CHAPTER 102
KIDNEY TUMOURS

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Introduction

A variety of benign and malignant tumours can arise in the kidney in children. With minor variations, the spectrum of tumours has worldwide distribution. Wilms' tumour (WT; also known as nephroblastoma) is the most common kidney tumour in childhood, and may represent the most common abdominal tumour presenting in infants and children in sub-Saharan Africa. In the past decade, considerable advances have been made in the management and elucidation of the molecular biology of Wilms' tumour. Multidisciplinary collaboration has led to the formation of cooperative study groups in Europe and North America, and has resulted in standardisation of treatment and a remarkable improvement in the outcome of this tumour.[1,2] The treatment of children with WT is considered the paradigm for management of most childhood tumours.

In Africa as well as some other developing countries, WT remains a challenge to the oncologist, with a significantly poorer outcome of treatment than in developed countries.[3–5]

This chapter highlights the demographics, aetiology, and pathology of this typical kidney tumour, followed by a presentation of the diagnosis, treatment, outcome, and challenges in Africa. A brief overview of other tumours of the kidney is also highlighted.

Demographics

The overall incidence of Wilms' tumour is 7.6 cases per million children younger than 15 years of age, or 1 case per 10,000 infants. In Africa, it accounts for about 4–26% of all malignant solid tumours in childhood.[6,7] The hospital-based reports suggest that 4 to 10 new cases of Wilms' tumour are seen every year in most tertiary referral centres.[5,7–9] The incidence in Africa is probably underestimated, however, because some of the affected children are not brought to the attention of trained medical practitioners.[3]

There is no gender predilection; the peak age at presentation is 2–5 years.[3,5] Other malignant renal tumours (e.g., rhabdoid tumour of the kidney; clear cell carcinoma; renal cell carcinoma) occur in older children.

Aetiology/Pathology

In about 10% of the cases, WT is associated with congenital syndromes, for example:

- isolated hemihypertrophy;
- Beckwith-Wiedemann syndrome (visceromegaly, hypoglycaemia, macroglossia, midline defects);
- WAGR (an acronym for WT, Aniridia, Genito-urinary malformations, mental Retardation); and
- Denys-Drash syndrome (protein-losing nephropathy, disorders of sexual development, WT).

These associations have led to the discovery of genetic mutations in WT. In WAGR patients, a deletion has been found on band p13 of chromosome 11, and it has been hypothesised that a Wilms' tumour suppressor gene, WT1, is located there. In Beckwith-Wiedemann patients, another deletion has been found on band p15 of chromosome 11, which has been designated as the WT2 gene. To date, there is no evidence that WT1 and WT2 are correlated with the prognosis, and research is ongoing in this field. Loss of heterozygosity of chromosome 16q has been observed in 15–20% of patients with WT and found to be associated with a 3.3 times higher relapse risk and a 12 times higher risk of death.[10]

The presence of embryonal nephrogenic rests (NR) increases the risk of developing WT. NR can be solitary or multiple (nephroblastomatosis). NR may regress, remain dormant, or become hyperplastic and progress to WT.

WT consists of three types of tissue: embryonal blastema, epithelial tissue, and mesenchymal tissue. Glassberg gives a thorough review on developmental aspects in relation to renal oncogenesis.[11]

According to the SIOP (Société Internationale d'Oncologie Pédiatrique) classification,[12] there are three risk categories for kidney tumours.

1. Low-risk tumours are mesoblastic nephroma and nephroblastoma that has become completely necrotic after chemotherapy (see the later section "When to Operate: NWTSG versus SIOP").

2. Intermediate-risk tumours are triphasic nephroblastoma, including those with focal anaplasia.

3. High-risk tumours are nephroblastoma with blastemal predominance or with diffuse anaplasia and other tumours such as clear cell sarcoma and rhabdoid tumour of the kidney.

Staging of WT in the SIOP and National Wilms' Tumour Study Group (NWTSG) protocol is established after surgery. SIOP staging is as follows:

Stage I:	tumours with an intact capsule that have been removed completely.
Stage II:	tumours with penetration of the capsule that have been removed completely without lymph node metastases.
Stage III:	tumours with microscopic residue, either because of rupture (before or during operation), intravascular extension, ingrowth into other organs that cannot be excised, or lymph node metastases.
Stage IV:	tumours with distant metastases, most common in the lungs but also in the liver or brain.
Stage V:	bilateral tumours, each of which should also be staged according to local characteristics.

The histological classification as well as clinico-pathological staging is correlated to the outcome. Hadley emphasized the relevance of this risk assessment in the Third World.[4] In the Western world, the prognosis for stage I and II with low- or intermediate-risk histology is excellent, with 95% survival.

Clinical Presentation

The main presentation is painless abdominal mass in an otherwise healthy child. The mass in the sub-Saharan African setting is in most cases of a considerable size (Figure 102.1). Other, less common presentations include weight loss, fever, haematuria, or hypertension. The presence of weight loss is common among African patients compared to caucasian children and may indicate an advanced stage of the disease at presentation.[3,5]

A significant number of children in Africa have delayed presentation. The average duration of symptoms before attendance to a mainstream hospital is reported to be 4.7 months.[3] This delay in presentation is related mainly to lack of knowledge or familiarity of the condition and resource deficiency. Some children may be taken initially by their parents to a herbalist and present to hospital only when there is no improvement with herbal treatment (Figure 102.2). The late presentation may thus be responsible for the unique distribution of the stages of the disease in Africa (Table 102.1).[3,7–9]

Table 102.1: Average distribution in Africa of the stages of Wilms' tumour at operation.

Stage of disease at operation	Average percentage
Stage I:	6.9
Stage II:	25.2
Stage III:	42.4
Stage IV:	22.9
Stage V:	2.6

Figure 102.1: A 4-year-old girl presenting with a 6-month history of abdominal mass. At operation, a 6.5-kg left Wilms' tumour was excised.

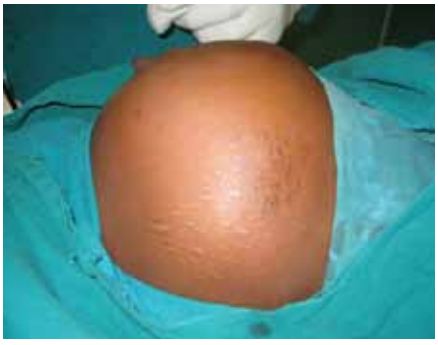

Figure 102.2: A 3-year-old boy with left Wilms' tumour. He presented with a 7-month history. The scarification was inflicted during herbal treatment.

In clinical evaluation of affected children, it may be necessary to exclude associated syndromes such as aniridia, hypospadias, macroglossia, intersex, and the recently described sex-linked Simpson-Golabi-Behmel syndrome (macroglossia, coarse facial features, viceromegaly, diaphragmatic and heart defects, and polydactyly).

Evaluation

Definition of the abdominal mass, status of the contralateral kidney, and involvement of surrounding or distant structures can be achieved with ultrasonography (US), intravenous urography (IVU), chest radiograph, computed tomography (CT), and magnetic resonance imaging (MRI). CT and MRI exceptionally characterise the tumour and the extent of spread, especially with respect to patients with intracaval involvement (Figure 102.3), and bilateral Wilms' tumour. Unfortunately, CT and MRI are not readily available in many centres in Africa. Surgeons working in those centres need a high index of suspicion and appreciation of the diagnostic findings on the readily available US, chest radiograph, and IVU. It is important to determine function on the contralateral kidney and to exclude other retroperitoneal tumours, and in the African setting this can be reasonably achieved by using IVU. A chest radiograph is required to exclude pulmonary metastasis.

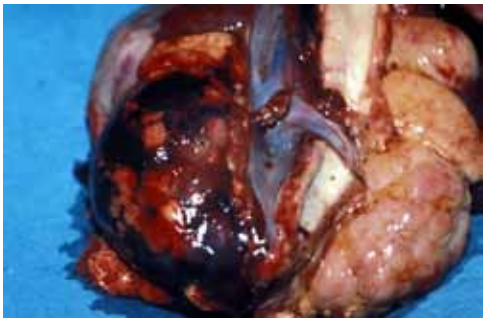

Figure 102.3: Autopsy specimen demonstrating extension of tumour along the right renal vein and into the inferior vena cava.

If any diagnostic uncertainty exists, needle biopsy (Trucut®) will help to confirm tissue diagnosis. This is particularly relevant in the evaluation of retroperitoneal masses to distinguish WT from Burkitt lymphoma.[13]

Treatment

Definitive treatment of Wilms' tumour involves surgery, chemotherapy, and radiotherapy. The treatment modalities used can be modified by stage of the disease, age of the patient, size of the tumour, and the clinical state of the patient. Prior to the commencement of therapy, it is imperative to correct anaemia and malnutrition, which are relatively common in the African setting.

Role of Surgery

Despite the advances in chemotherapy, surgery is still critical in the therapy of Wilms' tumour. Complete resection of the tumour and accurate staging of the disease, both of which are crucial in effecting cure, can be achieved only through surgery. Optimal outcome with surgery will require a generous transperitoneal incision, thorough exploration of the abdomen, biopsy of the lymph nodes in the renal hilum and along the vena cava or aorta, and nephroureterctomy. Migration of the tumour along the renal vein and into the vena cava requires proximal and distal venous control to permit temporary occlusion sufficient to allow removal of the intravascular tumour. Postoperative complications may include intestinal obstruction, haemorrhage, wound infection, and vascular injury.

Role of Chemotherapy

Based on a series of studies by NWTSG in North America and SIOP in Europe, standard chemotherapy regimens have been established. Effective agents currently in use include actinomycin-D, vincristine, cyclophosphamide, doxorubicin, iphosphamide, and etoposide. Unfortunately, these drugs are not readily available in some centres in Africa. Additionally, in a number of centres where the drugs are available, some patients may not be able to afford them.[3,5] These factors are considered responsible for poor compliance with therapy.

Chemotherapy can be administered preoperatively in all patients (SIOP) or in selected patients with solitary kidney, bilateral tumours, intravascular tumour extension, inoperable tumours, or tumour in a horseshoe kidney (NWTSG). Pretreatment biopsy may be necessary in these cases. Agents used include vincristine and actinomycin-D given weekly over a 4-week period.[14]

Adjuvant chemotherapy is advocated by all the protocols. Here the agents used and the duration of therapy depend on the stage of the disease and the histology of the tumour. Advanced stages and cases with unfavourable histology require more intense therapy (Table 102.2).

Role of Radiotherapy

Preoperative radiotherapy may be used to achieve the same effects as preoperative chemotherapy: minimise intraoperative tumour rupture; shrink huge tumours to respectable size; and preserve maximum renal parenchyma in bilateral, solitary, or horseshoe kidneys.

Postoperative radiotherapy has been shown to significantly reduce local recurrence in stages III and IV disease. Radiotherapy facilities and trained personnel are not available, however, in many centres in Africa. Some of the patients requiring this modality of treatment are therefore referred to centres where they are available. Because some of these centres are hundreds of miles away from the referral hospitals, compliance may be difficult to achieve.

Table 102.2: Postoperative treatment commonly used for various stages of Wilms' tumour.

Stage of disease at operation	Optimal treatment
Stage I:	Vincistine, actinomycin-D
Stage II:	Vincristine, actinomycin-D
Stage III:	Vincristine, actinomycin-D, doxorubicin, x-ray therapy (XRT)
Stage IV:	Vincristine, actinomycin-D, doxorubicin, cyclophosphamide, XRT

When to Operate: NWTSG versus SIOP

Whereas SIOP promotes the use of preoperative chemotherapy or radiotherapy for all cases of Wilms' tumour, NWTSG advocates preoperative therapy for only a select category of patients. Issues such as lack of staging information, modification of tumour histology, and potential for inappropriate use of chemotherapy in nonmalignant disease have been raised against the routine preoperative treatment.[15] A critical appraisal[9,16] of the clinical state of cases in Africa suggests that this SIOP protocol may indeed be suited for the African setting. Some centres have reported better outcome with SIOP protocol when compared with immediate nephrectomy.[8,9,16] Israels and Molyneaux have published several papers on this subject based on Malawi data.[17]

Prognosis and Outcome

In the West, the prognosis depends on the stage and histology (see the section "Aetiology/Pathology" for risk classification), but in Africa additional factors are equally important: nutritional and general condition of the child, comorbidity, availability of chemotherapy and radiotherapy, and compliance with completion of postoperative treatment. Some paediatric surgeons therefore advocate keeping these children in hospital from the start of preoperative chemotherapy until they have finished the postoperative courses.

Challenges in Africa

The results of treatment of WT in most centres in Africa are poor, with an overall survival of less than 50%. Although a few centres have reported overall survival approaching 70%, numerous challenges confront the management of this tumour in Africa. Prominent among these is late presentation, inadequate facilities and trained personnel, and poor compliance to therapy. Lack of multidisciplinary collaboration, inadequate drug supply, and comorbidity (human immunodeficiency virus/ acquired immune deficiency syndrome (HIV/AIDS), tuberculosis (TB)) may also play an important role.[4]

Prevention

There is no primary prevention for WT, but early detection is an important tool to improve outcome. Routine screening of patients with relevant syndromes (such as Beckwith-Wiedemann or WAGR) and immediate investigation of patients with abdominal masses have to be advocated by surgeons to paediatricians, general practitioners, under-five clinics staff, and other health care workers.

Ethical Issues

The balance between cost and benefit in WT in Africa is delicate. Expensive diagnostic procedures and drugs, sophisticated surgery, and extended postoperative treatment will place a heavy burden on the resources of the family and the country. However, in view of the good prognosis in children with stage I or II WT and favourable histology, an active surgical approach is commended. More debatable are patients with advanced disease, relapses, or with severe comorbidity (TB, HIV) because these patients will not only need more treatment but also have less of a chance of survival.

Other Kidney Tumours

With the exception of Burkitt lymphoma, the other tumours found in the kidney are extremely rare in Africa. They include mesoblastic nephroma, cystic nephroma, clear cell sarcoma, malignant rhabdoid tumour, renal cell carcinoma, and renal teratoma. These can be distinguished by histology of biopsy specimen. Sometimes differentiating between WT and retroperitoneal Burkitt may be challenging, especially in parts of Africa where Burkitt is endemic.[13] Definitive treatment is in accordance with the histology of the tumour. Burkitt lymphoma can be managed exclusively with chemotherapy with good outcome. The outcome of treatment for the other tumours is variable. For mesoblastic and cystic nephroma, the prognosis is quite good if completely excised. In contrast, the outlook for clear cell sarcoma and rhabdoid tumours is rather dismal; even with multimodal treatment.[18]

Evidence-Based Research

Table 102.3 presents the results of the 9th SIOP Wilms' tumour trial and study on the optimal duration of preoperative chemotherapy in Wilms' tumour.

Table 102.3: Evidence-based research.

Title	Optimal duration of pre-operative therapy in unilateral and nonmetastatic Wilms' tumour in children older than 6 months: Results of the Ninth International Society of Pediatric Oncology Wilms' tumour trial and study
Authors	Tournade MF, Com-Nougue C, de Kraker J, et al
Institution	SIOP
Reference	J Clin Oncol 2001; 19:488–500
Problem	Optimal duration of preoperative chemotherapy in WT.
Intervention	4 weeks vincistine and actinomycin-D.
Comparison/ control (quality of evidence)	8 weeks vincistine and actinomycin-D.
Outcome/ effect	No difference in event-free or overall survival.
Historical significance/ comments	Demonstrates that in Western settings, 4 weeks of chemotherapy is sufficient. Longer treatment may be associated with more complications.

Key Summary Points

1. Cytological or histological (needle biopsy) diagnosis of abdominal tumours in Africa may be an imperative addition to ultrasonography.
2. Preoperative chemotherapy will enable reduction of the bulk of most Wilms' tumours (WT), thereby reducing the risk of surgical complications, in particular tumour rupture.
3. The optimal duration of preoperative chemotherapy in Africa has yet to be established.
4. Surgery remains the only certain way to cure WT, and surgical technique is of utmost importance.
5. Every effort has to be made to complete the postoperative treatment.
6. Multidisciplinary, and multiinstitutional collaborations may help to standardise treatment in Africa.

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