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Nephron-sparing surgery for bilateral Wilms' tumours: A single-centre experience with 23 cases

A. J. W. Millar, A. Davidson[1], H. Rode, A. Numanoglu, P. S. Hartley[1], Farieda Desai[1]

ABSTRACT

Introduction: The challenge of management with bilateral Wilms' tumours is the eradication of the neoplasm, while at the same time preserving renal function. Surgical management with a variety of nephron-sparing techniques, combined with chemotherapy and occasionally supplemented by transplantation has evolved over the last 30 years to achieve remarkable success. We document the experience of a single centre in a developing country. **Material and Methods:** Twenty-three bilateral Wilms' tumours were seen in our service between 1981 and 2007. Treatment was, in most cases, according to National Wilms' Tumour Study Group protocols, with initial bilateral biopsy, neoadjuvant chemotherapy, and tumourectomy. Technique of nephrectomy included full mobilization of the tumour-involved kidney, topical cooling with slush ice, vascular exclusion, tumour resection and reconstruction of the remnant kidney. **Results:** Twelve patients are alive and free of disease one to 15 years after treatment, all with well-preserved renal function (lowest glomerular filtration rate was 65 ml/min per (1.73 m^2). None of the survivors have hypertension. Eleven have died (two of unrelated disease) including six of the seven with spread outside the kidney. All three with unfavourable histology are alive. Four of the five metachronous presentations are alive, as are eight of 12 patients with synchronous bilateral tumours who presented since 2000. **Conclusions:** Appropriate chemotherapy and nephron-sparing surgery can achieve good results with preservation of adequate renal function in nearly all cases. Unfavourable histology did not have a reduced survival in our series. Metastatic spread outside the kidney had a poor prognosis.

Key words: Bilateral, nephron-sparing surgery Wilms' tumour

Departments of Paediatric Surgery, [1]Paediatrics, Haematology-Oncology Service, Red Cross Children's Hospital, School of Child and Adolescent Health, University of Cape Town, Cape Town, South Africa

Address for correspondence:
Dr. A.J.W. Millar, Department of Paediatric Surgery, Red Cross Children's Hospital, School of Child and Adolescent Health, University of Cape Town, Cape Town, South Africa.
E-mail: Alastair.Millar@uct.ac.za

INTRODUCTION

Successful modern treatment for bilateral Wilms' tumour (BWT) requires preservation of functioning renal tissue in order to achieve a cure with the minimum of therapy-related morbidity. This can be particularly difficult with delayed presentation and advanced local disease, if there is poor response to chemotherapy, or after previous total nephrectomy as in metachronous presentation. Management is often complicated by the presence of multiple nephrogenic rests or areas of nephroblastomatosis, which are difficult to distinguish from Wilms' tumour (WT).[1] Hyperplastic rests can mimic WT on biopsy, and may even transform into WT.[2]

Reported cure rates have approached 80%,[3-5] but this has not been our experience with bilateral disease. By contrast, our results with unilateral Wilms' tumour (UWT) compare favourably with most major paediatric oncology centers.[6] Also, our operative techniques have become more sophisticated. Consequently, we decided to revisit our experience of the last two decades in light of recent surgical and technical innovations.[7]

MATERIAL AND METHODS

The case notes of all patients treated at our hospital for BWT since 1981 were reviewed. Synchronous presentations were managed according to the fourth National Wilms' Tumour Study (NWTS) protocol. At the outset, transperitoneal exploration with bilateral renal biopsies and lymph node sampling was performed prior to commencement of chemotherapy. Since 1999 this has been replaced in some cases of extensive bilateral tumours by percutaneous biopsy. Vincristine, dactinomycin and doxorubicin were used in all cases. Since 1999 cyclophosphamide and etoposide have been added for diffuse anaplasia[8] or poorly responding tumours that were not amenable to surgery at review. Radiotherapy to the kidney was not used as curative therapy.

Laparotomy was usually planned two to three months after initiating treatment with excision of tumour from the kidney with the least involvement. If this left a viable functioning kidney, the contralateral kidney was examined and removed if extensively involved. In the last decade we have been more surgically conservative, and if there was hope of some salvage, another biopsy was done, the extent of the tumour marked with titanium clips, and more chemotherapy given. Surgical exploration and tumourectomy or partial nephrectomy were then performed two to three months later. All attempts were made to avoid bilateral nephrectomy. Extensive bilateral nephroblastomatosis prevented partial nephrectomy or tumourectomy in two cases. These children were treated with three drugs only and achieved complete remission. Both these cases suffered local relapses, or perhaps better termed new lesions in areas of nephroblastomatosis, which were successfully excised and both are alive and disease-free. This approach is different to that advocated by Davidoff *et al.*,[9] who routinely perform bilateral nephron-sparing procedures at the same sitting to decrease the risk of therapy-resistant disease, and to spare the child a second surgical procedure. They argue that tumour size should not preclude an attempt at nephron-sparing since large lesions may compress adjacent normal kidney parenchyma such that there may be more viable kidney than was anticipated by preoperative imaging. We would strongly agree with this statement.

Surgical techniques for BWT varied over the study period and changed considerably in the last decade. Up to 1993 partial nephrectomy, and tumourectomy/enucleation were done by conventional techniques with vascular pedicle clamping for short periods. Since then surgical techniques have included full mobilization of the tumour-bearing kidney, topical cooling of the kidney with slush ice, as well as vascular control with tumourectomy or partial nephrectomy performed under bloodless conditions using bipolar diathermy or the ultrasonic scalpel with an attempt to resect just outside the tumour capsule.

Technique

After full mobilization of the kidney tumour mass, two large 3M Steri-drapes (3M, St Paul, MN), were placed adherent side to adherent side together with a slit cut for the vascular pedicle to act as a 'dam' to contain the crushed ice, which was packed around the renal tumour mass. The patient was insulated from the crushed ice with packing swabs. After the plastic dam and crushed ice were placed, the pedicle was clamped, and the kidney immersed in the crushed ice. A five to eight-minute wait time was allowed for cooling (depending on residual kidney and tumour size), before excision of the tumour commenced. Heparin at a 50% heparinization dose was administered intravenously in some cases prior to cross-clamping of the vessels and ureter. Using loop magnification (x 2.5) the tumour was resected with a thin margin of normal tissue as opposed to being enucleated. The pelvicalyceal system, if involved, could be easily identified and meticulously repaired with 6/0 absorbable sutures. Vascular structures in the remaining open 'fillet' of renal tissue were identified by intermittent partial vascular clamp release and observation of bleeding points, which were controlled with 6/0 absorbable sutures or bipolar diathermy. Cross-clamp time rarely exceeded 35 min; in only one of our cases was there evidence of any degree of acute tubular necrosis following surgery [Figure 2a-d].

On one occasion, bench surgery and orthotopic auto-transplantation was required in a very extensive tumour with rhabdomyomatous change not responding to chemotherapy.[6] In this case the whole kidney/tumour was removed with division of vessels and ureter and flushed with cold Euro Collin's organ preservation solution. The tumour/kidney mass was then placed in a tray of slush ice to maintain hypothermia at 4 degrees Celsius before tumour dissection and excision with reconstruction of the pelvicalyceal system and oversewing of visible vessels. After completion of the bench surgery the kidney was replaced in the renal fossa with end-to-end re-anastomosis of the renal vessels and ureter using interrupted 7/0 sutures for the artery and continuous sutures for the vein and ureter. This patient had a recurrence of tumour in the opposite

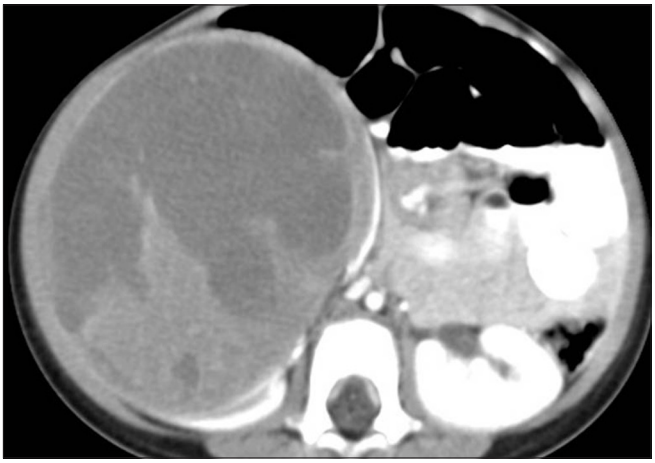


Figure 1: Axial CT with contrast of a 2 year old with bilateral Wilms' tumour after partial left nephrectomy. There is extensive tumour remaining in the right kidney 45% of renal function in this kidney. There was little response to chemotherapy and histology was of the rhabdomyomatous type

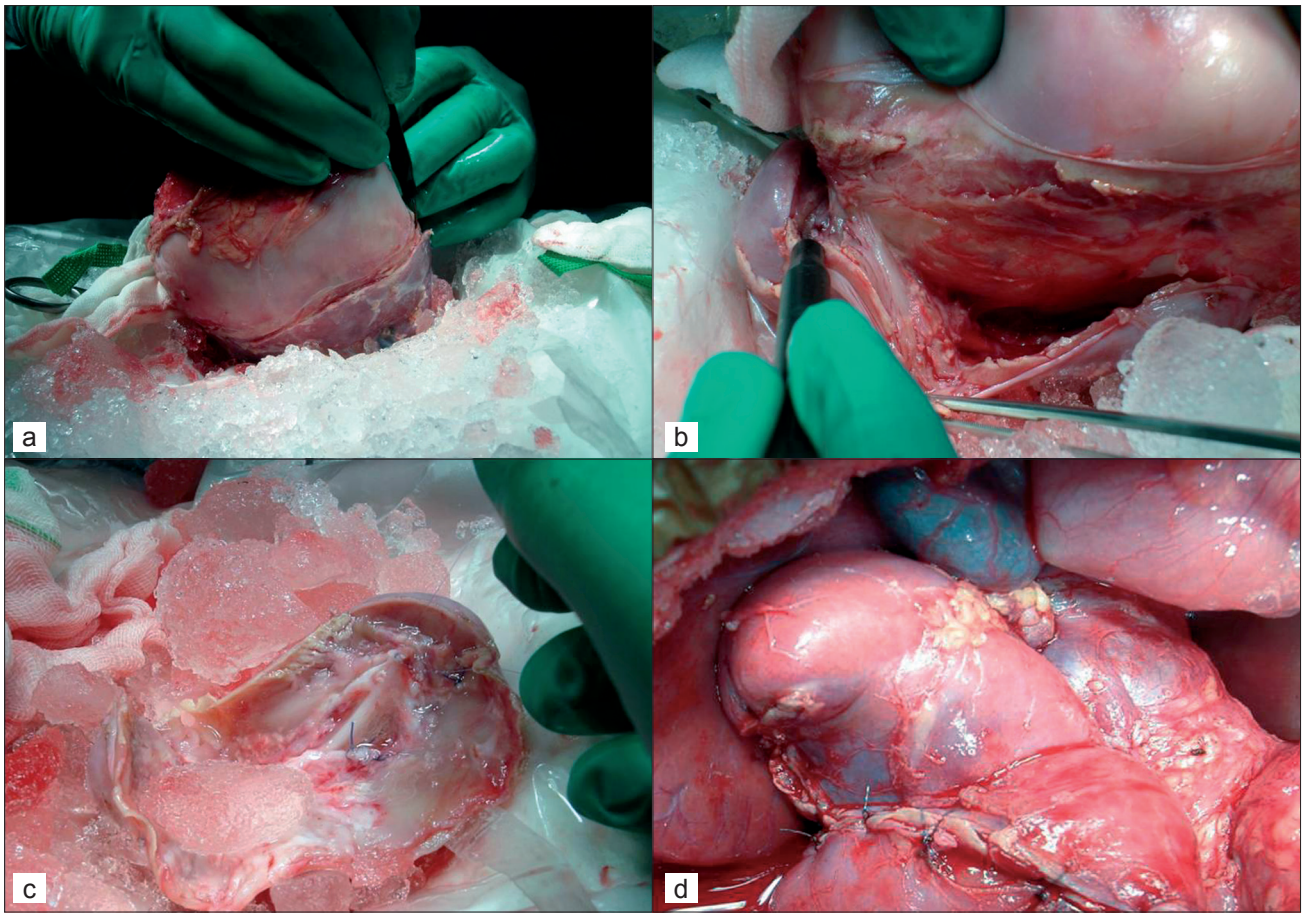


Figure 2: (a) Tumour excision line marked out prior to resection. There is complete vascular control and the residual functioning kidney remains immersed in slush ice during the surgery, (b) Resection of the tumour has commenced leaving a thin margin of renal tissue on the tumour, (c) The residual kidney tissue after repair of calyces and application of haemostatic sutures, (d) Reconstructed kidney after reperfusion. Note uniform perfusion and minimal blood loss. No stenting of the ureter was required. An axiom drain was placed for 48hrs. with minimal drainage.

kidney away from previous resection sites within an area of biopsy-proven nephroblastomatosis, which was successfully excised. He remains a long-term survivor without recurrence at five years post surgery despite tumour having had to be extracted from the renal pelvis at revision surgery.

The metachronous tumours were given chemotherapy and then tumourectomy was performed. Local renal bed radiotherapy was avoided completely for BWT. Radiotherapy was reserved for pulmonary metastases and local palliation.

RESULTS

Two hundred and forty-seven patients were diagnosed with WT between January 1981 and December 2007 with a mean age of 3.6 years (and a median of 3.3 years). There were 23 patients with bilateral tumours (eight boys and 15 girls) ranging in age from three months to eight years. Five (2%) were metachronous (mean age, 5.6 years) and 18 (7.3%) synchronous (mean age, 2.76 years). Most (18 or 78%) presented with an abdominal mass or distension, 12 (52%) had hypertension, two of these with cardiomyopathy. There were no patients with associated congenital abnormalities or syndromes in the bilateral group as opposed to 17 identified among those with UWT.

Of the 18 synchronous cases, 16 presented with the tumours confined to the kidneys (local Stage I or II). One patient had preoperative local rupture and another had liver metastases. Stage, histology, treatment, and outcome are detailed in Table 1. On histological examination, 16 were considered favourable and two had diffuse anaplasia (both local Stage II). Fourteen (78%) had nephroblastomatosis seen on biopsy or in the resected specimens.

Twelve patients achieved complete remission. In two cases, the response to chemotherapy was such that no further surgery was necessary after biopsy to one or

Table 1: Synchronous bilateral Wilms tumours

Age [years]	Local Stage	Metastases	Histology	NBL	Treatment	CR	Relapse Site	Treatment	Status	OS [months]	EFS [months]
0.73	II	nil	blastemal	Y	VAD	N			DD	5.6	4.1
1.99	II	nil	triphasic	Y	VAD/Bilateral PN	Y	Lung	VIE	DD	13.5	6.9
2.59	II	nil	triphasic	Y	VAD/ICE/RPN/LPN	Y	Local (bilateral)	Nil	DD	18.8	17.1
2.98	II	Lung	blastemal	Y	VADCyE/Bilateral B	N			DD	13	13
2.99	II	nil	blastemal	N	VAD/B/ICE/LPN	N			DD	16.8	16.8
3.52	I	nil	blastemal	Y	VAD/RPN/LPN	Y	Lung	M/VADC/PXRT	DD	46.6	18.1
4.01	II	nil	triphasic	Y	VADCyE/LPN	Y	Local and Liver	Nil	DD	19.4	16.4
5.27	II	nil	blastemal	Y	VAD/LN/RPN	N			DD	13.7	7
1.27	I	nil	triphasic	N	VADCy/RN/LXRT	N			DO	8	8
1.95	II	nil	triphasic	Y	VAD/Bilateral PN	Y			DO	47.1	47.1
0.6	II	nil	triphasic	Y	VADCyE/RBS/LPN	Y	Left Kidney	LT/VA	ADF	83.7	16
0.84	II	nil	blastemal	Y	VAD/Bilateral PN	Y			ADF	187.3	187.3
1.13	I	nil	mixed	Y	VAD/Bilateral B	Y	Left Kidney	LPN/VA	ADF	96.7	18.4
1.16	II	nil	triphasic	N	VAD/LPN/RT	Y			ADF	9.7	9.7
1.77	I	nil	blastemal	Y	VAD/Bilateral B	Y	Both Kidneys	Bilateral T/VA	ADF	92.3	29.6
3.31	II	nil	anaplastic	Y	VADCyE/Bilateral T	Y			ADF	73.2	73.2
5.73	III	nil	blastemal	N	LN/VAD/RT	Y			ADF	54.4	54.4
7.9	II	nil	anaplastic	Y	VAD/LPN/RPN	Y			ADF	92.9	92.9

NBL – Nephroblastomatosis; CR - Complete Remission; V – Vincristine; A – Actinomycin; D – Doxorubicin; Cy – Cyclophosphamide; C – Carboplatin, E – Etoposide; R – Right; L – Left; B – Biopsy; N – Nephrectomy; PN - Partial Nephrectomy, T – Tumourectomy; BS - Bench Surgery; M – Metastatectomy; LXRT - Local Radiotherapy; PXRT - Pulmonary Radiotherapy; ADF - Alive Disease Free; DD - Died Disease; DO - Died Other

both sides. While under treatment or after completion of protocol chemotherapy, four developed metastases (two pulmonary and two with local extra-renal spread, one of whom also developed liver metastases).

All patients with extensive extra-renal involvement died, as did the patients with lung and liver metastases. Two more patients died of unrelated disease, one because of anthracycline-induced cardiomyopathy and one from pneumonia. One patient failed to achieve remission despite three-drug induction, second-line treatment with ifosafamide, carboplatin and etoposide and several surgeries. He was not considered for bilateral total nephrectomies because of chemotherapy resistance. Of the eight synchronous patients who are alive and disease-free, three have had local recurrences in a kidney in areas of nephroblastomatosis away from previous resection sites. All three underwent successful revision tumourectomy and are survivors 72 to 85 months since relapse surgery.

The five metachronous tumours presented between 20 and 51 months after initial diagnosis (mean, 33 months). Three were originally Stage I and two were Stage II. Histology, treatment, and outcome are detailed in Table 2. Histologically, one patient had focal anaplasia, whereas the remainder had favourable histology; all had nephroblastomatosis. Three had their nephrectomies (two were right-sided) elsewhere. One of these patients had suffered a pulmonary relapse seven months after completing treatment of a Stage I WT. The pulmonary metastasis was removed, and four months after completing three-drug chemotherapy, she was referred to our centre with a small tumour in an area of nephroblastomatosis in the contralateral kidney. Management of the remaining kidney in four cases involved biopsy, further chemotherapy, and tumourectomy with a minimum of 60% kidney mass remaining. One from another hospital presented late with an obstructive uropathy of the remaining kidney requiring nephrostomy. He responded poorly to three-drug chemotherapy and was given palliative radiotherapy after an unsuccessful attempt at removing the tumour. The other four patients are alive and free of disease 81 to 249 months from their metachronous presentation.

Only three of the survivors had a degree of renal impairment defined here as a glomerular filtration rate (GFR) below 90 ml/min per 1.73 m^2 (these GFRs were (65, 83 and 85 ml/min per 1.73 m^2). Three had isotope GFR assessment after completion of surgical intervention and the other patients had their GFRs calculated from serum creatinine, height, and the Schwartz constant (k = 38). The GFRs ranged from 65 to 162 ml/min per 1.73 m^2. None of the survivors required dialysis or transplantation and none have hypertension [Figure 3].

Reviewing the whole group, 12 of 23 are alive and

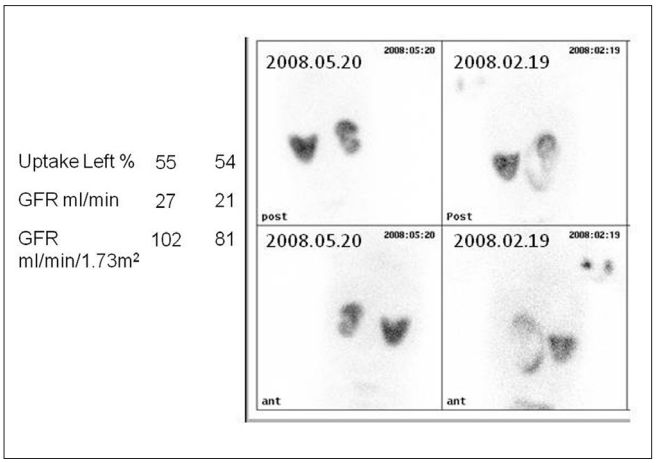


Figure 3: DMSA scan and chromium EDTA glomerular filtration rate (GFR) images and results after left partial nephrectomy (2008.02.19) and 2 months after right tumourectomy as shown in the previous figures (2008.02.20) confirming minimal change of % function

free of disease, four (36%) of 11 prior to 2000 and eight (67%) of 12 since that date, four months to 19 years since completion of treatment. Eleven have died, nine of disease and two of unrelated disease (cardiomyopathy and pneumonia). All three patients with unfavourable histology are alive, 73, 93 and 97 months since diagnosis. Overall and event-free survival was estimated by the method of Kaplan and Meier using Statistica 8.0 (Statsoft, Tulsa). Survival analysis yields an estimated five-year overall and event-free survival of 44.1% and 25.6%, respectively, for synchronous tumours compared with 80% and 80%, respectively, for metachronous tumours (log-rank *P* values, 0.22 and 0.05, respectively). Estimated five-year overall survival for patients with synchronous tumours diagnosed prior to 2000 was 29.2%, compared with 55.6% for patients since 2000 (log-rank *P* value, 0.43).

DISCUSSION

Early work clearly demonstrated that biopsy followed by neoadjuvant chemotherapy was superior to surgical reduction at diagnosis.[10] It then became increasingly clear that the first procedure after neoadjuvant chemotherapy should be partial rather than total nephrectomy. The use of partial nephrectomy or tumourectomy for BWT in NWTS-4[3] was associated with a local recurrence rate of only 8.2%; 16% if the margins were histologically positive and 6.3% if they were negative. Seventy-two percent of these kidneys were salvaged. A more recent report by Fuchs *et al.*,[11] advocated an extremely conservative approach: macroscopic tumour was resected with no attempt to obtain clear microscopic margins in a series of 14 cases of BWT. Renal salvage techniques included the use of longitudinal incisions with reconstruction of the renal pelvis. Thirteen of the 14 are alive and disease-free with no patients in chronic renal failure; the sole death was a patient with anaplastic histology. Davidoff *et al.*,[9] point out that despite advances in technique only 19.4% of synchronous BWT (sBWT) in NWTS-4 underwent nephron-sparing surgery.[3] They suggest that nephron-sparing surgery should always be attempted since the danger of positive margins does not necessarily decrease survival.

Although emphasis has been increasingly placed on nephron-sparing surgical approaches, it should be remembered that most deaths occur because of progressive disease of anaplastic tumours and usually in the first two years after diagnosis.[12] For sBWT, outcome is influenced by local stage with Stage I and II tumours faring better than those that are Stage III.[13] Results for metachronous BWT (mBWT) have been reported as inferior[13] or comparable[4] to sBWT. There appears to be a better outcome if the time to development of the second tumour is less than 18 months.[14]

Synchronous BWT represent 4-7% of all WTs, typically presenting at a younger age than UWT (mean age: 2.6 vs. 3.3 years).[15] About 10% of sBWT have unfavourable histology, and they are associated with genitourinary abnormalities, aniridia, hemihypertrophy, or one of the overgrowth syndromes in up to 20% of cases.[3,5] Variables for poor prognosis identified have been unfavourable histology, advanced local stage, and age over three years at diagnosis.[12] About 1% of UWTs develop subsequent contralateral disease; the risk is increased in children younger than 12 months with nephrogenic rests at diagnosis.[16] Nephrogenic rests may be seen in up to 90% of sBWT and 94% of mBWT;[17] about 70% of children with sBWT in the NWTS series had multiple nephrogenic rests or nephroblastomatosis.[3,5] sBWT comprised 7.3% of our series and mBWT 2%, with the synchronous tumours presenting at a mean age of 2.76 years (compared to 3.6 for the whole group). All but two were local Stage I or II. Fourteen (78%) sBWT and five (100%) mBWT had multiple nephrogenic rests or nephroblastomatosis, and two of the sBWT (11.1%) had diffuse anaplasia. Surprisingly, there were no associated congenital abnormalities or syndromes.

In our series, neither unfavourable histology nor metachronous presentation was associated with a poorer prognosis. However, when extra-renal disease developed, this was associated with reduced survival. Survival improved considerably from 36% before 2000 to 67% since that date.

The prime goal in the management of patients with BWT is to provide effective curative treatment while at the same time preserving sufficient functioning renal tissue for normal growth and development.[18] This 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. Accurate preoperative imaging is critical for successful nephron-sparing surgery and should take the form of multiplanar computerised tomography or magnetic resonance imaging.[19] It should not, however, replace careful visualization of the contralateral kidney.[20,21] Any nephroblastomatosis in a resected tumour should alert the physician to be particularly diligent in follow-up and monitoring. Where nephroblastomatosis is identified pre-or intra-operatively in UWTs, there may be a place for nephron-sparing surgery in a selected group of infants with well-circumscribed tumours, and the NWTS group has recommended that such an approach be formally studied.[16]

With metachronous presentation, there is only one kidney remaining, and an attempt at nephron-sparing surgery is indicated. The alternative is leaving the patient free of disease but anephric, requiring renal transplantation with all the consequences of lifelong immune suppression and drug toxicity. With sBWT, the current recommendations for treatment are biopsy followed by neoadjuvant chemotherapy and then renal salvage procedures (partial nephrectomy or tumourectomy).[3] Nephron-sparing is not advocated in the face of diffuse anaplasia,[22] nor in cases of the Denys-Drash syndrome.[23] Patients can be considered for transplant when they have achieved two years of disease-free survival after treatment, though this may be reduced to one year if there is a living-related donor.[23]

A number of innovations have facilitated nephron-sparing surgery. *In-situ* topical cooling or *ex-situ* perfusion with preservation solution, first described by Lilly and Starzl in 1975, allows careful and extensive dissection and reconstruction without loss of renal function from ischemia.[24] In most cases using *in-situ* topical cooling, the cross-clamp time is relatively short, and topical cooling with ice is sufficient to preserve renal function. In our experience the use of either bipolar diathermy forceps or the ultrasonic scalpel facilitated dissection, as they cut well in a wet environment, with the residual preserved part of the kidney remaining in ice while the tumour was resected. The Cavitron ultrasonic surgical aspirator (Cavitron Surgical Systems, Stanford, CA) has also been used effectively by others.[24] Both renal artery and vein are usually of increased size and length, as they have supplied a large tumour prior to chemotherapy and this allows for considerable mobilization of the kidney making surgical access relatively easy. Up to six tumours or nephrogenic rests were removed at one sitting.

Bench surgery with autotransplantation[25] can be performed in exceptional circumstances, as demonstrated in one of our cases. Vessel re-anastomosis can easily be done in the orthotopic position as the renal artery usually has an enlarged diameter. *Ex-vivo* perfusion does have the disadvantage, however, of making it very difficult to visually discriminate between tumour, nephroblastomatosis, and normal renal tissue. Multiple frozen-section biopsies may be required but can also be difficult for the histopathologist to interpret.

Tumours arising in areas of nephroblastomatosis tended to respond to chemotherapy. Two patients with extensive nephroblastomatosis achieved complete remission with chemotherapy only, a phenomenon that has been described in a child with Beckwith-Wiedemann syndrome.[26] Nephroblastomatosis in residual kidney tissue that is identified on imaging can be followed up with serial ultrasound but a rapid change in size would mandate definitive imaging prior to resection or biopsy.[19] Two patients with extensive rhabdomyomatous change had a poor response to chemotherapy. This phenomenon has been previously reported.[27] One had successful bench surgery and subsequent contralateral tumourectomy. Recurrence of tumour occurred in that kidney but after a second resection he remains a long-term disease-free survivor with good renal function. The other had bilateral extensive nephron-sparing surgery with our technique of ice-dam cooling without the need for bench surgery. If rhabdomyomatous histology is identified earlier surgery may be indicated.

A particularly difficult area is that of progressive or non-responding BWT. In NWTS-4 these tumours achieved an overall survival of only 66.8%.[28] Notably, only a small percentage had anaplastic histology or rhabdomyomatous change. In the event of a poor response to neoadjuvant chemotherapy early biopsy with early resection is recommended, and nephron-sparing techniques may not be feasible. Some workers have even advocated the use of brachytherapy (local treatment with radioactive implants) for these tumours.[22]

The use of radiotherapy for BWT has diminished

over time; 57% of patients on NWTS-2 and NWTS-3[5] received renal or renal-bed irradiation, compared with 42 (21.4%) of the 196 renal units registered on the renal salvage procedure arm of NWTS-4.[3] This supports our decision to avoid radiotherapy; significant survival advantage has not been demonstrated and its use could come at the cost of reduced renal function.

Other than cardiomyopathy and second malignant neoplasms, renal failure is the most common source of morbidity. The risk of renal failure increases with the loss of more than 50% of renal mass. Consequently, with the changing nature of treatment, the rate of renal failure in BWT has decreased from 16.4% in NWTS-1 and NWTS-2, to 9.9% in NWTS-3, and 3.8% in NWTS-4.[29] The preservation of renal function also has to be balanced against patient survival, and the excellent survival reported in institutional series such as Giel *et al*., from St Jude (88.2%)[30] reflects an ability to render some patients anephric, dialyse and await transplantation. In our hands that option would be reserved for those with suitable family donors. The absence of significant renal impairment and hypertension among our survivors is proof of the success of our techniques of nephron-sparing surgery, but all should have systematic follow-up of blood pressure, urine protein, and renal function.[9,18]

CONCLUSION

Bilateral Wilms' tumours that are confined to the kidney have a good prognosis and should be managed conservatively using nephron-sparing surgery. An individualized approach to management with stepwise biopsy, neoadjuvant chemotherapy and carefully planned surgery yields the best results. Tumours with extra-renal spread do poorly and need more intensive adjuvant chemotherapy with or without radiotherapy.

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