Nephroblastoma (Wilms’ tumour)
G S Arul

Abstract
Wilms’ tumour is a common extracranial solid tumour of childhood; it typically presents as a painless abdominal mass, haematuria or fever. In the UK, it is treated according to the European International Society of Paediatric Oncology protocols: initial imaging by CT and Trucut needle biopsy followed by preoperative chemotherapy. Surgery involves radical nephrectomy and lymph node sampling. Histological examination of the kidney determines the stage and the histological grade of the tumour; postoperative treatment is decided on these two criteria. The overall survival for Wilms’ tumour is about 90%.

Keywords nephroblastoma; Wilms’ tumour; radical nephrectomy; Beckwith–Wiedemann

In 1899, Max Wilms (Leipzig, Germany) became the first to describe nephroblastoma. The survival rate was 20% when surgery was the only means of treatment. Survival improved to 50% with the arrival of adjuvant radiotherapy; overall survival is >85% with modern multi-method therapy. Wilms’ tumour can arise in three clinical forms:
• sporadic
• associated with particular congenital syndromes
• familial (1–2% of cases, autosomal dominant inheritance with variable penetrance; at-risk patients have a 30% chance of developing Wilms’ tumour).

Incidence and epidemiology
The annual incidence of Wilms’ tumour in the UK is 0.8 per 100,000 population; it is slightly more common in children of black African origin and less common in children of Asian origin. The typical presentation is at a median age of 42 months; the male:female ratio is equal. Synchronous bilateral tumours occur in 7% of cases, but present earlier, at an average age of 30 months, with a male:female ratio of 1:2. Table 1 shows the association with various syndromes.

Anatomy
Wilms’ tumour is thought to arise within embryonic renal tissue (i.e. nephrogenic rests). Synchronous bilateral tumours can occur in 4–7% of cases. Extension of tumour into the renal vein occurs in 6% of cases and is usually asymptomatic.

Pathology
Classic Wilms’ tumour has a triphasic appearance, with varying proportions of three cell types (blastemal, stromal, epithelial); anaplastic Wilms’ tumour has a poor prognosis. Nephroblastomatosis is the finding in otherwise normal kidney tissue of one or more nephrogenic rests (persistent embryonic metanephric tissue); they are found in 1% of normal children, in 35% of unilateral Wilms’ tumour cases and in all bilateral tumours. They can predispose to tumours in the other kidney, and so may alter the chemotherapy given and indicate continued monitoring.

Genetics
Several genes have been implicated in the development of Wilms’ tumour, including WT1 (11p13), WT2 (11p15) and abnormalities in 16p, 1p and 17p. Mutations of the p53 tumour suppressor gene on chromosome 17p have been identified in anaplastic Wilms’ tumour. Knudson proposed a two-hit theory for the development of familial tumours. This means that two rate-limiting mutational steps must occur: the first event could be prezygotic i.e. familial inheritance of an affected gene; consequently only one new event (i.e. second mutation) need occur to lead to development of a tumour. The best example of the two-hit theory is retinoblastoma, but a similar (though more complex) scenario appears to occur in familial Wilms’ tumour.

Presentation
The typical presentation is parents observing a hard abdominal mass while bathing an otherwise asymptomatic child. Other presentations include tumour bleeding (pain, temperature, anaemia, haematuria), varicocele (secondary to obstruction of the gonadal vein) or discovered incidentally on screening because of a predisposing syndrome.

Screening
The guidelines of the UK Wilms’ Tumour Screening Working Group are that patients with significant risk factors should be referred to a clinical geneticist, who can carry out the necessary genetic tests and estimate risk. Regular (every three months) ultrasound should be done by a paediatric radiologist or radiographer. Screening should start at the time of diagnosis. The length of the screening period depends on the risks:
• WT1 mutations = 5 years
• 11p15 defects = 7 years
• GPC3 mutations = 7 years
• familial WT = 5 years (unless the affected child in the family was older than 5 years).

Diagnosis
History-taking and examination often give the clinical diagnosis; typically the child is well and thriving with a large palpable mass arising from the kidney.
Further imaging includes an ultrasound followed by a CT of the abdomen (Figure 1). A CT of the chest is essential to screen for lung metastases as part of the initial staging process. Imaging alone is associated with an error rate of 5%.

The differential diagnosis includes benign (e.g. multicystic dysplastic kidney) and neoplastic (e.g. clear cell sarcoma of the kidney) lesions, mesoblastic nephroma and malignant rhabdoid tumours. Neuroblastomas (see page 309) can also be confused with nephroblastoma, but they tend to arise from the adrenals and are locally invasive, tending to surround the vessels. In the UK, we tend to do Trucut needle biopsies to confirm the histological diagnosis before starting treatment; in Europe and North America diagnosis is based entirely on the initial imaging. There has been concern that Trucut needle biopsy may upstage the tumour, but no evidence supports this.

## Treatment

### Approaches

There are two approaches to the management of Wilms' tumour.

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**Table 1**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Affected gene</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beckwith–Wiedemann</td>
<td>WT2</td>
<td>Macroglossia, gigantism, exomphalos minor, neonatal hypoglycaemia, predisposition to abdominal tumours, risk of Wilms' tumour of 5–10%</td>
</tr>
<tr>
<td>WAGR</td>
<td>WT1</td>
<td>Wilms' tumour, aniridia, genitourinary malformations, mental retardation, risk of Wilms' tumour of 50%</td>
</tr>
<tr>
<td>Denys–Drash</td>
<td>WT1</td>
<td>Mesangial sclerosis leading to renal failure, pseudohermaphroditism, risk of Wilms' tumour of 50%</td>
</tr>
<tr>
<td>Congenital aniridia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemihypertrophy</td>
<td>‘Forme fruste’ of Beckwith–Wiedemann syndrome</td>
<td>Risk of Wilms' tumour of 3.5%</td>
</tr>
<tr>
<td>Fraser</td>
<td>WT1</td>
<td>Male sex reversal from gonadal dysgenesis, nephropathy and gonadoblastomas, risk of Wilms' tumour of 8%</td>
</tr>
<tr>
<td>Simpson–Golabi–Behmel</td>
<td>X-linked disorder of GPC3 mutations</td>
<td>Males, tall, distinctive facies, normal intelligence, coronary heart disease, skeletal and urogenital abnormalities, risk of Wilms' tumour of ≈10%</td>
</tr>
</tbody>
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**Figure 1**

a and b are CT images clearly showing Wilms' tumour.
The European approach of the International Society of Paediatric Oncology group is to offer preoperative chemotherapy; this is a four-week course of vincristine and actinomycin D for non-metastatic disease. Surgery is done at 5 weeks so that the tumour can be examined histologically; postoperative chemotherapy starts at week 7.

The North American National Wilms’ Tumour Study Group recommends a primary nephrectomy; staging is then done histologically and a course of chemotherapy agreed. Radiotherapy is reserved for patients with stage-3 disease because of:
- invasion beyond the tumour capsule
- tumour rupture at the time of surgery
- spread to local lymph nodes.

Studies: in an attempt to ascertain the best approach, the UK undertook the UKW-3 trial, which randomized patients between preoperative chemotherapy and primary nephrectomy. This showed no difference in survival, but there was a significantly higher incidence of tumour rupture in patients who had a primary nephrectomy; the UK approach is now to follow the International Society of Paediatric Oncology protocol of preoperative chemotherapy.

Surgical approach
Preoperatively, clotting should be checked because 8% of patients have an acquired von Willebrand’s disease.

Radical nephrectomy
Radical nephrectomy is done via the transperitoneal route using a large transverse muscle-cutting incision (Figure 2). The colon is reflected and, on the right, the duodenum may also need to be mobilized. Some surgeons place the small intestine in a plastic bag to reduce heat loss and fluid evaporation; and in the hope that postoperative ileus and adhesions are reduced. The tumour and the kidney are resected en masse; a pseudocapsule usually surrounds the tumour and it must not be breached.

The vessels must be carefully identified, particularly in enormous tumours, because the vessels to the other kidney may be accidentally damaged. The vein can be slung at the point it enters the inferior vena cava and the artery beneath this. Occasionally, there is more than one renal artery. The artery should be ligated and divided before the vein to prevent swelling, which would occur if the vein were ligated first. The renal vein on the right is very short and more difficult to divide and oversew than the vein on the left. Once the vessels are divided, the tumour kidney and Gerota’s fascia can be freed carefully from the surrounding structures and sent to the laboratory. The adrenal gland can usually be preserved. At least four lymph nodes should be sampled from the hilar and para-aortic region.

Controversies
Partial nephrectomy is not recommended in the UK for new presentations of Wilms’ tumour, but it may have a role in bilateral disease or in small tumours that are detected early in screening.

Intracaval extension of the tumour can be detected preoperatively by imaging. If intracaval extension is below the infrahepatic inferior vena cava, then it should be possible to sling the cava above the tumour and remove the tumour by cavotomy. If the extension is into the liver or even into the atrium, it may be necessary to consider a joint procedure involving cardiac bypass and total circulatory arrest to allow the atrium to be opened and the tumour removed.

Complications
Complications can be intraoperative, immediately postoperative or late. Intra-operative complications include damage to adjacent structures (e.g. liver, bowel, pancreas) and bleeding. The postoperative complications include infection and bleeding, but the classic complication in Wilms’ tumour surgery is ileo-ileal intussusception. This occurs in 10% of patients; the treatment is open reduction at laparotomy. Resection is rarely required.

Late complications include adhesive obstruction, chronic renal failure (<1%) and second malignancy (1.6%). Metachronous Wilms’ tumour can develop in the remaining kidney in 2% of patients so long-term surveillance is essential.

Staging
This is predominantly done by the pathologists after nephrectomy (Table 2). The protocols for localized disease after nephrectomy are summarized in Table 3.

### Staging after nephrectomy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Feature</th>
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<tbody>
<tr>
<td>I</td>
<td>Tumour confined to kidney and completely resected</td>
</tr>
<tr>
<td>II</td>
<td>Tumour extends beyond the kidney, is noted in the renal sinus or blood vessels, but is completely resected</td>
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<tr>
<td>III</td>
<td>Incomplete resection of tumour, involved abdominal lymph nodes, tumour rupture pre- or intraoperatively. Tumour biopsied by wedge biopsy before preoperative chemotherapy or definitive surgery</td>
</tr>
<tr>
<td>IV</td>
<td>Distal metastases (usually lung, liver, bone, brain)</td>
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<tr>
<td>V</td>
<td>Bilateral renal tumours at diagnosis</td>
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</tbody>
</table>

Table 2
Prognosis

Prognosis is good: survival for localized disease is 90% and for metastatic disease is 70%. Patients who relapse have a 60% chance of cure after salvage chemotherapy.

Table 3

<table>
<thead>
<tr>
<th>Protocols for localized disease after nephrectomy</th>
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<tbody>
<tr>
<td><strong>Stage I</strong></td>
</tr>
<tr>
<td>Low risk</td>
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<tr>
<td>Intermediate risk</td>
</tr>
<tr>
<td>High risk</td>
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</table>

AV-1 = 4-week course of actinomycin D and vincristine
AV-2 = 27-week course of actinomycin D and vincristine
AVD = 27-week course of actinomycin D, vincristine and doxorubicin
AV ± Dox (rand) = 27-week course of actinomycin D and vincristine with randomization to ± doxorubicin
High risk = 34-week course of carboplatin, cyclophosphamide, doxorubicin and etoposide

FURTHER READING