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Editorial Comment

Transatlantic controversies in the treatment of Wilms' tumour

*M.C.G. Stevens**

Institute of Child Life and Health, 6th Floor, UBHT Education Centre, Upper Maudlin Street, Bristol BS2 8AE, UK

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Survival of children and young people with most forms of cancer has improved substantially during the past 30 years. This can be largely attributed to the introduction of coordinated multimodality therapy and the efforts of collaborative clinical trial groups in the USA and Europe. As survival has improved, important late sequelae of treatment have been characterised, and it is no surprise that different opinions have emerged about the relative advantages and disadvantages of one approach to therapy over another. Wilms' tumour – described by Green as 'the paradigm for the treatment of a malignant solid tumour of children and adolescents'–is a case in point.[1]

A long standing difference of opinion about the optimal initial management for children with unilateral Wilms' tumour remains unresolved – the timing of nephrectomy.[2] This is not just a simple question of surgical expediency because decisions about further treatment are made according to staging based on the surgical and pathological information provided at and after nephrectomy. If patients are subject to chemotherapy before delayed nephrectomy, how do we know how to use and compare the findings with those obtained at primary nephrectomy in achieving the key objective in the management of Wilms' tumour – maintaining high cure rates whilst avoiding components of therapy which convey the greatest long term risk? This risk principally lies in the use of postoperative radiation therapy and the intensification of standard chemotherapy with doxorubicin.

Children with Wilms' tumour are almost always very young and usually have very large tumours. Primary nephrectomy is not always easy and there has been longstanding agreement that if a tumour ruptures, either before or during an attempt at resection, it is usually necessary to administer post operative radiotherapy. In practice this implies delivery of a radiation field to the flank, with incorporation of the adjacent section of vertebral column and lower chest. The long term implications are those of bone and soft tissue growth impairment, the inclusion of the lower portion of the heart in the field for a left side tumour and of the whole liver for a right sided tumour, and concern about an increased risk of second malignancy. Doxorubicin is added to the standard combination of vincristine and actinomycin D in cases with metastases, unfavourable histology or advanced post surgical local stage disease. It is well known that this conveys a long-term risk of cardiotoxicity but it is perhaps less recognised that anthracyclines may also contribute to the risk of second malignancy.[3]

Early nephrectomy, undertaken before commencing any other therapy, has been a long standing policy in the United States whereas the use of pre-nephrectomy chemotherapy has been practised in Europe for many years. Interestingly, paediatric oncologists in the United Kingdom had previously favoured the North American approach but changed their practice in line with that of their European colleagues following the experience gained in a randomised trial performed by the United Kingdom Children's Cancer Study Group (UKCCSG) comparing immediate versus delayed nephrectomy which was published in the *European Journal of Cancer* in 2006.[4] In his review, Green assesses the evidence for the optimal timing

* Tel.: +44 117 342 0205/0172; fax: +44 117 342 0193.
E-mail address: m.stevens@bristol.ac.uk
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of nephrectomy and poses some criticisms of the UKCCSG study.[1] Are these criticisms justified and where do we go from here?

One of the challenges and frustrations of paediatric oncology is the relatively long time it takes to undertake pivotal randomised phase III studies because of the relatively small number of patients available for recruitment. Over time other factors may evolve which impact on the ease with which data can be compared between studies – obvious examples are changes in imaging and pathological techniques which may have important effects on established prognostic factors such as staging systems and pathological sub grouping. We need, therefore, to be cautious about the transfer of observations from historical studies to the present day – and the earliest clinical trials in Wilms' tumour, on both sides of the Atlantic, date back over 30 years. More important than this, however, is the recognition that changes in treatment will themselves impact on an ability to interpret and compare prognostic factors. Post operative treatment in Wilms' tumour is determined by the surgical findings and by the pathological assessment of the resected specimen. Inevitably this will be altered by chemotherapy, making comparison with strategies that employ primary nephrectomy more difficult.

One of the most important opportunities to consider when planning chemotherapy for young children is to avoid, where possible, the use of anthracycline drugs. The UKCCSG study clearly showed a 'staging shift' with fewer stage III patients in the delayed chemotherapy group and this, together with the ability to assess early chemotherapy response, may help determine whether the addition of doxorubicin is necessary. The controversy here lies principally with the treatment of stage II patients but Green challenges the conclusion made by Mitchell et al. in suggesting that it is safe to avoid doxorubicin in patients with stage II tumours after delayed nephrectomy. In fact the value of doxorubicin in patients with stage II / III favourable histology Wilms' tumour (as assessed after immediate nephrectomy) is itself unclear[5] and the importance, or otherwise, of doxorubicin in stage II tumours after pre-nephrectomy chemotherapy is being explored in a randomised study currently being undertaken by the SIOP Wilms' tumour committee, in which the UKCCSG (now know as the Children's Cancer and Leukaemia Group) are engaged.

Although it seems likely, on the basis of the staging profile, that more patients will receive radiotherapy if treated with immediate nephrectomy, there is also the question of whether it is safe to reduce its use. Green quotes data from an earlier SIOP study in which there appeared to be an increased risk of local relapse in patients who did not receive radiotherapy. In fact, the final analysis of the data showed no difference in DFS between patients with stage II (node negative) disease who received RT and those who did not.[6] However, as the study was discontinued because the stopping rule was triggered, it is not clear if the final analysis was powered to address the original objectives.

Green calls some of the methodology in the UKCCSG study into question. As the authors admit, this was predicted to be a difficult randomisation and although only 39% of the eligible patient population was randomised, the surgeons involved should be congratulated in attempting a trial of this nature. Key issues raised by Green are whether the patients included in the analysis were truly representative of the whole study group and if it was reasonable to report the results by intention to treat rather than by the treatment actually received. The two groups were equivalent in terms of pathological subtype although it would be helpful to know whether other factors such as presenting tumour volume and other imaging characteristics could have had an influence on randomisation or an impact on outcome. It seems inevitable that there was an important subjective component to the assessment required to determine which patients were suitable for randomisation. Surgeons had to decide whether a tumour was potentially operable and it would be no great surprise if larger tumours were more frequently considered inoperable and therefore excluded from the randomisation. The randomisation was stratified by centre in order to limit the effect of surgical subjectivity but further analysis and publication of these data would be a useful contribution to the debate.

Analysis by intention to treat is preferred by statisticians and perhaps also conveys something of 'real life' as it will include those patients where, for whatever reason, treatment is not given as intended – a situation more likely to occur outside a clinical trial than within it. The number of protocol violations was small in both arms of the UKCCSG study and it seems unlikely that this could have an impact on their findings. Green also comments on the suggestion of an adverse trend for more relapses in patients who underwent delayed nephrectomy and although this was not borne out by the statistical analysis, and one needs to be cautious in interpreting trend (in either direction) when comparing small numbers of events.

One important difference remains between practice in the UK and that elsewhere in Europe, and this relates to initial biopsy. All patients in this study who were randomised to delayed nephrectomy underwent diagnostic needle biopsy. This should reduce the risk of a patient with a benign or alternative malignant diagnosis being treated as a Wilms' tumour and may help identify patients with unfavourable pathology at the outset. However, concern has been raised about the risk of recurrence arising by seeding along the biopsy track (although it is interesting that this is rarely, if ever, raised in discussions of other tumour types). Although the UKCCSG report states that no biopsy track relapses occurred, Green highlights the report of a case identified (in a previous publication) as being part of the trial.[7] This requires clarification and it remains at least a theoretical risk. The continuing experience of diagnostic biopsy before delayed nephrectomy in the UK should be further reviewed and reported.

Overall, and despite the findings of the UKCCSG study, it seems likely that a difference in approach between Europe and North America will remain for the foreseeable future.[8,9] It might seem unimportant to resolve this and that Wilms' tumour, with its high survival rate, is not a priority for further research but these are important issues to be resolved in achieving cure at least cost. This concept is not unique to Wilms' tumour and the trade-off between different approaches to therapy is seen across paediatric oncology.[10] The concept of the 'total burden of therapy' needs to be considered and quantified. There is much that the European and North American Wilms' tumour study groups could achieve in undertaking a meta analysis of long term survivors in relation to

treatment exposure and late effects. In order to do so, basic issues of definition in relation to staging, pathological assessment and treatment response need to be agreed both for patients who undergo primary nephrectomy and those who receive initial chemotherapy.

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