short review

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Radiotherapy update: current role of radiotherapy in the treatment of lymphomas

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Summary Radiotherapy (RT) remains an important modality in the modern treatment of lymphomas. In Hodgkin lymphoma (HL), its role is stage-dependent. In early stage favorable HL, RT is an essential component of combined treatment. In early unfavorable and advanced stage HL, RT can be omitted if patients are positron emission tomography-computed tomography (PET-CT) negative after chemotherapy. In non-Hodgkin lymphomas (NHL), RT can be used as definitive treatment of indolent lymphoma. In aggressive NHL, the role of RT is limited to consolidation therapy of bulky disease, extranodal involvement and in elderly patients. Overall, technology evolved from extended fields to involved-node (INRT) and involved-site radiotherapy (ISRT), with concurrent reduction in doses. This short review summarizes current evidence and provides a future outlook with regard to the role of RT in the treatment of lymphomas.

Keywords Hodgkin lymphoma · Non-Hodgkin lymphoma · Consolidation · Involved-site · Involved-node

Introduction

Radiotherapy is a highly effective treatment method for the majority of lymphomas. In the first half of the 20th century, patients with early stage Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) could be cured by radiotherapy alone; however, it was also associated with the development of late complications and increased mortality due to the need of extended fields and high dose levels.

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With the advent of effective and less toxic chemotherapy, the use of radiotherapy has gradually declined in terms of field size and dose. In several types of NHL, radiotherapy has become a secondary modality for consolidation and reduction of relapse risk after chemotherapy. For localized follicular lymphoma (FL) and mantel cell lymphomas (MCL) where chemotherapy is less effective, radiotherapy alone is still the treatment of choice.

The aim of this short review is to outline the current treatment approaches in radiotherapy of common lymphomas and to discuss their clinical relevance. Studies with direct implications on clinical practice guidelines are summarized in Table 1.

Hodgkin lymphoma

In HL, radiotherapy has traditionally been used as a primary treatment modality with excellent tumor control; albeit there were significant challenges due to treatment-related morbidity. While for some HL patients, radiotherapy alone still plays a role as a single modality in early stage lymphocyte-predominant HL, it is now mostly used in combination with chemotherapy with high cure rates. Five-year relative survival rates of 96.4% and 89.8% were reported for patients diagnosed at the age of 0–19 years and of 20–64 years, respectively [1]. In the combined treatment modality for HL, RT improves locoregional control and overall outcome. With increasing effectiveness of curative approaches, a reduction in late side effects and an increase in quality of life is gaining importance. Therefore, RT should maintain its effectiveness in local control, while minimizing radiation dose to normal tissue. Extended-field radiation, where adjacent regions are also treated, was replaced by involved-site and involved-node radiation fields regions, depending

Table 1 Studies with direct implications on clinical practice guidelines of RT in lymphomas

Study	Year	Design	Patient characteristics	Investigations	Patients receiving RT	Findings	Conclusion
Fuchs et al. [5] GHSG HD16	2019	Prospective, randomized, phase III	$n=1150$ with early stage favorable HL	2-arm randomization to standard 2 × ABVD +20 IFRT vs. 2 × ABVD and no RT after neg. PET scan	Overall $n=693$ PET-neg. $n=353$ PET-pos. $n=340$	PFS at 5 years was 93.4% in the RT group and 86.1% in the ABVD alone group with in-field recurrence rate of 2% vs. 9%, $p=0.0003$	RT cannot be omitted
Borchmann et al. [11] GHSG HD17	2021	Prospective, randomized, phase III	$n=1100$ with early stage unfavorable HL	2-arm randomization to standard 2 + 2 (2 × ABVD + 2 × B_{esc}) + 30 IFRT vs. 2 + 2 and no RT after neg. PET scan	Overall $n=588$ PET-neg. $n=353$ PET-pos. $n=340$	PFS at 5 years was 97.3% in the standard CMT group and 95.1% in the PET-guided group	RT can be omitted in PET-neg. patients
Engert et al. [12] GHSG HD15	2012	Prospective, randomized, phase III	$n=2182$ with advanced stage HL	3-arm randomization to 8 × B_{esc} vs. 6 × B_{esc} vs. 8 B_{14}. Additional RT (30 Gy) to PET-pos. lesions or residual disease ≥ 2.5 cm	$n=225$	Overall, 6 × B_{esc} showed better efficacy and fewer serious toxic effects than 8 × B_{esc}. The negative predictive value for PET at 12 months was 94.1%	6 × B_{esc} should be the treatment of choice. PET done after chemotherapy can guide the need for additional radiotherapy
Hoskin et al. [22] FORT	2014	Prospective, randomized, phase III	$n=548$ patients with 614 sites of indolent lymphoma	2-arm randomization to RT with 4 Gy vs. 24 Gy	299 sites with 24 Gy 315 sites with 4 Gy	91% with 24 Gy and 81% with 4 Gy had CR or PR ($p=0.00095$). No difference in OS	24 Gy is the standard of care for indolent lymphoma
Pfreundschuh et al. [25] UNFOLDER	2018	Prospective, randomized	$n=467$, patients with advanced stage DLBCL	2-arm randomization to 6 × R-CHOP-14 vs. 6 × R-CHOP-21 followed by either RT (39.6 Gy) or observation to bulky or extranodal disease or observation	Overall: $n=305$	EFS was significantly improved with RT ($p=0.004$) after an interim analysis observation arm terminated early; 3-year EFS was significantly worse with no RT (68% vs. 84%; $p=0.001$). No significant differences in PFS/OS	Worse EFS in the observation arm, but no difference in PFS and OS

RT radiotherapy, *HL* Hodgkin lymphoma, *IFRT* involved field radiotherapy, *PFS* progression-free survival, *CMT* combined modality treatment, *CR* complete response, *PR* partial response, *OS* overall survival, *DLBCL* diffuse large B-cell lymphoma, *EFS* event-free survival, *pos.* positive, *neg.* negative

on the quality and accuracy of the prechemotherapy imaging.

Early stage classical Hodgkin lymphoma

The protocol of the German HD10 trial with two cycles of ABVD followed by 20 Gy of INRT or ISRT is currently the state-of-the-art treatment approach [2, 3]. Attempts to reduce chemotherapy in the German HD13 trial and to omit radiotherapy in PET-CT negative patients after chemotherapy in the German HD 16 trial resulted in relevant loss of tumor control [4, 5]. The RAPID trial and the EORTC H10 trial confirmed these findings with a 3-year progression-free survival (PFS) of 97% in the radiotherapy group versus 90% in the group of no radiotherapy and a 5-year PFS of 99% versus 87% in PET-CT negative patients, respectively [6, 7].

Early stage classical Hodgkin lymphoma with unfavorable prognostic factors

The standard treatment in unfavorable HL was a combination of four cycles of chemotherapy and consolidation radiotherapy with a dose of 30 Gy [8, 9]. The German HD14 trial introduced an intensified chemotherapy regimen consisting of 2 cycles eBEACOPP plus 2 cycles ABVD (2 + 2) followed by 30 Gy involved field radiotherapy [10]. To further reduce late complications, the German HD 17 trial showed that consolidation radiotherapy could be omitted without a clinically relevant loss of tumor control in patients with a negative PET-CT after systemic therapy with the 2 + 2 regimen [11].

Advanced Hodgkin lymphoma

The main treatment modality of advanced Hodgkin lymphoma is combination chemotherapy. The German HD 15 trial found that the omission of radiotherapy in patients with a complete metabolic response was noninferior (4-year PFS 92%) compared to patients with a positive PET-CT after chemotherapy and additional RT (4-year PFS 86%) [12]. The RATHL trial confirmed these results by omitting radiotherapy in PET-CT negative patients without a loss of disease control [13]. Thus, the recommendation in the following HD18 trial remained radiotherapy for lesions of at least 2.5 cm in the largest diameter with residual fluorodeoxyglucose (FDG) uptake after chemotherapy [14].

Non-Hodgkin lymphomas

In the contemporary management of NHL, radiotherapy still plays an essential role in both aggressive

and indolent subtypes. For many localized indolent NHL, radiotherapy remains the standard of care, while most aggressive NHL are treated with systemic therapy alone and radiotherapy is partially used for consolidation. Modern guidelines recommend ISRT for the treatment of NHL, but if radiotherapy is used as definitive treatment without combined modality treatment, larger treatment volumes should be considered to encompass microscopic disease in the vicinity [15, 16].

Recently, RT has shown a promising role as a bridging strategy to chimeric antigen receptor (CAR)-T cell therapy for patients with relapsed/refractory NHL [17]. Upfront bridging RT to CAR-T cell therapy provides excellent local control rates of 86% after 1 year and response with a median duration of local response of 257 days [18].

Indolent lymphoma

In indolent lymphoma, RT provides excellent local control; however, its impact on overall survival may be limited and thus the role of RT is still debated. Concerning local tumor control of FL or MCL after radiotherapy alone, studies report high overall response rate (ORR) of >90% [19]. In a retrospective Australian/Canadian study of 365 early stage FL patients, active treatment versus observation was investigated [20]. Active treatment including radiotherapy was associated with better PFS, but no difference in overall survival (OS) was found. Both patients with radiotherapy alone and patients undergoing observation had similar time to transformation. In the modern era, the radiation dose for indolent NHL has been dramatically reduced from 40–50 Gy to 24–30 Gy and modern guidelines recommend small fields [15, 16]. Thus, morbidity has been reduced as well, and the indication for RT in indolent lymphoma should be decided on a case-by-case basis.

For palliative treatment intent, very low doses of RT (VLDRT) of 2×2 Gy have proven to be very effective [21]. Particularly for elderly or poor performance status patients, VLDRT can palliate lesions in a short treatment course irrespective of disease stage and delay the need for more standard-dose radiation or systemic therapy. The randomized phase III FORT trial investigated that VLDRT was significantly inferior in terms of local progression in comparison to the standard dose of 24 Gy [22]. Thus, a dose of 24 Gy remains the state-of-the-art in a curative setting and VLDRT with 4 Gy represents a good alternative in a palliative setting.

Aggressive lymphoma

In limited stage aggressive NHL, consolidation radiotherapy has a limited role and is considered in specific scenarios such as bulky disease, extranodal involvement and geriatric patients. The RECOVER-60 trial and the companion study observed that patients with bulky disease where RT was omitted had significantly decreased PFS and OS [23, 24]. The German UNFOLDER study confirmed these results, as the observation arm without RT of bulky disease or extranodal involvement was terminated prematurely [25]. Elderly patients with a greater risk of poor chemotherapy tolerance and cardiac toxicity from systemic therapy may have a benefit with improved outcome with consolidation radiotherapy [26].

In advanced stages of aggressive lymphoma, the use of consolidation radiotherapy is unclear and controversially discussed. A recent published meta-analysis including 4584 patients with diffuse large B-cell lymphoma (DLBCL) in 11 trials observed no evidence for a better survival outcome of a consolidation radiotherapy. Furthermore, patients with a complete morphologic remission after chemotherapy or initial bulky disease were unlikely to benefit from radiotherapy [27]. Additional future trials in the PET-CT era are needed to define the role of consolidation radiotherapy. In general, patients with advanced stage disease should be discussed in a multidisciplinary team to balance the advantages and disadvantages of RT, particularly with regard to toxicity.

Conclusion and future directions

To further improve radiotherapy of lymphomas, several aspects should be considered in the future. First, the use of advanced radiotherapeutic technologies and RT dose de-escalation promise reducing late treatment complications while maintaining high control rates. Concerning technological advances, conformal techniques such as intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT), inspiration breath-hold techniques, image-guided radiation therapy (IGRT) and 4D imaging may offer improved sparing of critical adjacent regions and are already in active use in many departments. On the other hand, the role of proton therapy is not well defined yet and the limited availability leads to case selection. Particularly, patients with mediastinal involvement may benefit from proton therapy in the future [28]. With regard to dose de-escalation, future research may aim to further reduce RT dose without compromising outcomes. For instance, a recent phase II study evaluated the feasibility of 20 Gy instead of 30 Gy in diffuse large B-cell lymphoma and observed stable local tumor control [29].

Second, the role of RT in the era of immunotherapy still needs to be investigated. Potentially, radiation doses may be further reduced if RT is added as an adjunct to immunotherapy. For example, the addition of low dose total skin electron therapy (12 Gy) to multimodality immunotherapy in patients with Sèzary syndrome may lead to better long-term clinical and molecular remissions [30].

In conclusion, both definitive and consolidation radiotherapy remain important pillars in modern era treatment of HL and NHL. While doses and fields are being successfully reduced leading to improved local tolerability, control rates remain excellent due to combination with standard chemotherapy protocols. Future directions include technological advances as well as the inclusion of immunotherapy into the treatment armamentarium.

Take home messages

- In early stage favorable Hodgkin lymphoma, consolidating radiotherapy is indispensable after initial chemotherapy. In other stages of Hodgkin lymphoma, radiotherapy can be omitted if PET-CT is negative following chemotherapy.
- In indolent lymphoma, radiotherapy alone can be provided as definitive treatment with excellent local control rates.
- Radiotherapy in aggressive lymphoma is offered in the setting of bulky disease, extranodal involvement and in elderly patients, although data are inconclusive and its role is controversially discussed.
- The continued reduction in dose and field, which became possible due to combination of radiotherapy with modern chemotherapy and immunotherapy, provides improved tolerability.

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