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Perspective

Evolution of Radiation Fields from Involved Field to Involved Site—A Summary of the Current Guidelines by the International Lymphoma Radiation Oncology Group

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Abstract: Radiation therapy has been proven to be highly effective in the treatment of lymphoma. With increasing rates of long-term survival, the reduction in toxicity has gained importance. The evolving understanding of the diseases' biology, as well as technical and conceptual advances, allows for a precise and individualized application of irradiation. Smaller treatment fields and safety margins make it possible to spare healthy neighbouring tissue (organs at risk). The International Lymphoma Radiation Oncology Group (ILROG) has developed several guidelines to optimize radiotherapy treatment in lymphoma patients. Since its introduction in 2013, involved site radiotherapy (ISRT) has been adopted as the standard of care in most treatment regimens in adult lymphoma. This article serves as a summary of the current ILROG guidelines, also considering contemporary developments and possible future directions.

Keywords: lymphoma; radiation therapy; ISRT; IFRT

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1. Introduction

Most lymphatic malignancies are sensitive to radiotherapy (RT), prompting the introduction of RT for lymphoma treatment. Curative treatment for this complex spectrum of diverse entities was made possible by the development of the linear accelerator by Henry Kaplan in the 1960s, using large extended fields such as "mantle field" or "inverted y" as part of total lymphoid RT for Hodgkin's lymphoma (HL). The underlying treatment volumes have since been adapted for other lymphoma entities (non-Hodgkin's lymphoma, NHL) and have been subject to considerable change over time [1].

Scientific effort and technical advances have led to improved outcomes in lymphoma patients, with high rates of disease control and long-term survival for a group of diseases previously considered fatal. Because of possible short- and long-term toxicity, the risk–benefit ratio of RT as a single- or part of a combined-modality treatment was constantly reevaluated in a series of treatment de-escalation trials. In addition to lower doses, the reduction in side effects was achieved via the use of smaller treatment fields, sparing normal tissue. Involved field radiotherapy (IFRT) replaced extended field RT (EFRT), marking the first step from uniform treatment towards individually tailored planning. Delineation of specific sites of disease necessitated the definition of corresponding anatomical landmarks [2].

Since then, further technological advances have increased the safety and accuracy of application of RT, rendering even smaller target volumes possible. Identification of lymphoma infiltration and monitoring of response via metabolic PET/CT-imaging, giving a precise representation of disease extension, has proven to be a valuable basis for RT and encouraged aspirations of achieving the smallest possible field size.

The International Lymphoma Radiation Oncology Group (ILROG), a board of experts founded in 2010, has devoted itself to the improvement as well as the harmonization and

standardization of RT lymphoma treatment by conducting clinical trials and developing guidelines for state-of-the-art treatment [3–10]. In 2014, their proposal of involved site radiotherapy (ISRT) further decreased IFRT fields. Today, this principle has become the standard of care for most lymphoma entities [11–13]. This paper serves as a summary of the underlying guidelines, the status quo, and possible future developments regarding the use of ISRT.

2. From Involved Field to Involved Site

IFRT was non-inferior to EFRT in a series of trials that combined RT with compatible chemotherapy regimens. While disease control was unchanged, combined-modality settings with de-escalated RT resulted in reduced treatment toxicity [2,14–16], but with continuing improvements in imaging (especially the emergence of PET/CT) and treatment delivery, further de-escalation seemed achievable: the origin of ISRT lies in the concept of involved node radiotherapy (INRT), which was introduced by the EORTC group of Girinsky et al. in 2006 [17], adapted by the German Hodgkin Study Group [18], and successfully applied in the corresponding EORTC H10-trial [19] and the HD17-trial [20] on patients with early-stage HL. This concept marks the furthest reduction in RT field size for lymphoma treatment to date. Leveraging pre-treatment imaging in the radiation application position allowed for delineation of small margins around initial tumour mass and lymph node remnants with sharp exclusion of organs at risk (OARs). The limitation of this concept lies in the ambitious prerequisites for baseline imaging requiring optimal co-registration of pre- and post-chemotherapy scans with the planning CT.

When comparing clinical trials to real-world scenarios, radiation oncologists are oftentimes confronted with a number of limitations concerning this concept, mainly due to differences in patient positioning (such as head and arm positioning, missing contrast enhancement, or divergent breathing). As a compromise, the ILROG introduced the concept of ISRT [4,5], recommending small treatment volumes of initially affected sites of disease with a high degree of normal tissue sparing, but slightly more generous margins to make up for uncertainties in image fusion. Figure 1 illustrates the reduction in size of the treatment fields.

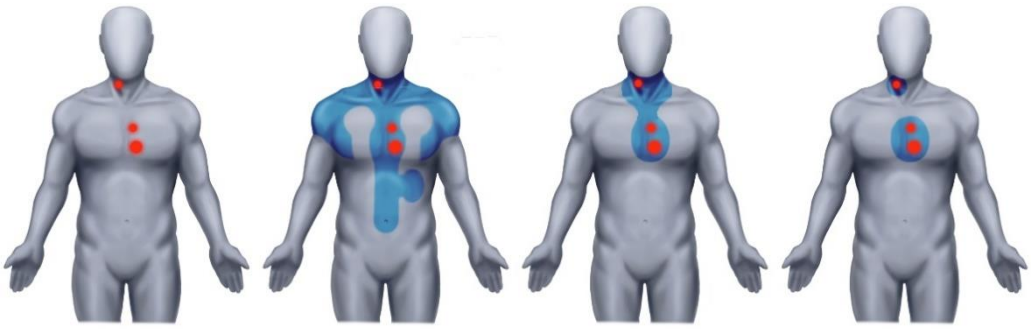

Figure 1. Exemplary depiction of lymphoma sites (red) and different radiation treatment fields (blue). (**A**) Disease location of mediastinal and cervical lymphoma manifestation; (**B**) field extension for EFRT; (**C**) field extension for IFRT; (**D**) field extension for ISRT. Image courtesy of Niklas Schwartz Illustration & Design.

3. Target Volume Definition for ISRT (Summary of ILROG Guidelines)

Today, ISRT is used in several settings: as part of combined-modality treatment or definitive RT (with no systemic treatment) in curative intent (i.e., early-stage follicular lymphoma, early-stage nodular lymphocyte-predominant Hodgkin's lymphoma (LPHL), marginal zone lymphoma, low-risk NK/T-cell nasal type lymphoma, and mantle cell lymphomas), as salvage treatment after failure of systemic therapy, or in palliative settings [21].

The ILROG guidelines specify dose and volume definitions for HL as well as NHL of nodal or extranodal location, but also give specific recommendations regarding NK/T-cell lymphoma. Underlying volume definitions as defined by the International Commission on Radiation Units [22] include the gross tumour volume (GTV) as a representation of macroscopic disease, the clinical target volume (CTV), also considering areas of subclinical infiltration, the internal target volume (ITV), and planning target volume (PTV), consisting of an additional margin to account for organ movement, set-up, and internal uncertainties.

The creation of these volumes relies heavily on FDG-PET/CT-imaging for lymphoma treatment. Metabolic imaging has not only demonstrated high value in diagnosis and response assessment [23–25], but is now the basis for RT planning in most lymphoma entities [20,26–28] even though some limitations remain [21,29]. Uncertainties in image interpretation can be a concern and should be discussed in an interdisciplinary setting since they may require additional extension of safety margins based on clinical judgment [3–5,21]. It is important to note that the definition of treatment volumes for ISRT as well as dose considerations (which are not discussed in this summary) do not solely depend on PET/CT-imaging data, but also consider factors like histology, stage, location, and extent of prior therapy in an individual assessment [21]. The requirements needed for planning of ISRT are summarized in Table 1.

Table 1. Requirements for planning/simulation of ISRT.

Requirements for Planning/Simulation of ISRT
• Mandatory fusion of initial, pre-therapeutic imaging (PET/CT, MRI) with the simulation study (of which at least one should be contrast-enhanced, in cases of GI lymphoma with and without additional oral contrast medium < 50 mL).
• If possible, acquire baseline imaging already in treatment position.
• Use respiratory motion management (i.e., 4D-CT simulation or deep inspiration breath hold) in areas of high mobility (e.g., mediastinum, abdomen).
• Use appropriate immobilization (e.g., thermoplastic mask).
• In cases of abdominal lymphoma, fasting for at least 4 h might be necessary.
• Slice thickness of planning study should be 3–5 mm.
• In cases of extranodal lymphoma, additional information of locoregional assessments such as slit lamp examination, ear, nose, and throat examination, esophago-gastroduodenoscopy, or MRI (especially in cases of cerebral and skull base involvement) should also be considered.
• In cases of exposed structures, consider special precautions (e.g., lens shield or bolus for ocular lymphoma, feeding tube for large cervical involvement, bite block, side-by-side renal function test in abdominal lymphoma).

Essentially, the GTV is defined as the initial extent of disease (pre-chemotherapy) while the CTV includes the sites of initial or remaining disease with consideration of anatomical changes after application of chemotherapy. In cases of definitive RT (without systemic treatment), adjacent visible nodes (even if not enlarged) might be included. In this setting, more generous margins are also advisable given the absence of systemic therapy to treat microscopic disease. Special caution is needed when defining pericardial or pleural disease extension [21,30]. The margin for the PTV should reflect institutional setup errors, with an extension of up to 10 mm being sufficient in most cases. Smaller margins can and should be used depending on the anatomical location as well as the availability and implementation of image guidance, tracking, and patient immobilization to reduce toxicity to organs at risk. CTV-to-PTV-margins should be as small as reasonably achievable without compromising treatment quality. Considering modern developments and increasing precision, they may be smaller than the exemplary margins given in this summary of the existing guidelines. Figure 2 gives an example of the target definition process with the resulting beam setup and dose distribution.

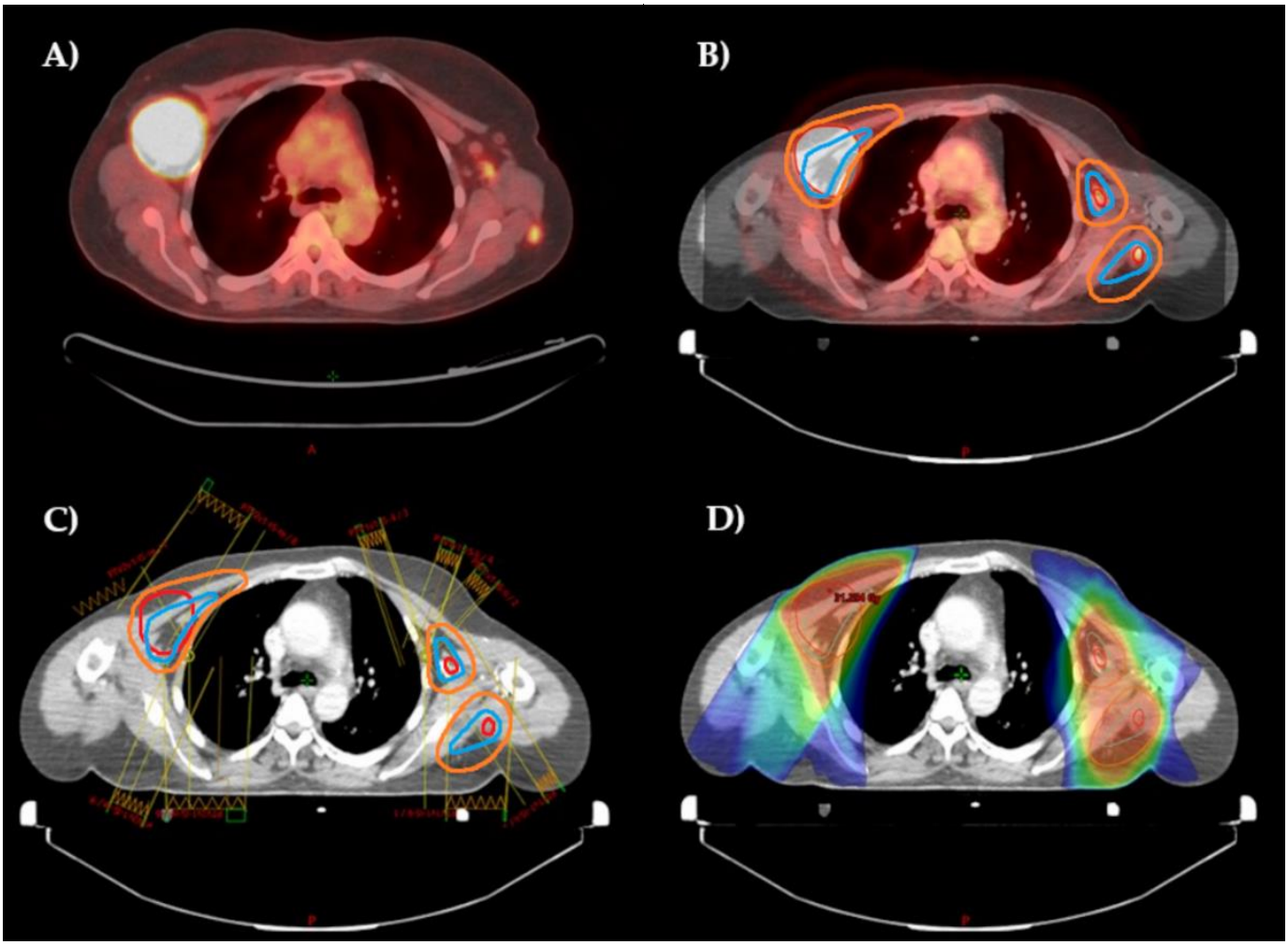

Figure 2. Target volume definition and field setup for ISRT in the thoracal region. (**A**) Initial PET/CT scan showing FDP avid manifestations in a patient with stage II HL. (**B**) Fusion of initial PET with planning CT scan for ISRT after two cycles of BEACOPPesc and ABVD with residual PET activity. Target volumes are defined as GTV = red, CTV = blue, PTV = orange. Notice the difference in arm positioning and table surface between initial PET/CT and planning CT; lymph nodes on the left are >5 cm apart, so they are treated individually. (**C**) Beam setup for sliding-window IMRT. (**D**) Resulting colour wash of dose distribution.

In the special case of nasal type NK/T-cell lymphoma (ENKTCL) or non-nasal type NK/T-cell lymphoma of the upper aerodigestive system (UADT ENKTCL), the CTV is often large due to extended macroscopic disease and/or continuous multisite spread. Additionally, the effectiveness of systemic therapy in ENKTCL is low compared to other lymphoma entities [9]. Here, the CTV comprises all involved primary sites and adjacent anatomic sites where infiltration is likely. Contrary to other lymphoma types, in cases of lymph node involvement, all regional lymph nodes are included, resulting in treatment fields that appear unusual in the context of lymphoma radiation, but reminiscent of solid head and neck tumours. Consulting the detailed ILROG guidelines by Qi et al. [9] is advised.

Even though this article does not cover the subject of dose prescription, it is important to note that all treatment field sizes as well as prescribed doses should consider uncertainties of disease localization, risk factors and possible toxicity resulting from surrounding organs at risk (OARs) on a case-by-case basis [21,31]. While the ILROG guidelines aim for the homogenization of treatment, they cannot fully replace the need for individual decisions based on clinical experience. An example is the in- or exclusion of lymph nodes of uncertain status (e.g., enlarged, but PET-negative) which is always subject to individual risk

assessment. Strict compliance with limitations of normal tissue is advised wherever possible, especially if long-term survival is likely (see Dabaja et al. [8] for further information on dose limitations).

Table 2 gives a summary of the key aspects of target definition for ISRT presented in the corresponding ILROG guidelines. Detailed information as well as exemplary depiction of volumes and field setups are given in respective publications as well and should be consulted for further detail.

Table 2. Summary of ILROG guidelines.

Key Aspects for ISRT Volume Definition in the ILROG Guidelines	
Guideline	**Key Aspects**
Treatment volumes for Hodgkin's lymphoma [5] and nodal non-Hodgkin's lymphoma [4]	**GTV Definition** • Primary treatment (e.g., LPHL): GTV is visualized in simulation. • Combined-modality treatment: GTV is affected due to upfront chemotherapy. The pre-chemo and post-chemotherapy/residual GTV extension should be defined in the simulation study. **CTV Definition** • The CTV comprises the pre-chemo GTV, but excludes OAR tissue with consideration of fusion accuracy, anatomical changes, and potential subclinical disease. • More generous margins and inclusion of directly adjacent lymph nodes (even if uninvolved) is advisable in cases of sole RT. • Nodes more than 5 cm apart can be treated in separate fields. • For irradiation of residual mass after chemotherapy in advanced disease, the CTV consists of the residual GTV (post-chemotherapy) with a margin of 10 mm (larger margins in areas of increased motion, see ITV). **ITV Definition** • ITV is defined on 4D simulation for chest and upper abdomen treatment with margins of 1.5–2 cm craniocaudal extension. **PTV Definition** • PTV definitions vary across institutions based on estimated setup errors. Typical margins around the CTV (or ITV) are 5–10 mm, but should be as small as clinically appropriate, based on individual treatment circumstances.
Extranodal non-Hodgkin's lymphoma [3]	**ISRT** can include the whole involved organ (especially in definitive RT) or just an affected part (as part of combined-modality treatment). **CTV** definitions are detailed below by organ. **PTV** definitions can vary based on setup (but margins are commonly 4–10 mm). CTV-to-PTV margins should be as small as clinically appropriate. **Primary central nervous system** • GTV definition is based on MRI and slit lamp examination. • CTV consists of the whole brain including C1-2 and the optical nerve bulbs. • If eyes are involved prior to systemic therapy, the entire globe should be included. • The role of a tumour site boost remains uncertain. • In cases of local treatment, margins < 4 cm seem to be associated with increased risk of failure [32]. **Primary intraocular lymphoma** • CTV includes the whole globe and optic nerve to the chiasm. • If suspicions of contralateral involvement arise, both globes should be treated. **Dura mater lymphoma** • CTV includes presurgical MRI volume with a margin along the dura. • In cases of multiple lesions, WBI with boost to the involved sites is advised.

Table 2. *Cont.*

Key Aspects for ISRT Volume Definition in the ILROG Guidelines	
Guideline	**Key Aspects**
Extranodal non-Hodgkin's lymphoma [3]	**Orbital (ocular adnexal) lymphoma** • CTV includes the whole bony orbit with inclusion of areas of suspected bone infiltration or extraorbital infiltration. Spare lenses if possible. • In cases only affecting conjunctiva or eyelid, RT (consider electrons) should cover the conjunctival reflection to the fornices but may spare the bony orbit. • For residual disease after systemic treatment for aggressive lymphoma, a local boost should be defined. **Lymphoma of the head and neck (excluding nasal type NK/T-cell lymphoma)** • CTV is based on initial GTV and mostly includes the entire involved subsite. • For lymphoma of the nasal cavity and paranasal sinuses, branched structures, based on PET and MRI as well endoscopic examination, are partially or completely included (based on certainty of infiltration). • For indolent pharyngeal NHL, the role of inclusion of the whole Waldeyer's ring remains unclear (and is not generally recommended). • For salivary gland involvement, the whole gland is included. **Thyroid lymphoma** • CTV is the whole thyroid, including the initial GTV extension. **Breast lymphoma** • CTV includes the whole breast without inclusion of uninvolved lymph nodes. • Partial breast irradiation might be considered in selected cases. **Lymphoma of the lung** • CTV and ITV include pre-intervention GTV sites with a margin based on suspected adjacent infiltration areas. **Gastric lymphoma** • CTV includes the complete gastric outline. ITV is advisable (10–20 mm margin). • Perigastric lymph nodes are usually included in the CTV. Further inclusion of portal/hepatic or para-aortic lymph nodes can be discussed. **Duodenum/small bowl lymphoma** • CTV for indolent NHL includes the whole duodenum. • For aggressive NHL, consider initial GTV extension with respect to anatomical changes and intraabdominal shift. • In select cases, consider a boost definition based on post-chemo GTV. **Lymphoma involving bladder and/or Gynaecological Organs** • CTV includes the whole organ. • Decision for full or empty bladder should be made individually. **Testicular lymphoma** • Preferred treatment is an anterior electron field. • A bolus might be advisable. **Lymphoma of the bone** • CTV includes sites of pre-chemo GTV with extension around uncertain areas of infiltration, based on PET/CT and MRI.

Table 2. *Cont.*

Guideline	Key Aspects
Key Aspects for ISRT Volume Definition in the ILROG Guidelines	
Nasal type NK/T-cell lymphoma [9]	**GTV Definition** • Based on imaging (MRI, CT, and PET/CT), endoscopy, and clinical examination. **CTV Definition** • CTV encompasses the initial GTV + 5 mm margin + areas with high risk of involvement with respect to anatomical borders (i.e., bones). • Anatomical volumes are treated as a whole, even if only partially involved (with exclusion of the orbit where only involved structures are included). • Include the whole Waldeyer's ring, if involved. • Include uncertain or first-echelon nodes based on clinical judgment. • Include bilateral cervical nodes if cervical lymph nodes are involved. **Additional aspects for non-nasal UADT ENKTCL:** • With primary disease in the upper aerodigestive tract, CTV includes the entire structure with a 2 cm margin and adjacent areas with suspected infiltration. • Prophylactic lymph node irradiation can be considered, even if not involved. • If lymph nodes are involved, bilateral cervical node stations are included.

4. Status Quo and Future Directions of ISRT

Overall, the developments in lymphoma treatment can be seen as a prime example of a scientific-driven process in the field of radiation oncology, continuously pushing the limits of the ALARA principle, the mantra of our profession, aiming for all application of ionizing irradiation to be "as low as reasonably achievable".

With image-guided and intensity-modulated therapy widely accessible today, radiation oncologists may challenge themselves to harness the potential of increasing treatment precision. The recent analyses regarding quality control of INRT application in large clinical trials (the German HD17-trial and the EORTC H10-Trial) show a high and increasing quality of compliance with the given treatment field definitions [33–35]. Nevertheless, incorrect definitions of treatment fields remain the primary source of protocol violations. In a real-world setting, the margin for clinically relevant errors grows smaller considering decreasing RT volumes. Interobserver variability in the interpretation of complex guidelines like the ones at hand are concerning and need to be taken seriously [36,37], to ensure a high standard in lymphoma RT.

With a growing arsenal of systemic agents and several trials aiming (mostly unsuccessfully) for the omission of RT from treatment regimens, the radiation oncologist's role remains challenging [38]. The effectiveness of RT in securing exceptional local control rates, resulting in better outcome or even translating to cure, is not debatable. At this point, treatment volumes can barely become any smaller and the benchmark for RT remains the tolerance of normal tissue. The switch from IFRT to INRT/ISRT has already proven effective in the reduction in treatment toxicity [39–41]. Additionally, rapidly evolving techniques for safer application and better sparing of OARs need to be explored and adapted in day-to-day practice: enhanced image fusion (e.g., with artificial intelligence (AI)-based deformed registration of PET/CT data) as well as optimized treatment positioning and beam setup (e.g., with 4D imaging, deep inspiration breath hold [42–45], and use of the optimal beam setup [38,46,47]) are just some branches that have already seen considerable improvements in individualization. It remains to be seen how the development of adaptive treatment with the possibility of high-frequency adjustments of volumes and the implementation of AI in the planning process might also benefit this development.

Despite the need for long-term follow-up, there is a lack of data regarding the long-term toxicity of current concepts. More data on the late sequelae of this new generation of precise individual treatment will lead to further optimization of the planning process. Optimization of IMRT planning happens on an individual basis, at the moment driven by

physics-centred parameters (DVH-based), but there is also progress to be expected from the ever-evolving insights into normal tissue complication probability modelling, rendering a more biologically driven approach possible [38].

With immunotherapy entering first-line treatment regimens [48], new synergies with RT may be established, comparable to solid tumours. Even in entities with decreasing use of RT (like primary central nervous lymphoma [49]), this treatment modality may witness a renaissance with more precise, less toxic, and well-combined concepts. In the future, personalized RT strategies may be possible.

5. Conclusions

RT plays a key role for lymphoma therapy, making long-term survival possible for low- and high-grade entities as part of single- or combined-modality treatment. The reduction in treatment field size from involved field to involved site is the basis for current and future developments to achieve maximum effectiveness with minimal toxicity. The guidelines of the ILROG, as summarized in this paper, give detailed information for modern state-of-the-art lymphoma treatment.

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