The involved field is back: issues in delineating the radiation field in Hodgkin’s disease

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During the last century, the role of radiation therapy in the treatment of Hodgkin’s disease (HD) has changed drastically. From a palliative treatment reserved for bulky lymph nodes of an incurable disease at the beginning of the century, to an exciting primary treatment used alone to cure most stages in the 1960s and 1970s, to the present more limited role as consolidation treatment after chemotherapy. Interestingly, the radiation field size has always influenced the evolution of treatment principles of HD. Over several decades, large or extended field radiotherapy has become synonymous with the successful treatment of HD. But the critical transformation from a single-modality to a combined-modality therapy, together with improvement in imaging and radiation planning techniques, mandates a reassessment of the delineation of appropriate radiation fields in HD. In this manuscript we review the comeback of the involved field, address design questions and offer field borders for common disease sites.

Key words: Hodgkin’s disease, involved field, radiation

Introduction

In 1902, reports on dramatic shrinkage of bulky Hodgkin’s disease (HD) tumors following exposure of the involved lymph nodes to the newly discovered X-rays, raised high hopes of curing the disease [1, 2]. Unfortunately, the limitations of the crude X-ray tubes available in those early years and the use of techniques that either administered a single large dose to a small field, or delivered weekly low doses to the whole trunk resulted in early local relapse and eventual systemic disease progression. Disappointingly, HD remained a universally fatal disease and radiation was reserved only for palliation. More than 50 years passed before a change in radiotherapy concepts coincided with improvement in ionizing radiation technology and allowed the cure of early stage HD with radiation alone.

In 1925, Rene Gilbert, a Swiss radiotherapist was the first to advocate the use of fractionated higher doses of radiation to larger fields encompassing not only the palpable nodes but also the surrounding clinically un-involved areas [3, 4]. Employing Gilbert’s concepts of larger field and higher fractionated dose, Vera Peters (1950) in Toronto was able to demonstrate an unprecedented 10-year survival rate of 79% following irradiation of patients with limited HD [5, 6]. Still, the concept of extended-field and high-dose for cure of HD was slow to be accepted. Indeed, it was the pioneering work of Henry Kaplan from Stanford in the early 1960s that had the most impact on the treatment of HD for decades [7–10]. Kaplan developed the linear accelerator, which could produce a large, penetrating and accurate beam that was most suitable for implementing the principles of the large field radiotherapy. Using new tools for imaging and staging, Kaplan and his team advanced the understanding of the spread of HD and defined the classical fields for its treatment. He advocated the treatment of multiple lymph nodes chains in continuity with as few fields as possible to avoid the gaps or overlaps within the field junctions. The large field called ‘mantle field’ was used to treat the lymph nodes in the upper part of the body, and the ‘inverted Y’ field for lymph nodes in the abdomen, pelvis and groins. The combination of both fields was termed total lymphoid irradiation (TLI), and if the pelvis was excluded, subtotal lymphoid irradiation (STLI). TLI and STLI have become the gold-standard fields in the treatment of stages I–III HD.

The advantage of the large field over the involved field, when radiation alone was used, was documented in prospective randomized studies at Stanford and other institutions [9]. The early randomized studies from Stanford documented not only the advantage of the extended-field over the involved field, but also demonstrated that the extended field can be successfully substituted with a smaller (‘involved’) field radiotherapy (IF-RT) if chemotherapy was added to the program [10]. The main reason that chemotherapy was not routinely used with IF-RT at that time was the acute and late toxicity (sterility, leukemia) associated with the prime chemotherapy combination of the time: mechlorethamine–oncovin–
procarbazine–prednisone (MOPP). Chemotherapy was reserved for salvage of radiotherapy failures. As less toxic combinations of chemotherapy, such as doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD), have proven to be even more effective than MOPP, combining chemotherapy and radiotherapy has become the standard approach in the treatment of favorable and unfavorable early stage HD patients. The potential advantage of combining the two modalities is not only the increased efficacy over radiotherapy alone or chemotherapy alone, but also the option to reduce the radiation dose and limit the radiation field and in parallel with reducing the number of chemotherapy cycles and thus decreasing dose-dependent complications (such as bleomycin pulmonary toxicity). This concept of reducing toxicity and enhancing efficacy was extended to the treatment of advanced-stage HD, where chemotherapy has always been the mainstay of treatment. A program such as Stanford V is based on a short (12 week) course of weekly chemotherapy supplemented with irradiation of lymph node sites that were originally 5 cm or larger [11]. Although the contribution of consolidation radiotherapy following full-length chemotherapy (e.g. MOPP/ABVD) of advanced-stage HD remains controversial, patients with bulky disease and/or incomplete or uncertain response are likely to benefit from IF-RT following completion of a full course of chemotherapy [12].

Although the treatment results obtained with chemotherapy and IF-RT were equivalent to or surpassed the results achieved with TLI/STLI in favorable early stage HD [13, 14], a comparison of chemotherapy plus STLI with the same chemotherapy plus IF-RT was still required. Several randomized studies were designed to answer this question. The French Cooperative study showed no difference in 6-year disease-free survival between MOPPX6 and IF-RT and MOPPX6 and extended field [15]. The more modern Istituto Nazionale Tumori Milan trial has provided the most clear data regarding the adequacy of radiation volume reduction. From 1990 to 1996, 140 consecutive patients with clinically staged early HD (I bulky and/or B; IIA, IIA bulky, and IIEA) entered a randomized trial. The trial compared four cycles of ABVD followed by STLI with the same regimen followed by IF-RT. The dose of RT ranged from 30 to 36 Gy to uninvolved and involved sites, respectively. The main characteristics were fairly well balanced between the two arms. After a median follow-up of 87 months, treatment outcome was as follows: complete remission (CR) 100% after ABVD + STLI versus 97% after ABVD + IF-RT; freedom from progression 97 versus 94%; and total survival 93 versus 94%, respectively. The long-term results of this trial indicate that four cycles of ABVD followed by IFRT can achieve results comparable to the same regimen followed by extensive radiotherapy [16]. The European Organisation for Research and Treatment of Cancer (EORTC) H₂U trial compared, in unfavorable patients, four cycles of MOPP/ABVD plus IF-RT (36–40 Gy) with the same chemotherapy followed by STLI (36–40 Gy). No difference in the 4-year treatment-failure-free survival (92% in each arm) between IF-RT and STLI was detected [17]. The German Hodgkin Study Group HD8 study randomized unfavorable early stage patients to receive two cycles of cyclophosphamide–oncovin–procarbazine–prednisone/ABVD followed by either extended or involved field. At a median follow up of 56 months, freedom from treatment failure was 86% (in each arm) and no difference in relapse rate or survival was observed. Acute side effects were more frequent in patients who received the extended field radiotherapy [18].

While the randomized studies clearly indicate that reduction of the field size has not compromised the efficacy of treatment, it may take another decade to demonstrate whether the decrease in irradiated volume will translate into a significant reduction in long-term side effects of therapy, the most concerning of which is second malignancies. It is critical that long-term data from the above-mentioned randomized studies will be collected and analyzed. Thus far, retrospective studies that analyzed the effect of field size on risk of second tumors have suggested that the risk was lower in patients treated with IF-RT compared with those treated with extended field radiotherapy [19–21].

Considerations in designing IF-RT following chemotherapy

The field terminology used for radiotherapy of HD and non-Hodgkin’s lymphoma (NHL) is quite confusing, and even the simple term IF-RT has a variety of interpretations in different studies. The many terms used by lymphoma oncologists to describe the radiation field (‘involved field’, ‘regional field’, ‘extended field’, ‘total or subtotal lymphoid irradiation’, ‘total nodal irradiation’, ‘mantle and mini-mantle’) have never had a clear and uniform definition. A survey was conducted among lymphoma radiotherapy experts (by Hoppe and Yahalom) for the Fifth International Symposium on Hodgkin’s Lymphoma in Cologne, Germany (September 2001). It was designed to examine the dose and field borders prescribed by the experts in different clinical scenarios. The study demonstrated a wide heterogeneity in outlining the field borders and dose prescription and thus emphasizes the need for an international consensus and clear directions for designing and interpreting studies that employ the involved field as well as more clear guidelines for practicing radiation oncologists.

While it is understood that the involved field should address an area smaller than the classical extended fields of mantle or inverted Y, it is not entirely clear how small should the field remain. Should only the area of the enlarged lymph node (with margins) be irradiated? Should a region of lymph nodes be addressed? And if yes, what are the borders of this region? Many use the lymph node region diagram that was adopted for staging purposes at the Rye symposium (1966) to define a region of lymph nodes [22]. However, this diagram was not developed for individual radiation field design, and strangely...
enough the chart distinguishes between a mediastinal and a hilar region, has a separate infraclavicular lymph region and does not provide the borders of individual sites. Other questions relate to the change in size (or complete resolution) of the lymph node after chemotherapy. Should the pre-chemotherapy volume be irradiated? Or should we spare the tissues (such as lung) that are no longer involved by the disease by irradiating the post-chemotherapy residual abnormality alone?

There are no definitive answers to the above questions and it is often the individual clinical situation that affects the field design. At the same time, uniform general guidelines are important for assuring high standard of treatment and are essential for collaborative group studies.

**Suggested guidelines for delineating the involved field in HD**

We (with the assistance of Giulia Cicchetti) have developed the following as guidelines for the Cancer and Leukemia Group B (CALGB) studies in HD.

In designing the involved field borders we employed the following considerations:

1. We treat a region, not an individual lymph node.
2. The main involved field regions are neck (unilateral), mediastinum (including the hilar regions bilaterally), axilla (including the supraclavicular and infraclavicular lymph nodes), spleen, para-aortic lymph nodes and inguinal (including the femoral and iliac nodes).
3. We use the initially involved pre-chemotherapy sites and volume, with the exception of the transverse diameter of the mediastinal and para-aortic lymph nodes, for which we use the reduced post-chemotherapy status. In these latter areas the regression of the lymph nodes is easily depicted by computed tomography (CT) imaging and the normal tissue saved by reducing the irradiated volume is critical.
4. The supraclavicular lymph nodes are considered as part of the cervical region and if involved alone or with other cervical nodes, the whole neck is unilaterally treated. Only if the supraclavicular involvement is an extension of mediastinal disease and the other neck areas are not involved (based on CT imaging with contrast and gallium/PET imaging when appropriate) is the upper neck (above the larynx) spared. This is to save on irradiating the salivary glands when the risk for the area is low.
5. All borders should be easy to outline (most are bony landmarks) and plan on with a two-dimensional standard simulation unit. CT data are required for outlining the mediastinal and para-aortic region and will also help in designing the axillary field.
6. Pre- and post-chemotherapy information regarding lymph node localization and size is critical and should be available at the time of planning the field.

**I. Unilateral cervical/supraclavicular region**

Involvement at any cervical level with or without involvement of the supraclavicular (SCL) nodes. Arm position: akimbo or at sides.

**Upper border**

1–2 cm above the lower tip of the mastoid process and midpoint through the chin.

**Lower border**

2 cm below the bottom of the clavicle.

**Lateral border**

To include the medial 2/3 of the clavicle.

**Medial border**

7. If the supraclavicular nodes are not involved, place the border at the ipsilateral transverse processes, except when medial nodes close to the vertebral bodies are seen on the initial staging neck CT scan. For medial nodes include the entire vertebral body.

8. When the supraclavicular nodes are involved, the border should be placed at the contralateral transverse processes. For stage I patients, the larynx and vertebral bodies above the larynx can be blocked (assuming no medial cervical nodes).

**Blocks**

A posterior cervical cord block is required only if the cord dose exceeds 40 Gy. Mid-neck calculations should be performed to determine the maximum cord dose, especially when the central axis is in the mediastinum.

A laryngeal block should be used unless lymph nodes were present in that location, in which case the block should be added at 1980 cGy.

**II. Bilateral cervical/supraclavicular region**

Treat both cervical and supraclavicular regions as described above regardless of the extent of disease on each side. Posterior cervical cord and larynx blocks should be used as described above. Use a posterior mouth block if treating the patient supine (preferably with an extended travel couch at >100 cm source skin distance) to block the upper field divergence through the mouth. The chin should be marked anteriorly with a radio-opaque material to aid in drawing the block.

**III. Mediastinum**

Involvement of the mediastinum and/or the hilar nodes. The field includes also the medial SCL nodes even if not clinically involved. Arm position: akimbo or at sides. The arms up position is optional if the axillary nodes are involved.
Upper border
C5–C6 interspace.
If supraclavicular nodes were also involved the upper border should be placed at the top of the larynx and the lateral border should be adjusted as described in the section on treating neck nodes.

Lower border
The lower of (i) 5 cm below the carina or (ii) 2 cm below the pre-chemotherapy inferior border.

Lateral border
The post-chemotherapy volume with 1.5 cm margin.

Hilar area
To be included with 1 cm margin unless initially involved where as the margin should be 1.5 cm.

IV. Mediastinum with involvement of the cervical nodes
When both cervical regions are involved, the field is a mantle without the axilla using the guidelines described above. If only one cervical chain is involved the vertebral bodies, contralateral upper neck and larynx can be blocked as described previously. Because of the increased dose to the neck (the isocenter is in the upper mediastinum), the neck above the lower border of the larynx should be shielded at 30.6 Gy.
If paracardiac nodes are involved, the whole heart should be treated with 14.4 Gy and the initially involved nodes should be treated with 30.6 Gy.

V. Axillary region
The ipsilateral axillary, infraclavicular and supraclavicular areas are treated when the axilla is involved. Whenever possible use CT-based planning for this region. Arm position: akimbo or arms up.

Upper border
C5–C6 interspace.

Lower border
The lower of (i) the tip of the scapula or (ii) 2 cm below the lowest axillary node.

Medial border
Ipsilateral cervical transverse process. Include the vertebral bodies only if the SCL are involved.

Lateral border
Flash axilla

VI. Spleen
The spleen is treated only if abnormal imaging was suggestive of involvement. The post-chemotherapy volume is treated with 1.5 cm margins. The left kidney should be outlined on the plan/film. CT-based planning should be used.

VII. Abdomen (para-aortic nodes)
Upper border
Top of T11 and at least 2 cm above pre-chemotherapy volume.

Lower border
Bottom of L4 and at least 2 cm below pre-chemotherapy volume.

Lateral borders
The edge of the transverse processes and at least 2 cm from the post-chemotherapy volume.

Note
The kidneys should be outlined and considered when designing the blocks.
The porta-hepatis region should be included if originally involved (this should be identified with CT-based planning).

VIII. Inguinal/femoral/external iliac region
These ipsilateral lymph node groups are treated together if any of the nodes are involved.

Upper border
Middle of the sacro-iliac joint.

Lower border
5 cm below the lesser trochanter.

Lateral border
The greater trochanter and 2 cm lateral to initially involved nodes.

Medial border
Medial border of the obturator foramen with at least 2 cm medial to involved nodes.
Note

If common iliac nodes are involved the field should extend to the L4–L5 inter-space and at least 2 cm above the initially involved nodal border.

Conclusion

In summary, the involved field has become the standard field for irradiating patients with early and advanced-stage disease following chemotherapy. Uniform and high quality irradiation should provide the patient with maximum local control while minimizing the radiation of low-risk areas and reducing acute and long-term morbidity.

References