Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: Concepts and guidelines

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Abstract

Background and purpose: To describe new concepts for radiation fields in patients with early stage Hodgkin lymphoma treated with a combined modality.

Patients and materials: Patients receiving combined modality therapy with at least 2 or 3 cycles of chemotherapy prior to radiotherapy. Pre- and postchemotherapy cervical and thoracic CT scans are mandatory and should be performed, whenever possible, in the treatment position with the use of image fusion capabilities. A pre-chemotherapy PET scan is strongly recommended to increase the detection of involved lymph nodes.

Results: Radiation fields are designed to irradiate the initially involved lymph nodes exclusively and to encompass their initial volume. In some cases, radiation fields are slightly modified to avoid unnecessary irradiation of muscles or organs at risk.

Conclusions: The concept of involved-node radiotherapy (INRT) described here is the first attempt to reduce the size of radiation fields compared to the classic involved fields used in adult patients. Proper implementation of INRT requires adequate training and an efficient prospective or early retrospective quality assurance program.

Keywords: Hodgkin lymphoma; Involved-node radiotherapy; Involved-field radiation treatment; Combined modality treatment

Radiation treatment remains a key component in combined modality therapy for patients with early stage Hodgkin lymphoma. Its use has been questioned due to late complications, which are dependent on the irradiated volume and radiation dose [1,2,7,10,11,14].

The efficacy of radiation doses below the conventional 36-40 Gy has gradually been demonstrated [3,4,12]. A decline in late complications is expected with lower radiation doses as their incidence is correlated with the amount of radiation [5,9]. It is noteworthy that the use of smaller doses has already been implemented by most centers and groups. Smaller radiation fields should also lead to a decrease in late complications as the amount of irradiated normal tissue is reduced. Recent data seem to suggest that these assumptions might be correct [5,9]. With effective chemotherapy, involved-field radiotherapy (IFRT) was shown to be sufficient [6]. However, the definition of IFRT was not always clear, and most often, lymph node regions were irradiated according to the Ann Arbor staging diagram, which was not designed to delimit radiation fields. A recent review of relapses in patients treated with chemotherapy alone showed that most recurrences occurred in the initially involved lymph nodes [13]. With modern sophisticated techniques, including better CT scan imaging, FDG-PET/CT scans and more accurate radiation technology, it is now possible to customize radiotherapy for each patient with accurate delivery of radiation to the initially involved volume while minimizing the radiation dose to normal tissues.

The concept of IFRT, which included the whole initially involved lymph node region can now be replaced by the
concept of involved-node radiotherapy (INRT), which only includes the initially involved lymph node(s). This new concept of INRT will be applied in the new EORTC-GELA randomized trial for patients with early stage Hodgkin lymphoma. In order to achieve this, radiation guidelines must be very clear, radiation oncologists must be adequately trained and early retrospective or even prospective quality assurance programs must be in place and fully functional. The purpose of this paper is to describe the radiation guidelines and to illustrate the possible advantages of INRT over IFRT.

Definitions and guidelines
To successfully implement the INRT concept, a few rules must be followed. Patients must be examined by the radiation oncologist before chemotherapy. All patients must have pre- and postchemotherapy cervical and thoracic CT scans (axillary lymph node areas must be clearly visible on thoracic CT scans). Whenever feasible, CT scans should be performed in the treatment position as well as the prechemotherapy PET-CT, which can help pinpoint previously undetected involved lymph nodes. Whenever possible, CT scans should be evaluated with a radiologist. Moreover, CT simulation, modern radiation techniques (such as 3D-conformal radiotherapy, IMRT or respiratory-gated radiotherapy) and immobilization devices are strongly recommended for proper implementation of INRT.

The remission status after chemotherapy should be determined for each initially involved lymph node exclusively using CT scans. Complete remission (CR) is defined as the complete disappearance of clinically and/or radiologically detectable disease. A CRu is defined as at least a 75% decrease in tumor size. A partial response (PR) is at least a 50% decrease in tumor size. Failure is less than a 50% decrease or any increase in tumor size.

Design of radiation fields
To achieve the best quality treatment it is strongly recommended that pre- and postchemotherapy CT scans be performed with patients in the treatment position. The same rules apply to FDG-PET/CT scans. Fusion possibilities, allowing the overlapping of the pre- and postchemotherapy CT scans are also strongly recommended. However, they must be used with caution owing to many assumptions underlying such techniques.
Initially involved lymph nodes in CR or CRu

**Cervical and axillary lymph nodes**

As initially involved lymph nodes are either no longer visible or of normal size or are in CRu, a CTV (clinical target volume) is contoured. The CTV is the initial volume of the lymph node(s) before chemotherapy. In other words, the CTV incorporates the initial location and the extent of the disease. However, normal structures that have been displaced by the enlarged lymph node(s) are not included in the irradiated volume (for example, a neck muscle) (Figs. 1 and 2). Whenever possible, blood vessels are not included in the CTV if involved lymph nodes are clearly located at a distance from them. In case of a CRu with a visible lymph node remnant, the lymph node remnant should be included in the CTV.

The PTV is the CTV with a margin taking into account organ movement and set-up variations. In most situations, a 1 cm isotropic margin is considered adequate.

**Mediastinal area**

As the mediastinal area is considered to be in complete remission or CRu, a CTV is contoured. The CTV is the initial volume of the mediastinal mass (in the case of a CRu, the lymph node remnant is considered part of the CTV). In the case of a CR, the normal mediastinum is contoured and the CTV should not exceed the lateral mediastinal boundaries. In the case of a CRu, the normal mediastinum is contoured and the CTV should not exceed the lateral mediastinal boundaries except where lymph node remnants are still present. Whenever possible, blood vessels should be avoided and in order to decrease lung toxicity, the length of the CTV is the length of the mediastinal mass or lymph node(s) before chemotherapy and the width of the CTV is the width of the mediastinal mass or lymph node(s) after chemotherapy (Figs. 3 and 4).

The PTV is the CTV with a margin taking into account organ movement and set-up variations. In most situations, a 1 cm isotropic margin is considered adequate.

Initially involved lymph nodes in PR (partial remission)

**Cervical and axillary lymph nodes**

As initially involved lymph nodes are in partial remission, the GTV is the lymph node remnant(s) alone and it should be contoured first. The CTV is the initial volume of the lymph node(s) before chemotherapy, as described earlier. Therefore, 2 PTVs should be outlined. The initial PTV (or PTV1) is the CTV including the GTV (i.e. initial tumor mass and lymph node remnant(s)) with a margin to take into account organ movement and set-up variations. In most situations, a 1 cm isotropic margin is considered adequate. The boost PTV (or PTV2) is the GTV alone with a margin to take into account organ movement and set-up variations. In most situations, a 1 cm isotropic margin is considered adequate.

**Mediastinal area**

As the initially involved lymph node(s) or the tumor mass is (are) in partial remission, a GTV, which is the lymph node remnant(s) or the remaining mass alone, should be contoured first. The CTV is the initial volume of the mediastinal mass (Figs. 5 and 6), as mentioned above. Whenever possible, blood vessels and the heart should be avoided and lung toxicity decreased. Two PTVs should be outlined: the initial PTV (or PTV1) is the CTV including the GTV (i.e. the initial tumor mass and the lymph node remnant(s)) with a margin to take into account organ movement and set-up variations. In most situations, a 1 cm isotropic margin is considered adequate. The boost PTV (or PTV2) is the GTV alone with a margin to take into account organ movement and set-up variations. In most situations, a 1 cm isotropic margin is considered adequate.

**Treatment and dose prescription**

The dose must be specified according to ICRU 50/62 recommendations [8] and the PTV must receive a dose.
Fig. 3. Clinical target contouring (CTV) of a mediastinal tumor mass in an unconfirmed complete remission (CRu). (A) Contouring of the initial tumor volume (pink color). (B) Initial tumor volume superimposed on an axial postchemotherapy CT scan (pink color). (C) Adequate CTV contouring taking into account the initial tumor volume on an axial postchemotherapy CT scan (blue color).

Fig. 4. Clinical target contouring (CTV) of a mediastinal tumor mass in an unconfirmed complete remission (CRu). (A) Coronal prechemotherapy CT scan of the initial tumor mass. (B) Contouring of the initial tumor volume (pink color). (C) Coronal postchemotherapy CT scan. (D) Initial tumor volume superimposed (pink color) on a coronal postchemotherapy CT scan and tumor mass remnant contouring (green color). (E) Adequate CTV contouring (blue color) taking into account the initial tumor volume on a coronal postchemotherapy CT scan.
comprised between 95 and 107%. If the initially involved lymph nodes are more than 5 cm apart, then separate fields should be devised. Otherwise, the involved lymph nodes should be included in the same radiation field.

It is strongly recommended that modern radiation techniques such as 3D-conformal radiotherapy, intensity modulated radiotherapy or respiratory-gated radiotherapy should be used, notably for mediastinal tumor masses. However, the final choice will be left to the discretion of the physician. If a conventional treatment is used with anterior and posterior fields, the size of the field should be at least $5 \times 5$ cm.

Radiation treatments should be delivered using five fractions of 1.8-2 Gy per week. Portal imaging of all fields should be performed consecutively, within the first 2 days of treatment and once a week thereafter. Whenever feasible, daily portal controls are recommended.

Monthly quality assurance meetings should be convened in large cancer centers or in any local treating facilities with all the radiation oncologists participating in the randomized trials.

**Discussion**

As chemotherapy has become more efficient, extended fields have been progressively replaced by involved fields. This was demonstrated to be sufficient in patients with early-stage unfavorable Hodgkin’s lymphoma by the German Hodgkin Study Group [5] and by the EORTC-GELA cooperative H8 trial [6]. A few years ago, the EORTC-GELA radiotherapy group decided to further the concept of radiation field reduction because late complications (notably cardiovascular and second cancers) were correlated with the size of radiation fields. This led to the concept of involved node radiotherapy (INRT) in which only initially involved lymph nodes are irradiated. This concept has been recently vindicated by Shahidi et al. [13] who showed that

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Fig. 5. Clinical target contouring (CTV) and gross volume contouring (GTV) of a mediastinal mass in partial remission. (A) Prechemotherapy axial CT scan. (B) Contouring of the initial tumor volume (yellow color). (C) Postchemotherapy axial CT scan. (D) Initial tumor volume superimposed on a postchemotherapy CT scan (yellow color). (E) Adequate CTV contouring (green color) taking into account the initial tumor volume. (F) Adequate GTV contouring (yellow color) for the radiation boost.
Fig. 6. Clinical target contouring (CTV) and gross volume contouring (GTV) of a mediastinal mass in partial remission. (A) Prechemotherapy coronal CT scan. (B) Contouring of the initial tumor volume (yellow color). (C) Postchemotherapy coronal CT scan. (D) Initial tumor volume (green color) superimposed on the postchemotherapy CT scan. (E) Adequate CTV contouring taking into account the initial tumor volume (blue color). (F) Adequate GTV contouring (yellow contouring) for the radiation boost.

Fig. 7. Comparison between dose distributions using either IFRT (A) or INRT (B) for involved cervical lymph nodes.
recurrences usually occurred in initially involved nodes in patients treated with chemotherapy alone.

The design of INRT also implies that the initial tumor volume should be irradiated. This design can be considered as an initial requirement but not necessarily as a final one. The decision to deliver radiation to the initial tumor volume was based on two major facts. First, it was considered an intermediate step between conventional involved-field irradiation and far more limited irradiation of the tumor remnants alone. Secondly, it was realized that by delivering radiation exclusively to tumor remnants, no radiation would be delivered to lymph nodes in complete remission. This attitude seemed to be premature and our decision to even deliver radiation to lymph nodes in CR was recently vindicated by the results of the H9 F trial [12].

It is noteworthy that gradually reducing the size of the radiation field will provide radiation oncologists with a transition period allowing learning and training.

The use of INRT implies greater accuracy in identifying and contouring involved lymph nodes. Therefore, all modern imaging technologies should be used to achieve this goal, notably the prechemotherapy PET scan. As fusion possibilities are recommended to delineate the initial tumor volume on the postchemotherapy CT scan, all radiological imaging should be best performed with the patient in the treatment position.

Better sparing of normal tissues (salivary glands, heart, coronary arteries, and breast in female patients) is expected with the use of INRT compared with conventional IFRT (Figs. 7 and 8) provided the initial tumor mass is not too large and involved lymph nodes are not too numerous.

Conclusions

INRT is expected to be as good as IFRT in terms of local control. Significantly fewer late complications are expected because of limited irradiation of normal tissue. Training and quality assurance programs will be crucial for the proper implementation of INRT guidelines. More details will soon be available on the EORTC website.

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