Chapter 5

Management of Bilateral Wilms Tumours

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Abstract

Synchronous bilateral Wilms tumours (BWTs) represent 4% to 7% of all Wilms tumours (WTs) and present at a younger age than unilateral WTs do. At least 10% of synchronous BWTs have unfavourable histology, and up to 22% are associated with genitourinary abnormalities, aniridia, WAGR (WT, aniridia, genitourinary anomalies, and retardation) syndrome, Denys–Drash syndrome, hemihypertrophy or one of the other overgrowth syndromes. The long-term disease-free survival rate of patients with unilateral WT is now approaching 90% and is around 70% for those with metastatic disease. For both synchronous and metachronous WTs, the prognosis is less favourable, with reported cure rates

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approaching 80% in the best centres but are often considerably less in resource-poor settings. Also, there is the potential for a reduced quality of life due to renal insufficiency and the possible need for renal transplantation. Thus, the major clinical challenge in BWTs is the preservation of functioning renal tissue, while achieving cure with the minimum of therapy-related morbidity. Although mortality is generally associated with progressive disease of anaplastic tumours, the emphasis of management has been increasingly placed on nephron-sparing surgical approaches in an attempt to reduce ultimate renal insufficiency. Chemotherapy followed by nephron-sparing surgery has been able, in most cases, to eradicate the tumour while preserving renal function. Radiotherapy has largely been avoided because of fear of long-term radiation injury to the residual functioning renal mass. Patient selection, appropriate pre- and post-operative chemotherapy, and skilful surgical techniques all contribute to excellent outcomes, where these are achievable.

Key words: Bilateral Wilms tumour; Nephroblastomatosis; Nephron-sparing surgery

Introduction

Nephroblastoma named after Max Wilms (1867–1918), a German surgeon, who published a monograph on 'Mixed tumours of the kidney' in 1899 while in Leipzig, working under the famous surgeon Professor Friedrich Trendelenburg, has become synonymous with the name "Wilms" (1). The tumour is an embryonal tumour derived from the metanephros containing epithelial, blastemal and stromal tissues. It is the third most frequently seen paediatric malignancy, is the most common renal tumour of childhood and is particularly seen in the under 5-year age group. It is associated with a number of 'overgrowth' syndromes mostly related to chromosome 11, as well as other genitourinary abnormalities.

Synchronous bilateral Wilms tumours (BWTs) make up 4% to 7% of all Wilms tumours (WTs) and present at a younger age than unilateral WTs (mean age, 2.6 vs ~3.3 years) (2, 3) do. Current results after the treatment of unilateral WT are excellent, even in some resource-limited settings, and protocols of management have been extensively interrogated on both sides of the Atlantic, in Children's Oncology Group (COG) and Société Internationale d'Oncologie Pediatrique (SIOP) trials. Both investigative groups have equivalent final outcomes with the 5-year overall survival in the region of 90% for favourable-histology unilateral WT, although there are differences between the groups in the approach to management, that is, in the use and timing of chemotherapy, surgery and radiotherapy. This has been emulated in some middle-income settings (4), but the outcome in patients with bilateral tumours is not as favourable, with the overall survival at 4 years varying between 81% for favourable histology and 55% for anaplastic histology in the National Wilms Tumor Study-5 trial (5, 6) and the overall 5-year survival being 85% in the SIOP-9 trial (7).

Predisposing factors

Nephrogenic rests are areas of embryonal metanephric tissue still present after the 36th week of life. Nephroblastomatosis refers to multiple or diffuse rests. While only a few will undergo clonal transformation into WTs, they are considered precursor lesions. Actively proliferating rests, termed hyperplastic rests, can cause the greatest diagnostic challenge and can appear radiologically and histologically similar to a WT (8). Rests, present on histological examination of resected tumours, increase the risk of a metachronous tumour developing in the other kidney, especially in the under 1-year age group. Diligence in follow-up and monitoring is thus required if nephroblastomatosis is present in a resected tumour. In a selected group of infants where unilateral tumours are well circumscribed and where nephroblastomatosis is identified pre- or intra-operatively, nephron-sparing surgery (NSS) may have a place. The NWTS group has recommended that this approach be assessed in a formal study. However, exclusion criteria for NSS such as those used in the SIOP 2001 protocol for unilateral WTs also need to be considered for BWT in order to stay oncologically safe (9). These are preoperative tumour rupture, abdominal lymph node metastases, tumour in the renal vein, multifocal tumour and infiltration into the renal pelvis (10). Nephrogenic rests may be seen in up to 90% of synchronous BWTs and 94% of metachronous BWTs (78% in our series) (11); about 70% of children with synchronous BWT in the NWTS series had multiple nephrogenic rests or nephroblastomatosis (12–14).

The prevalence of bilateral disease is higher among children with genetic predisposition syndromes such as WAGR (WT, aniridia, genitourinary anomalies and retardation), Beckwith–Wiedemann syndrome, hemihypertrophy and one of the overgrowth syndromes. These patients contribute to 22% of BWT series (15, 16).

Investigation

After investigation of history, blood pressure measurement, and physical examination looking specifically for signs of associated syndromes, all patients require routine testing of complete blood count, liver functions and renal functions and also urinalysis. Some centres advise coagulation studies because WT patients can develop acquired von Willebrand disease (17, 18).

Abdominal imaging includes a computed tomography (CT) scan with contrast or magnetic resonance imaging (MRI) (Figure 1a and b). Ultrasound scanning of the abdomen is often performed after clinical examination, which reveals a mass and guides more definitive imaging. In addition, ultrasound with Doppler may be the preferred method to assess intravascular extension of the tumour. MRI is of major value in the identification of nephrogenic rests. Nowadays metastatic workup includes a CT scan of the chest.

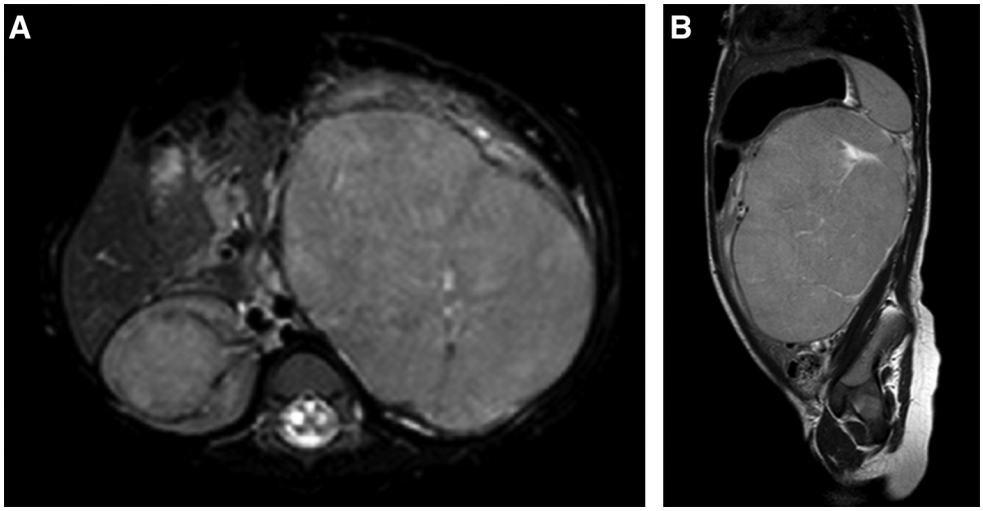

Figure 1. Axial (a) and sagittal (b) MRI scans of a 2-year-old child with bilateral Wilms tumours after 12 weeks of chemotherapy. Reprinted with permission from Red Cross War Memorial Children's Hospital Radiology Department.

There is only scarce evidence that an 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)-CT may be helpful in patients with bilateral disease (19). WT is 18F-FDG avid; 18F-FDG-PET-CT imaging adds clinically applicable information to conventional imaging, and avid areas correspond to histologically active disease, but currently there is no evidence that it will discriminate WT from nephroblastomatosis.

Management

The aim of BWT management is to achieve cure with a minimum treatment-related morbidity, with the challenge in BWT being the preservation of adequate functioning renal tissue (20, 21). Renal tissue preservation may, however, be particularly difficult in cases with a delay in presentation and advanced local disease, in cases in which the chemotherapy response is poor, or in cases of a metachronous presentation where a contralateral nephrectomy has already been performed. Management may also be complicated by the presence of multiple nephrogenic rests or areas of nephroblastomatosis, as these are difficult to clinically distinguish from WTs (8, 22).

Management should commence with early clinical diagnosis, and for those presenting with ostensibly unilateral disease, a very close look at the contralateral kidney with biopsy of any suspicious areas is essential (23). Preoperative imaging is increasingly accurate (24) but should not be relied on due to some inconsistencies in imaging characteristics (8) and should not replace careful visualization of the contralateral kidney (25).

Preoperative chemotherapy in synchronous tumours is now the standard of care on both sides of the Atlantic. Previous protocols allowed for primary resection of tumours followed by chemotherapy. While the overall survival in a study by the United Kingdom Children's Cancer Study Group was similar in those undergoing primary surgery followed by chemotherapy and those treated with neoadjuvant chemotherapy followed by surgery, the incidence of renal failure was 20% in the initial surgery group versus 6% in the initial chemotherapy group (26).

With synchronous BWT, the traditional approach has been bilateral renal biopsies and staging of each kidney, followed by neoadjuvant chemotherapy and then renal salvage procedures (partial nephrectomy or tumourectomy) (14, 22). However, data from NWTS-4 and NWTS-5 have shown conclusively that a significant number of patients have unfavourable histology, which is revealed at the time of definitive surgery following chemotherapy but missed during initial biopsy.

Because anaplasia is difficult to detect (27) and bilateral childhood renal tumours are most likely to be WTs, initial biopsy is now controversial in patients with BWT. The current COG study of BWT and of patients with unilateral WT predisposed to the development of bilateral tumours attempts to avoid upfront biopsy but mandates biopsy after 6 weeks of three-drug chemotherapy (AREN0534, National Cancer Institute) (19, 28). The COG studies have shown a higher risk of local recurrence in patients who had tumour spillage or rupture, irrespective of the cause or extent of the soiling (with tumour biopsy being included as a cause of spillage). Thus, in the COG studies, all patients with tumour spillage, including biopsy, are considered stage III. When performing a biopsy, it is important to biopsy all lesions in both kidneys as discordant pathology occurs in up to 20% of cases with favourable histology on one side and anaplastic histology on the other (27).

In suspected BWT, where doubt exists due to atypical imaging or with a patient older than 10 years, an upfront biopsy may be indicated to rule out a non-Wilms tumour (AREN0534) even though it may not rule out anaplasia (28).

While most deaths occur because of progressive disease especially in the case of anaplastic tumours and usually in the first 2 years after diagnosis, emphasis has been increasingly placed on nephron-sparing surgical approaches to avoid subsequent renal insufficiency (15, 16, 29, 30). Nephron sparing is contraindicated in the face of diffuse anaplasia (3) and in cases of the Denys–Drash syndrome (31).

With metachronous presentation, the contralateral kidney has been removed and only the affected side remains. In this scenario, an attempt at NSS is indicated. Alternatively, should excision be performed, the patient may be free of disease but anephric, requiring renal transplantation. This has lifelong consequences of immune suppression and drug toxicity.

Chemotherapy

The current COG BWT study protocol is a response-based protocol. Neoadjuvant chemotherapy consists of three drugs (vincristine, dactinomycin and doxorubicin) given for 6 weeks, with a provision for a further 6 weeks if NSS is not feasible. Surgery is mandated at week 12. This protocol does not require pretreatment biopsies because bilateral tumours are very rarely clear cell sarcoma or rhabdoid tumours of the kidney. They are invariably WT, and therefore, biopsy does not change the therapy. In addition, anaplasia is difficult to diagnose, and biopsy may upstage the tumour and increase the chance of local recurrence.

SIOP (32) uses vincristine and dactinomycin for preoperative chemotherapy for 8 weeks, adding doxorubicin after 4 weeks only if there is a poor response. Despite adequate neoadjuvant chemotherapy, there is a subgroup of patients with BWT with progressive or non-responsive disease. This non-responsiveness may be due to anaplasia, and thus insensitivity to administered therapy, necrosis and rhabdomyomatous or mature stromal differentiation (33, 34). While the second group of patients do not respond radiologically to therapy, they have improved outcomes when compared with those with anaplasia. It is thus crucial to establish the exact histology, and therefore, all such patients are best served by surgery.

Post-operative chemotherapy is based on the histology of the surgical specimen and the stage and is chosen according to the kidney with the highest risk. Cyclophosphamide, etoposide and carboplatin are added for unfavourable histology.

Surgery

The surgery for BWTs needs a multidisciplinary approach for diagnosis and treatment, and BWT patients benefit from surgery in the national centres of excellence with the most experience in BWT.

The decision to operate on both kidneys at the outset or to do so sequentially depends on the size and site of the tumours and their response to therapy. In every case, assessment of differential renal function by way of radionucleotide scan is mandatory prior to surgery. In cases with small peripheral tumours, both sides can be approached at the same laparotomy. When the tumours are very large and/or centrally placed, we prefer to operate on the difficult side first so that we are aware of how much renal function remains before operating on the relatively easier side.

Traditionally, these tumours are resected via a transabdominal approach. More recently, a retroperitoneal approach has been advocated, citing earlier post-operative recovery and slightly less associated surgical morbidity with equivalent outcomes when compared to the usual transabdominal approach, but this approach is yet to be widely adopted (35).

Several innovations have facilitated the NSS. In situ topical cooling with vascular pedicle cross-clamping or ex situ perfusion with preservation solution and 'bench surgery', first described by Lilly and Starzl in 1975 (36), allows careful and extensive dissection and reconstruction in a bloodless field without the loss of renal function from ischaemia (37). Using in situ topical cooling results in a relatively short cross-clamp time and topical cooling with ice is sufficient to preserve the renal function in most cases. Bilateral extensive NSS with our technique of ice-dam cooling (Figure 2) without the need for bench surgery does allow for better preservation of renal function and avoids significant acute tubular necrosis in most cases. However, some surgeons have preferred not to use any form of cooling (38).

It is important to avoid traction or torsion of the renal artery to prevent spasm, intimal damage and vessel occlusion. Some surgeons have specifically avoided using a clamp that may injure the vessels and have used finger occlusion instead (38). Either way, prior to commencing the resection, the kidney should be fully mobilized on its vascular and ureteric pedicle. The resection line is then marked on the tumour mass, identifying the normal renal tissue which is to be preserved, prior to any cross-clamp in an attempt to minimize the ischaemic time. Considerable mobilization of the kidney is possible as the renal vessels usually display an increased diameter, due to the increased needs of the growing tumour prior to chemotherapy, and this allows for making surgical access relatively easy. At this point, the renal hilar and peri-aortic nodes are sampled to rule out lymphatic spread. The renal vein and inferior vena cava should be palpated for evidence of tumour extension.

Gerota's fascia is opened, and the perirenal fat is dissected off the renal surface, excluding the fat attached to the tumour mass. If the tumour is peripherally situated or is well localized to an upper or lower pole, a wedge or guillotine tumourectomy or partial nephrectomy is performed. For large tumours, the outline of the tumour to be resected is scored with diathermy on the renal mass prior to proceeding with the surgery (Figure 3). The capsule is peeled back to expose the adjacent renal parenchyma. Using either fine bipolar cautery or the ultrasonic scalpel in our centre to facilitate dissection, as both cut well in a wet environment, we resect the tumour while the residual part of the kidney to be preserved remains in ice (Figure 4). Fuchs has described three zones of technical repair, with the cortex lending itself to cautery haemostasis, the medulla to suture/ligation haemostasis and the pelvicalyceal system to fine absorbable suture repair (39). After the pelvi-calyceal repair, a double J stent can be placed to ensure better urine drainage and thus reduce the chance of a urine leak. The Cavitron ultrasonic surgical aspirator (Cavitron Surgical Systems, Stanford, CA) has also been used effectively by Ritchey and Coppes (37). Where possible, the residual renal parenchyma is 'folded' on itself with suture reconstitution of the renal capsule to achieve a near-normal post-operative appearance (Figure 5).

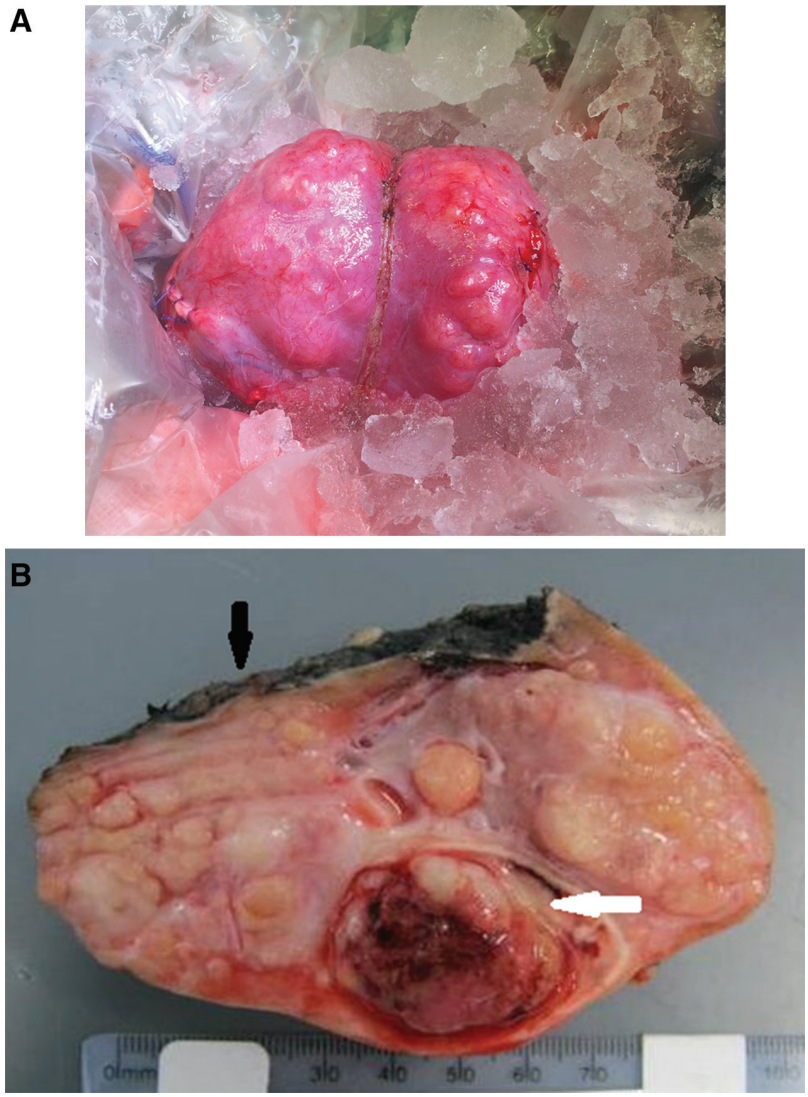

Figure 2. (a) Ice-bath kidney cooling in a 2-year-old child with bilateral nephroblastomatosis and an upper-pole Wilms tumour in the kidney. The score line indicating the line of dissection is clearly shown. (b) The resected specimen (cut surface shown by black arrow) shows the anaplastic Wilms tumour (white arrow) surrounded by nephrogenic rests. Reprinted with permission from Red Cross War Memorial Children's Hospital Surgery and Pathology Department.

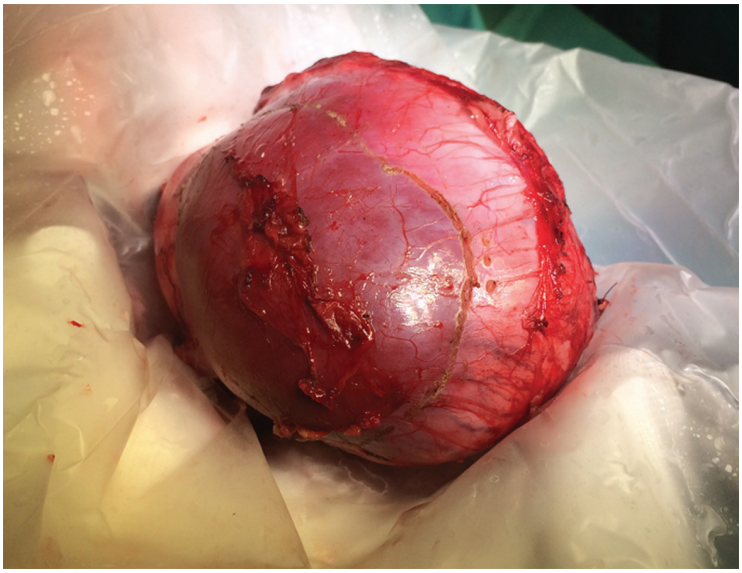

Figure 3. The left kidney of the child depicted in Figure 1. The kidney is cooled in an ice bath after dissection of the kidney to isolate the pedicle, and the outline of tumour to be resected is scored with diathermy on the renal mass. Reprinted with permission from Red Cross War Memorial Children's Hospital Surgery Department.

In exceptional circumstances, bench surgery with autotransplantation can be performed, as demonstrated in one of our cases (37, 40). Vessel re-anastomosis can usually be performed in the orthotopic position as the renal artery usually has an enlarged diameter; alternatively, the reconstructed residual kidney can be transplanted onto the iliac vessels. The disadvantage, however, is that it is very difficult to visually discriminate between tumour, nephroblastomatosis and normal renal tissue while performing ex vivo perfusion. In this situation, multiple frozen-section biopsies may be required. These are generally not satisfactory as these can also be difficult for the histopathologist to interpret. At the end of the procedure, a drain is inserted and a Foley catheter should remain in the bladder for a few days. The double J stent should be removed via cystoscopy in 4 to 6 weeks. If the surgical specimen reveals diffuse anaplasia and there is incomplete resection, additional surgery is indicated to ensure complete resection of the tumour (28). Successful bench surgery and subsequent contralateral tumourectomy were performed in one patient in our series. The patient then developed recurrence of tumour in that kidney, but he remains a long-term disease-free survivor with good renal function after a second resection.

Enucleation of the tumour by blunt dissection should only be considered for patients with favourable-histology WT. If anaplasia is present, enucleation is contraindicated as clear margins are mandated for anaplastic tumours (28).

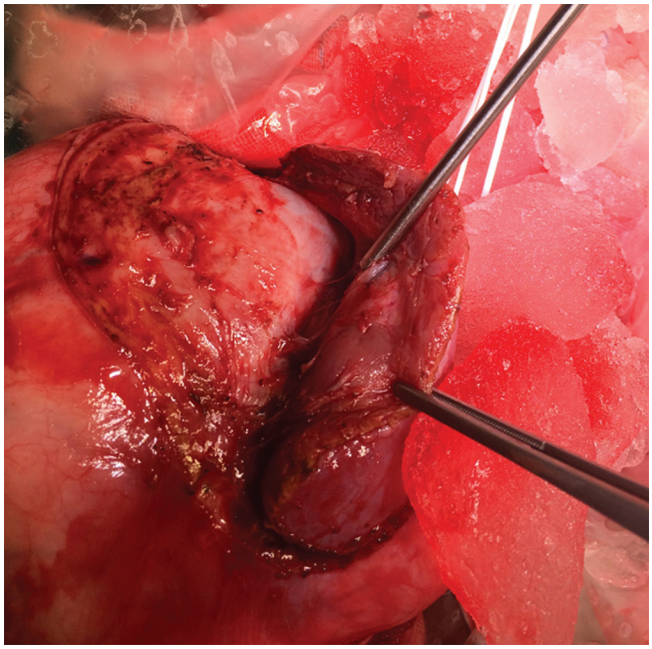

Figure 4. Dissection of the 'fillet' of normal renal tissue in the same child. Reprinted with permission from Red Cross War Memorial Children's Hospital Surgery Department.

Tumours not responding to chemotherapy and still not amenable to NSS may require nephrectomy. In this instance, the dissection plane is outside the Gerota's fascia. Unless the mass is in the upper pole or the adrenal is abutting the mass, the adrenal gland should be left in situ.

Resection of local recurrence in the residual kidney is possible, and it has shown some promising results (41). In our series, apart from the patient indicated above, there have been four other occasions where we have resected recurrences with good long-term results, two of which had tumour extending into the pelvi-calyceal system.

Radiotherapy

In BWT, radiotherapy use has decreased over the years; 57% of patients on NWTS-2 and NWTS-3 (12) received renal or renal-bed irradiation, while 42 (21.4%) of the 196 renal units registered on the renal salvage procedure arm of NWTS-4 were treated with radiotherapy (14). Radiation therapy is considered for abdominal stage III tumours or for stage II cases of anaplasia with involved margins at tumour resection. Its use could come at the cost of reduced renal function, particularly in young patients with the added toxicity of anthracycline chemotherapy (42). Fortunately, it has been shown that anthracyclines can be omitted

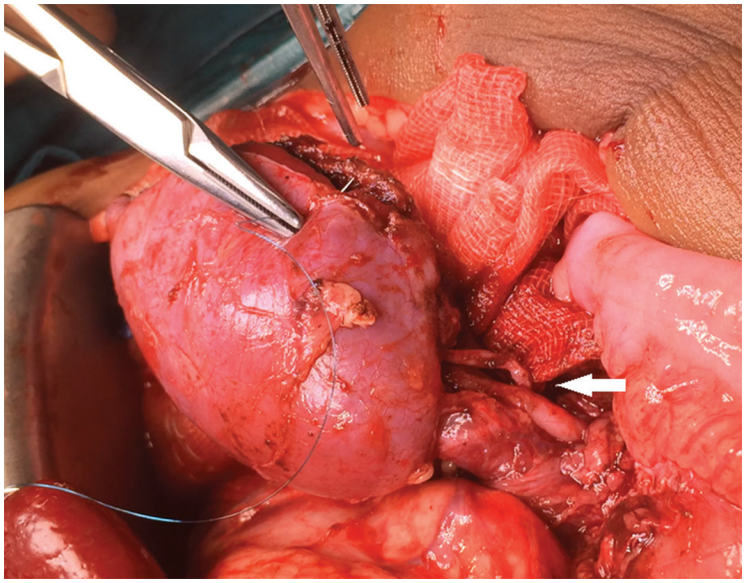

Figure 5. The residual kidney folded over to close the renal capsule with preserved renal artery and vein (arrow). Reprinted with permission from Red Cross War Memorial Children's Hospital Surgery Department.

in Intermediate risk stage III cases in SIOP; however, this needs to be determined in stage V cases (43). Other than cardiomyopathy and second malignant neoplasms, renal failure is the most common source of morbidity in BWT.

Prognosis

The variables identified for poor outcome have been unfavourable histology, advanced (local) stage and age over 3 years at diagnosis. Six of the seven patients in our series who presented with metastases died, although none had anaplastic histopathology (44). About 1% of unilateral WT will subsequently develop a contralateral tumour, with the risk for this tumour development being higher in children younger than 12 months who have nephrogenic rests at diagnosis (10).

Renal failure is an obvious concern in patients with BWT, the aetiology being multifactorial, and it can be due to the compounded effects of the inherent renal disease related to the patient's genetics, nephrotoxic chemotherapy, effects of radiotherapy and the loss of renal parenchyma. Risk factors for renal failure include Denys–Drash and other congenital syndromes, metachronous tumour and progressive disease in BWT with the need for bilateral nephrectomies and radiation nephritis, while the greatest risk factor is that of BWT (40, 45).

The risk of renal failure increases with the loss of more than 50% of renal mass. With the changing nature of treatment and the increasing efforts to preserve renal parenchyma, the rate of renal failure has decreased from 16.4% in NWTS-1 and NWTS-2 (1969–1979) to 9.9% in NWTS-3 (1979–1986) and 3.8% in NWTS-4 (1986–1998) (46). However, more recent long-term studies reflect a higher incidence of renal failure. The SIOP 9301 study reported a 14% rate of end-stage renal disease in 49 children treated from 1993 to 2001 (16). Dekkers et al. (47) showed that tumour nephrectomy, as well as radiotherapy, carries a higher risk of impaired renal function and hypertension. Nonetheless, the absence of significant renal impairment among most survivors is a proof of the success of NSS following initial chemotherapy. However, all BWT patients are eligible to be surveilled and to have systematic follow-up of blood pressure, urine protein and renal function.

In the few patients requiring bilateral nephrectomy, such as those with unresectable tumours or Denys–Drash syndrome, renal transplantation is usually performed between 1 and 2 years without the evidence of malignancy (34). The general consensus is to wait till at least 2 years of disease-free survival for a cadaver donor and 1 year for a living, related donor (34).

Conclusion

With appropriate patient selection and both pre- and post-operative chemotherapy and skilful surgical techniques, an excellent outcome can be achieved in most cases.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article.

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