Modern Radiation Therapy for Nodal Non-Hodgkin Lymphoma-Target Definition and Dose Guidelines From the International Lymphoma Radiation Oncology Group

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Radiation therapy (RT) is the most effective single modality for local control of non-Hodgkin lymphoma (NHL) and is an important component of therapy for many patients. Many of the historic concepts of dose and volume have recently been challenged by the advent of modern imaging and RT planning tools. The International Lymphoma Radiation Oncology Group (ILROG) has developed these guidelines after multinational meetings and analysis of available evidence. The guidelines represent an agreed consensus view of the ILROG steering committee on the use of RT in NHL in the modern era. The roles of reduced volume and reduced doses are addressed, integrating modern imaging with 3-dimensional planning and advanced techniques of RT delivery. In the modern era, in which combined-modality treatment with systemic therapy is appropriate, the previously applied extended-field and involved-field RT techniques that targeted nodal regions have now been replaced by limiting the RT to smaller volumes based solely on detectable nodalinvolvement at presentation. A new concept, involved-site RT, defines the clinical target volume. For indolent NHL, often treated with RT alone, larger fields should be considered. Newer treatment techniques, including intensity modulated RT, breath holding, image guided RT, and 4-dimensional imaging, should be implemented, and their use is expected to decrease significantly the risk for normal tissue damage while still achieving the primary goal of local tumor control. _ 2014 Elsevier Inc.

Introduction

The purpose of these guidelines is to provide a consensus position on the modern approach to radiation therapy (RT) delivery in the treatment of nodal non-Hodgkin lymphoma (NHL) and to outline a new concept of involved-site RT (ISRT), in which reduced treatment volumes are planned for the effective control of involved sites of disease. The present guidelines represent a consensus viewpoint following face to

face international meetings, examination of available evidence, and discussion within the Steering Committee of the International Lymphoma Radiation Oncology Group (ILROG). The guidelines are thus based on the best available evidence and, in its absence, on the experience and agreed consensus of ILROG members. Radiation therapy has been widely used in the management of malignant lymphomas and was responsible for many of the early cures (1). Radiation therapy continues to play an important role as a single modality for some lymphomas. More recently, combination chemotherapy and immuno-chemotherapy with the addition of rituximab has evolved with increasing efficacy and now plays a major role in the management of many B-cell NHLs. Radiation therapycontinues to have an important place in increasing locoregional control in combined treatment programs formany early-stage presentations, as well as for selected bulky and extranodal, advanced-stage, aggressive NHL presentations (2-5). Radiation therapy serves as the sole treatment modality in most early-stage indolent NHL (6). With effective curative treatment regimens there is increasing concern for 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 of surrounding normal tissues. Furthermore, it is recognized that most recurrences in patients treated for NHL are in sites of previous involvement and that RT is highly effective at reducing subsequent local recurrences (7, 8). Historic guidelines for lymphoma RT predated modern imaging techniques that identify sites of overt (gross) disease and effective chemotherapy that sterilizes covert (subclinical) sites. Therefore, guidelines for lymphoma RT based on involved fields defined by anatomic landmarks and encompassing adjacent uninvolved lymph nodes (9) are no longer appropriate for modern, morefocused RT delivery aimed at reducing normal tissue exposure. Although we acknowledge the lack of randomized evidence to support radiation field size reduction, there is increasing evidence to suggest effective local control with such reduced field sizes (10, 11). Here we have highlighted the application of advances in the technological expertise available in the planning and delivery of RT and provide radiation oncologists treating NHL with guidelines on imaging, volume determination, and treatment planning. The focus is on adult patients with localized nodal NHL, as well as patients with bulky sites and residual disease in advanced stages. The treatment approaches described include both aggressive and indolent lymphoma. Other clinical scenarios that are discussed include the role of RT in advanced-stage NHL, recurrent lymphoma, and palliation of nodal NHL.

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 (12), based on defining a gross tumor volume (GTV) and clinical target volume (CTV), which is expanded to create a planning target volume (PTV). The PTV is then used to define dose coverage. This approach allows direct comparison with the diagnostic imaging, increasing the accuracy with

which lymph node localization is defined. An important consideration in defining target volumes is whether RT is being used as a single treatment modality or, alternatively, whether RT is being delivered as a consolidation therapy. In patients with disease that is refractory to chemotherapy, RT may be administered to persistent or residual lymphomatous sites with a higher dose and larger volume in an attempt to obtain lasting local control, because chemotherapy has neither sterilized the identifiable disease nor the presumed adjacent subclinical or covert disease. Furthermore, RT is highly effective when administered to local residual or refractory lymphoma as a treatment component preceding or following a comprehensive salvage high-dose therapy program that includes stem cell transplantation (13, 14).

Radiation Therapy as Primary Treatment

Radiation therapy as a single modality can be curative for patients with localized indolent lymphoma and provides effective treatment for patients with localized aggressive nodal NHL who are unsuitable for primary chemotherapy because of serious comorbidities. Some patients with localized disease who remain refractory to chemotherapy may also be appropriately treated with localized RT. In most clinical situations that require RT as the primary modality, the GTV should be readily visualized during treatment preparation, and it is recommended that this is enhanced by the use of contrast. The CTV should be more generous in this clinical situation and also encompass lymph nodes in the vicinity that, although of normal size, might contain microscopic disease that will not be treated when no chemotherapy is given. The absence of effective systemic therapy in such cases should also influence RT dose decisions.

RT as Part of a Combined-Modality Approach

Radiation therapy is often part of the treatment program for localized aggressive nodal lymphomas and is delivered as consolidation therapy after systemic chemotherapy. A combined-modality approach with abbreviated chemotherapy may be particularly relevant in elderly patients, in whom chemotherapy is often poorly tolerated. A significant number of these patients are unable to tolerate the full dose and number of courses of chemotherapy, requiring significant dose, schedule, or cycle modifications and reductions. Many of these patients with localized disease are potentially cured with abbreviated chemotherapy and consolidation RT. For this group of patients the use of RT is particularly important, given the lack of effective salvage options in relapsed disease. Recent data suggest an important role of consolidation RT in improving outcome for patients when delivered to sites of initial bulky and extranodal disease, even in patients with advanced-stage disease that achieved a complete response after chemotherapy (2, 3). In this situation where consolidation ISRT is used, the GTV may be markedly affected by systemic chemotherapy, and it is therefore particularly important to review the

prechemotherapy imaging and outline the prechemotherapy volume on the simulation CT study as "prechemotherapy GTV."

Volume Definitions for Radiation Therapy Planning of Lymphoma

Volume of interest acquisition

Planning RT for lymphoma is based on obtaining a 3- dimensional (3D) simulation study using either a CT simulator, a positron emission tomography (PET)-CT simulator, or an MRI simulator. If PET and/or CT information has been obtained separately or before simulation, it should be fused 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 in the treatment position and using the planned immobilization devices.

Prechemotherapy (or presurgery) GTV

Imaging abnormalities suggestive of lymphomatous involvement obtained before any intervention that might have affected tumor volume should be outlined on the simulation study, because these volumes should (in most situations) be included in the CTV.

No chemotherapy or postchemotherapy GTV

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

CTV determination

The CTV encompasses in principle the original (before any intervention) GTV, even if extended beyond the involved tissue or organ. Yet normal structures such as lungs, kidneys, and muscles that were clearly uninvolved, though previously displaced by the GTV, should be excluded from the CTV according to 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; and adjacent organs constraints.
If distinct nodal volumes are involved but <5 cm apart, they can potentially be encompassed in the same CTV. However, if the involved nodes are >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

Internal target volume (ITV) is defined in ICRU report 62 (10) 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 (15). The optimal way is to use 4-dimensional (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 1.5-2 cm in the superior- inferior direction may be necessary. In sites that are unlikely to change shape or position during or in between treatments (eg, the head and neck), outlining the ITV is not required.

Determination of PTV

The PTV is the volume that takes into account the CTV (and 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 margins that depend on estimated setup variations that are a function of immobilization device, body site, internal organ motion, and patient cooperation. In general, margins for uncertainties are based on probability levels. Margins should not be added linearly because this will lead to large margins based on the most extreme and least likely situations (16).

Determination of organs at risk

The organs at risk (OARs) are critical normal structures that can manifest adverse effects from radiation, usually dependent on the radiation dose. The OARs relevant to treatment planning or the prescribed dose should be outlined on the simulation study. The planner should calculate dose-volume histograms, and the plan should be evaluated in consideration of the expected normal tissue complication probability.

RT dose considerations

Historically, doses for nodal NHL have varied between 30Gy and 55 Gy using conventional 1.8- to 2.0-Gy fractionation schedules. For aggressive NHL, radiation doses of up to 40-55 Gy after chemotherapy have been used in clinical trials (17). Most retrospective series on RT alone for follicular lymphoma and marginal zone lymphoma used doses of 35-45 Gy and 30 Gy, respectively. More recently, differences in the relative radiosensitivity of the commonest indolent lymphomas and aggressive lymphomas have been recognized. A large prospective, randomized trial was undertaken in the United Kingdom comparing 24 Gy with 40 Gy in “low-grade” (predominantly follicular) and 30 Gy with 40 Gy in “high grade” (predominantly diffuse large Bcell lymphoma). Importantly, most patients had also received

chemotherapy, and RT was given as consolidation. More than 1000 patients were randomized, and at a median follow-up of 5.6 years, no differences between the highand low-dose treatment arms within each lymphoma subtype were seen (6).

Radiation Treatment Planning

Role of imaging in radiation planning

Lymphoma staging and response assessment is based on 3D imaging, with CT supplemented by functional imaging using fluorodeoxyglucose-PET. Optimally, these images should be acquired with the patient in the radiation treatment position and with involvement of the radiation oncologist. The use of diagnostic contrast-enhanced CT is recommended to help to delineate nodal stations and differentiate nodes from vessels. In centers where PET/CT can be done with contrast, this can obviate the need for a separate contrast-enhanced investigation. PET/CT scans can be done with contrast without interfering with the attenuation correction (18). For abdominal and pelvic locations, oral contrast should be used. Four-dimensional CT imaging as part of the simulation may be helpful in determining the ITV for sites that move with respiration. Acquiring this high-quality imaging is fundamental to high-quality RT planning.

Immobilization

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

Treatment techniques

The treating radiation oncologist should make a clinical judgment as to which treatment technique to use, based on comparisons of treatment plans and dose-volume histograms with different techniques. In some situations, conventional anteroposterior-posteroanterior techniques may be preferred, because the smallest volume of normal tissue would be irradiated with this technique, albeit to the full-prescribed dose. In other situations more-conformal techniques, such as intensity modulated RT (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. The potential benefits and risks of proton therapy for patients with lymphoma are not yet fully understood and require further investigation. 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 lowest risk of significant late toxicity for that patient.

3D planning and RT approach

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 RT may offer significant and clinically relevant advantages and should be used. Image guided RT verification may be indicated for sites that are adjacent to critical dose-limiting normal structures, especially in situations that entail retreatment.

Intensity modulated RT

Intensity modulated RT plans may provide improved PTV coverage (Dmean, V95, conformity index) compared with 3D-conformal RT. In selected patients with mediastinal involvement, IMRT reduces pulmonary toxicity predictors (lower values for Dmean and V20) and allows for superior protection of the heart and coronary arteries. This dosimetric gain is normally more evident in situations in which a large PTV involves the anterior mediastinum (19, 20). Although the advantages of IMRT include the tightly conformal doses and steep gradient next to normal tissues, target definition and delineation 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 that the target is optimally covered during the administration of therapy. 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 relapsing patients without exceeding the tolerance of critical normal structures such as the spinal cord (21).

Techniques to deal with tumor motion in the thoracic region

The use of 4D imaging or deep-inspiration breath-hold technique for disease sites that are significantly affected by respiratory motion is encouraged. In patients with involvement of the mediastinum, irradiation of the mediastinum is frequently indicated. Several studies havedemonstrated that treatment in inspiration enables significant sparing of lung and heart, and this technique is recommended in selected cases (22).

Dose Constraints

Previous experience comes from patients treated over the last 5 decades, for whom extended fields and higher doses resulted in significant risks of morbidity and mortality (23, 24). Hence, it is important to use the ISRT treatment technique

described below and to choose the treatment planthat is estimated to provide the lowest risk of long-termcomplications for the individual patient. Consideration should be given to factors such as gender, age, andcomorbidities. 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, normal tissue complication probability models for all relevant risk organs with a special focus on the low-dose region of 20-40 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 (25). At 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 (26). The risk of late RT-induced side effects should always be balanced via multidisciplinary discussion associated with the risks to the patient of local recurrence if RT is not given. In many situations with aggressive nodal lymphoma, particularly in older age groups for example, the risk and morbidity of disease recurrence outweigh the unlikely risk of late effects such as secondary malignancies.

Aggressive Nodal Lymphomas

Involved-site RT

The concept of ISRT is that the prechemotherapy GTV determines the CTV as discussed in more detail in the ILROG guidelines on Hodgkin lymphoma (27). This concept assumes that chemotherapy eradicates adjacent or regional microscopic disease, and ISRT targets the identifiable prechemotherapy disease. The irradiated volume is significantly smaller with ISRT than with involved-field RT because all adjacent lymph nodes that appear grossly uninvolved are not purposely treated. However, ISRT accommodates cases in which optimal prechemotherapy imaging, specifically highquality imaging performed in the treatment-planning position, is not available to the radiation oncologist. In these situations it is not possible to reduce the CTV to the same extent as with optimal imaging. In ISRT, clinical judgment in conjunction with the best available imaging is used to contour a CTV that will accommodate the uncertainties in defining the prechemotherapy GTV in each individual case. For these reasons ISRT is a slightly larger irradiated volume than involved-node RT.In the situation in which prechemotherapy imaging (eg, CT, PET, or MRI) of all the initially involved lymphomasites 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. Allowances should be made for the uncertainty of the contouring and differences in positioning by including a larger volume in the CTV. The more uncertainty there is, the larger the contoured volume will need 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 clinical information as possible concerning the pre- and postchemotherapy location of the pathological lymph node(s). The CTV should be contoured taking into account all of this information, making generous allowances 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. The ITV should be added to the CTV only in situations in which internal organ movement is of concern. The CTV will be expanded further to create the PTV. In situations in which RT is the primary treatment, larger margins to encompass subclinical disease need to be applied. Examples of ISRT CTVs are shown for aggressive nodal lymphomas in the neck (Fig. 1), mediastinum (Fig. 2), and axilla (Fig. 3).

Larger-field RT

The role of larger-field RT is now limited essentially to salvage treatment in patients who fail chemotherapy and are unable to embark upon more-intensive salvage treatment schedules. Such salvage cases are usually addressed on a case-by-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 increased normal tissue toxicity and compromise the safety of subsequent therapy such as stem cell transplant.

Advanced-stage aggressive NHL

In patients with advanced-stage aggressive nodal NHL with sites of original bulky disease or extranodal disease, RT may be considered at the outset of combined-modality treatment planning (2, 5). In this clinical situation the prechemotherapy GTV should be considered in determining the CTV. In contrast, in cases of isolated or solitary residual PETpositive disease, RT is often recommended after systemic chemotherapy. In the latter situation, the CTV is defined as residual mass(es) containing PET-positive areas on the postchemotherapy scan. A dose of 30-40 Gy to sites of residual disease is recommended.

Refractory and recurrent aggressive NHL

Despite the success of primary therapy for aggressive NHL, a significant percentage of patients will manifest primary refractory disease or relapse after achieving a complete response. For this group of patients, salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT) is a common treatment approach. Radiation therapy to sites of recurrent or refractory disease may enhance local disease control (28-31). An example is shown in Figure 4. Patients with primary refractory disease unsuitable for transplantation may benefit from RT to doses up to 55 Gy (32-34). Patients with primary refractory disease unsuitable for transplantation may benefit from RT for symptom palliation or disease control to prevent symptoms; doses will depend on normal tissue tolerance. Patients who are candidates for salvage therapy may benefit from irradiation either before or immediately after ASCT to sites of dominant local recurrence or residual disease. In patients with complete response to salvage chemotherapy, a dose of 30-40 Gy before or after ASCT is recommended. If given after ASCT, there are no data to suggest the optimal timing of when the RT should be delivered, but established practice is to deliver RT as soon possible after the patient has recovered from the acute side effects of ASCT, ideally within 6-8 weeks after stem cell infusion (11, 12).
For peritransplant irradiation in patients with relapsed or refractory disease, the radiation volumes are constructed using the guidelines provided above but determined on an individual patient basis depending on the sites of disease at initial diagnosis and at relapse. Consideration is given to previous RT and to the radiosensitivity of normal tissues and organs that would be inadvertently irradiated. Radiation therapy volumes are localized to encompass the known site(s) of disease recurrence, without prophylactic inclusion of adjacent lymph nodal stations.

Indolent Nodal Lymphomas

Localized indolent lymphoma

For the potentially curative treatment of localized earlystage (I and II) disease, RT is used as the primary treatment approach. The CTV must be designed to encompass suspected subclinical disease based on the preintervention GTV imaging. The CTV should incorporate GTV and include as a minimum adjacent lymph nodes in that site and a generous margin dictated by the clinical situation. An example is shown in Figure 5. For potentially curative RT to stage IA/IIA disease a dose of 24-30 Gy in 12-15 fractions (6, 35) is recommended.

Advanced-stage indolent lymphoma

A number of retrospective cohort studies have demonstrated that patients with advanced or recurrent indolent lymphoma treated with very low doses of only 4 Gy in 2 fractions achieve high response rates, and the treatment provides effective palliation for localized symptomatic disease (36-41). Initial results from a prospective, randomized trial in the United Kingdom comparing 4 Gy with 24 Gy for follicular lymphoma (41) suggest that there is only a modest decrease in local control with the lower dose. In some cases patients may benefit from RT to sites of bulky disease, such as within the retroperitoneum where monitoring clinical progression is challenging and progressive disease may lead to organ failure. These patients require higher doses of 24-30 Gy to provide durable longterm local disease control.

Conclusion

Modern RT for nodal NHL 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 concept of ISRT represents a significant reduction in the volume included in the previously used involved-field RT.
Radiation oncologists treating NHL should be involved as part of the multidisciplinary team in the initial management plan and attempt to introduce imaging procedures up front before initiation of chemotherapy. Such an integrated collaborative multidisciplinary approach will enable the optimal outcome for patients with nodal NHL.

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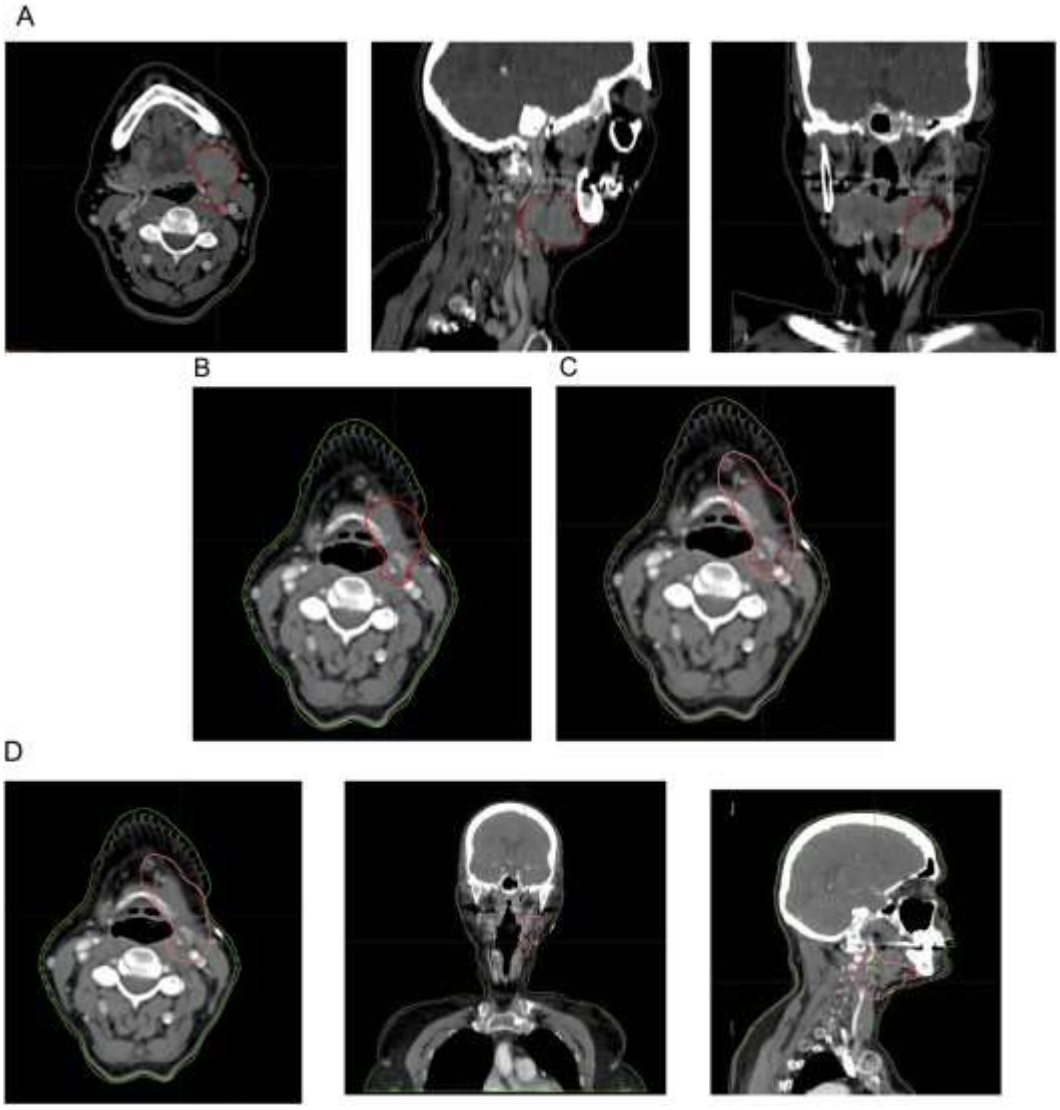

Fig. 1. (A-D) Patient with diffuse large B-cell lymphoma Clinical Stage (CS) 1A in the left neck. (A) Prechemotherapy CT scan with the contoured initially involved lymphoma volume (GTVCT) in red. (B) Postchemotherapy planning CT scan with the prechemotherapy GTVCT transferred by image fusion. (C) Postchemotherapy planning CT scan. The clinical target volume in pink is the tissue volume that contained lymphoma initially. It is created by modifying the GTVCT to take into account tumor shrinkage and other anatomic changes, allowing for uncertainties in contouring and differences in position. (D) The postchemotherapy planning CT scan with the final clinical target volume, which encompasses all of the initial lymphoma volume while still respecting normal structures that were never involved by lymphoma.

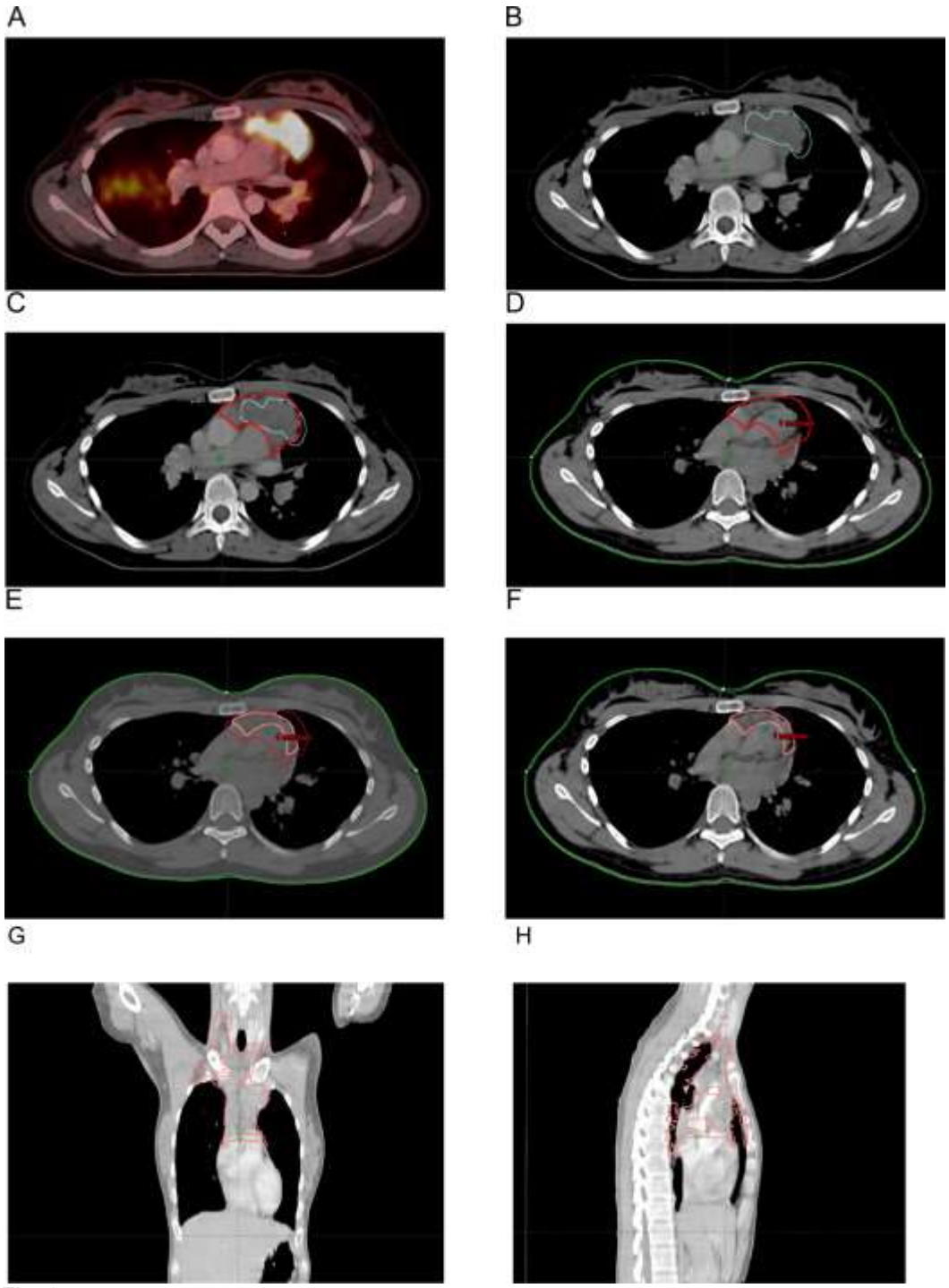

Fig. 2. (A-H) Patient with diffuse large B-cell lymphoma CS 2A with mediastinal involvement. (A) Prechemotherapy positron emission tomography (PET)/CT scan showing the initially PET-positive volume. (B) Prechemotherapy CT part of the PET/CT-scan with the contoured initially PET-positive involved lymphoma volume in blue. (C) Prechemotherapy CT scan with the contoured initially involved lymphoma volume (GTVCT) in red, including both PET-positive and PET-negative parts of the lymphoma. (D) Postchemotherapy planning CT scan with the prechemotherapy GTVCT transferred by image fusion. (E) Postchemotherapy planning CT scan. The clinical target volume in pink is the tissue volume that contained lymphoma initially. It is created by modifying the GTVCT to take into account tumor shrinkage and other anatomic changes, allowing for uncertainties in contouring and differences in position. (F) Postchemotherapy planning CT scan with the final clinical target volume, which encompasses all of the initial lymphoma volume while still respecting normal structures that were never involved by lymphoma. (G) Coronal image. (H) Sagittal image.

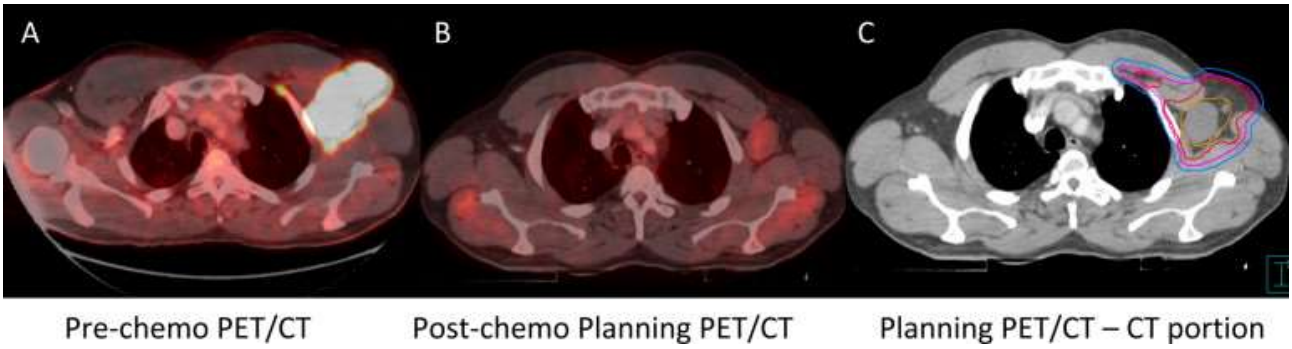

Fig. 3. (A-C) A 48-year-old man with stage 2AX diffuse large B-cell lymphoma of the left axilla presented with a rapidly growing underarm mass. (A) Baseline positron emission tomography (PET)/CT imaging shows extent of disease. (B) After 6 cycles of Rituximab-Cyclophosphamide, Adriamycin, Vincristine, Prednisolone (R-CHOP) fluorodeoxyglucose uptake resolved, leaving residual CT abnormality only. (C) Treatment volumes are outlined on the treatment planning scan according to International Commission on Radiation Units and Measurements guidelines; orange contour denotes postchemotherapy gross tumor volume, red denotes prechemotherapy gross tumor volume, pink denotes clinical target volume, and light blue denotes planning target volume.

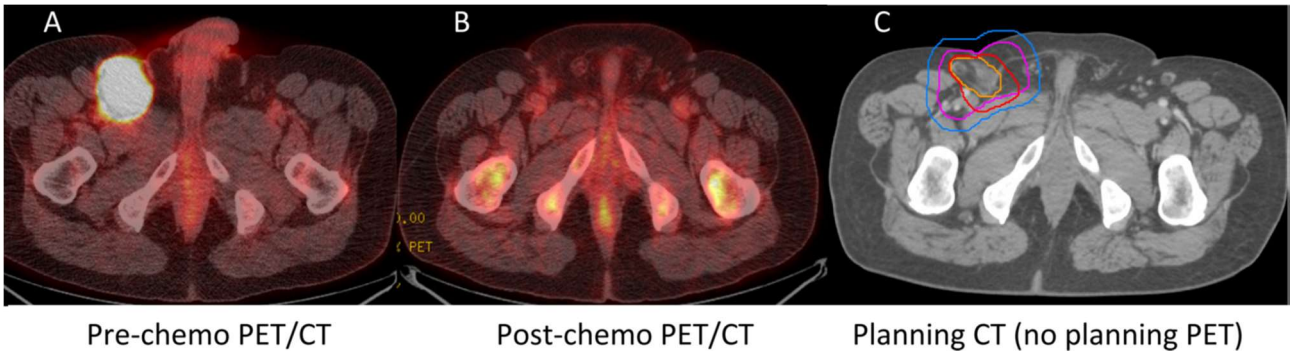

Fig. 4. (A-C) A 63-year-old man with relapsed diffuse large B-cell lymphoma involving the right groin. After salvage chemotherapy, he was referred for involved-site radiation therapy to the groin before stem cell transplant. (A) Baseline imaging at relapse. (B) Postchemotherapy imaging and (C) simulation imaging are performed with slight differences in patient positioning, in turn accounted for and reflected in a generously drawn clinical target volume (pink contour in C). In (C), the orange contour denotes postchemotherapy gross tumor volume, red denotes prechemotherapy gross tumor volume, and light blue denotes planning target volume. PET Z positron emission tomography.

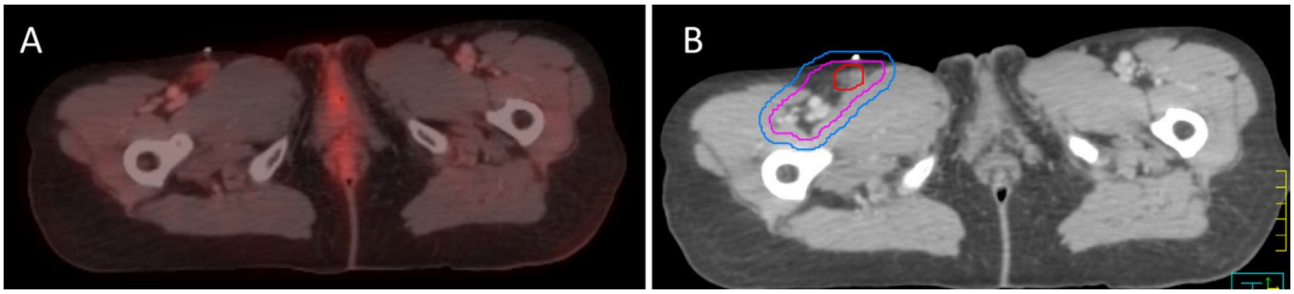

Fig. 5. (A, B) A 63-year-old woman with stage 1A follicular lymphoma of the right inguinal region presented with a selfpalpated right groin mass. Diagnosis was established upon excision by a general surgeon. At simulation the patient was placed in frog-leg position, and the scar was wired. Only CT abnormality remained (A). (B) Red contour denotes the prechemotherapy gross tumor volume, pink denotes clinical target volume, and light blue denotes planning target volume.