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Treatment of Early Stage Hodgkin Lymphoma

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1. Introduction

Hodgkin lymphoma (HL) is an uncommon lymphoid malignancy which accounts for about 0.5% to 1% of all cancers. In 2010, an estimated 8,490 new cases and 1,320 deaths will occur in the United States (Jemal, Siegel, Xu, *et al*, 2010). HL incidence appears to be stable over the past few decades, in contrast to the incompletely understood continued increase in frequency of non-Hodgkin lymphomas. HL has a bimodal incidence with most patients diagnosed in the third decade, followed by another peak in adults aged 55 years or older. There has been correlation between incidence of certain histologic subtypes of HL and age and sex; for example, nodular-sclerosis HL is more common in women and young adults in contrast to mixed cellularity HL which is more common in men and lymphocyte-rich HL which is more common in older males (Correa, O'Connor, Berard, *et al*, 1973).

The cause of HL remains unknown, but there has been some progress in identifying risk factors in development of HL. Factors associated with HL include genetic predisposition (increased incidence in certain ethnic populations such as Jews and in first degree relatives such as siblings, twins and children), viral exposures, and immune suppression (Bernard, Cartwright, Darwin, *et al*, 1987; Glaser & Jarrett, 1996; Lynch, Marcus & Lynch, 1992; Mack, Cozen, Shibata, *et al*, 1995). Epstein-Bar virus (EBV) has been implicated in the etiology of HL based on epidemiological and serologic studies (Weiss, Strickler, Warnke, *et al*, 1987), as well as by the detection of the EBV genome in tumor specimens of about half of HL nodes. Moreover, HIV-infected patients have been noted in many studies to have a significantly increased risk of HL with the majority of patients presenting with advanced stages, having extranodal involvement and unfavorable histological subtypes, and associated with a poorer outcome after initial therapy (Levy, Colonna, Tourani, *et al*, 1995; Tirelli, Errante, Dolcetti, *et al*, 1995).

The past few decades have seen major advances in treatment of HL using both, radiation therapy (RT) and chemotherapy. With advances in combination chemotherapy regimens and RT techniques over the past four-five decades, HL has changed from an incurable disease to one with the best survival rates to date among other cancers. HL is currently curable in 85% to 95% of cases, depending on disease stage at time of diagnosis and other risk factors (Diehl, 2007). In the H8-F trial, Ferme' *et al*. reported a 10-year overall survival (OS) estimates of 97% in early-stage disease (Ferme, Eghbali, Meerwaldt, *et al*, 2007). In fact, cure rates for HL have increased so extensively that the overriding treatment considerations often relate to long-term toxicity, especially for patients with early- or intermediate-stage disease (Hoppe, Advani, Ai, *et al*, 2011). For advanced disease, clinical trials still emphasize improvement in cure rates, but

the potential long-term effect of treatments remain an important consideration as well. New innovative treatment strategies are clearly needed for the refractory and recurrent disease, as the cure rates in these patients are still low, especially for those who relapse after autologous stem cell transplantation (ASCT).

In this chapter, we will discuss briefly the initial workup and staging at the time of diagnosis with brief review of the role of positron emission tomography (PET) scan in HL. We will then go through the revised response criteria, followed by a thorough review for the management of early stage HL including the various definitions of the favorable and unfavorable risk groups as determined by major study groups. Management of HL in specific populations such as the NLPHL, elderly, and pregnant patients will be reviewed in this chapter as well.

2. Diagnosis/staging

Hodgkin lymphomas are defined as lymphomas containing one of the characteristic types of Reed-Stenberg (RS) cells in a background of nonneoplastic cells. Based on the morphology and immunophenotype of the RS cells and the composition of the cellular background, the WHO classification system published in 2001 divided HL into two disease entities: classical HL (cHL) which accounts for 95% and nodular lymphocyte-predominant HL (NLPHL) which accounts for 5% of all HL cases. cHL is further divided into 4 subtypes: nodular sclerosis (grades I or II), mixed cellularity, lymphocyte depleted, and lymphocyte-rich cHL (Diehl V, 2005b; Harris, Jaffe, Diebold, *et al*, 1999; Jaffe ES, 2001). cHL and NLPHL share the same diagnostic workup, though they have different natural history and distinctive morphologic and immunophenotypic features (**Table 1**), and ultimately different approach of therapy.

	Classic HL	NLPHL
Pattern	Diffuse, interfollicular, nodular	Nodular, at least in part
Tumor cells	Diagnostic RS cells; mononuclear or lacunar cells	L&H or popcorn cells
Background	Lymphocytes (T cells > B cells), histiocytes, eosinophils, plasma cells	Lymphocytes (B cells > T cells), histiocytes
Fibrosis	Common	Rare
CD15, CD30	+	-
CD45 & CD57 + T cells	-	+
EMA	-	+
CD20	±	+
EBV (in RS cells)	+ (~50%)	-
Nuclear bcl-6 protein	-	+
Ig genes (single-cell PCR)	Rearranged, clonal, mutated, "crippled"	Rearranged, clonal, mutated, ongoing

EBV, Epstein-Barr virus; EMA, epithelial membrane antigen; Ig, immunoglobulin; L&H, lymphocytes and histiocytes; PCR, polymerase chain reaction; RS, Reed-Sternberg.

Adapted from De Vita et al. Cancer. Principles & practice of oncology. Philadelphia: Lippincott Williams and Wilkins; 2005.

Table 1. Morphologic and Immunophenotypic Features of cHL Compared to NLPHL.

Diagnosis of HL should always be established by a tissue biopsy; though a core needle biopsy may be adequate, an excisional lymph node biopsy is preferred and highly recommended. FNA alone is generally insufficient for the evaluation of architecture and for immunophenotyping, and should be avoided (Caraway, 2005; Hehn, Grogan & Miller, 2004; Meda, Buss, Woodruff, *et al*, 2000). Rarely, multiple LN biopsies may be necessary for the diagnosis, as the cytokines associated with HL can produce reactive hyperplastic changes in adjacent lymph nodes (Ansell & Armitage, 2006).

Though it might not be necessary for typical cases of cHL, immunohistochemistry staining is recommended for accurate diagnosis of any case of HL with atypical features and many cases of NLPHL. cHL is usually positive for CD15 and CD30, but negative for CD3 and CD45. NLPHL usually stains positive for CD45 and CD20, but negative for CD15, and rarely expresses CD30 (Hoppe, Advani, Ai, *et al*, 2011)(Table 1). Also, in contrast to NLPHL, the RS cells of cHL lack the nuclear bcl-6 protein associated with follicle center B cells (Falini B, 1995).

Staging of HL is based on the Ann Arbor staging system that was developed in 1971 (Carbone, Kaplan, Musshoff, *et al*, 1971) and further modified in 1989 through a consensus meeting held in Cotswolds, England (Lister, Crowther, Sutcliffe, *et al*, 1989) (Table 2).

Stage	Definition/Disease Involvement
I	Involvement of a single lymph node region (I) or a single extralymphatic site (IE).
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of only one extranodal organ or site and of ≥ 1 lymph node regions on the same side of the diaphragm (IIE).
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (III _s) or by localized involvement of an extranodal organ or site (IIIE) or both (III _s +E).
IV	Diffuse involvement of one or more extranodal organs or sites, with or without associated lymph node involvement.
Each Stage may be subdivided into:	
A	No symptoms.
B	General symptoms include any of the following: fever (unexplained temperatures $>38^{\circ}\text{C}$ over the preceding one month), drenching night sweats, unexplained loss of $>10\%$ body weight within the preceding 6 months.
X	Bulky disease which is defined by any nodal mass with a maximal dimension ≥ 10 cm or a mediastinal mass exceeding one third of the widest transverse transthoracic diameter measured on a standard PA chest radiography.
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site.

Table 2. Modified Ann Arbor Staging System for HL.

Initial staging evaluation starts with a detailed history and physical examination. History should focus on the presence or absence of systemic B symptoms (unexplained fevers $>38^{\circ}\text{C}$ within the preceding month, drenching night sweats, and unexplained weight loss of $>10\%$

body weight within the preceding 6 months), performance status, pruritus, alcohol intolerance, and any history of prior cancers and treatments received (chemotherapy and/or RT). Of notice, cHL compared to NLPHL, presents more commonly with B symptoms (about one third of patients with HL), pruritus, alcohol-induced pain, and extra nodal disease involvement. Physical examination should be focused on all lymphoid regions in addition to the liver and spleen.

The National Comprehensive Cancer Network (NCCN) established certain laboratory and radiographic studies which are recommended at the initial evaluation of patients with HL. These include (NCCN, v.2.2011) CBC with differential and platelets, ESR, LDH, albumin, liver and kidney function tests, and a pregnancy test for women of childbearing age. An adequate bone marrow (BM) biopsy should be performed for stages IB-IIB and stages III-IV disease. More invasive procedures such as liver biopsy, diagnostic laparotomy, or splenectomy are restricted to a very small subgroup of patients where initial staging is inconclusive. Radiographic studies should include at least chest x-ray and diagnostic computed tomography (CT) of the chest, abdomen and pelvis. CT-PET scan has become an integral part of initial staging as well. Neck CT is recommended if RT is planned.

2.1 Role of PET in HL

The role of PET in HL has been markedly evolving over the past few years. It has been used and shown to have high positivity and specificity for initial staging and restaging in patients with lymphoma (Isasi, Lu & Blaufox, 2005; Seam, Juweid & Cheson, 2007). In a review done by Juweid ME (Juweid, 2006a), the use of PET scan in HL results in a modification of disease stage (usually upstaging) in about 15-20% of patients with an impact on management in about 5-15%. However, it remains unclear whether patients would benefit from a subsequent change in the treatment plan, and therefore, the value of PET for initial staging of HL patients outside a clinical trial is still debatable. On the other hand, as reviewed by Juweid, response assessment after completion of therapy is currently the most widely utilized application of restaging PET in HL and can be considered the standard of care for post treatment assessment of patients with HL. In this setting, PET shows an excellent negative predictive value between 91 and 95% in several studies, but the positive predictive value is substantially lower and considerably more variable averaging approximately 65% (de Wit, Bohuslavizki, Buchert, *et al*, 2001; Juweid, 2006a; Weihrauch, Re, Scheidhauer, *et al*, 2001). To decrease the false positive results, the International Harmonization Project (IHP), recommends that PET not be performed for at least 3 weeks following chemotherapy and preferably 8-12 weeks after completion of radiotherapy (Juweid, 2006b). The role of PET scan for routine post therapy surveillance remains controversial, primarily because of the potential for a disproportionate fraction of false-positive findings, potentially resulting in increasing cost without proven benefit from earlier PET detection of disease compared to standard surveillance methods (Cheson, Pfistner, Juweid, *et al*, 2007; Jerusalem, Beguin, Fassotte, *et al*, 2003).

Another evolving and interesting use of PET scan is in the assessment of early response; interim PET scan findings has been significantly correlated with treatment outcomes in terms of progression-free survival (PFS) and OS. Recently, PET scanning was proposed to assist in determining the choice of therapy. Patients with negative PET scans after 2-3 cycles of

treatment are being considered for an abbreviated course of chemotherapy alone, whereas those with positive PET scan are treated in a more standard fashion with the combined modality. The ongoing United Kingdom (RAPID trial) is testing whether PET scanning can guide therapy in early HL after 3 cycles of chemotherapy; PET-negative patients are randomized to involved field RT (IF-RT) versus observation while PET-positive are treated with 4th cycle ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) followed by IFRT. The recently initiated EORTC/GELA H10 Intergroup trial is comparing 'standard therapy' to PET-based response-adapted therapy (i.e. PET after 2 cycles ABVD) for favorable and intermediate group patients with early-stage HL.

3. Response criteria

Uniform and standardized criteria for assessment of initial treatment response are essential since they guide for additional treatment and are required for interpreting and comparing clinical trials. Hence, the International Working Group (IWG) published guidelines for non-Hodgkin's lymphoma response criteria first time in 1999 (Cheson, Horning, Coiffier, *et al*, 1999; Cheson, Pfistner, Juweid, *et al*, 2007). The HL study groups have adopted these IWG criteria which were based on the size reduction of the enlarged lymph nodes (as measured with CT scan) and the extent of BM involvement; bone marrow aspirate and biopsy should only be performed to confirm a CR if they were initially positive or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear.

The IWG guidelines were revised in 2007, by the IHP, after incorporating the PET scans, immunohistochemistry, and flow cytometry in the definitions of response for both NHL and HL (**Table 3**). Using the revised system, response is simplified to complete response (CR), partial response (PR), stable disease (SD), relapsed disease, or progressive disease (PD) (see table 3). CRU (complete response uncertain) category was eliminated from the new guidelines, based on the improved ability of PET scans to distinguish between viable tumor and necrosis or fibrosis in residual masses present after treatment (Buchmann, Reinhardt, Elsner, *et al*, 2001; Jerusalem, Beguin, Fassotte, *et al*, 1999; Jerusalem, Warland, Najjar, *et al*, 1999; Wirth, Seymour, Hicks, *et al*, 2002).

More recently integrated PET/CT scan, which combines a PET and a CT scan in a single study, has been shown to provide at least equal information to that obtained separately by PET and CT scans. This is supported mostly by retrospective and small trials (Juweid, 2006a). The recent increase in use of combined PET/CT scans may further help in distinction between viable and nonviable tumors.

4. Treatment

4.1 Background

Traditionally, treatment modality for HL had been chosen based on clinical stage. Early-stage HL includes the limited stages I, II, and IIIA whereas advanced HL includes stage IIIB and stage IV, according to the Cotswolds modification of the Ann Arbor classification (Josting, Wolf & Diehl, 2000). Major advances in treatment modalities over past 3 decades made early stage HL highly curable with rates achieving up 97% after 10-year follow up as reported by Ferme *et al* (Ferme, Eghbali, Meerwaldt, *et al*, 2007). Such high cure rates for

Table 3. Revised Response Criteria/Definitions for Lymphoma.

Response	Definition	Nodal Masses	Spleen, Liver	
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	In bi m im ne
PR	Regression of measurable disease and no new sites	$\geq 50\%$ decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	$\geq 50\%$ decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Ir th sp
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by $\geq 50\%$ of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, $\geq 50\%$ increase in SPD of more than one node, or $\geq 50\%$ increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	$> 50\%$ increase from nadir in the SPD of any previous lesions	N

Abbreviations: CR, complete remission; FDG, [18F]fluorodeoxyglucose; PET, positron emission tomography; partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease. Source: Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J of Clin Oncol* 2007;25(5):57.

early stage HL made the focus of recent studies on minimizing acute and late therapy related toxicities without decreasing the excellent treatment outcomes. Hence, there have been various attempts to modify different treatment modalities such as omitting RT, decreasing the dose and/or field of RT, and modifying the chemotherapy. In order to maintain efficacy and decrease toxicity, clinical investigators, through major randomized studies, were able to identify adverse prognostic factors that may predict treatment outcomes in different groups of patients. We will discuss and define below these risk groups according to published data from major study groups in Europe and North America. Subsequently, we will discuss the management of early stage HL according to different risk groups.

4.2 Definitions of favorable and unfavorable early-stage HL

In addition to the clinical stage and B symptoms which have traditionally known to be of prognostic value, various other adverse factors have been identified based on large cohorts over several years. As there have been different approaches to treat HL among major study groups which ultimately lead to different prognostic variables, various definitions for different risk groups do exist among these cooperative research groups.

In Europe, three different risk groups are defined: early-stage favorable, early-stage unfavorable (intermediate) and advanced-stage HL (**Table 4**). The NCCN divides HL into 3 groups: early-stage favorable (stage I-II with no B symptoms or large mediastinal adenopathy), early-stage unfavorable (stage I-II with large mediastinal mass, with or without B symptoms; stage I-II with B symptoms; numerous sites of disease; or significantly elevated ESR), and advanced-stage disease (stage III-IV). However, some centers in Northern America define only two risk groups, namely limited-stage (IA and IIA without bulky disease) and advanced-stage HL [III and IV; B symptoms; bulky disease (≥ 10 cm)] (Fuchs, Diehl & Re, 2006).

NCCN unfavorable risk factors for stage I-II disease include bulky mediastinal disease (mediastinal mass ratio >0.33) or bulky disease >10 cm, B symptoms, ESR >50 and more than 3 nodal sites of disease. NCCN further classifies unfavorable stage I-II disease into stage I-II (unfavorable with bulky disease) and unfavorable stage I-II with bulky disease and unfavorable stage I-II with non-bulky disease. The European Organization for Research and Treatment of Cancers (EORTC) definitions of favorable and unfavorable early stage HL are very similar to those for early stage HL in the German HL Study Group (GHSG) (**Table 4**) (Carde, Burgers, Henry-Amar, *et al*, 1988; Loeffler, Pfreundschuh, Ruhl, *et al*, 1989; Mauch, Tarbell, Weinstein, *et al*, 1988; Tubiana, Henry-Amar, Carde, *et al*, 1989). The EORTC criteria differs by substituting age ≥ 50 years in place of the extra nodal disease criterion and specifying ≥ 4 involved regions rather than ≥ 3 , as in GHSG (Noordijk, Carde, Dupouy, *et al*, 2006). Moreover, the National Cancer Institute of Canada (NCIC) and the Eastern Cooperative Oncology Group (ECOG) subdivided early-stage HL into risk categories, with 'low risk' being NLPHL and nodular sclerosis histology, age <40 years, erythrocyte sedimentation rate (ESR) <50 , and ≤ 3 disease regions. 'High risk' group patients were all other cases with stage I-II disease, except those with bulky disease > 10 cm, which are assigned to advanced-stage disease (**Table 4**) (Evens, Hutchings & Diehl, 2008; Meyer, Gospodarowicz, Connors, *et al*, 2005).

	GHSG		EORTC/GELA		NCIC/ECOG		NCCN	
Risk Factors (RF)	A	Large mediastinal mass	A	Large mediastinal mass	A	Bulky disease >10 cm	A	Large mediastinal mass (MMR >0.33) or bulky disease (>10 cm)
	B	Extranodal disease	B	Age ≥50 y	B	Age ≥40	B	ESR ≥50, if asymptomatic
	C	ESR ≥50 or B symptoms ^a with ESR ≥30	C	Same as for GHSG ¹	C	ESR ≥50 or any B symptom ^a	C	B symptoms ^a
	D	≥3 involved nodal regions	D	≥4 involved nodal regions	D	>3 involved nodal regions	D	>3 involved nodal regions
					E	MCHL or LDHL		
Treatment groups								
Lymphocyte predominant	NLPHL histology in CS I-II with no RF		NLPHL histology in supradiaphragmatic CS I-II		Low risk early stage	CS I-II with no RF		
Early stage favorable	CS I-II with no RF		CS I-II supradiaphragmatic with no RF				CS I-II with none of the RFs	
Early stage unfavorable	CS I, CS IIA with any RF; CS IIB with C/D but without A/B		CS I-II supradiaphragmatic with any RF		High risk early stage	CS I-II with any RF except A	CS I-II with any of the RFs	
Advanced stage	CS IIB with A/B; CS III-IV		CS III-IV		CS I-II with A; CS III-IV		CS III-IV	

Abbreviations: CS, clinical stage; EORTC, European Organization for Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GELA, Groupe d'Etude des Lymphomes de l'Adulte; GHSG, German Hodgkin Study Group; LDHL, lymphocyte depleted HL; MCHL, mixed cellularity HL; MMR, mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter; NCIC/ECOG, National Cancer Institute of Canada/ Eastern Cooperative Oncology Group; NCCN, National Comprehensive Cancer Network; NLPHL, nodular lymphocyte-predominant Hodgkin's lymphoma; RF, risk factor

^aB symptoms include fever with temperature >38°C, drenching night sweats, and unexplained weight loss of >10% body weight within 6 months.

^bSource: Derived from Table 21.2 by Srour S.A. and Fayad L.E. (Srour & Fayad, 2010).

Table 4. Unfavorable Factors and Treatment Groups According to Major Study Groups and NCCN.

4.3 Treatment of early stage cHL

Treatment of HL is becoming more standardized in the current era of rapidly evolving medical literature and with the marked advances in high technique imaging studies. The

most accepted standard of care to date is the combined modality treatment (CMT) with chemotherapy and radiotherapy (Table 5). However, there has been some controversy about the best RT field/dose and/or the best chemotherapy regimens. We will discuss below some of these issues.

Histology	Prognostic Group	Recommended Treatment
Early Stage cHL	Favorable ^a	Chemotherapy ^{b, d} + 20 Gy to 30 Gy IF-RT (most commonly accepted protocol) or Chemotherapy alone with 4-6 cycles of ABVD (category 2B ^e per NCCN Guidelines)
	Unfavorable ^a	Chemotherapy ^{c, d} + 30 Gy to 36 Gy IF-RT
Early Stage NLPHL	CS IA	Local LN excision (limited data) or IF-RT alone (preferred option)
	CS IIA	Regional RT or IF-RT alone ^f (preferred option by most investigators)
	CS IB-IIB	Chemotherapy ^g followed by IF-RT

^aSee Table 4 for the definitions of favorable and unfavorable prognostic groups

^bFor favorable early stage cHL, the most commonly used regimens are the ABVD (2 to 4 cycles) and the Stanford V regimen (2 cycles)

^cFor unfavorable early stage cHL, either ABVD is given for 4 to 6 cycles or Stanford V for 3 cycles

^dSee Table x for the chemotherapy regimen abbreviations and dosages

^eCategory 2B, per NCCN, is defined as follows: the recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement)

^fIn the setting of non-bulky CS IIA NLPHL

^gGiven the rarity of NLPHL, no large randomized trials regarding the best chemotherapeutic regimen are done. ABVD is widely used based on data for cHL. Immunotherapy with rituximab has been shown recently to have excellent response rates in NLPHL. See text for further details.

CS, clinical stage; IF-RT, involved field radiation therapy; NCCN, National Comprehensive Cancer network; RT, radiation therapy

Table 5. Recommended Treatments for Early Stage HL Commonly Adopted in Europe and USA.

4.3.1 Radiotherapy alone

It was first noticed in 1950, by Peters (Peters, 1950), that aggressive RT might cure patients with limited stage HL. It was not then until early 1960's when extended field RT (EF-RT) was adopted as standard of care for early stage HL. However, EF-RT was complicated by high relapse rates (Horwich, Specht & Ashley, 1997) and serious long-term side effects including pulmonary dysfunction, heart disease and secondary cancers (Gustavsson, Osterman & Cavallin-Stahl, 2003). Hence, in an attempt to lessen toxicity and improve treatment outcomes, several studies over the past 3 decades addressed those concerns through modifying the radiation field/dose and/or incorporating chemotherapy to RT. Multiple randomized studies revealed that combined modality treatment (RT plus chemotherapy) has superior outcomes and less toxicity to RT alone. Of importance are the two randomized studies by Press et al (Press, LeBlanc, Lichter, *et al*, 2001) and Engert et al (Engert, Franklin, Eich, *et al*, 2007) which compared RT alone in early stage favorable HL to combined modality with chemotherapy followed by RT. Press et al compared 3 cycles of

chemotherapy (doxorubicin + vinblastine) followed by subtotal lymphoid irradiation (STLI) to STLI alone with freedom from treatment failure (FFTF) of 94% vs. 81% after 3 years of follow up in favor to combined modality arm. Engert et al compared EF-RT alone to combined modality with 2 cycles of ABVD followed by EF-RT. Superior outcomes were in favor to the combined therapy after 7 years of follow up with FFTF of 88% vs. 67%.

Therefore, treatment with large radiation fields alone has been abandoned and the availability of less toxic and more effective chemotherapy made the combined modality therapy the standard of care in treating early HL over the past 10-15 years. The only exception is those patients with stage IA NLPHL who might benefit from RT alone as will be discussed below.

4.3.2 Early stage favorable cHL

Almost all investigators in Europe and US now agree that patients with favorable early stages HL should receive combined modality therapy. However, there is still no consensus as to what chemotherapy should be used, how many cycles should be delivered, and how much RT should be administered, if at all. The application of chemotherapy prior to irradiation not only led to better treatment results but also enabled the reduction of EF-RT to IF-RT in this group of patients (Bonadonna, Bonfante, Viviani, *et al*, 2004; Diehl V, 2005a; Hagenbeek A, 2000; Noordijk EM, 2005) and also lead to a meaningful reduction (up to 50%) in the effective prescribed radiation dose (Yahalom, 2006).

Among other regimens (chemotherapy regimens abbreviations are listed in Tables 6-8), ABVD and Stanford V have been favored as frontline regimens in the combined modality with RT in the early stage HL (see **Table 6** for regimen details and dosages). ABVD was first introduced by Bonadonna et al in 1975 for patients who failed MOPP with very promising results. Hence, Santoro and colleagues (Santoro, Bonadonna, Valagussa, *et al*, 1987) compared then three cycles of MOPP vs. ABVD as frontline therapy followed by EF-RT and three additional chemotherapy cycles in an attempt to improve outcomes and decrease toxicities associated with MOPP. ABVD arm had superior outcomes with better freedom from progression (FFP) rates (81% vs. 63%) and lower rates of sterility and leukemia. Since then, many studies were conducted by major study groups in Europe and USA and compared the combination of either EF-RT or IF-RT with different chemotherapy regimens like ABVD, MOPP, MOPP/ABV, EBVP, COPP and BEACOPP, among others. **Table 7** summarizes some of the major studies addressed the combined modality treatment with the treatment outcomes.

The Stanford V regimen, which incorporated the active agents from ABVD and MOPP into a brief dose-intense regimen, is one of the relatively new regimens that also has been proven, combined with radiotherapy, to be highly effective in early stage favorable and unfavorable or locally extensive HL with low toxicity profile.

The number of chemotherapy cycles (2 to 4 ABVD versus 2 to 3 Stanford V), and the intensity of radiation, have been addressed by multiple randomized studies to date with major impact on current therapy guidelines. Bonadonna et al (Bonadonna, Bonfante, Viviani, *et al*, 2004) revealed a noninferiority outcomes with 4 cycles of ABVD followed by IF-RT compared to same chemotherapy followed by EF-RT after 12 years of follow up (FFP rates of 93% for ABVD followed by EF-RT vs. 94% for ABVD followed by IF-RT). Horning S (Horning SJ, 2004), in a single arm study, showed as well that the 8-week modified Stanford V chemotherapy (rather than the standard 12 -week cycle) followed by IF-RT has

Regimen	Dosage and schedule	Frequency ^a
ABVD^b		
Doxorubicin	25 mg/m ² IV on days 1 and 15	Repeat cycle every 28 days
Bleomycin	10 units/m ² IV on days 1 and 15	
Vinblastine	6 mg/m ² IV on days 1 and 15	
Dacarbazine ^b	375 mg/m ² IV on days 1-5	
Standard BEACOPP^c		
Bleomycin	10 units/m ² IV on day 8	Repeat cycle every 21 days
Etoposide	100 mg/m ² IV on days 1, 2, and 3	
Doxorubicin	25 mg/m ² IV on day 1	
Cyclophosphamide	650 mg/m ² IV on day 1	
Vincristine ^d	1.4 mg/m ² IV on day 8	
Procarbazine	100 mg/m ² PO on days 1-7	
Prednisone	40 mg/m ² PO on days 1-14	
Esc-BEACOPP^c		
Bleomycin	10 mg/m ² IV on day 8	Repeat cycle every 21 days
Etoposide	200 mg/m ² IV on days 1, 2, and 3	
Doxorubicin	35 mg/m ² IV on day 1	
Cyclophosphamide	1200 mg/m ² IV on day 1	
Vincristine ^d	1.4 mg/m ² IV on day 8	
Procarbazine	100 mg/m ² PO on days 1-7	
Prednisone	40 mg/m ² PO on days 1-14	
Filgrastim ^e	300 mcg/day starting on day 8	
STANFORD V^f		
Doxorubicin	25 mg/m ² IV on days 1 and 15	Repeat cycle every 28 days
Vinblastine ^g	6 mg/m ² IV on days 1 and 15	
Mechlorethamine	6 mg/m ² IV on day 1	
Vincristine ^g	1.4 mg/m ² IV on days 8 and 22	
Bleomycin	5 units/m ² IV on days 8 and 22	
Etoposide	60 mg/m ² IV on days 15 and 16	
Prednisone ^h	40 mg/m ² PO every other day	

^aThe duration of chemotherapy and number of cycles are determined by the stage of the disease and the prognostic stratification (see text for details)

^bABVD regimen was used first as described in the table by Bonadonna G et al (Bonadonna G et al., 1975). On subsequent studies, dacarbazine was administered on days 1 and 15 rather than on days 1-5 (Canellos GP et al., 1992)

^cDerived from Diehl V et al. 2003

^dMaximum dose 2 mg.

^eFilgrastim is given subcutaneously starting on day 8 and continuing until WBC $\geq 13,000/\text{mm}^3$ on 3 consecutive days. The dose is 300 mcg/day for patients with body weight < 75 kg and 400 mcg/day for those ≥ 75 kg

^fDerived from Bartlett NL et al. 1995

^gVinblastine dose reduced to 4mg/m² and vincristine dose to 1mg/m² during cycle 3 for patients 50 years of age or older

^hPrednisone is started on day 1 and continued every other day. It is tapered by 10 mg/dose every other day starting on day 14 of the third cycle

Table 6. Common Chemotherapy Regimens Used for the Treatment of HL in Europe and USA.

Trial/Study Group	Treatment Protocols	No. of Patients	Median Follow-up	Treatment Outcomes
Engert A et al. (2007) GHSG HD7	A: RT alone (30 Gy EF-RT or 40 Gy IF-RT)	311	87 months	7-yr FFTF, 67%; 7-yr OS: 92%
	B: 2 ABVD + RT (30 Gy EF-RT or 40 Gy IF-RT)	316		7-yr FFTF: 88%; 7-yr OS: 94%
Engert A et al. (2010) GHSG HD10, 1998-2003	A: 2 ABVD + IF-RT (30 Gy)	295	91 months for OS and 79 months for FFTF	8-yr FFTF: 85.5 8-yr OS: 93.6
	B: 2 ABVD + IF-RT (20 Gy)	299		8-yr FFTF: 85.9 8-yr OS: 95.1
	C: 4 ABVD + IF-RT (30 Gy)	298		8-yr FFTF: 87.2 8-yr OS: 94.4
	D: 4 ABVD + IF-RT (20 Gy)	298		8-yr FFTF: 89.9 8-yr OS: 94.7
Advani RH et al. (2010) Stanford ^a	A: Stanford V for 8 wk + IF-RT (mostly 30 Gy, but some with 20 Gy)	46 (favorable factors GHSG)	8.5 years	10-yr FFP: 100% 10-yr OS: 97%
Press OW et al. (2001) SWOG 9133/CALGB 9391	A: 3 (doxorubicin + vinblastine) + STLI (S) (36-40 Gy)	165	3.3 years	3-yr FFS: 94% 3-yr OS: 98%
	B: STLI (S) (36-40 Gy)	161		3-yr FFS: 81% 3-yr OS: 96%
Ferme C et al. (2007) EORTC/GELA H8F	A: 3 MOPP/ABV + IF-RT (36 Gy)	270	92 months	10-yr EFS: 93% 10-yr OS 97%
	B: STLI (S)	272		10-yr EFS 68%; 10-yr OS 92%
Horning SJ et al. (1999) Stanford ^a	Stanford V for 8 wk + modified IF-RT (30 Gy)	65	16 months	3-yr FFP: 94.6% 3-yr OS: 96.6%
Noordijk EM et al. (2006) EORTC/GELA H7F	A: 6 EBVP + IF-RT (36 Gy)	164	9 years	10-yr EFS: 88%; 10-yr OS: 92%
	B: EF-RT	165		10 yr FFTF: 78%; 10 yr OS: 92%
Meyer RM et al. (2005) NCIC-CTG/ECOG	A: EF-RT alone	64	4.2 years	5-yr EFS: 88% 5-yr OS: 100%
	B: 4-6 cycles of ABVD alone	59		5-yr EFS: 87% 5-yr OS: 97%
Eghbali H et al. (2005) EORTC-GELA H9-F	A: 6 EBVP + IF-RT (36 Gy)	239	51 months	4-yr EFS: 88% 4-yr OS: 99%
	B: 6 EBVP + IF-RT (20 Gy)	209		4-yr EFS: 85% 4-yr OS: 100%
	C: 6 EBVP alone	130		4-yr EFS: 69% 4-yr OS: 98%
Wirth A et al. (2011) ALLG/TTROG ^a	3 ABVD followed by 30 Gy IF-RT	?75	5.9 years	5-yr FFP: 97%

ABV, doxorubicin (Adriamycin), bleomycin, vinblastine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ALLG/TTROG, Australasian Leukaemia and Lymphoma Group/Trans-Tasman Radiation

Oncology Group; AV, doxorubicin and vinblastine; AVD, doxorubicin, vinblastine, dacarbazine; CALGB, Cancer and Leukemia Group B; EF-RT, extended-field radiotherapy; EBVP regimen, epirubicin, bleomycin, vinblastine, and prednisone; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; EORTC, European Organization for Research and Treatment of Cancer; FFP, freedom from progression; FFS, failure-free survival; FFTF, freedom from treatment failure; GELA, Groupe d'Etude des Lymphomes de l'Adulte; GHSG, German Hodgkin Study Group; IF-RT, involved-field radiation therapy; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; OS, overall survival; NCIC-CTG, National Cancer Institute of Canada Clinical Trials Group; RFS, relapse-free survival; RT, radiotherapy; Stanford V, mechlorethamine, doxorubicin, vinblastine, prednisone, vincristine, bleomycin, VP-16; STLI (S), subtotal nodal irradiation (splenic irradiation); SWOG, Southwest Oncology Group; VAPEC-B, doxorubicin, cyclophosphamide, etoposide, vincristine, bleomycin, prednisone; yr, year.

^aUsed GHSG definition for early stage favorable HL

Table 7. Selected Trials in Favorable Early Stage HL Derived from Major Study Groups.

comparable outcomes to more intense regimens with FFP of 96% and OS of 98% after a median follow-up of 5.7 years.

Furthermore, one of the recent “practice changing” important studies, the GHSG HD 10 trial by Engert A et al (Engert, Plutschow, Eich, *et al*, 2010), randomized 1370 patients (age range, 16 to 75) with early stage favorable HL in a 4 arm study into 2 or 4 cycles of ABVD followed by 20 or 30 Gy IF-RT. Favorable disease included patients with no bulky disease, no extranodal extension, and without elevated ESR (see Table 4 for definitions of risk groups). With a median follow-up of 79-91 months, there were no significant differences in FFTF and OS in the 4 arms with FFTF rates in the range of 85.5% to 89.9% and OS rates in the range of 93.6% to 95.1% (Table 7). Furthermore, patients who received only two cycles of ABVD and low dose of radiation have less adverse events and acute toxic effects.

The HD 13 randomized trial is trying to address the question, in order to decrease toxicity from ABVD, whether the number of drugs can be reduced. Patients in this study are randomly assigned to one of the 4 arms: ABVD, ABV, AVD, or AV chemotherapy followed by 30 Gy of IF-RT. An interim safety analysis in 2006 showed increased failure rates in the ABV and AV arms, hence those arms were closed. Until further evidence, dacarbazine should be considered an integral part of the ABVD regimen in early stage favorable HL. Future analyses of the HD 13 study would hopefully answer the question whether ABVD and AVD are equivalent or not (Borchmann & Engert, 2010).

4.3.3 Early stage unfavorable cHL

The standard of care based on multiple randomized studies remains the combined modality treatment with chemotherapy and RT, as for the early stage favorable HL. However, there has been a trend towards more intense therapy than early favorable stage HL with some investigators suggesting therapy approaches similar to those adopted for advanced HL. However, giving the high cure rates and prolonged CR rates, there have been many randomized studies trying to address the need for less intense chemotherapy and/or RT in order to decrease long term toxicity from RT and maintain the best response rates. Table 8 summarizes some of the major studies addressing the therapeutic approaches for early stage unfavorable HL with the associated response rates.

4.3.3.1 Brief historical background for chemotherapy use in early stage unfavorable cHL

Various chemotherapeutic regimens have been investigated in the combined modality treatment for early stage unfavorable HL since early 1980's. However, studies didn't identify significant survival advantages among different modalities. Based on data derived from major studies in advanced HL, ABVD has been favored in most recent studies as first line therapy combined with RT in this population. ABVD has been favored for its superior outcomes and low late toxicity profile compared to other more intense regimens. Stanford V has been studied as well with some promising data and more recently ABVD has been compared to more intense regimens such as BEACOPP in early stage unfavorable HL.

Earlier studies in unfavorable HL patients compared CMT with MOPP to ABVD and MOPP-like combinations. One of the earlier studies is the Milan study (Santoro, Viviani & Zucali, 1983) which randomized patients in a split fashion for 3 cycles of MOPP followed by subtotal nodal irradiation followed by another 3 cycles of MOPP versus same course but with ABVD rather than MOPP. No significant differences in FFP were noticed initially. However, the EORTC H6U trial (Cosset, Ferme, Noordijk, *et al*, 1996) showed a better 10-year FFTF with ABVD compared to MOPP, though there was no significant survival advantage as in many other subsequent studies.

In an attempt to improve efficacy and reduce toxicity, few studies were conducted with modified combinations such as reducing alkylating agents or total cumulative dosage of chemotherapy. However, inferior outcomes were noticed in the unfavorable early stage HL with these approaches (**Table 8**).

One of such experiences was the Cancer and Leukemia Group B 9051 phase II study (Wasserman, Petroni, Millard, *et al*, 1999) which tested three cycles of etoposide, vinblastine, and doxorubicin (EVA) followed by subtotal lymphoid irradiation in 59 patients with CS I-III disease and unfavorable features (bleomycin was eliminated). CR rate was about 66% with high relapse rate of 20%.

In a more recent study (the EORTC H7U trial) conducted by the EORTC group (Noordijk, Carde, Dupouy, *et al*, 2006), 389 patients with unfavorable prognosis early stage HL were randomized to receive CMT with six cycles of epirubicin, bleomycin, vinblastine, and prednisone (EBVP) and IF-RT versus 6 cycles of mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine (MOPP/ABV hybrid) and IF-RT. The EBVP regimen, given one time per month (compared with two times per month for ABVD), was anticipated to be a less toxic regimen. However, the 10-year EFS rate was 88% in the MOPP/ABV arm compared with 68% in the EBVP arm ($P < .001$), leading to 10-year OS rates of 87% and 79%, respectively ($P = .0175$). Also, the failure-free survival rate at three years was significantly lower with EBVP (72 versus 88 percent) and further entry into the trial was discontinued.

4.3.3.2 Popular chemotherapy regimens, number of cycles, and dose/field of radiation

Recent studies, focused on the more popular regimens such as the ABVD, Stanford V, and BEACOPP, and as well on the number of cycles and dose/field of RT in order to enhance the outcomes and decrease toxicities (**Table 8**).

Trial/Study Group	Treatment Protocols	No. of Patients	Median Follow-up	Treatment Outcomes
Cosset J et al. (1996) EORTC H6U	A: 3 MOPP + mantle RT + 3 MOPP	165		10-yr FFP: 68% 10-yr OS: 87%
	B: 3 ABVD + mantle RT + 3 ABVD	151		10-yr FFP: 90% 10-yr OS: 87%
Santoro A et al. (1983) Istituto Nazionale Tumori, Milan	A: 3 MOPP + STLI/TLI + 3 MOPP	33		5-yr FFP: 66%
	B: 3 ABVD + STLI/TLI + 3 ABVD	36		5-yr FFP: 72%
Pavlovsky S et al. (1997) GATLA	A: 3 CVPP + IF-RT (30 Gy) + 3 CVPP	92		5-yr EFS: 85% 5-yr OS: 95%
	B: 3 AOPE + IF-RT (30 Gy) + 3 AOPE	84		5-yr EFS: 66% 5-yr OS: 87%
Noordijk EM et al. (2006) EORTC H7U	A: 6 EBVP II + IF-RT (36 Gy)	194	9 years	10-yr EFS: 68%; 10-yr OS: 79%
	B: 6 MOPP/ABV + IF-RT	195		5-yr EFS, 88%; 5-yr OS 87%
Meyer RM et al. (2005) NCIC-CTG/ECOG	A: 2 ABVD followed by EF-RT	139	4.2 years	5-yr EFS: 88% 5-yr OS: 92%
	B: 4-6 ABVD alone	137		5-yr EFS: 85% 5-yr OS: 95%
Eich HT et al. (2010) GHSG HD11	A: 4 ABVD + IF-RT (30 Gy)	356	6.8 years	5-yr FFP: 85.3% 5-yr OS: 94.3%
	B: 4 ABVD + IF-RT (20 Gy)	347		5-yr FFP: 81.1% 5-yr OS: 93.8%
	C: 4 baseline BEACOPP + IF-RT (30 Gy)	341		5-yr FFP: 87% 5-yr OS: 94.6%
	D: 4 baseline BEACOPP + IF-RT (20 Gy)	351		5-yr FFP: 86.8% 5-yr OS: 95.1%
Advani RH et al. (2010) Stanford ^a	A: Stanford V for 8 wk + IF-RT (20 or mostly 30 Gy)	55	8.5 years	10-yr FFP: 89% 10-yr OS: 96%
Wirth A et al. (2011) ALLG/TTROG ^a	4 ABVD followed by 30 Gy IF-RT for: A. Stage IA-IIA with any risk factor B. Stage IB-IIB:	A. 47 B. 26	5.9 years	A. 5-yr FFP: 89% B. 5-yr FFP: 73%
Zittoun R et al. (1985)	A: 3 MOPP + IF-RT (40 Gy) + 3 MOPP	82		6-yr DFS: 87% 6-yr OS: 92%

Trial/Study Group	Treatment Protocols	No. of Patients	Median Follow-up	Treatment Outcomes
French Cooperation				
	B: 3 MOPP + EF-RT (40 Gy) + 3 MOPP	91		6-yr DFS: 93% 6-yr OS: 91%
Bonadonna G et al. (2004) Istituto Nazionale Tumori, Milan ^b	A: 4 ABVD + STLI	66	116 months	12-yr FFP: 93% 12-yr OS: 96%
	B: 4 ABVD + IF-RT	70		12-yr FFP: 94% 12-yr OS: 94%
Ferme C et al. (2007) EORTC/GELA H8U	A: 6 MOPP/ABV + IF-RT (36 Gy)	336	92 months	10-yr EFS: 82% 10-yr OS: 88%
	B: 4 MOPP/ABV + IF-RT (36 Gy)	333		10-yr EFS: 80% 10-yr OS: 85%
	C: 4 MOPP/ABV + STLI	327		10-yr EFS: 80% 10-yr OS: 84%
Engert A et al. (2003) GHSG HD8	A: 4 COPP/ABVD + 30 Gy EF-RT (+ 10 Gy to bulky disease)	532	54 months	5-yr FTF: 85.8% 5-yr OS: 90.8%
	A: 4 COPP/ABVD + 30 Gy IF-RT (+ 10 Gy to bulky disease)	532		5-yr FTF: 84.2% 5-yr OS: 92.4%

ABV, doxorubicin (Adriamycin), bleomycin, vinblastine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ALLG/TTROG, Australasian Leukaemia and Lymphoma Group/Trans-Tasman Radiation Oncology Group; AOPE, doxorubicin, vincristine, prednisone, etoposide; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; COPP, cyclophosphamide, vincristine, procarbazine, prednisone; CVPP, cyclophosphamide, vinblastine, procarbazine, prednisone; DFS, disease-free survival; EBVP, epirubicin, bleomycin, vinblastine, prednisone; ECOG, Eastern Cooperative Oncology Group; EF-RT, extended-field radiotherapy; EFS, event-free survival; EORTC, European Organization for Research and Treatment of Cancer; FFP, freedom from progression; FTF, freedom from treatment failure; GATLA, Grupo Argentino de Tratamiento de la Leucemia Aguda; GELA, Groupe d'Etude des Lymphomes de l'Adulte; GHSG, German Hodgkin Study Group; IF-RT, involved-field irradiation; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; NCIC-CTG, National Cancer Institute of Canada Clinical Trials Group; OS, overall survival; Stanford V, mechlorethamine, doxorubicin, vinblastine, prednisone, vincristine, bleomycin, VP-16; RT, radiation therapy; STLI, subtotal nodal irradiation; TLI, total lymphoid irradiation.

^aUsed GHSG definitions for favorable and unfavorable early stage HL

^bIncluded unfavorable stage I and all clinical stage II patients

Table 8. Selected Trials in Unfavorable Early Stage HL Derived from Major Study Groups.

Trying to address the number of cycles and/or radiation field, Ferme C, et al. randomized 996 patients with early unfavorable HL in the GELA H8U trial into one of the following three arms: six cycles of the hybrid MOPP/ABV regimen plus IF-RT versus four cycles plus IF-RT versus 4 cycles plus subtotal nodal irradiation (STNI). All arms had similar 5-year EFS and 10-year OS rates (Ferme, Eghbali, Meerwaldt, *et al*, 2007). Hence, 4 cycles of chemotherapy followed by IF-RT was proposed as standard treatment for early stage unfavorable HL. EF-RT versus IF-RT has been addressed as well by the large HD8 randomized trial from the German Hodgkin's Lymphoma Study Group (Engert, Schiller,

Josting, *et al*, 2003), where 1204 patients were randomly assigned to receive four cycles of COPP/ABVD followed by either IF-RT or EF-RT. At 5-years of follow-up, there was no significant difference in FTF and OS between the 2 groups, but increased acute toxicity with the EF-RT group (leukopenia, thrombocytopenia, and GI toxicities).

ABVD and BEACOPP have been compared head to head in early stage unfavorable HL. In the EORTC/GELA H9U study (Noordijk EM, 2005) patients were randomly assigned to 6 cycles of ABVD or 4 cycles of ABVD or 4 cycles of baseline BEACOPP, all followed by 30 Gy IF-RT. At an interim analysis with a median follow-up of 4 years, no EFS and OS differences were noted, but increased toxicity with baseline BEACOPP. More recently, the final analysis of the GHSG HD11 trial (Eich, Diehl, Gorgen, *et al*, 2010) has been published with similar results to the H9U study, but with more information about the RT dosage. In this 4-arm study, 1395 patients with early stage unfavorable HL were randomized to either 4 cycles of ABVD or 4 cycles of baseline BEACOPP. Patients in each group of chemotherapy were then randomized to either 20 or 30 Gy IF-RT. At a median follow-up of 7.5 years, the OS was similar in all 4 arms. FTF and PFS were similar as well between the 2 chemotherapy arms with the 30 Gy IF-RT. Baseline BEACOPP arm with 20 Gy IF-RT showed superior FTF compared to ABVD followed by same RT. However, treatment-related toxicity was more frequently observed in the baseline BEACOPP arm and hence the BEACOPP is not adopted as new standard of care.

More recently, Wirth and colleagues (Wirth, Grigg, Wolf, *et al*, 2011) reported the results of the Australian Leukemia and Lymphoma Group/Trans-Tasman Radiation Oncology Group which tested combined modality treatment in stages I-II HL with IF-RT, with the number of cycles of ABVD determined by risk group (according to GHSG). 150 patients were classified into three groups as follows: group 1 with no risk factors who received 3 cycles of ABVD and IF-RT, group 2 with stages IA-IIA disease and any of the risk factors and group 3 included patients with stage IB-IIB; groups 2 and 3 received the same therapy with 4 cycles of ABVD and IF-RT. With a median follow-up of 5.9 years, the 5-year FFP and OS were comparable to those in the HD10 and HD11 trials for groups 1 and 2, but not group 3 which showed lower 5-year FFP and OS of 73% and 85%, respectively. The lower rates in group 3 may be explained by the inclusion of stage IIBX disease (44% of patients) in this study (those were excluded from HD10 and HD11 studies).

As with ABVD and BEACOPP, clinical studies has shown promising response rates with the Stanford V regimen. Advani RH, *et al* (Advani, Hoppe, Baer, *et al*, 2009) updated recently the initial results of the G4 study published by Horning SJ *et al* (Horning SJ, 2004). Among the 87 patients with non-bulky stage IA-IIA HL, 47 patients had unfavorable risk factors (according to GHSG criteria). At a median follow-up of 9 years, the FFP and OS rates for the whole group were 94% and 96%, respectively. However, FFP was 100% for favorable disease patients compared to 89% of those with unfavorable factors, but with no significant OS differences. Hence, Stanford V (8 weeks; 2 cycles) and 30 Gy IF-RT is considered safe and highly effective in this group of patients.

Few other studies confirmed as well that combined modality with Stanford V regimen is highly effective for locally extensive and advanced HL with low toxicity profile. More recently, the MSKCC study (Edwards-Bennett, Jacks, Moskowitz, *et al*, 2010) tested 126 patients with either locally extensive or advanced disease with 12-week Stanford V chemotherapy regimen followed by 36 Gy IF-RT to bulky sites and/or macroscopic splenic

disease. The 5-and 7-year OS rates were 90% and 88%, respectively. On the other hand, at least 3 randomized trials were conducted comparing combined modality treatment with Stanford V versus ABVD. The final results confirm that ABVD should stay the standard therapy, but offers Stanford V as an acceptable and effective alternative (NCCN, v2.2011).

4.3.4 Chemotherapy alone

Giving the high cure rates and long term survivors of early stage HL with combined modality therapy, but with continued increased risk of long term complications from RT such as premature heart disease, lung toxicity, and secondary malignancies, many investigators have initiated randomized studies trying to omit RT in such good risk patients. Data from few randomized studies and as well few other single arm studies will be discussed briefly (these were summarized by a recent review by Straus DJ, 2011).

One of the earliest randomized studies is the prospective trial by Pavlovsky S, et al (Pavlovsky, Maschio, Santarelli, *et al*, 1988). A total of 104 patients with unfavorable clinical stages I-II HL were randomized for chemotherapy alone with 6 cycles of CVPP (cyclophosphamide, vincristine, procarbazine, and prednisone) versus 6 cycles of CVPP sandwiched with 30 Gy dose of IFRT. Combined modality treatment had higher rates of disease-free survival (75% vs. 34%) and a trend toward higher OS rates (84% vs. 66%).

Another prospective study was conducted by the Memorial Sloan Kettering Cancer Center (Straus, Portlock, Qin, *et al*, 2004) which randomized 152 patients with non-bulky stages I-II and stage IIIA disease to 6 cycles of ABVD with or without RT. There were no significant differences, but increased tendency for inferior outcomes in CR rates (87% vs. 91%), FFP rates (81 vs. 86%), and OS at 60 months (90% vs. 97%) for ABVD alone compared to the combined modality arm.

A phase II trial by the NCIC and ECOG study group (Meyer, Gospodarowicz, Connors, *et al*, 2005) randomized 399 patients with non-bulky early stage IA-IIB HL to 4-6 cycles of ABVD alone (favorable or unfavorable) vs. RT based therapy (STLI alone if favorable HL and ABVD followed by STLI if unfavorable). An interim analysis after median follow-up of 4.2 years revealed better outcomes (FFP and EFS) in the RT alone plus combined modality therapy arms compared to the chemotherapy alone arm, but no survival benefit. In a subset analysis of patients with unfavorable prognostic factors, FFP was superior for those treated with the combined modality compared to chemotherapy alone (95% vs. 88%), but with no survival differences.

The fourth 3-arm randomized study is the EORTC-GELA H9-F (Eghbali, Raemaekers & Carde, 2005) which randomized early stage favorable HL patients (total of 783 patients) to chemotherapy alone with epirubicin, bleomycin, vinblastine, and prednisone (EBVP) versus EBVP followed by 20 Gy of IF-RT versus EBVP followed by 36 Gy IF-RT. EBVP has an inferior outcome compared to the combined modality with both the 20 Gy and 36 Gy IF-RT with 4-year EFS rates of 69%, 85%, and 88%, respectively. The EBVP alone arm was then discontinued though there was no survival differences.

Of the retrospective analyses, Canellos GP et al (Canellos, Abramson, Fisher, *et al*, 2010) reported a PFS and OS of 92% and 100%, respectively, in a series of 75 patients with early stages IA-IIA and stage IIB disease (median follow-up was 52 months). Another nonrandomized study from Spain (Rueda Dominguez, Marquez, Guma, *et al*, 2004) included

unselected 80 patients with early stage HL treated with 6 cycles of ABVD. The progression-free and overall survival at 7 years reported in 65 patients without B symptoms or mediastinal bulky disease were 88% and 97%, respectively.

More recently, a systematic review with meta-analysis of randomized controlled trials comparing chemotherapy alone with CMT in patients with early stage HL. Randomized studies comparing chemotherapy alone to the same chemotherapy regimen plus RT were only included. A total of 1245 patients were included. Authors concluded that adding RT to chemotherapy improves tumor control and OS in patients with early stage HL (Herbst, Rehan, Skoetz, *et al*, 2011).

Until further randomized trials are published, there will be no consensus to adopt chemotherapy alone as front line therapy for early stage HL. Enrollment in randomized clinical trials should be highly recommended. Currently, there are few ongoing randomized studies trying to answer that question. Armitage (Armitage, 2010) summarized four major randomized clinical trials which are incorporating interim PET scans to guide further therapy with or without IF-RT.

Based on available data and until further studies show convincing evidence for the opposite, we think combined modality treatment with chemotherapy and RT should remain the standard of care for early stage HL. Exceptions can be made for individual cases with either chemotherapy alone or RT alone. Of significance, and as noted by Armitage (Armitage, 2010), it appears that the actual choice of treatment modality is greatly affected by a physician's comfort with a particular treatment and by cumulative clinical experience- not just by data published in the literature.

4.4 Treatment of early stage NLPHL

4.4.1 Introduction

As discussed above, NLPHL is a rare subtype of HL with distinctive morphologic and immunophenotypic features compared to cHL. NLPHL accounts for 5% of HL cases with around 500 new diagnoses in US annually. Many retrospective analyses showed different natural history and more indolent course than cHL. Given the rarity of NLPHL, there are no randomized studies to establish standard of care for management of NLPHL. It has been managed historically similarly to cHL, however distinctive features are more recognized currently with some changes in the approach of management.

4.4.2 Presentation and prognosis

Generally, NLPHL is characterized by early presentation (stages I-II), indolent course with no constitutional symptoms, favorable prognosis, and occasional late relapses. The extremely favorable prognosis on some cases is reflected by data which showed that patients with stage IA may be treated with LN excision followed by a "watch and wait" approach or with IFRT alone (Diehl, Sextro, Franklin, *et al*, 1999; Nogova, Reineke, Eich, *et al*, 2005; Schlembach, Wilder, Jones, *et al*, 2002; Wilder, Schlembach, Jones, *et al*, 2002; Wirth, Yuen, Barton, *et al*, 2005) and that some patients with Stages IIIA-IVA may benefit as well from the "watch and wait" approach until they become symptomatic without jeopardizing treatment outcomes.

The largest analysis to describe patients with NLPHL and identify certain prognostic factors is the recent report by Nogova, et al (Nogova, Reineke, Brillant, *et al*, 2008) who reviewed all NLPHL patients registered in the GHSG database, comparing patient characteristics and treatment outcome with cHL patients. A total of 394 patients with NLPHL were identified with 63 % having early stage favorable, 16 % has early stage unfavorable, and 21% has advanced stage. At a median follow-up of 50 months, FFTF (88% vs 82%) and OS (96% vs 92%) were found better with NLPHL compared to cHL, respectively. Among patients with NLPHL, FFTF were superior in patients with early favorable HL compared to those with early unfavorable HL and advanced HL (93% vs 87% vs 77%, respectively). The following factors were found negative prognostic factors: age (≥ 45), advanced stage, hemoglobin <10.5 g/dl, and lymphopenia. In another, but smaller series, Diehl V et al (Diehl, Sextro, Franklin, *et al*, 1999) reported similar favorable outcomes for early stage disease NLPHL compared to more advanced stages.

4.4.3 Treatment options

IF-RT or regional RT alone has been accepted by most investigators in Europe and US as a valid choice in the setting of non-bulky stage IA-IIA NLPHL, and is adopted as first line therapy by the NCCN guidelines. This is based on many retrospective analyses which showed excellent long term outcomes and no added benefit with combined modality therapy as for cHL. The Australasian Radiation Oncology Lymphoma Group (Wirth, Yuen, Barton, *et al*, 2005) described the long term outcomes of 202 patients with stage I-II NLPHL treated with RT alone. At a median follow-up of 15 years, the FFP and OS rates for the whole group were 82 % and 83 %, respectively. Various RT fields were used in this population with a median RT dose of 36 Gy. Another small series of 36 patients reported treatment outcomes with RT alone for non-bulky stage IA-IIA NLPHL (Schlembach, Wilder, Jones, *et al*, 2002). In this small series, 20 patients with stage IA received either IF-RT or EF-RT alone. At a median follow up of 8.8 years, the 5-year relapse-free and OS rates were 95% and 100%, respectively.

Treatment outcomes for early stage NLPHL with RT with or without chemotherapy have been reported in few other retrospective analyses. Chen RC et al (Chen, Chin, Ng, *et al*, 2010) reported recently the outcomes from 113 patients with stage I-II NLPHL treated with RT alone (93 patients), combined modality (13 patients), or chemotherapy alone (7 patients). Among the 106 patients treated with RT, 25 received limited-field, 35 regional-field, and 46 received EF-RT. At a median follow-up of 136 months, 10-year PFS rates were 85% (stage I) and 61% (stage II); overall survival (OS) rates were 94% and 97% for stages I and II respectively. PFS and OS did not differ among patients who received limited-field, regional-field, or extended-field RT. In contrast, six of seven patients who received chemotherapy alone developed early disease progression. In a multivariate analysis, extent of RT was not significantly associated with PFS. Addition of chemotherapy to RT didn't improve the outcomes as well.

Nogova L et al (Nogova, Reineke, Eich, *et al*, 2005) reported a retrospective analysis, from the GHSG, which included 131 patients with stage IA NLPHL treated with either IF-RT alone (45 patients), ER-FT alone (45 patients), or the RT combined with two to four cycles of ABVD chemotherapy (41 patients). At a median follow-up of 78 months for EF-RT, 17 months for the IF-RT, and 40 months for the combined modality, the estimated 24-month FFTF rates were 100, 92, and 97 percent, respectively for the three treatment groups. In

another small series (48 patients), but with longer median follow-up (9.3 years), the M.D Anderson study (Wilder, Schlembach, Jones, *et al*, 2002) showed no difference in treatment outcomes for early stage NLPHL with RT alone (37 patients) compared to combined modality (11 patients).

Based on current data and until future convincing evidence is available, we think IF-RT alone is the preferred first line treatment modality for early stage favorable NLPHL. There is a general agreement for now by most investigators to treat patients with early unfavorable or advanced-stage LPHL according to the treatment protocols for cHL. However, with more data investigating the role of the monoclonal anti-CD 20 antibody (Rituximab) in patients with NLPHL, many investigators recommend incorporating rituximab alone or combined with other treatment modalities for unfavorable early stage, advanced stage, and relapsed NLPHL.

5. Special cases

5.1 Treatment of elderly patients with HL

5.1.1 Introduction

HL is a disease of relatively young patients; however, about 15-30% of patients with HL are older than 60 years according to few population-based studies. Elderly patients are mostly defined as those above ages 60-65 years. Unfortunately, the reported rates of elderly HL patients enrolled in large randomized studies is much lower than its prevalence (<5% to 10%) (Evens, Hutchings & Diehl, 2008; Klimm, Diehl & Engert, 2007). There is paucity of randomized studies that targeted the elderly HL population alone. However, many retrospective analyses derived from large studies have addressed the elderly population.

5.1.2 Presentation and prognosis

Elderly patients tend to present with increased frequency of mixed cellularity histologic subtype, advanced disease, B symptoms, and Epstein-Barr virus-positive disease. Overall, patients older than 60 years tend to have poorer outcomes than the younger population as reported by most series. Poor outcomes may be attributed to various factors including multiple co-morbidities, poor performance and/or mental status, inability to tolerate aggressive therapy, and death due to causes other than HL, among other factors as discussed below (Evens, Hutchings & Diehl, 2008; Klimm, Diehl & Engert, 2007).

Kim HK *et al* (Kim, Silver, Li, *et al*, 2003) reported treatment outcomes of 86 elderly patients (60-93 years) among which 52 patients had early stage disease (stages IA-IIA) and 34 patients had advanced disease (stages IIB-IV). At a median follow-up of 75 months, the 10-year FFTF and OS rates for all patients were 62% and 30%, respectively. The 10-year FFTF and OS for early stage HL were 71% and 31% and for advanced stage HL were 49% and 26%, respectively. In this study, the recurrence of HL was found to have a significant negative impact on survival. In a more recent report by Engert A *et al* (Engert, Ballova, Haverkamp, *et al*, 2005), a comprehensive retrospective analysis from the GHSG data base was performed and yielded poorer outcomes for elderly patients. From 4251 patients, 372 (8.8%) were 60 years or older. The 5-year OS (65% vs. 90%) and FFTF (60% vs. 80%) rates

were significantly lower than those in younger patients. It was noticed in this study that the acute toxicity rate was higher in the elderly and that fewer elderly patients received the intended full dose chemotherapy. Hence, the authors concluded that the overall poorer outcome of elderly HL patients is attributed to the higher mortality during treatment and the lower dose-intensity therapy received. Of notice in this study, and as have been noticed with few other reports, adequately staged elderly patients receiving appropriate doses of therapy can achieve responses comparable to those of younger patients. However, older patients in general have a less favorable outcome which may be attributed to treatment-related deaths, shorter survival after relapse, death due to other causes, and others as mentioned above. Few other reports over the past 3-4 decades have been published with similar outcomes as above.

5.1.3 Treatment options

To date and until proven otherwise, there is an agreement among different investigators to treat the best fit elderly patients according to the management guidelines for the younger population, early stage HL with CMT and advanced stage disease with chemotherapy with or without RT as indicated. If chemotherapy is indicated, the widely used ABVD regimen would probably be the preferred regimen over the less commonly used and/or more intense-toxic regimens such as Stanford V and BEACOPP.

Over the past 10 years, attempts are being made to define the best therapeutic approach for elderly patients. Adjusting the chemotherapy and/or RT protocols to maintain high efficacy, but decrease the toxicity have been tried.

For patients with early stage unfavorable HL, Klimm et al. (Klimm, Eich, Haverkamp, *et al*, 2007) reported in 2007 the GHSC experience for the elderly early stage HL after CMT with 4 cycles of chemotherapy (COPP/ABVD) followed by EF-RT vs. IF-RT. From 1204 patients enrolled in the GHSG HD8 study, 89 patients were 60 years or older. Acute toxicity from RT was more pronounced in elderly patients receiving EF-RT compared to IF-RT. FFTF and OS rates were significantly lower in the elderly patients compared to younger population. However, more importantly, this study reported that elderly patients had poorer outcome when treated with EF-RT compared to IF-RT in terms of FFTF (58% vs. 70%) and OS (59% vs. 81%).

In regards of best chemotherapy regimen, data suggest that best outcomes in the elderly HL patients were received with adriamycin-based therapy. Weekes et al. (Weekes, Vose, Lynch, *et al*, 2002) reported that patients received anthracycline-containing regimen (ChIVPP/ABV) survived twice as long as patients given ChIVPP alone. Ballova et al. (Ballova, Ruffer, Haverkamp, *et al*, 2005), on the other hand in the HD9 elderly study, tried more intense regimen with baseline BEACOPP compared to COPP-ABVD in patients (>60 years) with advanced stage HL. Although there was better tumor control in the BEACOPP arm, that didn't translate into better outcome because of the higher toxicity.

More recently, and in an attempt to maintain dose intensity and avoid excessive toxicity, CHOP-21 regimen which is traditionally used for NHL has been studied as front line therapy for elderly HL patients with promising results (Kolstad, Nome, Delabie, *et al*, 2007).

There have been few other regimens tested in single arm phase II studies and others are being under investigation with various successes to date. Examples of such regimens include vinblastine, cyclophosphamide, procarbazine, etoposide, mitoxantrone and bleomycin (VEPEMB) (Levis, Anselmo, Ambrosetti, *et al*, 2004), vincristine, doxorubicin, bleomycin, etoposide and prednisone (ODBEP) (Macpherson, Klasa, Gascoyne, *et al*, 2002), prednisone, vinblastine, doxorubicin and gemcitabine (PVAG) (Boll, Bredenfeld, Gorgen, *et al*, 2011), and bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BACOPP) (Halbsguth, Nogova, Mueller, *et al*, 2010). However, randomized studies are highly recommended in this elderly heterogenous population in order to adopt any of the new regimens as standard of care compared to traditional regimens such as ABVD.

We do think that using a comprehensive geriatric assessment (CGA) model for elderly HL patients, addressing comorbidity and functional status prior to initiation of therapy, may guide medical providers in their decision for the intensity of therapy which usually predicts treatment outcomes. A similar approach has been studied in elderly patients with diffuse large cell lymphoma (Tucci A *et al*, 2009) where GCA was found to be an efficient method to identify elderly patients who may benefit from a curative approach with aggressive therapy (well fit patients) compared to unfit patients who have poor outcomes. Until more data is available, treatment of well fit elderly patients should follow same guidelines as for younger population given the potentially high cure rate of HL even in advanced disease status as compared to poor outcomes with other types of cancers.

5.2 Treatment of HL during pregnancy

5.2.1 Epidemiology and prognosis

As the HL high incidence rates coincides with the female reproductive age, it is not surprising to mention that it is considered the fourth most common cancer during pregnancy (Sadural & Smith, 1995). However, as the overall incidence/prevalence of HL is low compared to other cancers the association between pregnancy and HL is low as well with only few small series describing the clinical presentation and treatment outcomes in this population. Fortunately, most reports showed that pregnancy doesn't have a negative impact on the course of HL with long term treatment outcomes comparable to those who were treated while non-pregnant (Gelb, van de Rijn, Warnke, *et al*, 1996). The challenge in managing those cases is attributed to the increased risk on the fetus with the different diagnostic and/or therapeutic interventions. Adverse teratogenic effects from chemotherapy and/or RT depend mainly on the level of fetal maturation. The highest teratogenic effects with increased risk of fetal malformation and death are noticed in the first trimester. In the second and third trimester, complications from therapy are more subtle with adverse effects such as intrauterine growth retardation, impaired functional or mental development, microcephaly, and low birth weight, among others (Fisher & Hancock, 1996).

5.2.2 Presentation and staging

Clinical presentation of HL during pregnancy is generally similar to non-pregnant patients. Staging workup approach is similar as well; however, to avoid fetus exposure to RT, CT

scans should be avoided if possible. Instead, CXR and abdominal US and/or MRI may be used safely to complete staging (Nicklas & Baker, 2000).

5.2.3 Treatment options

There are no consensus guidelines to date that address standard of care. However, based on the available scattered reports there is an agreement to manage pregnant patients conservatively if possible until fetal maturation or delivery. Some authors suggested that in specialized cases (such as those with limited stage IA-IIA in their late second and third trimester), treatment may be deferred until mature fetal development and delivery, but patients should be followed then very closely for any signs of progression and proceed with delivery and/or therapy as indicated (Gelb, van de Rijn, Warnke, *et al*, 1996; Jacobs, Donaldson, Rosenberg, *et al*, 1981).

Patients who present with HL during the first trimester, in particular those with advanced disease, may be offered therapeutic abortion given the high risk of teratogenic effects associated with therapy. Data suggest that chemotherapy increases risk of fetal malformations to around 15% during the first trimester, with the greatest risk associated with the alkylating and antimetabolite drugs, as opposed to the lowest risk with vinblastine (Doll, Ringenberg & Yarbrow, 1989; Yahalom, 1990). Of notice, Doll DC *et al*. reported as well that there was low risk of fetal malformation in the second and third trimesters. In contrast, RT has been used more safely during pregnancy even in the first trimester. Yahalom J (Yahalom, 1990), in a series of 23 patients received supradiaphragmatic radiation therapy (five in the first trimester), reported no harm to the fetus. Based on these data and other similar reports, if treatment is indicated in the first trimester and can't be delayed for the second trimester, RT (with maximized uterine shielding) may be considered the best choice for supradiaphragmatic disease (with a dose of less than 10 Gy). However, for patients with infradiaphragmatic disease and/or advanced disease chemotherapy may be indicated with vinblastine-based therapy.

For second and third trimesters, treatment may be deferred until complete fetal development and safe delivery in specific asymptomatic localized stages. However, most patients would need treatment which may include RT alone (10 to 36 Gy in a mantle or IF-RT fashion) for supradiaphragmatic disease (with maximized uterine shielding) vs. chemotherapy for infradiaphragmatic and/or advanced disease as for the first trimester; however, in the second and third trimesters the use of chemotherapy is much safer than in the first trimester (Barnicle, 1992; Doll, Ringenberg & Yarbrow, 1989), but remote side effects on long term survivor babies remain of concern.

6. Novel treatments for early stage HL

Besides the increased use of the monoclonal anti-CD20 antibody (rituximab) in NLPHL, novel targeted therapy is rarely incorporated in the management of early stage HL. This is mainly because of the high cure rates achieved with traditional chemotherapy regimens. Novel therapies are being more studied in advanced and relapsed/progressive diseases and will be discussed separately.

7. Conclusion

The treatment of early stage classical HL is mostly, today a combined modality with chemotherapy and involved field radiation. Decreasing the long-term side effects of the treatment is a goal. Decreasing the dosing of radiation and improving the radiation techniques, may demonstrate less complications in long-term follow-up. Incorporation of PET scan as a tool may select patients who will have higher risk for relapse. It is imperative to consider the acute and long-term side effects of the current therapeutic modalities in the treatment planning and future clinical trials.

8. References

- Advani, R. H., Hoppe, R. T., Baer, D. M., *et al* (2009) Efficacy of Abbreviated Stanford V Chemotherapy and Involved Field Radiotherapy in Early Stage Hodgkin's Disease: Mature Results of the G4 Trial. *Blood (ASH Annual Meeting Abstracts)*, 114, 1670.
- Ansell, S. M. & Armitage, J. O. (2006) Management of Hodgkin lymphoma. *Mayo Clin Proc*, 81, 419-426.
- Armitage, J. O. (2010) Early-stage Hodgkin's lymphoma. *N Engl J Med*, 363, 653-662.
- Ballova, V., Ruffer, J. U., Haverkamp, H., *et al* (2005) A prospectively randomized trial carried out by the German Hodgkin Study Group (GHSG) for elderly patients with advanced Hodgkin's disease comparing BEACOPP baseline and COPP-ABVD (study HD9elderly). *Ann Oncol*, 16, 124-131.
- Barnicle, M. M. (1992) Chemotherapy and pregnancy. *Semin Oncol Nurs*, 8, 124-132.
- Bernard, S. M., Cartwright, R. A., Darwin, C. M., *et al* (1987) Hodgkin's disease: case control epidemiological study in Yorkshire. *Br J Cancer*, 55, 85-90.
- Boll, B., Bredendfeld, H., Gorgen, H., *et al* (2011) Phase II study of PVAG (prednisone, vinblastine, doxorubicin, gemcitabine) in elderly patients with early unfavorable or advanced stage Hodgkin lymphoma. *Blood*.
- Bonadonna, G., Bonfante, V., Viviani, S., *et al* (2004) ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. *J Clin Oncol*, 22, 2835-2841.
- Borchmann, P. & Engert, A. (2010) The past: what we have learned in the last decade. *Hematology Am Soc Hematol Educ Program*, 2010, 101-107.
- Buchmann, I., Reinhardt, M., Elsner, K., *et al* (2001) 2-(fluorine-18)fluoro-2-deoxy-D-glucose positron emission tomography in the detection and staging of malignant lymphoma. A bicenter trial. *Cancer*, 91, 889-899.
- Canellos, G. P., Abramson, J. S., Fisher, D. C., *et al* (2010) Treatment of favorable, limited-stage Hodgkin's lymphoma with chemotherapy without consolidation by radiation therapy. *J Clin Oncol*, 28, 1611-1615.
- Caraway, N. P. (2005) Strategies to diagnose lymphoproliferative disorders by fine-needle aspiration by using ancillary studies. *Cancer*, 105, 432-442.
- Carbone, P. P., Kaplan, H. S., Musshoff, K., *et al* (1971) Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res*, 31, 1860-1861.

- Carde, P., Burgers, J. M., Henry-Amar, M., *et al* (1988) Clinical stages I and II Hodgkin's disease: a specifically tailored therapy according to prognostic factors. *J Clin Oncol*, 6, 239-252.
- Chen, R. C., Chin, M. S., Ng, A. K., *et al* (2010) Early-stage, lymphocyte-predominant Hodgkin's lymphoma: patient outcomes from a large, single-institution series with long follow-up. *J Clin Oncol*, 28, 136-141.
- Cheson, B. D., Horning, S. J., Coiffier, B., *et al* (1999) Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol*, 17, 1244.
- Cheson, B. D., Pfistner, B., Juweid, M. E., *et al* (2007) Revised response criteria for malignant lymphoma. *J Clin Oncol*, 25, 579-586.
- Correa, P., O'Connor, G. T., Berard, C. W., *et al* (1973) International comparability and reproducibility in histologic subclassification of Hodgkin's disease. *J Natl Cancer Inst*, 50, 1429-1435.
- Cosset, J. M., Ferme, C., Noordijk, E. M., *et al* (1996) Combined Modality Treatment for Poor Prognosis Stages I and II Hodgkin's Disease. *Semin Radiat Oncol*, 6, 185-195.
- de Wit, M., Bohuslavizki, K. H., Buchert, R., *et al* (2001) 18FDG-PET following treatment as valid predictor for disease-free survival in Hodgkin's lymphoma. *Ann Oncol*, 12, 29-37.
- Diehl, V. (2007) Hodgkin's disease--from pathology specimen to cure. *N Engl J Med*, 357, 1968-1971.
- Diehl V, E. A., Mueller RP, *et al* (2005a) HD10: investigating reduction of combined modality treatment intensity in early stage Hodgkin's lymphoma. Interim analysis of a randomized trial of the German Hodgkin Study Group. *J Clin Oncol*, 23, 561S.
- Diehl V, H. N., Mauch PM (2005b) *Hodgkin's disease* (7th edn). Philadelphia: Lippincott Williams & Wilkins.
- Diehl, V., Sextro, M., Franklin, J., *et al* (1999) Clinical presentation, course, and prognostic factors in lymphocyte-predominant Hodgkin's disease and lymphocyte-rich classical Hodgkin's disease: report from the European Task Force on Lymphoma Project on Lymphocyte-Predominant Hodgkin's Disease. *J Clin Oncol*, 17, 776-783.
- Doll, D. C., Ringenberg, Q. S. & Yarbrow, J. W. (1989) Antineoplastic agents and pregnancy. *Semin Oncol*, 16, 337-346.
- Edwards-Bennett, S. M., Jacks, L. M., Moskowitz, C. H., *et al* (2010) Stanford V program for locally extensive and advanced Hodgkin lymphoma: the Memorial Sloan-Kettering Cancer Center experience. *Ann Oncol*, 21, 574-581.
- Eghbali, H., Raemaekers, J. & Carde, P. (2005) The EORTC strategy in the treatment of Hodgkin's lymphoma. *Eur J Haematol Suppl*, 135-140.
- Eich, H. T., Diehl, V., Gorgen, H., *et al* (2010) Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. *J Clin Oncol*, 28, 4199-4206.

- Engert, A., Ballova, V., Haverkamp, H., *et al* (2005) Hodgkin's lymphoma in elderly patients: a comprehensive retrospective analysis from the German Hodgkin's Study Group. *J Clin Oncol*, 23, 5052-5060.
- Engert, A., Franklin, J., Eich, H. T., *et al* (2007) Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin's lymphoma: final results of the GHSG HD7 trial. *J Clin Oncol*, 25, 3495-3502.
- Engert, A., Plutschow, A., Eich, H. T., *et al* (2010) Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med*, 363, 640-652.
- Engert, A., Schiller, P., Josting, A., *et al* (2003) Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol*, 21, 3601-3608.
- Evens, A. M., Hutchings, M. & Diehl, V. (2008) Treatment of Hodgkin lymphoma: the past, present, and future. *Nat Clin Pract Oncol*, 5, 543-556.
- Falini B, D. F. R., Pileri S (1995) BCL-6 gene rearrangement and expression in Hodgkin's disease. In *Third International Symposium on Hodgkin's Lymphoma*. Cologne, Germany.
- Ferme, C., Eghbali, H., Meerwaldt, J. H., *et al* (2007) Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *N Engl J Med*, 357, 1916-1927.
- Fisher, P. & Hancock, B. (1996) Hodgkin's disease in the pregnant patient. *Br J Hosp Med* 56, 529.
- Fuchs, M., Diehl, V. & Re, D. (2006) Current strategies and new approaches in the treatment of Hodgkin's lymphoma. *Pathobiology*, 73, 126-140.
- Gelb, A. B., van de Rijn, M., Warnke, R. A., *et al* (1996) Pregnancy-associated lymphomas. A clinicopathologic study. *Cancer*, 78, 304-310.
- Glaser, S. L. & Jarrett, R. F. (1996) The epidemiology of Hodgkin's disease. *Baillieres Clin Haematol*, 9, 401-416.
- Gustavsson, A., Osterman, B. & Cavallin-Stahl, E. (2003) A systematic overview of radiation therapy effects in Hodgkin's lymphoma. *Acta Oncol*, 42, 589-604.
- Hagenbeek A, E. H., Fermé C, *et al* (2000) Three cycles of MOPP/ABV hybrid and involved-field irradiation is more effective than subtotal nodal irradiation in favorable supra-diaphragmatic clinical stages I-II Hodgkin's disease: preliminary results of the EORTC-GELA H8-F randomized trial in 543 patients. *Blood*, 575a.
- Halbsguth, T. V., Nogova, L., Mueller, H., *et al* (2010) Phase 2 study of BACOPP (bleomycin, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) in older patients with Hodgkin lymphoma: a report from the German Hodgkin Study Group (GHSG). *Blood*, 116, 2026-2032.
- Harris, N. L., Jaffe, E. S., Diebold, J., *et al* (1999) World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. *J Clin Oncol*, 17, 3835-3849.

- Hehn, S. T., Grogan, T. M. & Miller, T. P. (2004) Utility of fine-needle aspiration as a diagnostic technique in lymphoma. *J Clin Oncol*, 22, 3046-3052.
- Herbst, C., Rehan, F. A., Skoetz, N., *et al* (2011) Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma. *Cochrane Database Syst Rev*, CD007110.
- Hoppe, R. T., Advani, R. H., Ai, W. Z., *et al* (2011) Hodgkin lymphoma. *J Natl Compr Canc Netw*, 9, 1020-1058.
- Horning SJ, H. R., Advani RH, *et al* (2004) Efficacy and late effects of Stanford V chemotherapy and radiotherapy in untreated Hodgkin's disease: mature data in early and advanced stage patients [abstract]. *Blood*, Abstract 308.
- Horwich, A., Specht, L. & Ashley, S. (1997) Survival analysis of patients with clinical stages I or II Hodgkin's disease who have relapsed after initial treatment with radiotherapy alone. *Eur J Cancer*, 33, 848-853.
- Isasi, C. R., Lu, P. & Blafox, M. D. (2005) A metaanalysis of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography in the staging and restaging of patients with lymphoma. *Cancer*, 104, 1066-1074.
- Jacobs, C., Donaldson, S. S., Rosenberg, S. A., *et al* (1981) Management of the pregnant patient with Hodgkin's disease. *Ann Intern Med*, 95, 669-675.
- Jaffe ES, H. N., Stein H (2001) Tumors of Hematopoietic and Lymphoid Tissues. *Lyon: IARC Press*.
- Jemal, A., Siegel, R., Xu, J., *et al* (2010) Cancer statistics, 2010. *CA Cancer J Clin*, 60, 277-300.
- Jerusalem, G., Beguin, Y., Fassotte, M. F., *et al* (2003) Early detection of relapse by whole-body positron emission tomography in the follow-up of patients with Hodgkin's disease. *Ann Oncol*, 14, 123-130.
- Jerusalem, G., Beguin, Y., Fassotte, M. F., *et al* (1999) Whole-body positron emission tomography using 18F-fluorodeoxyglucose for posttreatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. *Blood*, 94, 429-433.
- Jerusalem, G., Warland, V., Najjar, F., *et al* (1999) Whole-body 18F-FDG PET for the evaluation of patients with Hodgkin's disease and non-Hodgkin's lymphoma. *Nucl Med Commun*, 20, 13-20.
- Josting, A., Wolf, J. & Diehl, V. (2000) Hodgkin disease: prognostic factors and treatment strategies. *Curr Opin Oncol*, 12, 403-411.
- Juweid, M. E. (2006a) Utility of positron emission tomography (PET) scanning in managing patients with Hodgkin lymphoma. *Hematology Am Soc Hematol Educ Program*, 259-265, 510-251.
- Juweid, M. E., Stroobants, S., Mottaghy, F.M. (2006b) Recommendations of the imaging committee of the International Harmonization Project (IHP) for FDG-PET (PET) use in patients with lymphoma. *J Nucl Med*, 452.
- Kim, H. K., Silver, B., Li, S., *et al* (2003) Hodgkin's disease in elderly patients (> or =60): clinical outcome and treatment strategies. *Int J Radiat Oncol Biol Phys*, 56, 556-560.

- Klimm, B., Diehl, V. & Engert, A. (2007) Hodgkin's lymphoma in the elderly: a different disease in patients over 60. *Oncology (Williston Park)*, 21, 982-990; discussion 990, 996, 998 passim.
- Klimm, B., Eich, H. T., Haverkamp, H., *et al* (2007) Poorer outcome of elderly patients treated with extended-field radiotherapy compared with involved-field radiotherapy after chemotherapy for Hodgkin's lymphoma: an analysis from the German Hodgkin Study Group. *Ann Oncol*, 18, 357-363.
- Kolstad, A., Nome, O., Delabie, J., *et al* (2007) Standard CHOP-21 as first line therapy for elderly patients with Hodgkin's lymphoma. *Leuk Lymphoma*, 48, 570-576.
- Levis, A., Anselmo, A. P., Ambrosetti, A., *et al* (2004) VEPEMB in elderly Hodgkin's lymphoma patients. Results from an Intergruppo Italiano Linfomi (IIL) study. *Ann Oncol*, 15, 123-128.
- Levy, R., Colonna, P., Tourani, J. M., *et al* (1995) Human immunodeficiency virus associated Hodgkin's disease: report of 45 cases from the French Registry of HIV-Associated Tumors. *Leuk Lymphoma*, 16, 451-456.
- Lister, T. A., Crowther, D., Sutcliffe, S. B., *et al* (1989) Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol*, 7, 1630-1636.
- Loeffler, M., Pfreundschuh, M., Ruhl, U., *et al* (1989) Risk factor adapted treatment of Hodgkin's lymphoma: strategies and perspectives. *Recent Results Cancer Res*, 117, 142-162.
- Lynch, H. T., Marcus, J. N. & Lynch, J. F. (1992) Genetics of Hodgkin's and non-Hodgkin's lymphoma: a review. *Cancer Invest*, 10, 247-256.
- Mack, T. M., Cozen, W., Shibata, D. K., *et al* (1995) Concordance for Hodgkin's disease in identical twins suggesting genetic susceptibility to the young-adult form of the disease. *N Engl J Med*, 332, 413-418.
- Macpherson, N., Klasa, R. J., Gascoyne, R., *et al* (2002) Treatment of elderly Hodgkin's lymphoma patients with a novel 5-drug regimen (ODBEP): a phase II study. *Leuk Lymphoma*, 43, 1395-1402.
- Mauch, P., Tarbell, N., Weinstein, H., *et al* (1988) Stage IA and IIA supradiaphragmatic Hodgkin's disease: prognostic factors in surgically staged patients treated with mantle and paraaortic irradiation. *J Clin Oncol*, 6, 1576-1583.
- Meda, B. A., Buss, D. H., Woodruff, R. D., *et al* (2000) Diagnosis and subclassification of primary and recurrent lymphoma. The usefulness and limitations of combined fine-needle aspiration cytomorphology and flow cytometry. *Am J Clin Pathol*, 113, 688-699.
- Meyer, R. M., Gospodarowicz, M. K., Connors, J. M., *et al* (2005) Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. *J Clin Oncol*, 23, 4634-4642.
- Nicklas, A. H. & Baker, M. E. (2000) Imaging strategies in the pregnant cancer patient. *Semin Oncol*, 27, 623-632.

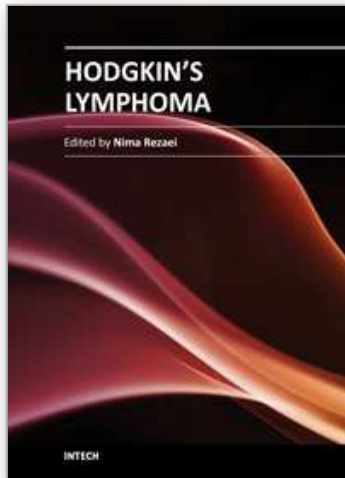
- Nogova, L., Reineke, T., Brillant, C., *et al* (2008) Lymphocyte-predominant and classical Hodgkin's lymphoma: a comprehensive analysis from the German Hodgkin Study Group. *J Clin Oncol*, 26, 434-439.
- Nogova, L., Reineke, T., Eich, H. T., *et al* (2005) Extended field radiotherapy, combined modality treatment or involved field radiotherapy for patients with stage IA lymphocyte-predominant Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Study Group (GHSG). *Ann Oncol*, 16, 1683-1687.
- Noordijk, E. M., Carde, P., Dupouy, N., *et al* (2006) Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. *J Clin Oncol*, 24, 3128-3135.
- Noordijk EM, T. J., Fermé C, *et al* (2005) First results of the EORTC-GELA H9 randomized trials: the H9-F trial (comparing 3 radiation dose levels) and H9-U trial (comparing 3 chemotherapy schemes) in patients with favorable or unfavorable early stage Hodgkin's lymphoma. *J Clin Oncol*, 23, 561S.
- Pavlovsky, S., Maschio, M., Santarelli, M. T., *et al* (1988) Randomized trial of chemotherapy versus chemotherapy plus radiotherapy for stage I-II Hodgkin's disease. *J Natl Cancer Inst*, 80, 1466-1473.
- Peters, M. (1950) A study of survivals in Hodgkin's disease treated radiologically. *Am J Roentgenol*, 63, 299.
- Press, O. W., LeBlanc, M., Lichter, A. S., *et al* (2001) Phase III randomized intergroup trial of subtotal lymphoid irradiation versus doxorubicin, vinblastine, and subtotal lymphoid irradiation for stage IA to IIA Hodgkin's disease. *J Clin Oncol*, 19, 4238-4244.
- Rueda Dominguez, A., Marquez, A., Guma, J., *et al* (2004) Treatment of stage I and II Hodgkin's lymphoma with ABVD chemotherapy: results after 7 years of a prospective study. *Ann Oncol*, 15, 1798-1804.
- Sadural, E. & Smith, L. G., Jr. (1995) Hematologic malignancies during pregnancy. *Clin Obstet Gynecol*, 38, 535-546.
- Santoro, A., Bonadonna, G., Valagussa, P., *et al* (1987) Long-term results of combined chemotherapy-radiotherapy approach in Hodgkin's disease: superiority of ABVD plus radiotherapy versus MOPP plus radiotherapy. *J Clin Oncol*, 5, 27-37.
- Santoro, A., Viviani, S. & Zucali, R. (1983) Comparative results and toxicity of MOPP vs ABVD com-bined with radiotherapy (RT) in PS IIB, III (A,B) Hodgkin's disease (HD). *Annual Meeting American Society of Clinical Oncology, San Diego, CA*.
- Schlembach, P. J., Wilder, R. B., Jones, D., *et al* (2002) Radiotherapy alone for lymphocyte-predominant Hodgkin's disease. *Cancer J*, 8, 377-383.
- Seam, P., Juweid, M. E. & Cheson, B. D. (2007) The role of FDG-PET scans in patients with lymphoma. *Blood*, 110, 3507-3516.

- Srouf, S. A. & Fayad, L. E. (2010) Treatment of Hodgkin Lymphoma. In *Neoplastic Hematopathology: Experimental and Clinical Approaches* (ed D. Jones), pp. 367-390: Humana Press.
- Straus, D. J., Portlock, C. S., Qin, J., *et al* (2004) Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. *Blood*, 104, 3483-3489.
- Tirelli, U., Errante, D., Dolcetti, R., *et al* (1995) Hodgkin's disease and human immunodeficiency virus infection: clinicopathologic and virologic features of 114 patients from the Italian Cooperative Group on AIDS and Tumors. *J Clin Oncol*, 13, 1758-1767.
- Tubiana, M., Henry-Amar, M., Carde, P., *et al* (1989) Toward comprehensive management tailored to prognostic factors of patients with clinical stages I and II in Hodgkin's disease. The EORTC Lymphoma Group controlled clinical trials: 1964-1987. *Blood*, 73, 47-56.
- Wasserman, T. H., Petroni, G. R., Millard, F. E., *et al* (1999) Sequential chemotherapy (etoposide, vinblastine, and doxorubicin) and subtotal lymph node radiation for patients with localized Hodgkin disease and unfavorable prognostic features: A phase II Cancer and Leukemia Group B Study (9051). *Cancer*, 86, 1590-1595.
- Weekes, C. D., Vose, J. M., Lynch, J. C., *et al* (2002) Hodgkin's disease in the elderly: improved treatment outcome with a doxorubicin-containing regimen. *J Clin Oncol*, 20, 1087-1093.
- Weihrauch, M. R., Re, D., Scheidhauer, K., *et al* (2001) Thoracic positron emission tomography using 18F-fluorodeoxyglucose for the evaluation of residual mediastinal Hodgkin disease. *Blood*, 98, 2930-2934.
- Weiss, L. M., Strickler, J. G., Warnke, R. A., *et al* (1987) Epstein-Barr viral DNA in tissues of Hodgkin's disease. *Am J Pathol*, 129, 86-91.
- Wilder, R. B., Schlembach, P. J., Jones, D., *et al* (2002) European Organization for Research and Treatment of Cancer and Groupe d'Etude des Lymphomes de l'Adulte very favorable and favorable, lymphocyte-predominant Hodgkin disease. *Cancer*, 94, 1731-1738.
- Wirth, A., Grigg, A., Wolf, M., *et al* (2011) Risk and response adapted therapy for early stage Hodgkin lymphoma: a prospective multicenter study of the Australasian Leukaemia and Lymphoma Group/Trans-Tasman Radiation Oncology Group. *Leuk Lymphoma*, 52, 786-795.
- Wirth, A., Seymour, J. F., Hicks, R. J., *et al* (2002) Fluorine-18 fluorodeoxyglucose positron emission tomography, gallium-67 scintigraphy, and conventional staging for Hodgkin's disease and non-Hodgkin's lymphoma. *Am J Med*, 112, 262-268.
- Wirth, A., Yuen, K., Barton, M., *et al* (2005) Long-term outcome after radiotherapy alone for lymphocyte-predominant Hodgkin lymphoma: a retrospective multicenter study of the Australasian Radiation Oncology Lymphoma Group. *Cancer*, 104, 1221-1229.

- Yahalom, J. (1990) Treatment options for Hodgkin's disease during pregnancy. *Leuk Lymphoma*, 2, 151.
- Yahalom, J. (2006) Favorable early-stage Hodgkin lymphoma. *J Natl Compr Canc Netw*, 4, 233-240.

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Hodgkin's Lymphoma is the book consisting of 11 chapters: Recent insights into the biology of Hodgkin's lymphoma, including historical aspects, epidemiology, pathophysiology, genetic defects, and prognostic indicators are explained in the intro chapters. After a translational chapter from tumor microenvironment to immunotherapeutic approach, treatment of early stage, advanced, and refractory Hodgkin's lymphoma are explained in the following chapters. MALT lymphoma and adverse effects of chemotherapy and radiotherapy in the affected patients are discussed in the subsequent chapters, while the final chapter is focused on survivorship in Hodgkin's lymphoma. The book is intended to present recent advances in the pathophysiology of Hodgkin's lymphoma as well as practical approach to diagnosis and management in clinical practice, which is hoped to be welcomed by the physicians, who wish to learn more about Hodgkin's lymphoma.

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