Radiotherapy in Early-Stage Favourable Hodgkin's Lymphom: Experiences of the German Hodgkin Study Group

Rolf-Peter Müller* and Hans Theodor Eich

Department of Radiation Oncology, University of Cologne, Germany, Radiotherapy Reference Center of the German Hodgkin Study Group (GHSG), Germany

Abstract: Since its beginning, more than 15.000 patients with Hodgkin's lymphoma (HL) have been enrolled into the multicentre randomized trials of the German Hodgkin Study Group (GHSG). Within 4 study generations the treatment of HL has been developed stepwise by using the results of the completed protocols. According to radiotherapy, the study group successfully evaluated different dose-effect relationships and could also prove the efficacy of involved field radiotherapy in early stages in combination with effective chemotherapy. According to the recent final analysis of the HD10 trial for patients with early-favourable HL, a radiation dose of 20 Gy to the involved lymph node areas preceded by short-term chemotherapy (ABVD x 2) is the standard for these patients. An extensive radiotherapy quality assurance program, performed by the GHSG radiotherapy reference centre in Cologne, has proven to be successful and necessary to ensure that with reduced radiation doses and volumes a precise treatment, as defined by the protocol, can be performed by the participating radiotherapy departments.

Keywords: Hodgkin lymphoma, involved field radiotherapy, radiation dose.

INTRODUCTION

The radiosensibility of Hodgkin's lymphoma (HL) is well established since 1902, when Pusey [1] was one of the first to publish about radiotherapeutical treatment of a HL.

In the early years, radiotherapy was the only curative treatment for this systemic disease, but the reports of Kaplan and Rosenberg [2] and Peters [3] in the fifties and seventies showed that irradiation of involved lymph node regions only resulted in high local and distant recurrences.

The introduction of linear accelerator based high dose extended field (EF)-radiotherapy by Kaplan in Stanford was a milestone in the evolution of definitive curative radiotherapy strategies. The application of the mantle field for supradiaphragmatic and the inverted Y (with or without including the spleen or splenic pedicle) for infradiaphragmatic disease resulted in a dramatic improvement of survival rates in the early stages I and II (Ann Arbor) from 25 – 30 % in the sixties to 65 – 80 % in the eighties [4]. Kaplan reported about a close relationship between radiation dose and cure rates in the case of definitive radiotherapy. A dose of at least 40 Gy resulted in local recurrences below 5% and is today the standard dose for radiotherapy only outside protocols. Despite complete remission rates after radiotherapy of 90 – 100%, the overall recurrence rate (including in-field, marginal and distant relapses) was between 20 and 30%. Analysis of the relapses revealed some stage migrating risk factors: large mediastinal mass, extra nodal involvement, number of involved lymph node areas ($\geq$ 3) and high ESR.

*Address correspondence to this author at the Department of Radiation Oncology, University of Cologne, Germany, Radiotherapy Reference Center of the German Hodgkin Study Group (GHSG), Germany; Tel: +49-221-478 5450; Fax: +49-221-478 6158; E-mail: rolf-peter.mueller@uk-koeln.de

The possibility of more accurate staging by using new imaging techniques like ultrasonography, CT and MRI as well as PET in the recent years resulted e.g. in the definition of early-favourable, early-unfavourable (intermediate) and high risk stages and more specific, risk adapted treatment strategies.

The objective of this article is to show recent achievements and developments in the management of early-stage favourable HL exemplified by the strategy of the German Hodgkin Study Group (GHSG), where radiotherapy still is an integral part within combined modality treatment.

CLINICAL RESULTS IN EARLY-FAVOURABLE STAGES

From a Single Radical Approach to a Combination of Mini Treatments

Treatment strategies in HL changed dramatically during the last recent years. For many decades the optimal and standard treatment for early-stage favourable HL was EF-radiotherapy. Today major study groups have changed from EF-radiotherapy to involved field (IF)-radiotherapy preceded by short-term chemotherapy to reduce the extent of late toxicities without the risk of lowering the overall survival rates (Fig. **1**).

The extension of the disease at the time of diagnosis still is the most important risk factor. Radiotherapy only resulted, as reported by the Stanford group [4] in the eighties, in complete remission rates of 100% and recurrent free survival of 80% in stages PS IA, IIA and IIB without large mediastinal tumour. Most of the recurrences could be treated successfully by polychemotherapy. These excellent results could not be confirmed by other well-recommended study groups.

2210-2892/10

The evolution of effective treatments for early-stage HL is best exemplified by the successive randomized trials of the GHSG. The first protocol with a radiotherapeutic question was the HD4 trial (1988-1994). The major aim of HD4 was to show whether the radiation dose to the non-involved EF could be reduced while maintaining effective tumour control. Thus patients in stage I or II without risk factors (large mediastinal mass, extra nodal extension, massive spleen involvement, $\geq$ 3 lymph node areas, high ESR) were randomized between standard treatment consisting of 40 Gy EF-radiotherapy (arm A) and 30 Gy EF-radiotherapy plus additional 10 Gy to the IF (arm B). Staging laparotomy was obligatory in this protocol. The results showed no statistically significant differences in recurrent free survival (RFS) and overall survival (OS) between the two treatment arms [5], but the overall recurrence rate approached 20 %. Due to a sufficient salvage therapy, RFS after seven years came up to 80 % and the overall survival was 93 %. A careful relapse analysis could show that the majority of recurrences occurred outside of the radiation fields and was rated as diagnostic error of the initial staging. In the HD4 protocol the GHSG initiated for the first time a successful quality assurance program. For all randomized patients a radiotherapy treatment plan was given by the radiotherapy reference centre based on the documentation of the disease extension on case report forms (CRF). After the end of the EF-radiotherapy, simulation and verification films of every individual patient as well as the treatment data were analysed by an expert panel. One important achievement of this retrospective quality control was to show that deviations of radiation treatment portals and radiation doses from prospective treatment prescriptions proved to be unfavorable prognostic factors for patients with early-stage HL [5-11].

To eradicate microscopic disease, in HD7 (1994-1998) patients were randomized between radiotherapy alone (30 Gy EF + 10 Gy IF) (arm A) or upfront 2 cycles ABVD followed by radiotherapy (30 Gy EF + 10 Gy IF) (arm B) for early stages PS IA, IIA, IIB without risk factors. Staging laparotomy was not obligatory and the spleen was irradiated with 36 Gy in both treatment arms. At 7 years there was no difference between treatment arms in terms of complete response rate (arm A: 95%, arm B: 94%) or OS (arm A: 92%, arm B: 94%; p = 0, 43). However, freedom from treatment failure (FFTF) was significantly different with 67% in arm A and 88% in arm B ($p \leq 0, 0001$). This was mainly due to significantly more relapses after EF-radiotherapy only (arm A: 22%; arm B: 3%) [6, 12, 13].

The aim of the HD10 trial (1998-2002) was to reduce acute and long term toxicities while maintaining optimal tumour control. According to radiotherapy, the HD10 trial represents a very decisive step, since irradiation was performed as IF-radiotherapy in all treatment arms [13]. The HD10 trial was designed to investigate the optimal intensity of both, chemotherapy and radiotherapy. Therefore patients in stages PS I or II without risk factors were randomized in a four-arm study between an IF-radiotherapy dose of 30 Gy versus 20 Gy and 2 versus 4 cycles of ABVD. To ensure that IF-radiotherapy was performed exactly according to the RT-prescriptions of the protocol, an extensive quality assurance program was performed. A prospective radiotherapy planning by the radiotherapy reference centre in Cologne on the basis of clinical and laboratory data as well as on the basis of all pre-treatment diagnostic imaging was initiated [14]. The recent final analysis of this large trial showed that the reduction of chemotherapy is possible and that there was no difference between the different radiation doses [15].

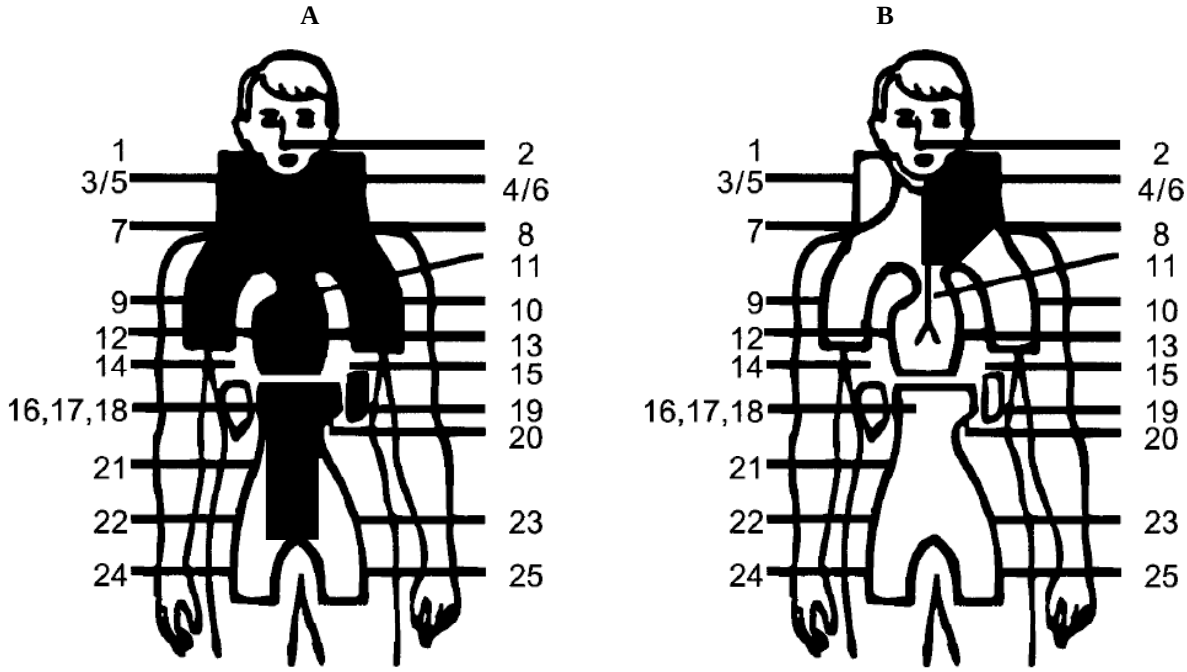

Fig. (1). Comparison of extended field radiation therapy (EFRT) vs. involved field radiation therapy (IFRT) for a patient with Hodgkin's lymphoma stage I in the left neck: disease involvement lower cervical region on the left side. (**A**) Typical EFRT-volume (mantle field plus the Paraaortic area, splenic hilar region, and spleen); (**B**) the IFRT-volume includes the whole left neck (upper and lower cervical region plus supra- and infraclavicular lymph nodes).

Thus, 2xABVD+20Gy IF-radiotherapy should be regarded standard of care in this patient population.

The current GHSG study for early-favourable patients (HD13, since 2003-still open) is testing the exclusion of bleomycin (pulmonary toxicity) and/or darcarbazine (questionable efficacy) from the shorter regimen, while maintaining IF-radiotherapy at 30 Gy.

In the EORTC/GELA-Intergroup study H10F for patients with early-favourable stages the IF-radiotherapy was recently replaced by the involved node (IN)-radiotherapy concept as a consolidation after ABVD chemotherapy. Since this concept has never been tested in a randomized trial the GHSG aims to compare it with standard IF-radiotherapy in their future study generation.

It is unlikely that the reduction of chemotherapy accomplished in HD10 and tested in HD13 could be possible without maintaining the radiotherapy component, and vice versa. At present, the combined modality treatment, consisting of chemotherapy upfront, followed by IF-radiotherapy is the standard treatment of the GHSG for early-favourable HL.

REFERENCES

[1] Pusey, W.A.; Cases of sarcoma and of Hodgkin's disease treated by exposures of x-rays: a preliminary report. *JAMA*, **1902,** *38*, 166-169.

[2] Kaplan, H.S.; Rosenberg, S.A. The management of Hodgkin's disease. *Cancer* **1975,** *36*, 796-803.

[3] Peters, M.; Middlemiss, K. A study of Hodgkin's disease treated by irradiation. *Am. J. Roentgenol.*, **1958,** *79*, 114-121.

[4] Rosenberg, S.A.; Kaplan, H.S. The evolution and summary results of the Stanford randomised clinical trials of the management of Hodgkin's disease: 1962-1984. *Int. J. Radiat. Oncol. Biol. Phys.*, **1985,** *11*, 5-22.

[5] Dühmke, E.; Franklin, J.; Pfreundschuh, M.; Sehlen, S.; Willich, N.; Rühl, U.; Müller, R.P.; Lukas, P.; Atzinger, A.; Paulus, U.; Lathan, B.; Rüffer, U.; Sieber, M.; Wolf, J.; Engert, A.; Georgii, A.; Staar, S.; Herrmann, R.; Beykirch, M.; Kirchner, H.; Emminger, A.; Greil, R.; Fritsch, E.; Koch, P.; Drochtert, A.; Brosteanu, O.; Hasenclever, D.; Loeffler, M.; Diehl, V. Low-dose radiation is sufficient for the noninvolved extended field treatment in favorable early-stage Hodgkin's disease: long-term results of a randomized trial of radiotherapy alone. *J. Clin. Oncol.*, **2001,** *19* (11), 2905-14.

[6] Müller, R.-P.; Eich, H.T. The developement of quality assurance of radiotherapy within the German Hodgkin Study Group (GHSG) - Introduction, continuing work and results of the radiotherapy reference panel. *Strahlenther. Onkol.*, **2005,** *181* (9), 557-566.

[7] Groscu, A.-L.; Piert, M.; Weber, W.A.; Jeremic, B.; Picchio, M.; Schratzenstaller, U.; Zimmermann, F.B.; Schwaiger, M.; Molls, M. Positron emission tomography for radiation treatment planning. *Strahlenther. Onkol.*, **2005,***181* (8), 483-499.

[8] Dörr, W.; Köst, S.; Keinert, K.; Glaser, F.H.; Endert, G.; Herrmann, T. Early intestinal changes following abdominal radiotherapy comparison of endpoints. *Strahlenther. Onkol.*, **2006**, *182* (1), 1-8.

[9] Trott, K.-R.; Kamprad, F. Estimation of cancer risks from radiotherapy of benign diseases. *Strahlenther. Onkol.*, **2006**, *182* (8), 431-436.

[10] Bölling, T.; Schuck , A.; Rübe, C.; Hesselmann, S.; Pape, H.; Dieckmann, K.; Pöllinger, B.; Kortmann, R.D.; Speiser-Held, I.; Meyer, F.M.; Martini, C.; Asadpour, B.; Timmermann, B.; Beck, J.D.; Langer, T.; Paulides, M.; Schmidt, B.; Willich, N. Therapy-associated late effects after irradiation of malignant diseases in childhood and adolescence. Feasibility analyses of a prospective multicenter register study. *Strahlenther. Onkol.*, **2006,** *182* (8), 443-449.

[11] Engert, A.; Schiller, P.; Josting, A.; Herrmann, R.; Koch, P.; Sieber, M.; Boissevain, F.; De Wit, M.; Mezger, J.; Dühmke, E.; Willich, N., Müller, R.-P., Schmidt, B.F., Renner, H., Müller-Hermelink, H.K., Pfistner, B., Wolf, J., Hasenclever, D., Loffler, M., Diehl, V. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavourable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's lymphoma Study Group. *J. Clin. Oncol.*, **2003,** *21*, 19: 3601-3608.

[12] Eich, H.T.; Haverkamp, U.; Engert, A.; Kocher, M.; Skripnitchenko, R.; Brillant, C.; Sehlen, S.; Dühmke, E.; Diehl, V.; Müller, R.P. Biophysical analysis of the acute toxicity of radiotherapy in Hodgkin's lymphoma – a comparison between extended field and involved field radiotherapy based on the data of the German Hodgkin Study Group (GHSG). *Int. J. Radiat. Oncol. Biol. Phys*., **2005**, *63* (3), 860-865.

[13] Müller, R.-P.; Eich, H.T. Current role of radiotherapy in the treatment of Hodgkin's disease. In *Update Principles and Practice of Radiation Oncology*; Perez CA, Brady L.W., Halperin E.C., Schmidt-Ullrich R.K., E.S.; Lippincott Williams & Wilkins **2005**; Vol. *6* Number 2, pp. 2-15.

[14] Eich, H.T.; Staar, S.; Gossmann, A.; Hansemann, K.; Skripnitchenko, R.; Kocher, M.; Semrau, R.; Engert, A.; Josting, A.; Franklin, J.; Krug, B.; Diehl, V.; Müller, R.P. Centralized radiation oncological review of cross-sectional imaging of Hodgkin's disease leads to significant changes of the required involved field – results of a quality assurance program of the German Hodgkin Study Group (GHSG). *Int. J. Radiat. Oncol. Biol. Phys*., **2004,** *58* (4), 1120-1126.

[15] Engert, A.; Diehl, V.; Pluetschow, A.; Eich, H.T.; Herrmann, R.; Doerken, L.K.; Greil, R.; Markova, J.; Fuchs, M.; Borchmann, P.; Müller-Hermelink, H.K.; Müller, R.P. *Two Cycles of ABVD Followed by Involved Field Radiotherapy with 20 Grey (Gy) Is the New Standard of Care in the Treatment of Patients with Early-Stage Hodgkin Lymphoma: Final Analysis of the Randomized German Hodgkin Study Group (GHSG) HD10*. 51. ASH Meeting New Orleans **2009**, *716*.

Received: April 12, 2010 Revised: July 08, 2010 Accepted: July 09, 2010