

# comments

## INTRODUCTION

The current management of Wilms' tumour has resulted in long-term survival rates of >90% for localized cancers and of ≈70% for metastatic disease. Large randomized controlled trials have been designed, managed and published by various collaborative groups, including the National Wilms' Tumour Study Group (NWTSG), The Société Internationale d'Oncologie Pédiatrique (SIOP) and the United Kingdom Children's Cancer Study Group (UKCCSG), and emphasis has now been diverted from successful treatment to reducing treatment-associated morbidity, without loss of efficacy. Collectively, these studies have enabled the treatment of Wilms' tumour to be modified to minimize morbidity for low-risk disease and to maximize the prognosis for high-stage high-risk patients.

The most important determinant of outcome in Wilms' tumour is the histological grade and stage of the tumour. Accurate staging is therefore required before surgery with CT (including examination of the contralateral kidney for tumour) and during surgery (inspection for evidence of local tumour extension, liver and nodal metastases, peritoneal seeding and nephrogenic rests) to adequately assess the requirements for intervention after surgery. Adverse prognostic factors for event-free survival in Wilms' tumour include stage IV disease, anaplastic histological subtype, absence of a pseudocapsule (composed of compressed atrophic renal tissue), presence of lymph node metastases and too few lymph nodes sampled at nephrectomy. Unfavourable histology accounts for only 10% of all patients with Wilms' tumour, but represents half of the mortality. At a molecular level, allelic loss at 1p and/or 16q and the presence of a *p53* mutation are emerging as useful predictors of outcome, but at present are purely experimental [1].

## CURRENT TRENDS IN THE MANAGEMENT OF WILMS' TUMOUR

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Although the fundamental treatment for almost all patients with Wilms' tumour is a transperitoneal radical nephrectomy, interestingly there is a significant difference in the timing of nephrectomy between Europe and North American clinicians. SIOP and UKCCSG recommend neoadjuvant chemotherapy to down-stage tumours before nephrectomy, such that only 15% of patients have stage III disease and half have stage I disease [2]. Successive SIOP trials also showed fewer surgical complications, especially peri-operative tumour-rupture rates [3], and a more favourable tumour stage distribution with this treatment regimen, leading to a lower overall burden of therapy [2]. By contrast, immediate nephrectomy followed by adjuvant treatment, if necessary, is standard practice according to the NWTSG, with the significant advantage of having histology present to determine further management. Amazingly, there are no major differences in clinical outcome between the regimens.

Also, notably in the SIOP studies, neoadjuvant chemotherapy was commenced solely on the basis that the lesion had the typical clinical and radiological features of Wilms' tumour and with no histological proof on biopsy. However, this approach is contentious and not generally accepted in the UK, because in the UKCCSG Wilms' Study 3, which involved confirmatory tumour biopsy before the start of chemotherapy, 1% of patients had a non-malignant lesion and 12% of lesions that seemed radiographically to be Wilms' tumours were shown not to be Wilms' tumours on biopsy before chemotherapy [4]. In this trial there was no evidence that percutaneous

biopsy resulted in a greater risk of tumour recurrence in the flank or biopsy tract [4].

Currently the role of partial nephrectomy is controversial, as few patients have suitably small, peripherally located tumours, and laparoscopic nephrectomy with lymph node sampling is possible, but long-term experience is lacking [5]. The mainstay of chemotherapy treatment is currently to use dactinomycin, vincristine and doxorubicin as first-line chemotherapy if indicated. In the UK and Europe, 4–8 weeks of preoperative chemotherapy is given. Stage I patients with favourable histology have an excellent prognosis and may require no postoperative chemotherapy. The recently reported SIOP 93–01 trial investigated patients with stage I intermediate-risk and anaplastic tumours, confirming that this group of patients requires standard preoperative chemotherapy followed by only 4 weeks of vincristine and dactinomycin. This short postoperative regimen has reduced acute and late side-effects, as well as the inconvenience for families, while maintaining treatment effectiveness and an event-free survival of 91.4% at 2 years [6]. Stage II tumours require two-agent chemotherapy after surgery (vincristine and dactinomycin). NWTSG showed that adding radiotherapy (20 Gy) gave no statistical improvement in 4-year recurrence-free or overall survival [7]. Stage III disease has a better outcome with adjuvant three-agent chemotherapy (dactinomycin, vincristine, doxorubicin) and low-dose radiotherapy (10 Gy) but has additional concerns over long-term toxicity of abdominal radiotherapy and heart failure

associated with doxorubicin. This regimen is supported by the sixth SIOP trial (with additional two-agent chemotherapy before nephrectomy), which studied stage II and stage III tumours, and reporting recurrence-free survival rates of 49% for two-agent chemotherapy vs 74% for three-agent chemotherapy ( $P=0.029$ ) [1]. Stage IV patients, with lung metastases, represent a unique group who require lung irradiation in conjunction with vincristine, dactinomycin and doxorubicin to improve survival [7]. Children entered into the UKCCSG Wilms' Study 2 received three-agent chemotherapy, delayed nephrectomy and 12 Gy of whole-lung irradiation. The 4-year event-free survival and overall survival was 70% and 75%, respectively [8]. Bilateral Wilms' tumour or stage V disease has a survival rate of  $\approx 70\%$  but a high incidence of renal failure. Therefore, before intervention, both kidneys should be biopsied to ensure an accurate diagnosis, followed by 6–8 weeks of chemotherapy. Each kidney can then be reassessed to determine the feasibility of resection. Any intervention should be monitored closely and nephron-sparing surgery should be considered. The prognosis for patients with relapsed Wilms' tumour is very poor. Therapeutic options include high-dose re-induction chemotherapy with ifosfamide, carboplatin and etoposide or autologous haematopoietic stem cells.

The last decades of the 20th century gave an evidence base for providing curative treatment for most children with Wilms' tumour. Less aggressive chemotherapeutic regimens are available for patients with validated good prognostic factors, such as low stage and favourable histology. Treatment may be optimized through stratification of patients according to tumour stage and histology. Management of relapsed disease remains problematic, but by elucidating the biological pathways involved in Wilms' tumour and defining novel therapeutic targets, we will hopefully generate further therapies. Further research in large randomized controlled trials in the collaborations already established will be required to refine treatment regimens and identify further the role of additional prognostic factors.

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Abbreviations: **NWTSG**, the National Wilms' Tumour Study Group; **SIOP**, the Société Internationale d'Oncologie Pédiatrique; **UKCCSG**, the United Kingdom Children's Cancer Study Group.

**HAEMATURIA IN PROSTATE CANCER: NEW SOLUTIONS FOR AN OLD PROBLEM**

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INTRODUCTION

Patients with advanced prostate cancer frequently develop prostatic bleeding which can significantly increase morbidity. There is relatively little evidence to guide the treatment of haematuria in prostate cancer. In this article, we discuss potential therapeutic strategies and future directions in the management of haematuria due to prostate cancer.

THERAPEUTIC STRATEGIES

HORMONAL MANIPULATION

Anecdotal experience suggests that hormonal manipulation is an effective treatment for prostatic bleeding in cancer, but there is no

published data to support this. The 5 $\alpha$ -reductase inhibitors (5ARIs) are effective treatments for haematuria in benign prostatic enlargement (BPE), probably by reducing microvascular density (MVD) in periurethral tissue [1]. Foley *et al.* [2] randomized 57 patients with chronic intermittent haematuria due to BPE to receive either finasteride 5 mg or placebo for 1 year. Haematuria recurred in 63% of the control group but only 14% in the treatment arm ( $P=0.05$ ). Surgery for bleeding was required by 26% of the controls but none of those on finasteride.

Most prostate cancers arise in the peripheral zone away from the urethra, but tumours causing haematuria must either encroach on the transition zone or bleed from coexisting BPE, so 5ARIs may be an effective treatment. Dutasteride reduces the MVD in prostate