Is Partial Nephrectomy Appropriate Treatment for Unilateral Wilms' Tumor?

By Catharina G.M. Moorman-Voestermans, Daniel C. Aronson, Chris R. Staalman, Jan F.M. Delemarre, and Jan de Kraker
Amsterdam, The Netherlands

Purpose: After nephrectomy for unilateral Wilms' tumor (WT), two potential hazards threaten the remaining kidney. The development of a metachronous WT (2% to 3%), and decrease in renal function after chemotherapy. Our study aims included: (1) to clarify how many WT patients could benefit from partial nephrectomy (PN) without jeopardizing the high cure rate, (2) to establish the function of the kidney remnant, and (3) to test the radiological criteria for preoperative selection of PN candidates.

Methods: A retrospective analysis of 90 consecutive cases of histologically verified WT (1982 to 1992) was carried out. Data were studied independently by the surgeon, the radiologist, and the pathologist. The preoperative selection criteria for PN were functioning kidney, tumor confined to upper or lower pole leaving two thirds of the kidney tumor free, and no hilar or vascular structures involved. After PN, renal function was estimated by a calculated creatinine clearance (CC) combined with the assessment of the relative function of each kidney by renal scintigraphy.

Results: There were 46 boys and 44 girls with median age at diagnosis of 3 years 6 months (range, 3 months to 16 years 7 months). Stage I disease occurred in 40 patients, stage II in 23, stage III in 16, and stage IV occurred in 11 patients. Nearly all patients received preoperative chemotherapy. Radiological analysis of 85 available data sets (5 missing) suggested that PN was possible in 13 patients, and data were inconclusive in two. All 13 patients selected by the radiologist appeared to be in agreement with the pathological criteria for resectability. Of these cases, complete resection by PN was performed in five, could have been possible in retrospect in two, and appeared impossible in six. In two more patients, PN was performed; in both cases the radiologist had predicted PN to be impossible. Median follow-up after PN was 61 months, range, 45 to 167 months. Two patients died of distant metastasis, and no local recurrence occurred. Five are in remission with a median CC level of 110 mL/min, range, 85 to 124. Relative functions of the kidney remnants were 20% to 50%. Contralateral nephrectomy for progressive obstruction was performed in one, but CC level remained normal (85 mL/min). Comparing the preoperative radiological prediction with the combined surgical and pathological findings in a 2 × 2 frequency table, the sensitivity of the radiological findings could be calculated to be 80%, the specificity 97%, and the accuracy 87%.

Conclusions: (1) Partial nephrectomy is safe in approximately 10% of Wilms' tumor patients. (2) The function of the kidney remnant remains well, and even permits contralateral nephrectomy. (3) Preoperative imaging shows an accuracy of 87% to predict the possibility for partial nephrectomy.
J Pediatr Surg 33:165-170. Copyright © 1998 by W.B. Saunders Company.

INDEX WORDS: Unilateral Wilms' tumor, partial nephrectomy, preoperative criteria.

THE CRUDE 3-YEAR SURVIVAL rate for children with nephroblastoma (Wilms' tumor), treated according to the International Society of Pediatric Oncology (SIOP) 9 protocol, is 90% (Tournade et al, unpublished data). In this respect, quality-of-life aspects become very important. In addition to a 2% to 3% chance that a metachronous Wilms' tumor may develop in the contralateral kidney later in life, a substantial risk of renal function loss is caused by various reasons, ie, trauma, obstruction, or in rare cases, chemotherapy and/or radiation, in view of a solitary kidney. Quality of life may therefore be improved by the preservation of as much functioning renal tissue as possible at the time of operation, provided that surgical oncological principles are not violated. How many and which patients could benefit from a partial nephrectomy (PN) without jeopardizing the high cure rate? Additionally, would the kidney remnant still have sufficient function?

This retrospective study was undertaken to answer these questions and to evaluate the preoperative selection

From the Departments of Pediatric Surgery, Pediatric Radiology, Pediatric Oncology, and Pathology, Academic Medical Center, University of Amsterdam, Emma Childrens' Hospital AMC, Amsterdam, The Netherlands.

Presented at the 28th Annual Meeting of the American Pediatric Surgical Association, Naples, Florida, May 18-21, 1997.

Address reprint requests to C.G.M. Moorman-Voestermans, MD, Academic Medical Center, University of Amsterdam, Emma Childrens' Hospital AMC, Department of Pediatric Surgery (G8-238), PO Box 22700, 1100 DE Amsterdam, The Netherlands.

Copyright © 1998 by W.B. Saunders Company
0022-3468/98/3302-0003$03.00/0

criteria for a partial nephrectomy in children with a unilateral Wilms' tumor.

MATERIALS AND METHODS

From 1982 to 1992, 93 consecutive children were operated on for Wilms' tumor at our Pediatric Surgical department. Three children with a stage V tumor were excluded from the study because they constitute a separate category. The study group consisted of 90 children with a median age at diagnosis of 3.6 years (range, 0.3 to 16.7 years), and contained 46 boys and 44 girls. Nearly all of them received preoperative chemotherapy during either 8 or 4 weeks according to the SIOP 6 and 9 protocols, respectively. SIOP staging criteria are equal to those used by the National Wilms' Tumor Study (NWTS), except for two differences. SIOP staging distinguishes stage II tumors into lymph nodes negative and lymph nodes positive, and staging occurs at operation after chemotherapy pretreatment. Stage II, lymph nodes positive tumors are treated like stage III tumors with postoperative radiotherapy.

The data for these 90 children were studied retrospectively by the pediatric surgeon (C.M.), the radiologist (C.S.), and the pathologist (J.D.). The clinical and follow-up data were collected by the pediatric surgeon using patients' charts, operative reports, and office notes. When partial nephrectomy (PN) was performed, evaluation of whether the surgical criteria for this procedure had been applied was done, and at follow-up of those cases, special emphasis was put to the local control status. When total nephrectomy (TN) was performed, evaluation was done as to whether the application of the surgical criteria would have led to the conclusion that PN would have been possible. The imaging studies were reevaluated by the radiologist who did not know the clinical data, or the type of surgery performed. All preoperative images and reports, especially those after pretreatment, were studied. The ultrasound examination (US), the intravenous urography (IVU), and, if available, the computed tomography (CT) scan, magnetic resonance imaging (MRI), cavograms or color Doppler US were scrutinized. Based on this reevaluation, the radiologist predicted the possibility of performing a PN using preset radiological criteria. The pathologist reevaluated the histology and screened the operation specimen as a "gold standard." When PN had been performed, the surgical margins were reevaluated. For TN, assessment was made as to whether the possibility of performing a PN had not been missed. At the time of the primary postoperative pathological investigation, the surgical specimens had been divided into two parts in longitudinal direction, after which the cut surfaces had been photographed. These photographs were reevaluated, and whenever photographs were missing, the primary macroscopic description was used. Because this pathological evaluation was limited to the local status in one midline section, the "true" gold standard in the assessment of the possibility to perform a PN was obtained by combining the surgical and pathological retrospective evaluation on a unanimous basis, as discussed by the pediatric surgeon and the pathologist.

Surgical selection criteria for partial nephrectomy included functioning kidney, tumor confined to one pole occupying less than one third of the kidney, no invasion in the renal vein (RV) or collecting system, and clear margins between tumor, kidney, and surrounding structures.[1-3] Radiological selection criteria for partial nephrectomy included solitary mass confined to the kidney, tumor boundary remote from hilum leaving two thirds of the kidney intact, relatively small area of contact between tumor and kidney, and no involvement of renal vein (RV) or inferior vena cava (IVC).[4] Pathological selection criteria for partial nephrectomy included tumor in upper or lower pole, normal part of the kidney at least two thirds, and no invasion in the collecting system or hilar region.

Assessment of the Predictive Value of the Preoperative Radiological Judgment Regarding a Possible Partial Nephrectomy

The sensitivity, specificity, and accuracy of the radiological preoperative prediction were calculated, using both the pathological findings as the gold standard, as well as the combined surgical and pathological findings as the true gold standard.

Assessment of Renal Function of the Kidney Remnant After Partial Nephrectomy

After PN, an assessment of the renal function of the kidney remnant was performed at the time of this study. The overall renal function was estimated by a calculated creatinine clearance (body length [cm] $\times$ 38, divided by serum creatinine [μmol/L]; normal value, >80 mL/min/L,73 m^2).[5] The contribution of each kidney to the renal function was assessed by renal scintigraphy.

RESULTS

Patient Characteristics

PN was performed in seven children (7.8%) with a median age of 3.4 years (range, 0.7 to 10.4 years) and a sex distribution of four boys and three girls. The median follow-up period was 61 months (range, 45 to 167 months). TN was performed in 83 children with a median age of 4.0 years (range, 0.3 to 16.7 years) and a sex distribution of 42 boys and 41 girls. The median follow-up period for the whole group was 101 months (range, 4 to 179 months).

Pathology and Staging

All patients had been treated for a histologically verified Wilms' tumor. A metachronous tumor in the contralateral kidney developed in three patients and was treated by PN. These three patients were included for the primary tumor (TN) but excluded for the secondary. Of the seven patients treated with PN, five patients had a stage I tumor, and two a stage III tumor (incomplete resection, but renal resection margins tumor free). Of the 83 patients treated with TN, 35 patients had a stage I tumor, 23 a stage II tumor, 14 a stage III tumor, and 11 a stage IV tumor.

Outcome

The 5-year survival rates were 95% for stage I, 82.6% for stage II, 81.2% for stage III, and 81.8% for stage IV tumors. Five-year survival rate was five of seven after PN, and 74 of 83 after TN. Statistical significance could not be calculated for differences in group size. At follow-up of the seven patients treated with PN, no local recurrence was found. Two patients died. One of these patients had a stage I tumor, and lung metastases developed at 20 months follow-up. He was treated with chemotherapy and radiotherapy, and underwent two thoracotomies. At his third relapse, the lung metastasis had become unresectable, and he died 49 months after his

primary operation without any sign of local recurrence at US and MRI studies. The second patient had a stage III tumor and died 46 months after the primary operation of unresectable metastases in the liver. At the referring center, she had undergone repeated diagnostic punctures that had gone through the right sided Wilms' tumor into the liver. She showed no local recurrence at explorative laparotomy.

Surgical Analysis

Of the seven PN cases, two had a lower pole tumor; three an upper pole tumor, of which one was a multilocular cystic tumor operated at diagnosis without preoperative chemotherapy; one an upper pole tumor in the left half of a horse shoe kidney; and one a lower pole tumor in a crossed ectopic kidney. In all seven PN patients, the renal plane of resection showed a tumor-free margin. In one of the two patients with a stage III tumor, a small metastatic node in the mesocolon appeared to be removed incompletely; the other showed a tumor-positive margin at the site of the diaphragm. These latter two patients had additional radiotherapy. Of the 83 TN cases, one PN had been planned, but was unsuccessful because of marginal perfusion of the kidney remnant during the procedure. In two cases, a PN could probably have been performed but was not even considered. In 52 cases, a PN proved, also in retrospect, to be impossible. The remaining 28 reports were inconclusive.

Radiological Analysis

Applying the radiological criteria, the radiologist found PN possible in 13 patients, PN impossible in 70 children, and data were inconclusive in two. In five children, the preoperative images were missing, and all underwent TN.

Pathological Analysis

Of the 83 TN specimens, the pathologist found that PN was possible in eight patients. In 73 patients, the pathological criteria for a kidney salvage procedure were not met. In two patients, the findings were inconclusive. In the PN specimen, histological evaluation of margins demonstrated tumor-free renal margins in all.

Comparison of the Surgical Radiological and Pathological Results

All 13 patients selected by the radiologist to be eligible for PN also met the pathological criteria (no false positives). In five, an actual PN had been performed (three stage I, two stage III); in one, it was attempted, but the procedure had to be stopped because of defective renal perfusion; and in one, the surgeon had deliberately not undertaken a PN in view of the presence of an undetermined process in the other pole of the kidney that eventually appeared to be a subcapsular hematoma (stage I). In four of the remaining six patients, however, in retrospect, the surgeon would not have performed a PN for solid surgical reasons: tumor too close to the hilar region in two patients (one stage I and one stage II tumor), multiple positive nodes in hilar and paraaortic region (stage III) in the third, and dubious infiltration of the wall of the renal vein (stage IV, locally stage I) in the fourth patient. In the remaining two patients selected by the radiologist, the surgical criteria for PN were positive retrospectively, but both had been missed by the surgeon as PN candidates. Of the 70 patients in whom the radiologist had predicted PN to be impossible, 2 had undergone PN, both in anatomically abnormal kidneys. Both were stage I tumors, and had thus been missed by the radiologist (false negatives).

Of the 8 TN specimens in which the pathological criteria for PN were positive, six had been detected by the radiologist, whose findings were inconclusive in the other two.

Assessment of the Predictive Value of the Preoperative Radiological Judgment Regarding a Possible Partial Nephrectomy

In 85 of 90 patients, preoperative radiological imaging was available for evaluation. There were no false-positive predictions regarding the possibility of performing PN and two false negatives. After comparison of the preoperative radiological prediction (test) with the pathological findings (the gold standard) in a 2 × 2 frequency table (Table 1), the sensitivity (a/a + c) of the preoperative radiological assessment was 87%, the specificity (d/c + d) 97%, and the accuracy (a + d/total) 93%.

Comparing the preoperative radiological prediction (test) with the combined surgical and pathological findings (the true gold standard) in a 2 × 2 frequency table, there were five false-positive predictions regarding the possibility of performing PN, and two false negatives (Table 2). The eight true positives are five patients in whom PN was performed, one in whom the surgeon had deliberately not undertaken a PN in view of the presence of an undetermined process in the other pole of the kidney that eventually appeared to be a subcapsular hematoma, and two whose diagnoses were missed by the

Table 1. The Radiological Predictive Data Compared With the Pathological Data as the Gold Standard

	Pathology				
Radiology	PN	TN	?	Total
PN	13 (a, b, c, d)	—	—	13
TN	2	66	2	70
?	—	2	—	2
Total	15	68	2	85

Table 2. The Radiological Predictive Data Compared With the Surgical and the Pathological Data as the True Gold Standard

	Surgery/Pathology					
Radiology	PN			TN	?	Total
PN	8			5	—	13
		a	b			
		c	d			
TN	2			66	2	70
?	—			2	—	2
Total	10			73	2	85

surgeon. The sensitivity of the radiological findings could be calculated to be 80%, the specificity 97%, and the accuracy 87%.

Renal Function of the Kidney Remnant After Partial Nephrectomy

Two of the seven PN patients died of disease, one because of lung metastases, and one because of liver metastases. In the remaining five patients, after a median follow-up of 88 months (range, 73 to 151 months), the overall renal function and the functional capacity of the kidney remnant could be assessed and were all within the normal range. The data are shown in Table 3.

DISCUSSION

Because a patient with a Wilms' tumor has a good prognosis, PN is only justified if the disease-free survival rate does not decrease, and the good quality of life is prolonged because of the preservation of more functioning renal parenchyma. Of course, it is evident that by performing a PN, a stage I tumor should not become a stage III tumor because of incomplete resection, which would increase morbidity and decrease survival rates. In the data presented, survival rates in both PN and TN patient groups can not be compared statistically because of the small number of patients treated with PN. In terms of renal function, the question can be raised whether it is useful and worthwhile to take an oncological risk by saving part of the kidney. Therefore, the functional assessment of the kidney remnant was performed. The overall creatinine clearance (CC) was within the normal range in all five patients, with a relative kidney-remnant function ranging from 24% to 50% (Table 3). The patient with the best kidney function (AO, Table 3) even had received abdominal radiotherapy, and still the radiated kidney remnant contributed 50% of the kidney function, which is of substantial value. In the patient who later had contralateral nephrectomy of a nonfunctional kidney caused by progressive obstruction (RK, Table 3) the CC of the kidney remnant was normal (85 mL/min), and saved him from dialysis. These functional results, together with the absence of an increased local recurrence rate, seem to justify this approach.

Table 3. Clinical Data

Case No.	Age at Diagnosis	Side of PN	Local Radiation	Δ Diagnosis RFA (mo)	CC‡ (mL/min/ 1.73 m²)	Renographic KRF§ (% of TRF) R	L
1	10 yr 4 mo	R	–	74	93.8	44	58
2	2 yr 4 mo	R	–	88	119.5	41	59
3*	5 yr 7 mo	L	+	73	123.7	50	50
4	7 mo	L	–	148	110	76	24
5†	3 yr 4 mo	L	–	151	85	—	100

Abbreviations: RFA, renal function assessment; KRF, kidney remnant function; TRF, total renal function.

*Case 3 (AO) received local radiation on the kidney remnant.

†Case 5 (RK) underwent contralateral nephrectomy for obstruction—the normal clearance reflects the function of the kidney remnant.

‡CC was estimated (body length [cm] ×38, divided by serum creatinine [μmol/L]; normal value, 80 to 110 mL/min).

§The percentage of function of each kidney was measured by renography.

Because the radiological images of five patients were missing, complete data could be studied in 85 patients, in one of whom the surgical as well as the pathological data were inconclusive. The pathologist's report confirmed tumor-free renal resection margins in all seven patients in whom PN had been performed. This reassures that the indication and technique applied had indeed been correct in these cases. This was confirmed by the follow-up findings that none of those patients experienced a local recurrence.

It is noteworthy that the radiologist seemed quite able to predict preoperatively which patient was suitable for a PN, as shown by the high sensitivity, specificity, and accuracy of the screening results. In preparing the operation, the surgeon should take this into account. However, in case of doubt, it remains the surgeon's responsibility to then refrain from a kidney-salvage procedure. The surgeon should be present at the preoperative radiological imaging to enhance the intensive interactive process with the radiologist, which will increase the preoperative predictive value.

The SIOP treatment strategy for Wilms' tumor, in which preoperative chemotherapy is given to all patients, has shown an increase in stage I tumors from 20% in the no pretreatment arm of the first study (SIOP-1), to 65% in the latest study (SIOP-9). It is the SIOP experience that by pretreating the patients, PN can be considered more often. It is questionable if PN should be considered in patients with positive lymph nodes or stage III tumors, because both categories are subjected to radiotherapy (Table 1). Radiation of the kidney remnant may thwart the advantage of a PN despite the findings in one of our patients (AO, Table 3). More patients are needed to

determine whether the added functioning of the radiated kidney remnant outweighs the increased risk from an oncological point of view.

Partial nephrectomy is applicable in approximately 10% of Wilms' tumor patients after preoperative chemotherapy as an oncologically safe procedure and does not lead to decreased local tumor control. The function of the kidney remnant remains rather well even after local radiotherapy and permits contralateral nephrectomy. Preoperative imaging shows an accuracy of 87% to predict the possibility for partial nephrectomy. The surgeon's presence at the preoperative imaging intensifies the necessary interaction between radiologist and surgeon and is strongly advocated.

REFERENCES

1. Gruner M, Chaouachi B, Bitker L, et al: La Place de la Chirurgie Conservatrice dans le Traitement des Néphroblastomes. Journal d'Urologie 88:223-229, 1982

2. Verga G, Parigi GB: Partial nephrectomy for Wilms tumor. J Urol 135:981-982, 1986

3. Wilimas JA, Magill L, Parham DM, et al: Is renal salvage feasible in unilateral Wilms' tumor?: Proposed computed tomographic criteria and their relation to surgicopathologic findings. Am J Pediatr Hematol Oncol 12:164-167, 1990

4. Wilimas JA, Magill L, Parham DM, et al: The potential for renal salvage in nonmetastatic unilateral Wilms' tumor. Am J Pediatr Hematol Oncol 13:342-344, 1991

5. Schwartz GJ, Haycock GB, Edelman CM, et al: A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 58:259-263, 1976

Discussion

T. Weber (St. Louis, MO): It wasn't clear whether all of the patients were treated with preoperative chemotherapy.

D.C. Aronson (response): Yes, that's part of the SIOP strategy. Every patient is treated with chemotherapy to shrink the tumor before surgery.

C.A. Burnweit (Miami, FL): Do you use frozen section in the operating room to clear your margins?

D.C. Aronson (response): No, we don't; only in case of doubt.

S.J. Shochat (Memphis, TN): This study clearly shows that only a few patients could have partial nephrectomies performed. Your 10% incidence is similar to other studies.

Did pretreatment radiological results correlate with your ability to perform partial nephrectomy? Did your chemotherapy-treated patients have their radiological studies done before they were operated on to see if they could have a partial nephrectomy?

D.C. Aronson (response): No, the radiological studies are done in the diagnosis phase so they are done before any treatment.

S.J. Shochat: In the United States, we don't pretreat most Wilms' tumor patients. Can you determine which patients before treatment would be candidates for partial nephrectomy.

D.C. Aronson (response): Our radiological analysis is performed twice. The first analysis is done before any treatment. The second radiological analysis is performed after pretreatment with chemotherapy but before surgery when the surgeons are with the radiologist in the radiological suite. It is at this point, when we decide whether partial nephrectomy can be performed. As our experience grows, we can usually tell from the first radiological analysis (before therapy) whether this patient could have a partial nephrectomy. But the real decision is made after pretreatment before surgery.

S.J. Shochat: So was the information you showed us before or after chemotherapy?

D.C. Aronson (response): The radiological information I showed you was after pretreatment and before surgery.

R.C. Shamberger (Boston, MA): I would like to pursue Dr. Shochat's question a little further. Prior studies have shown that preoperative chemotherapy does not significantly increase the percentage of children anatomically suitable for partial nephrectomy. What percentage of children in your group became suitable for partial nephrectomy after chemotherapy?

In the current NWTS V study, children with small primary tumors (<550 g), under 2 years of age, receive neither adjuvant chemotherapy nor radiotherapy. How many children in your study fall into that category, and by doing partial nephrectomy, have become exposed to either chemotherapy or radiation that they would not have received if they had a complete nephrectomy?

D.C. Aronson (response): I can't answer the question of how many patients partial nephrectomy could be performed on at the second imaging. We already had that opinion at the first imaging. I don't know the answer because I didn't evaluate the data that way. However, with growing experience, we regularly choose those patients for partial nephrectomy at the second imaging in whom we already thought this could be done at the first evaluation.

In the treatment protocol in this study, every patient received chemotherapy after surgery, and stage II node

positive and stage III patients also received postoperative radiotherapy. Every patient that had partial nephrectomy received the same postoperative adjuvant therapy as they would have received if they had been treated with total nephrectomy.

D. Tapper (Seattle, WA): My concern about the SIOP study is the lack of up-front biopsy. Some tumors in their study are not Wilms' tumors. In this study, all the pathology results that you showed pointed to Wilms' tumor. In patients in whom a partial nephrectomy was not successful, or not able to be done, was there a difference in histology? If so, what was the difference? Was it related to histology, or do you feel it was lack of response to chemotherapy? Would the difference be improved if you did up-front biopsies or changed your protocol?

D.C. Aronson (response): In the 25-year SIOP experience no up-front biopsy results were used to diagnose Wilms' tumors. Because benign tumors represent less than 1% of cases,—not doing an initial biopsy and treating with chemotherapy outweighs the increased risk for tumor rupture in case of primary excision, which increases the chances that the tumor converts from a stage I to a stage III tumor.

Regarding your second question, the ability to perform partial nephrectomy is unrelated to histology, but depends more on the anatomy. As long as the tumor is confined to either of the two kidney poles, leaving two thirds of the kidney (including all hilar structures) disease free then it is possible to perform partial nephrectomy with tumor-free renal margins.