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ORIGINAL ARTICLE

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Nephron-sparing procedures in 11 patients with Wilms' tumor

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Abstract ***Purpose***: In unilateral Wilms' tumor (WT), tumor nephrectomy is the standard surgical approach, whereas partial nephrectomy (PN) is controversially discussed. The aim of our retrospective study was to show that in selected cases of unilateral WT kidney-sparing operations could be a reasonable alternative to nephrectomy and to discuss the results of patients with bilateral WT treated by tumor enucleation. ***Materials and methods***: From 1981 to 1998, seven patients with unilateral nephroblastoma (four stage I, one stage III and two stage IV) had tumor resection by PN (five right side, two left side), which was planned when the tumor volume was reduced after 4 to 6 weeks of chemotherapy by at least 50%, when the tumor occupied one pole or was easily resectable, when 50% or more of the kidney tissue remained and when paraaortic lymph nodes were free by intraoperative histological examination. In four patients with bilateral WT (stage V) bilateral tumor enucleation was carried out—except in one patient in whom the contralateral kidney had to been removed because of extension of the tumor via the inferior vena cava to the right atrium. All patients ($n=11$) received pre- and postoperative chemotherapy followed by radiotherapy in four patients. ***Results***: All patients with unilateral WT ($n=7$) are still alive and disease free (follow-up time: mean 6.6 years, range: 28 months to 11 years) with normal renal function, although two patients with secondary nephrectomy revealed creatinine clearance levels at the lower range. In six patients primary PN was performed successfully. In a stage III tumor patient (intraperitoneal metastasis, free lymph nodes), secondary nephrectomy was necessary due to renal arterial thrombosis 2 days after PN. In one stage IV tumor patient (lung metastasis, free lymph nodes), the primary resection was not far enough away from the tumor margin so that an additional slice of tissue with then tumor-free margins had to be resected. This patient evolved a local relapse 19 months after PN and had to be nephrectomised thereafter. In the group of bilateral WT patients ($n=4$), one child died 2 months after surgery during chemotherapy because of central venous line sepsis. One patient who additionally suffered from inferior vena cava tumor thrombosis extending to the right atrium making nephrectomy of the right kidney necessary developed chronic renal failure 4.7 years postoperatively. The other two stage V tumor patients have creatinine clearance levels within the normal range. ***Conclusions***: Kidney-sparing procedures remain the operative approach of choice in patients with bilateral WT, but bear the risk of chronic renal failure when one kidney has to be removed. PN in children with unilateral WT, carried out by an experienced surgeon, is a reasonable alternative to nephrectomy if strict guidelines such as excellent tumor response to preoperative chemotherapy and easy resectability far away from the tumor margins through healthy kidney tissue are followed. Paraaortic lymph nodes must be free of tumor invasion in order to avoid local radiotherapy. PN prevents the patient from having to have dialysis in cases of contralateral nephrectomy resulting from metachronous WT or subsequent renal trauma.

Keywords Wilms' tumor · Partial nephrectomy · Tumor enucleation · Preoperative chemotherapy

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Introduction

In patients suffering from bilateral WT, kidney-sparing surgery by tumor resection or enucleation is accepted as the operative treatment of choice according to the

SIOP (Societe Internationale d'Oncologie Pediatrique) and NWTSG (National Wilms' Tumor Study Group) protocols [1, 2]. In contrast, tumor nephrectomy is recommended as the standard surgical treatment in patients with unilateral WT. Nephron-sparing surgery in adult patients with unilateral renal cell carcinoma is a well-established method [3], whereas in pediatric patients with unilateral nephroblastoma renal salvage procedures remain more controversial. As long as 18 years ago, Grunert et al. discussed the role of "La chirurgie conservatrice dans le traitement des nephroblastomes" in four bilateral and two unilateral tumors—one of them in a single kidney [4]. Since then a number of authors published their experiences with partial nephrectomy in patients with unilaterlal WT [5, 6, 7, 8, 9, 10]. The purpose of this retrospective study was a review of the clinical course and outcome of 11 patients with WT treated in this institution by kidney-sparing operations.

Subjects and methods

From June 1981 to December 1998, 11 patients (eight female, three male) suffering from nephroblastoma underwent a renal salvage strategy (Table 1). Seven patients (four female, three male) with unilateral WT (five right, two left) were operated on at the mean age of 4.2 years (range: 1 year to 10.5 years), whereas four patients with bilateral WT were operated on at the mean age of 2.6 years (range: 8 months to 6 years).

Initial symptoms were abdominal pain in six children and painless abdominal distension in four patients. In one child a blunt abdominal trauma led to the diagnosis.

One infant suffered primarily from a massive bilateral nephroblastomatosis, which evolved to a unilateral WT at the age of 44 months, after primary normalization of the kidney size with treatment according to the SIOP-93 protocol for nephroblastomatosis. The family history in this patient revealed a hemihypertrophic grandfather who was operated on for nephroblastoma during childhood.

In terms of clinical and pathological staging we used the criteria of the SIOP, differentiating among stage I to V nephroblastomas and among favourable, intermediate and unfavourable histology, respectively. Clear cell sarcoma and rhabdoid tumor, initially subgroups of WT, were seen as different entities from nephroblastoma and therefore were not included in this study [13, 14].

Four patients had stage I WT, one stage III, two stage IV and four stage V—one of them with intravascular extension of the tumor to the right atrium. Preoperatively, in one patient (no. 6) a unilateral lung metastasis and in another patient (no. 7) bilateral lung metastases combined with liver metastases were diagnosed. Histology was intermediate in all nephroblastomas.

Preoperatively, a plain X-ray film of the abdomen and the chest and abdominal sonography combined with computed tomography scan (CT) of the abdomen and the lung were performed routinely in our patients—except in two patients with bilateral nephroblastoma, who instead had excretory pyelography and angiography (according to the Austrian Wilms' Tumor Protocol 1981). The reduction rate of tumor volume by preoperative chemotherapy in our unilateral nephroblastoma patients was assessed by weekly abdominal sonography.

Over the years the patients were submitted to three Wilms' Tumor treatment protocols: the Austrian Wilms' Tumor Protocol 1981, $n = 2$; the Austrian/Hungarian (A/H) Wilms' Tumor Protocol 1989, $n = 5$, and the SIOP 93–01, $n = 4$. Preoperatively, all patients received chemotherapy according to the treatment protocols (i.e., actinomycin D and vincristine). At the age of 13 months, in patient no. 1, biopsy of both kidneys via laparotomy confirmed the diagnosis of bilateral nephroblastomatosis. As mentioned above, this patient developed a unilateral WT of the left kidney after complete shrinkage of nephroblastomatosis as a result of primary chemotherapy.

In patient no. 7 a preoperative biopsy of the tumor via laparotomy revealed histologically an undifferentiated tumor. Therefore, this patient received a chemotherapy regimen for sarcoma (EVAIA protocol). The tumor size shrunk by 75%, so that partial nephrectomy was possible. Definite histology showed an intermediate nephroblastoma.

Laparotomy was conducted by a wide supraumbilical transverse transperitoneal incision with the possibility to extend the incision to the other side. In patients with unilateral disease partial nephrectomy was considered when (1) tumor volume could be

Table 1 Patient characteristics. *A.a.o.*age at operation in months, *TR* tumor volume reduction rate in % sonographically, *C.C.*creatinine clearance in ml/min 1.73 m^2, *PN* partial nephrectomy, *RN* rest nephrectomy

Patient	Sex	Stage	A.a.o	Metastases	Operations	TR	C.C.	Complications
No. 1	M	I	44		PN after primary bilateral nephroblastomatosis, open biopsy	76	111	
No. 2	M	I	12		PN	87	128	
No. 3	F	I	49		PN	97	102	
No. 4	F	I	56		PN	82	94	
No. 5	M	III	56	Peritoneum	PN, resection of metastatic implant	84	74	Renal arterial thrombosis, RN
No. 6	F	IV	40/59	Lung	PN, wedge resection of lung metastasis	49	70	Local relapse, RN, lung metastases
No. 7	F	IV	126	Lung, liver	PN, open biopsy	75	100	
No. 8	F	V	8		Bilateral tumor enucleation		90	
No. 9	F	V	34		Tumor enucleation + contralateral nephrectomy		47	Chronic renal failure
No. 10	F	V	72		Bilateral tumor enucleation		75	
No. 11	F	V	12		Bilateral tumor enucleation			Died of sepsis at the age of 14 months

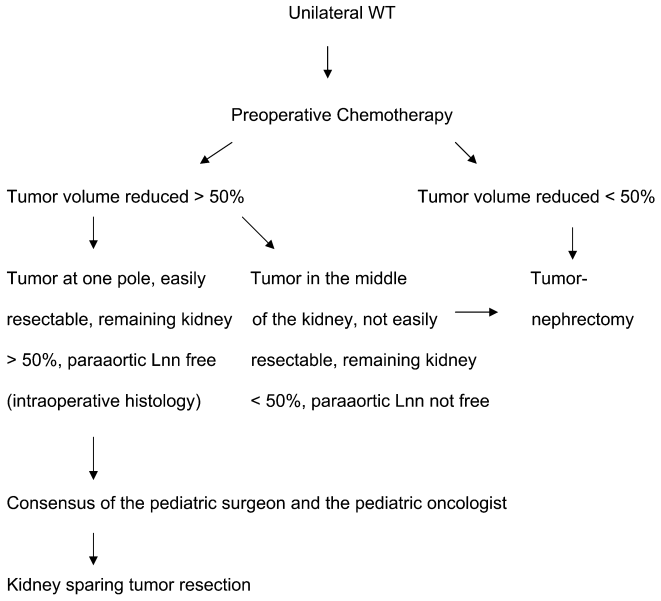

Fig. 1 Algorithm in unilateral Wilms' tumors with preoperative chemotherapy. Nephron-sparing surgery is only indicated when paraaortic lymph nodes are free and no local radiation therapy is necessary

reduced by preoperative chemotherapy sonographically by at least 50%, (2), when the tumor occupied one pole or turned out to be easily resectable and when 50% or more kidney tissue remained and (3) when paraaortic lymph nodes were free by intraoperative histological examination (Fig. 1). After inspection of surrounding organs, unilateral nephroblastomas were resected together with a rim of normal kidney tissue, while bilateral nephroblastomas were removed by tumor enucleation in three cases. In one stage V case—tumor thrombosis via vena renalis and inferior vena cava extending to the right atrium—unilateral nephrectomy, contralateral tumor enucleation and extraction of the intracaval tumor supported by cardiopulmonary bypass were necessary. In patient no. 5, who showed no metastases in preoperative abdominal and chest CT scans, a peritoneal implant metastasis next to the tumor was removed. In patient no. 6 a metastasis of the left lung was removed by wedge resection via thoracotomy 2 months after partial nephrectomy. Lung and liver metastases of patient no. 7 disappeared after preoperative chemotherapy.

Postoperatively, chemotherapy and/or radiotherapy were performed according to appropriate Wilms' Tumor treatment protocols. Renal function was evaluated by measurement of creatinine clearance (normal >70 ml/min 1.73 m2) and renal scintigraphy (the remaining part of the kidney should have at least a function rate of one-third of total renal function).

Results

Unilateral WTs

The initial mean tumor volume of unilateral nephroblastomas estimated by ultrasonography ($n=7$) was 720.5 ml (range, 17.8 ml to 1,346 ml). After 4 to 6 weeks of preoperative chemotherapy the mean tumor reduction rate was 79% (4.2 ml to 594 ml, mean 162.3 ml).

Primary tumor resection in unilateral WT was successfully performed in six patients. In patient no. 5 (stage III due to a local peritoneal implantation metastasis with complete regression on surgery and free lymph nodes), the spared half kidney had to be taken out 2 days after primary surgery because of a renal arterial thrombosis. The intraoperative histological analysis in patient no. 6 (stage IV because of a lung metastasis, free lymph nodes) showed that the primary resection margin was not radical and an additional slice of tissue had been resected to include a rim of healthy kidney tissue. Nineteen months later, this particular patient developed a metastatic implant cranial from the remaining kidney, which was then resected together with the remaining kidney.

Tumor bed irradiation with a dosage up to 1,500 rads was carried out in patients nos. 5 and 6 after secondary nephrectomy. Patient no. 6 developed lung metastases and had high-dose chemotherapy with autologous peripheral stem cell transplantation followed by bilateral lung irradiation.

All patients in the group of primary unilateral partial nephrectomy are alive and disease-free at a mean follow-up time of 6.6 years (range: 28 months to 11 years). The mean creatinine clearance was 97 ml/min/1.73 m2 (range: 70 to 128 ml/min/1.73 m2). The postoperative renal scintigraphy revealed a 40% kidney remnant function rate.

Bilateral WTs

In the group of stage V tumor patients, patient no. 11 died 2 months postoperatively during chemotherapy because of central venous line sepsis. The mean follow-up time of the remaining three patients was 12.5 years (range: 7 to 18.5 years). Patient no. 9 with intracardial tumor extension in which the left-sided tumor was enucleated and the right kidney was removed received radiotherapy of the whole abdomen up to 12 Gy. Additionally, the site of ureteronephrectomy was irradiated up to 19 Gy. This child suffers from chronic renal failure with a creatinine clearance of 47 ml/min/1.73 m^2 4.7 years postoperatively. The creatinine clearance levels of the two other patients (nos. 8 and 10) with residual kidneys on both sides are within the normal range (90 ml/min/1.73 m2 and 75 ml/min/1.73 m2).

Discussion

Wilms' tumor or nephroblastoma comprises 87% of all pediatric renal tumors. With 600 new cases annually in the USA, it is the most common genitourinary malignancy in children [11, 12, 13]. The tumor is classified by the SIOP and NWTSG into five stages according to extent, infiltration of neighboring organs, local or distant metastases and bilateral involvement. The treatment of WT, including chemotherapy, surgery and radiotherapy (when appropriate) differs substantially between the NWTSG protocol recommending primary

surgery and the SIOP protocol favoring preoperative chemotherapy [14, 15, 16].

The protocols by which our patients have been treated over the years were closely related to the SIOP strategies preferring primary chemotherapy without biopsy and secondary surgery in all WT patients. A preoperative open biopsy was performed only in patient no. 1 to confirm the diagnosis of bilateral nephroblastomatosis and in patient no. 7 with uncertain clinical diagnosis (Table 1). In the latter patient the result of the histological diagnosis favored an undifferentiated tumor. Therefore, a chemotherapy regimen for sarcoma (EVAIA protocol) was initiated. Nevertheless, the tumor response rate was excellent and only the postoperative histology confirmed a nephroblastoma.

Kidney-sparing surgery by tumor enucleation or resection of at least one kidney after preoperative chemotherapy is the recommended approach in bilateral WTs according to both study groups—the European and the North American. A recent published study showed a good outcome with a 5-year survival rate of 73% and a 10-year survival rate of 70% [17]. One out of four of our patients died 2 months after surgery of central venous line sepsis during postoperative chemotherapy. However, Montgomery et al. reported a small portion of children with stage V tumor developing renal failure. The author considered the cumulative effect of surgical reduction of functioning kidney tissue, chemotherapy and/or radiotherapy responsible for renal dysfunction [17]. Our stage V tumor patient no. 9 (Table 1) with inferior vena cava thrombosis extending to the right atrium developed postoperative chronic renal failure, which possibly would have been avoided by tumor enucleation/resection instead of unilateral nephrectomy.

In contrast to bilateral WT patients, total nephrectomy is recommended in unilateral cases as the surgical procedure of choice. Based on the excellent survival rate of more than 90% the question must be asked whether some carefully selected forms of unilateral nephroblastomas—easily resectable tumors, confined to one kidney pole, and excellent response to preoperative chemotherapy—could be treated by kidney tissue sparing surgery with the same favorable outcome. In the group of patients with unilateral WT presented here, we followed a renal salvage surgical strategy removing the tumor together with a rim of healthy renal parenchyma [18]. The major argument to prefer kidney-sparing surgery in selected patients comes from the local situs during surgery, when only a rather small and/or easily resectable remaining tumor is situated on one kidney pole. Resection of the tumor through distant healthy kidney tissue, thereby sparing at least half of the kidney, is a very strong option in these cases. Local radiotherapy should not be necessary, therefore it is important that paraaortic lymph nodes are free of tumor invasion.

The danger of focal glomerulosclerosis caused by hyperfiltration after unilateral ureteronephrectomy is discussed in a controversial manner in the literature [19]. Ritchey et al. reported a low risk of renal failure in children and adolescents with unilateral nephrectomy ranging from 0.2% to 0.4% [20]. On the other hand microalbuminuria, proteinuria and a decreased glomerular filtration rate could be seen in adults as long-term sequelae of renal agenesis or unilateral nephrectomy [21, 22]. In our group of patients no child had reduced renal function after partial nephrectomy, but patients nos. 5 and 6, after secondary nephrectomy, revealed creatinine clearance levels at the lower range of normality. Thus, kidney-sparing surgery in unilateral WTs may minimize the risk of late glomerulosclerosis and reduced kidney function.

A further argument for renal salvage procedures in unilateral nephroblastomas is the advantage of renal tissue preservation in the case of secondary contralateral nephrectomy, i.e., due to metachronous WT. Moorman-Voestermans reported a patient suffering from unilateral WT who was saved from dialysis by partial nephrectomy because the contralateral kidney had to be removed after a renal trauma [6].

The major argument of critics concerning renal salvage procedures in unilateral WT is that partial nephrectomy bears the risk of leaving a tumor remnant in situ; especially, when the tumor is anaplastic, the outcome would be markedly worse [23, 24]. It has to be pointed out that a characteristic of anaplastic nephroblastomas is their resistance to conventional chemotherapy. Therefore, in our selected group of patients only unilateral nephroblastomas with excellent response to preoperative chemotherapy ($>50\%$ tumor volume reduction rate) have been considered for partial nephrectomy. We have learned a lesson from patient no. 6, suffering from local stage I WT, in whom the partial nephrectomy was initially not far enough away from the tumor, so that a further slice of tissue had to be resected, with then healthy kidney tissue margins. Nineteen months later this particular patient evolved a local metastatic implant cranial from the remaining kidney and resection of the local metastasis combined with a total nephrectomy was performed. Thus, intraoperative opening of the tumor is similar to tumor rupture with local spillage, which then needs postoperative radiotherapy of the tumor bed [10, 20]. Therefore, concerning the surgical technique in partial nephrectomy, it is important to be radical, which means that the surgeon always has to resect a rim of normal renal tissue. If the resection margin turns out to be uncertain, intraoperative ultrasound should be carried out to clearly mark the resection line.

In contrast, tumor enucleation is preferred in bilateral WT. Cozzi recommends this procedure as nephron-sparing surgery in unilateral WT, too, whereas Gulielmi et al. showed that tumor enucleation of an unilateral WT is a ''nononcologic'' procedure, because only in cases with a thick, histologically confirmed tumor pseudocapsule was complete tumorectomy predictable [10, 25].

Detailed histories of 18 children with unilateral nephroblastoma (13 stage I, 2 stage II, 3 stage III) who underwent a renal salvage procedure have been described in the literature since 1983 (Table 2) [4, 5, 6, 7, 8, 9, 10]. Three of these patients died [5, 6]: One stage I patient developed lung metastases 20 months after the operation and two children with stage III tumor died as a result of metastatic disease. One stage I tumor patient presented with local recurrent disease, making nephrectomy of the initially preserved kidney necessary [5]. The latter and all other patients are still alive, disease free and have normal renal function.

As mentioned above, an important indicator concerning the feasibility of partial nephrectomy is the tumor response rate after preoperative chemotherapy of at least 50% [26]. In these cases even patients suffering from very large tumor masses can be treated by partial nephrectomy. In patient no. 2 (Table 1) the initial tumor volume was 1,346 ml. After preoperative chemotherapy the tumor volume reduced to 175 ml (tumor reduction rate of 87%) (Fig. 2a and b). This patient was successfully operated on by a kidney-sparing procedure without long-term sequelae at follow-up (Fig. 3).

Moorman-Voestermans et al. described a 87% accuracy rate in predicting the possibility of renal salvage procedures in unilateral nephroblastomas by preoperative imaging techniques [6]. However, our experience showed that only the intraoperative situs is decisive for the definitive surgical approach. Moreover, we have learned that some nephroblastomas (i.e., patient no. 7), which have responded well to primary chemotherapy, but remain a relatively large mass preoperatively and therefore are determined for tumor nephrectomy, can present intraoperatively as a resectable tumor with the possibility of preservation of at least 50% of the healthy renal tissue. It is our policy for the surgeon and pediatric oncologist to make the definite decision intraoperatively whether a PN is feasible and safe without opening the tumor. The promising results of nephron-sparing surgery in unilateral WT was acknowledged in the recent SIOP protocol offering this type of procedure in selected cases as an option that is not considered as a violation of the protocol [18].

Table 2 Overview of 18 children with unilateral WT operated on by PN

		Stage	Survived
Gruner et al. [4]	1985	I ($n=2$)	2
Verga et al. [7]	1986	I ($n=1$)	1
McLorie et al. [5]	1991	I ($n=1$)	1
		II ($n=2$)	2
		III ($n=1$)	0
Cozzi et al. [10]	1996	I ($n=3$)	3
Morales et al. [9]	1997	I ($n=1$)	1
Moorman et al. [6]	1998	I ($n=5$)	4
		III ($n=2$)	1

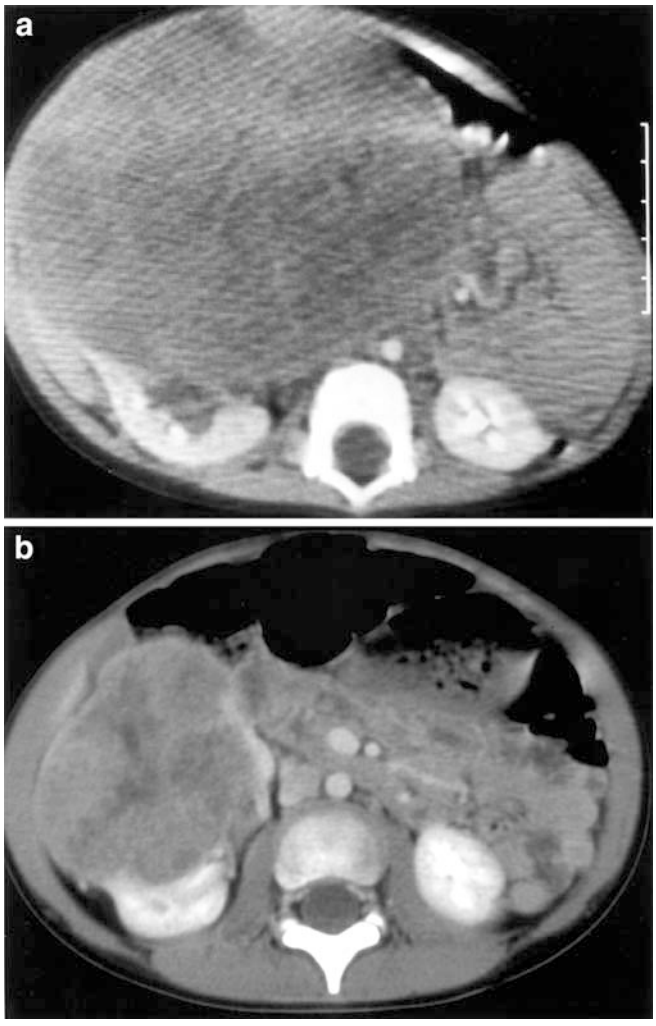

Fig. 2 **a** Patient no. 2. Initial tumor volume (1,346 ml). **b** Patient no. 2. Tumor volume after 6 weeks of preoperative chemotherapy (175 ml)

Conclusion

PN in unilateral WT in general cannot be recommended yet, but promises to be a reasonable alternative surgical strategy to tumor nephrectomy in some patients. It preserves renal tissue and potentially can save the child from dialysis in cases of contralateral nephrectomy resulting from renal trauma or metachronous WT. However, resection through healthy kidney tissue is mandatory, because tumor spillage due to incomplete resection bears the risk of local relapse, which would make nephrectomy and postoperative local radiotherapy necessary. Important prerequisites for a decision for a partial nephrectomy in unilateral WT are a preoperative tumor volume reduction rate of at least 50% measured by abdominal ultrasonography, confinement of the tumor to one renal pole and/or easy resectability, preservation of at least 50% of the renal tissue and histologically free paraaortic lymph nodes. While tumor enucleation in unilateral WT

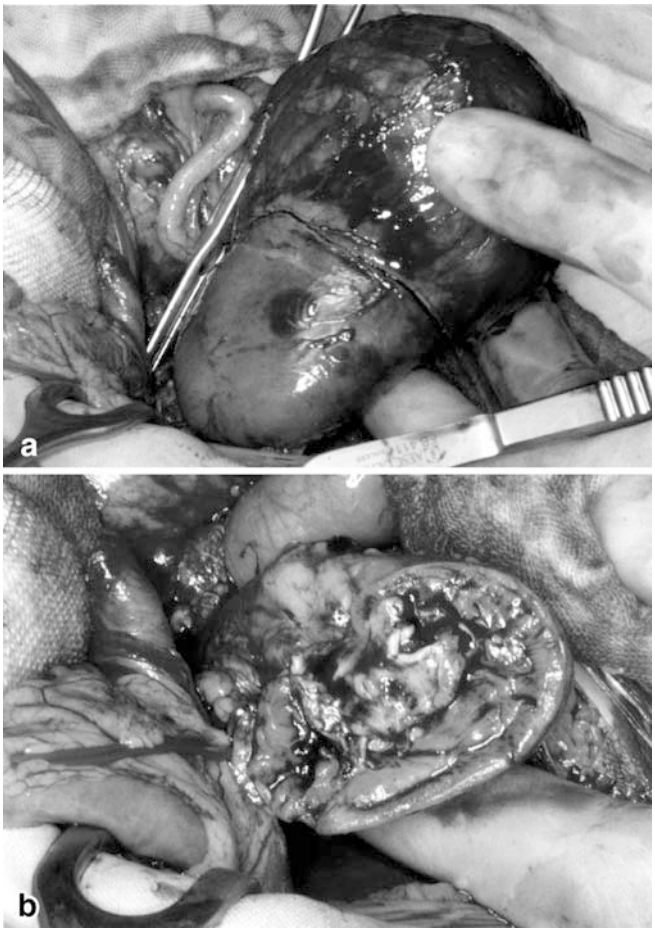

Fig. 3 Patient no. 2. Resected nephroblastoma

cannot be recommended as a safe strategy, in bilateral WT, tumor enucleation or kidney-sparing resection after preoperative chemotherapy remains the surgical procedure of choice, because it prevents the child from having dialysis and renal transplantation.

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