred more frequently than with radical nephrectomy, complications were easily managed, suggesting an aggressive use of nephron-sparing surgery should be considered in these patients.

Figure 1. Kaplan-Meier estimates of recurrence (A) and survival (B) comparing patients who underwent nephron-sparing surgery (NSS) or radical nephrectomy (RN).

Table 1.**Descriptive Statistics of Radical and Partial Nephrectomy Patients**

	Overall (n=109)	RN (n=54)	NSS (n=55)	P-Value
Age at Diagnosis				<.001
Mean (SD)	3.51(3.08)	4.73(3.72)	2.32(1.58)	
Median (Range)	2.80(0.26~17.75)	3.67(0.26~17.75)	2.16(0.33~5.97)	
Gender				0.907
Male	43 (39.45%)	21 (38.39%)	22 (40%)	
Female	66 (60.55%)	33 (61.11%)	33 (60%)	
Tumor Stage (per kidney) ^a				0.008
I	66 (45.2%)	15 (27.8%)	51 (55.4%)	
II	21 (14.4%)	12 (22.2%)	9 (9.8%)	
III	59 (40.4%)	27 (50.0%)	32 (34.8%)	
Tumor Histology (per kidney) ^b				0.971
Favorable	127 (88.8%)	47 (88.7%)	80 (88.9%)	
Anaplastic	16 (11.2%)	6 (11.3%)	10 (11.1%)	
Blood Loss (mL)				<.001
N	101	54	47	
Mean (SD)	373.71(379.27)	278.15(390.25)	483.51(337.92)	
Median (Range)	250(20~2100)	100(20~2100)	380(150~1650)	
Margin Status				0.037
N	104	54	50	
Negative	72 (66.1%)	42 (77.8%)	30 (54.5%)	
Positive	32 (29.4%)	12 (22.2%)	20 (36.4%)	
Recurrence	17 (15.6%)	8 (14.8%)	9 (16.4%)	0.824
Survival	97 (89.0%)	49 (90.7%)	47 (85.5%)	0.540
Follow Up (years)				
Median (Range)	3.40(0.02~16.71)	2.98(0.02~8.46)	4.10(0.02~16.71)	

^a54 observations in Radical, 92 observations in NSS.

^b53 observations in Radical, 90 observations in NSS.

Table 2.

Postoperative Complications in Radical vs. Nephron-Sparing Nephrectomies

Complication	Overall (n=109)	RN (n=54)	NSS (n=55)	P Value
Prolonged Urine Leak				0.003
No	100 (91.7%)	54 (100.0%)	46 (83.6%)	
Yes	9 (8.3%)		9 (16.4%)	
Infection				0.234
No	97 (89.0%)	50 (92.6%)	47 (85.5%)	
Yes	12 (11.0%)	4 (7.4%)	8 (14.5%)	
Intussusception				1.000
No	103 (94.5%)	51 (94.4%)	52 (94.5%)	
Yes	6 (5.5%)	3 (5.6%)	3 (5.5%)	
Renal Insufficiency				1.000
No	108 (99.1%)	54 (100.0%)	54 (98.2%)	
Yes	1 (0.9%)		1 (1.8%)	