Risk adaptive treatment in Hodgkin's lymphoma: reduction of radiation dose and irradiated volume

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Summary

Treatment–related late complications on non-target normal tissues and appearance of secondary malignancies are well known side-effects induced by effective treatment regimens currently used in the curative approach of early and advanced Hodgkin's lymphoma. Radiotherapy (RT) and chemotherapy (CT) can lead to these late complications. Efforts have been conducted to reduce the morbidity and mortality related to these treatments. In particular there has been a progressive shift from radiotherapy used as sole modality to chemotherapy as first line followed by consolidation radiotherapy. As the side-effects of radiotherapy are linked to dose, volume and interaction with chemotherapy, trials have been launched to assess the impact of modifying the characteristics of the radiation treatment. For early-stage Hodgkin's lymphoma radiotherapy cannot be avoided but dose and volume can be reduced. In advanced Hodgkin's lymphoma omitting radiotherapy seems reasonable only in case of complete response (CR). The clinical trials allowing such a paradigm shift are highlighted in this review.

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Introduction

Radiotherapy (RT) has long been used for the curative treatment of Hodgkin's Lymphoma (HL). The pioneering work and establishment of the basic principles of ionizing irradiation in HL were performed at Stanford University by Henri Kaplan in the early 1960's.[1] From this approach based on the use of RT alone with curative intent, there has been a paradigm shift to CT alone or to combined modality treatment.

Chemotherapy evolved rapidly from first generation multi-agent schedules such as MOPP and ChlVPP to the second generation schedules with ABVD as the "gold standard". This was followed by a third generation consisting of hybrid schedules (examples: MOPP-ABVD, COPP-ABVD, ChlVPP-EVA, MOPP/ABV). Rapidly after introducing the MOPP "hybrids" in clinical practice, there was concern about induction of acute leukaemia (AL) and bone marrow dysplasia. More recently a fourth generation of CT appeared aiming at shortening and intensifying the treatment course (Stanford V, BEACOPP, escalated BEACOPP, VAPEC-B). Most of those recent fourth generation schedules are designed to reduce the toxicity of the full-dose ABVD or hybrid schedules, especially by lowering the cumulative doses of doxorubicin, bleomycin and mustard and by shortening the overall treatment time.[2] The fourth generation exploits the concept of increasing dose-intensity and dose density. Investigators are not only trying to reduce toxicity and risk of second malignancy (SM), but are also interested in preservation of fertility especially in the young patient population. This latter is one of the reasons why there has been a progressive shift to non-alkylating CT to avoid the dismal effect of alkylating agents on male fertility.[3]

The field became even more complex as in parallel there has been a continuous effort to evaluate the possible positive or negative impact of RT combined

with CT. Combining CT and RT increases treatment intensity and hence the probability of disease control, at the cost of an increase in late toxicity. It became rapidly evident that those highly effective combinations in term of survival, were linked to major risks, especially at the level of heart diseases (coronary artery disease, pericarditis), gonadal dysfunction, fatigue and last but not least, induction of secondary cancer. Similar to the experience in paediatric HL, it has been demonstrated that within the first 10 to 15 years after treatment there is an increase of the incidence of secondary leukaemia, myelodysplastic syndromes and highly malignant non-Hodgkin's lymphoma (NHL). After 15 years of follow-up there is an increased risk of solid tumours such as lung cancer, the largest component of secondary cancer risk in the Collaborative British cohort, as well as breast cancer, gastro-intestinal cancer, thyroid cancer, bone and soft tissue cancer and an increased risk of melanoma, head and neck cancer and central nervous system tumours.[4] Age at treatment is important as the increase of the relative risk of several malignancies is greater for patients who have been treated at a younger age.[4] One should be aware that those patients need life-time follow-up. If the relative risk is constant over the years, and this is not necessarily the case, this will result in a large absolute risk of cancer at a later age.

A recent meta-analysis of randomized trials in HL estimated the odds ratios for second malignancy and tried to compare the impact of respectively RT versus CT+RT, CT versus CT+RT, and IF-RT (involved field radiotherapy) versus EF-RT (extended field radiotherapy).[5] This analysis has been performed on individual patient data in contrast to numerous other "retrospective" reports. An overall analysis of SM as well as a separate analysis of three classes (AL, NHL and solid tumours) was made. From this analysis one can conclude that RT alone increases the odds ratio for SM overall as compared to CT+RT. However, this can be explained by the greater rate of progression or relapse requiring intensive salvage CT. The dismal effect vanishes when the analysis is censored at progression or relapse.

Nowadays, a general effort is being made to reduce the incidence of late toxicity and the risk of SM, without hampering disease control. Emphasis is put especially on reduction of radiation-induced late damage. Risk-adapted treatment incorporates changes in treatment paradigms with a reduction of treatment indications as far as radiotherapy is concerned and changes in radiation volumes and doses. One should not forget, however, that CT is not devoid of inducing SM in HL and this issue has been discussed in particular for gastro-intestinal cancer and for lung cancer.[4,6]

The paradigm shift

Because of the late toxicity related to RT, several randomized trials have been conducted to evaluate the efficacy of CT alone or combined with reduced intensity RT. *How can we reduce the intensity of RT? Three options are available: to shrink the volume of irradiated tissue, to shrink the total dose of RT and to shrink both volume and dose.*

First of all the intensity of RT can be reduced through field-size reduction. The smallest possible field includes the clinically involved nodes of a given region (called involved field = IF), whereas the extended field (EF) includes the IF and the adjacent lymph node regions. In the early work of *Kaplan*, the importance of EF was highlighted, but at this time no effective chemotherapy was available. The issue of EF or IF has obviously been revisited since the more systematic use of chemotherapy for HL. In the meta-analysis there is no significant difference in SM rate between EF-RT and IF-RT, with the exception of breast cancer with an odds-ratio of 3.25. When the analysis is censored at progression or relapse, there is a borderline increase in SM in case of EF-RT.[5]

In a recent paper, *Girinsky et al* developed new guidelines that are currently used in the design of the radiotherapy protocol of the ongoing EORTC/GELA H10 trial.[7,8] In this trial the concept of "*involved-node*" radiotherapy (INRT) has been introduced. Only the initial tumour volume will be treated with RT, allowing more sophisticated, highly conformal radiation therapy techniques (intensity modulated radiation therapy = IMRT and dose-painting) as well as respiratory gating. However, this approach requires a pre- and post-chemotherapy computed tomography and FDG-PET (positron emission tomography with [^{18}F]-2-Deoxy-2 glucose) in treatment position in order to allow adequate definition of the volume of interest by the radiation oncologist.[7] This philosophy is based on the analysis of the site of recurrence in patients treated with CT alone.[9] Indeed, most recurrences (83%) are located in the initially involved nodes and in 45% of the patients this is the sole site of recurrence.

Second, the intensity of RT can be reduced by reduction of the radiation dose. Several trials have

been designed to investigate this option. Already in the era of exclusive RT there has been a debate on the optimal dose to be given to cure HL.[10] A compilation of dose control data issued from trials conducted in the 60s to 90s shows that in-field control rates of 98% can be reached with doses in the range of 36Gy instead of what has been thought to be required, i.e. 44Gy. A re-analysis of those data fails to demonstrate any dose-response relationship at doses higher than 32,5Gy. Moreover, the total elapsed treatment time is not of major importance, at least up till seven weeks, which is in contrast to the time-effect observed for other solid tumours.[11] These data consolidate the concept of dose-reduction in modern trials where CT and RT have been combined.[12]

A third option is to avoid RT in the general management of HL and this has been investigated especially in children and young adults.[13] The question remains open whether this can be considered as a standard.

The paradigm shift in early-stage HL

Reduction of treatment volume in early stage HL

Trials such as the SWOG (South-West Oncology Group) study in which a comparison has been performed between subtotal nodal irradiation (sTNI) alone and 3 cycles of vinblastin, doxorubicin and sTNI (36 to 40 Gy) in patients with supra-diaphragmatic clinical stage IA and IIA HL, have accelerated the paradigm shift from exclusive RT to a combined approach. The failure free survival at three years was significantly higher in the CT+RT arm as compared to RT alone (94% versus 81%).[14]

One of the first randomized trials designed to assess the possibility of volume reduction in early clinically staged HL (stage CS IA, IB and IIA) is the *Milan trial*.[15] In the era of ABVD, sTNI has been compared to IF-RT. The final analysis of the trial shows that the 12-year freedom from progression and OS are similar in both arms. However, the trial was underpowered to test really for non-inferiority of IF-RT compared to sTNI.

Other attempts have been made for volume reduction in early HL and have been successful. The *EORTC H7 trial* has been designed to show that it is possible to replace sTNI (36 uninvolved area to 40Gy involved area) as the sole treatment in early favourable HL by EBVP followed by IF-RT (36 to 40Gy).[16] For early unfavourable HL a randomization has been performed between the above mentioned experimental arm and the hybrid MOPP/ABV combined with IF-RT. The idea is obviously to tailor the treatment intensity according to the projected clinical outcome. The EBVP is developed to be less cardiotoxic because of the replacement of doxorubicin by epirubicin, and should induce less nausea and vomiting as dacarbazine has been replaced by prednisone. The 10-year OS is high in both arms in favourable HL patients (92%), and therefore sTNI can be replaced by EBVP and IF-RT. For the unfavourable HL group, however, the combination of MOPP/ABV is significantly more efficacious (10-year OS 87% versus 79%).[16] In this latter group EBVP and IF-RT cannot replace MOPP/ABV and IF-RT.

In the *EORTC H8-U trial* two questions have been raised: first there has been a comparison between 6 cycles of MOPP/ABV versus 4 cycles and second sTNI has been challenged by IF-RT (36-40Gy). At 4 years the FFTF (Freedom from treatment failure) and OS are similar.[17]

The *GHSG (German Hodgkin's Lymphoma Study Group) HD8 trial* clearly illustrates that there is no change nor in 5-year OS (90.8% versus 92.4%), neither in FFTF (85.8% vs 84.2%) when one compares patients submitted to alternating chemotherapy COPP-ABVD, followed after two cycles by radiotherapy of 30 Gy EF plus 10 Gy to bulky disease or 30 Gy IF plus 10 Gy to bulky disease.[18] Patients were eligible for this trial if they presented with early unfavourable HL, i.e. stage I or II with one or more risk factors, or stage IIIA. Risk factors were defined as large mediastinal mass (at least one third of thorax diameter), extranodal disease, massive spleen involvement, elevated Erythrocyte Sedimentation Rate (ESR $\geq$ 50mm/h if no B-symptoms, or ESR $\geq$ 30mm/h if B-symptoms are present), and more than two lymph node areas involved. The German trial, allows to rule out an inferiority of >6% in terms of FFTF. The toxicity is superior after EF as compared to IF, which could obviously be expected. It remains to be determined whether the volume reduction in the GHSG HD8 trial will translate into a significant reduction of long-term side effects and especially a reduction of the risk of induction of secondary cancer. A recent subgroup analysis of the elderly patients (60 years or older) introduced in the *HD8 trial* illustrates the potential deleterious effect of EF with a 12% reduction in FFTF and a 22% reduction in OS at 5 years.[19] This can be explained by the fact that elderly patients have a poorer tolerance to treatment and hence receive lower dose intensity.

Table 1. Trials testing the concept of reduced-volume irradiation in early-stage HL.

Name of trial		stage	Schendule	OS	FFTF EFS
Milan Trial		Early stage	4x ABVD + IF-RT 4x ABVD + sTNI	94% 96%	94% 93%
EORTC[1]	H7-F	CS I and II Favourable	EF-RT (sTNI) 6x EBVP + IF-RT	92% 92%	78% 88%
			p-value	0.79	0.011
EORTC[1]	H7-U	CS I and II Unfavourable.	6x EBVP + IF-RT 6x MOPP/ABV + IF-RT	79% 87%	68% 88%
			p-value	0.018	<0.001
EORTC GELA	H8-F		3x MOPP/ABV + IF-RT sTNI	99% 77%	
EORTC GELA	H8-U		6x MOPP/ABV + IF-RT 4x MOPP/ABV + IF-RT 4x MOPP/ABV + sTNI	90% 95% 93%	94% 95% 96%
GHSG[4]	HD8	Early-stage Unfavourable.	2x COPP/ABVD + EF-RT 2x COPP/ABVD + IF-RT	90.8% 92.4%	85.8% 84.2%
			p-value	NS	NS

In the EORTC H7-U and EORTC/GELA H8-U there is no comparison with an arm containing an EF-RT. For the Milan trial, data are given at 12 years. For the EORTC H7 study, data are given at 10 years [Noordijk 2006]. For the GHSG, the data are given at 5 years. For the EORTC H8-F and EORTC H8-U the data are given at 4 years.

Moreover, mortality and toxicity are significantly higher in elderly patients after EF-RT, as well as the incidence of SM (13% EF versus 9.3% IF). The corresponding numbers for SM in younger patients are 3.7% and 2.2%. For the GHSG investigators *the take home message for elderly patients* is or to reduce the field size to residual lesions only or no RT at all. A concise overview of these clinical trials is given in *Table 1*.

Reduction of radiation dose in early stage HL

Dose reduction in early HD can be performed without ultimately altering the FFTF. *The GHSG HD4 trial* is a randomized trial testing whether 30 Gy alone is enough as compared to 40 Gy to control the clinically non-involved areas of the EF in favourable early-stage HL (stage I or II without risk factors). The involved areas received 40 Gy. EF-RT alone achieves CR in 98% of the cases with a 7-year FFTF of 78% (40Gy arm) and 83% (30Gy arm), the difference being not significant.[20]

Dose reduction is even more important in the context of CT+RT. *The GHSH HD1 study* has been designed to compare 40 Gy versus 20 Gy EF after response is obtained after two cycles of COPP/ABVD for intermediate stage HL (clinical stage / pathological stage I, II, IIIA, with risk factors i.e. large mediastinal mass, massive spleen involvement or more than five focal lesions or extranodal involvement). The subsequent *HD5 trial* establishes 30 Gy as a safe dose after two cycles of COPP/ABVD.[21] *Bulky disease always receives 40 Gy*. The results of the *HD1 and HD5 trials* can best be summarized as follows: *the local control rate in the EF/IF is similar for 20, 30 and 40 Gy*. If relapse occurs, this relapse is mainly located in extranodal sites and/or at the site of the initial bulky disease. Therefore, these relapses are more linked to the intensity of the systemic treatment rather than to the intensity of the locoregional treatment. In the *HD1 & HD5 studies* the higher radiation dose seems to be linked to higher rates of acute and late complications.

Based on these studies IF at a dose level of 30 Gy is considered standard in the GHSG. In the *GHSG HD10 trial*, designed for early favourable HL, the investigators are testing a reduction of the number of ABVD cycles (4 versus 2), as well as a reduction of the radiation dose (30 Gy versus 20Gy).[22] The interim analysis at 4 years shows a similar FFTF at 20 Gy compared to 30 Gy. This pushes even further the dose-reduction concept in favourable early stage HL.

Table 2. Overview of the preliminary results of the recent EORTC/GELA and GHSG trials.

				OS	FFTF
EORTC/GELA	H9-F	Early-stage favourable	6x EBVP + IF-RT 36Gy 6x EBVP + IF-RT 20Gy 6x EBVP + no RT	98% 100% 98%	88% 85% 69%*
EORTC/GELA	H9-U	Early-stage unfavourable	6x ABVD + IF-RT 36-40Gy 4x ABVD + IF-RT 36-40Gy 4x BEACOPP + IF-RT	95% 94% 93%	91% 87% 90%
GHSG	HD10	Early-stage favourable	4x ABVD + IF-RT 30Gy 2x ABVD + IF-RT 30Gy 4x ABVD + IF-RT 20Gy 2x ABVD + IF-RT 20Gy		
GHSG	HD11	Early-stage unfavourable	Overall*	98.5%	96.6%
			4x ABVD + IF-RT 30Gy 4x ABVD + IF-RT 20Gy 4x BEACOPP + IF-RT 30Gy 4x BEACOPP + IF-RT 30Gy		
			Overall (#) ABVD BEACOPP IF-RT 30Gy IF-RT 20Gy	96% 97% 96% 97% 97%	87% 87% 88% 90% 87%

These trials do raise the question on dose reduction of RTH in favourable and unfavourable HL. The standard volume in these trials is IF. For the EORTC/GELA H9-F and H9-U OS and EFS results are given at 4 years. The no RT arm in the EORTC/GELA H9-F has been closed prematurely at an interim analysis. For the GHSG HD11, the results are given after a median observation time of 2 years (*) and 3 years (#).

In the *GHSG HD11 trial*, patients with unfavourable early stage HL are randomized between 30 Gy and 20 Gy IF after four cycles of CT. The interim analysis after a median observation time of 3 years shows no sequential significant difference in outcome with an OS of 96% and a FFTF of 87%.[23]
The *EORTC/GELA H9-F* trial compares 36 Gy to 20 Gy and a control arm without RT. Interestingly, the no RT arm has been closed prematurely illustrating that chemotherapy alone in early stage HL is still experimental.[24] The preliminary results do show that in favourable early stage HL, the omission of IF-RT leads to an unacceptable failure rate (i.e. >20% of events). The EORTC/GELA study HD10 is evaluating whether 36 Gy or 30 Gy is an effective treatment in patients with favourable or unfavourable early stage HL, who are considered in CR after induction treatment. The CR will be estimated with FDG-PET after two cycles of ABVD.[16] A concise overview of these studies is given in *Table 2*.

Can RT be avoided in early stage HL?

Is there any evidence that RT is necessary after full dose ABVD? The National Cancer institute of Canada Clinical Trials Group (NCIC) and the Eastern Cooperative Oncology Group (ECOG) *HD-6 trial* compares 4 cycles of ABVD alone with a strategy that includes RT therapy in patients with early HL (CS I to IIA and absence of bulky disease). Patients randomized in the RT alone group and categorized into the favourable group, received sTNI (35 Gy in 20 fractions), whereas those categorized in the unfavourable cohort were submitted to two cycles of ABVD followed by sTNI. Overall, the investigators observed an increase in FFTF in patients allocated to the arm containing RT (95 vs 88%, p=.004), but there was no difference in OS (92 vs 95%, p=0.3).[25] *From these results, one can conclude* that 4 cycles of ABVD do not provide the same disease control as compared to a strategy with RT. Therefore, the NCIC-ECOG investigators shifted to a new standard consisting of combined-modality therapy that includes IF-RT. The lack of impact on survival has been explained by the fact that the increase in FFTF is offset by death due to causes other than progressive HL. The re-analysis of the

Overview of abbreviations for chemotherapy regimens

ABVD	Chemotherapy consisting of Doxorubicin® (Adriamycin), Bleomycin, Vinblastin and Dacarbazin
ABVPP	Chemotherapy consisting of Doxorubicin® (Adriamycin), Bleomycin, Vinblastin and Procarbazin and Prednisone
BEACOPP	Chemotherapy consisting of Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristin (Oncovin®), Procarbazin and Prednisone
ChlVPP-EVA	Hybrid chemotherapy consisting of Chlorambucil, Vinblastin, Procarbazin, Prednisolone and Etoposide, Vincristin and Doxorubicin® (Adriamycin)
COPP	Chemotherapy consisting of Cyclophosphamide, Vincristin (Oncovin®), Procarbazin and Prednisone
EBVP	Chemotherapy consisting of Epirubicin, Bleomycin, Vinblastin, Prednisone
MOP-BAP	Chemotherapy consisting of nitrogen Mustard, Vincristin (Oncovin®), Prednisone, Bleomycin, Doxorubicin® (Adriamycin), and Procarbazin
MOPP/ABV	Chemotherapy consisting of Mechlorethamine, Vincristin (Oncovin®, Procarbazin, Prednisone, Doxorubicin® (Adriamycin), Bleomycin, and Vinblastin.
MOPPEBVCAD	Chemotherapy consisting of Mechlorethamin, Vincristin (Oncovin®, Procarbazin, Prednisone, Epidoxorubicin, Bleomycin, Vinblastine, Lomustin, Melphalan, Vindesin.
PVACE-BOP	Chemotherapy consisting of Prednisolone, Vinblastin, Doxorubicin, Chlorambucil, Etoposide, Bleomycin, Vincristin, Procarbazin.
Stanford V	Chemotherapy consisting of doxorubicin, vinblastin, mechlorethamin, vincristin, bleomycin, etoposide, and prednisone
VAPEC-B	Vincristin, Doxorubicin ® (Adriamycine), Prednisolone, Etoposide, Cyclophosphamide, and Bleomycin

relapse pattern in the inter-group study *NCIC CTG HD.6 / ECOG JHD06 trial* shows that ABVD alone in limited stage HL results in an increased risk of relapse at sites which should have been covered by IF-RT. However, salvage therapy is effective as there is no difference in the proportion of patients alive without secondary progression.[25,26]

This is not the only trial investigating the role of RT in early HL. *The Memorial Sloane Kettering Cancer Center (MSKCC) trial* showed no difference in FFTF or OS between 6 cycles of ABVD alone and 6 cycles of ABVD combined with IF-RT.[27] The trial however was underpowered as only a difference of <20% could be detected.

The Indian trial investigates whether RT is of any benefit in patients in CR after 6 cycles of ABVD.[28] The EFS (event free survival) and OS at 8 years are both significantly improved. But the interpretation of this trial is difficult as most of the patients were younger than 15 and there was a great proportion of patients presenting with stage III and IV HL.

The *EORTC-GELA H9-F trial*, already mentioned, confirms the necessity of RT in early stage HL in CR after EBVP. The trial arm without RT has been closed prematurely because of the high incidence of events.[24] In favourable early stage HL, patients who achieve CR after 6 cycles of EBVP, do benefit from IF-RT. In the *EORTC/GELA H9-U trial*, the combination of 4 cycles of ABVD and IF-RT can be considered standard with a 4-year EFS and OS of respectively 87% and 94% at the time of interim analysis.[29]

Particularly in children and young adults, there have been numerous attempts to avoid RT. The *CCG study* is one of these trials.[30] After the induction of CR with risk-adapted combination CT, the children have been randomized between low-dose IF-RT (21 Gy in 12 fractions) or no RT at all. There was a significant increase in the EFS in favour of low-dose IF-RT used as consolidation treatment. Hence, combined modality treatments remains the standard of care for children and adolescents with HL.

The *GPOH-HD 95 trial* evaluates the impact of response adapted radiotherapy in pediatric HL. The reduction of dose and volume as a function of the response to the initial CT results in an excellent OS and EFS.[13] However, the failure rate is unacceptable (9.2%) for patients with advanced stage disease in CR after induction CT. The follow-up is too short to estimate the real impact of the response adapted radiotherapy on late toxicity and SM.

The paradigm shift in advanced-stage HL

Consolidation with RT after CT for advanced HL

Poly-chemotherapy is standard in the treatment of advanced HL. One can expect a CR rate of 70-90% but nevertheless one third of the patients reaching a CR will ultimately relapse.[31] The majority of those relapses are located within the initially involved nodes, whether those nodes were bulky or not prior to treatment.

The role of adjuvant RT after CT is controversial in stage IIIB and IV.[32] A meta-analysis based on individual patient records, shows that additional RT after CT, yields an overall improvement in tumour control of 11% at 10 years (c.i. 4-18%, p=0.0001) without any apparent difference in survival. Prolonging CT (using either more cycles of the same CT or regimens that contain additional drugs), does not modify the control rate. There is, however, a significant difference in survival in favour of the patients receiving a treatment without RT (8% difference at 10 years, c.i. 1-15%, p= 0.045).[12]

In a *German study* as well as in a *SWOG study*, the addition of RT did not yield a survival advantage.[33,34] In the German study there is no benefit seen of adding further CT or RT (20 Gy IF-RT) as consolidation after CR with COPP/ABVD. The 5-year DFS and OS were similar.[33,35]

In the *SWOG study*, the investigators aimed at defining the role of low-dose IF-RT after CR induction with 6 cycles of MOP-BAP in stage III or IV HL. Radiation consisted of 20 Gy to lymph node areas or 10-15 Gy to other involved organs. There was a significantly higher remission duration seen after RT in several subgroups, being prominent in patients with the nodular sclerosis subtype, although this was not the case in the overall analysis.

In the *TATA Mountain Hospital study*, both OS and relapse free survival were improved with consolidation RT applied after induction with six cycles of ABVD in patients in CR.[28] This is one of the few larger trials (N=179) showing a survival benefit with RT as consolidation. The trial has been designed to detect a 10% difference in EFS and OS assuming a 75% 5-years EFS and 85% OS in the observation arm with an α of 0.05 and a β of 0.20. However, this trial can be criticized for several reasons: first, 8 and not 6 cycles of ABVD are standard CT; second, there is a large variation in radiation dose levels (20-44Gy) as well as volume (84% received IF-RT); third, nearly half of the population is younger than 15 years of age.

In the *CCG-521 phase III trial*, children with advanced HL (pathologically verified stage III and IV) were randomized between ABVD followed by MOPP versus ABVD followed by low-dose EF-RT.[36] OS and EFS are better in the group treated with low-dose EF-RT, but the difference is not considered statistically significant. One should be aware however, that the patient number is limited to 111. However, the real conclusion is that MOPP chemotherapy can be safely omitted in young patients.

In early stage unfavourable disease (stage I and II with bulky disease) and stage III and IV HL, the comparison between a hybrid schedule (ChlVPP-EVA) and an intensified schedule (VAPEC-B), shows a significantly better OS and FFTF in favour of the hybrid schedule.[37] Interestingly, the results with the VAPEC-B regimen are poor compared to the outcome which could be expected after a similar intensified MDR (such as the Stanford V) in a comparable group of patients (the 5-years FFTF is only 62% compared to a 6-years FFTF of 89%).[2] The major difference between these two trials is the radiotherapy applied to patients: 58% of the patients treated with VAPEC-B did receive radiotherapy whereas 86% of patients treated with the Stanford V regimen were submitted to ionizing irradiation (36 Gy to initial sites of bulky i.e. (>5cm) or macroscopic splenic disease).

More recently the data from the randomized EORTC-20844 have been published. In this trial, the investigators have compared hybrid chemotherapy (MOPP/ABV) with the same CT completed with RT. The radiotherapy was tailored according to the response to MOPP/ABV. Patients in CR were randomized between no further treatment or IF-RT (24 Gy to nodal areas and 16-24 Gy to extranodal sites). Patients in PR (partial response) were treated with IF-RT (30 Gy to nodal areas and 18-24 Gy to extranodal sites).[38] The IF-RT did not improve the outcome in patients in CR after MOPP-ABV. Patients in PR after six cycles of MOPP-ABV, have an 8-year OS and EFS which is comparable to patients

in CR. This suggests a definite role of IF-RT in patients with advanced HL in PR after CT.[39]
Recently, the long-term results of the *H89 trial* have also been published.[40,41] In this trial patients with advanced HL (stage IIIB and IV) are randomized between MOPP/ABV or ABVPP. Patients in CR or with a PR of at least 75% after six cycles of CT are further randomized between two cycles of consolidation CT or sTNI (30 Gy, plus 5 Gy to the initially involved areas, plus 5 Gy to the site of residual mass after CT). The investigators of the GELA (Groupe d'Etude des Lymphomes de l'Adulte) confirm that RT does not offer a survival advantage over CT as consolidation after CR or PR≥75%.[40,41] Moreover, ABVPP is inferior to MOPP/ABV and ABVPP together with consolidation radiotherapy is an independent prognostic factor for death. Nowadays, ABVD is considered "standard" given the increased incidence of acute toxicity and an increased risk of SM while using the hybrid regimen.[42]

CT with optional RT in advanced HL

Very Recently the results of the Italian lymphoma Study Group (ILSG) have been published. The *ILSG study* is a prospective randomized trial comparing Stanford V, MOPPEBVCAD and ABVD. The MOPPEBVCAD chemotherapy is a shortened, hybridized and intensified schedule. Radiotherapy (36 – 42 Gy) has been limited to sites of bulky involvement or to areas that have not responded to CT.[43] Only in the case of an unequivocal CR, RT has been omitted in this trial. The idea of the Italian investigators was to select which CT regimen would best support a reduced RT program. First of all, if CT is used with a policy of optional response-oriented RT, the results in response rates and PFS (Progression Free Survival) are better with ABVD and MOPPEBVCAD as compared to Stanford V, but results in OS are comparable. However, patients are less irradiated if treated with MOPPEBVCAD. The toxicity of the latter CT schedule results in the final conclusion that ABVD is still the best choice when it has to be combined with a policy of limited RT. However, this study can be criticized: irradiation was only given to patients who had no more than two involved sites to irradiate. Hence, those patients who presented with few unconfirmed CR or PR sites and who could benefit most of RT, did not receive it.[44] Moreover, the ABVD schedule in the study of the ILSG only consists of 6 cycles, whereas the standard in advanced HL is eight cycles. The important information emerging from the ILSG trial is that the role of RT depends heavily on the CT schedule used.
Interestingly, in the ILSG trial the overall incidence of AL and myelodysplasia is only 2.9% at 10 years. The 10-year cumulative incidence of solid tumours is 2.3%. This is in line with other modern schedules but it should be noted that in the Italian series 20% of the patients are older than 50 years. This should be kept in mind as age at treatment is an important risk factor in the occurrence of SM.
A comparable approach has been published by the investigators of the *LY09 (United Kingdom Lymphoma Group 09) trial*. In this open-label, randomized trial ABVD has been compared with two other MDR (multidrug regimens). Again, ABVD remains the standard of care in advanced HL. Those with incomplete response are eligible for RT to residual or initially bulky sites. Patients in the ABVD arm were more likely to receive consolidation radiotherapy compared with the other MDR regimens but these latter have more adverse effects.[45] The authors conclude that ABVD is still standard and they implicitly accept a higher rate of consolidation RTH. These data are in line with the previously mentioned EORTC trial in which patients with PR are all submitted to RT and for whom OS is comparable to The OS of patients in CR after CT alone.[38] In fact, RT is equivalent to two more cycles of CT as shown in the EORTC/GELA trial.[40,41]

HD-CT as an alternative to RT in advanced HL?

Some investigators have analyzed whether high-dose chemotherapy (HDCT) followed by autologous stem-cell transplantation (ASCT) is a valid alternative to 4 cycles of ABVD in patients with unfavourable HL in CR or PR after 4 cycles of conventional front-line chemotherapy containing doxorubicin. In a randomized comparison the addition of HDCT-ASCT did not demonstrate any benefit in survival as compared to the standard approach.[46] *The Scotland and Newcastle Lymphoma Group Study (SNLG HD III)*, comparing three courses of intensive chemotherapy (PVACE-BOP) followed by auto-transplant with five courses of the same chemotherapy in a patient population consisting of poor risk Hodgkin's disease patients, did not highlight a significant improvement in outcome. Hence, the authors do not recommend the use of auto-transplant as part of the primary treatment.[47]

Radiotherapy for recurrent or relapsed HL

The incidence of CR after initial standard treatment for HD can reach 95%. Rescue treatment in case of relapse includes different strategies such as salvage chemotherapy (sCT) at conventional doses or high-dose CT followed by stem-cell transplantation (HDCT/SCT). Randomized trials do show superiority of HDCT/SCT. In a selected subgroup of patients some authors do demonstrate that salvage RT (sRT) alone is a viable option yielding an OS rate of approximately 50% and a FFTF at 5 years of about 30%.[48] The most important prognostic factors for OS from the multivariate analyses of this large series of 100 patients treated with sRT are the absence of B-symptoms and stage at the time of relapse. For FF2F (Freedom From second Failure) and duration of first remission, the Karnofsky index is predictive.

The impact of IF-RT after salvage with HDCT and progenitor cell transplant has been discussed: two observations deserve our attention. First of all there is a trend towards an improved survival although EFS basically remains unchanged. Second, the addition of IF-RT after the salvage treatment does not increase the risk of acute mortality neither the incidence of late events.[49] However, the true benefit of IF-RT after HDCT still needs to be defined within well designed, prospective, randomized trials. In most retrospective series the patient populations are heterogeneous and treatment schedules are extremely variable, not allowing definite conclusions.

Risk-adapted lymphoma treatment: the value of FDG-PET

Treatment decisions are based on prognostic factors. *In case of HL, the pre-treatment prognostic factors are: clinical disease stage, number of involved regions, B symptoms, extranodal disease, bulky disease, patient age, blood counts and biochemical parameters.* A seven factor prognostic scoring system has been constructed in 1998 to predict freedom from progression in HL.[50] The factors with independent prognostic effect in this model are: a serum albumin level of less than 4 g per deciliter, a haemoglobin level of less than 10.5 g per decilitre, male sex, an age of 45 years or older, stage IV disease (according to the Ann Arbor classification), leukocytosis (a white cell count of at least 15′000 per cubic millimeter), and lymphocytopenia (a lymphocyte count of less than 600 per cubic millimeter, a count that was less than 8% of the white cell count, or both). One should realize that even with this scoring system, based on routinely available and documented clinical characteristics, it was not possible to identify a distinct group of patients at very high risk. A possible alternative which is currently frequently investigated in clinical practice is the use of FDG-PET, which is based on avid uptake of glucose by metabolically active cells, coupled with computed tomography (FDG-PET-CT).

Basically, FDG-PET can be used for several purposes in HL: staging, restaging after treatment (to distinguish between viable cells and necrosis or fibrosis), surveillance after treatment, monitoring of response to treatment (in order to provide an early assessment of treatment efficacy and allow tailored therapy), and last but not least, when combined with computed tomography, to increase diagnostic accuracy.

Classical methods for response evaluation and prognosis are based on conventional imaging techniques such as reduction of tumour size on computed tomography scans. This is not predictive for outcome as the tumour volume does not only represent HL cells but also a large amount of connective tissue which obviously will not change after treatment. The worst prognosis has been observed in patients with primary refractory HL as well as in those patients presenting with early relapse. Those patients require high-dose salvage chemotherapy with haematopoietic stem cell transplantation (HSCT) in order to improve their outcome. The aim of early evaluation of response is to select subgroup of patients for risk adapted treatment. As conventional radiology, inclusive computed tomography, does not offer a clue for prediction of outcome based on early response assessment, FDG-PET has been investigated as an alternative approach. FDG-PET offers a unique opportunity to detect residual viable cells during treatment and hence allows potentially "adaptive treatment" to optimize outcome. *Several studies have shown that early response assessment with FDG-PET – assessment made after 2 to 3 cycles of chemotherapy - is highly predictive of survival.*[52] The ongoing EORTC/GELA H10 is tailoring the treatment as a function of response assessed by PET after two cycles of ABVD.[17,52]

The optimal timing of this assessment has still to be defined, but obviously, if one considers adaptation of treatment as a function of response, an evaluation late in the course of treatment will not allow any treatment modification. The first prospective study using FDG-PET after two cycles of chemotherapy to estimate prognosis, confirms its independent value in prediction of outcome. Combined with para-

Key messages for clinical practice

1. Chemotherapy is the standard of care in HL.
2. In early stage HL currently there is no evidence that RT can be avoided albeit there is clear evidence in favour of volume and dose reduction. The true impact of dose and volume reduction on risk is still unclear.
3. Radiotherapy can be avoided in advanced stage HL if a CR is obtained after 8 cycles of ABVD.

meters such as clinical stage and extra nodal disease, there is a possibility to identify a subgroup of patients with a very high risk of disease progression.[52] The effectiveness of FDG-PET for evaluating response to treatment in both HD and non-Hodgkin lymphoma has led to *In summary* revision of the criteria initially proposed by the International Working Group. FDG-PET is now recommended in routine practice for evaluating the disease status at the end of the treatment in HD and DLBCL (diffuse large B-cell lymphoma), and in clinical trials for assessing the therapeutic response in all pathological subtypes of lymphoma.[53]

Although it is possible to use semi-quantitative measurements such as standardized uptake value (SUV), or even to measure the absolute net influx of FDG through kinetic modelling, current guidelines recommend using the simple visual analysis for assessing the response to treatment.[54]

Moreover, FDG-PET combined with simultaneous computed tomography is a powerful tool for delineation of target volumes in radiotherapy planning. Paradoxically, a study performed in Denmark shows that FDG-PET/CT results in larger IF-RT treatment volumes. Therefore, the introduction of this technique in the treatment planning will require a more general change in treatment strategy in order to avoid larger volumes to be treated and hence a greater risk of SM and toxicity.[55,56] The clue to success might well be to advocate involved node radiotherapy and FDG-PET/CT guided IMRT.[7,57]

Conclusions

As the field of radiation oncology is continuously evolving towards the use of more sophisticated treatment planning and delivery, one may expect that treatment with ionizing irradiation might well continue to play an important role in the risk-adaptive treatment of early as well as advanced stage HL. For the early-stage HL, the most recently developed randomized trials of the EORTC/GELA and GHSG will allow addressing the question of dose-response. "No dose" of radiotherapy should not be considered as has been shown by the unacceptable rate of events in the EORTC/GELA H9-F trial as well as by other randomized trials. The volume of RT can be restricted to the involved nodes and this concept is introduced in the guidelines of the ongoing EORTC/GELA trial. It remains to be determined whether the reduction of dose and/or volume will at the long run end up in similar control rates and reduction of late toxicity.

The exact role of RT in advanced stage HL is difficult to assess from published data. However, it seems reasonable to omit RT in patients with a CR after standard ABVD of 8 cycles. In contrast, patients with uncertain CR or PR, or patient with bulky disease or patients treated on brief CT programs, seem to benefit from consolidation RT without an increase in toxicity. This consolidation RT should be limited in dose and volume.

Risk-adapted treatment, tailored by early response assessment with FDG-PET, may allow reduction of treatment intensity in patients prone to an excellent response and intensification of CT, and/or RT for the others. Development of selective agents targeting lymphoma is pending and might enhance the current treatment paradigms even more.

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