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Paediatric Update

Paediatric Hodgkin's Disease

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INTRODUCTION

Paediatric Hodgkin's Disease (HD) is an outstanding example for a paediatric malignancy which can now be cured in the vast majority of children without a significant risk of adverse side-effects mostly achieved by combination treatment. The evolution of staging and treatment strategies have been based on the progress in diagnostic imaging as well as in planning and performance of radiotherapy. Treatment strategies have been increasingly tailored to the individual risk of relapse. The therapeutic ratio can be improved by reducing the burden of each treatment modality which results in avoidance of major side-effects. These strategies developed for paediatric HD have recently even become an example for strategies to be studied in adult HD. Deeper insight into the molecular process of HD now allows a better understanding of the malignant transformation process.

EPIDEMIOLOGY

The overall incidence rate of paediatric HD is 14 per 100 000 under the age of 15 years. The incidence of HD has a characteristic bimodal distribution with regard to age. In Western countries (European Union U.S.A.) rates are low in early childhood rise steeply with an early peak occurring in the age range between 20 and 29 years decreasing thereafter and reaching a second peak beyond the age of 50 years. In developing countries a higher incidence is found in childhood with a similar incidence in young adults. HD is rarely detected in children younger than 5 years of age in Western countries. Overall there is a slight male predominance which is pronounced in children younger than 10 years (male:female ratio of approximately 4:1). Nodular sclerosis shows a unimodal age incidence and accounts for the peak seen in young adults in Western countries. Mixed cellularity type HD is more common in children and in developing countries. Nodular sclerosis type HD is associated with higher socioeconomic status. HD of mixed cellularity type is seen with decreasing incidence with increasing social class [1].

There is a large body of evidence that HD is associated with an infectious agent. Several epidemiological studies and currently additional experimental studies highlight the fact that Epstein–Barr Virus (EBV) seems to play an important role in the pathogenesis of HD. Mixed cellularity is much more likely to be associated with EBV than with nodular sclerosis. This is also reflected by the more frequent incidence of EBV in childhood HD compared with HD in young adults [2].

PATHOLOGY BIOLOGY AND AETIOLOGY

HD was described more than 160 years ago [3]. The definitive description of its histological features is now around 100 years old [4 5]. The most widely accepted classification was introduced in Rye [6]. Based on morphological features visible in standard histological sections four subtypes were distinguished: lymphocyte predominance (LP) lymphocyte depletion (LD) nodular sclerosis (NS) and mixed cellularity (MC). This Rye-classification is still in common use for clinical work-up and clinical trials. The recently published revised European–American lymphoma classification [7] now includes HD. In this classification additional immunological and genetic markers were added to discriminate between various forms of HD.

Modern techniques have led to the recognition of the LP subtype of HD as a distinct clinicopathological entity termed 'Lymphocyte Predominance HD' (LP HD) or 'Nodular Paragranuloma'. When compared with the other subtypes of HD this entity seems to be associated with a long natural history a typical clinical presentation and an extremely favourable prognosis. In LP HD similar to LD HD the differential diagnosis from NHL in particular from anaplastic large cell lymphoma can sometimes be difficult especially in composite lymphomas. In NS HD a subdivision into two subtypes (NSI/NSII) has been proposed based on the number of RS-cells atypia and the extent of fibrosis [8]. Although controversial this subdivision seems to be supported by some studies which show a worse prognosis for the NSII-type HD.

Until recently little has been known about the aetiology and pathophysiology of HD mainly because it is a common feature of all subtypes of HD that a very small number of tumour cells (Hodgkin and Reed–Sternberg (HRS) cells) are surrounded by a huge number of reactive lymphocytes and histiocytes.

Efforts in the last few years have been successfully undertaken to identify the nonmalignant counterpart of the HRS cell at least for LP HD. Lymphocytic and histiocytic (LH) cells which are the HRS equivalent in LP HD express

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several B-lineage associated surface markers such as CD19 CD20 CD22 and CD79a and are therefore considered to be of B cell origin. Using single cell PCR of the V_H gene locus several authors [9] have demonstrated the clonal origin of LH cells from germinal centre B cells. Consequently LP HD is considered to be a B cell lymphoma [7]. Whether or not there is a transformation of LP HD into large cell lymphomas is still controversial [10].

The questions regarding origin and clonality of the HRS cells in the 'classical' subtypes of HD are much less settled. There is however growing evidence coming from single cell PCR analysis of the V_H gene [11 12] that the HRS cells are monoclonal in at least 50% of the 'classical' cases of HD. In most cases the majority of the HRS cells seems to originate from germinal centre B cells [13] which have apparently lost their ability to produce immunoglobulines by somatic mutations in the V_H gene [14]. There are reports which describe T cell markers such as CD3 on some HRS cells in a few patients [15]. So in a minor subgroup of patients with 'classical' HD the HRS cells might be of T cell origin.

The likely origin of HRS cells from germinal centre B cells and the crippling somatic mutations in their V_H genes offer a tempting explanation for a pathogenic mechanism of HD. Under physiologic conditions B cells with such mutations are unable to produce antibodies or T cell receptors and are therefore eliminated by apoptosis. Therefore the development of HD disease requires that the HRS cells have found mechanisms to evade apoptosis. The well-known 14;18 translocation which leads to overexpression of the anti-apoptotic protein Bcl-2 and which is considered to be an important factor in the aetiology of follicular lymphomas could be found only in a few cases of HD [16]. The high expression of various cytokines and cell surface receptors on HRS cells [17] prompted the search for an activated transcription factor which was found to be NFκB [18]. NFκB a dimeric transcription factor is able to protect hepatocytes from apoptosis during embryonic development. It has been demonstrated that downregulation of NFκB activity in an HRS cell line almost completely inhibits tumour growth in SCID mice [19]. The reason for NFκB activation might be the lack of activity of the inhibitory molecule IκBα. Another explanation for the activation of NFκB might be the latent membrane protein 1 (LMP1) of the EBV which is expressed in more than 70% of the cases of HD [20]. LMP1 is able to activate NFκB via the Tumour Necrosis Factor Receptor Associated Factor 1 (TRAF1). LMP1 is also able to upregulate anti-apoptotic proteins of the Bcl-2 family. There is evidence that the latter mechanism is not of importance in HRS cells [21].

Although HRS cells seem to have deactivated some apoptotic pathways other parts of the apoptotic machinery are still intact. This can be concluded from expression data of proteins involved in the apoptotic signal transduction pathways [22] and from the efficiency of radiation therapy the effects of which partially depend on the induction of apoptosis [23].

STAGING

The purpose of initial staging (pathological and clinical staging) is to define the extent of detectable disease. Stage according to the Ann Arbor definition [24] in combination with certain risk factors (e.g. bulky disease) is most important for the natural history and the prognosis of disease and forms the basis for treatment decisions. Pathological staging has been of crucial importance during the period when single modality treatment was mainly applied in early and intermediate stage disease and also for appropriate staging in risk adapted combination treatment. With the widespread use of high quality sectional imaging and the systematic combination of chemotherapy and radiotherapy—also in early disease—pathological staging with staging laparotomy has practically lost its relevance during the last decade in particular in European practice. However it has to be kept in mind that clinical staging based on modern imaging is associated with a significant rate of false-positive and false-negative results in nodal areas and in liver (negative) and spleen (negative) (altogether up to more than 30% [25–28]. Nevertheless it may be argued that within the combination treatment setting chemotherapy controls microscopic deposits adequately. However patients with false-positive results would be overtreated by local radiotherapy and—because of 'overstaging'—by too much chemotherapy. According to results from major recent trials (e.g. GPOH AIEOP SFOP) which incorporated modern imaging based clinical staging—despite a significant limitation in accuracy—it seems to be sufficient to delineate suspected macroscopic disease for defining subgroups (stage extranodal involvement) including certain risk factors (e.g. bulky disease number of involved regions) for overall risk adapted individual treatment planning in particular for the decision on the amount of chemotherapy and radiotherapy. Sectional imaging based clinical staging is most important for planning local involved field (IF) radiotherapy.

The staging system for Hodgkin's disease currently in use is basically still the Ann Arbor Classification [24]. Some revisions have been proposed at the Cotswolds Meeting [29] which are given in brackets in Table 1 and also applies for paediatric HD.

B-symptoms include recurrent drenching night sweats unexplained weight loss of at least 10% of the body weight within the preceding 6 months unexplained recurrent or persistent fever above 38°C.

The subscript 'X' now indicates bulky disease for a mass which is defined as 10 cm or more in its largest dimension (abdomen/peripheral nodes) and for a mass > one third of the internal transverse diameter of the thorax at the level T5/T6 [29].

Table 1. *Ann Arbor classification of Hodgkin's Disease*

Stage I	Involvement of a single lymph node region or lymphoid structure (e.g. spleen) or a single extranodal site.
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm or involvement of one extranodal site and one lymph node region at the same side of the diaphragm (number of lymph node regions to be indicated by a subscript e.g. II_3).
Stage III	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm (a subdivision has been introduced for upper abdominal involvement as III_1—spleen splenic hilar coeliac portal—or lower abdominal involvement as III_2—paraaortic iliac mesenteric [29]).
Stage IV	haematogenous spread to multiple extranodal sites (visceral involvement).

For the more appropriate evaluation of remission a new category has been proposed as 'uncertain complete remission' or CR_u indicating some residual mass on radiological examination with no clinical evidence of residual or recurrent disease [29].

The following procedures for work-up for staging are recommended to be performed at present:

1. History complete clinical examination in particular of the lymph node bearing regions and the abdomen (hepatosplenomegaly).
2. Histology including immunophenotyping with traditional and new classification.
3. Basic laboratory tests as complete blood cell count erythrocyte sedimentation rate (ESR) alkaline phosphatase liver function parameters serum albumin and LDH are widely accepted. The value of additional work-up like the assessment of EBV-serology immune status (B T4/T8 lymphocytes NK cells) monoclonal antibodies (CD 30) cytokines adhesion molecules and oncogenes will be hopefully clarified in near the future [30].
4. Noninvasive diagnostic imaging procedures have a moderate overall accuracy depending on a large variety of parameters which may be estimated to be somewhere between 70 and 90%. Few precise overall data are given in the literature for the various regions except for the abdomen. The noninvasive imaging procedures include chest radiographs and chest CT abdominal CT and ultrasound including the pelvis ultrasound for peripheral lymph nodes. Sectional imaging is mainly based on the (pathological) size of lymph nodes with a mass >1.5 cm regarded as involved [29] which varies to some degree in the different regions. In Europe lymphography is hardly used any more although it is superior in detection of pathological lymph node structures in retroperitoneal lymph nodes [26]. The overall additional value of MRI remains still to be proven. For specific indications like extranodal spread into soft tissue MRI seems to be the method of choice [31]. Nuclear medicine investigations such as gallium 67 scans are not widely accepted because of their high rate of false-positive results [32]. Biological imaging like PET SPECT and immunoscintigraphy may become interesting additional imaging tools in the future for staging and monitoring.
5. Invasive diagnostic procedures such as laparotomy for pathological staging in the abdomen have lost their relevance with the systematic introduction of combination treatment. However invasive procedures should be performed in very specific situations (e.g. extranodal disease) which need clarification for therapeutic decisions in terms of burden of treatment. For specific situations in the abdomen (e.g. accurate assessment of pelvic disease for sparing the ovaries from radiation fields) pathological staging by staging laparotomy remains the gold standard. Laparotomy could so far not be replaced by laparoscopy for various reasons.
6. Bone marrow biopsy remains an important integral part of staging in advanced disease. Bone marrow involvement correlates with clinical risk factors which are stage B-symptoms elevated ESR alkaline phosphate and LDH.
7. For toxicity assessment and monitoring heart and lung function tests and endocrine function tests (thyroid and gonadal function) are recommended before the start of treatment.

PLANNING AND PERFORMANCE OF RADIOTHERAPY

Treatment planning in HD for target definition has been increasingly based on information from sectional imaging studies (in particular CT) during the last two decades. Nevertheless for specific planning of radiotherapy the traditional fluoroscopy based approach with conventional X-rays is still used taking into account information from sectional images for individualised target definition with individual blocking. In the 'large field approach' e.g. with modified mantel field techniques two opposite photon beams with individual blocking have been the most appropriate treatment techniques. Within systematic combination treatment the target concept covering the whole classically defined lymph node region has been questioned [33]. If only the area of macroscopic disease has to be treated by radiotherapy within such combination treatment the target can be more individually tailored to the spread of disease. Consequently the treated volumes will conform more to the target sparing as much normal tissue as possible. In such a setting there will be more place for 3-dimensional (3-D) treatment planning and conformal 3-D radiotherapy in paediatric HD in near future resulting in a more adequate coverage of highly individualised targets by treated volumes which can spare more normal tissue than has been possible in the traditional opposite beam technique covering whole lymph node regions. Maybe there will even arise an indication for unconventional beams like protons with their ability to spare even more normal tissue behind the target (due to Bragg-peak effect) compared with 3-D photon conformal radiotherapy.

TREATMENT

Until the 1960s treatment of HD in general—including paediatric HD—was regarded as mainly palliative although a high response rate to X-rays (orthovoltage radiation) was known since the beginning of the century (neck: [34] (boy age 4 years) mediastinum: [35]).

1960*s to early* 1970*s*

With a better understanding of the natural history of the disease as a contiguous spread to adjacent lymph node areas and the systematic use first of orthovoltage radiotherapy [36 37] then of megavoltage radiotherapy (linear accelerators telecobalt machines) in superficial and deep-seated adjacent areas localised HD (stage I-III) became a curable disease [38 39]. Extended field radiotherapy (EF RT) was delivered up to a dose of 40 to 44 Gy in 4–5 weeks. In the late 1960s and early 1970s the high responsiveness of HD to various cytotoxic drugs became evident: alkylating agents (mechlorethamine (M) cyclophosphamide (C) chlorambucil (Chl) procarbazine (P) dacarbazine (D)); vincristine (O)/vinblastine (V); prednisone (P); anthracylines (A); bleomycin (B). The M(C)OPP and ABVD regimens resulted in high continuous remission rates in advanced HD approximately 50% in stage IIIB/IV [40 41]. As the natural history and biology of paediatric HD were regarded as similar to adult HD the translation of adult HD treatment concepts into the paediatric setting was performed which was high-dose EF RT

with 40–45 Gy in localised disease [42] and intensive multiagent chemotherapy with additional RT in advanced disease. Nevertheless substantial radiation related morbidity was soon recognised in particular musculosceletal growth inhibition after 40–44 Gy [43].

Late 1970s to early 1980s

A wide variety of specific strategies taking mainly into account radiation-related morbidity was developed for the treatment of paediatric HD in the late 1970s and early 1980s including:

- Combination chemotherapy and low-dose EF RT with 15–25 Gy [44–47] or medium dose EF RT with 30–36 Gy [48 49];
- Combination chemotherapy and low-dose IF RT [50–53] or medium dose IF RT [54];
- Chemotherapy alone [55 56]; and
- Involved field (IF) RT alone [57 58].

Based on growing experience with combination chemotherapy and radiotherapy different toxicities were increasingly recognised. After treatment with alkylating agents and RT second malignant neoplasms (SMN) and infertility (from pelvic RT in girls from alkylating agents in boys) were reported [59–63]; cardiomyopathy and coronary heart disease after high-doses of anthracyclines and high-dose RT to the inferior mediastinum [64]; pulmonary disease after high-doses of bleomycin (in combination with RT) [51 65]; thyroid abnormalities after high- and medium-dose RT [66]. A significant number of infections sometimes with fatal outcome were associated with the intensity of treatment (number of chemotherapy cycles EF RT) and with splenectomy [48 61 67 68].

LATE 1980S TO THE PRESENT

Currently the major challenge has become the avoidance of treatment related morbidity above all fatal events which have mostly been attributed to SMN (ANLL and certain solid tumours) and to overwhelming sepsis (rarely to pulmonary or cardiac disease) and to minimise any significant impairment in quality of life caused by somatic or psychoscial late effects. Therefore the current strategies (late 1980s to 1990s) aim at further reducing the burden of treatment from radiotherapy and chemotherapy and from diagnostic procedures (staging laparotomy in particular splenectomy).

EARLY DISEASE

Localised nodal disease (stage IA-IIIA) was recognised as early as the 1970s as associated with a 5-year overall survival (OS) of 89–95% and a relapse free survival (RFS) of 57–66% [42 69]. This was achieved with high-dose EF RT with 40–46 Gy according to the effective treatment schedules in adult HD. Because of the well-known radiation related adverse side-effects in particular in soft tissue and bone growth different groups soon introduced additional combination chemotherapy derived from the experience in adult advanced disease: first MOPP ABVD then OPPA COPP and ChlVPP. RT was increasingly applied as involved field (IF) RT with medium or low radiation doses (15–25/30–35 Gy) [50 68 70]. Results after such combination treatment improved with the most favourable results reported at 7 years as 100% OS and 98% event free survival (EFS) in 100 children in stage IA/B IIA [54 71].

As these excellent results for obvious reasons could not be improved any more the major challenge then became to design treatment strategies with an optimal balance between maximum efficacy and minimum toxicity. For radiotherapy this meant dose and volume reduction in order to minimise growth disturbances infertility cardiac complications and above all the induction of SMN. For chemotherapy this meant a reduction in cumulative dose or elimination of alkylating agents (SMN infertility in boys) anthracyclines (cardiac complications) and bleomycin (pulmonary complications). Also staging laparotomy and splenectomy has been questioned and finally abandoned. The burden of treatment was to be as low as possible because it has been associated with serious infections and impairment in quality of life (e.g. 'fatigue' [61]).

Combination treatment

The most challenging treatment strategies for localised disease currently include combination treatment without invasive staging procedures with the use of an initial chemotherapy regimen (with little potential of long term toxicity) and IF or local radiotherapy with doses between 15 and 25 Gy. The most beneficial chemotherapy regimen in terms of therapeutic range reduce or even eliminate alkylating agents and/or anthracyclines and/or bleomycin. Italian and French cooperative groups have successfully investigated the ABVD regimen with 3–4 cycles of ABVD and low-dose IF RT (Italian group EF in IIA) with cumulative doses for doxorubicin of 150–200 mg/m^2 and bleomycin of 60–80 mg/m^2 resulting in progression and disease-free survival of 89–95% respectively [46 72].

The most data have been collected in the German–Austrian trial group (DAL/GPOH) with 2×OPPA (HD 82 HD 90 for girls) or OPA (HD 85/87) or OEPA (HD 90 for boys) and IF RT (from 35 Gy in HD 82 to 25 Gy in HD 90) given to 516 patients from 1982–1995 [73]. The respective cumulative doses for doxorubicin was 160 mg/m^2 for procarbazine (for girls in 2×OPPA) 3000 mg/m^2 and for etoposide (for boys in 2×OEPA) 1200 mg/m^2 all well below the so far clinically recognised long term toxicity levels for the different endpoints. The respective OS and EFS at 5 years (cS IA/B IIA) were 98–100% and 80–98%. The volume of radiation has been further reduced since the HD 90 trial modifying the radiation fields to radiotherapy of local nodal involvement [33]. Because of their low potential morbidity and their high efficacy these combination treatment schedules seem to represent a very beneficial approach.

A chemotherapy regimen very similar to OEPA has been reported by O'Brien [74] with VEEP (epirubicin etoposide). Another recently introduced challenging approach is being carried out by the French group (SFOP) introducing an initial chemotherapy regimen without anthracyclines and without alkylating agents consisting of four cycles of VBVP (vinblastin bleomycin (40 mg/m^2) etoposide (2000 mg/m^2) prednisone) and IF RT of 20 Gy in case of a good response. Results reported so far are promising with an EFS at 2 years of 97% [75].

Because of its significant impact on SMN induction and sterilising effects mechloretamine is now increasingly abandoned for treatment of early disease although it had been proven to be very efficient in a large number of different mono- and multicentre trials [44 50 52 53 76].

Higher radiation dose ('boost' dose) with an additional 10–20 Gy resulting in a total dose of 30–40 Gy has been used in bulky disease at diagnosis and/or in insufficient partial

remission with a significant residual mass. Currently a radiation boost is mostly only applied for cases of 'no sufficient partial remission' after initial chemotherapy. According to the SFOP and GPOH experience this insufficient partial remission has been defined as less than 70–75% volume reduction and/or a residual mass >>50 cm^3 and accounts for approximately 5–15% of all patients [72 77].

Single modality treatment

IF RT alone seems to represent another reasonable option for selected prognostic favourable patients e.g. CS I involvement of the upper neck lymphocytic predominance. In favourable patients (CS I peripheral lymph node involvement) IF RT alone with radiation doses of 35 Gy results in 98% OS and 85% EFS according to the British experience (UKCCSG) [57].

In all stage I/IIA patients (including any pattern of involvement) IF RT alone as investigated by the CCSG from 1977–1981 [52] resulted in a low rate of relapse free survival (41%) but still in a high rate of 95% OS at 5 years. Nevertheless 59% of all patients required intensive salvage treatment so such treatment cannot be recommended taking into consideration the significant burden of long-term treatment-related morbidity in a large number of patients.

If medium-dose IF RT alone is considered the potential of long term radiation morbidity has to be carefully considered. In peripheral lymph node treatment (mostly neck) this means thyroid function impairment and soft tissue and bone retardation which is most pronounced after medium and high-dose radiotherapy in young children [78].

Chemotherapy alone as proposed by different groups is also to be judged from the long term morbidity. Six cycles of ABVD alone [79] with cumulative doses of doxorubicin of 300 mg/m^2 and of bleomycin of 120 mg/m^2 resulting in an EFS of 10/12 (crude rate 83%) are efficient but not attractive in terms of their potential for long-term cardiac and pulmonary morbidity. The same applies for chemotherapy alone regimens using high cumulative doses of alkylating agents such as that used in the UKCCSG trial with 6–8 cycles of ChlVPP [80] with significant cumulative doses of chlorambucil (504–672 mg/m^2) and procarbazine (8400–11200 mg/m^2) or that used in the Australian trial (4–12 cycles of ChlVPP or MOPP [81]) which have a high potential for long term morbidity in terms of (male) infertility and SMN induction [59 60]. Such regimens for stage II disease result in 80% EFS and 94% OS at 5 years but with a high probability of infertility at least for boys and a significant risk of SMN induction they cannot be recommended. A similar comment applies for the POG 8625 study on early disease which included 3 cycles of MOPP and 3 of ABVD in the chemotherapy alone arm after pathological staging. Although results have been rather favourable (EFS 88% at 8 years [82 83]) this treatment as for other reported chemotherapy alone regimens seems to be excessive for early stage disease as it bears a significant potential for long-term morbidity.

Future

Future strategies will certainly try to refine radiation therapy and chemotherapy for this patient group that accounts for approximately half the paediatric HD patient population. Using a gold standard of combination treatment high cure rates approaching 100% and EFS rates >90% are now achievable in non selected CS I and IIA children staged without laparotomy and splenectomy treated with 2 cycles of chemotherapy e.g. OPPA OEPA VEEP VPVB combined with low-dose IF RT thus with a low potential of treatment related long-term morbidity. This highlights the fact that an optimal treatment strategy in this early disease group seems to be almost complete.

One future option is to reduce the indication for RT in selected favourable patients. This can be done by using the treatment response after 2 cycles of chemotherapy as a selection criterion for further treatment which means for example to stop further treatment (radiotherapy) in cases of a complete response after chemotherapy. It does not seem advisable to replace RT by further chemotherapy because this might add chemotherapy-related morbidity. This issue is at present under investigation in the current GPOH HD 95 protocol [84].

Another future option is to reduce radiotherapy further in terms of dose (10–15 Gy) and volume (local involvement only). In particular radiotherapy targeted to the involved nodes only as detected by modern sectional imaging which has been successfully pioneered in the HD 90-trial [33] is a challenging approach in terms of reduction of treated radiation volume without jeopardising excellent treatment results.

The use of new non-cytotoxic biological drugs in this favourable subgroup is currently not probable at least in the near future.

INTERMEDIATE DISEASE (LOCALISED DISEASE WITH ADVERSE PROGNOSTIC FACTORS)

Adverse prognostic factors in paediatric HD

Compared with the extensive experience in adult HD few data are available in paediatric HD on the prognostic risk factors which can classify unfavourable localised disease. This seems to be a consequence of the excellent treatment results (EFS about 90%) in particular after combination treatment—which has become almost routine practice within the last two decades in paediatric HD. For obvious reasons it is difficult to detect prognostic relevant parameters in a rare disease with an excellent outcome. Adverse prognostic parameters have been mainly derived from experience in adult HD after high-dose EF RT alone where they have been successfully used for the assignment to different treatment groups in particular for EF RT alone in localised favourable disease and combination treatment in localised unfavourable disease [85]. These prognostic factors have been above all stage and B-symptoms then width of mediastinal mass and bulk of disease number of involved lymph node regions splenic involvement erythrocyte sedimentation rate histology primary infradiaphragmatic disease and anaemia. On the whole these risk factors have never been widely verified in the paediatric population with the exception of stage B symptoms and to some extent mediastinal mass and bulk of disease [77 86 87].

Risk adapted treatment based on stage

Treatment strategies in the paediatric population have been mainly tailored to stage. Widely accepted are the low and high risk groups: early nodal disease classified as stage IA/IIA and advanced disseminated disease classified as stage IVA/B. This is reflected in the dichotomy of treatment strategies with for the majority of institutions and cooperative groups only two alternatives one for 'early' and one for 'advanced' disease. There is no consensus however on how

to classify and how to treat children in an intermediate risk group who are considered to be between the low and high risk groups as for example children with (compare [29] for the suffices): B-symptoms (CSIB/IIB/IIIB) bulky disease ($CSII_x$ $CSIII_x$) 3 or more involved lymph node regions (e.g. CS II_3/ $CSII_4$/$CSII_5$) infradiaphragmatic involvement (CSIII CS III_1/III_2) splenic involvement ($IIIA_S$) any additional extranodal disease (e.g. II_E. or III_E). These differences are not trivial but have so far been poorly represented in the assignment to different risk or treatment groups.

The Italian and the German–Austrian cooperative groups have consequently tried to define an intermediate risk and treatment group which has been based in particular on Ann Arbor stage (stage IIIA) on the presence of B-symptoms (IIB) and on extranodal involvement (I_EA I_EB II_EA); in the Italian group bulky mediastinal disease and spleen involvement have been added. Both the Italian and the German–Austrian cooperative groups have so far been able to present excellent treatment results (EFS between 81 and 94%) with risk adapted treatment strategies including more chemotherapy (4 versus 2 cycles (DAL-GPOH) or 6 versus 3 cycles (AIEOP)) and more radiotherapy in terms of dose (GPOH) or volume (AIEOP) in intermediate disease compared with early disease [46]. In the British study the chemotherapy alone regimen was supplemented with local RT in case of bulky mediastinal disease.

One of the major challenges of future treatment strategies will be the better definition of risk groups in order to better tailor treatment strategies of different intensity to the individual risk.

ADVANCED DISEASE STAGE IIIB-IV

Results in advanced (unfavourable) disease reported so far from single institutions have been significantly worse than in early (favourable) disease. These results have been difficult to interpret because of rather small patient numbers and different treatment regimens: in the Stanford Toronto and Boston studies low patient numbers with stage IV disease were treated in different time periods from about 1969–1992 resulting in a 7–10 year OS of 65–85% and DFS of 60–69% [44 50 88 89]. The majority of these patients were treated with MOPP regimen (six cycles)—except the late series from Stanford with 6 alternating MOPP/ABVD cycles [89]—and low-dose RT (15–30 Gy (Stanford/Toronto)). IF RT was used in the Stanford; EF RT in the Toronto and Boston series.

Advanced disease has only been studied recently in significant patient numbers by large cooperative groups in particular within five German–Austrian DAL/GPOH trials (HD 78/82/85/87/90) one SIOP trial (SIOP IV) and three CCSG/POG trials (521-P/8426 8725). The DAL/GPOH strategy was based since 1982 on initial chemotherapy (2×OPPA plus 4×COPP) and IF nodal and extranodal low-dose RT (12–25 Gy) in patients with stage IIEB IIIEA IIIB IIIEB IV. These consecutive prospective clinical trials from 1982–1995 accruing 300 children resulted in OS of 83–100% and EFS of 83–91% except in HD85 with 46% EFS/ 100% OS without procarbazine [68].

The GPOH/SIOP trial (SIOP IV) based on an identical approach to the DAL/GPOH strategy produced similar OS of 95% and EFS of 79% at 4 years in 97 stage IV patients [90].

The CCSG/POG strategy was based on very intensive chemotherapy in combination with low-dose RT. The first trial started with 12 cycles of ABVD and regional RT (CCSG 521-P 1984–1985 [51]). The POG trial 8426 investigated 4×MOPP combined with 4×ABVD followed by low-dose RT (total nodal irradiation (TNI) subtotal nodal irradiation (STNI) (21 Gy) plus extranodal RT) leading to 3-year EFS of 77% and OS of 91% in 62 patients [47]. The latest POG randomised trial (1987–1992 8725) examined the additional value of radiotherapy with initial 4×MOPP combined with 4×ABVD followed or not by low-dose RT (TNI STNI plus extranodal RT). The overall results in 179 pts were 92% for OS and 79% for EFS at 5 years with no significant difference between the two arms on an 'intent to treat' basis [91] (compare also the criticism of Donaldson [92]).

The therapeutic results of these different trial traditions for advanced disease are excellent and seem to be comparable. Nevertheless the potential long-term toxicity of the different regimens have to be considered. The DAL/GPOH strategy for example seems to carry much less risk of adverse late effects than is to be expected from the POG regimen. This applies for chemotherapy (leukamogenic effects and induction of sterility by mustargen pulmonary toxicity by bleomycin) for radiotherapy (larger radiation portals if treated) and intestinal morbidity and immunosuppression caused by laparotomy and splenectomy in a significant number of patients.

Based on these favourable results it seems to be worthwhile even for advanced disease to tailor further treatment intensity to the individual risk of different patient groups. This applies both for chemotherapy and radiotherapy.

Response to chemotherapy may be among others one of the important prognostic parameters [91]. This issue is being studied at present in the current GPOH-HD 95 protocol. Patients with a complete response (CR) at the end of chemotherapy receive no further radiotherapy treatment. According to the data collected so far in this protocol 18/110 patients achieved a CR at the end of chemotherapy and only 1 relapsed resulting in an EFS for this group of 94 versus 86% for the 92 patients without CR [84].

SALVAGE TREATMENT FOR RELAPSED AND REFRACTORY DISEASE

The experience with salvage treatment in paediatric HD is limited due to the low number of treatment failures. Nevertheless the overall results of salvage treatment approaches the range of results from primary treatment [93].

The standard of primary treatment has evolved to be induction chemotherapy (two to eight cycles dependant on the risk group) in combination with low-dose IF radiotherapy. After such risk adapted treatment in localised disease (two to four cycles of chemotherapy and low-dose IF RT) there is consequently—in case of first relapse—again the option of an effective combination treatment with chemotherapy and IF/EF radiotherapy. This is also true although to less extent in case of first relapses after advanced disease.

Often proposed as salvage treatments are alternative chemotherapeutic agents to those used in primary treatment: e.g. ifosfamide etoposide CCNU prednimustine. Nevertheless highly effective agents in HD such as anthracylines or alkylating agents should in any case be reconsidered within a salvage regimen. From the German–Austrian trial experience an effective salvage treatment consisting of IEP (ifosfamide etoposide prednisone) in combination with ABVD/COPP after OPPA/COPP for primary treatment resulted in the

majority of patients in a second continuous complete remission [93 94]. Thus cure can be achieved in a significant number of patients based on such conventional treatment schedules with only moderate risks of long-term adverse side-effects.

There seems to be little indication for high-dose chemotherapy with stem cell support in case of first relapse after risk adapted primary treatment due to the good results of conventional salvage treatment on the one hand and the significant toxicities of high-dose chemotherapy on the other hand. In case of insufficient response an increase in conventional chemotherapy and local radiotherapy should be considered as the first choice high-dose chemotherapy only as the second.

The few patients who progress during primary treatment (1–2%) and who experience an early second relapse have a relatively poor prognosis. In this patient group with refractory disease high-dose chemotherapy with ABMT (autologous bone marrow transplantation) similar to the regimen used in adult treatment is to be considered for salvage treatment [95] and results in progression free survival of approximately 40% [96]. A precondition for an effective high-dose chemotherapy programme however is a significant or a complete remission which has to be achieved first by induction chemotherapy preferably in combination with IF radiotherapy.

There have been few publications on prognostic parameters in relapsed paediatric patients. Based on some clinical evidence it may nevertheless be assumed that—similar to adult HD—good prognostic parameters in relapsed children are a long duration of first remission and relapses in nodal (not irradiated) sites whilst poor prognostic parameters are a short initial CR relapses in extranodal sites and stage IV at diagnosis.

FUTURE

The aim of further improvement of treatment strategies will be mainly to avoid or minimise adverse side-effects (chronic medical as well as psychosocial) which may be caused by diagnostic or therapeutic means and at the same time not to jeopardise substantially the excellent treatment results which have been achieved so far. In paediatric HD this main goal will be achieved through further reduction of morbidity-associated treatment which applies both for radiotherapy and chemotherapy. In addition invasive staging procedures associated with morbidity will be abandoned and hopefully replaced by more accurate non-invasive procedures. In order to reach the goal of an appropriate 'cost: benefit ratio' in terms of achieving cure and avoiding adverse effects it will be necessary to improve the tailoring of different treatment strategies in regard to their intensity to the different subsets of risk groups which need better definition. In addition it may be of some advantage if new therapeutic approaches can be introduced which are less toxic than the present ones. However in near future no direct translation of the insights gained into molecular pathophysiology of HD into effective clinical treatment strategies seems likely although this field represents one of the most challenging issues for future basic and clinical research.

1. Glaser SL Jarrett RF. The epidemiology of Hodgkin's disease. In Diehl V ed. *Hodgkin's Disease Baillière's Clinical Haematology Vol.* 9 No. 3. London Baillère Tindall 1996 401–417.
2. Jarrett AF Armstrong AA Alexander E. Epidemiology of EBV and Hodgkin's lymphoma. *Ann Oncol* 1996 **7** 5–10.
3. Hodgkin T. On some morbid appearances of the absorbant glands and spleen. *Med Chir Trans* 1832 **17** 68–114.
4. Reed DM. On the pathological changes in Hodgkin's disease with special reference to its relation to tuberculosis. *Johns Hopkins Hosp Rev* 1902 **10** 133–196.
5. Sternberg C. Über die eigenartige unter dem bilde der pseudoleukämie verlaufende tuberculose des lymphatischen apparates. *Z Heilk* 1898 **19** 21–90.
6. Lukes R Butler J Hicks E. Natural history of Hodgkin's disease as related to its pathological picture. *Cancer* 1966 **19** 317–344.
7. Harris NL Jaffe ES Stein H *et al*. A revised European–American classification of lymphoid neoplasms: a proposal from the International Lympoma Study Group. *Blood* 1994 **84** 1361–1392.
8. Bennett MH MacLennan KA Easterling MJ Vaughan Hudson B Vaughan Hudson G Jelliffe AM. Analysis of histological subtypes in Hodgkin's disease in relation to prognosis and survival. In Quaglino D Hayhoe FGJ eds. *The Cytobiology of Leukaemias and Lymphomas*. New York Raven Press 1985 15.
9. Braeuninger A Kuppers R Strickler JG Wacker HH Rajewsky K Hansmann ML. Hodgkin and Reed–Sternberg cells in lymphocyte predominant Hodgkin disease represent clonal populations of germinal center-derived tumour B cells. *Proc Natl Acad Sci USA* 1997 **94** 9337–9342.
10. Pan LX Diss TC Peng HZ Norton AJ Isaacson PG. Nodular lymphocyte predominance Hodgkin's disease: a monoclonal or polyclonal B-cell disorder? *Blood* 1996 **87** 2428–2434.
11. Kamel OW Chang PP Hsu FJ Dolezal MV Warnke RA van de Rijn M. Clonal VDJ recombination of the immunoglobulin heavy chain gene by PCR in classical Hodgkin's disease. *Am J Clin Pathol* 1995 **104** 419–423.
12. Manzanal AI Santon A Acevedo A Aguilera B Oliva H Bellas C. Molecular analysis of the IgH gene in 212 cases of Hodgkin's disease: correlation of IgH clonality with the histologic and the immunocytochemical features. *Mod Pathol* 1997 **10** 679–685.
13. Delabie J Tierens A Gavriil T Wu G Weisenburger DD Chan WC. Phenotype genotype and clonality of Reed–Sternberg cells in nodular sclerosis Hodgkin's disease: results of a single cell study. *Br J Haematol* 1996 **94** 198–205.
14. Kanzler H Kuppers R Hansmann ML Rajewsky K. Hodgkin Reed–Sternberg cells in Hodgkin's disease represent the outgrowth of a dominant tumor clone derived from (crippled) germinal center B cells. *J Exp Med* 1996 **184** 1495–1505.
15. Papadimitriou CS Bai MK Kotsianti AJ Costopoulos JS Hytiroglou P. Phenotype of Hodgkin and Sternberg–Reed cells and expression of CD57 (LEU7) antigen. *Leuk Lymphoma* 1995 **20** 125–130.
16. Gupta RK Lister TA Bodmer JG. The t(14;18) chromosomal translocation and Bcl-2 protein expression in Hodgkin's disease. *Leukemia* 1994 **8** 1337–1341.
17. Hsu SM Hsu PL. The nature of Reed–Sternberg cells: phenotype genotype and other properties. *Crit Rev Oncog* 1994 **5** 213–245.
18. Bargou RC Leng C Krappmann D *et al*. High-level nuclear NF-kappa B and Oct2 is a common feature of cultured Hodgkin/Reed–Sternberg cell. *Blood* 1996 **87** 4340–4347.
19. Bargou RC Emmerich F Krappmann D *et al*. Constitutive nuclear factor-kappaB-RelA activation is required for proliferation and survival of Hodgkin's disease tumor cells. *J Clin Invest* 1997 **100** 2961–2969.
20. Herbst N Niedobitek G. Epstein–Barr virus and Hodgkin's disease. *Int J Clin Lab Res* 1994 **23** 13–18.
21. Jiwa NM Oudejans JJ Bai MC *et al*. Expression of bcl-2 protein and transcription of the Epstein–Barr virus bcl-2 homologue BHRF-1 in Hodgkin's disease: implications for different pathogenic mechanisms (see comments). *Histopathology* 1995 **26** 547–553.
22. Messineo C Jamerson MH Hunter E Braziel R Bagg A Irving SG Cossmann J. Gene expression by single Reed–Sternberg cells: pathways of apoptosis and activation. *Blood* 1998 **91** 2443–2451.
23. Dewey WC Clifton CL Meyn RE. Radiation induced apoptosis: relevance to radiotherapy. *Int J Radiat Oncol Biol Phys* 1995 **33** 781–790.
24. Carbone PP Kaplan HS Musshoff K *et al*. Report of the committe on Hodgkin's disease staging classification. *Cancer Research* 1971 **31** 1860–1861.
25. Mendenhall NP Cantor AB Williams JL *et al*. With modern imaging techniques is staging laparotomy necessary in pediatric

Hodgkin's disease? A Pediatric Oncology Group Study. *J Clin Oncol* 1993 **11** 2218–2225.
26. Baker LL Parker BR Donaldson SS. Staging of Hodgkin Disease in children: comparison of CT and lymphography with laparotomy. *AJR* 1990 **154** 1251–1255.
27. Hays DM Fryer CJ Pringle KC *et al*. An evaluation of abdominal staging procedures performed in pediatric patients with advanced Hodgkin's disease: a report from the Childrens Cancer Study Group. *J Ped Surg* 1992 **27** 1175–1180.
28. Schellong G Lietzke S Strauch S Kuhne B Schneider B. Bedeutung sonographischer computertomographischer und klinischer befunde für die erkennung eines abdominalbefalls beim morbus Hodgkin im kindesalter—eine retrospektive statistische analyse bei 145 patienten der therapiestudie DAL-HD-82. *Klin Pädiat* 1986 **198** 147–154.
29. Lister TA Crowther D Sutcliffe SB *et al*. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds Meeting. *J Clin Oncol* 1989 **7** 1630–1636.
30. Carde P. Diagnostic procedures. In Diehl V ed. *Hodgkin's Disease. Baillière's Clinical Haematology Vol* 9 No. 3. London Baillère Tindall 1996 479–501.
31. Skillings JR Bramwell V Nicholson RL *et al*. A prospective study of magnetic resonance imaging in lymphoma staging. *Cancer* 1991 **67** 1838–1843.
32. Hagemeister FB Fesus SM Lamki LM Haynie TP. Role of the gallium scan in Hodgkin's disease. *Cancer* 1990 **65** 1090–1096.
33. Pötter R Dieckmann K Hofmann J *et al*. Individualisation of radiation fields based on modern sectional imaging within combination treatment of pediatric Hodgkin's Disease (HD): evaluation of 386 patients from the German-Austrian multicenter trial (HD-90). *Int J Radiat Oncol Biol Phys* 1995 **32**(Supp1.) Abstract 81.
34. Pusey WA. Cases of sarcoma and of Hodgkin's Disease treated by exposure to X-Rays—a preliminary report. *JAMA* 1902 **38** 166–169.
35. Holzknecht G. Drüsentumoren. *Wiener klinische Wochenschrift*. 1905 418.
36. Gilbert R. Radiotherapy in Hodgkin's Disease (malignant granulomatosis). Anatomic and clinical foundations; governing principles; results. *Am J Roent and Radium Therapy* 1939 **41** 198–241.
37. Peters V. A Study of Survivals in Hodgkin's Disease treated radiologically. *Am J Roent and Radium Therapy* 1950 **63** 299–311.
38. Peters V. Prophylactic treatment of adjacent areas in Hodgkin's disease. *Cancer Research* 1966 **26** 1232–1243.
39. Kaplan HS. The radical radiotherapy of regionally localized Hodgkin's disease. *Radiology* 1962 **78** 553–561.
40. DeVita VT Serpick A Carbone PP. Combination therapy in the treatment of advanced HD. *Ann Inter Med* 1970 **73** 881–895.
41. Bonadonna G Zucali R Monfardini S *et al*. Combination chemotherapy of Hodgkin's Disease with adriamycin bleomycin vinblastine and imidazole carboxamide versus MOPP. *Cancer* 1975 **36** 252–259.
42. Donaldson SS Glatstein E Rosenberg SA *et al*. Pediatric Hodgkin's disease: II. Results of therapy. *Cancer* 1976 **37** 2436–2447.
43. Probert JC Parker BR. The effects of radiation therapy on bone growth. *Radiology* 1975 **114** 115–162.
44. Jenkin D Doyle J Berry M *et al*. Hodgkin's disease in children: treatment with MOPP and low-dose extended field irradiation without laparotomoy. Late results and toxicity. *Med Ped Oncol* 1990 **18** 265–272.
45. Jenkin RDT Chan H Freedman M *et al*. Hodgkin's disease in children: treatment results with MOPP and low dose extended-field irradiation. *Cancer Treat Rep* 1982 **66** 439–459.
46. Vecchi V Pileri St Burnelli R *et al*. Treatment of pediatric Hodgkin disease tailored to stage mediastinal mass and age. *Cancer* 1993 **72** 2049–2057.
47. Weiner MA Leventhal BG Marcus R *et al*. Intensive chemotherapy and low-dose radiotherapy for the treatment of advanced-stage Hodgkin's disease in pediatric patients: a Pediatric Oncology Group Study. *J Clin Oncol* 1991 **9** 1591–1598.
48. Breu H Schellong G Grosch-Wörner I *et al*. Abgestufte chemotherapie und reduzierte strahlendosis beim morbus Hodgkin im kindesalter—ein bericht über 170 patienten der kooperativen therapiestudie HD 78. *Klin Pädiat* 1982 **194** 233–241.
49. Fossati-Bellani F Gasparini M Kenda A *et al*. Limited field and low-dose radiotherapy + ABVD chemotherapy for childhood Hodgkin's disease. Abstract XVIIth SIOP Meeting Venice 1985 323–324.
50. Donaldson SS Link MP. Combined modality treatment with low-dose radiation and MOPP chemotherapy for children with Hodgkin's disease. *J Clin Oncol* 1987 **5** 742–749.
51. Fryer CJ Hutchinson JR Krailo M *et al*. Efficacy and toxicity of 12 courses of ABVD chemotherapy followed by low-dose regional radiation in advanced Hodgkin's disease in children: a report from the Childrens Cancer Study Group. *J Clin Oncol* 1990 **12** 1971–1980.
52. Gehan EA Sullivan MP Fuller LM *et al*. The intergroup Hodgkin's Disease in Children. *Cancer* 1990 **65** 1429–1437.
53. Oberlin O Boilletot A Leverger G Sarrazin D Lemerle J. Clinical staging primary chemotherapy and involved field radiotherapy in childhood Hodgkin's disease. *Eur Paed Haematol Oncol* 1985 **2** 65–70.
54. Schellong G Brämswig J Ludwig R *et al*. Kombinierte behandlungsstrategie bei über 200 kindern mit morbus Hodgkin: abgestufte chemotherapie involved-field-bestrahlung mit erniedrigten dosen und selektive splenektomie. *Klin Pädiat* 1986 **198** 137–146.
55. Behrendt H van Bunningen B van Leeuwen EF. Treatment of HD in children without radiotherapy. *Cancer* 1987 **59** 1870–1873.
56. Radford M Barrett A Martin J Cotterill S. Treatment of Hodgkin's disease in children. Study HDI. *Med Ped Oncol* 1991 **19** 400.
57. Barrett A Crennan E Barnes J *et al*. Treatment of clinical stage I Hodgkin's disease by local radiation therapy alone. *Cancer* 1990 **66** 670–674.
58. Jereb B Tan C Bretsky S He SQ Exelby P. Involved field (IF) irradiation with or without chemotherapy in the management of children with Hodgkin's disease. *Med Ped Oncol* 1984 **12** 325–332.
59. Meadows AT Obringer A Marrero O *et al*. Second malignant neoplasms following childhood Hodgkin's disease: treatment and splenectomy as risk factors. *Med Ped Oncol* 1989 **17** 477–484.
60. Brämswig JH Heimes U Heiermann E *et al*. The effects of different cumulative doses of chemotherapy on testicular function. *Cancer* 1990 **65** 1298–1302.
61. Donaldson SS Kaplan HS. Complications of treatment of Hodgkin's disease in children. *Cancer Treat Rep* 1982 **66** 977–989.
62. Hancock SL Tucker MA Hoppe RT. Breast cancer after treatment of Hodgkin's disease. *J Natl Cancer Inst* 1993 **85** 25–31.
63. Bhatia S Robison LL Oberlin O *et al*. Breast cancer and other second neoplasms after childhood Hodgkin's disease. *N Engl J Med* 1996 **21** 745–751.
64. Hancock SL Tucker MA Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. *JAMA* 1993 **270** 1949–1955.
65. Mefferd JM Donaldson SS Link MP. Pediatric Hodgkin's disease. Pulmonary cardiac and thyroid function following combined modality therapy. *Int J Radiat Oncol Biol Phys* 1989 **16** 679–685.
66. Constine LS Donaldson SS McDougall R Cox RS Links MP Kaplan HS. Thyroid dysfuncion after radiotherapy in children with Hodgkin's disease. *Cancer* 1984 **53** 878–883.
67. Hudson MM Poquette C Luo X *et al*. Fatal late events after treatment for pediatric Hodgkin's disease. *Med Pediatr Oncol* 1997 **29** Abstract O-63.
68. Schellong G. Treatment of children and adolescents with Hodgkin's Disease: the experience of the German–Austrian Paediatric Study Group. In Diehl V ed. *Hodgkin's Disease. Baillière's Clinical Haematology Vol* 9 No. 3. London Baillère Tindall 1996 619–634.
69. Jenkin RDT Brown TC Peters MV Sonley MJ. Hodgkin's Disease in Children. A retrospective analysis: 1958–73. *Cancer* 1975 **35** 979–990.

70. Dionet C Oberlin O Habrand JL *et al*. Initial chemotherapy and low-dose radiation in limited fields in childhood Hodgkin's disease: results of a joint cooperative study by The French Society of Pediatric Oncology (SFOP) and Hôpital Saint-Louis Paris. *Int J Radiat Oncol Biol Phys* 1988 **15** 341–346.
71. Brämswig JH Hörnig-Franz I Riepenhausen M Schellong G. The challenge of pediatric Hodgkin's disease—where is the balance between cure and long-term toxicity? *Leukemia and Lymphoma* 1990 **3** 183–193.
72. Oberlin O Leverger G Pacquement H *et al*. Low-dose radiation therapy and reduced chemotherapy in childhood Hodgkin's disease: the experience of the French Society of Pediatric Oncology. *J Clin Oncol* 1992 **10** 1602–1608.
73. Schellong G Riepenhausen M Hörnig-Franz I *et al*. Morbus Hodgkin bei kindern: kombinierte behandlungsstrategie mit involved-field-radiotherapie für die studien IA IB und IIA. *Klin Onkol* 1994 **94/95** 62–66.
74. O'Brien MER Pinkterton CR Kingston J *et al*. "VEEP" in children with Hodgkin's disease—a regimen to decrease late sequelae. *Br J Cancer* 1992 **65** 756–760.
75. Landmann-Parker J Oberlin O Pacquement Y *et al*. Localized childhood Hodgkin's disease: response adapted treatment by chemotherapy (CT) regimen with VP16 bleomycin vinblastin and prednisone (VBVP) before low-dose radiation therapy (RT). Results of the study by the French Society of Pediatric Oncology (SFOP). *Med Ped Oncol* 1997 **29** Abstract O-135.
76. Kung FH Behm FG Falletta J *et al*. Reduced dose chemoradiotherapy in early stage Hodgkin's disease of childhood. *Med Ped Oncol* 1993 **21** Abstract 58.
77. Dieckmann K Pötter R Heinzl H. Influence of bulky disease on local control in the German–Austrian Pediatric Hodgkin Study HD-90. *Med Ped Oncol* 1997 **29** Abstract O-136.
78. Willmann KY Cox RS Donaldson SS. Radiation induced height impairment in pediatric Hodgkin's disease. *Int J Radiat Oncol Biol Phys* 1993 **28** 85–94.
79. Behrendt H Brinkhuis M Van Leeuwen EF. Treatment of childhood Hodgkin's disease with ABVD without radiotherapy. *Med Pediatr Oncol* 1996 **26** 244–248.
80. Martin J Radford M. Current practice in Hodgkins Disease. The United Kingdom Children's Cancer Study Group. In Kamps WA Humphrey GB Poppema S eds. *Hodgkin's Disease in Children: Controversies and Current Practice*. Boston Kluwer 1989 263–275.
81. Ekert H Waters KD Smith PJ *et al*. Treatment with MOPP or ChIVPP chemotherapy only for all stages of childhood Hodgkin's disease. *J Clin Oncol* 1988 **6** 1845–1850.
82. Chauvenet A Gieser P Kung F *et al*. Pediatric Oncology Group (POG) Hodgkin's disease studies: experience with 630 children/adolescents treated with combined modality therapies from 1984–1993. *Leukemia & Lymphoma* 1998 **29** Abstract 0–7.
83. Leventhal BG. Management of Stage I–II Hodgkin's disease in children. *J Clin Oncol* 1990 **8** 1123–1124.
84. Dörffel W Albrecht M Lüders H *et al*. Multinationale therapiestudie für den morbus Hodgkin bei kindern und jugendlichen GPOH-HD 95. Zwischenbericht nach 2 1/2 jahren. *Klin Pädiatrie* 1998 **210** 212–219.
85. Tesch H Sieber M Diehl V. Treatment of intermediate stages. In Diehl V ed. *Hodgkin's Disease. Baillière's Clinical Haematology Vol.* 9 No. 3. London Baillère Tindall 1996 543–551.
86. Maity A Goldwein JW Lange B D'Angio G. Comparison of high-dose and low-dose radiation with and without chemotherapy for children with Hodgkin's disease: an analysis of the experience at the Children's Hospital of Philadelphia and the Hospital of the University of Pennsylvania. *J Clin Oncol* 1992 **10** 929–993.
87. Rostock RA Siegelmann SS Lenhard RE Wharam MD Order SE. Thoracic CT scanning for mediastinal Hodgkin's disease; results and therapeutic implications. *Int J Radiat Oncol Biol Phys* 1983 **9** 1451–1457.
88. Bader SB Weinstein H Mauch P Silver B Tarbell NJ. Pediatric stage IV Hodgin disease long-term survival. *Cancer* 1993 **72** 249–257.
89. Hunger SP Link MP Donaldson SS. ABVD/MOPP and low-dose involved-field radiotherapy in pediatric Hodgkin's disease: the Stanford experience. *J Clin Oncol* 1994 **12** 2160–2166.
90. Oberlin O Hörnig-Franz I Pacquement H *et al*. for the SIOP Hodgkin's Disease Study Group. Stage IV Hodgkin's disease: results of the study of the International Society of Paediatric Oncology. *Abstract Fifth International Conference on Malignant Lymphoma*. Lugano 1993 **71**.
91. Weiner MA Leventhal B Brecher ML *et al*. Randomized study of intensive MOPP-ABVD with or without low-dose total-nodal radiation therapy in the treatment of stages IIB IIIA2 IIIB and IV Hodgkin's disease in pediatric patients: a Pediatric Oncology Group Study. *J Clin Oncol* 1997 **15** 2769–2779.
92. Donaldson SS Lamborn KR. Radiation in pediatric Hodgkin's disease. *J Clin Oncol* 1998 **16** 391–394.
93. Hörnig-Franz I Schellong G Riepenhausen M Pötter R. Salvage therapy in Hodgkin's disease incorporating etoposide/ifosfamide/prednisone (IEP). A multi-center trial of the Geman Pediatric Study Group DAL-HD. *Med Ped Oncol* 1992 **20** 441 (P198).
94. Schellong G Hörnig I Brämswig J *et al*. Zur bedeutung des procarbazins in der chemotherapie des morbus Hodgkin—ein bericht der kooperativen therapiestudie DAL-HD-85. *Klin Pädiatr* 1988 **200** 205–213.
95. Gause BL Longo DL. Treatment of relapsed Hodgkin's disease. In Diehl V ed. *Hodgkin's Disease. Baillière's Clinical Haematology Vol* 9 No. 3 401-17. London Baillère Tindall 1996 559–572.
96. Williams CD Goldstone AH Pearce R *et al*. Autologous bone marrow transplantation for paediatric Hodgkin's disease: a case-matched comparison with adult patients by the European Bone Marrow Transplant Group Lymphoma Registry. *J Clin Oncol* 1993 **11** 2242–2249.

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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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