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Contemporary Use of Nephron-Sparing Surgery for Children with Malignant Renal Tumors at Freestanding Children's Hospitals

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Abstract

Purpose—It is widely accepted that, when feasible, nephron-sparing surgery (NSS) is preferable to radical nephrectomy (RN) for treatment of renal tumors in adults. However, RN is more frequently used in children. We sought to compare in-hospital outcomes after NSS and RN for malignant pediatric renal tumors.

Patients & Methods—The Pediatric Health Information System (PHIS) combines data from over 40 North American pediatric hospitals. We queried PHIS to identify children with malignant renal tumors who underwent surgery from 2003 to 2009. We examined whether outcomes (complication rates, cost and length of stay) differed by procedure type. Multivariate regression models were used to adjust for confounding and generalized estimating equations were used to adjust for hospital clustering.

Results—We identified 1,235 children with renal tumors who underwent RN (91%) or NSS (9%). Patients undergoing RN and NSS had similar median co-morbidity scores (p=0.98), hospital length of stays (each 6.0 days, p=0.54), in-hospital charges, ($25,700 v. $37,000, p=0.11), and surgical complication rates (16.4 v. 20.5%, p=0.24). These outcomes remained similar after adjusting for other patient and hospital factors.

Conclusions—The majority of children with malignant renal tumors treated at children's hospitals undergo RN. RN and NSS use were not significantly different in terms of their length of hospital stay, in-hospital charges, and complication rates. While oncologic outcomes are lacking, these data suggest that NSS may be performed in selected children with malignant renal tumors without significantly increasing their hospital charges, length of stay, or surgical complication rates.

Keywords

Kidney Neoplasms; Wilms Tumor; Renal Cell Carcinoma; Pediatrics

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INTRODUCTION

Beginning in the 1980s, radical nephrectomy (RN) was challenged as the standard of care for management of malignant renal tumors by several reports demonstrating favorable results with nephron-sparing surgery (NSS) in select adult patients.[1,2] Since then, numerous reports have demonstrated that NSS is an effective alternative to RN, leading many experts to conclude that NSS now represents the standard of care for most adult renal tumors, even in the setting of a normal contralateral kidney.[3-6] The merits of this approach become more apparent in light of recent data suggesting a survival benefit to preserving maximal renal function.[6-8]

While NSS use has increased for managing renal tumors in adults, RN remains the standard of care in children with renal tumors. Potential roadblocks to pediatric NSS use include oncologic concerns regarding local recurrence due to organ preservation and technical considerations such as the relatively large size of most pediatric renal tumors. Recent reports demonstrate that NSS can be successfully applied in selected pediatric patients without compromising oncologic outcomes.[9-19] It is unclear whether these results have led to increased utilization of NSS in children with malignant renal tumors, or whether in-hospital outcomes such as charges or complication rates differ between the two surgical techniques.

The purpose of this study was to analyze practice trends and in-hospital outcomes in children with malignant renal tumors. We used a national database of children's hospitals to compare NSS with RN in terms of surgical outcomes such as surgical complication rate, length of hospital stay, and in-hospital charges.

PATIENTS AND METHODS

Data Source

We analyzed the Pediatric Health Information System (PHIS), a national database of administrative and billing data from freestanding North American children's hospitals affiliated with the Child Health Corporation of America (Shawnee Mission, KS). The PHIS database is composed of over 1,000,000 pediatric patient encounters annually, including data from inpatient admissions, ambulatory medical and/or surgical short-stay areas, and emergency department visits. PHIS data accuracy is screened on a quarterly basis through the joint efforts of the Child Health Corporation of America, an independent data manager (Thomson Healthcare, Durham, NC), and each participating hospital. Data are accepted into PHIS only when classified errors occur in less than 2% of a hospital's quarterly data. In total, data from 41 hospitals were used.

Patient Population

We queried PHIS in order to identify all hospital or outpatient surgeries occurring between January 2003 and September 2009 (inclusive) for patients less than 18 years of age with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code for malignant renal neoplasm (189.0). We then defined our treatment groups based on procedure codes for RN (55.5, 55.51, 55.52, 55.53, or 55.54) or partial nephrectomy/NSS (55.4).

In order to verify database findings, a nested chart review was performed of all children who received treatment at our institution. Patient records were reviewed in detail in order to verify tumor histology, tumor stage, and procedure type.

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Variable Selection

The primary endpoints of the study were in-hospital outcomes: surgical complications, length of hospital stay, and hospital charges. Surgical complications were defined by PHIS as in-hospital surgical issues such as prolonged postoperative ileus, small bowel obstruction, or wound infection, based on ICD-9-CM codes. Length of stay and hospital charges were tabulated beginning on the day of the surgery.

Predictor variables and covariates were selected based on biologic plausibility and/or demonstrated associations in the literature. Our primary predictor variable was surgical procedure (NSS vs. RN). Other model covariates included patient age, gender, race/ethnicity, insurance type (private vs. public), patient severity, procedure year, hospital census, hospital teaching status, United States census region, and metropolitan area population. Patient co-morbidity was estimated using the All Patient Refined Diagnosis Related Group (APR-DRG) severity level, version 20 (3M Health Information Systems, Salt Lake City, UT) and was categorized as Minor, Moderate, Major, and Extreme. As fewer than 5% of study patients were in the Minor (n=5, 0.4%) or Extreme (n=53, 4.4%) categories, we dichotomously defined patients as being in low-severity (Minor and Moderate) or high-severity (Major and Extreme) groups.

Statistical Methods

Initial bivariate tests of association were performed using Fisher's exact test, Mantel-Haenszel chi square trend test, t-test, or Wilcoxon rank-sum test as appropriate based on data characteristics and distribution. Based on these results, logistic (complication rates) and Poisson (cost, length of stay) regression models were constructed in order to further examine associations between the predictor of interest – procedure type – and the outcome variables 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 model were patient age, gender, hospital census, and metropolitan area population. Generalized estimating equations were used to adjust for hospital-level clustering. In addition, we constructed a logistic regression model in order to define any associations between procedure type and the above-listed covariates. Model diagnostics revealed no significant violations of regression assumptions. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). All tests were two-sided and p-values of 0.05 or less were considered significant.

Institutional Review Board approval and PHIS administrative approval were obtained prior to data collection or analysis.

RESULTS

Bivariate Analysis

We identified 1,235 children with renal tumors who underwent surgery for a malignant renal tumor, 1,118 (91%) of whom received RN and 117 (9%) of whom received NSS. Table 1 details the demographic characteristics of the cohort by procedure type. NSS patients more likely to be female (63 v. 51%, p=0.01) than RN patients. No differences were noted between procedure types in terms of mean patient age (4.8 vs. 4.3 years, p=0.13), race/ethnicity (p=0.60), insurance type (p=0.48), or co-morbidity level (p=0.98). There was no significant change in procedure use over time, with NSS accounting for 12% of procedures in 2003 and 10% of procedures in 2009 (p=0.23 for trend).

Of the 41 included PHIS hospitals, 35 hospitals performed both RN and NSS during the study period. The number of procedures performed by each hospital was highly variable

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(p=0.0008), ranging from 0 to 16 (mean 2.9) for NSS and 9 to 55 (mean 27.3) for RN. Procedure type was also associated with hospital size (p=0.04), but not with teaching status (p=0.35), metropolitan area population (p=0.58), or census region (p=0.69). There was no discernible trend in procedure type per hospital over time (p=0.34).

Post-procedure outcomes are detailed in Table 2. Patients undergoing RN and NSS had similar hospital lengths of stay (median 6.0 v. 6.0 days, p=0.54), in-hospital charges (median $25,700 v. $37,000, p=0.11), in-hospital complication rates (16.4 v. 20.5%, p=0.24), and in-hospital mortality rates (0.24 vs. 0.0%, p=0.57).

Multivariate Analysis – Associations with In-Hospital Outcomes

After adjusting for confounding by other hospital and patient factors as well as hospital-level clustering, surgical procedure type (RN vs. NSS) remained unassociated with hospital length of stay (p=0.77), in-hospital charges (p=0.92), patient co-morbidity levels (p=0.57), or in-hospital complication rates (p=0.46).

Multivariate Analysis – Associations with Procedure Type

NSS use was independently associated with a larger hospital size (p=0.02) and female gender (p=0.008). Patient age (p=0.09), metropolitan area population (p=0.7), and the individual hospital (p=0.18) at which a patient was treated were not associated with use of a particular procedure after correcting for confounding by other factors.

Nested Chart Review

In order to verify this administrative data, we performed a nested chart review of the 45 patients at our institution. PHIS codes for procedure type were accurate in 43 (96%) patients, with one RN and NSS patient each having been miscoded. Tumor pathology was accurately coded in PHIS as malignant in 44 (98%) patients: 36 (80%) patients with Wilms' tumor (WT), 3 (7%) with renal cell carcinoma (RCC) or translocation carcinoma, 2 (4%) with neuroblastoma, 2 (4%) with rhabdoid tumor and 1 (2%) with a desmoplastic small round blue cell tumor. One patient (2%) was diagnosed with a cystic nephroma. Among WT patients, 3 of 36 (8%) were noted to have diffuse anaplasia. Median WT stage was stage II (range I-IV), which did not differ between procedures (stage II vs. stage III, p=0.3). Among all tumors, median tumor size was 11.0 cm (interquartile range, 7.5-13.0 cm), which also was not significantly different between RN and NSS (11.5 vs. 9.0 cm, p=0.5). Similarly, procedure type was not associated with tumor histology (p=0.7), tumor stage (p=0.5), or physician type (p=1.0).

COMMENT

It is widely accepted that, when feasible, NSS is preferable to RN for the treatment of renal tumors in adults.[5,6,8] In children, however, RN is more frequently used, due in part to the relatively large size and technical difficulty of NSS for most pediatric renal tumors. As such, the use of NSS is chiefly limited to children with bilateral disease or other imperative indications.

In light of recent data suggesting that adults undergoing RN may have decreased long-term survival as compared to NSS patients,[6,8] and given the small but measurable increased risk of death from renal disease in long-term WT survivors,[20,21] it seems reasonable to reconsider the role of NSS in children. Multiple series have reported successful NSS use in children with malignant renal tumors, particularly WT and RCC.[9-19] However, a common theme in many series – particularly older reports - has been an increased local recurrence rate for NSS as compared to RN. Drawing on data from the Fourth National Wilms' Tumor

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Study, Horwitz *et al*. reported that 8.2% of patients with bilateral WT undergoing NSS suffered a local recurrence.[15] Given that local recurrences have been linked to increased mortality rates in WT,[22] this issue is of significant concern and should not be quickly dismissed. However, it is important to note that NSS technique has evolved with time: contemporary reports of NSS document recurrence rates of 0 to 2.5% in well-selected patients with WT or RCC.[9,11,23] Giel *et al*. recently reported an 88% overall survival rate in a single-institution series of 17 patients with bilateral, synchronous WT – 3 of whom had anaplasia and 2 of whom had distant metastases at the time of diagnosis.[24] This compares favorably with survival rates from other large WT series,[25] implying that the application of contemporary NSS surgical techniques to well-selected patients may not necessarily raise the risk of local recurrence or cancer-specific mortality. However, this finding awaits confirmation in larger, multi-institution studies.

In the current study, we noted an association between increased NSS use and increased hospital size. Given our retrospective, observational study design, this association is difficult to interpret; however, it seems likely that larger children's hospitals are referred higher volumes of pediatric renal tumors overall, making it more likely that they would perform a higher volume of NSS. Based on these data alone, however, it is unclear whether characteristics such as increased surgical volume truly play a role in determining surgery type in otherwise similar patients.

This study should be interpreted in light of its limitations. First, PHIS is an administrative database, with the attendant potential for clerical errors and lack of clinical detail which is associated with all such databases. However, PHIS data is independently reviewed on a quarterly basis to ensure quality standards; this is consistent with the 96-98% coding accuracy which we discovered following our nested chart review of patients at our hospitals. While a review of all 1,235 patient records would clearly have been ideal, PHIS regulations and privacy guidelines prevent investigators from accessing medical records at other institutions. As such, we must extrapolate our institution's coding accuracy to all patients, presuming that such an extrapolation is reasonable. Similarly, our definition of complications was limited by our data source. PHIS does not currently classify surgical complications as recommended by many authors and organizations,[26,27] which limits our comparisons of the types of surgical complications.

Second, this study examines only in-hospital surgical outcomes of NSS and RN, not oncologic outcomes such as long-term event-free survival, overall survival, or local recurrence rates. Clearly, in children with malignant renal tumors, the ultimate goal of therapy is to maximize cancer-specific survival. As such, this study should not be construed as proof that NSS is a superior oncologic procedure to RN in children with renal tumors. Rather, our intent was to compare the in-hospital outcomes of each procedure and thus to determine whether NSS compared favorably with RN in terms of these strict criteria. Clearly, if a procedure is prohibitively expensive or complication-prone, it is unlikely to be practically superior to the current gold standard. In this case, we found that NSS compares quite favorably with RN, implying that in well-selected patients, NSS may be a reasonable treatment option for malignant renal masses in children – provided that long-term data demonstrate that oncologic outcomes are not compromised with NSS.

Third, given the non-random treatment allocation, it is likely that selection bias played a role in our findings. As such, these results should be interpreted with caution, as it is clear that not all patients are suitable candidates for NSS. However, as noted above, the intent of this study was not to determine the superiority of RN or NSS for the management of pediatric malignant renal tumors, but rather to determine whether the two procedures were associated with reasonably comparable surgical and technical outcomes. Further study of suitable

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patients (*e.g.*, those with smaller tumors or favorable pathology) would be needed before any recommendations of changes to current clinical practice would be indicated.

Despite its limitations, however, this analysis reveals that NSS as currently used in U.S. children's hospitals is associated with in-hospital outcomes that are comparable to those achieved with RN. After nearly two decades of follow-up, only a relatively small fraction of children with unilateral, non-syndromic WT involved in National Wilms' Tumor Study Group studies progressed to end-stage renal disease.[20] Nevertheless, at 6% of all late effects deaths, renal disease was the third most common cause of death among long-term Wilms' tumor survivors in those same studies.[21] Given the impressive body of literature supporting the use of NSS among adults with renal tumors, and given that a dose-response effect can be seen between the degree of renal insufficiency and all-cause mortality risk,[7] we submit that further study of NSS would seem appropriate.

CONCLUSIONS

The majority of children with malignant renal tumors treated at children's hospitals undergo RN, although a significant minority undergo NSS. Patients undergoing RN and NSS were not significantly different in terms of their length of hospital stay, in-hospital charges, and complication rates. These data suggest that NSS may be performed in well-selected children with malignant renal tumors without significantly increasing their hospital charges, length of stay, or surgical complication rates. Long-term data on oncologic outcomes are lacking, however, and this issue clearly requires further study before implementing management changes in children with malignant renal tumors.

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Table 1

Demographic Characteristics of Study Population, by Procedure Type

	Radical Nephrectomy	Partial Nephrectomy	p Value
Total patients (n,%):	1,118 (91%)	117 (9%)	-
Age in years (Median, IQR):	3.5 (1.8-5.3)	3.5 (2.2-6.1)	0.15‡
Age Category (n,%):			
0-1 years	138 (12%)	8 (7%)	0.12†
1-3 years	330 (30%)	41 (35%)	
3-6 years	425 (38%)	36 (31%)	
6-12 years	170 (15%)	23 (20%)	
12-18 years	55 (5%)	9 (8%)	
Gender (n,%):			
Female	571 (51%)	74 (63%)	0.01*
Male	547 (49%)	43 (37%)	
Race (n,%):			
White	619 (55%)	68 (58%)	0.60*
Black	180 (16%)	22 (19%)	
Hispanic	164 (15%)	15 (13%)	
Other	155 (14%)	12 (10%)	
Insurance Type (n,%):			
Private Insurance	433 (39%)	41 (36%)	0.48*
Public Insurance	671 (61%)	74 (64%)	
Co-morbidity Level (n,%):			
Low co-morbidity	460 (41%)	48 (41%)	0.99*
High co-morbidity	658 (59%)	69 (59%)	
Average Hospital Census Size (Median, IQR):	206 (181-282)	241 (180-334)	0.03‡
US Census Region (n,%):			
Northeast	150 (13%)	12 (10%)	0.69*
Midwest	362 (32%)	43 (37%)	
South	361 (32%)	37 (32%)	
West	245 (22%)	25 (21%)	

*Fisher's exact test

‡Wilcoxon rank-sum test

†Mantel-Haenszel chi-square test

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Table 2

In-Hospital Surgical Outcomes, by Procedure Type

	Radical Nephrectomy	Partial Nephrectomy	p Value
Length of Stay, in Days (Median, IQR):	6 (4-7)	6 (4-8)	0.54‡
Hospital Charges (Median, IQR):	$44,849 ($32,636-60,907)	$38,284 ($27,207-57,897)	0.02‡
Surgical Complications (n,%):			
Yes	183 (16%)	24 (21%)	0.24*
No	935 (83%)	93 (79%)	

*Fisher's exact test

‡Wilcoxon rank-sum test