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Immediate nephrectomy versus preoperative chemotherapy in the management of non-metastatic Wilms' tumour: Results of a randomised trial (UKW3) by the UK Children's Cancer Study Group

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ABSTRACT

Purpose: To determine if patients receiving preoperative chemotherapy with vincristine and actinomycin D for non-metastatic Wilms' tumour have a more advantageous stage distribution and so need less treatment compared to patients who have immediate nephrectomy, without adversely affecting outcome.

Methods: Between 1991 and 2001, a total of 205 patients with newly diagnosed non-metastatic renal tumours, of which 186 had Wilms' histologies, were randomly assigned either to immediate surgery or to 6 weeks preoperative chemotherapy and then delayed surgery. Both groups of children received postoperative chemotherapy according to tumour stage and histology determined at the time of nephrectomy.

Results: There was a significant improvement in the stage distribution for patients with Wilms' histologies receiving delayed surgery compared to those having immediate nephrectomy (stage I: 65.2% versus 54.3%; stage II: 23.9% versus 14.9%; stage III: 9.8% versus 29.8%, χ^2 test for trend = 7.02, $p = 0.008$). This improvement resulted in 20% fewer children

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receiving radiotherapy or doxorubicin yet event-free and overall survivals at 5 years of 79.6% and 89.0%, respectively, were similar in the two groups.

Conclusion: Six weeks of preoperative chemotherapy with vincristine and actinomycin D results in a significant shift towards a more advantageous stage distribution and hence reduction in therapy, while maintaining excellent event free and overall survival in children with non-metastatic Wilms' tumour. Around 20% of survivors were therefore spared the late-effects of doxorubicin or radiotherapy. Our results suggest that all children with non-metastatic Wilms' tumour should receive chemotherapy prior to tumour resection.

1. Introduction

Early advances in the treatment of Wilms' tumour relied on improvement in surgical and anaesthetic techniques, but owed little to the consistent and structured use of postoperative chemotherapy or radiotherapy. The prognosis for children with Wilms' tumour improved steadily from the 1960s until the early 1980s, as a consequence of cooperative multicentre clinical trials, but there was relatively little change in the cure rates after the introduction of doxorubicin in the 1970s. More recently, with overall long-term survival now exceeding 80%, investigators have instead focussed on reduction of short- and long-term toxicities, especially in those patients who have biologically favourable disease. The third United Kingdom Children's Cancer Study Group (UKCCSG) Wilms' tumour trial (UKW3) reported here is a further example of this genre of studies but is unique in that it was designed to investigate the relative merits of two contrasting philosophies of treatment.

The timing of surgery for Wilms' tumour has been a subject of lively debate for many years. The North American National Wilms' Tumour Study Group (NWTSG) (now the Renal Tumours Committee of the Children's Oncology Group, COG) has always favoured immediate surgery, with subsequent chemo- and radiotherapy based on a carefully defined pathological staging system that assesses both the extent of tumour spread and the success of surgical resection at the time of operation.[1–4] Using this approach, histological response to chemotherapy is not possible.

The International Society of Pediatric Oncology (SIOP) Nephroblastoma Trial Group, by contrast, has advocated and employed preoperative chemotherapy, usually 4–8 weeks of vincristine (Vcr) and actinomycin D (Act D). Postoperative treatment is determined by postoperative stage and histological subtype, as in NWTSG studies, and also the degree of histological response to the preoperative chemotherapy.[5–7]

The two previous UK studies for Wilms' tumours (UKW1 and UKW2) have recommended immediate nephrectomy for patients without metastases at the time of diagnosis. UKW1[8] included children with all stages and both the favourable histology (FH) classical triphasic Wilms' tumour and the unfavourable histological (UH) subtypes, anaplastic Wilms' tumour, malignant rhabdoid tumour (RTK) and clear cell sarcoma of the kidney (CCSK). For younger children with stage I FH tumours, Vcr alone was as effective as Vcr and Act D combined,[9] and fractionation of Act D was shown to be unnecessary. Outcomes for stage III tumours were comparable to contemporary NWTSG trials but were inferior for stage IV and UH patients.[10,11] UKW2[12] showed that further refinement of treatment for stages I and II FH tumours was possible. The duration of Vcr 'monotherapy' for stage I FH patients was reduced from 26 to 10 weeks; abdominal radiotherapy was omitted for stage II FH tumours without adversely affecting the outcome. UKW1 results for stage III FH tumours were consolidated; outcome for patients with tumours deemed inoperable at diagnosis and for patients with stage IV tumours was improved.[13]

Though the NWTSG and SIOP philosophies differ, there is no obvious difference in the event-free (EFS) and overall survival (OS) between contemporaneous studies such as NWTS 4[14] and SIOP 9.[15] Thus, preoperative chemotherapy might permit identification of patients with chemo-responsive tumours who might be cured with less overall treatment. In an era of 'cure at least cost' for children with cancer, the SIOP approach was increasingly appealing to UKCCSG investigators; it seemed timely to compare its approach with that of the NWTSG in a randomised trial to determine if treatment reduction was possible. A major difference between UKCCSG and SIOP investigators, however, was that a tissue diagnosis – via a percutaneous biopsy – was considered essential before a patient could be included in the delayed surgery arm of the UKW3 trial. This procedure was included to ensure that no child with a non-malignant condition received chemotherapy and that children with other types of tumours received the most appropriate treatment from the outset. The main aim of the UKW3 randomised trial was to determine whether delayed surgery with preoperative chemotherapy might improve the tumour stage distribution of patients with Wilms' tumour, as assessed by the local pathologist, thus leading to a greater proportion avoiding abdominal radiation and anthracycline therapy, without compromising outcome. A secondary aim was to reduce surgical morbidity and mortality.

2. Patients and methods

UKW3 was open to all participating centres of the UKCCSG in Ireland and the UK, as well as Oslo, Norway, and Adelaide and Sydney, Australia, between October 1991 and March 2001. Agreement for centre participation was obtained from the relevant local research ethics committee. Informed consent was obtained from the parents and, where appropriate, the patient.

Eligible patients were aged between 6 months and 16 years, with a newly diagnosed intrarenal tumour and no evi-