Current Role and Future Developments of Radiotherapy in Early-stage Favourable Hodgkin's Lymphoma

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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 (≥ 3) and high ESR.

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 Treatment

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.

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 tumor. Most of the recurrences could be treated successfully by polychemotherapy. These excellent results could not be confirmed by other well-recommended study groups.

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 noninvolved EF could be reduced while maintaining effective tumor control. Thus patients in stage I or II without risk factors (large mediastinal mass, extranodal extension, massive spleen involvement, ≥ 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 center 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 unfavourable prognostic factors for patients with early-stage HL (Figure1) [5–10].

Key Words: Hodgkin's lymphoma · Involved field radiotherapy · Combined modality treatment · Quality assurance

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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 tumor 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, chemotherapyy 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 center 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]. After 4 years, FFTF was similar in all groups – 94%, and overall survival was 97%. Reducing chemotherapy appeared safe, and at this point, there was no difference between the different radiation doses (Table 1).

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.

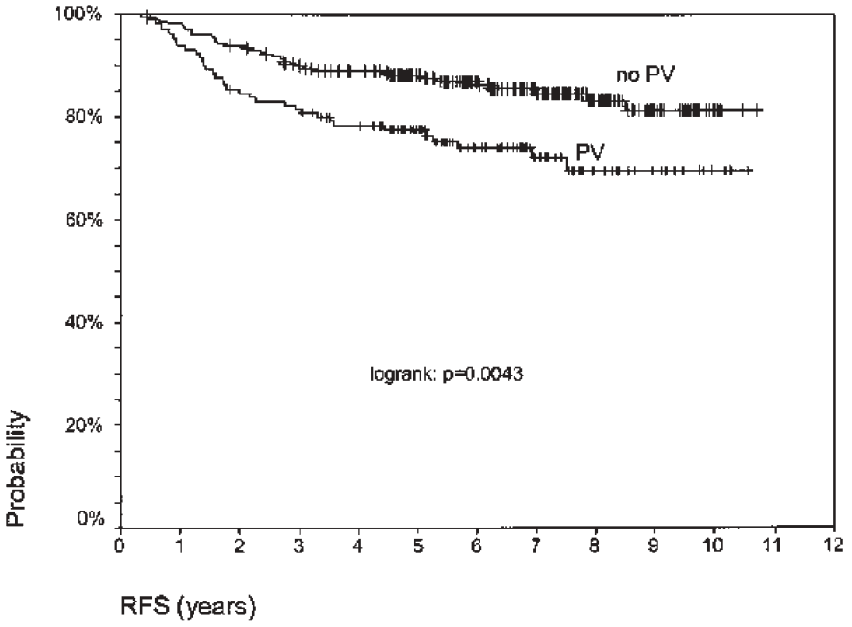

Figure 1. Relapse-free survival to presence (n=127) or absence (n=242) of a relevant radiotherapy protocol violation (PV). Results of the HD4 trial of the GHSG.

Table 1. Results of clinical trials for patients with early-stage favourable Hodgkin's lymphoma.

Trial	Treatment	# Pat.	Results
SWOG #9133	A. 3 (dox.+vinbl.) + STLI (36-40 Gy) B. STLI (36-40 Gy)	165 161	94% (FFTF);98% (SV); 81% (FFTF); 96% (SV); [3 years]
Stanford V (CSI-IIA)	8 weeks Stanford V + modified IF RT (30 Gy)	65	94.6% (FFP); 96.6% (SV) [16 months]
Milan 1990–97	A. 4 ABVD + STLI B. 4 ABVD + IF RT	65 68	97 % (FFP); 93% (SV) 97 % (FFP); 93% (SV); [5 years]
EORTC/ GELA H7F	A. 6 EBVP + IF RT (36 Gy) B. STNI	168 165	90 % (RFS); 98% (SV) 81 % (RFS); 95% (SV); [5 years]
EORTC/ GELA H8F	A. 3 MOPP/ABV + IF RT (36 Gy) B. STNI	271 272	99 % (RFS); 99% (SV) 80 % (RFS); 95% (SV); [4 years]
EORTC/ GELA H9F	A. 6 EBVP + IF RT (36 Gy) B. 6 EBVP + IF RT (20 Gy) C. 6 EBVP		reached final recruitment, arm C was closed earlier due to more recurrences
GHSG HD7	A. EF RT 30 Gy (40 Gy IF) B. 2 ABVD + EF RT 30 Gy (40 Gy IF)	305 312	75% (FFTF); 94% (SV); 91% (FFTF); 94% (SV); [5 years]
GHSG HD10	A. 4 ABVD + IF RT (30Gy) B. 4 ABVD + IF RT (20Gy) C. 2 ABVD + IF RT (30Gy) D. 2 ABVD + IF RT (20Gy)	1370	no final analysis available 4-years-FU: 94%(FFTF) 97% (SV)
GHSG HD13	A. 2 ABVD + IF RT (30Gy) B. 2 ABV + IF RT (30Gy) C. 2 AVD + IF RT (30Gy) D. 2 AV + IF RT (30Gy)		ongoing trial

GHSG: German Hodgkin Study Group; EORTC: European Organization for Research and Treatment of Cancer, GELA: Groupe d'Etude des Lymphomes de l'Adulte; EF/IF RT: Extended/Involved field radiotherapy; STLI: Subtotal lymphoid irradiation; STNI: Subtotal nodal irradiation; FFTF: Freedom from treatment failure; RFS: relapse free survival; FFP: freedom from progression; SV: overall survival.

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 [15].

References

1. Pusey WA. Cases of sarcoma and of Hodgkin's disease treated by exposures of x-rays: a preliminary report. JAMA 1902;38:166–169.
2. Kaplan HS, Rosenberg SA. 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 SA, Kaplan HS. 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, et al. 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 HT. 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 WA, et al. Positron emission tomography for radiation treatment planning. Strahlenther Onkol 2005;181 (8): 483–499.
8. Dörr W, Köst K, Keinert K, et al. 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, et al. 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, et al. 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 HT, Haverkamp U, Engert A, et al. 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 HT. Current role of radiotherapy in the treatment of Hodgkin's disease. In: Perez CA, Brady LW, Halperin EC, Schmidt-Ullrich RK (eds.). Update Principles and Practice of Radiation Oncology. Lippincott Williams & Wilkins 2005; Vol 6 Number 2:2–15.
14. Eich HT, Staar S, Gossmann A, et al. 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 Biopl Phys 2004;58(4):1120–1126.
15. Eich HT, Hansemann K, Müller R-P. Behandlung früher Stadien des Hodgkin-Lymphoms unter dem Aspekt der Qualitätssicherung. Onkologe 2005;11: 924–932.

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