

Expanding the Use of Nephron-Sparing Surgery for Wilms Tumor

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ABSTRACT

Radical nephrectomy combined with contemporary chemotherapeutic and radiation therapy protocols has drastically improved outcomes for children with Wilms tumor. Patients with bilateral disease and a syndrome predisposing to tumor development have necessitated the use of nephron-sparing surgery in select cases. Success in managing these patients has increased the indication for partial nephrectomy, although current guidelines for unilateral Wilms tumor are limited. Given that children are being cured with increasing success, recent focus has shifted to long-term health outcomes in addition to tumor treatment. Specifically, renal function has an impact on long-term cardiovascular health and events. Adult outcomes with partial nephrectomy provide a guideline for a paradigm shift in the management of children with Wilms tumor, particularly with advances in imaging and adjuvant therapy. The data are limited for children undergoing partial nephrectomy for unilateral Wilms tumor and outcomes for larger tumors will need to be studied closely in future trials. Increased utilization of neoadjuvant chemotherapy could further expand the number of patients eligible for partial nephrectomy.

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Wilms tumor (WT) is the most common malignant renal tumor in childhood. Of approximately 1 in 10,000 children who are diagnosed with WT, 5% to 10% have either synchronous or metachronous bilateral disease.¹ Bilateral WT tends to occur in children at younger ages, more often in girls, and is an important risk factor for the development of renal failure. Specifically, those born with a *WT1* mutation portend a poor prognosis for renal function.² Survival has dramatically improved over the past several decades, largely because of the adoption of treatment guidelines and clinical trials from both the National Wilms Tumor Study Group (NWTSG) and the International Society of Pediatric Oncology (SIOP).

Although the clinical goal of these 2 groups is aligned, the approach has fundamental differences. In general, the recommendation from NWTSG for treatment of unilateral disease is total radical nephrectomy (RN) at diagnosis followed by chemotherapy and possibly radiation therapy (RT), depending on the stage of the tumor. Alternatively, SIOP recommends neoadjuvant chemotherapy followed by delayed nephrectomy. Regardless of the approach, surgical resection is a mainstay of treatment. Although nephrotoxicity from chemotherapy, radiation, and intrinsic renal disease are thought to contribute to the eventual development of renal failure in some patients, the loss of renal mass from tumor resection is also a potential factor.²

Current Indications for Partial Nephrectomy

Nephron-sparing surgery (NSS), or more specifically partial nephrectomy (PN), has been advocated in cases of bilateral Wilms tumor (BWT), multifocal unilateral disease, or with Wilms predisposition syndromes (eg, Beckwith-Wiedemann, WAGR, Denys-Drash, Perlman).^{3,4} Underlying genetic anomalies can predispose patients to dysplastic renal tissue or premature tissue loss.² There is a delicate balance between tumor management while maximizing renal parenchymal preservation. For bilateral cases, the only alternatives are bilateral PN, unilateral PN, and contralateral RN or bilateral RN, leaving the patient anephric. In these instances, preoperative vincristine, dactinomycin, and doxorubicin is given 6 to 12 weeks prior to surgery to maximize tumor shrinkage in hopes of performing a PN. It is not simply the tumor that mandates maximal parenchymal preservation but also

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the risk of nephrogenic rests and subsequent tumor development.

Despite the complexity of tumor volume and multifocal disease, we have seen favorable outcomes for PN. Several studies have examined outcomes of NSS for BWT, while a recent systematic review summarized this diverse group.⁵ The review analyzed 66 studies, with 4,002 patients undergoing either RN or PN. Although limited by the quality of data from several studies, comparing RN and PN suggests that the most important factors, namely tumor rupture, tumor recurrence, and overall survival, are equivalent for either approach. Importantly, PN was more likely to be used for smaller masses. The authors highlighted the need for a properly conducted prospective, randomized trial to address the efficacy of increasing the use of PN.

A single-institution outcomes evaluation of PN in patients with a predisposing syndrome included 42 patients with bilateral WT: 39 underwent a bilateral PN and 3 underwent a PN and contralateral RN.⁶ The 3-year cancer-free survival rate was 64%, but overall survival was 86%; 5 of 6 patients who died had anaplasia. Repeat PN was required in 9 patients, whereas 2 developed metastatic disease at follow-up. A prolonged urine leak occurred in 10 patients, whereas 30% developed hypertension long term. Our own early series of 12 patients over 7 years did not identify prolonged leak nor recurrence at a median follow-up of 36 months.⁷ A meta-analysis of 20 studies with 5,246 patients (297 PN; 4,897 RN) had similar conclusions of preserved renal function and survival rates of PN versus RN.⁸

Additional treatment with chemotherapy and RT can further decrease renal function beyond the setting of tumor removal.^{9,10} Patients with positive nodes and a remnant kidney will receive RT, as will patients with negative nodes but a positive surgical margin. The question remains whether the radiated renal remnant will add better overall function than no renal remnant at all.

SIOP has inclusion criteria that permit NSS for unilateral WT (UWT). The most recent iteration of the SIOP protocol (UMBRELLA) has recommendations for PN, specifically small tumor burden (<300 mL), an expected significant amount of residual renal tissue, and no concern for positive lymph nodes.¹¹ When these tumor characteristics are present, the UMBRELLA protocol leaves PN as a surgeon's choice for UWT. Perhaps most importantly, the UMBRELLA protocol recognizes the variability in descriptors used in the surgical approach to PN, creating specific nomenclature to define their technique. Current concerns are that PN is performed in small numbers across many centers and that surgeons use many terms—such as wedge resection, heminephrectomy, margin sampling, including a rim of parenchyma—increasing the variability of treatment. As we increase the indications for PN, use of a standard surgical description

will be vital to assess outcomes across individual institutions and surgeons.

Benefits of PN

A query of the Nationwide Readmissions Database compared outcomes for 2,200 patients (focusing on children aged <10 years) undergoing RN versus PN for renal tumors and showed a similar length of stay and cost.¹² Of note, this analysis was based on coding data and lacks the granularity to determine tumor size or histology, but the age range is suggestive of WT. A total of 249 of 2,200 children (11%) underwent a PN and the rate of readmission and complications did not differ between the groups.

Because of the young age of most patients with WT, they are at long-term risk of renal insufficiency and end-stage renal disease (ESRD)-related morbidity. In addition to elevated serum creatinine levels, hypertension can occur as a result of nephrectomy. In a small study of BWT, patients undergoing PN and contralateral RN (8/12; 66%) were more likely to develop hypertension requiring medical therapy during follow-up compared with those undergoing bilateral PN (2/10; 20%).¹³ As expected, there was greater renal parenchymal volume after bilateral PN, although compensatory hypertrophy did occur in patients (aged <8–9 years) with a solitary kidney after PN. In an earlier effort by Davidoff et al,¹⁴ 7 of 10 patients (70%) undergoing bilateral PN developed hypertension requiring medical therapy.

There is risk for a more complicated postoperative course after PN. The possibility of positive margins in residual renal parenchyma, urine leak, and the need to remove an indwelling ureteral stent are unique to PN and are not concerns with RN. Despite these concerns, studies to date comparing PN and RN in WT have revealed nearly equivocal surgical complication rates.^{6,15}

Extension of PN for UWT for nonsyndromic patients revealed preserved glomerular filtration rate (GFR) in appropriately matched patients undergoing RN versus PN.¹⁶ Tumors were significantly larger in the RN group, but the overall and recurrence-free survival were not statistically different between the groups; this effort, however, was not sufficiently powered to achieve a conclusion.

Long-Term Concerns for RN

The crux of the argument favoring PN over RN is preservation of renal function. Compromised renal function can lead to anemia, hypertension, an increased risk of cardiovascular disease, and death.¹⁷ Although few studies have examined this benefit in children, extensive work has been performed in the treatment of adults with renal tumors, mainly with renal cell carcinoma (RCC), which has some obvious fundamental differences in biology and presentation compared with WT, including tumor size and risk of tumor spillage. The rate of ESRD 20 years after RN in patients with nonsyndromic UWT is low at

0.7%.² The risk drastically increases with BWT and those who develop metachronous disease, for whom the rates are 4% and 19.3%, respectively, albeit only 20 years after diagnosis. Another study examined long-term renal function after unilateral RN in nonsyndromic patients.¹⁸ At 28 years of follow-up, GFR was similar to that of controls, except for those who received RT, and no patients developed ESRD. There was, however, a significant increased risk for hypertension in those with WT.

Several studies have compared outcomes in treating adults with RN versus PN. Retrospective studies have identified RN as a risk factor for the development of chronic kidney disease (CKD) when used to treat small renal masses.^{3,19} Conflicting data emerged from a randomized trial by Van Pappel et al²⁰ that failed to identify a significant survival benefit in patients being treated with PN for RCC. In fact, overall survival was improved in patients undergoing RN despite a higher GFR in those undergoing PN. This result was surprising and subsequent studies have reached conflicting conclusions. A systematic review of 21 studies suggested that PN resulted in a significant reduction of overall mortality, severe CKD development, and cancer-specific mortality.³ RN has a direct and negative impact on overall renal function.¹⁰ Given the lack of benefit of PN in the aforementioned article, others have refined the definition of CKD beyond GFR, including hypertension, proteinuria, and renal size discrepancy on imaging. Larger tumor size, preoperative renal function, patient age, and presence of proteinuria identify a subpopulation at higher risk for more rapid deterioration. Likewise, increased time from surgery leads to progressive renal function loss.²¹ However, PN was not completely protective against development of progressive renal loss, as there is a substantial number of patients who will develop CKD progression even after PN.²²

These consequences of RN for RCC provide a paradigm in our efforts to treat WT. Our patients are younger and have a longer anticipated lifespan compared with adults being treated for RCC. Although oncologic control is our central focus and RN has remained the gold standard in treating WT to date, a global view of the patient must include the long-term impact of this therapy on quality of life and morbidity. If PN can be performed with equal oncologic outcomes for WT, it could provide similar benefits in the pediatric population as it does in adults.

Contemporary oncologic management has increased lifespan after therapy completion. Over the past 30 years, it is estimated that there are now >500,000 survivors of childhood cancer, and this number is increasing.^{23,24} As the focus shifts from cancer survival to improved quality of life, issues facing patients after completing therapy include recurrent cancer, chronic pain, fertility, and organ dysfunction. It is estimated that >50% of survivors will develop a severe medical condition by age 50 years, such as cardiac, renal, or other organ dysfunction.²⁵ Despite oncologic advances,

there is still a significant decrease in overall survival of these patients compared with their peers, particularly when RT is included.²⁴ As renal function is a key aspect of cardiovascular health, PN with renal preservation will take on a more prominent role in the management of WT. Patients who develop a metachronous WT fare worse than those who present with synchronous lesions at diagnosis given the push for NSS in these patients.² Children diagnosed with WT prior to 1 year of age have an increased risk for developing contralateral disease, although this is only true if these patients also have nephrogenic rests (NRs), especially perilobar nephrogenic rests (PLNRs).²⁶ NWTSG reported that PLNRs were more commonly associated with synchronous BWT, whereas intralobar nephrogenic rests (ILNRs) were more common in patients with metachronous BWT.²⁷ The matched case control study suggests a particularly high risk of developing metachronous BWT among children aged <12 months found to have PLNR in the renal tissue removed for UWT. Because NWTSG has demonstrated that the median age at diagnosis with WT and PLNR is substantially older (36 months) than for WT and ILNR (16 months), the occurrence of PLNR in children aged <12 months is rare.²⁸ Yet, this combination seems to carry the highest risk of contralateral disease development. Thus, patients with a predisposition to WT and those with NR pose a particular challenge after tumor excision. Although these patients will be under a strict surveillance protocol, initial management with PN increases the management flexibility should a recurrence occur.

Improving Success of PN

The SIOP protocols differ from the COG protocols in the use of neoadjuvant chemotherapy. This approach significantly reduces tumor size, decreases the rate of intraoperative tumor spillage, and facilitates tumor removal.²⁹ Even with the use of neoadjuvant chemotherapy, it is estimated that only 3% of tumors are amenable to a PN, although this is with the fairly strict criteria mentioned earlier.³⁰ More widespread use of neoadjuvant chemotherapy has obvious potential benefits with the need for tumor manipulation and dissection when performing a PN. It can also provide indication for a more favorable histology based on the tumor response to chemotherapy, although stromal predominant tumors (and certainly anaplasia) may not shrink as much in response to chemotherapy.³¹

Improved outcomes can be tied to our ability to refine treatment modalities based on the clinical appearance of the mass as well as the biologic factors it exhibits. Personalized management based on mass size, location in relation to the collecting system and vasculature, response to chemotherapy, histology, mRNA analysis, and chromosomal analysis for loss of heterozygosity at 1p and 16q can potentially be used to determine the feasibility of PN.^{11,32,33}

Cross-sectional imaging is imperative in the diagnosis and management of WT. Improved imaging techniques and refinement in MRI modalities yield a more precise assessment of the tumor size, correlation with histologic subtype and response to chemotherapy, as well as anatomic considerations related to PN.^{34,35} Tumor extension beyond the kidney, rupture, suspicious lymph nodes, and vascular extension is readily detectable in cross-sectional imaging and would suggest more aggressive disease, potentially precluding PN. In the setting of NR, imaging can provide the dividing line between the need for resection and the ability to continue with observation.³⁶

In adults with RCC, a number of scoring systems have been developed to risk-stratify the tumors undergoing PN in terms of surgical complexity and with the goal to improve reporting.³⁷ The RENAL nephrometry score has been validated and is the most widely used system. It

assigns complexity scores based on radius, exophytic/endophytic extent, proximity to the collecting system, anterior/posterior location, and polar involvement of the tumor to stratify masses into low, medium, or high complexity. This score has been shown to correlate to tumor biology, resectability, and complications.³⁸ Our own experience of 33 pediatric renal tumors for planned PN, independently scored by both pediatric urologists and radiologists, showed high interobserver reliability for this scoring system. Most tumors were of high-intermediate complexity yet successfully underwent PN.³⁹ Utilization of validated surgical complexity scoring systems will be essential for preoperative planning and when comparing literature on outcomes of pediatric PN.

A significant advancement in our ability to perform PN in complex WT has been the use of 3D models. The postchemotherapy MRI images are reviewed and the

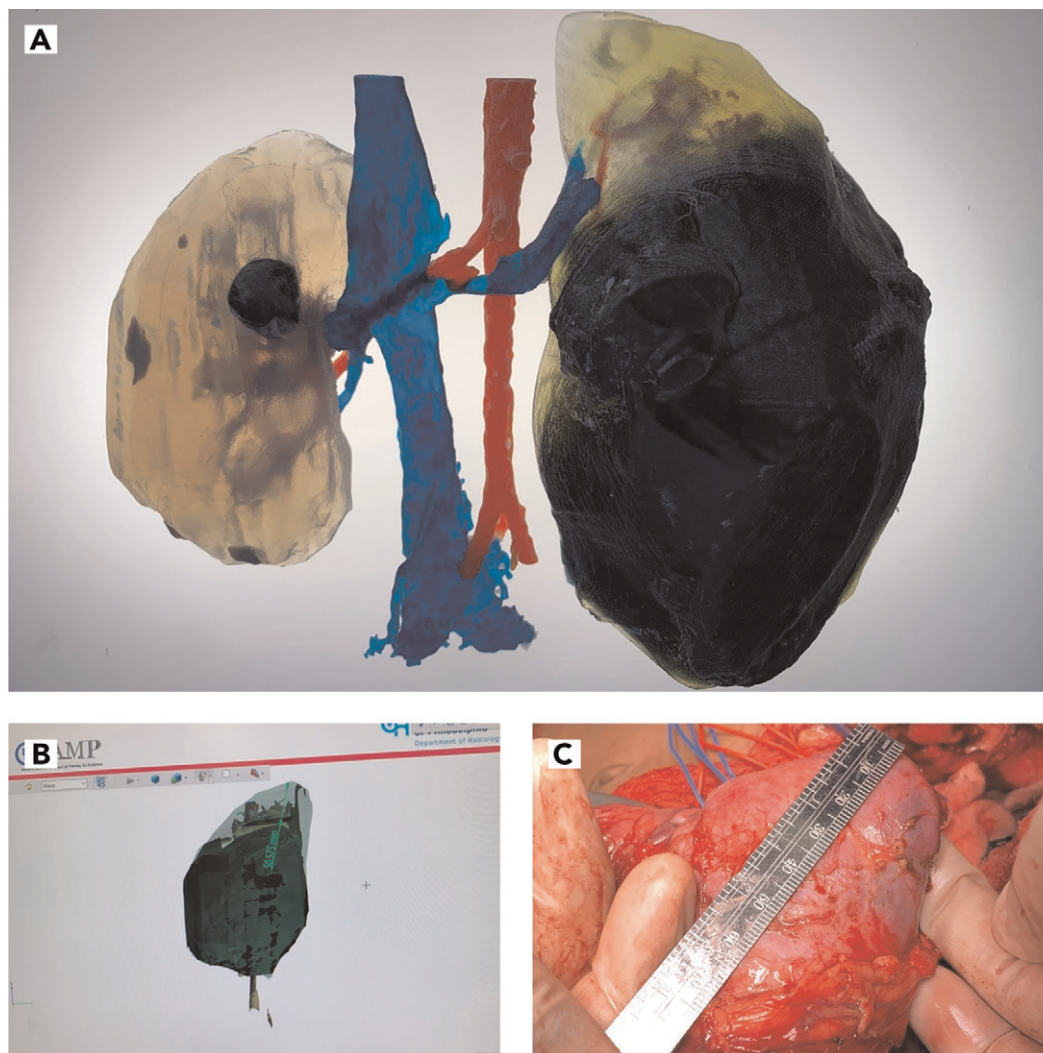


Figure 1. (A) Re-created MRI 3D model of kidneys with Wilms tumors and critical vasculature and intraoperative manipulation of PDF form (B) allowing real-time measurement (C) of normal parenchyma and tumor for excision.

relevant anatomy is identified and defined during a collaborative discussion by the radiologist, urologist, and engineer. A dynamic PDF is created on which the anatomy is manipulated to be viewed from different planes or have certain anatomy added/subtracted to better understand anatomic relationships.⁴⁰ After further review with the surgeon, a 3D model is printed to facilitate presurgical planning and for intraoperative reference (Figure 1). Use of such models in clinical practice, particularly in complex tumor resection, is invaluable in understanding anatomic relations of the tumor, but the future will show whether this will facilitate PN rates.⁴¹

The technical aspects of PN for WT are challenging and require strict adherence. Generally, WT presents as larger masses than adult RCC. During NSS, we have used traditional renal surgical techniques, including intricate hilar vascular isolation (Figure 2), partial direct compression of parenchyma with the surgeon's fingers and aided by a vascular clamp or an umbilical tape Rummel tourniquet to optimize a bloodless field (Figure 3), and Bovie electrocautery to divide the parenchyma. We favor direct compression of only the affected tumor parenchyma

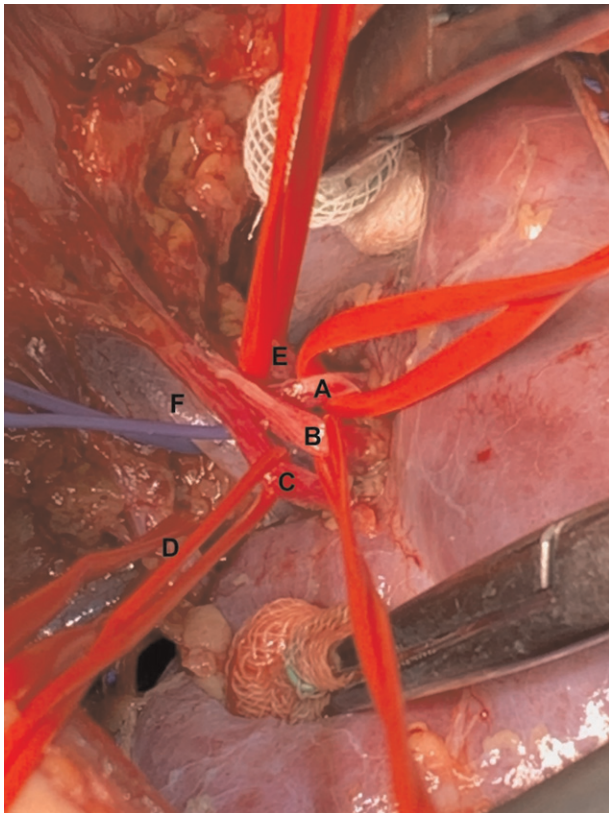


Figure 2. Renal hilum vasculature dissected to allow precise tumor isolation. Segmental arterial blood supply showing the apical artery (A), superior anterior artery (B), inferior anterior artery (C), inferior artery (D), posterior artery (E), and renal vein (F).

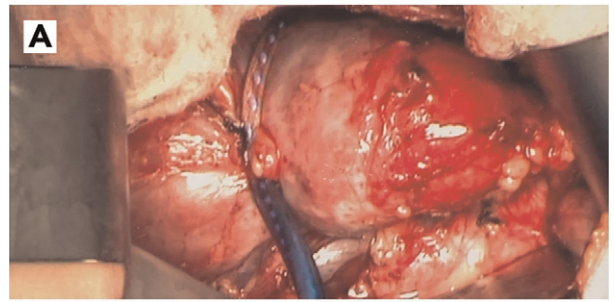


Figure 3. Renal parenchyma compression techniques of digital compression and (A) vascular clamp and (B) umbilical tape Rummel tourniquet.

while maintaining blood supply to the rest of the kidney, as opposed to whole-kidney warm or cold ischemia. Attention is directed toward meticulous repair of all violations of the collecting system with absorbable suture, liberal use of oxidized cellulose and argon beam

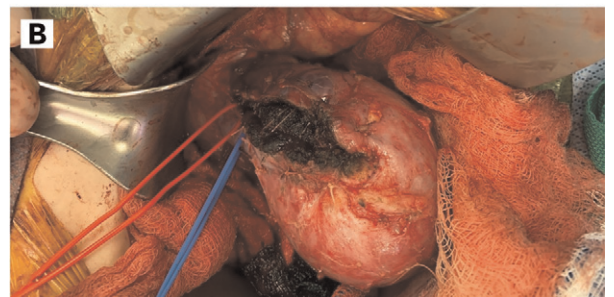


Figure 4. Renal parenchyma repair posttumor excision. (A) Argon beam coagulation and (B) direct mattress suture approximation of the renal parenchyma/capsule over oxidized cellulose.

coagulation on the excised parenchyma, and direct mattress suture approximation of the renal parenchyma/capsule whenever possible (Figure 4). In all cases of reconstruction of the collecting system, we use externalized drains and internal ureteral stents. Tumor and normal parenchyma sections are evaluated not only histologically but also genetically for genome-wide single nucleotide polymorphism microarray analysis.⁴²

We believe it is also important to adhere diligently to sound surgical oncology principles, including en bloc resection, avoidance of frank spillage, and resection of a 1-cm margin of normal parenchyma (rather than enucleating the tumor without a margin). Tumors that are indistinctly palpable or that encroach on the renal hilum are further evaluated using intraoperative ultrasound to delineate the deep extent of the tumor, including correlation with the 3D model. After full resection, we use intraoperative frozen section for margins as standard technique. Although we naturally find tumors arising in the lower pole of the kidney technically easier to resect with these techniques, we do not consider tumors located medially, posteriorly, or in the upper pole as a contraindication to NSS. Another technical concern regarding PN that is not present with RN is the role of surgical margins. It is imperative that intraoperative margins are negative from the tumor resection bed. A lymph node dissection is imperative, as with any approach to tumor resection for WT.⁴³

Conclusions

Great strides have been made in increasing survival in patients with WT. Although RN has remained the gold standard in the management of WT, the use of NSS has increased in patients with BWT and syndromic WT. Although the data to date do suggest a low risk of ESRD in patients with nonsyndromic UWT at 20 years of follow-up, given the benefits of PN in adults with renal masses and the impact on cardiovascular health, a paradigm shift toward increased use of NSS for WT is warranted. Improvement in preoperative cross-sectional imaging, including the use of 3D models and interactive dynamic PDFs, provide the surgeon with increased understanding of anatomic relationships and risk prior to entering the operating room. Adoption of neoadjuvant chemotherapy can lead to both tumor shrinkage and expanded use of PN for more WT while ensuring that we still achieve equivalent oncologic outcomes.

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