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Commentary

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THE GRATIFYING outcome for children with Hodgkin's disease has been observed worldwide and has now formed the template for current trials in the management of adults with Hodgkin's disease. Professor Pötter has succinctly and accurately summarised many decades of clinical research and experience in his accompanying comprehensive review article. Many lessons can be learned from careful scrutiny of this

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updated article on the current status of paediatric Hodgkin's disease. Perhaps most noteworthy is that there is easy agreement and few controversies in this remarkable success story.

WHAT ACCOUNTS FOR THE SUCCESS?

The early use of combined modality therapy introduced high event-free and overall survival rates in Hodgkin's disease in children. The concept of low-dose, involved field radiation therapy was first designed to achieve cure, but to do so while addressing the specific problems of children, most notably avoidance of age-related toxicity, complications and adverse sequelae [1–3]. With the recognition of musculoskeletal problems related to high-dose radiotherapy [4] came the concept of reduction of radiotherapy volume and dose and the subsequent avoidance of these growth abnormalities [5]. Simultaneously, the problems of surgical complications and infections explained by staging laparotomy and splenectomy, prompted investigators to rely on clinical staging in the setting of combined modality therapy, as opposed to pathological staging [6]. Along with differing drug combinations, cycles and durations of chemotherapy, paediatric oncologists worldwide have learned the value of risk-adapted combined modality therapy and have witnessed continually rising survival and event-free survival rates. The German–Austrian multicentre studies are the most impressive in demonstrating improved cure rates while gradually refining therapy according to risk groups [7].

DEFINITION OF RISK GROUP?

Professor Pötter correctly focuses on the challenge to improve the definition of risk groups. The concept of risk-adapted therapy based on stage has evolved over successive paediatric Hodgkin's disease studies and deserves special comment. The impressive German–Austrian protocols have used three treatment groups (TG)—TG 1: I, IIA; TG 2: IIB, IIIA, I_E, II_EA; TG 3: II_EB, III_E, IIIB, IV—and have defined risk-adapted therapy based on these three TGs [7]. It is noteworthy that these TGs have not utilised tumour bulk or size in determining stage–risk group. Most, if not all, other paediatric Hodgkin's disease studies have attempted to include tumour bulk into risk groups, although definition of risk has varied widely. The staging proposal from the Cotswolds meeting [8] has not been uniformly adopted for paediatric studies. There is much disagreement among leaders in the field as to how to define bulky disease and no suggestion from paediatric studies that $\geq$10 cm for abdominal or peripheral nodal disease is the appropriate definition of bulk for a child. One can argue, considering tumour/body ratio, that a 10 cm mass in a child represents a very different proportion tumour burden than the same size mass in a fully developed adult.

In addition, the category of Uncertain Complete Remission (CR_u) has not been tested in paediatrics. Sectional imaging studies of $\geq$1 cm are considered abnormal when interpreting imaging studies. Furthermore, a strict size criterion is problematic for children who may have lymphadenopathy on the basis of reactive changes.

Involved field radiotherapy alone as used for select favourable patients with clinical stage I lymphocyte predominant Hodgkin's disease (CSI LPHD) in the United Kingdom Children's Cancer Study Group (UKCCSG) studies [9] are only reasonable for adolescents and young adults in whom growth and development are not issues. When CS I LPHD presentations are observed in children, not infrequently they are in a youngster in whom 35 Gy to an upper neck/Waldeyer's field would be expected to carry unacceptable musculoskeletal, oral cavity and dental morbidity.

The use of involved field radiotherapy alone for stage I–IIA patients as used in the American Intergroup Hodgkin's disease study of 1977–81 [10] is particularly unattractive. While it resulted in an unacceptably low 5-year relapse-free survival (41%), the higher 5-year overall survival (95%) does not reflect the adverse complications which come with the use of retrieval therapy. Late effects are not usually expressed until beyond 5 years following treatment. Many paediatric studies now show that the most serious late effects such as cardiovascular sequelae and second malignant tumours are most apt to occur in the setting of relapse of Hodgkin's disease and the subsequent necessity of aggressive salvage therapy in an attempt to achieve cure [11]. Thus, the goal of risk-adapted combined modality therapy emerges as the most appropriate initial therapy for the vast majority of children with Hodgkin's disease.

The American paediatric Hodgkin's disease investigators are currently proposing definitions of risk groups as shown in Table 1.

IMPACT OF HISTOLOGY

The uniformly good results from current therapy in children with Hodgkin's disease has diminished the impact of histological subtypes as based on the Rye classification [12]. Today terminology of classical Hodgkin's disease is much more appropriate [13]. The recognition that nodular lymphocyte-predominant Hodgkin's disease arises as a clonal proliferation of B-cells of germinal centre origin and seems to be distinct from classical Hodgkin's disease has caused some oncologists to question the appropriate therapy for this disorder when affecting children. Currently, we believe there may be differences in the pathogenesis of these disorders, but have no clinical data upon which to suggest there should be differences in therapy. Thus, it is appropriate to include children with lymphocyte-predominant Hodgkin's disease on specific Hodgkin's disease protocols until the impact of the histological, genetic and immunophenotypic features are better understood and clarified.

Table 1. *Definition of risk groups designated by the American paediatric Hodgkin's disease investigations*

Risk group	Disease stage
Low risk	IA-IIA No bulky mediastinal lymphadenopathy (mediastinal ratio $<$33%) No extranodal extension No B symptoms $\leq$2 involved regions
Intermediate risk	I-IIA With bulky mediastinal disease (mediastinal mass ratio $\geq$33%) With extranodal extension $\geq$3 involved nodal sites IB-IIB IIIA
High risk	IIIB IVA-B

SUMMARY

With the gratifying cure rates now achieved using refined and risk-adapted combined modality therapy in children with Hodgkin's disease, there exists the potential to become somewhat complacent and cavalier with respect to the management of these children. The best outcomes in children have come from teams of investigators working together who are knowledgeable in the biology and natural history of the disease, expert in the interpretation of clinical staging, and accomplished in the complexities of the risk-adapted combined modality protocols. Strict adherence to timing and intensity of drug delivery is essential to the improved outcome. Use of conformal, three-dimensional radiotherapy techniques may also optimise radiation treatment. Success continues to come from those most accomplished in the art, as well as the science, of managing children with Hodgkin's disease. Professor Pötter provides an outstanding review of the tremendous gains which have been achieved over recent decades, gains which have occurred from large groups of investigators working together in clinical trials. Further refinement in treatment strategies requires entry into clinical trials in order to achieve the goal of cure without the adverse effects. We must not be content with the accomplishments of the past but must focus our energies on the basic and clinical research issues and challenges of the future.

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