Surgical Consideration for Wilms' Tumors and Other Neoplastic Renal Lesions

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Abstract

Wilms' tumor (WT) of the kidney, or nephroblastoma, represents one of the great success stories in pediatric cancer therapy. Outcomes for children with Wilms' tumor have improved dramatically over the last 50 years with long-term survival in both North America and European trials approaching 85 %. Furthermore, many of the low-stage tumors have survival rates between 95 and 99 %. WT is named after Carl Max Wilhelm Wilms (November 5, 1867–May 14, 1918), a German pathologist and surgeon. He published his findings in 1897 in an influential 1899 monograph titled Die Mischgeschwülste der Niere.

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11.1 History of Surgery for Wilms' Tumor

Wilms' tumor (WT) of the kidney, or nephroblastoma, represents one of the great success stories in pediatric cancer therapy. Outcomes for children with Wilms' tumor have improved dramatically over the last 50 years with long-term survival in both North America and European trials approaching 85 %. Furthermore, many of the low-stage tumors have survival rates between 95 and 99 % (Grundy et al. 2005; Kalapurakal et al. 2004). WT is named after Carl Max Wilhelm Wilms (November 5, 1867–May 14, 1918), a German pathologist and surgeon. He published his findings in 1897 in an influential 1899 monograph titled Die Mischgeschwülste der Niere (Wilms 1897, 1899).

Surgery was the first effective treatment for nephroblastoma and continues to be the backbone of successful multimodality therapy. Although Wilms is credited with describing the tumor, anecdotal reports on successful excision of renal tumors in children and their possible cure appeared in the end of the nineteenth century. Dr. Thomas Jessop (1837–1903), on June 7, 1877, probably performed the first successful nephrectomy on a 2-year-old child with hematuria and a tumor of the kidney (Willets 2003; Gross 1953). At the beginning of the 1900s, survival for a child with WT was 5 %. Surgery carried with it a high operative mortality. In the late 1930s, Ladd and Gross described removing renal tumors in selected children and increase in survival. This technique included large transverse transabdominal approach and early ligation of the renal vessels. This modification improved the outcome in children with nonmetastatic nephroblastoma up to 32.2 % at 3 years. In addition, operative mortality was reduced from 23 to 7 %. Today the current oncological nephrectomy currently used for Wilms' tumor is still very similar to that postulated by Ladd and Gross (Gross 1953; Kung and Nyhan 1982; Othersen et al. 1999).

Over the last 50 years, large clinical trials using surgery in combination with chemotherapy and radiotherapy have improved survival and reduced morbidity from WT. The majority of the randomized clinical studies for the treatment of children with WT have been conducted by two large clinical cooperative groups. These are the Children Oncology Group (COG – formerly the National Wilms' Tumor Study Group [NWTS]) and the Société Internationale d'oncologie Pédiatrique (SIOP). The COG/NWTS is primarily based in North America whereas SIOP is a European consortium. Since 1969 the COG/NWTS in North America and since 1971 the SIOP in Europe tested several aspects of the multimodal risk-adapted therapy. One of the primary philosophical differences is that COG/NWTS recommends primary nephrectomy in nearly all unilateral patients. The SIOP advocates preoperative chemotherapy following imaging-based diagnosis which could be supplemented with fine or core needle biopsy in case of doubts, then nephrectomy. Interestingly, nearly the same results were achieved using different policy of the initial approach (Ehrlich 2001, 2007a; de Kraker et al. 2001; D'Angio et al. 1976; Lemerle et al. 1983; Tournade et al. 2001).

11.2 Surgical Implications of Primary Nephrectomy and Primary Chemotherapy

Although similar cure rates are achieved by both SIOP and COG/NWTS studies, there are differences between these two groups that affect staging and classification that is critical to understand when interpreting outcome studies for children with Wilms' tumor. The approach used by each group affects the staging and the subsequent risk-based therapy. For example, stage III patients on COG protocols are different than those on SIOP protocols.

11.2.1 The Philosophical Arguments for Primary Nephrectomy

Primary nephrectomy (when possible) has the following potential advantages. First, the primary tumor burden is removed. The morbidity and

mortality in the modern age associated with renal surgery is low. Second, the pathology of the tumor will be determined before initiating adjuvant therapy. When treatment is started without tumor pathology, benign tumors or nonneoplastic lesions will be encountered. Misdiagnosis rates as high as 8 % and using the wrong chemotherapy in 5.2 % have been reported although this has dropped to below 1 % recently (de Kraker et al. 1999; Schenk et al. 2006; Vujanic et al. 2009). It is also important to consider that not all tumors respond to chemotherapy. Although removing big tumors is challenging, the size of the tumor does not always mean the risk of metastatic disease. In COG/NWTS protocols, if the tumor is not removed primarily, the patient will be stage III and receive three drug chemotherapy and radiation. A primary nephrectomy with a stage I or II tumor would avoid this increased therapy. Another consideration is that in a child less than two with a tumor less than 550 g who is stage I may not require any adjuvant therapy for a cure. Chemotherapy also changes tumor pathology, and the COG/NWTS staging system does not at present take this into account. Primary nephrectomy allows for initial assessment of lymph node status. This is very important in the COG/NWTS protocols. The treatment regimens for the COG protocols is risk based using age, stage, and LOH as key determinants. Preoperative chemotherapy results in a loss of important staging data, particularly lymph node status. For example, patients with favorable histology WT treated on SIOP 9301 and 2001 who were stage III and LN positive after preoperative chemo have a 5-year EFS of 82 %. Those that were stage III LN negative after preoperative chemotherapy, 5-year EFS is 82 %. Alternatively, the COG/NWTS data shows that stage III patients who are LN positive also have a 5-year survival of 81 %. In contrast, the COG/NWTS patients who are stage III but LN negative have a 5-year EFS of 91 % (Grundy 2009).

11.2.2 The Philosophical Arguments for Preoperative Chemotherapy

Preoperative chemotherapy, historically, proved its importance in decreasing the tumor rupture rate and inducing very favorable stage distribution at secondary surgery (Fig. 11.1). Also, the rate of surgery-related complications is low. The problem appears in very extensive or very fragile tumors. Heroic resections are followed more frequently by surgery-related complications. Incomplete resection implies more aggressive and also more toxic postoperative chemotherapy and radiotherapy. Surgical complications appear to be lower in pretreated patient. SIOP-9 reported an 8 % surgical complication rate as compared to NWTS-3 which had a 19.8 % complication rate. However, for NWTS-4 the complication

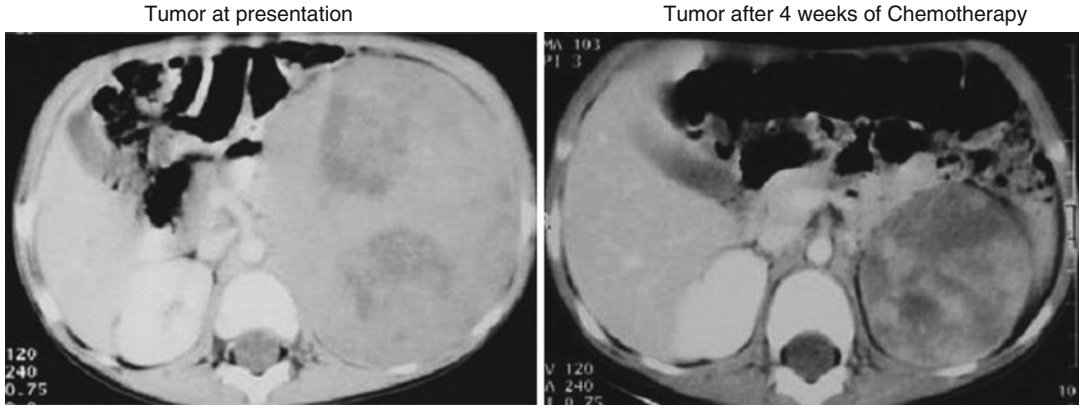

Fig. 11.1 Computed tomography scans demonstrating a picture of a Wilms' tumor at presentation and following 4 weeks of chemotherapy

rate was 12.7 %. It is also important to consider that what is considered as rupture or spill under SIOP is different in the COG/NWTS protocols. For example, in SIOP protocols, preoperative or intraoperative tru-cut or fine-needle punctures are not considered as spill, whereas in the COG/NWTS, they are considered spill. One relevant point is to look at whether a surgical spill resulted in patient being upstaged due to that spill. For NWTS-5 that was 1.4 % and for SIOP-9 that was 2.8 %, statistically there is no difference (Ehrlich et al. 2005; Godzinski et al. 1998). Tumor rupture and spillage during surgery is undoubtedly a bad event and needs to be avoided supporting an argument for pretreatment (Shamberger et al. 1999).On the other hand, those who have initially low staged tumor can benefit from lesser therapy if operated on primarily (D'Angio et al. 1976; Godzinski et al. 1998; Shamberger et al. 1999; Ritchey et al. 1992a, 2001; Kaste et al. 2008). Another argument for preoperative chemotherapy is that tumor staging does not occur until after initial chemotherapy and this results in lower rate of flank radiation in SIOP studies as compared to the COG/NWTS studies. This is an important consideration due to the late effects of radiotherapy.

Preoperative chemotherapy also preselects patients responding well to chemotherapy. That influences the histological classification which includes favorable 100 % necrotic subtype of nephroblastoma and unfavorable patients with blastema persisting the pretreatment. Also, initial extension of the disease has probably limited impact on final outcome if it regresses under the pretreatment, and, according to the SIOP experience, postoperative part of the therapy may be based upon the situation found at secondary surgery. That implies less aggressive postoperative therapy and avoidance of radiotherapy in a number of patients. On the other hand, primary chemotherapy for renal tumor diagnosed by imaging only implies certain number of treatments given to nonmalignant conditions or tumors other than nephroblastoma. Initial surgical biopsy is not recommended; however, fine-needle aspiration and tru-cut are the methods which decrease the risk of misdiagnosis (Godzinski et al. 1998, 1999; Shamberger et al. 1999; Ritchey et al. 1992a, 2001; Ritchey 1999).

11.3 Staging Aspects and the Problem of Comparing Outcomes

It is important when thinking about the potential advantages and disadvantages of each strategy to remember that outcomes are similar, but comparing patients is difficult due to the staging of patients prior to and after chemotherapy. Rather than thinking about which is better, it is more important to look at how each therapy addresses and answers some of the problems faced by any multidisciplinary groups that treat children with WT. The SIOP stages are induced by chemotherapy and separate good responders from poor responders, whereas the COG/NWTS staging systems are based on disease state prior to therapy using molecular markers such as LOH. These differences complicate markedly any direct comparisons of results, which in general should only be done very carefully and thoughtfully (Kaste et al. 2008; Godzinski et al. 1999, 2005; Brisse et al. 2006)

11.4 Nephrectomy

Surgery plays an important part of the multidisciplinary therapy for children with Wilms' tumor (WT). Regardless of timing of the renal surgery, there are several key issues that all surgeons must remember when performing operations on children with WT. These are: (a) perform safe operation, (b) understand what constitutes a complete procedure, and (c) recognize that the surgeon plays an important role in accurately staging the disease which is essential in directing future therapy. Under-staging can increase a child's risk of relapse, and over-staging could result in unnecessary chemotherapy or radiation. Intraoperative events that negatively affect patient survival include tumor spill, deficient operations, incomplete tumor removal, not assessing for

extrarenal tumor extension, and surgical complications (Ehrlich et al. 2005; Shamberger et al. 1999; Ritchey et al. 2001).

The surgeon must document everything she/he does or finds in the operative note. This includes any tumor spill or rupture. Studies have shown a higher risk of recurrence in patients who had tumor spills or ruptures irrespective of the cause or extent of the soiling (Ehrlich et al. 2005; Shamberger et al. 1999; Ritchey et al. 2001). "Spill" refers to a break in the tumor capsule during operative removal whether accidental, unavoidable, or by design. Spill is also considered to have occurred if the renal vein or ureter was transected when they contain tumor. *(In the Children Oncology Group [COG] protocols, spill is also considered to have occurred if a preoperative or intraoperative needle/open biopsy was performed. This is not the case for those patients treated following Société Internationale d'Oncologie Pédiatrique protocols.)* "Rupture" refers to either the spontaneous or posttraumatic rupture of the tumor preoperatively with the result that tumor cells are disseminated throughout the peritoneal or retroperitoneal space (Grundy et al. 2007). Bloody peritoneal fluid is considered a sign of rupture, whether or not gross or microscopic tumor is identified in the fluid. Rupture is also considered to have occurred if the tumor penetrates the kidney capsule, with open raw neoplastic tissue surface being in free communication with the peritoneal cavity. All of these situations must be carefully documented in the operative note.

11.5 Technical Considerations

For a child with two normal kidneys and a unilateral renal tumor, the recommended surgical procedure is a unilateral radical ureteronephrectomy with lymph node sampling (Grundy et al. 2006; Ladd 1938). The incisions associated with the best exposure and lower complication rates are transverse transabdominal, transperitoneal, or thoracoabdominal (Ritchey et al. 1992a, b, 2001; Fuchs et al. 2009a). Large tumors or for those that come off the superior pole and extend up to the diaphragm, a thoracic extension of the incision through the eighth or ninth rib helps with exposure, although this is rarely required (Fig. 11.2). After entering the peritoneal cavity, evaluation of the peritoneal surfaces, liver, renal vein, and IVC for tumor extension is needed. Routine exploration of the contralateral kidney was originally mandated. Due to improvement in imaging, especially spiral CT scans, this is not necessary if imaging is satisfactory and does not suggest a bilateral process (Ritchey et al. 1995, 2005). If the initial imaging studies were suggestive of a possible lesion on the contralateral kidney, the contralateral kidney should be formally explored to rule out bilateral involvement. This should be done prior to nephrectomy. In addition, any evidence of a preoperative or intraoperative tumor rupture should be clearly documented in the operative report. *(In the past, the COG/NWTSG made a distinction a local and a diffuse spill. For COG protocols, this distinction is no longer made* (Shamberger et al. 1999; Kalapurakal et al. 2010). *For COG protocols, in any preoperative or intraoperative tumor biopsy, preoperative*

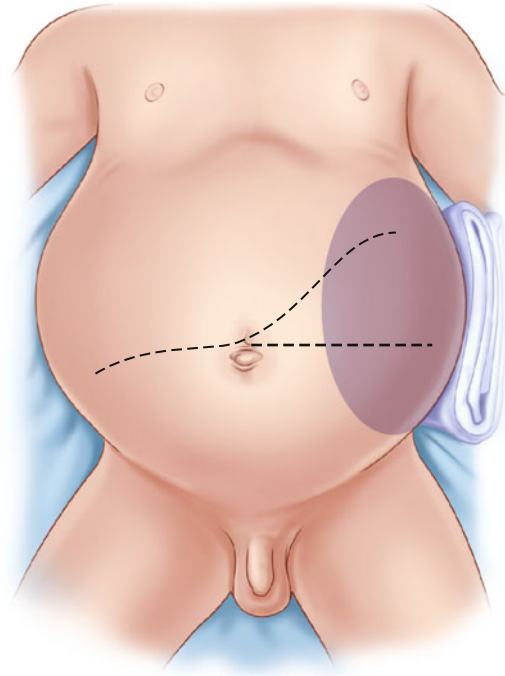

Fig. 11.2 A sketch showing patient positioning and typical abdominal incisions used for Wilms' tumor surgery

or intraoperative tumor rupture is considered a spill and is stage III. This is not the case for those patients treated following Société Internationale d'Oncologie Pédiatrique protocols: fine-needle punction or tru-cut needle punction is allowed in this study; however, surgical incisional biopsies are considered as ruptures, automatically staged III and contraindicated.)

To help expose the primary tumor, the lateral peritoneal reflection is opened, and the colon is reflected medially. For right-sided tumors, a Kocher procedure is also helpful. An attempt should be made to dissect, expose, and ligate the renal vessels in order to lessen the chance of hematogenous spread of tumor before mobilizing the tumor. The renal artery should be ligated first, then the renal vein. That prevents increasing the intrarenal and tumor blood pressure. However, because WT can be quite large, *preliminary ligation should not be pursued if technically difficult or dangerous*. For tumors that are pretreated with chemotherapy and respond, ligation of the renal vessels is often easy (Fig. 11.1). WT, as opposed to neuroblastomas, tends to displace vessels and organs. When dividing the vessels it is important for the surgeon to make sure the contralateral renal vessels, aorta, vena cava, iliac, and superior mesenteric arteries have not been ligated (Ritchey et al. 1992b). The adrenal gland may be left in place if it is not abutting the tumor, but if the mass arises in the upper pole of the kidney, the adrenal gland should be removed with the neoplasm. The ureter is ligated and divided as low as conveniently possible (Ritchey et al. 2008). The tumor and the uninvolved portion of the kidney are mobilized and removed intact. The tumor and kidney should be handled gently to avoid tumor spill as this results in a increase in local abdominal relapse (Shamberger et al. 1999, 2001; D'Angio et al. 1989).The renal vein and IVC should be palpated to look for tumor. Any suspicious areas that could represent metastases should be biopsied and marked with titanium clips. Although it is recognized that with improved CT and MRI imaging, the use of marking titanium clips may not be necessary. In addition, there is concern that clips may lead to artifacts on imaging.

WT can be large; however, in most cases there is no invasion by the tumor into contiguous organs, but typically the tumor displaces or is adherent to adjacent organs. This allows the tumor to be separated from the organs in most cases. When the surgeon does encounter a clinical situation with invasion, radical en bloc resection, e.g., partial hepatectomy, or colectomy is not warranted as a primary therapy and is associated with an increased frequency of complications (Shamberger et al. 1999; Ritchey et al. 2001). A small section of diaphragm, psoas muscle, or tip of the pancreas is acceptable. WT is very chemosensitive, and in these situations prior adjuvant therapy will allow for a safer resection.

There are clinical situations where it is agreed that primary nephrectomy poses too great a risk. These are (a) when there is extension of tumor thrombus above the level of the hepatic veins, (b) the tumor involves contiguous structures whereby the only means of removing the kidney tumor requires removal of the other structures (e.g., spleen, pancreas, colon but excluding the adrenal gland), (d) bilateral tumors, (e) or if there is pulmonary compromise due to extensive pulmonary metastases, (f) and if it is the surgeons' judgment that nephrectomy would result in significant or unnecessary morbidity/mortality, diffuse tumor spill, or residual tumor. Studies conducted by the large cooperative groups have shown that pretreatment with chemotherapy almost always reduces the bulk of the tumor (Lemerle et al. 1983; Mitchell et al. 2006; Tournade et al. 1993, 2001). This makes tumor removal easier and may reduce the incidence of surgical complications (Godzinski et al. 1998). Preoperative chemotherapy does not result in improved survival rates, and it may result in the loss of staging information and changes the histology of the tumor as noted above (Green et al. 1993; Weirich et al. 2001). It is a very rare situation when a tumor cannot be removed if pretreated. Some exceptions, however, happen. Inoperability for pretreated tumor implies a very poor outcome. In the COG protocols, a biopsy is recommended first for unilateral tumors. In SIOP protocols, this is not always the case. The COG/NWTS biopsies

can be performed open, tru-cut, or imaged guided. The SIOP protocols do not recommend open biopsy. Tru-cut, under "eye control" or US guided, but still rather from posterior side and passing via portion of uninvolved kidney (if exists) is SIOP options for tumors which appeared intraoperatively impossible to remove.

11.6 Lymph Node Documentation

Pathological assessment of hilar and regional lymph nodes is critical to accurately stage a child with renal tumor (Ehrlich et al. 2005; Shamberger et al. 1999). Unfortunately, failure to sample lymph nodes (*whether dealing with a unilateral or bilateral tumor*) is the major technical errors noted in Wilms' tumor surgery (Ehrlich et al. 2005). Furthermore, studies have demonstrated a higher risk of recurrence in children who did not have lymph node status documented at the time of nephrectomy (Shamberger et al. 1999). Routine lymph node sampling from the renal hilum, the pericaval, or the para-aortic areas must be performed. Simply looking at the lymph nodes to determine whether they are positive is highly inaccurate (Othersen et al. 1990).

11.7 Management of Tumor Extension in the Renal Vein, Inferior Vena Cava, and Atrium

WT patients may present with tumor extension through the renal vein to the IVC and even up to the right atrium. This is found in between 4 and 11 % of children. Surgical treatment is dependent on the extent of vascular invasion. These are usually clinically asymptomatic, and many are detected preoperatively by US, CT, and/or MRI scans. However, those that extend just into the renal vein may only be detected at operation, reinforcing the need to palpate the renal vein and IVC at the time of nephrectomy (Shamberger et al. 2001; Ritchey et al. 1993, 1994). As noted above, a primary resection when tumor thrombus extends into the inferior vena cava at the level of the liver or higher is contraindicated. We recommend that these patients be managed initially with preoperative chemotherapy. This approach will often achieve significant shrinkage of the intravascular thrombus facilitating subsequent surgical removal (Shamberger et al. 2001; Ehrlich 2007b). Although the outcomes of the patients with vascular extension is similar with a primary or delayed resection, the severity and number of operative complications are reduced with preoperative chemotherapy for those with vascular extension above the hepatic veins. Alternatively, if the tumor extends only into the renal vein or renal vein and IVC below the level of the liver, the tumor and tumor thrombus can in most cases be removed en bloc with the kidney (Fig. 11.3).

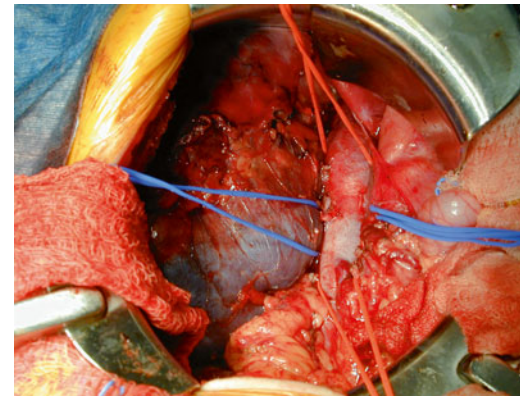

Fig. 11.3 This is an operative photo of a Wilms' tumor with vascular extension. Vessel loops are around the major vascular structures

An accurate description of the technique of removal should be given in the operative note. Control of renal veins and caval above and below the tumor with vessel loops is necessary using standard vascular surgery techniques. The tumor should not be transected, if possible, as this will result in spill and upstaging of the patient. In some cases, the tumor may be fixed to the vascular lumen. A similar technique used for removing plaque for a carotid endarterectomy is helpful to lift the tumor off the vein wall. It must be stated in the operative report if the intravascular tumor extension was removed en bloc or if tumor was transected, as well as if the tumor thrombus is removed completely and if there is evidence of

either adherence or invasion of the vein wall. If after preoperative chemotherapy the tumor still extends above the hepatic veins, cardiopulmonary bypass is needed to remove the vascular extent of the tumor.

11.8 Management of Tumor Extension in the Ureter

Extension of Wilms' tumor into the ureter is a rare event (Ritchey et al. 2008). In NWTS-5, the incidence of ureteral extension was 2 %. In only 30 % of these patients did preoperative imaging detect ureteral extension; the rest were discovered at operation. Clinical presentations included gross hematuria, passage of tissue per urethra, hydronephrosis, and a urethral mass. The diagnosis should be suspected in these patients, and cystoscopy with retrograde ureterogram may aid in preoperative diagnosis in these patients. If ureteric extension is detected or suspected, the ureter should be with clear margins.

11.9 Horseshoe Kidneys, Single Kidneys, and Nonfunctioning Kidneys

Resection of a WT in a child with a horseshoe kidney presents unique challenges (Fig. 11.4). Children with horseshoe kidneys and WT must be carefully imaged prior to any surgery (Ritchey 2005). The blood supply to a horseshoe kidney can be variable and must be documented prior to any surgical procedure. At the time of operation, the blood supply to the kidney as well as the ureters must be identified and isolated. Exposure and mobilization of the kidney on the side of the tumor is carried out as if one is performing a unilateral resection. The side of the kidney containing the tumor, the isthmus, and the ipsilateral ureter are resected. As with other unilateral procedures, the lymph node groups are sampled for staging purposes. Children with a single kidney, or a situation where a tumor occurs in one kidney but the second kidney is nonfunctioning, should be managed using a renal-sparing approach with preoperative chemotherapy to facilitate surgery and save more renal tissue.

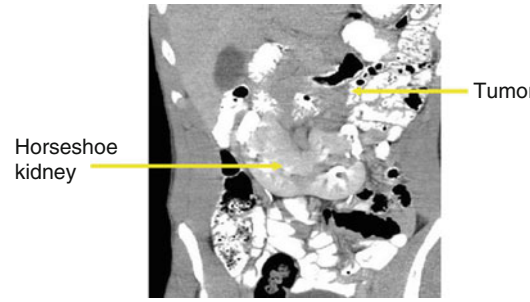

Fig. 11.4 A computed tomography scan showing a horseshoe kidney and a tumor in the upper pole of the left kidney

11.10 Surgical Management in Metastatic and Recurrent Disease

Metastatic disease (stage IV) is recognized as a poor prognostic factor for children with Wilms' tumor (Dome et al. 2006a). The primary sites of metastatic spread are to the liver and lungs. An important surgical point to remember is that the presence of lung or other site metastasis does not make the renal tumor unresectable. The abdominal tumor should be removed and staged locally as appropriate.

Lung metastases are the most common site of stage IV disease in children with Wilms' tumor. Depending on the treatment protocol, children with lung disease may be treated with just chemotherapy or both chemotherapy and radiation therapy. Historically, patients treated on COG/NWTS studies have been treated with radiotherapy in combination with either two or three drug therapy. Event-free survival for patients treated on NWTS-5 with lung metastasis was 76 % (72 %, 80 % CI 95 %). Review of the SIOP material by Jan de Kraker and co-workers evidenced overall survival and event-free survival of 83 % at 4 years for patients with pulmonary metastasis. Best outcomes were observed in those in whom metastasis disappeared after preoperative chemotherapy (23/27 alive and in CR) or were completely

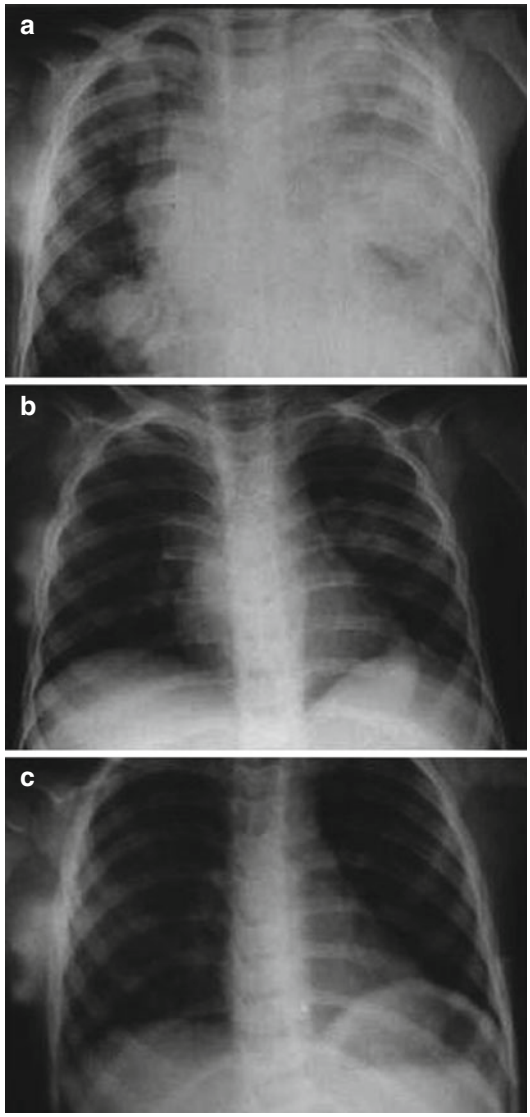

Fig. 11.5 (**a**) A chest radiograph in a patient with Wilms' tumor presenting with pulmonary disease. (**b**) The same patient's chest radiograph after 4 weeks of chemotherapy with vincristine, actinomycin D, and doxorubicin. (**c**) The same patient's chest radiograph after 4 more weeks of chemotherapy and radiotherapy

resected (5/5 CR) (de Kraker et al. 1990) (Fig. 11.5). Nearly the same results were reported by Steven Warmann and colleagues recently (Warmann et al. 2009).

Early treatment protocols assessed lung disease through a chest radiograph. However, current studies use CT and lesions are found on CT scan that are not found on CXR (Mankowski et al. 2004; Green 2002). These lesions have been managed in a variety of ways. The COG/NWTS analyzed these patients, and an inferior relapse-free survival was seen when children were treated with vincristine and actinomycin D only, whether or not they received pulmonary irradiation, compared to those who received doxorubicin. Thus, there appears to be no additional beneficial effect of lung irradiation on the outcome of some of these children when chemotherapy was taken into consideration. A second study examined the pathology of lung lesions seen only on CT scan in children from the NWTS-4/5 study (Owens et al. 2002). The results demonstrated that small lesions are usually but not invariably tumor. Based on these and other results, a current COG trial (ARENO533) for children with pulmonary lesions gives upfront chemotherapy followed by imaging at 6 weeks. If the lesions are still present, more intensive therapy including radiotherapy will be given.

There may be several times a surgeon may be asked to intervene in a child with a pulmonary lesion. The first is at diagnosis if there is uncertainty about pulmonary lesions. The second may occur after the first round of chemotherapy if lesions shrink but do not go away completely. If there is a concern about a lesion, it would be valuable to assess the histology of the lesion prior to giving radiotherapy. The third situation is if tumor remains after both chemotherapy and radiotherapy requiring surgical resection for cure. In the current SIOP 2001 protocol, if lesions remained after pretreatment, a metastasectomy is recommended. The suggested technical modalities include wedge resections or, rarely, lobectomies. Most WT metastases are peripheral and superficial, and many of these lesions can now be fully excised by video-assisted thoracic surgery (Fig. 11.6). Neither heroic, very extensive resections as bilobectomy or pneumonectomy nor surgery on progressing patients is recommended (de Kraker et al. 2001; Kaste et al. 2008; Ehrlich et al. 2006).

The approach to liver disease is less straightforward. Recent reports suggested that liver involvement at diagnosis in infants and children with Wilms' tumor indicated a worse prognosis than lung or other sites of stage IV disease (Varan

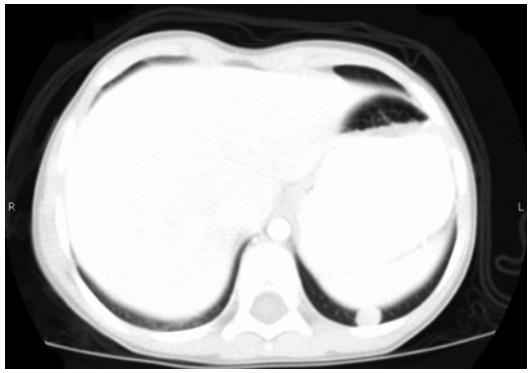

Fig. 11.6 Computed tomography scan showing peripheral lung lesions

et al. 2005; Szavay et al. 2006; Fuchs et al. 2008). The International Society of Pediatric Oncology (SIOP) and the German Pediatric Oncology Group (GPOH) studied 29 patients with liver metastasis at diagnosis (Szavay et al. 2006). The overall survival was less than 60 %, but all patients who had complete resection of the hepatic lesions survived. Another report from Varan et al. of 18 patients with liver metastases also noted a poorer outcome than for patients with pulmonary disease (50.2 % vs. 16.6 %) (Varan et al. 2005). These authors suggested, based on the poor outcomes of patients with liver metastases, that more intensive chemotherapy and more aggressive surgical treatment were warranted.

The COG also recently published their results of patients presenting with liver disease at diagnosis (Ehrlich et al. 2009). The estimated 5-year EFS (95 % confidence interval [CI]) for 634 patients with metastatic FH Wilms' tumor was 75 % (71, 78 %). The 5-year EFS (95 % CI) by stage IV category was: lung only 76 % (72, 80 %) (513 patients); liver, not lung, 76 % (58, 87 %) (34 patients); liver and lung 70 % (57, 80 %) (62 patients); and other sites 64 % (42, 79 %) (25 patients). There were no significant differences among stage IV categories ($p = 0.60$). Event-free survival was not different for the patients with liver metastases and a primary resection of the liver metastases compared to those who did not undergo primary resection of the liver metastases. The COG conclusion was that an initial aggressive approach to liver disease was not warranted. All agree that those patients whose disease does not completely go away or does not respond to therapy should undergo a liver resection (Ehrlich et al. 2009).

Metastases locate mainly in lungs and in liver. Other locations are rare (Kaste et al. 2008; Godzinski et al. 1991, 2001). Patients on SIOP-9 with extrapulmonary and hepatic metastasis have been reviewed. For SIOP-9 patients, the key variable appears to be the pathology variant, with very poor outcome for anaplastic nephroblastoma (Godzinski et al. 2001). More data and study is needed to help determine the role and timing of surgery in the management of extrapulmonary and extrahepatic metastasis.

11.11 Relapse

One of the major challenges in the treatment of children with WT is the management of a child who relapses. Although the overall relapse rate for children with WT has decreased to less than 15 %, the long-term survival for patients with recurrent disease remains between 30 and 45 %. The role of surgery in the treatment of relapsed disease has not been elucidated. For NWTS-5 a specific treatment protocol for relapsed patients was available. The study design was to determine if alternating cycles of cyclophosphamide/etoposide and carboplatin/etoposide improved the event-free survival (EFS) of children with WT who relapsed after chemotherapy with VAD and radiation therapy (DD-4A). All patients received induction therapy. Those who showed at least minimal response to therapy went on to have surgical resection of the tumor followed by radiation therapy of all sites of disease. Four-year event-free survival (EFS) and overall survival (OS) were 42.3 and 48.0 %, respectively, for all patients and were 48.9 and 52.8 % for those who relapsed in the lungs only. Sixty were analyzed. Unfortunately, details of the surgical procedure and extent of resection as well as complications have not been published. In 2008 the SIOP published their outcome of relapses of nephroblastoma patients

registered in the SIOP/GPOH trials. One hundred and seventy relapses were evaluated, 28 % were local, metastatic in 57 %, and combined in 15 %. No specific treatment protocol was used, but patients with isolated distant metastasis had a significantly better outcome than those with local and combined relapses ($p = 0.001$). Similar to the COG/NWTS study, the details of the surgical treatment for these patients have not been analyzed. Taken together, it makes it too difficult to determine what role and how aggressive surgeons should be in the treatment of relapsed disease.

11.12 Nephron-Sparing Surgery (NSS) and Minimal Invasive Nephrectomy (MIN) for Unilateral Nephroblastoma

Partial nephrectomy for unilateral tumors is an area of controversy. The goal of preserving renal tissue is laudable, but it is balanced against reducing survival and coupled with the knowledge that the long-term renal failure in patients after nephrectomy is exceedingly low. Nevertheless, experience gained in the treatment of bilateral tumors indicates that partial nephrectomy may be sufficient local therapy (Fuchs et al. 2009b; Herrera et al. 1996; Gentil Martins and Espana 1989; Moorman-Voestermans et al. 1994, 1998; Cozzi and Zani 2006).

Better pediatric care with wide access to imaging sometimes allows for very early discovery of low staged renal tumors. Some of those, if submitted to the preoperative chemotherapy, appear limited to polar or peripheral parts of the kidney. Currently, available CT or MRI makes possible precise imaging of the involved kidney and planning or excluding the patient as a candidate for NSS. On the other hand, status of the regional lymph nodes and pathology variant of tumor, incorrect interpretation, or technical problems at NSS which is more complicated than classical nephrectomy, all elevate the risk of relapse in this otherwise favorable group of patients. In what subset of patients the benefits of conservative surgery leaving more functional renal tissue outweighs the risk of the oncological failure is still an unanswered question. The SIOP started to register unilateral patients submitted to NSS in 2001. The safety measures included the list of contraindications which had to be respected to include the case in the study. Protocol clearly suggested to consider this technique in patients suffering from contralateral nephrological or urological disorders and syndromes of an increased risk of Wilms' tumor rather than in classical unilateral nephroblastoma (de Kraker et al. 2001; Kaste et al. 2008; Cozzi and Zani 2006).

11.13 Contraindications for NSS in Unilateral Nephroblastoma (de Kraker et al. 2001)

- Preoperative tumor rupture or biopsy
- Tumor infiltrating extrarenal structures
- Intra-abdominal metastases or lymph nodes seen on preoperative imaging
- Thrombus in the renal vein or vena cava
- Tumor involving more than 1/3 of the kidney (at least 50 % of renal tissue should be spared after the tumor resection with a margin of healthy tissue, to give any worthwhile protection against hyper perfusion)
- Multifocal tumor
- Central location
- Involvement of calyces
- Hematuria
- Little experience in partial nephrectomy.

The interim analysis made on cases registered thus far seems to emphasize the role of tumor stage. Preliminarily, of 41 analyzed patients submitted to NSS, 5 relapsed at 24-month follow-up but none of the 18 who were staged 1. Regarding pathology variants, of 6 patients with anaplastic nephroblastoma, 3 relapsed, but again not the case staged 1. Those results and review of literature look encouraging but only if the adequate safety rules are applied. The central review of the preoperative imaging and qualification of the candidates for NSS by the panel of dedicated and

experienced surgeons are probably the correct way to find the adequate balance between risk and benefit of conservative surgery. The oncological experience of the treating center and the experience and skills of the operating surgeon are of great value. Technique of NSS does not differ from that modalities used for bilateral tumors. The balance of risk and benefit suggests using very simple techniques of partial nephrectomy assuring adequate margin of healthy tissue. Sophisticated resections justified in bilateral tumors, if there is no other possibility to save at least a portion of the functional kidney, are not recommended for unilateral patients.

At this point the COG strongly recommends against partial nephrectomy. The outcomes are excellent with unilateral tumors. The tumors tend to be larger prior to chemotherapy and many will not fit criteria for NSS. In addition, as mention above the importance of lymph nodes sampling and the risk of relapse are too high to justify. Whether the preoperative chemotherapy may sufficiently decrease this risk in responding patients needs further studies.

11.14 Minimal Invasive Nephrectomy (MIN)

Another option currently discussed is minimally invasive nephrectomy (MIN) for renal tumors. It is not easy to see any crucial benefit of this technique over the open access surgery. The procedure is far more difficult than the classical one. It is especially important in the regional lymph nodes sampling and manipulating the larger tumors covering aorta and/or vena cava. Abdominal incision, wherever located, must be large enough to gently sort out the tumor. The potential group of candidates resemble that for NSS, but NSS offers more benefit to the child than the minimally invasive surgery. According to our experience, a limited group of relatively small, not covering central vessels and centrally located tumors, which excludes NSS, are candidates for MIN.

The place of minimal invasive surgery in metastatic patients appears a little different. Thoracoscopy or VATS may be a good and safe methods of exploring and resecting the subpleural metastatic nodules. Those, however, must be well imaged on high-quality CT to avoid missing the parenchymal metastasis. One shall remember that the metastases progressing under the treatment nearly always are not a surgical target regardless of technique used (de Kraker et al. 1990, 1997, 2001; Ehrlich et al. 2006).

11.15 Bilateral Wilms' Tumor and Surgery

Bilateral Wilms' tumors (BWT) can be synchronous or metachronous. Children with synchronous BWT account for 5–7 % of all patients with Wilms' tumor (Breslow et al. 1993; Coppes et al. 1989; Petruzzi and Green 1997; Ritchey 2008). (Fig. 11.7) They occur more frequently in girls (sex ratio 0.6:1) and at a younger age (mean age 2.5 years). There is a higher incidence of nephrogenic rests, genetic malformations, and predisposing syndromes in children with BWT (Dome et al. 2006a) Patients with metachronous bilateral WT present with unilateral WT and subsequently develop contralateral disease. The incidence of metachronous bilateral Wilms' tumor ranges from 1.0 to 1.9 % (Coppes et al. 1989; Blute et al. 1987; Shearer et al. 1993). As in synchronous

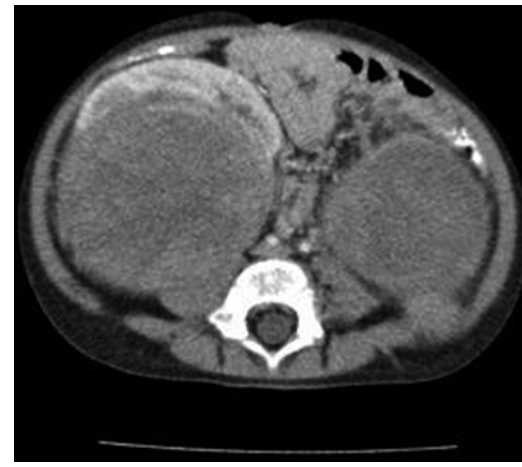

Fig. 11.7 A computed tomography scan demonstrating the typical appear of a bilateral Wilms' tumor

disease, the incidence is higher in girls and in young children (less than 12 months) with nephrogenic rests. Beckwith-Wiedemann syndrome, hemihypertrophy, or congenital aniridia seems to have a higher risk of developing a metachronous tumor than children with other syndromes or congenital anomalies known to predispose to the development of WT. (Coppes et al. 1999)

Imaging of BWT is best performed by CT or MRI. Computed tomography (CT) scan of the abdomen will confirm the renal origin of the mass and determine whether there are bilateral tumors. Early generations of CT scans missed 7–10 % of bilateral lesions, and it was always mandated to explore the contralateral side prior to doing a nephrectomy (Ritchey et al. 1995). A recent review of WT cases with modern helical CT scans demonstrated that only 0.25 % of bilateral tumors were missed, all of which were less than 1 cm (Ritchey et al. 2005). The SIOP currently recommends using MRI for all bilateral lesions, but there is no data comparing the two modalities in this situation.

The outcomes for most children with WT are outstanding. This is not the case, however, for children with bilateral Wilms' tumor (BWT) where survival is poor and the potential for late effects such as renal failure is great (Coppes et al. 1989; Shearer et al. 1993; Malogolowkin et al. 2008; Paulino et al. 1996; Weirich et al. 2004). In 1998, United Kingdom Children's Cancer Study Group (UKCCSG) published their experience with 70 BWT patients (Kumar et al. 1998). Conservative surgical treatment with initial biopsy followed by chemotherapy and delayed tumor resection was done in 57 children. Thirteen underwent primary surgical resection followed by chemotherapy. Overall survival was 69 % with similar survival in the conservatively treated and initial surgical resection groups. BWT with an unfavorable histology was associated with poorest prognosis. In 2004, Weirich reported BWT outcomes on 28 BWT patients from SIOP-9. Although therapy was individualized, all 28 patients with BWT were treated with preoperative therapy. Only three were anaplastic histology. Survival was 85.1 % for those with low-risk histology (95 % CI 71.6–98.6 %; four deaths, 2/3 anaplastics) and relapse-free survival 80.5 % (95 % CI 65.2–95.8 %; five relapses) (Weirich et al. 2004). The most recent survival for the 158 patients treated on NWTS-5 with BWT was 61 %, 80.8 % with favorable histology, and 43.8 % for a child with anaplastic histology. Data from SIOP 9301 compared bilateral partial nephrectomy with other resections used (mainly unilateral partial + total) and showed no decrease in survival in patients submitted to partial nephrectomy on both sides, although these comparisons are difficult due to possibly different extents of tumors in each group. Thus, the suggestion – do bilateral partial nephrectomy whenever "oncologically" possible – seems justified. It also reinforces the need for formal studies of BWT patients (Godzinski J, 2010, Results of surgery for bilateral Wilms tumors from SIOP 9301. Ehrlich PF, personal communication).

In addition to survival, renal failure is a major concern for patients with BWT. Factors that contribute to renal failure include progressive renal disease related to a genetic predisposition, inadequate renal parenchyma after one or more tumor resections, the nephrotoxic effects of chemotherapy and radiation, and the potential for hyperfiltration injury to the remaining renal parenchyma (Breslow et al. 2005; Feusner et al. 2008; Ritchey et al. 1996). In UKCCSG study BWT patients treated between 1980 and 1995, renal function (at follow-up) was normal in 80 % of the patients. Renal mass was 45 and 35 % in the conservatively treated and initial resection groups, respectively, with a trend toward better preservation in those treated conservatively (Kumar et al. 1998). The SIOP studies have reported renal failure in 3.8 % of all patients. A specific evaluation of stage V patients is currently being prepared. On NWTS-1–4 BWT was the greatest risk factor for renal failure (16.4 % for NWTS-1 and -2, 9.9 % for NWTS-3, and 3.8 % for NWTS-4). Other risk factors identified were: Denys-Drash syndrome, progressive tumor in the remaining kidney, and radiation nephritis (Ritchey et al. 1996). Breslow reported 20-year end-stage renal disease (ESRD) outcomes in children treated for WT (Breslow et al. 2005). Fifty-five of 379 (14.5 %) of patients with BWT developed ESRD at 20 years. The

incidence of ESRD after diagnosis of bilateral Wilms' tumor was 50 % for the Denys-Drash syndrome (6 patients), 90 % for WAGR (10), 25 % for genito-urinary anomalies (25), and 11.5 % for BWT alone. Thus, preservation of renal tissue without sacrificing long-term survival is of particular importance for those with BWT.

A major factor contributing to the suboptimal outcomes for children with BWT has been lack of a formal clinical trial. This has produced a variability of treatment schemes, many with prolonged and intensified therapy. In July 2009, the COG opened the first BWT study ARENO534 – Treatment for Patients with Bilateral, Multicentric, or Bilaterally-Predisposed Unilateral Wilms' Tumor. However, results from this study will not be known for some time.

Prolongation and intensification of therapy may increase the risks of treatment-related complications and may provide the opportunity for metastasis. Shamberger et al. reviewed and highlighted the pitfalls of continued therapy in a study of progressive or nonresponsive disease (PNRD) in 38 children with BWT. (Shamberger et al. 2006) Of the 38, chemotherapy was given for a median of 7 months (range: 2–29 months) before definitive resection. Thirty-six children went on to a second regimen, and of these, 21 children received a third regimen before resection. Eleven patients received radiation to one or both kidneys. Pathology at resection revealed previously undiagnosed anaplasia in 3 patients (2 diffuse and 1 focal) treated for 14, 15, and 15 months before resection. A fourth patient developed a diffusely anaplastic tumor 13 months after therapy.

Tumor volume may not change after chemotherapy due to tumor differentiation or anaplastic tumor histology (Weirich et al. 2001; Bocconn-Gibod et al. 2000; Zuppan et al. 1988). Chemotherapy can result in tumor necrosis, rhabdomyomatous differentiation, or mature stromal differentiation without significant changes in tumor size. Despite not responding to chemotherapy, children with these differentiated tumors with limited mitotic activity have good outcomes (Anderson et al. 2002). Therefore, tumors with limited mitotic activity may have minimal shrinkage with continued therapy and are best served with resection. Anaplastic tumors also respond poorly to chemotherapy. Furthermore, discordant pathology can be seen in children with BWT, and this may result in one kidney responding to chemotherapy and the other does not (Kumar et al. 1998; Dome et al. 2006b; Green et al. 1994a; Hamilton et al. 2006) Therefore, continuing therapy without reevaluating tumor pathology in both kidneys in a patient with BWT seems counterproductive. Figure 11.8 shows a case of progressive disease in a child with BWT despite prolonged chemotherapy. The pathology in this case was stromal predominant.

In both the current COG ARENO534 study and the SIOP guidelines, surgery occurs after a maximum of 12 weeks of chemotherapy. These observations highlight the issue of drawn-out therapy without response but also raise the question about how long therapy should be considered prior to biopsy or a definitive resection. Results from SIOP-9 help answer this question: patients with unilateral tumors were randomized to receive either 4 or 8 weeks of actinomycin and vincristine preoperatively. There was a 48 % reduction in tumor volume after 4 weeks that increased to 62 % after 8 weeks of chemotherapy (Tournade et al. 2001; Graf et al. 2000).

11.16 Surgical Considerations for Patients with Bilateral Wilms' Tumor

11.16.1 Renal Biopsies

Upfront biopsy of children with BWT may not be necessary before starting chemotherapy but renal biopsies play an important role in direct therapy, especially in those tumors which are nonresponsive. When considering tissue samples in children with bilateral tumors, the biopsies should be done from each kidney due to the high rate of discordant pathology (Hamilton et al. 2006). One of the reasons to perform a biopsy is to detect anaplastic tumors. This can be difficult and is often missed on percutaneous or core biopsies;

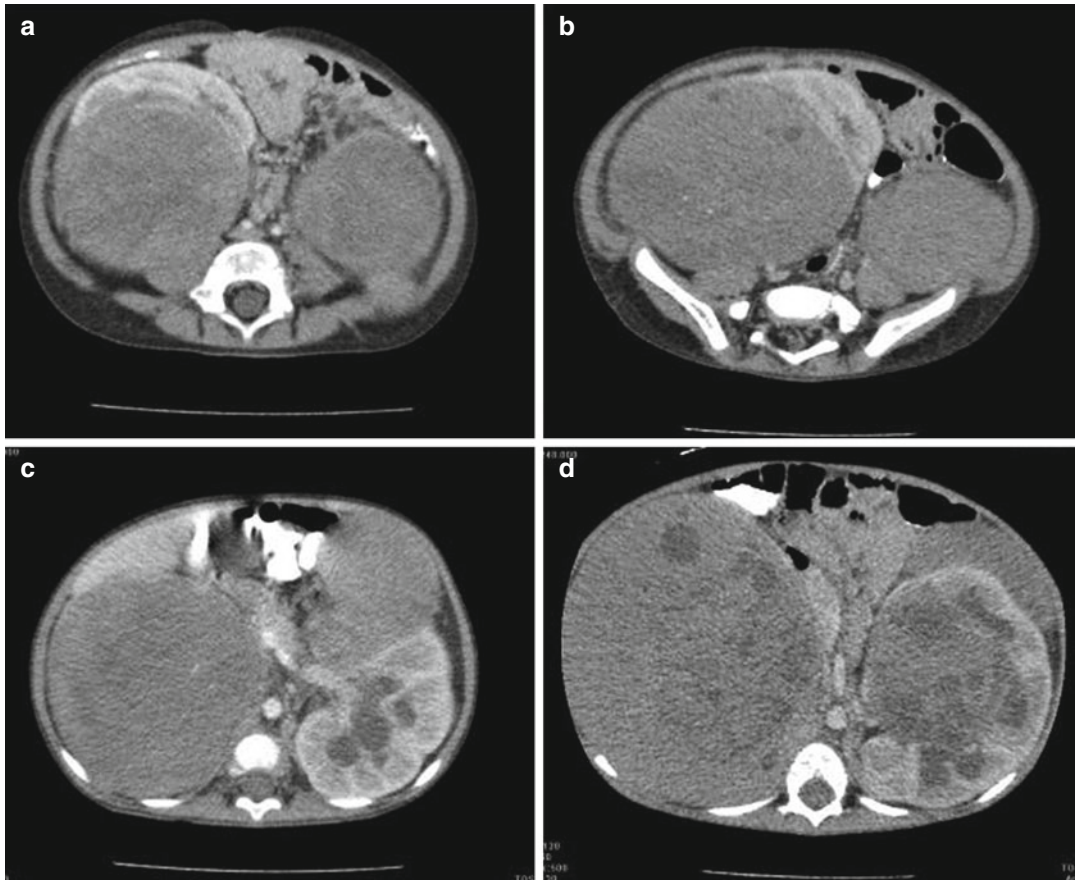

Fig. 11.8 (**a**, **b**) Computed tomography scans at presentation of a 1.5-year-old girl with aniridia and bilateral Wilms' tumor. (**c**, **d**) Comparison computed tomography scans after 8 weeks of chemotherapy demonstrating no response to therapy but pathology showed a stromal variant

thus a formal open biopsy is preferred in the COG protocol. (Hamilton et al. 2006) After 12 weeks of therapy both COG and SIOP option is to force resection rather than perform open biopsy in stage V nonresponsive cases.

11.16.2 Renal-Sparing Surgery

Despite the variability of treatment approaches, nephron-sparing surgery is an important consideration for all children with BWT. Both SIOP and COG agree that preoperative chemotherapy is the best first line of treatment for BWT followed by renal-sparing surgery. The two exceptions are those with extensive tumor thrombus that does not respond to therapy and patients with anaplastic histology where clear margins cannot be obtained. In patients with anaplastic histology where clear margins cannot be obtained with a partial nephrectomy, a complete nephrectomy is required. Anaplastic histology in BWT is difficult to diagnosis, and with preoperative chemotherapy, the pathology variant is usually unknown at surgery (Hamilton et al. 2006). This illustrates how crucial is correct planning of every nephron-sparing resection.

Preoperative imaging is valuable to help plan the operation. Three-dimensional computed tomography or MRI reconstructions are extremely useful in planning the operation. In addition, intraoperative ultrasound can be very helpful. Although by imaging large lesions may appear unresectable, they may just be

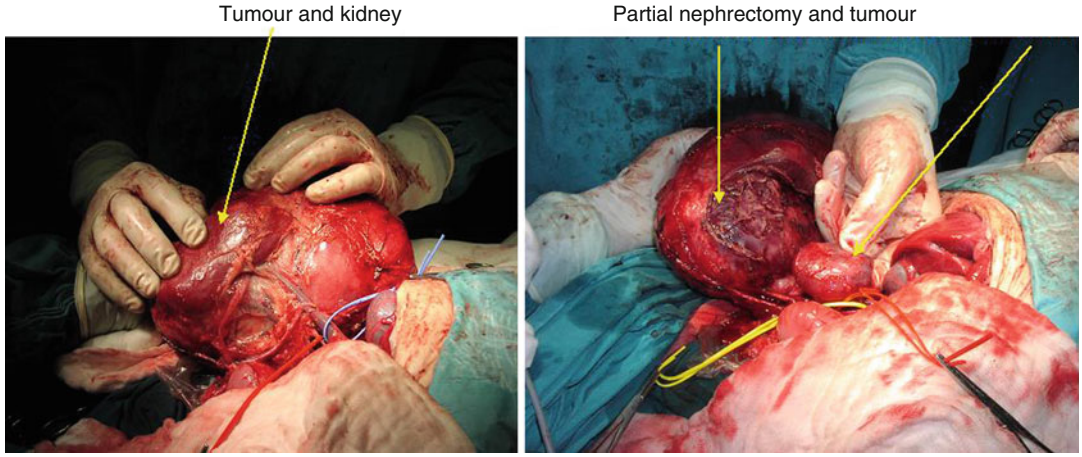

Fig. 11.9 Operative photographs of a patient with bilateral Wilms' tumor undergoing a partial nephrectomy. Spared part of the kidney (*Yellow arrow*)

compressing adjacent normal kidney where substantially more viable renal parenchyma exists than may have been anticipated by the preoperative imaging studies. This situation argues for attempting nephron-sparing surgery for all lesions (Ritchey 2008; Cozzi and Zani 2006; Davidoff et al. 2008). Figure 11.9 shows an example of partial nonanatomic renal resection.

Once the tumor is removed, the kidney volume can appear remarkably normal as these patients are followed over time. Atypical resections and unconventional tumor resections of localized lesions have also salvaged several kidneys that would have been sacrificed by traditional criteria. An interesting and promising technique of nephron-sparing resection for tumors extending to the renal hilum was proposed by Joerg Fuchs (Fuchs et al. 2009b). The technique included transection of the kidney and tumor resection performed longitudinally followed by extensive reconstruction of pyelon. Surgery was performed in vascular exclusion of the kidney and extrarenal cooling. All 5 reported cases were in CR for mean follow-up of 26.6 months (3.5–66) (Fuchs et al. 2009b).

Several different renal preservation strategies have been described and can be considered depending on the extent of resection and the location of the tumor. Clamping of the renal artery is safe with warm ischemia for approximately a half hour. Surface cooling with ice slush allows an hour of safe occlusion of renal artery. However, the layer of ice that must be packed around the kidney can interfere with the technical aspects of the surgery. Continuous in situ cold perfusion with solutions, which are in common use during organ transplantation, has also been reported in a patient with multifocal BWT. (Cozzi and Zani 2006; De Backer et al. 1995) However, the arteriotomy and the venotomy that are needed for in situ perfusion increase the risk of renal artery thrombosis and/or tumor spillage from the renal vein. Cases using ex vivo tumor dissection followed by autotransplantation in an attempt to preserve functioning renal tissue have also been described (Desai et al. 1999). In many instances, temporary vascular occlusion is not required.

The peritoneal cavity is entered through a standard transverse upper abdominal incision. Any suspicious lesion should be biopsied and frozen section obtained prior to starting the kidney resection. The kidney should be mobilized completely and elevated on its vascular pedicle without traction as it can result in vascular thrombosis, especially in very young patients. In most cases, identification of the lesions is relatively easy. If there is some concern, intraoperative ultrasound is useful. After lesions to be excised are identified, the capsule of the kidney is scored with electrocautery to outline the planned extent of resection. The most difficult lesions are those located near the hilum. A rim of normal kidney (~1 cm) should be taken around the lesion when possible.

Hemostasis in most cases can be achieved with electrocautery and digital compression but can be assisted by a ligature, harmonic scalpel, or argon-beam coagulation. Surgicel™ or another procoagulant is also helpful in maintaining hemostasis (Johnson and Johnson 2009). It is very important to remember to remove regional lymph nodes from each kidney to obtain accurate staging data, as each kidney is staged independently.

Injecting a dilute solution of methylene blue into the renal pelvis after temporarily occluding the ureter will help visualize defects in the collecting system after resection. Some leaks may benefit from placement of a double J stent. The decision to place a ureteral stent is based on the degree of disruption of the collecting system and the complexity of its closure. An open, rather than a closed, suction drain is commonly placed in surgical resection site, but this is primarily a surgeon preference issue. Closing the renal defect can often be difficult in a kidney that has been pretreated with chemotherapy as they are much less pliable than normal kidney. Perirenal fat, omentum, or oxidized cellulose can help close the renal defect.

In rare circumstances, enucleation of the tumor is possible to preserve renal function. This is only for patients with favorable histology Wilms' tumor. A problem with tumor enucleation is an unrecognized pseudocapsule penetration and spill (Green et al. 1994b; Green 1997). Furthermore, enucleation increases the risk of local tumor spillage.

Early complications from partial nephrectomy include urine leaks, pyelonephritis, renal failure, and positive surgical margins. Delayed complications have included bowel obstructions, hydronephrosis, and scar tissue causing an ureteropelvic junction obstruction and end-stage renal disease (Davidoff et al. 2008).

References

Anderson J, Slater O, McHugh K et al (2002) Response without shrinkage in bilateral Wilms tumor: significance of rhabdomyomatous histiology. J Pediatr Hematol Oncol 24:31–34

Blute ML, Kelais PP, Offord KP et al (1987) Bilateral Wilms tumor. J Urol 138:968–973

Boccon-Gibod L, Rey A, Sandstedt B et al (2000) Complete necrosis induced by preoperative chemotherapy in Wilms tumor as an indicator of low risk: report from the International Society of Pediatric Oncology(SIOP) Nephroblastoma Trial and Study 9. Med Pediatr Oncol 34:190

Breslow N, Olshan A, Beckwith JB, Green DM (1993) Epidemiology of Wilms tumor. Med Pediatr Oncol 21:172–181

Breslow N, Collins AJ, Ritchey ML et al (2005) End stage renal failure in patients with Wilms tumor: results from the national wilms tumor study group and the United States renal data system. J Urol 174:1972–1975

Brisse H, Schleiermacher G, Helfe S (2006) Evaluation of 61 nephroblastoma patients with clinical and/or radiological sign of tumor rupture- a single institution study. Pediatr Blood Cancer 47:364

Coppes MJ, de Kraker J, van Dijken PJ (1989) Bilateral Wilms' tumor: long-term survival and some epidemiological features. J Clin Oncol 7:310–315

Coppes MJ, Beckwith JB, Ritchey ML, D'Angio GJ, Green DM, Breslow N (1999) Factors affecting the risk of contralateral wilms tumor development (A report from the national Wilms tumor study group). Cancer 85:1616–1625

Cozzi DA, Zani A (2006) Nephron-sparing surgery in children with primary renal tumor: indications and results. Semin Pediatr Surg 15:3–9

D'Angio GJ, Evans AE, Breslow N, Beckwith JB et al (1976) The treatment of Wilms' tumor. Cancer 38:633–646

D'Angio GJ, Breslow N, Beckwith JB et al (1989) Treatment of Wilms' tumor. Results of the Third National Wilms' Tumor Study. Cancer 64:360

Davidoff AM, Giel GW, Jones DP et al (2008) The feasibility and outcome of nephron-sparing surgery for children with bilateral Wilms tumor. The St Jude Children's Research Hospital experience: 1999–2006. Cancer 112:2060

De Backer A, Lamote J, Keuppens F et al (1995) Bilateral Wilms' tumor: in situ cooling of the kidney facilitates curative excision of tumors, with preservation of renal function. J Pediatr Surg 30:1338–1340

de Kraker J, Lemerle J, Voute PA et al (1990) Wilms tumor with pulmonary metastases at diagnosis: the significance of primary chemotherapy. J Clin Oncol 8:1187–1190

de Kraker J, Tournade MF, Weirich A et al (1997) Wilms tumour stage IV. A report from the SIOP-9 study. Med Pediatr Oncol 29:370

de Kraker J, Delemarre JF, Lilien MR, Tournade MF (1999) Misstaging in nephroblastoma. causes and consequences. A report of the sixth nephroblastoma trial and study of the International Society of Paediatric Oncology. Eur J Pediatr Surg 9(3):153–157

de Kraker J, Graf N, Pein F et al (2001) Society of international paediatric oncology (SIOP) Wilms tumor protocol http://web.visu.uni-saarland.de/rtsg/

Desai D, Nicholls G, Duffy PG (1999) Bench surgery with autotransplantation for bilateral synchronous

Wilms tumor: a report of three cases. J Pediatr Surg 34(4):632–634
Dome JS, Perlman EJ, Ritchey ML, Coppes MJ, Kalapurakal J, Grundy PE (2006a) Renal tumors. In: Pizzo PA, Poplack DG (eds) Principles and practice of pediatric oncology. Lippincott Williams and Wilkins, Philadelphia, pp 905–932
Dome JS, Cotton CA, Perlman EJ (2006b) Treatment of anaplastic histology Wilms' tumor: results from the fifth National Wilms' Tumor Study. J Clin Oncol 24:2352–2358
Ehrlich PF (2001) Wilms tumor: progress to date and future considerations. Expert Rev Anticancer Ther 1(4):555–564
Ehrlich PF (2007a) Wilms tumor: progress and considerations for the surgeon. Surg Oncol 16:157–171
Ehrlich PF (2007b) Re: Intracaval and intracardiac extension of Wilms' tumor. The influence of preoperative chemotherapy on surgical morbidity. Int Braz J Urol 33:847–848
Ehrlich PF, Ritchey ML, Hamilton TE et al (2005) Quality assessment for Wilms' tumor: a report from the National Wilms' Tumor Study-5. J Pediatr Surg 40:208–212
Ehrlich PF, Hamilton TE, Grundy PE et al (2006) The value of surgery in directing therapy of Wilms tumor patients with pulmonary disease. A Report From The National Wilms Tumor Study Group (NWTS –5). J Pediatr Surg 41:162–167
Ehrlich PF, Ferrer F, Ritchey ML et al (2009) Hepatic metastasis at diagnosis in patients with Wilms tumor is not an independent adverse prognostic factor for stage iv Wilms tumor. A report from the children's oncology group/national wilms. Ann Surg 250:642–648
Ehrlich PF, Anderson JR, Ritchey ML et al (2013) Clinicopathologic findings predictive of relapse in children with stage III favorable-histology Wilms tumor. J Clin Oncol 20;31(9):1196–1201
Feusner JH, Ritchey ML, Norkool PA (2008) Renal failure does not preclude cure in children receiving chemotherapy for Wilms tumor: a report from the National Wilms Tumor Study Group. Pediatr Blood Cancer 50:242–245
Fuchs J, Szavay P, Luithle T et al (2008) Surgical implications for liver metastasis in nephroblastoma- data from the SIOP/GPOH study. Surg Oncol 17:33–40
Fuchs J, Kienecker K, Furtwängler R (2009a) Surgical aspects in the treatment of patients with unilateral wilms tumor: a report from the SIOP 93-01/German Society of Pediatric Oncology and Hematology. Ann Surg 249:666–671
Fuchs J, Szavay P, Scheel-Walter H et al (2009b) Longitudinal partial nephrectomy for stage V nephroblastoma with extension into the renal hilus. Pediatr Blood Cancer 53:715–716
Gentil Martins A, Espana M (1989) Partial nephrectomy for nephroblastoma – a plea for less radical surgery. Med Pediatr Oncol 17:320
Godzinski J, Tournade MF, de Kraker J et al (1991) Stage IV nephroblastoma with extra pulmonary metastatic involvement in the SIOP 6 and 9 Study. Med Pediatr Oncol 19:371
Godzinski J, Tournade MF, de Kraker J, Lemerle J, Voute PA (1998) Rarity of surgical complications after postchemotherapy nephrectomy for nephroblastoma. Experience of the International Society of Paediatric Oncology-Trial and study "SIOP-9". International Society of Paediatric Oncology Nephroblastoma Trial and Study Committee. Eur J Pediatr Surg 8(2): 83–86
Godzinski J, Tournade MF, de Kraker J et al (1999) The role of preoperative chemotherapy in the treatment of nephroblastoma -the SIOP experience. Semin Urol Oncol 17:28–32
Godzinski J, de Kraker J, Weirich A et al (2001) Local treatment for extrapulmonary metastases in the SIOP-9 initial stage IV Wilms' tumour patients. Med Pediatr Oncol 37:338
Godzinski J, Heij H, Cecchetto G et al (2005) Does pretreatment tumor rupture influence the outcome in patients with nephroblastoma submitted to preoperative chemotherapy. Pediatr Blood Cancer 45:387
Graf N, Tournade MF, de Kraker J (2000) The role of preoperative chemotherapy in the management of Wilms tumor. The SIOP studies. Urol Clin North Am 443–454
Green DM (1997) Enucleative surgery for stage I nephroblastoma with a normal contralateral kidney. J Urol 185:548–549
Green DM (2002) Use of chest computed tomography for staging and treatment of Wilms' tumor in children. J Clin Oncol 20:2763–2764
Green DM, Breslow N, D'Angio GJ et al (1993) The treatment of children with unilateral Wilms' tumor. J Clin Oncol 11:1009–1010
Green DM, Beckwith JB, Breslow N et al (1994a) Treatment of children with stages II to IV anaplastic Wilms Tumor : a report from the National Wilms' Tumor Study Group. J Clin Oncol 12:2126–2131
Green DM, Beckwith JB, Weeks D et al (1994b) The relationship between microsubstaging variables, age at diagnosis, and tumor weight of children with stage I/ favorable histology Wilms' tumor. A report from the National Wilms' Tumor study. Cancer 74:1820
Gross R (1953) Embryoma of the kidney (Wilms tumor). In: Gross R (ed) The surgery of infancy and childhood. WB Saunders, Philadelphia, pp 588–605
Grundy PE, Perlman EJ, Ehrlich PF et al (2005) Current issues in Wilms tumor management. Curr Probl Cancer 29:221–260
Grundy PE, Dome JD, Perlman EJ et al (2006) Renal tumors classification, biology, and banking study. https://members.childrensoncologygroup.org/Prot/AREN03B2/AREN03B2DOC.pdf
Grundy PE, Dome JS, Ehrlich PF (2007) Renal tumors classification, biology and banking studies. https://members.childrensoncologygroup.org/Prot/AREN03B2/AREN03B2DOC.pdf, pp 18–33
Hamilton TE, Green DM, Perlman EJ et al (2006) Bilateral Wilms' tumor with anaplasia: lessons from

the National Wilms' Tumor Study. J Pediatr Surg 41:1641–1644
Herrera JM, Gauthier F, Tournade MF et al (1996) Bilateral synchronous Wilms' tumour (WT): is it a good model of conservative surgery for unilateral WT? Med Pediatr Oncol 27:219
Johnson and Johnson. Surgicel (2009) http://www.jnj.com/connect/
Kalapurakal JA, Dome JS, Perlman EJ, Malogolowkin M, Haase GM, Grundy PE, Coppes MJ (2004) Management of Wilms' tumour: current practice and future goals. Lancet Oncol 5:37–46
Kalapurakal JA, Li SM, Breslow N et al (2010) Intraoperative spillage of favorable histology Wilms tumor cells: influence of irradiation and chemotherapy regimens on abdominal recurrence. A report from the National Wilms Tumor Study Group. Int J Radiat Oncol Biol Phys 76:201–206
Kaste S, Dome JS, Babyn PS et al (2008) Wilms Tumor :prognostic factors, staging, therapy and late effects. Pediatr Radiol 38:2–17
Kumar R, Fitzgerald R, Breatnach F (1998) Conservative surgical management of bilateral wilms tumor: results of the United Kingdom children's cancer study group. J Urol 160:1450–1453
Kung FH, Nyhan WL (1982) Wilms tumor. In: Holland JF, Frei E (eds) Cancer medicine. Lea and Feiger, Philadelphia, pp 2181–2192
Ladd WE (1938) Embryoma of the kidney (Wilms' tumor). Ann Surg 108:885–902
Lemerle J, Voute PA, Tournade MF (1983) Effectiveness of preoperative chemotherapy in Wilms' tumor: results of an international society of pediatric oncology (SIOP) clinical trial. J Clin Oncol 1:604–609
Malogolowkin M, Cotton CA, Green DM et al (2008) Treatment of Wilms tumor relapsing after initial treatment with vincristine, actinomycin D, and doxorubicin. A report from the National Wilms Tumor Study Group. Pediatr Blood Cancer 50:236–241
Mankowski P, Godzinski J, Jankowski A et al (2004) Minimal invasive pulmonary metastasectomy in stage IV malignancies in children. Pediatr Blood Cancer 43:334–335
Mitchell C, Pritchard-Jones K, Shannon R (2006) Immediate nephrectomy versus preoperative chemotherapy in the management of non-metastatic Wilms' tumour: results of a randomised trial (UKW3) by the UK Children's Cancer Study Group. Eur J Cancer 42:2554–2562
Moorman-Voestermans CGM, Staalman CR, Delamarre JFM (1994) Partial nephrectomy in unilateral Wilms' tumour is feasible without local recurrence. Med Pediatr Oncol 23:218
Moorman-Voestermans CGM, Aronson DE, Staalman CR et al (1998) Is partial nephrectomy appropriate treatment for unilateral Wilms' tumour? J Pediatr Surg 33:165–170
Othersen HB, Delorimier A, Hrabovsky E, Kelalis P, Breslow N, D'Angio GJ (1990) Surgical evaluation of lymph node metastases in Wilms tumor. J Pediatr Surg 25:330–331
Othersen HB, Hebra A, Tagge E (1999) Nephroblastoma and other renal tumors. In: Grosfeld JL (ed) The surgery of childhood tumors. Arnold, Philadelphia, pp 107–139
Owens CM, Veys PA, Pritchard J et al (2002) Role of chest computed tomography at diagnosis in the management of Wilms' tumor: a study by the United Kingdom Children's Cancer Study Group. J Clin Oncol 20:2768–2773
Paulino AC, Wilimas J, Marina N et al (1996) Local Control in synchronous bilateral wilms tumor. Int J Radiat Oncol Biol Phys 36:541–548
Petruzzi MJ, Green DM (1997) Wilms tumor. Pediatr Clin North Am 44:939–952
Ritchey ML (1999) The role of preoperative chemotherapy for Wilms tumor; the NWTSG perspective. Semin Urol Oncol 17(1):21–27
Ritchey ML (2005) Renal sparing surgery for Wilms tumor. J Urol 174:1172–1173
Ritchey ML (2008) Renal sparing surgery for children with bilateral Wilms tumor. Cancer 112:1877–1878
Ritchey ML, Kelalis P, Breslow N et al (1992a) Surgical complications after nephrectomy for Wilms tumor. Surg Gynecol Obstet 175:514
Ritchey ML, Lally KP, Haase GM et al (1992b) Superior mesenteric artery injury during nephrectomy for Wilms' tumor. J Pediatr Surg 27:612–615
Ritchey ML, Kelalis P, Haase G (1993) Preoperative therapy for intracaval and atrial extension of Wilms tumor. Cancer 71:4104–4110
Ritchey ML, Pringle K, Breslow N (1994) Management and outcome of inoperable Wilms tumor: a report of the national Wilms tumor study group. Ann Surg 220:683–690
Ritchey ML, Green DM, Breslow N (1995) Accuracy of current imaging modalities in the diagnosis of synchronous bilateral Wilms tumor. A report from the National Wilms' Tumor Study Group. Cancer 75:600–604
Ritchey ML, Green DM, Thomas PRM (1996) Renal failure in Wilms tumor patients: a report from the National Wilms Tumor Study Group. Med Pediatr Oncol 26:75
Ritchey ML, Shamberger RC, Haase G, Horwitz J, Bergemann TL (2001) Surgical complications after primary nephrectomy for Wilms' tumor: report from the National Wilms' Tumor Study Group. J Am Coll Surg 192:63–68
Ritchey ML, Shamberger RC, Hamilton TE, Haase G (2005) Fate of bilateral renal lesions missed on preoperative imaging: a report from the National Wilms Tumor Study Group. J Urol 174:1519–1521
Ritchey ML, Daley S, Shamberger RC et al (2008) Ureteral extension in Wilms' tumor: a report from the National Wilms' Tumor Study Group (NWTSG). J Pediatr Surg 43:1625–1629
Schenk JP, Schrader C, Zieger B et al (2006) Reference radiology in nephroblastoma: accuracy and relevance for preoperative chemotherapy. Rofo 178:38–45
Shamberger RC, Guthrie KA, Ritchey ML, Haase G, Taskashima BA, Beckwith JB, D'Angio GJ, Green

DM, Breslow N (1999) Surgery related factors and local recurrence of Wilms tumor in the national Wilms tumor study 4. Ann Surg 229:292–297

Shamberger RC, Ritchey ML, Haase G, Bergemann TL, Loechelt-Yoshioka T, Breslow N, Green DM (2001) Intravascular extension of Wilms tumor. Ann Surg 234(1):116–121

Shamberger RC, Haase GM, Argani P (2006) Bilateral Wilms' tumors with progressive or nonresponsive disease. J Pediatr Surg 41:642–657

Shearer P, Parham DM, Fontanesi J et al (1993) Bilateral Wilms tumor. Review of Outcome, associated anomalies and late effects in 36 patients treated at a single institution. Cancer 72:1422–1426

Szavay P, Luithle T, Graf N (2006) Primary hepatic metastases in nephroblastoma–a report of the SIOP/GPOH Study. J Pediatr Surg 41:168–172

Tournade MF, Com-Nougue C, Voute PA, Lemerle J, de Kraker J (1993) Results of the sixth International Society of Pediatric Oncology Wilms' tumor trial and study: a risk-adapted therapeutic approach in Wilms' tumor. J Clin Oncol 11(6):1014–1023

Tournade MF, Com-Nougue C, de Kraker J et al (2001) Optimal duration of preoperative chemotherapy in unilateral non metastatic Wilms tumor in children older than six months. Results of the ninth International Society of Pediatric Oncology tumor trial. J Clin Oncol 19:488–500

Varan A, Büyükpamukçu N, Caglar M (2005) Prognostic significance of metastatic site at diagnosis in Wilms' tumor: results from a single center. J Pediatr Hematol Oncol 27:188–191

Vujanic G, Sandstedt B, Kelsey A, Sebire NJ (2009) Central pathology review in multicenter trials and studies: lessons from the nephroblastoma trials. Cancer 115:1977–1983

Warmann S, Nourkami N, Seitz G et al (2009) Lung metastases in children with Wilms' tumor: data from SIOP9, SIOP 93–01, and SIOP 2001/GPOH. Pediatr Blood Cancer 53(5):753

Weirich A, Leuschner I, Harms D et al (2001) Clinical impact of histologic subtypes in localized non-anaplastic nephroblastoma treated according to the trial and study SIOP-9/GPOH. Ann Oncol 12:311–319

Weirich A, Ludwig R, Graf N (2004) Survival in nephroblastoma treated according to the trial and study SIOP-9/GPOH with respect to relapse and morbidity. Ann Oncol 15(5):808–820:5–808

Willets IE (2003) Jessop and the Wilms tumor. J Pediatr Surg 38:1496–1498

Wilms M (1897) Diagnostischer und therapeutischer Werth der Lumbalpunction. Druckbestimmung mit Quicksilvermanometer. Munch Med Wochenschr 3:53–57

Wilms M (1899) Die Mischgeschwülste der Niere. Verlag von Arthur Georgi, Leipzig

Zuppan CW, Beckwith JB, Luckey DW (1988) Anaplasia in unilateral Wilms tumor. A report from the National Wilms Tumor Study Pathology Center. Hum Pathol 19:1199–1209