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Review

Role of modern radiation therapy in early stage Hodgkin's lymphoma: A young radiation oncologists' perspective

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ABSTRACT

The role of radiotherapy is well established in combined modality programs for early stage Hodgkin's lymphoma, but still debated with regards to late toxicity issues. Modern radiotherapy prescribing attitudes include lower doses and smaller fields, together with the implementation of sophisticated and dedicated delivery techniques. Aim of this review is to briefly discuss the current role of radiotherapy in this field and the potential future developments. Major trials conducted in recent years in early stage Hodgkin's lymphoma are critically reviewed and discussed with a focus on radiotherapy-related issues and with an attention to current treatment options by a "young" radiation oncologists' perspective.

1. Background

For patients with Hodgkin's lymphoma (HL) in any stage, the primary goal of therapy is cure. In recent studies, the survival rate in early stages has consistently been 90% or higher. In studies with long-term follow-up, treatment-related complication deaths exceed the number of cancer-related deaths. The frequency of late complications is dependent on the treatment used. Radiation-related cardiac disease (coronary artery disease, myocardial injury, valvular disease, pericardial fibrosis) and second malignancies (breast and lung cancer) may occur many years after thoracic irradiation and are dependent on radiation doses and volumes. The risk of late complications after chemotherapy (cardiac toxicity, second malignacies) appears to be dependent on the type of drugs prescribed (alkylating agents, anthracycline, bleomycin) and on the cumulative dose. Treatment strategies in HL changed therefore dramatically during recent years, with current clinical protocols focusing, especially on early stage HL, on minimizing the intensity of treatment to avoid late potentially fatal toxic effects, without the risk of lowering overall survival rates.

1.1. *Radiotherapy in the cure of Hodgkin's lymphoma*

For many decades, the optimal and standard treatment for early stage HL was extended field radiotherapy (EF-RT), totally replaced right now with a combination of short-term chemotherapy with involved field radiotherapy (IF-RT). The evolution of effective treatments for early stage HL is best exemplified by the successive randomized trials of the

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German Hodgkin's Study Group (GHSG), as discussed in a paper by Hans Theodor Eich and Rolf-Peter Müller in 2007.[1] The first protocol dealing with a radiotherapy-related endpoint was the HD4 trial, designed in the early eighties (1988–1994). The major aim of HD4 was to show whether the radiation dose to the non-involved lymphatic regions could be reduced while maintaining effective tumour control. This trial was conceived as an effort towards a further improvement of results obtained in 1962–1984 by the Stanford group in early stages with radiotherapy, showing complete remission rates of 100% and recurrence free survival of 80% in stages IA, IIA and IIB without large mediastinal tumour (excellent results unconfirmed by other groups). In HD4, 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, but the overall recurrence rate approached 20%, as reported by the Stanford studies. Due to an effective salvage therapy (polychemotherapy), RFS after seven years went up to 80% and the overall survival was 93%.[2] The pattern of relapse in this study showed interesting results, with the majority of recurrences documented outside high dose radiation fields, probably due to errors in initial staging or in radiotherapy prescription. Due to the crucial importance of good quality radiotherapy in such studies, German Hodgkin Study Group promoted the creation of a task force for radiotherapy quality assurance, and for all patients enrolled in the study a treatment plan was given by the radiotherapy reference centre based on the documentation of the disease extension on case report forms (CRF), and after completion of the EF radiotherapy, simulation and verification films of every individual patient as well as treatment data analysis by an expert panel. This retrospective quality control study showed that deviations of radiation treatment portals and radiation doses from prospective treatment prescriptions were unfavourable prognostic factors for patients with early-stage HL.[3] Next research step of GHSG was a trial designed to keep the approach of low-dose EF of HD4 while trying to eradicate microscopic disease with chemotherapy and improving Relapse-Free Survival. 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%).[4]

HD10 trial (1998–2002) was designed to eliminate the EF approach, including IF only and with the primary aim of reducing acute and long term toxicities while maintaining optimal tumour control. This trial also incorporated results of major studies published in the nineties by North-American, European/French and Italian Groups, focusing on the role of chemotherapy and including the "involved fields" concept. All these studies showed a complete equivalence for the brief chemotherapy + IF vs. EF alone or chemotherapy + EF approach. As well pointed out by HT Eich and RP Muller, the HD10 trial represents a very decisive step, since irradiation was performed as IF radiotherapy in all treatment arms. The HD10 is the first trial designed to investigate the optimal intensity of chemotherapy and radiotherapy. The whole treatment strategy is based upon a selection of patients with favourable prognostic factors, in whom reduced treatment intensity should offer very good results in terms of disease control while reducing toxicity. Therefore, patients in stages I or II without risk factors (no bulky disease, less than 4 involved sites, low ESR values) 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 make sure that IF-radiotherapy was performed exactly according to the RT-prescriptions of the protocol, an extensive quality assurance program was performed. Results of HD10 were published in 2010[5]: the 2 chemotherapy regimens did not differ significantly with respect to freedom from treatment failure ($P = 0.39$) or overall survival ($P = 0.61$). At 5 years, the rates of freedom from treatment failure were 93.0% (95% confidence interval [CI], 90.5–94.8) with the four-cycle ABVD regimen and 91.1% (95% CI, 88.3–93.2) with the two-cycle regimen. When the effects of 20-Gy and 30-Gy doses of radiation therapy were compared, there were also no significant differences in freedom from treatment failure or overall survival ($P = 0.61$). HD10 demonstrated that treatment with two cycles of ABVD followed by 20 Gy of involved field radiation therapy is as effective as, and less toxic (acute toxicity) than, four cycles of ABVD followed by 30 Gy of involved-field radiation therapy. A parallel but different study is ongoing in early stage favourable and unfavourable patients, designed by EORTC/GELA/IIL, the H10 trial, comparing a treatment strategy based on interim (after 2 ABVD cycles) 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and on the introduction of an innovative radiotherapy concept, the so-called "Involved Nodes Radiation Therapy" (INRT). This trial is now closed and final results will be available in next years. Two major trials investigating the role of chemotherapy alone (ABVD) were published some years ago, showing that CT alone is a feasible option for patients with non-bulky early-stage Hodgkin's lymphoma.[6,7] An increased freedom from progression was shown for the combined-modality arms when compared with chemotherapy alone (86% vs. 81% and 93% vs. 87%, respectively), and since current recommended approaches towards relapse after primary therapy include autologous stem cell transplant, the current dilemma facing clinicians is whether all patients should be irradiated to prevent progression in 5–6% of cases or whether it is justified to withhold radiation, knowing that patients with progression will be referred to high-dose chemotherapy.

For patients with unfavourable early stage disease presentation (bulky disease, multiple involved sites, high ESR values), the treatment approach was similar but results should be evaluated separately; all major trials investigated a combination of at least 4 chemotherapy cycles (however 6 cycles