Management of Wilms’ tumour: current practice and future goals

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Most patients with Wilms’ tumour in Europe and North America can be cured with treatment and subsequently lead a normal adulthood. However, for some, therapy as applied today results in long-term side-effects and creates a substantial burden on quality of life. Therefore, investigators involved in the management of patients with Wilms’ tumour are increasingly focusing their efforts on curtailing the long-term sequelae of therapy. This aim has been achieved by lowering the total amount of chemotherapy, radiotherapy, or both administered to patients who have characteristics associated with favourable outcome. Although excellent survival has been maintained, many patients receive less therapy today than patients with similar characteristics did a decade or two ago. Better understanding of the biological processes that lead to this childhood cancer will allow further improvements in its management.

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Wilms’ tumour is the most common childhood renal tumour (figure 1), accounting for about 6% of all paediatric malignant disease. With an overall annual incidence of 8·1 per million children, about 650 new cases can be expected each year in North America.1 The multidisciplinary management of Wilms’ tumour has resulted in a striking improvement in survival from 30% in the 1930s to more than 85% nowadays and has become a paradigm for successful cancer therapy. Now that overall good outcomes have been achieved, the primary objective of clinical trials on Wilms’ tumour has shifted towards refinement of therapy for children with low-risk tumours so that they can be spared from modalities resulting in unwanted long-term side-effects without compromising the excellent cure rates. At the same time, investigators continue to look for novel strategies, including treatment intensification, for patients with high-risk tumours for whom outcome might be further improved. We review the progress that has been achieved in the management of Wilms’ tumour, current understanding of its biology, and the future goals for research on this disorder.

Diagnosis

Clinical presentation

A functional review of patients with Wilms’ tumour does not show any tumour-specific symptoms. The most common presentation is with a symptomless abdominal mass, although about a third of patients present with abdominal pain, anorexia, vomiting, malaise, or a combination of these symptoms. Physical examination reveals hypertension in about 25% of patients and congenital anomalies (aniridia, genitourinary malformations, hemihypertrophy, or signs of overgrowth) in 13–28% of children, depending on whether they have unilateral or bilateral disease.2 The syndromes associated with the highest risk of developing Wilms’ tumour include the syndrome of aniridia, genitourinary malformation, mental retardation (generally referred to as WAGR syndrome), the Beckwith-Wiedemann syndrome, and the Denys-Drash syndrome. Other syndromes that have been associated with Wilms’ tumour are shown in table 1. Up to 30% of patients have haematuria and less than 10% have coagulopathy.

Figure 1. Wilms’ tumour consists of varying proportions of three cell types: tubular (a), blastemal (b), and stromal (c) components. Stained with haematoxylin and eosin.
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Imaging

Most patients with Wilms’ tumour undergo abdominal ultrasonography and CT at diagnosis. In addition, either radiography or CT of the chest is done to seek lung metastases. The clinical significance of tumours noted on CT but not visualised on a chest radiograph remains unclear.1,4 The value of MRI in this disorder has yet to be established, but two recent reports have indicated that MRI can help to distinguish between nephrogenic rests (see below) and Wilms’ tumour.15,16

Staging

Wilms’ tumours are staged on the basis of anatomical tumour extent, and therapy is currently based on stage and histology. However, genetic markers are expected be included in risk assessment and therapy in the future. Classifications based on tumour extent have evolved over the years. For example, after careful analysis of the prognostic significance of several clinicopathological factors documented during the first two trials by the North American National Wilms’ Tumor Study Group (NWTSG), NWTS-1 and NWTS-2, use of a grouping system was abandoned in favour of a staging system, which has been used from NWTS-3 onwards. Patients with lymph-node involvement, previously included in group II disease, are now classified as having stage III disease, and those with local tumour spill were moved from group III to stage II disease. Refinements to the inclusion criteria for stages I and stage II disease (see panel) were introduced in the current NWTS-5 study. Previously, one of the criteria for stage II disease was either renal-capsular penetration or extension of the tumour past the hilar plane, an imaginary boundary marked by the medial border of the renal sinus. The hilar-plane criterion was replaced with renal sinus vascular invasion.

Histopathology

Non-Wilms’ tumours

Initially most paediatric renal tumours were classified as Wilms’ tumour, with either favourable or unfavourable histology. After careful histopathological examination of all unfavourable-histology tumours registered in the first two NWTSG studies, pathologists from the study group recognised that certain tumours represented separate disease entities. Therefore from NWTS-3 onwards, clear-cell sarcoma of the kidney and rhabdoid tumour of the kidney were excluded from trials on Wilms’ tumour, although the NWTSG continues to organise separate therapeutic trials for these disease entities. These two types of renal tumour are not discussed further in this review.

Favourable histology in untreated Wilms’ tumour

Most Wilms’ tumours are solitary lesions, although a substantial proportion are multifocal, with 6% involving both kidneys, and another 12% arising multifocally within a single kidney.1 The classic untreated Wilms’ tumour consists of varying proportions of three (triphasic) cell types: blastemal, stromal, and epithelial, commonly recapitulating various stages of normal renal development (figure 1). Less commonly, heterologous epithelial or stromal components are identified, including mucinous or squamous epithelium, skeletal muscle, cartilage, osteoid, or fat.1 Not all specimens are triphasic; biphasic and monophasic patterns are frequently encountered. Many monophasic blastemal Wilms’ tumours are highly invasive and may raise the differential diagnosis of other small round blue-cell tumours, such as primitive neuroectodermal tumour, neuroblastoma, and lymphoma. Similarly, monophasic undifferentiated stromal Wilms’ tumour can mimic primary sarcomas such as clear-cell sarcoma of the kidney, congenital mesoblastic nephroma, or synovial sarcoma. Other differentiated stromal Wilms’ tumours show a predominance of skeletal-muscle differentiation, varying from well-differentiated (rhabdomyomatous) to poorly differentiated (rhabdomyoblastic) skeletal muscle. Lastly, purely tubular and papillary Wilms’ tumour can be difficult to distinguish from papillary renal-cell carcinoma.6

Table 1. Syndromes and genetic loci associated with Wilms’ tumour

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Locus</th>
<th>Implicated genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAGR</td>
<td>11p13</td>
<td>WT1</td>
</tr>
<tr>
<td>Denys-Drash</td>
<td>11p13</td>
<td>WT1</td>
</tr>
<tr>
<td>Beckwith-Wiedemann</td>
<td>11p15</td>
<td>IGF2, H19, p57&lt;sup&gt;mm&lt;/sup&gt;</td>
</tr>
<tr>
<td>Simpson-Golabi-Behmel</td>
<td>Xq26</td>
<td>GPC3</td>
</tr>
<tr>
<td>Li-Fraumeni</td>
<td>17p13</td>
<td>p53</td>
</tr>
<tr>
<td>Hyperparathyroid jaw tumour</td>
<td>1q21–q31</td>
<td>HRPT2</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>17q11</td>
<td>NF1</td>
</tr>
<tr>
<td>Sotos</td>
<td>5q35</td>
<td>NSD1</td>
</tr>
<tr>
<td>Bloom</td>
<td>15q26</td>
<td>BLM</td>
</tr>
<tr>
<td>Perim�</td>
<td>? ?</td>
<td>?</td>
</tr>
<tr>
<td>Mosaic variegated aneuploidy</td>
<td>? ?</td>
<td>?</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>18</td>
<td>?</td>
</tr>
</tbody>
</table>

NWTSG staging system for renal tumours

Stage I

Tumour confined to the kidney and completely resected; no penetration of the renal capsule or involvement of renal sinus vessels.

Stage II

Tumour extends beyond the kidney but is completely resected (negative margins and lymph nodes); at least one of the following has occurred:
- penetration of the renal capsule
- invasion of the renal sinus vessels
- biopsy of tumour before removal
- spillage of tumour locally during removal

Stage III

Gross or microscopic residual tumour remains postoperatively including:
- inoperable tumour, positive surgical margins, tumour spillage involving peritoneal surfaces, regional lymph-node metastases, or transected tumour thrombus.

Stage IV

Haematogenous metastases or lymph-node metastases outside the abdomen (eg, lung, liver, bone, brain).

Stage V

Bilateral renal Wilms’ tumours.
Anaplastic untreated Wilms’ tumour

The histological feature of greatest clinical significance in untreated Wilms’ tumour is anaplasia, which is defined by the presence of greatly enlarged polyploid nuclei (figure 2). The frequency of anaplasia is about 5% and is correlated with patients’ age. It is rare in the first 2 years of life, then the frequency increases to about 13% in patients older than 5 years. It is far more frequent in African-American than in white patients and has been strongly linked with the presence of p53 mutations.

Anaplasia is judged to be a marker of resistance to chemotherapy, but whether it also confers increased aggressiveness or tendency to disseminate still remains unclear. This recognition has resulted in a distinction between tumours showing anaplastic changes that are focal from those that are diffuse. The diagnosis of focal anaplasia requires that cells with anaplastic nuclear changes are confined to sharply circumscribed regions within the primary tumour and surrounded on all sides by non-anaplastic tissue. The diagnostic criteria for diffuse anaplasia include any of the following: presence of anaplasia in any extrarenal site; its presence in a random biopsy specimen; unequivocal polyploid mitotic figures; or an unequivocally gigantic tumour-cell nucleus, may be sufficient to establish the diagnosis in small biopsy specimens. Stained with haematoxylin and eosin.

Histology of previously treated Wilms’ tumour

Tumours that have been subjected to chemotherapy before nephrectomy differ in histopathological findings from those resected at diagnosis. Most notably, about 6% of such tumours show massive necrosis, a feature rarely seen in specimens obtained at diagnosis. A comparison of the histopathological subtypes noted in untreated and pretreated Wilms’ tumours is given in table 2.

Nephrogenic rests

The existence of precursor lesions to Wilms’ tumour has been recognised for many years. These lesions consist of abnormally persistent embryonal nephroblastic tissue with small clusters of blastemal cells, tubules, or stromal cells (figure 3). Nephrogenic rests can be subclassified by their position within the renal lobe and histological appearance (table 3): perilobar nephrogenic rests are limited to the periphery of the renal cortex and intralobar nephrogenic rests occur randomly throughout the renal lobe. The different types of nephrogenic rests are associated with variants clinical and histological tumour features (table 3). The term nephroblastomatosis is used to refer to the presence of multiple nephrogenic rests. There are several possible fates for nephrogenic rests. Only a small number develop a clonal transformation into Wilms’ tumour. Some become hyperplastic, with striking enlargement that preserves the rectangular shape of the preceding rest, yet lacks the peritumoral pseudocapsule characteristic of Wilms’ tumour. Most nephrogenic rests become dormant or involute spontaneously. The presence of nephrogenic rests within a kidney resected for a Wilms’ tumour indicates the need for monitoring the contralateral kidney for tumour development, particularly in young infants.

Biology

The biological characterisation of Wilms’ tumour has provided the foundation for our understanding of key concepts in cancer genetics, including the roles of tumour suppressor genes and relaxation of genomic imprinting in tumorigenesis. Although Wilms’ tumour was one of the high-stage epithelial-predominant tumours limits the analysis, these results suggest a better outcome for advanced-stage diffuse blastemal Wilms’ tumour than for advanced-stage epithelial-predominant Wilms’ tumour. More recently, preliminary analysis of the group assigned no adjuvant chemotherapy in a trial of young children with small stage I tumours provides further support for the excellent prognosis of confined epithelial differentiated Wilms’ tumours, and the increased risk of relapse and subsequent responsiveness of blastemal-predominant Wilms’ tumours. Future therapeutic protocols will probably continue to define a subset of tumours that can be treated with surgery alone. These include cystic partially differentiated nephroblastoma among others. Although much of the past success of the NWTSG has relied on the accurate histological subclassification of Wilms’ tumours into high-risk and low-risk types, further risk classification will probably depend on molecular genetic features.
original examples in Knudson’s two-hit model of cancer development, subsequent research has shown that multiple genes and several genetic events contribute to the formation of this malignant disorder (figure 4). The molecular changes that have been described in Wilms’ tumour can be classified as primary events predisposing to the tumour or secondary events associated with malignant progression.

**WT1**

Initial insights into the molecular biology of Wilms’ tumour were derived from the observation that in patients with aniridia, genitourinary malformations, and mental retardation (WAGR syndrome), the risk of developing the tumour is more than 30%. Cytogenetic analysis of individuals with this syndrome showed deletions at chromosome 11p13, which was later found to be the locus of a contiguous set of genes including PAX6, the gene causing aniridia, and WT1, one of the Wilms’ tumour genes. The WT1 gene encodes a transcription factor that is crucial to normal kidney and gonadal development. Although several target genes of WT1 have been identified, its precise role in tumour suppression remains to be elucidated. The Denys-Drash syndrome, which is characterised by pseudohemaphroditism, glomerulopathy, renal failure, and a 95% chance of Wilms’ tumour development, is caused by point mutations in the zinc-finger DNA-binding region of the WT1 gene, resulting in a protein with a dominant-negative effect. Although several target genes of WT1 have been identified, its precise role in tumour suppression remains to be elucidated. The Denys-Drash syndrome, which is characterised by pseudohemaphroditism, glomerulopathy, renal failure, and a 95% chance of Wilms’ tumour development, is caused by point mutations in the zinc-finger DNA-binding region of the WT1 gene, resulting in a protein with a dominant-negative effect. Although WT1 has a clear role in tumorigenesis of Wilms’ tumour in patients with the WAGR and Denys-Drash syndromes, only a minority of patients with sporadic Wilms’ tumour carry WT1 mutations in the germline (<5%) or in tumour tissue (6–18%). These observations indicate that other genes are involved in Wilms’ tumour development.

**WT2**

The Beckwith-Wiedemann syndrome is an overgrowth disorder manifested by large birthweight, macrosomia, organomegaly, hemihypertrophy, neonatal hypoglycaemia, abdominal-wall defects, ear abnormalities, and predisposition to Wilms’ tumour and other malignant disorders. About 5% of individuals with this syndrome develop Wilms’ tumour. Beckwith-Wiedemann syndrome maps to chromosome 11p15, a locus sometimes called WT2, because loss of heterozygosity at this locus has been detected in Wilms’ tumour. Although the precise WT2 gene remains undefined, there is a cluster of genomically imprinted candidate genes, including insulin-like growth factor 2, H19, and p57 at this locus.

**FWT1 and FWT2**

Familial predisposition to Wilms’ tumour is rare, affecting only 1.5% of patients with the tumour. Analysis of families has revealed familial Wilms’ tumour predisposition at FWT1 (17q) and FWT2 (19q) loci.

**Other potential Wilms’ tumour susceptibility genes**

In addition to its well-established association with the WAGR, Beckwith-Wiedemann, and Denys-Drash syndromes, Wilms’ tumour has been reported in rare individuals with other genetic disorders (table 1). The genes causing most of these disorders have been cloned, but their role in Wilms’ tumorigenesis is unknown. Secondary genetic changes in Wilms’ tumour have been reported in the p53 gene and at chromosomes 1p and 16q. A primary objective of the NWTS-5 trial was to assess prospectively the prognostic significance of loss of heterozygosity at the 16q and 1p loci in a large cohort of patients.

**Table 2. Histological subtypes in favourable-histology Wilms tumour that did or did not receive preoperative chemotherapy**

<table>
<thead>
<tr>
<th>Histology subtype</th>
<th>Immediate surgery</th>
<th>Preoperative chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial predominant</td>
<td>15-5%</td>
<td>3-1%</td>
</tr>
<tr>
<td>Stromal predominant</td>
<td>0</td>
<td>14-0%</td>
</tr>
<tr>
<td>Blasstomal predominant</td>
<td>39-4%</td>
<td>9-3%</td>
</tr>
<tr>
<td>Mixed</td>
<td>45-1%</td>
<td>29-4%</td>
</tr>
<tr>
<td>Regressive predominant</td>
<td>0</td>
<td>37-6%</td>
</tr>
<tr>
<td>Completely necrotic</td>
<td>0</td>
<td>6-6%</td>
</tr>
</tbody>
</table>
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**Table 3. Nephrogenic rests: perilobar versus intralobar**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Intralobar</th>
<th>Perilobar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location within renal lobe</td>
<td>Random; many central</td>
<td>Peripheral</td>
</tr>
<tr>
<td>Associated syndromes</td>
<td>WAGR, Denys-Drash syndrome</td>
<td>Beckwith-Wiedemann syndrome,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perman syndrome, trisomy 13,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hernihyperplasty, trisomy 18.</td>
</tr>
<tr>
<td>Interface with kidney</td>
<td>Intermingling</td>
<td>Distinct</td>
</tr>
<tr>
<td>Dominant histological component</td>
<td>Triphasic, prominent stroma</td>
<td>Blastemal, epithelial</td>
</tr>
<tr>
<td>Number</td>
<td>Single in most cases</td>
<td>Multiple in many cases</td>
</tr>
</tbody>
</table>

**Treatment**

**Surgery**

Primary surgical resection of Wilms’ tumour remains the standard initial therapy undertaken in North America after appropriate clinical and imaging assessment. Some investigators have argued that “the resolution of contemporary ultrasound, CT, and MR imaging equipment allows discrimination of intrarenal masses several millimeters in size”.27 The most recent NWTSG study recommended a transperitoneal approach to provide adequate exposure for complete local-regional staging.28 This procedure includes mobilisation and inspection of the contralateral kidney to exclude bilateral disease before nephrectomy if possible. It also permits inspection of hilar and regional nodes, which remain a crucial factor in staging. Although suspicious lymph nodes are excised irrespective of location, a formal lymph-node dissection is not beneficial or recommended.

Most Wilms’ tumours that appear to involve contiguous structures actually only compress or adhere to the adjacent organ without invasion. Therefore, radical en-bloc resection in these tumours, which is associated with increased surgical complications, can be avoided. However, wedge resection of infiltrated structures such as the diaphragm, liver, or psoas muscle can be undertaken if all disease can be completely removed with little operative morbidity. This procedure is advantageous because the tumour can be downstaged to stage II and subsequent therapy reduced. Tumour extension into the renal vein and proximate inferior vena cava can in most cases be removed en-bloc with the kidney. However, primary resection of extension into the inferior vena cava to the hepatic level or into the atrium is associated with higher operative morbidity. In these circumstances, preoperative chemotherapy decreases the size and extent of the tumour thrombus without increasing its adherence to the vascular wall, thereby facilitating subsequent excision.

Tumour spillage remains an important concept in the surgery of Wilms’ tumour. Surgeons must be aware of any tumour-capsule violation with contamination of the peritoneal cavity during attempt at local tumour control. This event can happen by accident (ie, during operative removal), may be unavoidable (ie, preoperative rupture), or can occur by design (ie, planned biopsy). The accurate assessment of a local spill (stage II) from diffuse contamination (stage III) is difficult; therefore, treatment assignment may be altered. Nevertheless, peritoneal soilage definitely increases the risk of local and abdominal recurrence, although current data suggest that overall survival is not adversely affected.29

Some tumours are initially judged to be unresectable or to pose too great a surgical risk because of massive size. The surgeon is best suited to make this decision, and initial exploration to assess operability and obtain adequate biopsy material from the tumour is recommended. The error rate of imaging in the preoperative diagnosis of renal masses is 5–10%,30 and the histological diagnosis based on needle biopsy material is similarly inaccurate.31 In the truly inoperable cases, preoperative chemotherapy is successful in decreasing the primary tumour mass and generally renders it resectable.

Partial nephrectomy as a primary tumour resection strategy remains controversial and is probably not indicated in routine treatment of Wilms’ tumour. A recent review of patients with unilateral tumours showed a low incidence of renal failure after 6 years of follow-up, and most of these patients had intrinsic renal diseases not related to their tumour.32 In fact, most Wilms’ tumours are too large or centrally located for partial nephrectomy to be considered at initial presentation. If strict surgical criteria were applied, such that the lesion was limited to one pole of the kidney without collecting-system involvement and with separation between the tumour and kidney to allow clear resection margins, less
than 5% of patients would be eligible for partial nephrectomy at the time of diagnosis.\textsuperscript{19} Even after preoperative chemotherapy only about 10% of patients would be suitable for a renal-parenchyma-sparing procedure.\textsuperscript{34} Furthermore, the use of partial nephrectomy carries other risks including unique surgical complications and failure to identify and include nephrogenic rests in the surgical specimen. Therefore, at present, renal-sparing procedures for patients with unilateral Wilms’ tumour are suitable only for those with a solitary kidney, synchronous or metachronous bilateral disease, renal insufficiency of any aetiology, and children at risk of multiple neoplasms such as in Beckwith-Wiedemann syndrome.

**Chemotherapy**

Three highly effective drugs are used in the first-line therapy of Wilms’ tumours: dactinomycin, vincristine, and doxorubicin. Four other drugs are used in patients who experience relapse or do not respond to the combination of dactinomycin, vincristine, and doxorubicin. These include cyclophosphamide, ifosfamide, carboplatin, and etoposide.

The best combination of agents and duration of therapy has been developed by several cooperative clinical-trial groups worldwide, including the Société International d’Oncologie Pédiatrique (SIOP), the UK Children’s Cancer Study Group (UKCCSG), the German Pediatric Oncology (GPO) group, the Brazilian Pediatric Oncology Group, the French Société d’Oncologie Pédiatrique (SOPF), and the NWTSG. Through successive clinical trials these groups have continued to refine therapy and decrease the acute and long-term morbidity associated with the treatment of Wilms’ tumour.

**SIOP studies**

In the SIOP studies, the therapeutic approach has been focused on developing stage-specific strategies after prenephrectomy therapy. Stage classification and histopathological diagnosis are delayed until surgery, which occurs several weeks after clinical and imaging diagnosis. The use of prenephrectomy therapy facilitates surgery in most tumours, because they shrink after the administration of radiotherapy or chemotherapy. This approach reduces the incidence of perioperative tumour rupture,\textsuperscript{1,29} chemotherapy being as effective as radiotherapy.\textsuperscript{27} In addition, chemotherapy-induced tumour shrinkage results in a different stage distribution of patients who undergo immediate nephrectomy to that of patients who receive prenephrectomy chemotherapy by the NWTSG surgical pathological staging system.\textsuperscript{39} Moreover, it allows assessment of whether the histopathological features that characterise Wilms’ tumours after chemotherapy (eg, epithelial predominant, stromal predominant, blastemal predominant, mixed) are associated with tumour shrinkage, stage, or outcome.\textsuperscript{27,39} Finally, this approach establishes in vivo the efficacy of the chemotherapeutic agents used, allowing consideration of other chemotherapeutic agents after surgery for patients whose tumours did not show signs of response. A drawback of administering prenephrectomy chemotherapy is that treatment is initiated without histopathological tissue confirmation.

The first and second SIOP trials showed that preoperative irradiation reduces the incidence of tumour rupture and recurrence-free survival but not overall survival.\textsuperscript{35,36} SIOP-5 showed that preoperative chemotherapy with vincristine and dactinomycin is as effective as preoperative irradiation plus dactinomycin in preventing tumour rupture.\textsuperscript{37} SIOP-6 showed that there was no difference in survival when children with SIOP stage I disease were randomly assigned either 17 weeks or 38 weeks of postoperative chemotherapy with vincristine and dactinomycin. Among SIOP stage II patients with negative lymph nodes who were randomly assigned no radiotherapy, there was a higher recurrence rate.\textsuperscript{38} In SIOP-9, the main objective was to find the optimum duration of preoperative chemotherapy (4 weeks or 8 weeks), to increase further the rate of SIOP stage I tumours and reduce the number of SIOP stage II and III tumours requiring more aggressive therapy. No advantage was noted for 8 weeks of therapy. Among SIOP stage II patients with negative lymph nodes, the rate of abdominal relapse was reduced by the addition of epirubicin without radiotherapy.\textsuperscript{36} In SIOP-93-01, postoperative therapy was based on stage and pathological response to chemotherapy. From postoperative histology, tumours were classified as low, intermediate, or high risk according to the Stockholm working classification of renal tumours.\textsuperscript{39} The final results of that study have not yet been published.

Since therapy is initiated without histopathological tissue confirmation, the approach advocated by SIOP must be balanced against the risks involved with the administration of chemotherapy without tissue diagnosis, the modification of tumour histology, and the loss of accurate staging information.

**UKCCSG**

Like the NWTSG, the UKCCSG initially used postoperative treatment regimens stratified by stage and histology after primary nephrectomy. Their first study (UKW1) showed that vincristine alone for 6 months was as effective as vincristine and dactinomycin for patients with stage I favourable-histology Wilms’ tumour. The results for stage III favourable-histology patients were similar to those reported by NWTSG investigators, but the 6-year survival for stage IV patients with lung metastases (65%) was significantly worse than the 4-year survival (82%) reported by the NWTSG.\textsuperscript{40} This discrepancy was attributed to the routine inclusion of lung irradiation in all lung stage IV patients on NWTSG treatments.\textsuperscript{40} In UKW2, patients with stage I favourable-histology Wilms’ tumour treated with ten weekly doses of vincristine had similar outcome (95% 4-year survival rate) to that noted for comparable patients registered on the NWTSG trials. However, more careful analysis suggested that the excellent outcome in stage I favourable-histology Wilms’ tumour does not apply for children aged four years or older.\textsuperscript{19} For these children, the UKCCSG does not recommend a 10-week course of postoperative vincristine monotherapy. Finally, although better than that reported for UKW1, the 4-year overall survival for stage IV patients in UKW2 (75%)\textsuperscript{40} remained inferior to that reported by the NWTSG.\textsuperscript{40}
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Table 4. Treatment regimens used in NWTS-5

<table>
<thead>
<tr>
<th>Stage</th>
<th>Histology</th>
<th>Radiotherapy</th>
<th>Chemotherapy regimen</th>
<th>Duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I–II</td>
<td>Favourable</td>
<td>No</td>
<td>EE4A</td>
<td>18</td>
</tr>
<tr>
<td>I</td>
<td>Anaplastic</td>
<td>No</td>
<td>EE4A</td>
<td>18</td>
</tr>
<tr>
<td>III–IV</td>
<td>Favourable</td>
<td>Yes</td>
<td>DD4A</td>
<td>24</td>
</tr>
<tr>
<td>II–IV</td>
<td>Focal anaplasia</td>
<td>Yes</td>
<td>DD4A</td>
<td>24</td>
</tr>
<tr>
<td>II–IV</td>
<td>Anaplastic</td>
<td>Yes</td>
<td>I</td>
<td>24</td>
</tr>
<tr>
<td>I–IV</td>
<td>CCSK</td>
<td>Yes</td>
<td>I</td>
<td>24</td>
</tr>
<tr>
<td>I–IV</td>
<td>RTK</td>
<td>Yes</td>
<td>RTK</td>
<td>24</td>
</tr>
</tbody>
</table>

NWTS\G

The first three NWTS\G trials showed that postoperative abdominal radiotherapy was unnecessary for patients with stage I favourable histology or anaplastic histology or for those with stage II favourable histology, when treated with vincristine and dactinomycin after nephrectomy. The addition of doxorubicin to the combination chemotherapy decreased the risk of relapse but did not improve overall survival for children with stage III favourable-histology Wilms’ tumour. Moreover, the dose of abdominal irradiation could be decreased to 10-8 Gy for stage III favourable-histology patients receiving the three-drug regimen. The addition of cyclophosphamide to the combination of vincristine, dactinomycin, and doxorubicin did not improve the outcome for patients with stage IV favourable-histology Wilms’ tumour, but it did improve relapse-free and overall survival in patients with stage II to IV anaplastic-histology Wilms’ tumour. The fourth NWTS\G study investigated the efficacy, toxicity, and cost of different schedules of dactinomycin and doxorubicin administration, finding that dactinomycin could be given safely in 1 day rather than over 5 days and doxorubicin in 1 day rather than over 3 days. These so-called pulse-intensive regimens were as effective as the standard courses but were accompanied by less severe haematological toxicity and fewer health-care encounters. As a consequence pulse-intensive therapy (table 4) has become the standard of care for treatment of Wilms’ tumour in North America.

Having almost reached cure for most patients, NWTS\G investigators have felt the need to refine risk categories further before embarking on new treatment strategies. The major aim of the just closed non-randomised NWTS-5 trial was to assess the prognostic value of loss of heterozygosity at chromosomes 1p and 16q and DNA ploidy. Data from NWTS-5 are currently being analysed.

Synchronous bilateral Wilms’ tumour

About 6% of all children with Wilms’ tumour present with simultaneous bilateral tumours (stage V) at the time of diagnosis. Although more than 70% survive, these children are at high risk of renal failure. This risk has led to the recommendation that such patients undergo bilateral renal biopsy with staging of each kidney followed by chemotherapy to shrink the tumour and facilitate renal-sparing procedures. Primary excision of the tumour masses is not recommended.

After 6–8 weeks of chemotherapy, the patient is reassessed and the feasibility of resection assessed. A second-look procedure may be indicated. Additional chemotherapy or radiotherapy may be needed, but surgery should not be delayed indefinitely. In general, definitive surgery should be done within 12–16 weeks of diagnosis to limit the risk of chemoresistant clonal expansion.

Relapsed Wilms’ tumour

The historical long-term survival for patients with recurrent Wilms’ tumour is less than 30%, but this survival does not reflect the use of agents such as cyclophosphamide, ifosfamide, carboplatin, and etoposide, which have shown substantial activity against the tumour. The use of modern multiagent intensive salvage regimens has improved survival to the 50–60% range. Favourable prognostic factors include initial stages I or II, treatment with vincristine and dactinomycin only, no previous radiotherapy, favourable histology, and relapse longer than 6 months after initial diagnosis. All other patients have a high risk of treatment failure. Recent studies with high-dose chemotherapy followed by autologous stem-cell rescue have also shown encouraging results. However, an adequately powered randomised trial of conventional chemotherapy versus high-dose chemotherapy followed by autologous bone-marrow rescue is needed to investigate whether this approach offers any advantages over conventional second-line therapies.

Radiotherapy

Treatment with radiation continues to have an important role in the management of Wilms’ tumour. The past decade has witnessed remarkable technical innovations in radiation delivery systems and treatment planning software. The use of three-dimensional treatment planning systems based on CT and MRI will enable accurate tumour targeting and superior protection of adjacent normal structures. This technology could be used to deliver conformal radiotherapy for abdominal tumour recurrences and for metastatic sites in the brain, lung, and liver.

Flank/abdominal irradiation

Successful NWTS trials have refined the indications for radiotherapy. The first study of Wilms’ tumour showed that radiotherapy conferred no advantage in children younger than 24 months with group I tumours who also received 15 months of dactinomycin. That study also showed that in group III tumours, with local tumour spill or previous biopsy, there was no need for irradiation of the whole abdomen, thus sparing them the toxicity associated with such irradiation. NWTS-2 showed that radiotherapy could be avoided in all children with group I Wilms’ tumour if they received vincristine and dactinomycin. In NWTS-1 and NWTS-2, an age-adjusted dose schedule was used for flank irradiation: 18–24 Gy for children younger than 8 months;
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24–30 Gy for those aged 19–30 months; 30–35 Gy for those aged 31–40 months; and 35–40 Gy for children older than 40 months. The abdominal relapse rate was 3–5% in group II and III tumours, and there was no dose-response relation across these dose ranges. The third NWTS study proved that radiotherapy could be avoided in children with stage II tumours if vincristine and actinomycin were given. This study also showed that children with stage III favourable-histology tumours who received 10·8 Gy radiotherapy and vincristine, actinomycin, and doxorubicin had similar tumour control to those who received 20 Gy with vincristine and actinomycin. This was an important finding because it eliminated the need for an age-adjusted dose schedule and significantly reduced the recommended dose of radiation.69

In NWTS-2, the predisposing factors for local tumour recurrence were unfavourable histology, delay of 10 days or longer before starting radiotherapy, and small radiation-field size.24 The issue of whether timing of irradiation affects outcome was reanalysed recently. NWTS investigators showed that a delay of 10 days or longer did not significantly influence flank or abdominal tumour recurrences among children with favourable-histology tumours treated on NWTS-3 and NWTS-4.49 However, owing to the rather narrow range of 8–12 days after nephrectomy by which time radiotherapy was administered, the possibility of detecting a meaningful difference in recurrence was limited. Children with abdominal tumour relapse fared poorly; in NWTS-3, 87% of children with a local tumour recurrence died of the disease.39

In NWTS-4, the frequency of abdominal tumour recurrence in children with local tumour spill and stage II tumours of all histologies was 16·5%.29 These children did not receive flank irradiation according to the revised guidelines in NWTS-4. Survival after local recurrence was poor, with only 43% surviving at 2 years. The incidence of tumour recurrence for patients with stage III tumours with local spill after irradiation was only 7·8%.39

Although diffuse anaplastic tumours are resistant to chemotherapy, and presumably radiotherapy, these tumours have not shown a radiation dose response between 10·8 Gy and 40 Gy.41 The optimum radiation dose for anaplastic Wilms’ tumour remains unknown.

The current standard of care includes flank/abdominal irradiation (10·8 Gy in six fractions) for stage III favourable-histology tumours and stage II–III diffuse anaplastic Wilms’ tumours.

Whole lung irradiation

In children with lung metastases detected on chest radiograph, whole lung irradiation (12 Gy in eight fractions) continues to be administered, leading to high cure rates. In NWTS-3, the 4-year relapse-free survival was 71·9%, and the 4-year survival was 78·4% in children with favourable-histology Wilms’ tumour and lung metastases.68 These results are slightly superior to those reported by investigators from the UKCCSG. In their report, the UKCCSG investigators noted that only 37 of 59 patients with pulmonary metastases received radiotherapy as prescribed by the protocol and questioned whether omission of whole lung irradiation had affected outcome in this group of patients.66 SIOP investigators continue to advocate the omission of radiotherapy for patients whose lung metastases disappear completely after 6 weeks of prenephrectomy chemotherapy with vincristine, actinomycin, and doxorubicin. The UKCCSG experience showed overall 6-year survival of only 65% for such patients.46 Given the superior survival obtained with pulmonary radiotherapy, we agree with the UKCCSG investigators who suggested that the omission of radiotherapy is probably not warranted given the negligible expected long-term side-effects of 12 Gy to the lungs.

In children with pulmonary metastases visible on CT but not chest radiograph, the role of pulmonary irradiation is unclear. In such patients treated on NWTS-3 and NWTS-4, the 4-year event-free survival was 89% with irradiation and 80% with chemotherapy alone, a difference that was not significant.62 The pulmonary relapse rate was 4% (two of 53) after irradiation compared with 16% (six of 37) with chemotherapy alone. Although there are genuine concerns about radiation toxicity, the poor outcome in children who relapse after initial treatment necessitates a critical assessment of the role of pulmonary irradiation in these patients.

Long-term sequelae

As the follow-up of successfully treated children increases, data are emerging on the late consequences of treatment. The type of late sequelae and their severity depends on the age and sex of the child, extent of surgery, chemotherapy drugs, and radiation-related factors. Several organ systems should be considered, including the kidneys, heart, and gonads. The most common cause for renal failure in patients with Wilms’ tumour is bilateral nephrectomy, and the second leading cause of renal insufficiency is radiation-induced damage and surgical complications involving the remaining kidney. The frequency of renal failure in bilateral Wilms’ tumour was 16·4% for NWTS-1 and NWTS-2, 9·9% for NWTS-3, and 3·8% for NWTS-4.32 The frequency of renal failure in unilateral Wilms’ tumour remained stable. Congestive heart failure is a well-known complication after the administration of anthracyclines and the risk is further increased when associated with whole-lung irradiation. Consequently, patients with advanced-stage Wilms’ tumour who are receiving doxorubicin should be monitored for cardiac dysfunction.46 Pulmonary function can be affected in those receiving radiotherapy to the lungs, particularly those treated bilaterally. In these patients, total lung capacity and vital capacity can be expected to decrease by 30–70% of predicted. Gonadal function can be endangered in women who have received abdominal radiotherapy for Wilms’ tumour. The NWTS has clearly shown that such women are at high risk of adverse pregnancy outcomes.64 Finally, some children treated for Wilms’ tumours are at increased risk of developing a second malignant neoplasm, whether solely as a result of their carcinogenic treatment or as a result of an inherited predisposition to cancer, or both. Most second tumours have occurred in irradiated areas. The risk factors for second neoplasms include radiation exposure, radiation doses, organs at risk (sensitivity of breast and thyroid gland being the highest), and the use of chemotherapy agents especially

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Search strategy and selection criteria

Data for this review were identified by searches of MEDLINE and PubMed with the search terms ‘Wilms’ tumour’ and ‘nephroblastoma’. Further papers relating specifically to surgery, pathology, radiation oncology, and biology were identified by each author, reflecting his or her specific area of expertise. Abstracts and reports from meetings were not included. Except for eight seminal reports published between 1976 and 1985, only papers published in English after 1985 were included.

Conclusions and future goals

At present, more than 85% of children with Wilms’ tumour are being cured and in our current treatments about 75% do not require radiotherapy or doxorubicin chemotherapy. Despite this success, several challenges remain. For patients with low-risk disease, acute and long-term toxicities of treatment must be limited. For patients with high-risk disease, such as tumours with anaplastic histology, novel therapies must be identified to improve survival. The role of high-dose chemotherapy in children with recurrent tumours needs to be defined. The biological characterisation of Wilms’ tumour will also enable clinicians to define more accurately a patient’s risk of recurrence and to select the best therapy. Future clinical trials will use genetic markers in addition to clinical staging and pathological classification for treatment stratification. As the pathways of Wilms’ tumorigenesis are elucidated, novel molecular therapeutic targets are likely to be identified. The progress of research endeavours in the different disciplines, coupled with a critical analysis of the ever-growing body of evidence accumulated by the clinical cooperative groups, promises a future of hope and optimism for the affected children and treating physicians alike.

Conflicts of interest

None declared.

References

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