Estimated risk of cardiovascular disease and secondary cancers with modern highly conformal radiotherapy for early-stage mediastinal Hodgkin lymphoma

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Background: Hodgkin lymphoma (HL) survivors have an increased morbidity and mortality from secondary cancers and cardiovascular disease (CD). We evaluate doses with involved node radiotherapy (INRT) delivered as 3D conformal radiotherapy (3D CRT), volumetric modulated arc therapy (VMAT), or proton therapy (PT), compared with the extensive Mantle Field (MF).

Patients and methods: For 27 patients with early-stage, mediastinal HL, treated with chemotherapy and INRT delivered as 3D CRT (30 Gy), we simulated an MF (36 Gy), INRT-VMAT and INRT-PT (30 Gy). Dose to the heart, lungs, and breasts, estimated risks of CD, lung (LC) and breast cancer (BC), and corresponding life years lost (LYL) were compared.

Results: 3D CRT, VMAT or PT significantly lower the dose to the heart, lungs and breasts and provide lower risk estimates compared with MF, but with substantial patient variability. The risk of CD is not significantly different for 3D CRT versus VMAT. The risk of LC and BC is highest with VMAT. For LYL, PT is the superior modern technique.

Conclusions: In early-stage, mediastinal HL modern radiotherapy provides superior results compared with MF. However, there is no single best radiotherapy technique for HL—the decision should be made at the individual patient level.

Key words: Hodgkin lymphoma, cardiovascular disease, highly conformal radiotherapy, involved node radiotherapy, secondary cancers

introduction

The overall prognosis is excellent for early-stage Hodgkin lymphoma (HL) patients. Combined modality treatment with chemotherapy followed by 20–30 Gy of radiotherapy (RT) is now considered the standard of care [1]. As most early-stage HL patients achieve durable complete remission and become long-term survivors, it is important to reduce the risk of treatment-induced late effects. HL survivors are known to have an increased morbidity and mortality, primarily due to cardiovascular disease (CD) and secondary cancers [2–6]. However, the available long-term morbidity data stem from a time when extended field RT [typically a mantle field (MF)] was used and radiation dose was higher.

RT for HL has changed dramatically over the last few decades in terms of both irradiated volumes and dose [7, 8]. Several critical points are currently under investigation: a reduction in total delivered dose [7, 8], a shrinkage of treatment volumes towards the involved node RT (INRT)-strategy [9, 10] and the use of highly conformal RT techniques such as intensity-modulated RT (IMRT) or volumetric modulated arc therapy (VMAT) [11–14], as well as proton therapy (PT) [15]. Smaller treatment volumes and improved dose distribution can reduce the amount of healthy tissue exposed to radiation with potential clinically significant consequences. The question is whether modern highly conformal RT will lead to a reduced rate of late effects. This is especially relevant for HL patients with mediastinal disease as their disease is in close proximity to critical thoracic structures, i.e. heart, lungs, and breasts.

In this study, we evaluate the estimated doses to the heart, lungs, and breasts using INRT with conventional 3D conformal RT (3D CRT), VMAT and intensity-modulated spot-scanned PT for patients with early-stage, mediastinal HL treated with combined modality. We compare these with the extensive MF of the past. For each patient, we also estimate the absolute excess lifetime risk of cardiac mortality (CMort),
cardiac morbidity (CMorB), myocardial infarction (MI), valvular disease (VD), lung cancer (LC), and breast cancer (BC) attributable to each RT technique, and we compare these risk estimates on a common scale by applying a method for life years lost (LYL) [16].

**materials and methods**

We included patients receiving RT as part of combined modality treatment for clinical stage I–II HL from 1 January 2006 till 30 August 2010. The inclusion criteria were supradiaphragmatic disease, classical histology, age ≥15 years, planning computed tomography (CT) scanning including both the neck and the mediastinum. The exclusion criteria were lymphocyte predominance-histology, chemotherapy given at other institutions, and unplanned modifications in radiotherapy. To identify patients who would benefit the most from highly conformal RT, we selected patients who received a mean dose to the heart or any heart substructure of ≥15 Gy with INRT, which is currently recommended as the maximum dose [17].

**initial treatment protocol**

All patients received the adriamycin, bleomycin, vinblastin, dacarbazine-chemotherapy regimen followed by INRT, delivered according to the guidelines [18]. All patients underwent a pre-chemotherapy 18-fluorodeoxyglucose positron emission tomography/CT scan as well as a post-chemotherapy CT scan, slice thickness of 3.0 or 2.5 mm and contrast enhanced. Images were acquired in the supine treatment position. The two CT scans were fused and adjusted to the post-chemotherapy anatomical outlines. Patients were prescribed 30.6 Gy to initially involved lymph nodes in 1.8 Gy fractions, 5 fractions/week. INRT was planned with 3D CRT.

**contouring**

We defined the organs at risk (OARs) as the heart, heart valves, coronary arteries, lungs, and breasts. The OARs were delineated on the original treatment CT scan. The heart, heart valves, and coronary arteries were contoured according to the published guidelines [19].

**VMAT simulations**

A planning target volume (PTV) was created for VMAT simulations. The PTV was generated from the clinical target volume; 1 cm margin in all directions, but below the C7 with 1.5 cm in the inferior direction to account for motion in the thorax. A virtual volume was constructed to help lower the dose to adjacent risk organs [20]. The field setup was constructed in Eclipse™ v. 8.9 (Varian Medical Systems) with 30.6 Gy to initial nodes in 1.8 Gy fractions, 5 fractions/week. The doses to OARs were kept as low as possible at all times (normal tissue objectives are listed in supplementary Table S1, available at *Annals of Oncology* online).

**proton simulations**

In the PT planning, the same PTV, virtual volume, prescription dose, and normal tissue objectives as above were used. We used a radiobiological correction factor of 1.1 and a co-planar isocentric field set-up with as few fields as possible. A 5.7 cm water equivalent range-shifter was used when needed. Plans were simulated in Eclipse™ v. 8.9 (PT2 Varian Proton Therapy machine).

**MF reconstruction**

The reconstruction of MF plans has been described elsewhere [21]. The prescribed dose was 36 Gy in 1.8 Gy fractions, 5 fractions/week.

**risk estimations**

For each patient, we estimated the lifetime excess risk of developing CMorB, CMorB, MI, VD, LC, and BC from the different techniques. Dose–response relationships were derived from clinical series with long-term follow-up of HL survivors [5, 6, 22, 23], and are described in detail elsewhere [16, 21]. We used logistic dose–response models for CMorB, CMorB, MI, and VD, and linear models for LC and BC. Our risk estimates were conditioned on the long-term survival after HL according to the published survival curve by Ng et al. [3], while treating death from other causes as competing risks. The survival function was assumed to follow the US general population after the last point in the curve. Based on our risk estimates, we derived the LYL attributable to RT using a previously published method [16].

**statistical analysis**

Repeated-measures analysis of variance (rANOVA) was carried out for determining global differences between the mean doses to OARs and risk estimates with 3D CRT, VMAT, PT, and MF treatment with a two-tailed significance level of 0.05, using the Greenhouse–Geisser correction. We carried out post hoc analyses to compare results among the three modern techniques. All statistical analyses were carried out in SAS v. 9.3.

**results**

Twenty-seven out of 46 patients received ≥15 Gy to the heart or any cardiac substructure. The patient characteristics are presented in supplementary Table S2, available at *Annals of Oncology* online. Figure 1 demonstrates the treatment plans across the four techniques for two different patients.

**dose to OARs**

All doses are calculated as mean dose and reported as median values for the 27 patients. The mean dose to the heart, lungs, and breasts with 3D CRT, VMAT, PT, and MF is shown in Figure 2A, C, and E. (A) illustrates how the mean dose to the heart differs substantially for the individual patients between the different modern techniques but not with the MF. The median mean dose to the heart for the whole group is 9.9, 10.1, 8.2, and 27.2 Gy with 3D CRT, VMAT, PT, and MF (P < 0.0001), respectively. However, in post hoc tests there is no statistically significant difference between the mean dose to the heart with 3D CRT versus VMAT (P = 0.335), whereas the difference is significant with 3D CRT versus PT and VMAT versus PT (both P < 0.0001). For the whole group, VMAT gives the higher and PT the lower heart mean dose compared with 3D CRT (B); however, for both comparisons the upper whisker is positive and the lower negative, illustrating the variation between patients. The mean dose to the lungs is highest with MF (20.0 Gy) and also, for most patients, higher with VMAT (11.4 Gy) compared with 3D CRT (8.6 Gy) and PT (7.3 Gy), P < 0.0001 (C). The difference is also significant in the pair-wise comparisons (all P < 0.0001). VMAT gives a higher mean lung dose to all patients as both the upper and lower whiskers are positive (D). With PT, some patients receive a higher mean lung dose compared with 3D CRT.

In the analyses of mean dose to the breasts, only the 13 female patients are included. The mean dose to the breasts is 3.0, 7.5, 1.1, and 20.1 Gy with 3D CRT, VMAT, PT, and MF.
In post hoc tests, the mean breast dose is statistically different between all treatment plans. In (F) the patient variability is seen again, as some patients benefit from 3D CRT compared with VMAT ($P = 0.002$), whereas all receive a lower mean breast dose with PT compared with 3D CRT ($P = 0.003$), some patients substantially as illustrated by the lower whisker.

**Risk estimations**

The risk estimates are reported as median values in Table 1. All estimates are calculated as absolute values, based on the individual treatment plans. With modern techniques all risk estimates are significantly lower compared with MF. However, some patients are still at a significant risk of late effects with modern techniques, as the range is considerable, and for some patients risk estimates are comparable with those seen for MF.

Comparing the risk estimates on a common scale, MF provides the highest LYL. VMAT is the inferior modern technique and PT the superior. When comparing the three modern techniques, 25 patients had a lowest total LYL with PT, and 2 patients (both women) with 3D CRT. If only comparing between 3D CRT and VMAT treatment, 25 patients had a lowest total LYL with 3D CRT, and 2 patients (both men) with VMAT.

**Discussion**

To our knowledge, this is the largest study to compare the potential clinical benefits of INRT with 3D CRT, VMAT, or PT compared with the extended MF of the past. We focus on 27 HL patients with lymphoma close to the heart, lungs, or breasts as they are especially at risk of late effects due to the anatomical location of their disease. These patients all received a mean dose of $\geq 15$ Gy to the heart or any heart substructure in their initial RT plan.

Evidence exists that lowering both the radiation dose and the irradiated volume will reduce the risk of secondary cancers as well as cardiac complications [4, 22]. At our institution, all early-stage HL patients are treated with INRT, and so a further reduction in treatment volume is not possible. We do not believe that omission of radiotherapy is warranted by the current literature [1]. Also, lowering the dose is not recommended in the unfavorable group [7]. Therefore, the only way to further reduce the risk of radiation-induced late effects is more conformal radiation techniques such as different IMRT-methods or PT.

We show how the INRT-strategy applied with different RT techniques could provide a substantially reduced dose to the heart, lungs, and breasts for patients with mediastinal lymphoma compared with older techniques. The use of VMAT instead of 3D CRT does not significantly lower the dose to the heart for the group as a whole, but the individual variation is substantial as seen in Figure 2. For the lung, the mean dose is significantly higher with VMAT compared with 3D CRT or PT for all patients due to the low-dose bath. Applying PT would significantly reduce the mean dose to the heart, lungs, and breasts.

The underlying assumptions of our comparison is that INRT is as effective in achieving local control as more extensive fields, which is supported by our retrospective analysis [9], and

![Figure 1](image_url)
that our plans are the best possible. Our mean dose to the heart, lungs, and breasts with 3D CRT are in concordance with Koeck et al. [13], but they are higher than the doses reported for 3D CRT and VMAT by Fiandra et al. [12] and Campbell et al. [11], and the doses for VMAT by Weber et al. [14]. This could be due to the difference in patient characteristics and numbers: both Fiandra, Campbell, and Weber report on 10 female HL patients, Koeck included 20 unfavorable patients. Our PT doses are in agreement with the study by Hoppe et al. [15] where the primary objective was to spare the heart.

We chose to model risk estimates of relevant late effects, by applying observations from cohort and case-control studies, to

Figure 2. The left panels illustrate the mean dose to the heart (A), lungs (C), and breasts (E) with 3D CRT, VMAT, PT and MF (black lines: individual patients, red line: group median). The right panels show boxplots (boxes: 25–75 quartiles, whiskers: 10–90 percentiles, red dots: outliers), illustrating the difference in mean dose to the heart (B), lungs (D), and breasts (F) between VMAT versus 3D CRT, proton versus 3D CRT, and MF versus 3D CRT, respectively. When the difference in mean dose is positive, there is a benefit using 3D CRT, whereas a negative difference signifies a benefit with the comparison technique.
relate the dose to important OARs to a more clinically relevant measure. Although modeling is limited by its simplifying assumptions and the quality of the clinical input data, it is the only way of estimating the risk of late effects from current highly conformal RT. Also, risk modeling enables individualized risk estimates, which is extremely important due to the large variability in patient anatomy and disease location, as illustrated by the patients in our cohort where some patients have an estimated high risk of late effects regardless of the RT technique. Not surprisingly, reducing the field size and dose with modern conformal treatment lowers the estimated risk of late effects by at least half compared with the extensive MF. The improved conformity by VMAT, however, does not translate into a lower estimated cardiac complication risk which can be explained by the inherent nature of this patient group with lymphoma in close proximity to the heart. In our series, the highest risk estimates for LC and BC was seen with VMAT, contradicting the linear model by Weber et al. [24].

With the LYL, we compare our different risk estimates on a common scale. In daily clinical practice, this is done intuitively by clinicians, which makes comparisons between different treatment plans and clinicians very qualitative and difficult to reproduce. The LYL provides an easy-to-understand-and-compare measure as it incorporates the age at exposure, life expectancy, and prognosis of the different late effects. The LYL, thereby, penalizes late effects seen in young persons whose primary disease has a favorable prognosis, the most. In our LYL estimates, PT is the superior choice for all but two patients. However, the uncertainties associated with PT in the thorax are significant. Also, proton facilities are not available to the majority of patients. When comparing 3D CRT only with VMAT, VMAT provides more LYL for 25 of 27 patients.

There are several limitations to our study. We chose to compare 3D CRT with VMAT and PT. The VMAT technique has previously been found superior to IMRT when applying the INRT strategy [14], although Fiandra et al. [12] conclude that no optimal IMRT technique exists when considering multiple OARs simultaneously. The proton plans were generated with as few fields as possible in order to minimize the low-dose volume, enabling a direct comparison between 3D CRT and PT. We have used the same PTV for VMAT and PT planning, assuming that the increased uncertainty with PT lowers the dose to the heart, lungs, and breasts and provides lower estimated risks of late effects compared with Mantle Field (MF) treatment. However, the low-dose volume, enabling a direct comparison between 3D CRT and PT. We have used the same PTV for VMAT and PT planning, assuming that the increased uncertainty with PT lowers the dose to the heart, lungs, and breasts and provides lower estimated risks of late effects compared with Mantle Field (MF) treatment. However, the low-dose volume, enabling a direct comparison between 3D CRT and PT. We have used the same PTV for VMAT and PT planning, assuming that the increased uncertainty with PT lowers the dose to the heart, lungs, and breasts and provides lower estimated risks of late effects compared with Mantle Field (MF) treatment. However, the low-dose volume, enabling a direct comparison between 3D CRT and PT. We have used the same PTV for VMAT and PT planning, assuming that the increased uncertainty with PT lowers the dose to the heart, lungs, and breasts and provides lower estimated risks of late effects compared with Mantle Field (MF) treatment. However, the low-dose volume, enabling a direct comparison between 3D CRT and PT. We have used the same PTV for VMAT and PT planning, assuming that the increased uncertainty with PT lowers the dose to the heart, lungs, and breasts and provides lower estimated risks of late effects compared with Mantle Field (MF) treatment. However, the low-dose volume, enabling a direct comparison between 3D CRT and PT. We have used the same PTV for VMAT and PT planning, assuming that the increased uncertainty with PT lowers the dose to the heart, lungs, and breasts and provides lower estimated risks of late effects compared with Mantle Field (MF) treatment. However, the low-dose volume, enabling a direct comparison between

<table>
<thead>
<tr>
<th>Risk estimates (%)</th>
<th>3D CRT</th>
<th>VMAT</th>
<th>PT</th>
<th>MF</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac mortality (CMort)</td>
<td>1.0 (0.2–2.7)</td>
<td>1.1 (0.3–2.1)</td>
<td>0.9 (0.1–1.9)</td>
<td>2.9 (2.2–3.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac morbidity (CMorb)</td>
<td>1.3 (0.5–7.1)</td>
<td>1.3 (0.6–4.0)</td>
<td>1.1 (0.5–3.3)</td>
<td>8.6 (4.6–14.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial infarction (MI)</td>
<td>5.5 (0.7–30.1)</td>
<td>5.9 (1.1–23.8)</td>
<td>4.7 (0.4–20.4)</td>
<td>19.8 (6.9–37.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Valvular disease (VD)</td>
<td>0 (0–0.2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.4 (0–3.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Radiation-induced lung cancer (LC)</td>
<td>4.4 (2.4–9.7)</td>
<td>6.0 (3.1–11.4)</td>
<td>3.3 (1.4–9.7)</td>
<td>10.5 (6.3–15.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Radiation-induced breast cancer (BC)</td>
<td>3.7 (0.2–11.8)</td>
<td>8.0 (0.6–13.4)</td>
<td>1.4 (0–8.1)</td>
<td>23.0 (7.5–34.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Life years lost (LYL)</td>
<td>Total LYL</td>
<td>0.9 (0.2–1.6)</td>
<td>1.1 (0.2–2.3)</td>
<td>0.7 (0.1–1.6)</td>
<td>2.1 (0.6–3.6)</td>
</tr>
</tbody>
</table>

*P values found using repeated-measures ANOVA with post hoc tests for pair-wise comparisons.

3D CRT, 3D conformal radiotherapy; VMAT, volumetric modulated arc therapy; PT, proton therapy.
HL patients, we advise that new treatment techniques should not be implemented based on dose planning studies with a small number of patients. There is no such thing as a single best radiotherapy technique when treating HL—the decision should be made at the individual patient level.

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disclosure

The authors have declared no conflicts of interest.

references