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Advanced Stage Hodgkin and Diffuse Large B-Cell Lymphomas: Is There Still a Role for Consolidation Radiotherapy in the PET Era?

Mario Levis,* and Michael Oertel†

The role of radiotherapy in the treatment of lymphoma is rapidly evolving. The development of modern systemic therapies and the adoption of FDG-PET-scanning as metabolic prognosticators are leading to a process of refinement of the treatment regimens. In this scenario, radiotherapy utilization is decreasing in several settings, including lower risk patients, to prevent the risk of long-term complications. Over the last decade, the most relevant changes in the treatment landscape are evident for advanced stage Hodgkin lymphoma and diffuse large B cell lymphoma. The main purpose of this paper is to review radiotherapy indications in these settings, to highlight pros and cons of a PET-guided strategy for radiotherapy recommendations, and to introduce future perspectives on the combination of radiotherapy and modern systemic therapies in both frontline and relapsed setting of advanced stage Hodgkin and diffuse large B cell lymphomas.
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Introduction

Traditionally, the indication for radiotherapy (RT) in advanced stage classical Hodgkin lymphoma (cHL) and diffuse large B cell lymphoma (DLBCL) was based on pre-chemotherapy risk factors such as the presence of bulky disease or extranodal disease involvement. The avalanching development of new systemic agents has significantly changed the prognosis of cHL and DLBCL and the treatment landscape is rapidly evolving. Simultaneously, the role of radiotherapy RT has been investigated in several settings. Debate on the refinement of the treatment schedules is currently ongoing.[1-3]

In particular, with the improved efficacy of systemic therapy resulting in higher rates of complete metabolic response, the contribution of RT is questioned in patients with advanced stage cHL or DLBCL treated with a full course of systemic therapy. Historically, the prevention of long-term complications, such as secondary neoplasms[4,5] and cardiovascular complications,[6-8] motivated trials to study RT de-escalation and, eventually, RT omission. In the recent years, the accuracy of RT planning and the precision of RT dose delivery have significantly improved through the developments of modern RT techniques, leading to a significant decrease of the toxicity burden.[9-16] Despite these advancements, largely described in several quality-assurance studies[17-19] and international guidelines,[20-23] the ongoing trend is to find alternative chemotherapy-only solutions and to limit RT to selected cases, or to push it in the relapse/refractory setting as induction or consolidation of salvage treatments for patients with high risk features.[24-28]

In particular, the growing trend is to guide RT administration based on metabolic response to the systemic therapy, estimated according to the Deauville Score (DS) criteria.[29-31] Here, we cover the relevant aspects of modern RT integration in advanced stage cHL and DLBCL.

Advanced Stage Hodgkin Lymphoma

Indications for Consolidation Radiotherapy—Historical Data on First Line Setting Before the PET Era

Before the advent of functional imaging, consolidation RT was a key component of frontline treatment for selected adult patients with advanced-stage cHL bearing unfavorable

*Department of Oncology, University of Torino, Torino, Italy
†Department of Radiation Oncology, University Hospital Muenster, Muenster, Germany
Address reprint requests to Mario Levis, MD, PhD, Department of Oncology, University of Torino, Via Genova 3, 10126, Torino. E-mail: mario.levis@unito.it

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features. In particular, the efficacy of RT was demonstrated for patients with a bulky lesion at baseline or in those with a partial morphologic remission at the end of the systemic treatment. Historically, many studies on advanced stage cHL included also stage IIB patients with unfavorable factors. Several studies also demonstrated that the role of consolidation RT was reliant on the intensity of the systemic regimen and the morphologic response.[32-35] The nonrandomized UK LY09 trial, which showed no difference between multidrug alternating regimens with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), also demonstrated a clear benefit for consolidation RT (30 to 35 Gy) to bulky sites or residual masses at the end of chemotherapy. Moreover, the impact of RT on PFS was confirmed after adjustment for confounding factors in the multivariate analysis (MVA) and was found to be more pronounced for patients in incomplete response after chemotherapy at the CT scan evaluation (HR = 0.25).[34] On the other hand, different results were seen when the more intensified $BEACOPP_{escalated}$ (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen is applied instead of ABVD. The GHSG HD12 trial showed that consolidation RT improves disease control in patients with residual disease site measuring ≥1.5 cm, but not in patients with a baseline bulky site achieving complete morphologic response after BEACOPP regimen.[36] These 2 trials suggest that the contribution of RT may be related to the intensity of chemotherapy and the benefit from consolidation RT to original bulky sites after ABVD is not seen after intensive BEACOPPesc in cases with complete remission.

Indications for Consolidation Radiotherapy—Recent Data on PET-Adapted Strategies

Treatment protocols of advanced cHL are changing in the modern era after the introduction of metabolic imaging. In fact, positron emission tomography (PET)- computed tomography (CT) scan improves baseline staging accuracy and, in particular, chemotherapy response assessment. Several studies have demonstrated the predictive role of a PET scan repeated after 2 cycles of chemotherapy (PET2) in patients with advanced stage Chl,[37-39] leading to a new generation of PET-response-adapted studies, with either intensification of systemic therapy for PET2 positive patients[40-42] or de-escalation of the therapeutic burden for PET2 negative patients.[43,44] Roughly 25% of patients (range 19%-42%) included in most new-generation studies[38,40,41,43,44] were diagnosed with stage IIB cHL, as well as for historical studies. The favorable outcomes of PET2 negative patients in recent studies, (2-year PFS rates >80%), led to the hypothesis-generating observation that the achievement of a complete metabolic response (CMR) could counteract the negative prognostic effect of clinical factors such as the presence of a baseline bulky lesion. Table 1 summarizes the results of the studies that investigated the role of consolidation RT in advanced stage cHL. In the GHSG HD15 trial, consolidation RT was given only to patients with a remnant measuring ≥2.5 cm, not achieving a CMR (defined as a DS ≥3) after 6-8 cycles of $BEACOPP_{escalated}$. In this study, patients with a residual disease ≥2.5 cm in CMR after chemotherapy had very similar PFS rates in comparison to patients in complete morphological remission (4-year PFS = 92% vs 93%, respectively). These results demonstrated the safety of omitting RT if patients achieve a CMR, regardless of the presence of bulky site and of the dimension of any residual site after $BEACOPP_{escalated}$. In the minority of patients achieving a partial metabolic remission (26%) in the final PET scan at the end of chemotherapy, RT should be offered, leading to a favorable PFS rate of 86% at 4 years. This outcome compares favorably to PET-negative patients (86% vs 93%, p = 0.02) and avoids the need for high dose salvage chemotherapy. However, it is important to avoid extrapolation of these results to patients treated with less intensive chemotherapy (eg ABVD).[45]

Several trials applied a similar PET-response-guided approach in patients treated with ABVD regimen.[40-43] In the RATHL trial, patients with negative PET2 were randomized to ABVD or a modified regimen omitting bleomycin (AVD regimen) in the remaining 4 cycles, while PET2 positive patients underwent chemotherapy intensification with $BEACOPP_{escalated}$.[43] Consolidation RT to bulky or to residual sites achieving CMR was left to the discretion of the treating physicians but was generally discouraged. Only 3% of these patients received consolidation RT; therefore no definitive conclusion can be drawn. At the MVA, the presence of baseline bulky lesion was not associated with treatment failure in the PET2 negative cohort, but a bulky lesion was present in only 28% of these patients, while it was recorded in 46% of PET2 positive patients who then received an intensification of the chemotherapy regimen. This suggests that bulky sites are less likely to achieve a CMR at the PET2 evaluation, thus requiring more intensified chemotherapy at the price of higher rates of toxicity. It remains unsettled if patients with baseline bulky sites not achieving a CMR at the PET2 could achieve the same favorable outcomes with a continuation of ABVD followed by consolidation RT instead of intensifying the systemic treatment.[46] Moreover, it is unknown which treatment (intensification of the systemic agents or consolidation RT) may result in a higher toxicity burden.

Two similar Italian randomized trials that investigated the efficacy of early intensification of the systemic treatment in PET2 positive patients, also evaluated the role of consolidation RT to baseline bulky sites (≥5 cm) in patients that attained a negative PET after 2 (PET2) and 6 cycles of ABVD (PET6).[47,48] Both studies published similar results, showing no benefit for consolidation RT in the overall population. In the GITIL HD0607 trial, 296 patients with a bulky lesion at baseline were randomized to receive RT (148 patients) or to be observed (148 patients). The 6-year PFS was not statistically different between the 2 groups (92% vs 90%, respectively, $P = 0.48$).[47] In the FIL HD0801 trial, only 116 patients were randomized to consolidation RT vs follow-up (58 vs 58 patients). Again, no significant difference was observed in favor of RT (2-year per protocol PFS: 94% vs 86%, $P = 0.5$).[48] Both studies demonstrated that patients achieving a CMR at both the PET2 and the final-PET after 6

Table 1 Summary of the Studies Investigating the Role of RT in Advanced Stage HL

Study	Patient Age	N	Patients Receiving RT (%)	Randomization	RT Indication	Bulky Definition	Dose	EFS	PFS/TTP	OS	Key Message
Studies published before the PET era											
EORTC 20884[32]	15-70 y	739	172 (23%)	Randomised: RT vs no RT	IFRT	>10 cm or >1/3 of TT ratio	24 Gy to sites in CR; 30 Gy +/− 10 Gy boost to sites in PR	5-y: 79% for RT vs 84% for no RT; (*P* = n.s)	–	5-y: 85% for RT vs 91% for no RT; *P* = n.s.)	Consolidation RT does not improve outcomes in CR. Patients with incomplete response may benefit from the addition of RT
Tata Memorial Hospital[33]	<70 y	251*	95 (38%)	Randomised: RT vs no RT in patients achieving a CR after ABVD x 6	IFRT (84%) or EFRT (16%)	>7 cm or >1/3 of TT ratio	20-44 Gy	8-y: 88% for RT vs 76% for no RT (*P* = 0.01)	–	8-y: 100% for RT vs 89% for no RT (*P* = 0.002)	RT improves EFS and OS in patients achieving a CR, especially when aged <15 years or when B symptoms or a bulky site are present at baseline.
UKLG LY09[34]	≥ 18 y	788	300 (38%)	Retrospective non-randomized comparison of RT vs No RT	RT recommended for incomplete response or bulky	>10 cm or >1/3 of TT ratio	≥30 Gy	–	5-y: 86% for RT vs 71% for no RT; (*P* < 0.001)	5-y: 93% for RT vs 87% for no RT; *P* < 0.001)	Consolidation RT improves the outcomes in patients with advanced HL
GHSD HD12[36]	16-65 y	1670	755 (45%)	Randomised: RT vs no RT to bulky sites or residual disease in patients responding to either BEACOPPbaseline or BEACOPPescalated	Bulky sites or residual disease (≥ 1.5 cm)	≥ 5 cm	30 Gy	–	5-y: 91% for RT vs 86.5% for no RT (−5.8%, 95% CI: −10.7 to −1.0%) in patients with residual disease. |No significant difference between RT and no RT for patients with bulky sites achieving a complete response after BEACOPP	–	RT can be safely omitted in patients with initial bulky who achieve CR after BEACOPP. RT cannot be omitted in patients with residual disease.
PET guided studies in patients treated with ABVD chemotherapy											
FIL HD0801[48]	18-70 y	519	49 (9%)	RT vs no RT in patients achieving a CMR after both 2 and 6 ABVD	Bulky sites	≥ 5 cm	25-40 Gy	2-y (PP): 90% for RT vs 86% for no RT (*P* = 0.7)	2-y (PP): 94% for RT vs 86% for no RT (*P* = 0.5)	–	RT does not improve PFS in this setting
FIL HD0607[47]	18-60 y	782	148 (19%)	RT vs no RT in patients achieving a CMR after both 2 and 6 ABVD	Bulky sites	≥ 5 cm	24-36 Gy	–	6-y: 92% for RT vs 90% for no RT (*P* = 0.5)	6-y: 99% for RT vs 98% for no RT (*P* = 0.6)	RT does not improve PFS in this setting
FIL-ROUGE[52]	18-60 y	503	106 (21%)	No randomization	Bulky sites or PET+ residual disease in standard arm (ABVD) only PET+ sites in experimental arm (intensified ABVD)	>10 cm or >1/3 of TT ratio	30 Gy	–	3-y (ITT) in patients with mediastinal bulk: 72% for standard arm vs 87% for experimental arm (*P* = 0.5)	–	Intensified ABVD followed by consolidation RT only to PET+ residual improves PFS compared to standard ABVD followed by consolidation RT to all bulky sites
PET guided studies in patients treated with BEACOPPescalated chemotherapy											
GHSG HD15[45]	18-60 y	2126	225 (11%)	No randomization	Residual disease sites (≥ 2.5 cm) not achieving a CMR	n.a.	30 Gy	–	4-y: 93% for patients in complete remission vs 92% for patients with PET negative residual masses vs 86% for patients with PET+ remnants receiving RT	–	Consolidation RT can be limited to patients with PET+ remnants after BEACOPP chemotherapy
GHSG HD18[44]	18-60	2101	155 (9%)	No randomization	Residual disease sites (≥ 2.5 cm) not achieving a CMR	n.a.	30 Gy	–	–	–	Confirms the results of HD15 on the role of consolidation RT in this setting

* Included also patients with Stage I HL.
Abbreviations: HL, Hodgkin lymphoma; RT, radiotherapy; EFS, event free survival, PFS, progression free survival, TTP, time to progression; OS, overall survival; TT, transthoracic; IFRT, involved-field radiotherapy; EFRT, extended-field radiotherapy; PR, partial response; n.s., not significant; CMR, complete metabolic response; n.a., not available; PP, per protocol; ITT, intention to treat.

ABVD, have a favorable outcome without the addition of consolidation RT to bulky sites. Unfortunately, both studies suffered from statistical shortcomings that limit the extrapolation of these results and suggest a careful interpretation. The GITIL HD0607 trial had no power calculation and the overall PFS rates were surprisingly high compared to similar studies, challenging a comparison with real life data. The HD0801 trial was designed with the overrated hypothesis of a 2-year EFS superiority of 20% for the RT arm, resulting in a small sample size that was underpowered to detect any difference in EFS or PFS <10%.

Moreover, the definition of bulk for cHL has changed over time and is still not universal. Limiting the analysis to recent PET-guided studies, the RATHL,[43] SWOG 0816[43] and GHSG HD18[44] trials adopted the more classical definitions of bulk, which include the maximum width of the tumor equal or greater than 1/3 of the thoracic diameter at the level of T5/T6 on a chest X-ray or a maximum axial measurement of 10 cm of any mass evaluated by any diagnostic imaging. On the other hand, the Italian HD0607[41] and HD0801[42] trials set a cut-off for bulky sites ≥5 cm. In addition, a maximum diameter >7 cm was a predictor of worse PFS in the HD0607 trial and the same cutoff was found to be optimal to detect bulky sites in early-stage cHL, with a possible mitigation of its prognostic role with the addition of RT.[49] The complex association between bulk and outcome was also investigated in a recent multi-institutional International study. The authors observed a better OS in patients with a mediastinal bulk than patients with a bulky lesion located outside of the mediastinum, showing the possible impact of other clinical factors not directly related with the tumor burden.[50] These differences prevent a universal definition of bulk in routine clinical practice and requires knowledge of the specific definition used in each treatment approach. In addition, the interaction of bulk with intensity of systemic treatment and response needs to be taken into account.

What brings together all PET-guided studies, despite the differences in bulk definition, type of chemotherapy regimen and role of consolidation RT, is that patients achieving CMR at PET2, then confirmed at the end of chemotherapy (eg after 6 ABVD cycles or after 4 $BEACOPP_{escalated}$), have a very good outcome without the addition of consolidation RT. Looking in detail at the literature data, we cannot exclude that some of these patients could benefit from consolidation RT, but the actual selection criteria require a rethinking.

On the other hand, the PET-guided intensification of systemic treatment for patients not achieving a CMR at the interim evaluation could obscure the prognostic relevance of the bulky lesions and leave unsolved the question on the possible role of consolidation RT to improve the outcomes of this subgroup of patients. It is also unclear if patients continuing standard ABVD despite having an incomplete metabolic response at PET2 could achieve favorable outcomes with the addition of consolidation RT. In the HD0801 trial, among the 15 PET2 positive patients who completed 6 ABVD, 11 patients (73%) had CMR at the end of treatment, with 4 of them (36%) achieving CMR after consolidation RT.[40] Furthermore, a substantial minority of patients (<10%) with a negative PET2 had a positive end-of-treatment PET (ePET). It is uncertain if this should be considered as incomplete response, disease progression, or reactive benign uptake. In the GHSG HD18 trial, a limited number of patients (n=31, 3%) had negative PET2 but positive ePET and were uniformly treated with consolidation RT to remnants ≥2.5 cm after completion of $BEACOPP_{escalated}$ chemotherapy.[44] In the HD0801 trial, most patients with this constellation (negative PET2 and positive ePET) were treated with high dose salvage chemotherapy, followed by autologous stem cell transplantation (ASCT). Interestingly, only 4 patients did not receive intensified chemotherapy regimen but were treated with consolidation RT. All were still alive and in complete remission after a median follow-up of 27 months.[51] Thus, RT may help in restoring a CMR in the limited proportion of patients with a metabolic reactivation between PET2 and ePET, at least when the uptake is limited to a site that can be included in a target volume.

More recently, the final results of the FIL-ROUGE trial were presented at the Lugano meeting in 2023.[52] Patients were randomised to receive 6 PET-response-adapted ABVD cycles or 6 intensified ABVD cycles (ie 35 mg/m^2 of doxorubicin per cycle, repeated every 21 days instead of 28 days) without PET-adaptation. Consolidation RT was mandated to bulky (≥10 cm) or residual sites (DS≥3 and residual ≥2.5 cm) in the standard intensity arm, but was only given to residual sites in the intensified arm. The study met its primary endpoint of improved 3-year PFS by >10% in the intensified ABVD arm (86.7% vs 73.2%, P = 0.0001). This study sheds some light on the role of consolidation RT in relation to chemotherapy intensity. In the intensified ABVD arm, the PET-guided RT policy was effective and demonstrated the feasibility of omitting RT in patients with bulky sites achieving a CMR (3-year PFS 87% vs 72% in the conventional ABVD arm). Again, this result is contingent on adopting a more intensive chemotherapy regimen to replace consolidation RT. Moreover, we do not know if PFS would have been even better in the intensified arm if bulky sites in CMR received RT. (see *Fig. 1* for a treatment example).

Indications for Radiotherapy—Future Perspectives in Combination With Modern Systemic Regimen

In the future, it will be even more complicated to address the role of RT in advanced cHL, as systemic agents are rapidly evolving. The ongoing strategy to improve the therapeutic ratio is to replace particular chemotherapy agents with novel agents that may have higher efficacy and lower the overall toxicity profile. The ECHELON trial has shown superior PFS[53] and even overall survival (OS)[54] rates for patients treated with the combination of the anti-CD30 conjugated antibody Brentuximab Vedotin (BV) + AVD, compared to ABVD for 6 cycles. More recently the results of the SWOG S1826 phase III randomized trial were presented at the Lugano Meeting,[55] showing a further improvement of PFS

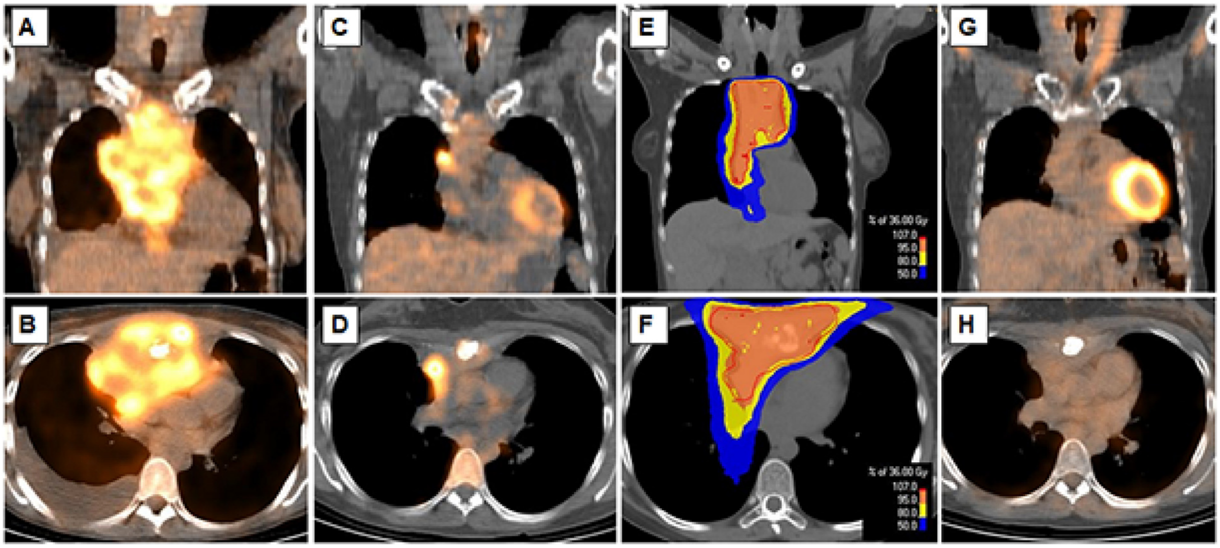

Figure 1 Consolidative Radiotherapy for an advanced stage HL with PET-positive residuals after chemotherapy. (A, B) Prechemotherapy PET-CT of a 40 year-old lady diagnosed with a stage IIB nodular sclerosis cHL, with a bulky mediastinal mass. (A) coronal view and (B) axial view. The patient was enrolled in a prospective phase III trial and received 6 cycles of intensified ABVD. (C, D) PET-CT after 6 cycles of intensified ABVD reveals a PMR response with 3 FDG-avid foci in the original mediastinal mass (3-times > liver uptake on central PET review: Deauville Score 5). (C) coronal view; (D) axial view. (E, F) Dose distribution of consolidation RT to the residual metabolically active disease site within the morphologic remnant of the original bulky site, as per study protocol. RT dose = 36 Gy. (E) Coronal color-wash dose distribution of the 6 MV photon VMAT plan (F) Axial color-wash dose distribution. The patient achieved CMR on the repeat PET 3 months after RT (G, H) and is in durable remission 5 year after the end of treatment.

with the combination of anti-PD-1 inhibitor Nivolumab + AVD for 6 cycles over the combination of BV-AVD for 6 cycles (1-year PFS 94% vs 86%, $P = 0.0005$). However, the use of consolidation RT was not planned in the ECHELON trial, and <1% of patients received consolidation RT in the S1826 trial. Therefore no definitive conclusion can be given on the role of radiation after these regimens. Additional studies are needed in the future to further refine the role of RT in this setting based on the systemic regimens adopted.

Advanced Stage Diffuse Large B-Cell Lymphoma

Role of Consolidation Radiotherapy—Overview on Historical Data and Current Management

Diffuse large b-cell lymphoma (DLBCL) is the most common entity of Non-Hodgkin lymphoma representing ca. 31 % of adult cases.[56,57] In contrast to the aforementioned cHL, DLBCL presents at a higher age (median: 7th decade of life) and reveals higher relapse rates with a long-term survival of 70 %[56,58,59] With the affected patients being older, secondary malignancies associated to therapy are of lesser concern, but patients may also not be suitable for intense primary or salvage treatment. The mainstay of treatment is based on immunochemotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[58,59] Recent attempts to implement modern, targeted drugs into first-line treatment have been unsuccessful apart from the POLARIX trial adding the anti-CD79b antibody-drug conjugate polatuzumab vedotin.[60] This led to an amelioration of PFS with no significant impact on OS.[60] Radiotherapy serves as a consolidative treatment for high-risk patients often using a dose of 30-40 Gy in conventional fractionation[21,61,62] (see Table 2). A main challenge in the modern era is to identify those patients benefiting from RT in the context of multimodal imaging. Traditionally, the indication for RT is based on prechemotherapy risk factors such as bulky disease or extranodal disease involvement.[63-65] More recent study designs utilize a PET-stratified approach, limiting RT to patients with PET-positive results only.[66,67]

There is a broad consensus to administer RT to patients with PET-positive residuals after immunochemotherapy, but for patients with PET-negative results after immunochemotherapy, international guidelines fail to formulate decisive recommendations considering either subsequent RT or mere observation.[21,62,68-70] Importantly, there is no randomized trial addressing patients with PET negative results, so it is currently unknown whether RT may have the potential to further reduce relapse rates in this setting.

Therefore, the detailed knowledge of recent publications on advanced-stage DLBCL is of pivotal importance to navigate the complex therapeutic decisions for this entity. Relevant aspects are covered in the following (sub) sections.

Table 2 Pivotal Publications on Radiotherapy for Diffuse Large B-Cell Lymphoma

Study	Patients	N	RT Indication	Randomization	Dose	EFS	PFS/TTP	OS	Key Message
Lowry et al.[61]	≥ 18 y (indolent and aggressive subgroup)*	476 aggressive lymphoma (82 % DLBCL)	80 % consolidative RT; 13.2 % r/R	40-45 Gy vs 30 Gy	See Randomization	5-y Freedom from local progression: 83.5 % vs 82.2 %; $P = 0.68$	5-y: 54 %; no significant difference between groups ($P = 0.66$)	5-y: 68 % vs 64 %; $P = 0.29$	RT de-escalation to 30 Gy is efficient and shows reduced skin toxicities
RICOVER-60[65]	61-80 y	1222	bulk (≥ 7.5 cm) Extranodal	No RT randomization	36 Gy	3-y: 66.5 %	3-y: 73.4 %	3-y: 78.1 %	6 x R-CHOP is standard of care
RICOVER-noRTH[63]	61-80 y	166	None	Prospective comparison to the best study arm of RICOVER-60	None	Pat. with bulky disease 3-y: 54% vs 80%; $P = 0.001$†	Pat. with bulky disease 3-y: 62% vs 88%; $P < 0.001$†	Pat. with bulky disease 3-y: 65% vs 90 %; $P = 0.001$†	RT is recommended in elderly patients with bulky disease
MegaCHOEP[79]	≤ 60 y; aaIPI: 2-3	261	bulk (≥ 7.5 cm) Extranodal	No RT randomization	36 Gy	Pat. with bulky disease 10-y: 64 % vs 35 %; $P < 0.001$	Pat. with bulky disease 10-y: 68 % vs 47 %; $P = 0.003$	Pat. with bulky disease 10-y: 72 % vs 59 %; $P = 0.011$	RT is recommended in young, high-risk patients with bulky disease
Held et al.[83]	Pooled meta-analysis of 9 trials	292 (7.6%) of 3,840 patients with skeletal involvment	recommended to extranodal	Retrospective comparison RT vs No RT	36 Gy	3-y: 75 % vs 36 %; $P < 0.001$	-	3-y: 86 % vs 71 %; $P = 0.064$	RT may be benefical for patients with skeletal involvment
OPTIMAL>60 (interim analysis)[66]	61-80 y	187	Pat. with PET+ within an initial bulk (≥ 7.5 cm)	Comparison to RICOVER-60	39.6 Gy	-	2-year: 79% vs 75% (n. s.)	2-year: 88% vs 78% (n. s.)	RT for bulky disease may be limited to PET-positive results
Freemann et al.[67]	≥ 18 y Advanced stages	723	Pat. with PET+ (Deauville 4-5) after 6-8 x R-CHOP	None	30-40 Gy	-	3-y: 83% (PET-) vs 76% (PET+ and RT; n. s.) vs 34% (PET+ without RT; $P < 0.001$)	3-y: 87% (PET-) vs 80% (PET+ and RT) vs 44% (PET+ without RT)	RT may be limited to patients with PET+ results patients. Bulky disease (≥10 cm), skeletal or craniofacial involvement were no independent risk factors.

* Classification according to BNLI classification.[54]
† As treated analysis.Abbreviations: DLBCL, diffuse large B-cell lymphoma; RT, radiotherapy; EFS, event free survival, PFS, progression free survival, TTP, time to progression; OS, overall survival; r/R, relapsed/refractory n.s., not significant.

Role of Consolidation Radiotherapy—Bulky Disease and Extranodal Involvement Before the PET Era

Varied definitions of bulky disease have been used in the past. In a post-hoc analysis of the German MinT-Trial, any threshold above 6.0 cm could be used to stratify distinctive subgroups of patients treated with R-CHOP resulting in significant OS-differences.[71] In a retrospective analysis of 96 patients with primary extranodal DLBCL treated with R-CHOP, 7.5 cm was identified as a significant stratification value for PFS and OS.[72] This value is also being used in the studies of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL, now part of the German Lymphoma Alliance.[63-66]

Retrospective studies provide supporting evidence for the use of consolidative RT in advanced-stage DLBCL.[73-76] These studies uniformly demonstrate an excellent local control of > 90 % with the use of RT, but conflicting results on PFS or OS.[73-76]

In regard to randomized trials, the RICOVER-60 trial explored the optimal systemic treatment, for elderly patients (61-80 years of age) testing 6 vs 8 cycles of CHOP vs R-CHOP in a 2 × 2 design, respectively.[65] The addition of rituximab to CHOP-chemotherapy significantly improved event-free (EFS), PFS and OS, whereas the extension to 8 cycles led to no further therapeutic improvement. Radiotherapy was stipulated for initial (prechemotherapy) bulky disease (maximum lymphoma diameter ≥ 7.5 cm) or extranodal disease with 36 Gy involved-field RT. The impact of RT was not evaluated, but toxicity results demonstrate no increase in secondary malignancies with the use of RT (5 % vs 5 %; $P = 0.6536$). Importantly, a prospective protocol by the same study group using 6 cycles of R-CHOP without RT shows a significant prognostic deterioration for elderly patients with bulky disease.[63] In a per-protocol analysis, significant declines in EFS, PFS and OS were found when RT was not administered in this sub-group (hazard-ratios EFS: 2.7; $P = 0.011$, PFS: 4.4; $P = 0.001$, and OS: 4.3; $P = 0.002$).

Likewise, the radiotherapy analysis of the MegaCHOEP-study advocates for the use of RT in young patients with aggressive B-cell lymphoma and bulky disease. In this study, young (<60 years), high-risk (age-adjusted international prognostic index [aaIPI]=2-3) patients were randomized between a standard immunochemotherapy incorporating 8 cycles of R-CHOEP and a dose-intensified strategy with high-dose chemotherapy (MegaCHOEP) necessitating subsequent autologous stem cell transplantations.[77] Neither in the initial publication, nor in the long-term follow-up analysis, a prognostic advantage of the more intense regimen could be demonstrated.[77,78] The post-hoc RT analysis of this trial is the only work accounting for young, high-risk patients in the context of a randomized trial.[79] After a median follow-up of 9.3 years, RT significantly ameliorated EFS, PFS and, in particular, OS in patients with bulky disease (EFS: 64% vs 35%; $P < 0.001$; PFS 68% vs 47%; $P = 0.003$; OS: 72% vs 59%; $P = 0.011$). Acute toxicities were mostly mild to moderate and RT led to no significant increase in secondary malignancies.[64] Indications and dose prescriptions for radiotherapy were the same as in the RICOVER-protocol without mandatory end-of-treatment PET-CT.

Role of Consolidation Radiotherapy in the PET Era

With the routine use of PET/CT in response assessment, the question arose whether RT could be omitted in patients with PET-negative results and be limited only to patients with PET-positive findings. To date, there has been no randomized studies testing the omission of RT, but there have been 2 studies employing a PET-guided approach for RT, which do not answer the question of whether there is a benefit or not from consolidation RT in patients with PET-negative results.

The OPTIMAL-Trial, being the successor of the RICOVER-60 trial, introduced a PET-stratified approach and RT was limited to patients with bulky disease and PET-positive results after immunochemotherapy (see *Fig. 2* as a treatment example). Preliminary results of this trial are only available as an abstract[66]. In the reported 187 patients, 48 % remained PET-positive after systemic therapy, 78 % of which were irradiated.[66] In comparison to RICOVER-60, no significant differences in PFS and OS could be found (2-year PFS and OS in OPTIMAL>60: 79% and 88% vs RICOVER-60: 75% and 78 %). This may be first hint for a PET-stratified approach of RT-indication, which is further corroborated by a retrospective analysis from British Columbia.[67] Freeman et al. reported on 723 patients with a mandatory FDG-PET-scan after 6 cycles of R-CHOP. Consolidative RT was limited to patients with PET-positive results after immunochemotherapy, resulting in a significant improvement of 3-year OS (87% vs 80% vs 44% for PET-negative patients, PET-positive patients treated with RT, and PET-positive patients not treated with RT, respectively). Bulky disease (≥10 cm) did not influence the prognosis in addition to PET-status. However, it has to be kept in mind that only 53 % of patients with PET-positive findings were actually irradiated and that the study protocol provides no insights whether to administer additional RT to PET-negative patients.

Iso-effective dose reduction has been a major focus of interest in recent years. A pivotal phase-II study utilized a reduced dose to 19.5 Gy-20.0 Gy for consolidative RT in 62 patients with DLBCL or primary mediastinal b-cell lymphoma and a complete remission to systemic therapy.[80] This resulted in a freedom from local failure of 98.0 % at 5 years, a 5-year PFS of 83 % and OS of 90 %. Based on the promising experience of this single-institutional study, ILROG is currently running a multi-institutional phase II study to confirm the safety of a RT dose de-escalation from 30 Gy to 20 Gy in this setting for patients achieving a CMR after chemoimmunotherapy.

Results of the British Columbia study[67] suggests that outcome of patients with PET-positive results receiving RT is close enough to patients with a metabolic remission after systemic therapy. Now that chimeric antigen receptor t-cell (CAR-T) salvage is available for 2nd line treatment for

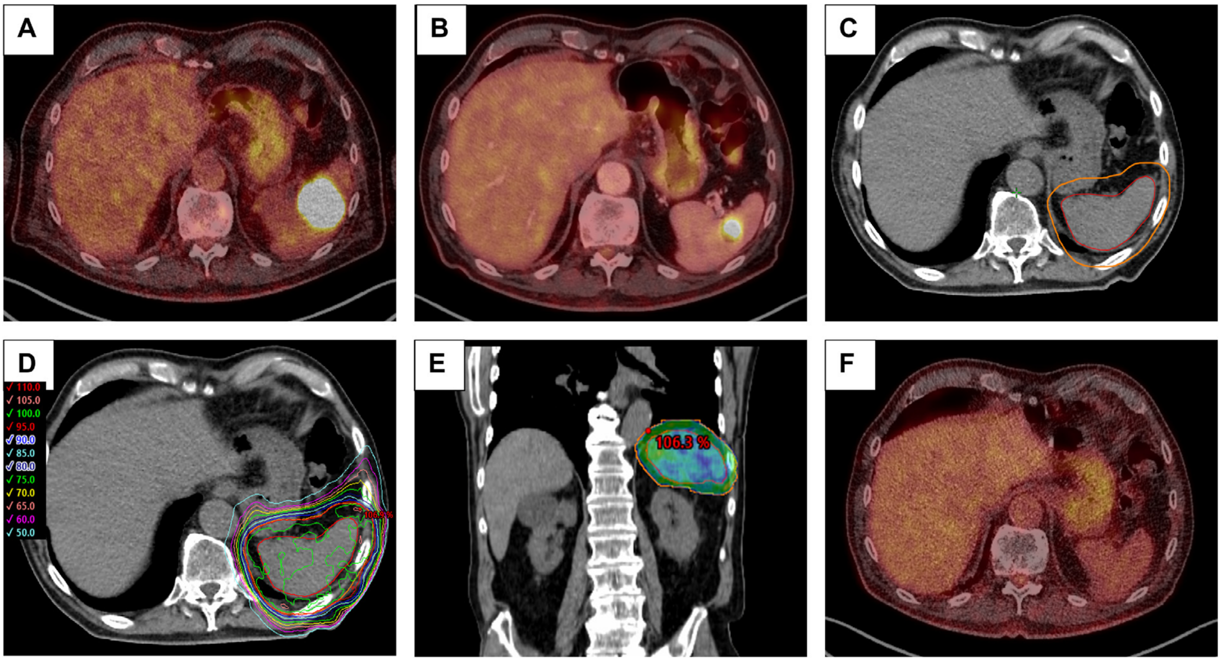

Figure 2 Consolidative Radiotherapy for an advanced stage DLBCL with PET-positive residuals after immunochemotherapy. (A) Prechemotherapy PET-CT of a 78 year-old gentleman with stage III nodal DLBCL with splenic involvement. (B) PET-CT after 6 cycles of R-CHOP reveals a reduction of the splenic disease, with a remaining Deauville 5 focus. Tumor board opted for radiation therapy. (C) Planning-CT indicating the GTV (red) and PTV (orange). (D): Isodose lines for a 6 MV FFF photon VMAT plan (prescribed dose: 39.6 Gy in fractions of 1.8 Gy) (E) Coronal slice 95 %-isodose as color-wash representation of RT-plan. (F) Follow-up PET-CT 6 weeks after RT demonstrates a complete morphological and metabolic response. **(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)**

refractory disease[81,82] there is a need to exercise a careful selection of cases who will do well with just RT and cases which need CAR-T.

Review of Selected Extranodal Sites—Bone, Testis and Central Nervous System

Amongst various extranodal disease sites of DLBCL, a particular focus has been on skeletal involvement, based on a pooled analysis by Held et al. of 9 prospective studies by the DSHNHL.[83] Skeletal involvement was associated with a significant deterioration in EFS in patients treated with R-CHOP (3-year EFS: 57 % with vs 72 % without skeletal involvement; $P = 0.002$). On the other hand, use of consolidative RT to skeletal sites resulted in a significant improvement in EFS in the total study population (3-year EFS: 75 % with vs 36 % without RT; $P < 0.001$); an effect which persisted when adjusting for IPI risk factors and bulky disease as well as in a subgroup analysis of advanced-stage patients. Opposed to that finding, the aforementioned retrospective analysis by Freeman et al. did not identify osseous involvement as an independent prognostic factor in addition to the metabolic status.[67] Importantly, PET-evaluation within the bone is challenging and may be obscured by false-negative or -positive findings, respectively.[31,84] Therefore, a careful evaluation is advocated[31,84] and the definitive impact of osseous involvement in the modern PET-era is yet to be determined.

Primary testicular lymphoma is an aggressive form of lymphoma constituted predominantly by DLBCL, which has a high-risk of extranodal recurrences, especially in sanctuary sites as brain or the contralateral testis.[85] Standard of care includes unilateral orchiectomy followed by anthracycline-based chemotherapy with rituximab, central nervous system −directed prophylaxis and RT.[86] Previous analyses revealed that prophylactic radiotherapy to the contralateral, uninvolved testes ± regional lymph nodal radiation improves survival.[86-89] According to recent guidelines, the involved testis should be included within the radiation field if no orchiectomy has been performed.[62]

If central nervous system (CNS)-involvement occurs during the course of disease as a secondary CNS-lymphoma, RT may be utilized both for consolidation or palliation to enable local control and ameliorate neurological deficits.[90,91] Overall, RT may be suitable treatment strategy especially in isolated CNS-recurrences or for consolidation but the limited prognosis of these patients has to be considered to formulate treatment recommendations.

Conclusions

Despite the advent of modern, targeted systemic therapies, RT remains an important and effective instrument in the therapeutic armamentarium for advanced-stage DLBCL or cHL. Due to individualized planning strategies and a high radiosensitivity of the underlying diseases, feasible radiotherapy strategies with a low-toxicity burden are now at hand. The implementation of PET-adapted strategies is the actual standard in several settings. Anyway, this approach cannot fit, itself, to the needs of all patients. The main goal in the future will be to adopt tailored approaches and to implement multifactorial scores able to integrate also additional radiological details (eg morphological response to systemic therapy) and clinical features. This trend will continue with the increasing understanding of molecular biology and the ability to tailor RT even further in a risk-stratified way. Implementation of advanced RT treatments like adaptive planning coupled with artificial intelligence will be powerful tools along this road with the goal to optimize RT treatment for the individual patient.

Conflict of interest

Both authors declare that they do not have any conflict of interest to disclose.

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