www.redjournal.org

Clinical Investigation

Modern Radiation Therapy for Hodgkin Lymphoma: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group (ILROG)

Lena Specht, MD, PhD,* Joachim Yahalom, MD,[†] Tim Illidge, MD, PhD,[‡] Anne Kiil Berthelsen, MD,[§] Louis S. Constine, MD,^{||} Hans Theodor Eich, MD, PhD,[¶] Theodore Girinsky, MD,[#] Richard T. Hoppe, MD,** Peter Mauch, MD,^{††} N. George Mikhaeel, MD,^{‡‡} and Andrea Ng, MD, MPH^{††}, on behalf of ILROG

*Department of Oncology and Hematology, Rigshospitalet, University of Copenhagen, Denmark; [†]Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York; [‡]Institute of Cancer Sciences, University of Manchester, Manchester Academic Health Sciences Centre, Christie Hospital NHS Trust, Manchester, United Kingdom; [§]Department of Radiation Oncology and PET Centre, Rigshospitalet, University of Copenhagen, Denmark; ^{II}Department of Radiation Oncology and Pediatrics, James P. Wilmot Cancer Center, University of Rochester Medical Center, Rochester, New York; [¶]Department of Radiation Oncology, University of Münster, Germany; [#]Department of Radiation Oncology, Institut Gustave-Roussy, Villejuif, France; **Department of Radiation Oncology, Stanford University, Stanford, California; ^{††}Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard University, Boston, Massachusetts; and ^{‡‡}Department of Clinical Oncology and Radiotherapy, Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom

Received Apr 25, 2013. Accepted for publication May 1, 2013.

Radiation therapy (RT) is the most effective single modality for local control of Hodgkin lymphoma (HL) and an important component of therapy for many patients. These guidelines have been developed to address the use of RT in HL in the modern era of combined modality treatment. The role of reduced volumes and doses is addressed, integrating modern imaging with 3-dimensional (3D) planning and advanced techniques of treatment delivery. The previously applied extended field (EF) and original involved field (IF) techniques, which treated larger volumes based on nodal stations, have now been replaced by the use of limited volumes, based solely on detectable nodal (and extranodal extension) involvement at presentation, using contrast-enhanced computed tomography, positron emission tomography/computed tomography, magnetic resonance imaging, or a combination of these techniques. The International Commission on Radiation Units and Measurements concepts of gross tumor volume, clinical target volume, internal target volume, and planning target volume are used for defining the targeted volumes. Newer treatment techniques, including intensity modulated radiation therapy, breath-hold, image guided radiation therapy, and 4-dimensional imaging, should be implemented when their use is expected to decrease significantly the risk for normal tissue damage while still achieving the primary goal of local tumor control. The highly conformal involved node radiation therapy (INRT), recently introduced for patients for whom optimal imaging is available, is explained. A new concept, involved site radiation therapy (ISRT), is introduced as the standard conformal therapy for the scenario, commonly encountered, wherein optimal imaging is not available. There is increasing evidence that RT doses used in the past are higher than

Reprint requests to: Lena Specht, MD, PhD, Department of Oncology, Section 5073, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark. Tel: (45) 35453969; E-mail: lena.specht@regionh.dk Supported by the Connecticut Sports Foundation and the Global Excellence Program of the Capital Region of Denmark.

Conflict of interest: none.

Acknowledgment—The authors thank Ms. Jessi Shuttleworth for coordinating the ILROG guidelines committee.

Int J Radiation Oncol Biol Phys, Vol. 89, No. 4, pp. 854–862, 2014 0360-3016/\$ - see front matter © 2014 Elsevier Inc. All rights reserved. http://dx.doi.org/10.1016/j.ijrobp.2013.05.005 necessary for disease control in this era of combined modality therapy. The use of INRT and of lower doses in early-stage HL is supported by available data. Although the use of ISRT has not yet been validated in a formal study, it is more conservative than INRT, accounting for suboptimal information and appropriately designed for safe local disease control. The goal of modern smaller field radiation therapy is to reduce both treatment volume and treatment dose while maintaining efficacy and minimizing acute and late sequelae. This review is a consensus of the International Lymphoma Radiation Oncology Group (ILROG) Steering Committee regarding the modern approach to RT in the treatment of HL, outlining a new concept of ISRT in which reduced treatment volumes are planned for the effective control of involved sites of HL. Nodal and extranodal non-Hodgkin lymphomas (NHL) are covered separately by IL-ROG guidelines. © 2014 Elsevier Inc.

Introduction

The purpose of these guidelines is to provide a consensus position on the modern approach to the delivery of radiation therapy (RT) in the treatment of Hodgkin lymphoma (HL) and to outline a new concept of involved site radiation therapy (ISRT) in which reduced treatment volumes are planned for the effective control of involved sites of disease. The present guidelines represent a consensus viewpoint of the Steering Committee of the International Lymphoma Radiation Oncology Group (ILROG). The guidelines are based on the best available evidence and the experience of ILROG members (1).

RT has been widely used in the management of malignant lymphomas and was responsible for many of the early cures of HL. Although RT continues to play an important role as a single modality for some HL patients, in most HL patients, RT is used in combination with chemotherapy. Combination chemotherapy has evolved with increasing efficacy to play a major role in the management of HL. RT continues to have an important place in ensuring locoregional control and improving overall outcome in the combined modality treatment programs for HL. With effective curative treatment regimens, there is increasing concern about the late effects of treatment and the quality of "survivorship." Therefore, it is of paramount importance in the delivery of RT to maintain high rates of long-term local control while minimizing radiation exposure to surrounding normal tissues. Furthermore, it is recognized that most recurrences in patients treated for HL occur in sites of previous involvement, and that RT reduces local recurrence. Advances in imaging, treatment planning, and RT delivery have made it possible to better define and further decrease RT fields in many situations. The current guidelines for involved field RT based on anatomic landmarks and encompassing adjacent uninvolved lymph nodes (2) are no longer appropriate for modern, more focused RT delivery aimed at reducing normal tissue exposure.

In this article, we highlight the application of advances in the technologic expertise available in the delivery of RT. These developments include the routine use of crosssectional imaging for RT planning, accurate dosimetry using modern algorithms that adjust for tissue inhomogeneities, complex beam shaping with multileaf collimation, and intensity modulated beam delivery in the treatment of HL.

The purpose of this document is to provide radiation oncologists treating HL with guidelines for imaging and treatment planning. The focus is on adult patients with localized HL and on bulky sites in advanced-stage and residual/relapsed/refractory disease in all stages.

Treatment Volume Principles

Modern RT planning in lymphoma incorporates the current concepts of volume determination as outlined in the International Commission on Radiation Units and Measurements (ICRU) Report 83 (3). It is based on defining a gross tumor volume (GTV) and a clinical target volume (CTV) that is expanded to a planning target volume (PTV). The PTV is then used to define beam coverage. This approach allows direct comparison with the diagnostic imaging, increasing the accuracy with which lymph node volumes are defined.

An important consideration is whether RT is being used as a primary treatment modality or, alternatively, whether it is being delivered as consolidation therapy. In patients with refractory disease after chemotherapy, RT may be administered to residual lymphoma to a higher dose and larger volume to obtain lasting local control. Furthermore, RT is highly effective when administered to local residual or refractory lymphoma as a component preceding or after a comprehensive salvage high-dose therapy program that includes stem cell transplantation.

Radiation Therapy as Primary Treatment

As a single modality in HL, RT is relevant for early-stage lymphocyte-predominant Hodgkin lymphoma (LPHL). It may also be relevant in selected cases of early-stage classic HL in patients who are not candidates for primary chemotherapy because of having serious comorbidities.

In most clinical situations that require RT as the primary modality, the GTV should be readily visualized during simulation. In this situation, the clinical target volume (CTV) should be more generous because microscopic or subclinical disease is more likely to be present without chemotherapy. The absence of effective systemic therapy in such cases should also influence dose decisions.

Radiation Therapy as Part of a Combined Modality Approach

In early-stage classic HL, RT is often part of the treatment program after adequate systemic chemotherapy in all age groups. RT improves freedom from treatment failure even in patients with negative positron emission tomography (PET) scans (4, 5) and allows treatment with fewer chemotherapy cycles (6). In a recent systematic review, combined modality treatment was found to improve tumor control and overall survival in patients with early-stage HL (7). In patients with advanced-stage disease, localized RT may be used for residual lymphoma after full chemotherapy, or RT may be an integral part of some regimens for advanced-stage disease (8).

In this situation, the GTV may be markedly affected by systemic chemotherapy, and it is therefore particularly important to review the prechemotherapy imaging and to outline the prechemotherapy volume on the simulation computed tomographic (CT) study as "prechemotherapy GTV."

Volume Definitions for Planning Radiation Therapy for Lymphoma

These principles apply whether ISRT or involved node radiation otherapy (INRT) is applied (see below). The difference between them is the quality and accuracy of the prechemotherapy imaging, which determine the margins needed to allow for uncertainties in the contouring of the CTV.

Volume of interest acquisition

Planning RT for lymphoma is based on obtaining a 3dimensional (3D) simulation study using either a CT simulator, a PET/CT simulator, or a magnetic resonance imaging simulator. If PET and/or CT information has been obtained separately or before simulation, it is best to fuse electronically with the CT simulation study so original volumes of interest can be displayed on the simulation study. Alternatively, careful manual transfer of volumes may be carried out if electronic transfer is not possible. Ideally, imaging studies that may provide planning information should be obtained with the patient in the treatment position and using the planned immobilization devices.

Determination of gross tumor volume

Prechemotherapy (or presurgery) GTV

Imaging abnormalities obtained before any intervention that might have affected lymphoma volume should be outlined on the simulation study, inasmuch as these volumes should (in most situations) be included in the CTV.

No chemotherapy or postchemotherapy GTV

The primary imaging of untreated lesions or postchemotherapy residual GTV should be outlined on the simulation study and is always part of the CTV.

Determination of clinical target volume

In principle, the CTV encompasses the original (before any intervention) GTV. Yet, normal structures such as lungs, kidneys, and muscles that were clearly uninvolved should be excluded from the CTV based on clinical judgment. In outlining the CTV, the following points should be considered:

Quality and accuracy of imaging Concerns of changes in volume since imaging Spread patterns of the disease Potential subclinical involvement Adjacent organs constraints

If separate nodal volumes are involved, they can potentially be encompassed in the same CTV. However, if the involved nodes are more than 5 cm apart, they can be treated with separate fields using the CTV-to-PTV expansion guidelines as outlined below.

Determination of internal target volume

The internal target volume (ITV) is defined in the ICRU Report 62 (9) as the CTV plus a margin taking into account uncertainties in size, shape, and position of the CTV within the patient. The ITV is mostly relevant when the target is moving, most commonly in the chest and upper abdomen with respiratory movements. The optimal way is to use 4D CT simulation to obtain the ITV margins. Alternatively, the ITV may be determined by fluoroscopy or estimated by an experienced clinician. In the chest or upper abdomen, margins of 1.5 to 2 cm in the superior-inferior direction may be necessary. In sites (eg, the neck) that are unlikely to change shape or position during or between treatments, outlining the ITV is not required.

Determination of planning target volume

The PTV is the volume that takes into account the CTV (or ITV, when relevant) and also accounts for setup uncertainties in patient positioning and alignment of the beams during treatment planning and through all treatment sessions.

The practice of determining the PTV varies across institutions. The clinician and/or treatment planner adds the PTV and applies standard margins that depend on estimated setup variations that are a function of immobilization device, body site, and patient cooperation. In general, margins for uncertainties should be added quadratically to avoid excessive margins based on the most extreme (and least likely) situations (10).

Determination of organs at risk

The organs at risk (OARs) are critical normal structures that, if irradiated, could experience significant morbidity and might influence treatment planning or the prescribed dose. They should be outlined on the simulation study. Dose–volume histograms (DVH) and normal tissue complication probability (NTCP) should be calculated by the planner and the plan vetted by the clinician in consideration of this information.

Radiation Therapy Dose Considerations

The determinants of dose prescription for HL include the histologic subtype (classic HL vs LPHL) and clinical risk factors.

For patients with early-stage classic HL in CR after chemotherapy, the dose to the CTV is determined on the basis of the results of the German Hodgkin Studies HD 10 and 11 (6, 11). For patients with favorable characteristics according to the German criteria, the dose is 20 Gy, whereas for patients with unfavorable characteristics it is 30 Gy.

For patients with early-stage LPHL, no advantage has been shown for doses over 30 to 35 Gy, which is the recommended dose to the CTV (12).

For patients with residual lymphoma after chemotherapy, the residual mass may represent a more refractory disease, and increasing the dose to the CTV to 36 to 40 Gy should be considered.

Radiation Therapy Planning

Role of imaging in radiation therapy planning

Lymphoma staging and response assessment is based on 3D imaging, with CT supplemented by functional imaging using ¹⁸F-fluorodeoxyglucose (FDG)-PET. Optimally, these images should be acquired with the patient in the radiation treatment position and with the involvement of the radiation oncologist (Fig. 1).

The use of diagnostic contrast-enhanced CT is essential to delineate nodal stations and differentiate nodes from vessels. In centers where PET/CT can be done with contrast medium, this can obviate the need for a separate contrastenhanced investigation. PET/CT scans can be done with contrast medium without interfering with the attenuation correction (13). For abdominal and pelvic locations, oral contrast medium should be used. 4D CT imaging as part of the simulation may be helpful in determining the ITV for sites that change with respiration. Acquiring this highquality imaging is fundamental to high-quality RT planning.

Immobilization

A planning CT scan should be taken with the patient having appropriate immobilization. In the case of disease in the head-and-neck region, a customized thermoplastic mask should be used. Contiguous slices with a slice thickness of no more than 3 to 5 mm should be taken through the region of interest.

Treatment techniques

The treating radiation oncologist makes a clinical judgment as to which treatment technique to use, based on comparisons of treatment plans and DVHs with different techniques. In some situations, conventional anteroposterior-posteroanterior techniques may be preferred, because the smallest volume of normal tissue will be irradiated, albeit to the full prescribed dose (Fig. 2). In other situations, more conformal techniques such as IMRT, arc therapy, or tomotherapy may offer significantly better sparing of critical normal structures, usually at the price of a larger total volume of normal tissue irradiated, albeit to a lower dose (Fig. 3). The role of proton therapy has not yet been defined, and it is not widely available. Recommendations as to which technique to use in the individual case cannot be made, and careful consideration must be given to choosing the technique that the clinician considers to offer the minimum risk of significant late toxicity for that patient.



Fig. 1. Patient having the initial staging positron emission tomography/computed tomography scan in a position suited for later radiation therapy. Notice immobilization devices (face mask and body support) and on the left an intravenous contrast pump for computed tomography.

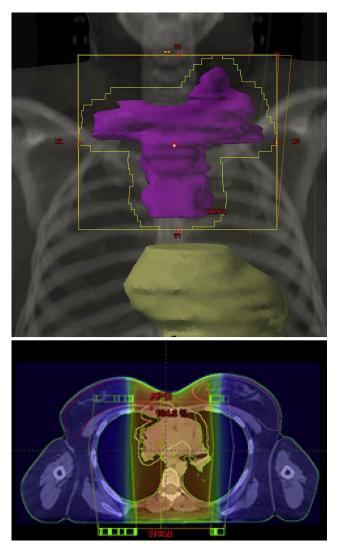


Fig. 2. Involved site radiation therapy with anteroposterior-posteroanterior technique, field (above) and dose distribution (below).

Three-dimensional planning

The use of 3D outlining is highly recommended and is essential for determining the CTV, PTV, and OARs. Standard 3D conformal treatment is appropriate in many cases. However, in some clinical scenarios, IMRT, inspiration breath-hold techniques, and image-guided radiation therapy (IGRT) may offer significant and clinically relevant advantages and should be used. The use of 4D imaging or deep-inspiration breath-hold technique for disease sites that are significantly affected by respiratory motion is encouraged. IGRT verification may be indicated for sites that are adjacent to critical dose-limiting normal structures, especially in situations of retreatment.

Intensity modulated radiation therapy

IMRT plans provide improved planning target volume coverage (D_{mean} , V95, conformity index) compared with

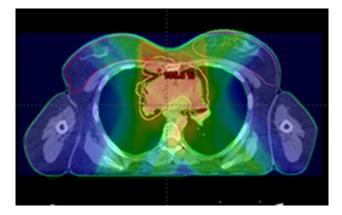


Fig. 3. Involved site radiation therapy with intensity modulated technique, dose distribution.

3D conformal RT. In selected patients with mediastinal involvement, IMRT reduces pulmonary toxicity predictors (lower values for D_{mean} and V20) and allows for a better protection of the heart and coronary arteries. This dosimetric gain is normally more evident in case of a large PTV involving the anterior mediastinum.

Although the advantages of IMRT include the tightly conformal doses and steep gradient next to normal tissues, target definition and treatment delivery verification need even more attention than with conventional RT to avoid the risk of tumor geographic miss and subsequent decrease in tumor control. Image guidance may be required to ensure full coverage during the whole treatment. For IMRT in mediastinal lymphoma, the use of 4D CT for simulation and the adoption of strategies to deal with respiratory motion during treatment delivery may be important.

The highly conformal treatment techniques enable retreatment of patients experiencing relapse without exceeding the tolerance of critical normal structures such as the spinal cord (14). Figure 4 shows a treatment plan for a patient with supradiaphragmatic recurrence after previous radiation therapy to 36 Gy to a modified mantle field.

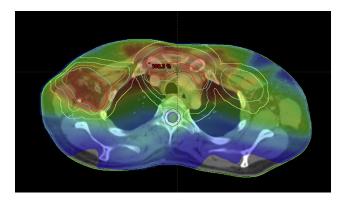


Fig. 4. Treatment plan for a patient with supradiaphragmatic recurrence after previous radiation therapy to 36 Gy to a modified mantle field.

Breath-hold techniques

In patients with classic HL, irradiation of the mediastinum is frequently indicated. Several studies have demonstrated that treatment in inspiration enables significant sparing of the lung and heart, and this technique is recommended (15). Figure 5 shows treatment plans for a patient with extensive mediastinal disease in free breathing and inspiration breathhold.

Dose Constraints

Previous experience comes from patients treated over the past 5 decades, where extended fields and higher doses resulted in significant risks of morbidity and mortality. Hence, it is important to use the ISRT treatment technique described below and to choose the treatment plan that is estimated to lead to the lowest risk of long-term complications for the individual patient. Consideration should be given to factors such as sex, age, and comorbidities.

An integral part of calculating conformal treatment plans is the use of dose constraints for different normal tissues. However, the dose constraints used for treatment planning of solid tumors are in most cases not well suited for the planning of RT for lymphomas because the prescribed dose to the target is much lower.

Radiation doses to all normal structures should be kept as low as possible to minimize the risk of long-term complications, but some structures are more critical than others. Ideally, NTCP models for all relevant risk organs with a special focus on the low-dose region of 20 to 40 Gy should be combined for each treatment plan. At present, no validated guidelines exist that allow optimization based on weighted estimates of risks of different long-term complications. Research into the development of methods for this purpose, based on the available dose-response data for different tissues and endpoints, is ongoing (16). As a minimum, however, the doses to normal structures should at least conform to well-documented dose constraints that are applied to the treatment of solid tumors (17).

The risk of late side effects needs always to be balanced by the risk of local recurrence if RT is not given for the individual patient. In many situations, particularly in the older age group, the risk and morbidity of disease recurrence outweighs the unlikely risk of late effects such as second malignancy.

Involved Site Radiation Therapy in Early-Stage HL

The concept of ISRT was developed on the basis of the INRT concept. INRT was introduced and implemented by the European Association for Research and Treatment of Cancer (EORTC) Lymphoma Group and is detailed later in the document (18, 19).

In both INRT and ISRT, the prechemotherapy GTV determines the CTV, and the irradiated volume is significantly smaller than with IFRT. However, ISRT accommodates cases in which optimal prechemotherapy imaging is not available to the radiation oncologist. In these situations, it is not possible to reduce the CTV to the same extent as with INRT because the prechemotherapy GTV information may not be optimal. In ISRT, clinical judgment in conjunction with the best available imaging is used to contour a larger CTV that will accommodate the uncertainties in defining the prechemotherapy GTV.

In the situation where prechemotherapy imaging (eg, CT, PET, or MRI) of all the initially involved lymphoma sites of disease is available, but image fusion with the postchemotherapy planning CT scan is not possible, the radiation oncologist will have to contour the target volume on the planning CT scan. The prechemotherapy images are used for contouring on the CT scan. Allowance should be made for the uncertainty of the contouring and differences in positioning by including a larger volume in the CTV. The

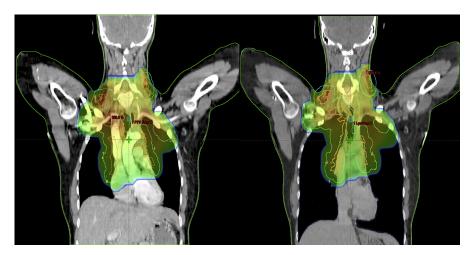


Fig. 5. Treatment plans for a patient with extensive mediastinal disease in free breathing (left) and inspiration breath-hold (right). Mean lung dose in free breathing was 15.7 Gy; in inspiration breath-hold it was 11.2 Gy.

more uncertainty there is, the larger the contoured volume will have to be.

If no prechemotherapy imaging is available (eg, patients presenting with neck disease but whose staging fails to include imaging of the neck), the situation is more challenging. The radiation oncologist must gather as much information as possible from the description of the prechemotherapy physical examination of the patient, the location of scars and scar tissue on the postchemotherapy planning CT scan, and the patient's and the family's recollections of the location of the presenting lymph node(s). The CTV should be contoured taking into account all of this information, making generous allowance for the many uncertainties in the process.

Clinical target volume

The CTV encompasses the original lymphoma volume, modified for normal tissue boundaries and expanded to accommodate uncertainties in determining the prechemotherapy volume as outlined above. In situations where RT is the primary treatment, larger margins to encompass subclinical disease need to be applied.

The ITV should be added to the CTV only in situations where internal organ movement is of concern. The CTV (or ITV if used) will be expanded further to create the PTV.

Involved Node Radiation Therapy in Early-Stage Classic HL

The concept of INRT for early-stage classic HL was developed and implemented by the EORTC and replaced the traditional larger IFRT that was used in previous studies by the EORTC and other groups. The INRT technique reduces the treated volume to a minimum, but to be safe, optimal imaging both before and after chemotherapy is needed (18, 20). INRT can therefore be regarded as a special case of ISRT wherein optimal imaging is available. It has been demonstrated that PET/ CT is the most accurate imaging method for determining disease extent in HL, and thus up-front PET/CT is mandatory for INRT design (21). To enable image fusion of the prechemotherapy and the postchemotherapy planning images, the prechemotherapy PET/CT scan should be acquired with the patient in the treatment position and using the same breathing instructions that will be used later for RT. Ideally, the patient should be scanned on a flat couch top, with the use of appropriate immobilization devices, and using markers at skin positions that are visible in the imaging. However, an ordinary diagnostic PET/CT scan with the patient lying in approximately a position that is suitable for later RT will usually suffice.

After the completion of chemotherapy, a response assessment using PET/CT or contrast-enhanced CT should be performed, if this is not being performed during the chemotherapy. INRT should be commenced 3 to 4 weeks after the completion of chemotherapy. A planning CT scan is acquired with the patient in the same position as in the prechemotherapy CT scan.

The contouring process is now as follows:

- 1. The CT images of the prechemotherapy PET/CT are used to delineate the initially involved lymphoma volume, the GTV_{CT} as determined by morphology on CT. This volume is depicted in red in Figure 6A.
- The PET images of the prechemotherapy PET/CT are used to delineate the initially involved lymphoma volume, the GTV_{PET} as determined by FDG uptake, depicted in blue in Figure 6B.
- The prechemotherapy PET/CT is fused with the postchemotherapy planning CT scan, and the GTV_{CT} and GTV_{PET} are imported to the planning CT images, depicted in Figure 6C and D.
- 4. The postchemotherapy tissue volume, which contained the initially involved lymphoma tissue, is contoured using information from both prechemotherapy PET and prechemotherapy CT, taking into account tumor shrinkage and other anatomic changes. This is the CTV, depicted in purple in Figure 6E. The CTV encompasses all of the initial lymphoma volume while still respecting normal structures that were never involved by lymphoma, such as lungs, chest wall, muscles, and mediastinal normal structures.

Once the CTV has been defined, the planning process is as described above with ISRT.

This highly conformal treatment technique has been shown to be safe, provided strict adherence to the principles described here is maintained (1, 22). INRT represents a special case of ISRT, in which prechemotherapy imaging is ideal for postchemotherapy treatment planning.

Irradiation of Residual Mass After Full Chemotherapy for Advanced Disease

In advanced disease (classic HL and LPHL), many centers treat patients with chemotherapy alone (especially in the absence of bulky disease) and only if a CR is not achieved will RT be used. The target in this situation is the residual mass (GTV) after chemotherapy.

Once the GTV has been contoured, the planning procedure is as described previously. A margin is added to account for uncertainties and motion. Usually a margin of 1 cm is sufficient, but in the chest and upper abdomen a larger margin in the superior-inferior direction is needed to compensate for respiratory motion.

Irradiation of Early-Stage LPHL

When RT is used as the only treatment modality, the CTV must be designed to encompass suspected subclinical disease. However, no advantage has been demonstrated with EFRT as opposed to more limited treatment fields (23). The CTV should incorporate the GTV and include as a minimum adjacent lymph nodes in that site and a generous margin dictated by the clinical situation. The scenario is similar to RT for localized indolent NHL.

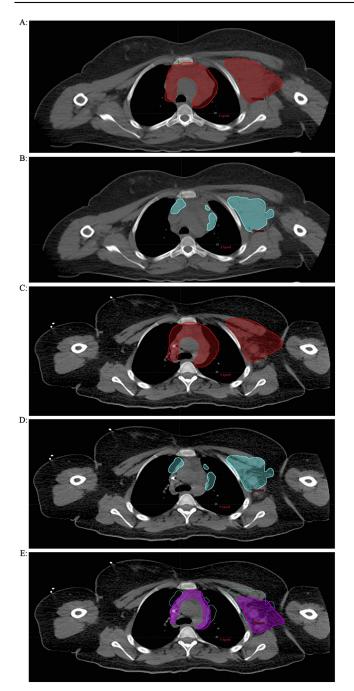


Illustration of the method of contouring the initially Fia. 6. involved lymphoma gross tumor volume (GTV) on the postchemotherapy planning computed tomography (CT) scan, with information from fusion with the prechemotherapy positron emission tomography/CT scan. (A) Prechemotherapy GTV_{CT} on prechemotherapy CT scan. (B) Prechemotherapy GTV_{PET} on prechemotherapy CT scan. (C) Prechemotherapy GTV_{CT} on postchemotherapy CT scan. (D) Prechemotherapy GTV_{PET} on postchemotherapy CT scan. (E) Clinical target volume, created by modifying GTV_{CT} and GTV_{PET}, on the postchemotherapy CT scan. (Reprinted with permission from Hutchings M, Berthelsen AK, Barrington SF. The role of imaging in radiotherapy for Hodgkin lymphoma. In: Specht L, Yahalom J, eds. Radiotherapy for Hodgkin Lymphoma. Heidelberg: Springer; 2011. pp. 81-89).

Larger Field RT

The role of larger field RT is now limited essentially to salvage treatment in patients in whom chemotherapy is unsuccessful and who are unable to embark on more intensive salvage treatment schedules. Such salvage cases are usually addressed on a case-to-case basis and it is not feasible to produce guidelines, given the diversity of individual cases. As such, there are no data to support the use of extended fields that can cause toxicity and compromise the safety of subsequent therapy such as stem cell transplantation.

Refractory and Relapsed HL

Salvage RT plays an important role in local control for patients who have primary refractory disease dominated by a local site. Salvage RT is also important for patients who experience relapse after achieving a CR with initial therapy, where RT is generally used as part of combined modality therapy along with salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT).

A small group of patients with localized disease and no systemic symptoms enjoy prolonged disease-free survival with RT alone (24). RT should also be considered as a salvage option in the setting of ASCT failure, after relapse, or after progression, wherein a significant proportion of patients could still achieve high response rates with salvage RT to doses up to 40 Gy, and a few may even enjoy long-term disease-free survival of over 5 years (25). Salvage RT yields high response rates and high local control rates in refractory and relapsed HL (24) and in relapses after ASCT, where it can play an important role in the palliation of incurable HL (25, 26). However, systemic failures remain the commonest problem in this setting, underlining the need for improved systemic therapy in combination with salvage RT.

RT plays an important role as cytoreduction and consolidation therapy in the peritransplantation period in some transplantation programs (27), and it results in low numbers of ASCT failures in patients who received RT in singleinstitution studies. Patients who are candidates for salvage therapy with ASCT may benefit from RT either before or after ASCT to dominant sites of local recurrence. In patients with CR or near-CR to salvage chemotherapy, a dose of 30 to 36 Gy after ASCT is recommended. When given after ASCT, RT should be delivered as soon as the patient has recovered from the acute side effects of ASCT, and ideally within 6 weeks after stem cell infusion. Consideration is given to previous RT and to the radiosensitivity of normal tissues and organs that would be inadvertently irradiated (Fig. 4). RT volumes are localized to encompass the known site(s) of disease recurrence, without prophylactic inclusion of adjacent lymph nodal stations.

Conclusion

Modern RT for HL is a highly individualized treatment restricted to limited treatment volumes. Modern imaging and RT techniques should be used to limit the amount of normal tissue being irradiated, thus minimizing the risk of long-term complications. The newly defined fields of ISRT represent a significant reduction in the volume included in the previously used IFRT. Radiation oncologists treating HL should be involved as part of the multidisciplinary team in the initial management plan and attempt to introduce imaging procedures up front before the initiation of chemotherapy. Such an integrated multidisciplinary approach will enable the optimal outcome for patients with HL.

References

- Maraldo MV, Aznar MC, Vogelius IR, et al. Involved node radiotherapy: An effective alternative in early stage Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys* 2013;85:1057-1065.
- Yahalom J, Mauch P. The involved field is back: Issues in delineating the radiation field in Hodgkin's disease. *Ann Oncol* 2002;13(Suppl 1): 79-83.
- DeLuca P, Jones D, Gahbauer R, et al. Prescribing, recording, and reporting photon-beam intensity-modulated radiation therapy (IMRT). *J ICRU* 2010;10:1-106.
- Andre MPE, Reman O, Federico M, et al. Interim analysis of the randomized EORTC/LYSA/FIL intergroup H10 trial on early PETscan driven treatment adaptation in stage I/II Hodgkin lymphoma [Abstract]. *Blood* 2012;120:549.
- Radford J, Barrington S, Counsell N, et al. Involved field radiotherapy versus no further treatment in patients with clinical stages IA and IIA Hodgkin lymphoma and a 'negative' PET scan after 3 cycles ABVD. Results of the UK NCRI RAPID trial [Abstract]. *Blood* 2012;120:547.
- Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med* 2010; 363:640-652.
- Herbst C, Rehan FA, Brillant C, et al. Combined modality treatment improves tumour control and overall survival in patients with early stage Hodgkin lymphoma: a systematic review. *Haematologica* 2010; 95:494-500.
- Bartlett NL, Rosenberg SA, Hoppe RT, et al. Brief chemotherapy, Stanford V, and adjuvant radiotherapy for bulky or advanced-stage Hodgkin's disease: A preliminary report. *J Clin Oncol* 1995;13:1080-1088.
- ICRU. International Commission on Radiation Units and Measurements. Prescribing, recording, and reporting photon therapy. (Supplement to ICRU Report 50). ICRU Report 62. 1999.
- van Herk M. Errors and margins in radiotherapy. Semin Radiat Oncol 2004;14:52-64.
- Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dosereduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: Final analysis of the German Hodgkin Study Group HD11 trial. J Clin Oncol 2010;28:4199-4206.

- Wirth A, Yuen K, Barton M, et al. Long-term outcome after radiotherapy alone for lymphocyte-predominant Hodgkin lymphoma: A retrospective multicenter study of the Australasian Radiation Oncology Lymphoma Group. *Cancer* 2005;104:1221-1229.
- Berthelsen AK, Holm S, Loft A, et al. PET/CT with intravenous contrast can be used for PET attenuation correction in cancer patients. *Eur J Nucl Med Mol Imaging* 2005;32:1167-1175.
- Goodman KA, Toner S, Hunt M, et al. Intensity-modulated radiotherapy for lymphoma involving the mediastinum. *Int J Radiat Oncol Biol Phys* 2005;62:198-206.
- 15. Paumier A, Ghalibafian M, Gilmore J, et al. Dosimetric benefits of intensity-modulated radiotherapy combined with the deep-inspiration breath-hold technique in patients with mediastinal Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys* 2012;82:1522-1527.
- Brodin NP, Vogelius IR, Maraldo MV, et al. Life years lost: Comparing potentially fatal late complications after radiotherapy for pediatric medulloblastoma on a common scale. *Cancer* 2012;118:671-676.
- Marks LB, Ten Haken RK, Martel MK, et al. Quantitative analyses of normal tissue effects in the clinic. *Int J Radiat Oncol Biol Phys* 2012; 76:1-160.
- Girinsky T, van der Maazen R, Specht L, et al. Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: concepts and guidelines. *Radiother Oncol* 2006;79:270-277.
- Girinsky T, Ghalibafian M, Specht L. Target definition for Hodgkin lymphoma: The involved node radiation field concept. In: Specht L, Yahalom J, editors. Radiotherapy for Hodgkin Lymphoma. Heidelberg: Springer; 2011. p. 91-122.
- Girinsky T, Specht L, Ghalibafian M, et al. The conundrum of Hodgkin lymphoma nodes: To be or not to be included in the involved node radiation fields. The EORTC-GELA lymphoma group guidelines. *Radiother Oncol* 2008;88:202-210.
- Hutchings M, Loft A, Hansen M, et al. Positron emission tomography with or without computed tomography in the primary staging of Hodgkin's lymphoma. *Haematologica* 2006;91:482-489.
- Paumier A, Ghalibafian M, Beaudre A, et al. Involved-node radiotherapy and modern radiation treatment techniques in patients with Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys* 2011;80:199-205.
- 23. Nogova L, Reineke T, Eich HT, et al. Extended field radiotherapy, combined modality treatment or involved field radiotherapy for patients with stage IA lymphocyte-predominant Hodgkin's lymphoma: A retrospective analysis from the German Hodgkin Study Group (GHSG). Ann Oncol 2005;16:1683-1687.
- 24. Josting A, Nogova L, Franklin J, et al. Salvage radiotherapy in patients with relapsed and refractory Hodgkin's lymphoma: A retrospective analysis from the German Hodgkin Lymphoma Study Group. J Clin Oncol 2005;23:1522-1529.
- 25. Goda JS, Massey C, Kuruvilla J, et al. Role of salvage radiation therapy for patients with relapsed or refractory Hodgkin lymphoma who failed autologous stem cell transplant. *Int J Radiat Oncol Biol Phys* 2012;84:e329-e335.
- Vose JM, Bierman PJ, Anderson JR, et al. Progressive disease after high-dose therapy and autologous transplantation for lymphoid malignancy: Clinical course and patient follow-up. *Blood* 1992;80: 2142-2148.
- Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: Analysis by intent to treat and development of a prognostic model. *Blood* 2001;97:616-623.