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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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ARTICLE INFO

Article history:
Received 22 December 2011
Received in revised form
27 March 2012
Accepted 27 May 2012

Keywords:
Hodgkin's lymphoma
Radiotherapy
Combined modality therapy

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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http://dx.doi.org/10.1016/j.rpor.2012.05.003

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

Table 1 – Temporal evolution of radiation therapy for Hodgkin's lymphoma.

RT approach	Years	Dose	Technique	Tools	Facilities
EFRT	1960–1990	40–44 Gy	2D RT	2D planning	Cobalt Units; first LINACs
IFRT	1995 to present	30–36 Gy	3DCRT Static-IMRT	Forward planning Inverse planning	LINACs with cerrobend blocks LINACs with MLC
IFRT-INRT	2008 to present	20–30 Gy	3DCRT Static-IMRT Arc-therapy Tomotherapy	Forward planning Inverse planning Biologic optimization Multimodality imaging Dose painting IGRT	LINACs with MLC IGRT/dynamic IMRT dedicated LINACs

in the majority of treatment arms) + EF or IF radiotherapy (EORTC H7U, EORTC/GELA H8U, EORTC/GELA H9U), showing that the IF approach is safe and equivalent to EF and that, globally, the results of combined modality therapy are inferior to those in favourable stages, with FFTF rates in the range of 84–94%. In this setting, a reduction in treatment intensity did not demonstrate any equivalence in terms of disease control. The recently published GHSG HD11 trial[8] was designed to specifically investigate this issue. With a total of 1395 patients included, BEACOPP was more effective than ABVD when followed by 20 Gy of IFRT (5-year FFTF difference, 5.7%; 95% CI, 0.1–11.3%), however, there was no difference between BEACOPP and ABVD when followed by 30 Gy of IFRT (5-year FFTF difference, 1.6%; 95% CI, −3.6% to 6.9%). Similar results were observed for the radiotherapy question: after 4 cycles of BEACOPP, 20 Gy was not inferior to 30 Gy (5-year FFTF difference, −0.8%; 95% CI, −5.8% to 4.2%), whereas inferiority of 20 Gy cannot be excluded after four cycles of ABVD (5-year FFTF difference, −4.7%; 95% CI, −10.3% to 0.8%). At the moment, in unfavourable early stage HL, 4 ABVD followed by 30 Gy IF-RT continues to represent a standard clinical approach (waiting for the final results of HD17 on 2 ABVD + 2 BEACOPP + IFRT 30 Gy).

Table 1 summarizes the time-trend in radiotherapy changes in Hodgkin's lymphoma in recent years.

1.2. *Open issues and future developments*

As briefly discussed, currently radiotherapy in early favourable and unfavourable presentations is an essential component of the standard treatment, as confirmed by a recent study by the Cochrane Collaboration Group on the outcome of combined modality therapy vs. chemotherapy alone (primary endpoint overall survival).[9] This important message is incorporated in therapeutic indications within international guidelines (such the ones from NCCN or ESMO) where combined modality treatment still represents a mainstay option as HL therapeutic strategy.[10,11] Globally and independently from the treatment approach, the issue of late toxicity still remains crucial. In almost all trials with long-term follow-up, the number of patients who die from other causes exceeds the number of patients dying from lymphoma. Second malignancies and fatal cardiac events are the main causes of death in a cohort of patients who presently show a relapse-free survival probability of approximately 90%. Due to the established toxicity of extended field radiotherapy, especially in patients receiving mediastinal irradiation, several studies were designed in recent years in order to decrease toxicity either by reducing or avoiding radiotherapy, trying to show a superior overall survival rate in chemotherapy only arms secondary to a reduction of RT-related deaths. An example of this research strategy is the already cited NCIC HD6 trial, designed with the aim of comparing chemotherapy only (4–6 ABVD cycles) to RT only or with 2 ABVD cycles (according to risk groups), with subtotal nodal irradiation of 35 Gy. A New England Journal of Medicine special issue dedicated to haematology-related studies was edited in December 2011 concurrently with the 2011 ASH Annual Meeting, and the main paper of this issue is the final report of this study.[12] Results were very disappointing for the radiotherapy arm. The median length of follow-up was 11.3 years. At 12 years, overall survival rate was 94% among those receiving ABVD alone, as compared with 87% among those receiving subtotal nodal radiation therapy. The rates of freedom from disease progression were 87% and 92% in the two groups, respectively, and the rates of event-free survival were 85% and 80%, respectively. Among the patients randomly assigned to ABVD alone, 6 died from Hodgkin's lymphoma or an early treatment complication and 6 died from other causes; among those receiving radiation therapy, 4 deaths were related to Hodgkin's lymphoma or early toxic effects from the treatment and 20 were related to other causes. An obvious critical point in this trial is that the subtotal nodal radiation therapy is no longer employed and radiation induced toxicity is expected to be less relevant in the future with modern radiotherapy strategies and techniques (IF-RT, IN-RT, IMRT, IGRT, CT-PET-driven contouring) employed in recent years. Comments in the Editorial by David J. Straus[13] are focused on the final demonstration that ABVD only is probably a better approach, taking into account that efficient salvage therapies can compensate the higher relapse rate of chemotherapy only. In this complex scenario, as briefly shown, many other groups tested different strategies, based on toxicity reduction by means of radical modification of radiotherapy doses and volumes. These approaches are based on the assumption that late toxicity data on radiation therapy from historical trials cannot be fully translated to current protocols, and probably it is unrealistic that every kind of radiation therapy strategy is harmful at the same level. A new radiation oncology question, such as the possibility of a further reduction of radiation fields compared to the classical involved field concept, limiting irradiation only to the single nodal station involved by the disease at diagnosis (IN-RT) rather than the whole anatomical region, is under investigation by the already cited EORTC-GELA-IIL H10 trial and by the ongoing GHSG HD17 trial, quite recently

opened to accrual. Below the INRT concept, the technological break-troughs in radiation oncology led to the employment of new treatment techniques such as Intensity Modulated Radiotherapy (IMRT) also in the field of hemato-oncology.[14] The extended fields of the past limited the radiation technique to simple parallel-opposed anterior-posterior fields, but reduced and better defined radiation volumes allow for the utilization of more conformal radiation therapy, based on more consistent imaging and advanced radiation delivery techniques. These recently introduced radiotherapy planning and delivery techniques have already demonstrated better sparing of the heart, coronary arteries, lung and breast. The achievable dose reduction can be protective for normal tissues for well known dose-related radiotherapy late effects such as radiation pneumonitis/fibrosis or coronary artery disease, with an open issue regarding the impact on secondary malignancy risk.[15,16] As pointed out by Paumier et al. in 2011, the optimal combined modality approach in early stage HL should encompass minimal chemotherapy and subsequent minimal radiotherapy with simultaneous effort to decrease late complication rate without jeopardizing clinical outcome results.[17] It has been demonstrated that the risk of radiation-induced second malignancies (particularly breast and lung cancer) is linearly dependent on delivered dose and becomes of a detectable magnitude at 20–30 Gy.[18] Both IMRT technique and INRT concept are able to reduce the volume of normal tissue receiving high doses and consequently might reduce the risk of second malignancies due to 'high doses' and 'extended fields'. Historically, the shrinkage of radiation fields from EF-RT to IF-RT has been shown to decrease the risk of second cancers, as reported by De Bruin et al.[19] Hence, this effect might be postulated also whenever shifting from IF-RT to IN-RT is performed. However, as a matter of fact, IMRT techniques increase low-radiation dose bath to normal tissues. The clinical implications of this issue in terms of carcinogenetic risk are difficult to assess, as is the magnitude of this effect. Some well-known deterministic dose-related effects of radiotherapy, such as heart diseases (mainly coronary arteries disease, but also myocardic damage leading to late heart failure) or hypothyroidism, should be drastically reduced with low-dose INRT (eventually with IMRT planning and further reduction in normal tissues exposure); regarding this issue, apart from some very interesting dosimetric studies,[20,21] we currently do not have enough data to clearly demonstrate a clinical benefit. Joachim Yahalom underlined in his recent paper that although it will take more years of careful follow-up of patients in randomized studies to display the full magnitude of risk tapering by current reduction of radiation fields and doses, recent data suggest that this is likely to be the case.[22]

As young Radiation Oncologists involved in the multidisciplinary Lymphoma Team, we assume that these different approaches to the issue of late toxicity (no RT at all, modified low-toxicity RT) are not necessarily mutually exclusive. A consistent effort in trying to understand if new RT modalities are able to reduce the negative impact on survival of second malignancies and cardiac events should be done by monitoring late toxicity in clinical practice and not only in clinical trials, and an effort in optimizing radiation therapy planning and delivery with the primary endpoint of reducing toxicity should be implemented. In a parallel view, new combined modality protocols such as, for example, ABVD x 2 cycles + IFRT-INRT 20 Gy in favourable presentations, should be prospectively tested against chemotherapy only, with overall survival as primary endpoint. Currently, it is very difficult to assess whether a low-dose, small-volume RT + 2 cycles of chemotherapy combination is more toxic than 4–6 ABVD cycles (in the Canadian trial 10 out of 196 patients in the CT-only arm developed a second malignancy and 16 a cardiac event, with 6/12 non Hodgkin's related deaths), even if the two options are likely to be similar in terms of disease control (comparing global results of GHSG HD10 study and the chemotherapy only arm of NCIC HD6 trial, with OS rates of respectively 95% an 94% and FFS rates of respectively 87.1% and 87% at 8 years). The rate of second malignancies in the HD10 study was globally 4.6%, without significant differences between treatment arms, but the follow-up time is probably too short to be conclusive, as we are not certain that the low-dose approach will be less carcinogenetic. We also do not know about long-term results of INRT. To conclude, in our opinion the majority of patients should be possibly included in clinical trials; outside these studies, combined modality should remain a standard therapeutic approach, as specified in several International Guidelines, with a thoughtful attention on late effects and on the possibilities of lowering cardiac toxicity and probable second malignancy risk with low-dose programs for favourable patients and/or with the employment of new RT techniques in critical presentations.

Conflict of interest

None declared.

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