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Variation in use of nephron-sparing surgery among children with renal tumors

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Abstract

Objective—Given the negative long-term effects of renal insufficiency, nephron-sparing surgery (NSS) is increasingly discussed for the treatment of pediatric renal tumors. We sought to examine variation in practice patterns of NSS among children with renal tumors.

Materials and methods—We performed a retrospective cohort analysis of claims data for pediatric inpatient admissions captured by the Kids Inpatient Database (1997–2009). We identified children with renal tumors who underwent surgery, including radical nephrectomy (RN) and NSS. We used multivariable logistic regression to assess the relationship between use of NSS and various clinical, demographic, and geographic predictors of interest.

Results—We identified 10,108 pediatric inpatient admissions for renal tumors. Of these, 1,657 were surgical admissions, with 1,501 patients (90.5%) undergoing RN and 156 (9.5%) undergoing NSS. On multivariable analysis, NSS was associated only with a concomitant diagnosis of renal insufficiency (relative ratio [RR] 3.37, $p = 0.01$) and surgery in the Northeastern USA (RR 3.07, $p = 0.03$). Race/ethnicity, age, payer type, procedure year, and other non-clinical factors were not significantly associated with NSS.

Conclusion—In a large, nationwide pediatric cohort, RN remains the most common surgical intervention for renal tumors. NSS is significantly associated with a diagnosis of renal insufficiency, but not non-clinical factors such as patient gender or race.

Keywords

Pediatrics; Kidney neoplasms; Nephrectomy; Practice pattern variations

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Conflict of interest JSW currently serves on the pediatric urology working group for RTI International Best Hospitals Project which is a consultant to *US News and World Report* magazine regarding their ranking of pediatric urology hospitals. JSW also has served on an advisory panel for Glaxo Smith Kline. None of the remaining authors have any conflict of interest, financial or otherwise, to disclose.

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Introduction

In adults, controversy remains regarding whether nephron-sparing surgery (NSS) is the optimal management strategy for renal tumors [1,2], even as some note a recent rise in utilization of NSS [3]. What is not as controversial, however, are the negative effects of chronic kidney disease (CKD), including increased risk for future cardiovascular events and death [4].

Preserving kidney function is potentially even more significant in children, whose longer life expectancy leads to more years at risk of CKD [5]. Current recommendations from the Children's Oncology Group (COG) support the use of radical nephrectomy (RN) in a non-syndromic child with a normal contralateral kidney. However, recent reports suggest that NSS can be safely applied to carefully selected children with comparable survival outcomes as RN [6–16]. Additionally, renal function in children undergoing NSS appear to be better preserved compared with those undergoing RN [17–19]. Hence, it is unclear whether and to what extent these conflicting signals have affected the utilization of NSS across time and geographic regions.

The objective of this study was to analyze variation in surgical practice patterns among children with renal tumors; we hypothesized that patients with predisposing clinical features (such as bilaterality or some degree of renal insufficiency) would be more likely to undergo NSS than RN, and that other non-clinical factors (such as patient race or gender) would be unlikely to impact on rates of RN versus NSS. We used a national database of inpatient pediatric admissions to assess temporal trends and compare geographic, demographic, and clinical predictors of NSS compared with RN utilization.

Methods

Data source

The Kids' Inpatient Database (KID) is a product of the Healthcare Cost and Utilization Project, sponsored by the Agency for Healthcare Research and Quality (Rockville, MD, USA). The KID is a triennial, stratified sample of pediatric discharges from all community, non-rehabilitation hospitals in participating states (from 2,521 hospitals in 22 states in 1997 to 4,121 hospitals from 44 states in 2009) [20]. The sampling design includes 10% of uncomplicated births and 80% of all other pediatric discharges annually, generating excellent power for the detection and characterization of rare conditions. In 1997, pediatric discharges were defined as those involving patients aged 18 years or younger at their admission date. Subsequently, pediatric discharge criteria were expanded to include patients aged 20 years or younger at admission.

We combined the latest four editions of the KID (2000–09), which contained 2.5, 2.9, 3.1, and 3.4 million pediatric discharges, respectively. This study was defined as exempt by our institutional review board.

Patient and predictor selection

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes were used to identify patients with a diagnosis of a renal mass (ICD-9-CM 189.0). Patient-level demographics captured in our model included age (grouped using standard American Academy of Pediatrics age categories), race/ethnicity (white, black, Hispanic, Asian/Pacific Islander, or other), ZIP code median income by quartile, and primary insurance payer (public or private). Hospital-level factors included size (number of beds), teaching/children's hospital designation, and hospital ownership (government, private non-profit, or private for-profit), as well as geographic location and population setting. Children's hospital designation was defined by the National Association of Children's Hospitals and Related Institutions. Teaching hospital designation was defined by the American Hospital Association Annual Survey of Hospitals. Geography was defined as US census bureau region (Northeast, South, Midwest, and West) and population setting was designated as urban or rural, also based on US census definitions.

Outcome selection

We broadly defined both diagnoses and surgical interventions based on ICD-9-CM procedure codes. We defined RN to include nephroureterectomy (55.51) or nephrectomy of a solitary kidney (55.52); transplant nephrectomy (55.53) patients were excluded. We defined NSS to include partial nephrectomy (55.4) and percutaneous ablation (55.32). In an effort to reduce double-counting of patients, we excluded those children who underwent only an open renal biopsy (55.24) or needle biopsy (55.23).

Renal insufficiency was defined based on ICD-9-CM or Clinical Classification Software diagnostic/procedure codes for acute renal failure, chronic renal failure, dialysis, or renal transplant. We attempted to identify bilateral tumors based on codes for bilateral nephrectomy (55.54); dual codes for partial nephrectomy; or codes for both RN and NSS. Unfortunately, coding for bilateral tumors lacked adequate granularity to be included in the multivariable analysis.

Statistical analysis

Initial bivariate tests of association were performed using Fisher's exact, chi-square, Cochran-Armitage trend, or Wilcoxon rank-sum tests based on data characteristics. We then constructed our multivariable logistic regression model; covariates were a priori selected based on biological plausibility and/or a p -value ≤ 0.2 in bivariate analysis. Patient-level covariates considered for our model included patient age, gender, race/ethnicity, insurance payer, median income of the patient's home ZIP code, year of admission, and diagnosis of renal insufficiency. Hospital-level covariates included admitting hospital, geographic region, and teaching/children's hospital designations. Ultimately, the final model included patient age, race, insurance payer, children's hospital designation, hospital region, and renal insufficiency diagnosis. Model diagnostics revealed no significant violations of regression assumptions. We corrected for hospital-level clustering using generalized estimating equations with hospital as a random effect.

All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). All tests were two-sided and p -values of ≤ 0.05 were considered to be significant.

Results

Demographics

Of the combined admissions in the 2000, 2003, 2006, and 2009 KID, we identified 10,108 admissions with diagnostic codes corresponding to renal tumors. We excluded 8,459 records; of these, the majority were non-surgical admissions ($n = 8,073$), or underwent transplant nephrectomy ($n = 3$) or renal biopsy only ($n = 383$). This resulted in a cohort of 1,657 surgical admissions, during which a total of 1,676 surgical procedures were performed. To reduce double-counting of patients who underwent more than one procedure during an admission, each admission was counted only once toward an overall number of procedures for a total final cohort of 1,657 procedures.

Of the included children (Table 1), 53% were girls, 50% were toddlers (2–5 years old), 57% were non-Hispanic whites, 59% were privately-insured, and 33% were from the South. Most patients were treated at urban teaching hospitals (90%), though urban non-teaching (9%) and rural (1%) hospitals were also represented. Admissions were spread fairly evenly across study years, with a slight preponderance of children being distributed in the more recent versions of KID.

Inpatient nephrectomy outcomes

Of the 1,657 renal surgical procedures, 1,501 (90.5%) were RN and 156 (9.5%) were NSS. Of the children in the radical resection group, the vast majority underwent nephroureterectomy with a small proportion undergoing nephrectomy of solitary kidney (9/1501, 0.6%) and bilateral nephrectomy (4, 0.3%).

Regional distribution of NSS and RN procedures was significantly varied (Fig. 1). On bivariate analysis, a diagnosis of renal failure and surgery in the Northeast compared with the Midwest were significant predictors of NSS. These associations remained significant on multivariable analysis (Table 2), with NSS again being associated only with diagnoses of renal failure (relative ratio [RR] 3.37, $p = 0.01$) and also surgery performance in the Northeast (RR 3.07, $p = 0.03$). Race, age, payer type, year of procedure, and children's hospital designation were not significant predictors of NSS on multivariable analysis.

Discussion

In adults and children with malignant renal tumors, the balance between oncologic control and preservation of functional renal parenchyma must be carefully weighed. RN may reduce the risk of local recurrence, but NSS reduces the risk of hyperfiltration injury and long-term CKD. In particular, children constitute a distinct subpopulation at potentially higher risk than adults for CKD owing mainly to their younger age and thus increased number of years at risk. Ultimately, each surgical option has associated risks and benefits, but the final choice requires a joint and informed decision-making process.

As in adults, children with bilateral synchronous Wilms' tumors (WT) or tumors in solitary kidneys were historically more likely to undergo NSS versus RN [6–11, 19]. Recently, the Children's Oncology Group developed a formal ongoing protocol (AREN0534) to study NSS outcomes in these high-risk patients. Nevertheless, the current recommended treatment for children with a unilateral tumor and a normal contralateral kidney remains RN. Fear of local recurrence clearly influenced this decision-making process to recommend RN, with ample historical justification; the fourth National Wilms' Tumor Study (NWTS4), closed in 1994, showed a local relapse rate of 8.2% in children with bilateral synchronous WT who had initially undergone NSS [21]. Given that children who suffered a local recurrence had an overall survival of 43% at 2 years, there was great pressure to prevent recurrences [22].

However, local recurrence rates have sharply declined in the modern era, with improvements in NSS techniques likely contributing to the overall improved outcomes in more contemporary series [23]. Recent studies have demonstrated excellent oncologic outcomes and survival with NSS, comparable with RN outcomes, in unilateral renal tumors with a normal contralateral kidney [12–18]. Syndromic patients also have been shown to benefit from a NSS approach, with the Toronto group finding no local recurrences and normal creatinine values in six syndromic patients who underwent NSS [24]. As such, recent recommendations on management of bilateral synchronous WT emphasize the primary objective of surgical treatment to be preservation of renal parenchyma after initial preoperative chemotherapy [25]. Although in the current study tumor bilaterality lacked adequate coding granularity to factor into the multivariable analysis, we still noted a higher-than-expected rate of NSS at 11% of pediatric renal tumors—more common than would be expected if NSS were used solely in bilateral or syndromic renal tumors.

The rise of NSS in pediatric renal tumors is not limited only to WT. Cook et al. [12] reported on five pediatric patients with renal cell carcinoma (RCC) who underwent NSS and had 100% disease-free and overall survival at a mean follow-up of 61 months. However, the authors did not evaluate postoperative renal function. Among studies that have compared postoperative kidney function following NSS versus RN for any etiology, all demonstrated better renal function with NSS, as measured by change in estimated glomerular filtration rate (eGFR) [17], serum creatinine levels [18], or creatinine clearance over time [19]. Cozzi et al. [17] recently reviewed their single-institution series of 25 patients with unilateral WT and normal contralateral kidney. Of 15 patients treated with RN, eight had stage II CKD at 12 years follow-up, with five of the eight demonstrating no compensatory increase in their eGFR following RN. By contrast, only one of 10 patients treated with NSS was found to have stage II (or worse) CKD at long-term follow-up.

In the current study, we found that presence of renal failure influenced selection of NSS. We also found regional variation in utilization of NSS over RN for pediatric renal tumors. Children undergoing surgery for their kidney tumors were more likely to receive NSS over RN in the Northeast region of the USA relative to the Midwest. A previous study using the Pediatric Health Information System (PHIS) showed no geographic association with NSS over RN [23]. However, the databases differ in that PHIS consists only of free-standing children's hospitals, whereas KID includes discharges from a broader range of hospitals. Thus, KID may more accurately represent the true contemporary practice trends for surgical

management of pediatric renal tumors. As children with renal tumors are presumably referred to centers of excellence with more experience in the treatment of pediatric tumors, the surgical predilection of certain high-volume hospitals may explain the observed regional variation.

Importantly, we found neither temporal trends in practice patterns, nor any effect of race, socioeconomic status, insurance payer, age, or hospital type on utilization of NSS over RN in KID for management of pediatric renal tumors. The lack of a temporal trend is notable, given that increasing NSS rates have been demonstrated amongst the adult population for small renal masses [3]. However, this can be explained by a fundamental difference between pediatric and adult urologic oncology. Management of pediatric renal tumors is primarily protocol-driven; as such, pediatric care patterns may not be as predisposed as adults to variations in individual surgeon preferences. Interestingly, we did not find a difference in effect of age on likelihood of undergoing NSS. In theory, younger patients with renal tumors should be more likely to have RN performed, secondary to increased incidence of congenital mesoblastic nephroma and tumors with worse prognosis, such as rhabdoid tumor or clear cell sarcoma. However, younger patients also have a higher incidence of bilateral WT and thus may actually undergo NSS at a higher rate than their older contemporaries. As more data emerge on outcomes of pediatric RCC, WT, and other renal tumors, and as techniques for NSS are further refined, we suspect pediatric NSS utilization rates will increase over time in a fashion similar to adults.

Our results must be viewed in light of their limitations. First, our findings rely on the validity of the database used. KID is an administrative database and thus inherently lacks patient-specific information, including recurrence rates, prior chemotherapy use, and estimates of renal function. Additionally, KID is not a longitudinal database and, as such, we analyzed admissions, not patients—a fact that is presumably offset by the low rate of re-resections these children will undergo. We therefore stress that these data cannot be used to evaluate the superiority of either NSS or RN. The goal of our study was not to define a best practice, but rather to examine practice patterns of surgical management of pediatric renal tumors. In addition, it is important to note that we did not use KID-specific weights for any of our analyses; because of the very small size of our sample compared to the overall large size of the KID database, we were concerned that we would introduce significant bias by weighting based on a non-representative sample. In order to verify that we did not introduce significant bias by *not* weighting our sample, we did perform a weighted sensitivity analysis. Using KID-specific weights gave generally similar results to our non-weighted analysis and did not change our conclusions (data not shown).

Second, beyond diagnosis of renal failure, KID also lacks specific clinical criteria such as tumor size, location, or focality, which clearly should influence surgical approach. However, Cost et al. [26] recently reviewed specimens from children who underwent pre-chemotherapy RN for unilateral WT; using strict pathological criteria to identify candidates for NSS, they demonstrated that as many as one in four children have tumors favorable for a nephron-sparing approach. This suggests that NSS may be substantially underutilized.

Third, in KID the diagnosis of renal insufficiency is not defined clearly by serum creatinine level, eGFR, or creatinine clearance. Instead, the diagnosis is based on ICD-9-CM codes, which hinge on accurate documentation. While renal insufficiency is a serious enough issue that it may be less frequently miscoded, it is nonetheless possible that poor coding could have influenced our results.

Lastly, selection bias or unrecognized confounding bias may influence our results, particularly given the nonrandom treatment allocation inherent to this and any other observational study. Prospective studies (ideally through COG or SIOP) are needed before any definitive changes to current treatment paradigms can or should be suggested.

Conclusion

In conclusion, given the relatively rare incidence of pediatric renal tumors, KID provides a large data framework ideal for examining regionalization and clinical predictors of NSS versus RN. We have demonstrated a significant association of presence of renal insufficiency and regional variation in the utilization of NSS. With the primary goals in the management of many renal tumors now shifting to include maximal preservation of renal parenchyma, we expect and eagerly await further dissemination of NSS as a viable option in appropriately-selected children with appropriately-selected renal tumors.

In a large, nationwide pediatric cohort, RN remains the most common surgical intervention for renal tumors. However, NSS is significantly associated with a diagnosis of renal insufficiency.

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Figure 1.
Regional trends in surgical procedures.

Table 1

Patient demographics by hospital admission.

Characteristic	Radical nephrectomy n (%)	Partial nephrectomy n (%)	<i>p</i>
Total	1501 (100)	156 (100)	—
Age (y)			
< 1	158 (11)	14 (9)	0.71
1	200 (13)	26 (17)	
2–5	749 (50)	79 (51)	
6–11	253 (17)	18 (12)	
12–18	103 (7)	13 (8)	
19–21	38 (3)	6 (4)	
Sex			
Male	707 (47)	70 (45)	0.95
Female	790 (53)	84 (55)	
Race			
Non-Hispanic white	659 (56)	70 (58)	0.54
Non-Hispanic black	194 (16)	14 (12)	
Hispanic	215 (18)	25 (21)	
Other	108 (9)	12 (10)	
Zip code median income (\$)			
< 25,000	306 (21)	24 (16)	0.12
25,000–34,999	356 (24)	48 (31)	
35,000–44,999	369 (25)	29 (19)	
> 45,000	436 (30)	52 (34)	
Payer			
Public	635 (42)	58 (37)	0.18
Private	863 (58)	98 (63)	
Hospital census region:			
Northeast	270 (18)	36 (23)	0.54
Midwest	338 (23)	29 (19)	
South	522 (35)	51 (33)	
West	371 (25)	40 (26)	
Hospital type			
Non-childrens	196 (14)	27 (20)	0.25
Pediatric general	565 (41)	53 (38)	
Pediatric unit	617 (45)	58 (42)	
Study year			

Characteristic	Radical nephrectomy n (%)	Partial nephrectomy n (%)	<i>p</i>
2000	288 (19)	29 (19)	0.51
2003	368 (25)	37 (24)	
2006	398 (27)	51 (33)	
2009	447 (30)	39 (25)	
Renal insufficiency			
No	1463 (97)	146 (94)	0.01
Yes	38 (3)	10 (6)	

Table 2

Multivariate associations with partial nephrectomy.

Characteristic	Adjusted RR	Adjusted 95% CI	<i>p</i>	Wald <i>p</i>
Age (y; vs. age < 1)				0.80
1	1.08	0.60–1.96	0.79	
2–5	0.88	0.45–1.69	0.69	
6–11	0.66	0.32–1.38	0.27	
12–18	1.14	0.53–2.46	0.73	
19–21	0.82	0.21–3.16	0.77	
Race (vs. white)				0.25
Black	0.55	0.28–1.10	0.09	
Hispanic	1.22	0.72–2.06	0.46	
Other	1.10	0.58–2.08	0.77	
Payer (vs. public)				0.57
Private	1.12	0.77–1.62	0.57	
Hospital type (vs. pediatric unit)				0.36
Non-childrens	1.42	0.77–2.62	0.26	
Pediatric general	1.40	0.83–2.34	0.20	
Hospital region (vs. Midwest)				0.02
Northeast	3.07	1.08–8.72	0.03	
South	1.47	0.54–4.05	0.45	
West	2.05	0.76–5.56	0.16	
Renal insufficiency diagnosis	3.37	1.30–8.74	0.01	0.01

Note. RR = relative ratio; CI = confidence interval.