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Commentary

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RICHARD WOMER'S commentary makes stimulating reading and reflects the complexity of the management of children with soft tissue sarcoma. The contrasting scenarios he offers for the future of this difficult group of diseases contain elements of truth. However, much is now being done, at a clinical level, to clarify the interpretation of principles of

management and interpretation of treatment results between the major collaborative study groups. The chief area for confusion relates to tumour staging and risk group allocation.

The purpose of staging is to classify tumours into categories for which treatment can be planned and prognosis predicted. It is also important to be able to compare the outcome of different treatment strategies between groups of patients with similar disease. The two main approaches used in staging rhabdomyosarcoma (RMS)—the postsurgical Clinical Grouping system developed by the North American IRS Group, and a TNM system used by the SIOP MMT committee—have been discussed in international workshops [1] and the groups on both sides of the Atlantic now collect information which allows cross-reference between groups of patients with similar pretreatment characteristics. This effort at standardisation is not yet evident in published literature nor always apparent in the dialogue at international meetings, but international workshops continue to be held between the IRSG and the European groups in an effort to share knowledge and improve understanding (the last, exploring the treatment of orbital RMS, was held in Stuttgart this year).

The definition of treatment strategy must not only take into account the extent of the disease at first presentation, but also the impact of initial surgery on residual disease before chemotherapy, i.e. a consideration of both pre- and postsurgical staging. These are both incorporated into the staging system promoted by the SIOP group, although its language is complex and not always completely understood. Dr Womer's critique of the factors which influence the (more popular and less complicated!) IRS postsurgical Clinical Grouping system is particularly welcome as insufficient attention is paid to the issues involved in staging and in treatment stratification. The proposed consensus view of low-, intermediate- and high-risk groupings is a welcome simplicity, but it may be difficult to adhere to when writing a protocol. The most important point, however, is the need to recognise that the nature of treatment itself has a major role in determining prognosis. The efficacy of a particular treatment schedule in one clinical trial may significantly affect the importance of previous prognostic variables in subsequent studies. For example, the results of IRS III did not identify alveolar histology as an independent prognostic factor in patients with localised tumours, in contrast to findings in IRS I and II. It is likely that intensification of treatment for patients with alveolar histology in IRS III eliminated its independent prognostic importance. It will be important to recognise this effect when new biological variables are used for refining treatment stratification.

Despite the slow (but not insignificant) progress in improving cure rates for the majority of patients, there are still anxieties about the possible overtreatment of patients with a good prospect for cure. It is in this context that important differences in treatment philosophy have emerged, especially in the arena of local tumour control. Controversies here relate to the method and timing of local treatment and, more specifically, to the place of radiotherapy in guaranteeing local control for patients who appear to achieve complete remission with chemotherapy ± limited surgery. As Dr Womer indicates, this represents an important philosophical difference between the SIOP studies and those of the IRSG. Whilst local relapse rates are higher in the SIOP studies than those experienced elsewhere, the SIOP experience has shown for the first time that it is possible to cure some patients without radiotherapy who would otherwise have received this. It is also clear that a significant number of patients who relapse may be cured with alternative treatment. In this context overall survival rather than disease-free or progression-free survival becomes the most important criterion for measuring outcome. However, the 'cost' of survival must take into account the predicted late sequelae of treatment and the total burden of therapy experienced by an individual patient. This must include an assessment of all the treatment used, including that used for treatment of relapse, hence the need for longer follow-up. It is for this reason that data from the SIOP trials are slow in coming to publication, although a definitive report of the MMT 84 study has now been submitted for publication. It will be seen that the overall survival rate (68% ± 3% SE at 5 years) is similar to those achieved in IRS II, yet only one third of patients received intensive local treatment. Dr Womer points to the potential for dose reduction in radiotherapy, but does not question whether a reduction of dose from 45 to 50 Gy, to 40 or even 36 Gy is likely to spare late effects—particularly as the majority of patients are very young. It will be interesting to know how the omission of local treatment for children with apparent clinical complete remission will compare with lower dose radiotherapy, both in outcome and sequelae. Perhaps the greatest challenge for those who accept the validity of the SIOP philosophy will be to define measures by which local therapy can be more confidently omitted in children who show a complete response to chemotherapy: biology may be as important as any conventional clinical factor in determining this.

The optimal choice of chemotherapy in the majority of patients with so-called 'intermediate risk' disease is well reviewed in the update. If the 'ifosfamide versus cyclophosphamide' dilemma looks likely to be resolved by IRS IV, the role for anthracyclines is more complicated. Indeed, there is relatively poor single-agent phase II data for several drugs in current use, but simply to re-visit such studies is unlikely to be particularly illuminating as most drugs are likely to show effect against a tumour which is generally chemosensitive. However, the achievement of response, or even of a complete remission, is not the point of failure for most patients and the importance of drug resistance (and its possible modulation) deserves more attention, particularly as no further results have followed those published from Toronto in 1990 [2].

The treatment of other (non-RMS) soft tissue sarcomas (STS) has never received the attention deserved by a group of tumours which can pose considerable management difficulties and show a variable natural history. There is now considerable data within the European studies which, in contrast to the IRSG, have systematically collected information in their clinical trials about all STS. Experience with chemotherapy is now much better defined and allows the classification of tumours into those with proven, possible or unlikely chemosensitivity [3]. The influence of histological grade has been incompletely assessed but is highly prognostic in adult STS and requires further evaluation. Furthermore, the study of other biological variables which may account for the influence of age on tumour behaviour in some diagnoses (for example, infantile fibrosarcoma and haemangiopericytoma) may be illuminating. Finally, the management of 'borderline' diagnoses such as the fibromatoses can also present considerable difficulties and requires elucidation.

In his update, Richard Womer rightly focuses attention on tumour biology as a way to the future, but in the meantime

there is still work to be done in evaluating different philosophies of therapy.

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