Minimising critical organ irradiation in limited stage Hodgkin lymphoma: a dosimetric study of the benefit of involved node radiotherapy

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Received 1 June 2011; revised 16 August 2011; accepted 24 August 2011

Background: Chemotherapy plus radiotherapy is the standard of care for patients with limited stage Hodgkin lymphoma (HL). Radiotherapy is evolving from involved field radiotherapy (IFRT) to involved node radiotherapy (INRT) to decrease radiotherapy-related morbidity. In the absence of long-term toxicity data, dose–volume metrics of organs at risk (OAR) provide a surrogate measure of toxicity risk.

Patients and methods: Ten female patients with stage I–IIA supradiaphragmatic HL were randomly selected. All patients had pre-chemotherapy computerised tomography (CT) and CT–positron emission tomography staging. Using CT planning, three radiotherapy plans were produced per patient: (i) IFRT, (ii) INRT using parallel-opposed beams and (iii) INRT using volumetric modulated arc therapy (VMAT). Radiotherapy dose was 30.6 Gy in 1.8 Gy fractions. OAR evaluated were lungs, breasts, thyroid, heart and coronary arteries.

Results: Compared with IFRT, INRT significantly reduced mean doses to lungs ($P < 0.01$), breasts ($P < 0.01$), thyroid ($P < 0.01$) and heart ($P < 0.01$), on Wilcoxon testing. Compared with conventional INRT, VMAT improved dose conformity but increased low-dose radiation exposure to lungs and breasts. VMAT reduced the heart volume receiving 30 Gy (V30) by 85%.

Conclusions: Reduction from IFRT to INRT decreased the volumes of lungs, breasts and thyroid receiving high-dose radiation, suggesting the potential to reduce long-term second malignancy risks. VMAT may be useful for patients with pre-existing heart disease by minimising further cardiac toxicity risks.

Key words: dosimetry, Hodgkin lymphoma, INRT, involved node radiotherapy, organs at risk, toxicity
introduction

The standard of care for patients with limited stage Hodgkin lymphoma (HL) is combined chemotherapy and radiotherapy [1], typically achieving 10-year survival rates of 90% [2]. Historically, radiotherapy has been associated with significant risks of toxicities and second malignancies in long-term survivors: an international retrospective study by the National Cancer Institute of 32 591 HL patients with 1111 25-year survivors demonstrated a 25-year actuarial risk of solid malignancy of 21.9% [3]. To improve the therapeutic ratio, radiotherapy fields in limited-stage HL have evolved from extended field radiotherapy (EFRT) to involved field radiotherapy (IFRT) and more recently to involved node radiotherapy (INRT) [2, 4], aiming to decrease radiotherapy-induced toxicity while maintaining high cure rates.

Retrospective evidence supports this trend, demonstrating that INRT retains the efficacy of conventional IFRT [2]. However, the proposed reduced late toxicity with INRT is yet unproven.

Unfortunately, clinical limitations make it problematic to determine the rates of radiation-induced long-term morbidities. First, very long follow-up is required to quantify the effect of reduced radiotherapy volumes on late toxicity rates. Second, large patient numbers are required to accurately determine the risks of less common radiation-induced toxic effects. Therefore, dose–volume metrics of organs at risk (OAR) are used as surrogate indicators for radiation-induced late toxicity rates. This is based on clinical observations that normal tissue complication rates are a function of both dose and volume. Thus, it is expected that improvements in the dose–volume metrics of OAR will translate into lower rates of corresponding radiotherapy-induced late toxicities and second malignancies. In this study, we aim to quantify the advantages of INRT over IFRT for clinically relevant OAR: lung, breast, thyroid, heart and coronary arteries.

Technological advances in the planning and delivery of radiotherapy offer improved dose conformity and relative sparing of adjacent OAR from high-dose radiation exposure. Three-dimensional radiotherapy techniques are now routinely used in the management of solid malignancies, and inverse planning has since developed as a means to meet the dose-limiting constraints of critical OAR. However, these techniques have been more slowly adopted in HL treatment due to concerns about the long-term effects of increased low-dose radiation to OAR in younger patients [5, 6]. Volumetric modulated arc therapy (VMAT) is a newer technology that utilises radiotherapy arcs and inverse planning to deliver highly conformal three-dimensional radiotherapy, which reportedly reduces the volumes of OAR exposed to high-dose radiation [7].

This study firstly compares the dosimetric effects on OAR of INRT versus IFRT in limited-stage HL, using conventional radiotherapy techniques. We then compare the dosimetric outcomes of INRT using conventional beam arrangements with VMAT.

patients and methods

patients

Ten female patients with limited-stage supradiaphragmatic HL were randomly selected from records at Peter MacCallum Cancer Centre (PMCC). Eligibility required histological diagnosis of HL, Ann Arbor stage I–II, largest mass <10 cm in diameter and absence of B symptoms. All patients received chemotherapy with ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) or ABVD-like regimens, plus radiotherapy. Additionally, all eligible patients had pre-chemotherapy computerised tomography (CT) and positron emission tomography (PET), plus confirmed complete response on post-chemotherapy CT–PET before radiotherapy. All patients had CT simulation carried out at PMCC, with 3–5 mm slice thickness. Ethics approval was obtained from PMCC Ethics Committee.

definitions of radiotherapy fields

Three radiotherapy plans were created per patient:

1. ‘IFRT’ was defined as parallel-opposed anterior and posterior photon beams to conventional IFRT fields encompassing the pre-chemotherapy involved nodal group [8, 9] (Figure 1a);
2. ‘Conventional INRT’ was defined as parallel-opposed anterior and posterior photon beams with target volumes reduced to cover the pre-chemotherapy involved nodes only (Figures 1b and 2a);
3. ‘VMAT’ was used to treat the same target volumes as conventional INRT (Figure 2b).

radiotherapy fields for IFRT

One qualified radiation oncologist marked all IFRT fields, using the definitions of the German Hodgkin Study Group HD10 protocol [9]. If the disease distribution was not clearly addressed in this protocol, then the guidelines of Yahalom and Mauch [10] were used.

volume definitions for INRT

To avoid interobserver variation, one qualified radiation oncologist was responsible for contouring OAR and clinical target volumes (CTVs) for all 10 patients. The CTV was defined as the volume of the pre-chemotherapy involved nodes as seen on CT and CT–PET, within post-chemotherapy anatomical boundaries. An additional margin was added to the CTV to form the planning target volume (PTV); this margin accounted for physiological movement and set-up error, thus incorporating the internal target volume (ITV) and set-up margin (SM), respectively. As respiratory movement varies between anatomical sites, the following margins were applied to the CTV:

(a) Mediastinal and hilar lymph nodes [11]—for the ITV, a 1 cm margin was applied craniocaudally and 0.5 cm margin radially. An additional 1 cm was added for SM;
(b) Other lymph node sites—in nodal sites not subject to respiratory motion, no additional margin was required for ITV. A 1 cm was added for SM.

anterior and posterior parallel-opposed fields for IFRT and conventional INRT

One radiotherapist planned all IFRT and conventional INRT plans. For INRT planning, anterior and posterior fields were devised using the Varian Eclipse V8.9 beams-eye-view feature, placing the 0.5 cm multileaf collimator leaves 1 cm from the PTV. For IFRT and conventional INRT plans, the maximum point dose was specified as 110%; where this was not obtainable with standard parallel-opposed photon beams, beam modifiers or field-in-field techniques were permitted to keep the maximum point dose within tolerance.

VMAT for conformal INRT

One radiotherapist designed all VMAT plans. Using Varian Rapidarc™ planning system, a single arc was used to deliver each fraction, with
Figure 1. Conventional radiotherapy fields*. (a) Conventional involved field radiotherapy (IFRT). (b) Conventional involved node radiotherapy (INRT). * Conventional radiotherapy technique with parallel opposed, anterior and posterior beams: the planning target volume is marked in blue, and the field edge is marked in orange.

Figure 2. INRT dosimetry: volume receiving ≥20 Gy (V20)*. (a) Conventional, parallel-opposed, anterior and posterior beams. (b) Volumetric modulated arc therapy (VMAT) using a single 360 degree arc. *Compared to the parallel-opposed beam arrangement, VMAT improves the conformality to the mediastinal planning target volume (outlined in red) and reduces the V20 of lungs (outlined in yellow) and breasts (outlined in pink).
modulation of dose rate, gantry speed and multileaf collimators. Evaluation of VMAT plans is sensitive to the adequacy of PTV coverage and dose constraints placed on OAR; in this study, VMAT plans were optimised using the dose constraints and priority weightings published by Girinsky et al. [8] (Table 1).

**prescribed dose and dose constraints**
The prescription dose was 30.6 Gy in 1.8-Gy fractions. Acceptable dose homogeneity across the PTV was defined as within +7% and −5% of the prescribed dose. All plans used 6-MV photon beams and the analytical

**contouring OAR**
For contouring, the lungs and thyroid were easily delineated on the non-contrast planning CT. Contouring of breasts, heart and coronary artery origins was guided by a cross-sectional anatomical CT atlas and an experienced radiologist. The breasts were delineated on CT datasets using a standard window (40) and width (600) level. Breast volumes were limited posteriorly, anteriorly, superiorly, inferiorly, medially and laterally by the pectoralis muscle, skin, midclavicular head, xiphoid process, sternum, and the anterior portion of latissimus dorsi, respectively [7]. The heart contour included all cardiac chambers; the most superior extent was defined as one CT slice (3–5 mm) below the completed branching of the pulmonary trunk. Individual coronary arteries are difficult to delineate on non-contrast CT, therefore, contouring was prospectively defined as the outer circumference of the proximal aorta, extending 2.0–2.5 cm superiorly from the tip of the heart auricles [7].

**radiotherapy plan evaluation**
Dose–volume histograms (DVHs) and mean organ doses were calculated for OAR using the Varian Eclipse treatment planning system. For the purposes of the DVH, the OAR were defined as the contoured volumes minus the PTV. The term ‘Vx’ reflects the volume (%) of tissue receiving x Gray or greater. The term ‘Dx’ reflects the dose (Gy) received by x percent of the tissue. Dose–volume metrics calculated for OAR were as follows:

- Bilateral lungs—mean dose, V1, V5, V20, D50;
- Bilateral breasts—mean dose, V1, V4, V20, D50;
- Thyroid—mean dose, V1, V4, V20, D50;
- Heart—mean dose, V30, D50;
- Coronary artery origins—mean dose, D50.

For each radiotherapy technique, the mean values for the above dose–volume metrics were calculated. The relative reductions in each of these mean dose–volume metrics were calculated to quantify the difference in radiation exposure received by the OAR by the two different field sizes (from IFRT to conventional INRT; Figure 1) and the two different radiotherapy techniques (from conventional INRT to INRT by VMAT; Figure 2).

| Table 1. Dosimetric constraints used for volumetric modulated arc therapy |
|--------------------------|-------------------------------------------------------------------------------|
|                         | D1 (Gy) | D33 (Gy) | D50 (Gy) | Priority |
| Planning target volume  |          |          |          |          |
| Breast                  | 20       | 10       | 5        | 2        |
| Lung                    | 20       | 10       | 5        | 3        |
| Heart                   | 30       | 15       | 7.7      | 4        |
| Thyroid                 | 30       | 25       | 18       | 5        |

To quantify the volumes receiving high-dose radiation, the volume receiving 95% of the prescribed dose (V95%) was determined per plan. The ratio of the V95% for IFRT and INRT was then determined per patient, and the mean of these ratios was calculated, thus indicating the average volume reduction of tissue receiving high-dose radiation.

The conformity of the two INRT planning techniques was compared using the conformity index for the PTV. The conformity index was defined as the overlap of the fraction of the PTV enclosed by the 95% isodose curve (PTV95%), with the fraction of the body volume covered by the same isodose (V95%). The following equation was used to calculate the conformity index [12]:

\[
\text{Conformity index} = \left( \frac{\text{PTV95%}}{\text{PTV}} \right) \times \left( \frac{\text{PTV95%}}{\text{V95%}} \right)
\]

**results**

**patient characteristics**
Ten female patients with supradiaphragmatic, limited-stage HL were randomly selected. Patient characteristics were as follows: median age 32 (range 23–48) years; stage IA, three and stage IIA, seven; four or less cycles of chemotherapy, eight and more than four cycles of chemotherapy, two. The number of involved nodal groups was one in three patients, two in five patients and more than two in two patients. Of the 10 patients, mediastinal node involvement was present in 9, supraclavicular node involvement in 8, neck node involvement above the supraclavicular fossae in 5, hilar node involvement in 1 and pericardial node involvement in 1. One patient had extranodal (thymic) involvement.

**radiotherapy plan evaluation: IFRT versus INRT**
Reducing the radiotherapy field size from IFRT to INRT reduced the proportion of tissue receiving higher radiation doses. For the IFRT plans, the mean V95% was 2625.9 cm³ (range 1010–4286). For the conventional INRT plans, the mean V95% was 1474.6 cm³ (range 800–2946). The ratio of these two volumes was calculated per patient, and the mean of these ratios was 1.9. Thus, reducing the field size from IFRT to INRT decreased the volume of tissue receiving ≥95% of prescribed dose by a factor 1.9.

**radiation exposure of OAR: IFRT versus INRT**
Reducing the field size from IFRT to conventional INRT was associated with relative reductions in the mean doses received by lungs, breasts, thyroid, heart and coronary arteries by 0.29, 0.33, 0.55, 0.35 and 0.08, respectively. The greatest benefit was seen in the D50 of the OAR, with relative reductions of 0.51 for lungs, 0.44 for breasts, 0.59 for thyroid and 0.55 for heart. The results of comparisons of the dose–volume metrics are presented in Table 2 and Figure 3.
Coronary arteries
Heart
Thyroid
Breast
Lung

breast and thyroid compared with conventional INRT, involved field radiotherapy; INRT, involved node radiotherapy; VMAT, volumetric modulated arc therapy.

very small (Figure 3c), although the thyroid dose constraints over conventional parallel-opposed beam arrangement were in favour of VMAT, the absolute and relative benefits of VMAT the mean V20 for thyroid was significant on Wilcoxon testing breast V20 by 0.95 and heart V30 by 0.85 (Figure 3). Although resulting in relative reductions in the mean lung V20 by 0.56, coronary artery dose– reductions in cardiac mean dose, D50 and V30 of 0.37, 0.55 and 0.85, respectively (Figure 3d). However, coronary artery dose–volume metrics were not improved by the use of VMAT (Figure 3e). Comparisons of the INRT dose–volume metrics are presented in Table 2.

INRT plan evaluation: conventional parallel-opposed beams versus VMAT

For each patient, the conformality of the two INRT plans was determined by calculating the conformality index of the radiotherapy dose to the PTV. The mean conformality indices were 0.26 (95% CI 0.23–0.29) for conventional INRT and 0.72 (95% CI 0.67–0.76) for VMAT. Therefore, compared with conventional INRT, VMAT improved the conformality to the PTV.

radiation exposure to OAR: conventional INRT versus VMAT

The optimised dosimetry produced by VMAT reduces the volumes of OAR receiving high-dose radiation (Table 2), resulting in relative reductions in the mean lung V20 by 0.56, thyroid V20 by 0.95 and heart V30 by 0.85 (Figure 3). Although the mean V20 for thyroid was significant on Wilcoxon testing in favour of VMAT, the absolute and relative benefits of VMAT over conventional parallel-opposed beam arrangement were very small (Figure 3c), although the thyroid dose constraints were given low priority during the VMAT planning and were not as restrictive as other OAR (Table 1). In contrast, VMAT was associated with increased low-dose exposure to lungs, breast and thyroid compared with conventional INRT planning, contributing to increased mean D50 in these OAR (Figure 3). Notably, the use of VMAT resulted in relative reductions in cardiac mean dose, D50 and V30 of 0.37, 0.55 and 0.85, respectively (Figure 3d). However, coronary artery dose–volume metrics were not improved by the use of VMAT (Figure 3e). Comparisons of the INRT dose–volume metrics are presented in Table 2.

discussion

In 2006, Girinsky et al. [4] coined the term ‘involved node radiotherapy’ (INRT), defined as radiotherapy fields that cover only the initially involved lymph nodes and exclude the adjacent uninvolved nodal groups. This approach is based on the observation that after treatment with chemotherapy alone, recurrences of HL typically occur in sites of initial nodal involvement [14]. Importantly, INRT is currently a concept in evolution, and published guidelines highlight the lack of consensus regarding INRT margins [8, 11, 15]. This is largely due to (i) variable accessibility of modern technologies between institutions, leading to variation in the sensitivity, precision and reproducibility of radiotherapy planning and delivery processes; (ii) variable physiological movement between anatomical sites. Despite the lack of

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<th>Table 2. Dose parameters (mean) ± standard deviations for organs at risk, with corresponding P values on Wilcoxon non-parametric testing</th>
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*Wilcoxon non-parametric tests.

IFRT, involved field radiotherapy; INRT, involved node radiotherapy; VMAT, volumetric modulated arc therapy.
consensus on INRT margins, the concept of INRT has been adopted by the European Organisation for Research and Treatment of Cancer, the Groupe d’Etude des Lymphomes de l’Adulte and the German Hodgkin Study Group for use in randomised trials of favourable-risk limited-stage HL [4].

The rationale for INRT is to reduce radiotherapy-induced morbidity in patients with limited-stage HL treated with chemoradiotherapy while maintaining the excellent disease control achieved by conventional IFRT [2]. Second malignancy and cardiac toxicity are the most concerning of these radiation-induced late morbidities, constituting the most common causes of non-lymphoma death in long-term HL survivors [16]. The dosimetric advantages of reducing the radiotherapy field size to INRT are twofold: first, to reduce the volumes of the OAR exposed to radiation, and second, to reduce the total doses of radiation received by the OAR.

Figure 3. Comparing the dosimetric effects on the organs at risk from a reduction in the radiotherapy field size from conventional IFRT to conventional INRT and from a change in INRT technique from conventional radiotherapy to VMAT: (a) lungs; (b) breasts; (c) thyroid; (d) heart and (e) coronary artery origins. IFRT, involved field radiotherapy; INRT, involved node radiotherapy; VMAT, volumetric modulated arc therapy.
Although limited, the available published data support an association between radiotherapy volume and the risk of radiation-induced morbidity in long-term survivors of HL. Clinical studies have demonstrated that reducing the radiotherapy field size from EFRT to IFRT decreases the incidence of secondary malignancies [17–20]. A meta-analysis of 10 randomised studies found that breast cancer risk was significantly higher in survivors of HL treated with EFRT compared with IFRT (odds ratio 3.25, *P* = 0.04) [19]. Also, in a retrospective series of 1122 female HL survivors, De Bruin et al. [20] reported that the risk of breast cancer was 2.7-fold higher in patients treated with mantle radiotherapy compared with mediastinum only. Additionally, mathematical dosimetric risk-modelling has been used to estimate the second malignancy risks from EFRT and IFRT [21, 22]. Researchers predict that reducing supradiaphragmatic radiotherapy fields from EFRT to IFRT reduces the excess relative risk of breast and lung cancers in females by 65% and lung cancers in males by 40% [21]. Therefore, it is reasonable to extrapolate that further reductions in radiotherapy field size to INRT will result in further reductions in second malignancy risk.

Large retrospective studies have also shown a relationship between the incidence of late radiotherapy-induced morbidities and radiotherapy dose in long-term survivors of HL [23–25]. However, these studies mostly utilised outdated radiotherapy techniques and chemotherapy regimens and therefore cannot be readly translated to the modern treatment era. Radiobiological and mathematical models have also been applied to second malignancy risks in HL patients treated with radiotherapy: overall, these models predict for higher breast and lung cancer risks with increasing radiation doses received by these tissues [21, 22]. Interestingly, one model also predicts that it is the component of high dose to the lung that contributes the most to the lung malignancy risk, whereas for breast cancer the model predicted a bimodal distribution with the largest predicted contribution occurring at 1–3 Gy and a smaller peak occurring at higher doses [21]. Although this model has not been confirmed in *vivo*, the results highlight a concern that low-dose exposure may raise the risk of second malignancy in the breast, which has implications for multi-field conformal radiotherapy techniques like VMAT.

Our findings support the hypothesis that reducing the radiotherapy field size from IFRT to INRT reduces the radiation exposure to OAR. Filippi et al. [26] reported on the dosimetric effect of reducing the field size from IFRT to INRT, using parallel-opposed photon beams, in five patients with limited-stage HL. As we found, INRT was associated with a reduction in the mean dose and D50 for lungs, breast and thyroid; however, the dosimetric advantages in mean dose and D50 were very small for coronary artery origins. Additionally, our study revealed that INRT reduces both low-dose and high-dose exposure to lung, breasts and thyroid, supporting our hypothesis that INRT is likely to lower the risks of late toxic effects and second malignancies in these OAR. However, as there was no dosimetric benefit to coronary artery origins, we postulate that INRT is unlikely to improve the risk of ischaemic heart disease.

Other groups have also investigated the technical aspects of INRT using different state-of-the-art techniques [7, 8, 27]. Intensity-modulated radiotherapy (IMRT) is arguably the most well-known technology for creating highly conformal radiotherapy plans, however, at the cost of a more diffuse distribution of low-dose radiation. This is illustrated in a dosimetric study of INRT comparing IMRT with conventional parallel-opposed radiotherapy and three-dimensional conformal radiotherapy in 12 patients with mediastinal HL: IMRT produced the best PTV coverage, at the cost of higher breast V5 and whole-body D50 [8]. The authors concluded that it was ‘difficult to demonstrate that IMRT treatment plans might be superior to conventional treatment’ [8]. To date, no published studies have evaluated low-dose parameters (for example, V1), which may have greater associations with breast cancer [21, 28] and thyroid cancer [28] risks than high-dose radiation.

VMAT is a recent technology that has some notable advantages over other conformal techniques. Compared with IMRT, VMAT reduces treatment delivery time and uses less monitor units/fraction, thus reducing the integral dose to OAR [7]. Comparing the dosimetry of INRT, Weber et al. [7] found that VMAT lowered the mean V10 of lungs, breasts and thyroid compared with IMRT. However, to our knowledge, VMAT dosimetry has not previously been compared with conventional parallel-opposed photon beam arrangements. In this cohort, the increased conformity of VMAT resulted in smaller volumes of lungs, breasts and heart receiving high-dose radiation, however, at the cost of increased low-dose exposure (Figure 3). We acknowledge that these analyses are sensitive to the dose constraints placed on the OAR. For patients with specific toxicity concerns, VMAT offers the advantage of further reducing high-dose exposure to OAR by tightening the dose constraints and prioritisation of the OAR. In this study, VMAT resulted in an impressive 85% relative reduction in the mean V30 for heart, which is likely to be advantageous for patients with pre-existing cardiac dysfunction where the risk of further cardiac morbidity needs to be minimised. Thus, the opportunity to individualise radiotherapy plans makes VMAT an attractive technique that may allow for further reductions in the incidence of radiation-induced toxicities in high-risk groups.

In conclusion, decreasing the field size from IFRT to INRT reduces the radiation exposure to lungs, breasts and thyroid in this cohort of patients with supradiaphragmatic limited-stage HL. We hypothesise that these dosimetric improvements are likely to translate into lower rates of radiotherapy-induced toxicity in these OAR, including the risk of second malignancy. However, we extrapolate that INRT is unlikely to decrease the risk of coronary artery disease in long-term survivors.

Volumetric modulated arc therapy for INRT may have a useful role in individualising INRT for patients at high risk of radiotherapy-induced morbidity from pre-existing co-morbidities or predispositions; however, this is at the cost of increased low-dose exposure to some OAR.
acknowledgements

These results were presented in an oral presentation at the 8th International Symposium of Hodgkin Lymphoma, 23–26 October 2010, in Cologne, Germany.

disclosure

The authors declare no conflict of interest.

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