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Treatment of early-stage Hodgkin lymphoma

Andreas Engert[a,*], John Raemaekers[b,c]

[a] Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany
[b] Department of Internal Medicine, Rijnstate Hospital, Arnhem, The Netherlands
[c] Department of Hematology, Radboud University Medical Center Nijmegen, Nijmegen, The Netherlands

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ABSTRACT

Hodgkin lymphoma (HL) has become one of the best curable malignancies today. This is particularly true for patients with early-stage disease. Today, most patients in this risk group are treated with a combination of chemotherapy followed by small-field radiotherapy. More recent clinical trials such as the German Hodgkin Study Group (GHSG) HD10 study demonstrated, that even two cycles of ABVD followed by 20 Gy involved-field radiation therapy (IF-RT) are sufficient and result in more than 90% of patients being cured. The current treatment for early unfavorable patients is either four cycles of ABVD plus 30 Gy IF-RT or two cycles of $BEACOPP_{baseline}$ followed by two cycles of ABVD plus IF-RT. Here, the European Organization for Research and Treatment of Cancer (EORTC) demonstrated that in positron emission tomography (PET)-positive patients after two cycles of ABVD, treatment switched to two cycles of $BEACOPP_{baseline}$ plus radiotherapy results in significantly improved outcomes. Other aspects including attempts to further reduce intensity of treatment will be discussed.

1. Background

Based on clinical data and prognostic factors, most groups now allocate newly diagnosed patients with Hodgkin lymphoma (HL) into early favorable, early unfavorable, and advanced stages. Patients in early favorable stages are usually those in stages I/II without clinical risk factors. Risk factors include large mediastinal mass, extranodal disease, high erythrocyte sedimentation rate (ESR), or more than three or four nodal areas involved. Patients with at least one of these risk factors in stages I and II and selected stage IIB patients are included in the early unfavorable risk group (Table 1). Treatment of early-stage patients has included radiotherapy alone or combined modality treatment (CMT). More recent experimental approaches used chemotherapy alone for those who became positron emission tomography (PET)-negative after two cycles of chemotherapy or escalated treatment in patients who were PET-positive after two cycles of ABVD. The use of PET-guided treatment in PET-negative early favorable and early unfavorable HL patients is one of the current controversies in the treatment of this. In this article, we will describe the historical development of treatment in early stage patients, give an update on treatment outcome and an overview on late effects for both, early favorable and early unfavorable HL patients. We will also give a brief overview on new concepts for the treatment of early favorable, and unfavorable HL patients.

2. Radiotherapy in Hodgkin lymphoma

The historical mainstay of treatment in HL patients was radiotherapy shortly after the discovery of x-rays [1,2]. Subsequently, the Canadian Vera Peters pioneered clinical studies using higher doses and larger fields resulting in the cure or patients with early-stage disease [3]. After the advent of medical linear accelerators, Henry Kaplan and Saul Rosenberg became the godfathers of modern radiation therapy and many early-stage patients became disease-free [4]. With the discovery of the contiguous spread to nodal sites, radiotherapy was also applied to clinically non-involved adjacent areas. This technique, termed subtotal nodal irradiation, was mainly used in the 1970s and 80s [5]. However, this large-field radiation given in doses of 40 Gy or more was subsequently found to be associated with an increased mortality that exceeded the Hodgkin-related mortality after 10–15 years [6]. Side effects of radiotherapy depend on the volume irradiated, dose administered, and technique employed. In addition, the toxicity also depends on the choice and number of cycles of chemotherapy received. Radiation doses of

* Corresponding author. Department I of Internal Medicine, University Hospital of Cologne, Kerpener Str 62, D-50937 Cologne, Germany. Tel.: +49-221-478-0; fax: +49-221-478-3778.
E-mail address: a.engert@uni-koeln.de (A. Engert).

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Table 1
Definition of favorable and unfavorable (intermediate) early-stage Hodgkin lymphoma.

	EORTC	GHSG	NCIC/ECOG
Risk factors	(a) Large mediastinal mass (b) Age ≥ 50 years (c) ESR ≥ 50 without B symptoms or ≥ 30 with B symptoms (d) ≥ 4 nodal areas	(a) Large mediastinal mass (b) Extranodal disease (c) ESR ≥ 50 without B symptoms or ≥ 30 with B symptoms (d) ≥ 3 nodal areas	(a) Histology other than LP/NS (b) Age ≥ 40 years (c) ESR ≥ 50 (d) ≥ 4 nodal areas
Favorable	CS I—II (supradiaphragmatic) without risk factors	CS I-II without risk factors	CS I-II without risk factors
Unfavorable	CS I-II (supradiaphragmatic) with ≥ 1 risk factors	CS I or CS IIA with ≥ 1 risk factors, CS IIB with (c) or (d) but without (a) and (b)	CS I-II with ≥ l risk factors

EORTC European Organisation for Research and Treatment of Cancer, *GHSG* German Hodgkin Study Group, *NCIC* National Cancer Institute of Canada, *ECOG* Eastern Cooperative Oncology group, *ESR* erythrocyte sedimentation rate, *LP* lymphocyte predominance, *NS* nodular sclerosis, *CS* clinical stage.
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40–44 Gy were used in earlier studies even in patients achieving a complete remission with chemotherapy [7].

3. Combined modality treatment

After the advent of effective multi-agent chemotherapy such as MOPP (mustargen, vncristine, procarbazine, prednisone), COPP (cyclophosphamide, oncovin, procarbazine, prednisone), or ABVD (doxorubicin, beomycin, vinblastine, dacarbazine), a number of larger clinical trials investigated the reduction of both, radiation dose and field size [8]. Smaller radiation fields such as the involved-field (IF-RT) were given after combination chemotherapy (Fig. 1). In the European Organization for Research and Treatment of Cancer (EORTC)-Groupe d'Étude des Lymphomes de l'Adulte (GELA) H8F trial, a total of 542 patients were randomized between subtotal nodal irradiation given at doses of 36 Gy or three cycles of MOPP/ABV followed by IF-RT also at 36 Gy [9]. This trial demonstrated a clear superiority of CMT with an event-free survival (EFS) of 93% at 10 years as compared to 68% with radiation only; the overall survival was also significantly better for the CMT approach (97% *v* 92%; $P = .001$) (Fig. 2). The German Hodgkin Study Group (GHSG) HD7 trial reported similar results in a total of 650 early favorable patients with newly diagnosed HL [10]. In this study, there was also a significantly improved tumor control at 7 years with 88% of patients tumor-free when treated with CMT as compared to 67% treated with extended-field radiation therapy (EF-RT) (Fig. 3). The GHSG follow-up trial, HD10, then compared four cycles of ABVD with only two cycles as well as 30 Gy IF-RT with 20 Gy IF-RT [11]. In this trial with a 2 × 2 factorial design, which included 1,204 patients, there was no difference between four cycles of ABVD as well as 20 or 30 Gy IF-RT (Fig. 4). Thus, two cycles of ABVD followed by 20 Gy IF-RT has become the standard of care within the GHSG and has subsequently been adapted by many other groups and countries. In the GHSG follow-up trial, HD13, the GHSG continued to evaluate further dose reduction and deleted bleomycin, dacarbazine, or both from the ABVD backbone [12]. In this trial with more than 1600 patients randomized, the arms in which dacarbazine was deleted had to be closed early due to higher number of progressive disease and early relapses. A total of 1,243 patients were randomized between ABVD and the bleomycin-deleted AVD. There was a 4.3% difference in the progression-free survival (PFS) at 5 years (Fig. 5). Formally, we were unable to demonstrate that two cycles of AVD were non-inferior to two cycles of ABVD each followed by 30 Gy IF-RT. Fortunately, there

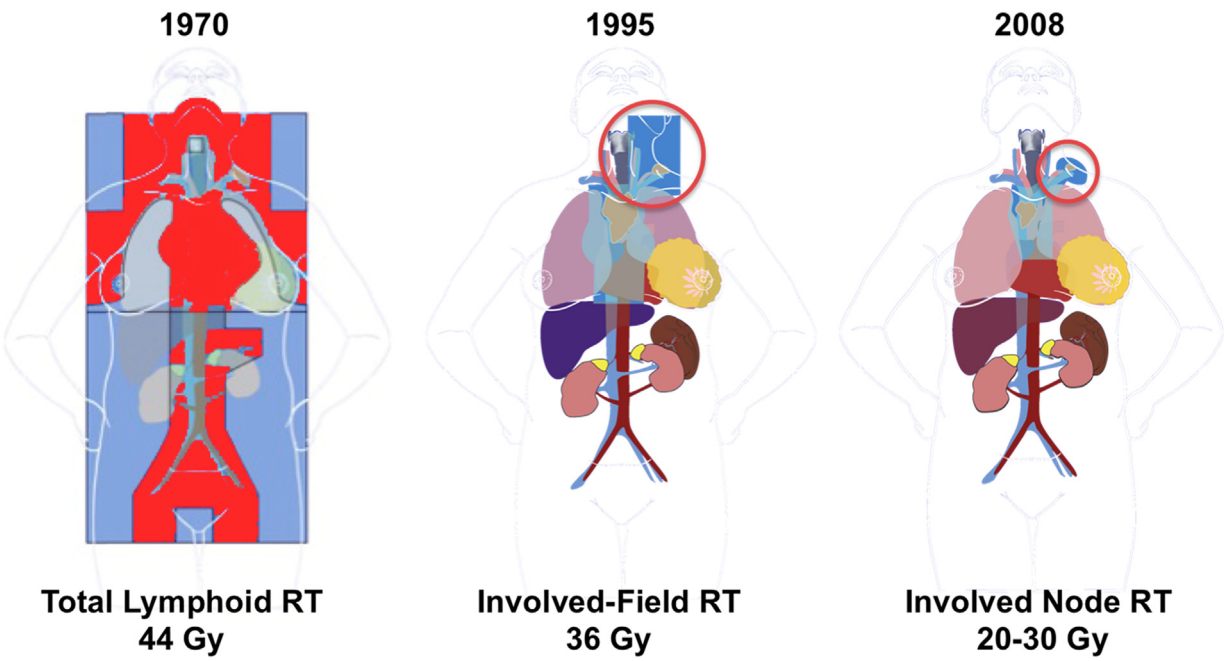

Fig. 1. Evolution of radiotherapy in HL. Adapted from Yahalom, Lugano, 2008. © Yahalom, J.