The need for individualized studies to compare radiogenic second cancer (RSC) risk in proton versus photon Hodgkin Lymphoma patient treatments

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Abstract

For Hodgkin Lymphoma (HL), proton therapy has been shown to potentially reduce therapeutic dose to healthy tissue and therefore the risk of developing a radiogenic second cancer (RSC) relative to photon therapy. Currently, commercial treatment planning systems (TPS) do not account for stray radiation doses for these treatments and their risks of late effects. Treatment plans were created and therapeutic doses were calculated with commercial TPSs for the breast, lung, and thyroid of nine HL patients. Stray dose contributions were added by thermoluminescent dosimeter (TLD) measurements in an anthropomorphic phantom for the intensity modulated radiation therapy (IMRT) treatments and personalized Monte Carlo simulations for the proton treatments. The mean relative risk (RR) of developing a RSC following HL treatment with proton therapies was then calculated and compared to photon IMRT, and reported with the metric ratio of relative risk (RRR). Results showed generally lower RSC risks after proton therapy than photon IMRT when averaged over all patients in the cohort for the breast (RRR = 0.84±0.03), lung (RRR = 0.77±0.03), and thyroid (RRR = 0.83±0.05), but were not universal across all patients examined. Our findings revealed that it is important to include stray dose contributions when comparing the RSC risks for different HL treatment techniques and demonstrated the importance of personalized dose and risk calculations for modern HL radiotherapy.

Keywords: Hodgkin Lymphoma; In-Silico Clinical Trial; Proton Therapy; Photon Therapy; Radiation Risks, Monte Carlo Simulations; Measurements

Original Article

1. Introduction

Hodgkin Lymphoma (HL) is the most common cancer diagnosis amongst adolescents (15% of all new cases)1 and young adults (12% of all new cases)2 in the United States. The 10-year survival rate is approximately 90% for cases diagnosed during childhood and adolescence.3 Consequential treatment-related side effects include radiogenic second cancers (RSC)3,5, which are the leading cause of death for HL survivors6,7. One strategy to reduce
the incidence and severity of late effects is to reduce the dose to healthy tissues by using advanced-technology treatment techniques, such as photon intensity modulated radiotherapies (IMRT) or proton treatments. Studies have shown proton treatments may reduce dose to healthy tissue in HL studies while maintaining equal dosimetric coverage of the tumor compared to photon treatments. These studies, however, did not include accurate assessments of stray radiation outside the therapeutic field. Its presence delivers unwanted dose to healthy tissue in the body and increases RSC risks. Additionally, previous studies have not conducted RSC risk calculations on a sample of HL patients. Inter-patient variation in anatomy and tumor location and volume are large in supra-diaphragmatic HL patients; the impact of these variations on RSC risk was not known.

The main objective of this study was to assess how predicted RSC risks depend on treatment techniques (photon versus proton radiotherapies) and on inter-patient variations in tumors and normal anatomy. To accomplish this we conducted a paired data, in-silico study for both proton and photon treatments on nine female HL patients, including full consideration of therapeutic and stray radiation exposures and risks.

2. Materials and Methods

Nine patients were selected using the consecutive sampling method. Inclusion criteria were female patients who received proton therapy at our institution between July 2007 and December 2011 with supra-diaphragmatic Classical Nodular Sclerosis Hodgkin Lymphoma. Data were retrospectively collected under a protocol approved by our Institutional Review Board. Patient data were anonymized using the technique described by Newhauser et al.

In this study, the total prescribed proton dose was 36.0 Gy relative biological effectiveness (RBE) (32.7 Gy × 1.1). An RBE of 1.1 was used following the recommendations on dose prescription and reporting in International Commission on Radiation units and Measurements Report 78. The prescribed photon dose was 36.0 Gy.

2.1 Therapeutic radiation

The therapeutic dose was calculated by a commercial treatment planning system (TPS) (Eclipse, Version 8.9.08 Varian Medical Systems, Palo Alto, CA). New treatment plans were developed to enhance consistency across patients and treatment modalities. Plans were reviewed and approved by a board certified radiation oncologist.

Both photon and proton HL treatments used involved-field radiation therapy (IFRT) target volumes.Photon treatment plans utilized 6-MV step-and-shoot IMRT treatment arrangements, with either five- or six-beam co-planar field arrangements. For proton plans we evaluated both passively-scattered proton therapy (PSPT) and intensity modulated proton therapy (IMPT) plans. For a given patient, the number of fields and their orientations for PSPT and IMPT plans were equal.

2.2 Stray radiation

For photon therapy, the TPS either did not accurately calculate or does not attempt to calculate stray absorbed dose below the 5% isodose line. Instead, stray doses were determined using supplemental approaches. Specifically, stray radiation doses from photon therapy were calculated following the methodology from Howell et al., which uses an analytical model to predict absorbed dose derived from TLD measurements of a HL IMRT treatment delivered to an anthropomorphic phantom.

Stray neutron radiation dose from proton therapy was assessed using patient specific simulations with the previously described MCNPX-based Monte Carlo Proton Treatment Planning System (MCPRTP). In this work, neutron dose was partitioned into two components, named external (those originating outside of the patient) and internal (those originating inside of the patient). The external neutron component is negligible in IMPT plans and therefore was not simulated. Internal neutrons, which originate inside the patient, were simulated in PSPT and IMPT plans. The mean neutron radiation weighting factor (neutron $w_R$) = 20 was chosen for this work as previous studies have reported values between 10 and 30.

2.3 Risk

We used risk models from the National Academy of Sciences Biological Effects of Ionizing Radiation (BEIR) VII – Phase 2 Report. These are organ-specific linear non-threshold (LNT) risk models. We calculated excess relative risk ($ERR$) for several organs using an in-house computer program validated against BEIR VII itself. Because organs were not irradiated uniformly, risk calculations were performed on a voxel-by-voxel basis.

$ERR$ values were calculated for the breasts, lungs, and thyroid as a function of sex, dose to organ, age at exposure, and attained age. To reduce variability within the cohort, the age at exposure for all patients was assigned a value of 26 years, which was the mean age of our patient cohort. The attained age of all patients was assigned a value of 46 years, which is 20 years after exposure, and is roughly equivalent to the median time for a RSC to develop in an HL patient treated with radiation.

Each organ of interest used the whole-organ LNT risk coefficient provided by BEIR VII to calculate $ERR$ on a voxel-by-voxel basis, where the value in the $i$th voxel is denoted by $ERR_i$. This approach follows that reported by Zhang et al. The majority of studies of medically irradiated populations have reported the risk of developing RSCs in most organs increases linearly with dose. The impact of possible non-linearities in dose
response models will be explored in a companion study.

ERR was then converted to relative risk (RR)\(^2\) for each voxel. The RR for the \(i\)th voxel (RR\(_i\)) was calculated using

\[ RR_i = ERR_i + 1 \] (1)

The mean RR for \(j\)th OAR was found using

\[ \overline{RR}_j = \frac{1}{L} \sum_{i=1}^{L} RR_i \] (2)

where, \(\overline{RR}_j\) is the mean RR for the \(j\)th OAR for a given treatment plan, \(RR\) is the RR for the \(i\)th voxel contained within the \(j\)th OAR, and \(L\) is the total number of voxels contained within the \(j\)th OAR.

### 2.4 Ratio of relative risk (RRR)

The endpoint of this work and the metric we used to determine which treatment plan provided the lowest risk of developing a RSC, was the ratio of relative risk (RRR). RRR was calculated by dividing the RR for a given treatment plan by the RR of the IMRT photon treatment plan, which will be our baseline treatment plan, or

\[ RRR = \frac{RR_{Treatment\ Plan}}{RR_{IMRT\ Photon\ Plan}} \] (3)

where, \(RR\) \(_{Treatment\ Plan}\) is the relative risk of a specified proton treatment plan, and \(RR\) \(_{IMRT\ Photon\ Plan}\) is the relative risk of the IMRT photon treatment plan for the same patient. The mean RRR was calculated for a given organ using

\[ \overline{RRR}_{j,k} = \frac{1}{L} \sum_{i=1}^{L} RRR_{i,j,k} \] (4)

where \(\overline{RRR}_{j,k}\) is the \(\overline{RRR}\) for all voxels, \(i\), contained in a given OAR, \(j\), and a given patient, \(k\).

The mean RRR in Eq. 4, denoted by \(\overline{RRR}_{j,k}^{\prime}\), was averaged over all patients, or

\[ \overline{RRR}_j = \frac{1}{N} \sum_{k=1}^{N} \frac{1}{L} \sum_{i=1}^{L} RRR_{i,j,k} \] (5)

Where, \(\overline{RRR}_j\) is the \(\overline{RRR}\) for all voxels, \(i\), all patients, \(k\), for a given OAR, \(j\) and \(N\) is the total number of patients.

### 2.5 Uncertainties and statistical significance

The sign test was used to determine the statistical significance of \(\overline{RRR}_{j,k}^{\prime}\) for each OAR considered. A \(\overline{RRR}_{j,k}^{\prime}\) value less than 1 indicates a lower RSC risk for the proton plan. Greater than 1 indicates a lower RSC risk for the photon plan. To account for uncertainty in the \(\overline{RRR}_{j,k}^{\prime}\) calculations, standard error propagation methods were applied. We adapted the formula for the \(\overline{RRR}_{j,k}^{\prime}\) uncertainty from Rechner et al.\(^2\)

### 3. Results

The host and treatment factors for all nine patients are listed in Table 1 for each patient and their respective OARs and clinical tumor volumes (CTV).

Figure 1 shows the source dose contributions for a subset of the patient cohort. This illuminates the wide range of variation between the patients and the different treatment modalities for each patient. While proton plans usually deposited less total dose to each organ, this was not always the case, and in some instances, was reversed due to neutron contributions.

Figure 2 shows the \(\overline{RRR}_{j,k}\) for all nine patients for the three OARs examined. The majority of comparisons again indicated a reduction in RSC risk for proton compared to photon plans; however, one third of the OARs indicated a reduced RSC risk for the corresponding photon treatments. Of note, the patients with the lowest \(\overline{RRR}_{j,k}\) (Patient #3 and #6) had only 1 field proton plans and patients with the highest \(\overline{RRR}_{j,k}\) (Patients #7, #8, and #9) were markedly younger than the average age of the cohort (ages 15, 10, and 15, respectively).

Figure 3 shows superior RSC risk reduction when the \(\overline{RRR}_{j,k}\) (mean RRR value for a given OAR for all patients) was calculated for either the proton PSPT or IMPT plans compared to the photon IMPT plans. As expected, the IMPT plan has a lower \(\overline{RRR}_{j,k}\) compared to the PSPT plan due to the lack of external neutron dose contributions. This graph highlights a contrast to Figure 2, which showed that individualize patients may or may not follow the class solution seen in Figure 3.

Table 2 shows the results of the sign test. The PSPT plan showed no significant decrease in RSC risk compared to the IMRT plan, while the IMPT plan showed a significant decrease in RSC risk compared to the IMRT plan for breast and lung.
Table 1: Host and Treatment Factors – Includes anatomical volumes, number of treatment fields, and gantry angles for all treatment plans.

<table>
<thead>
<tr>
<th>Patient Information</th>
<th>Breast</th>
<th>Lung</th>
<th>Thyroid</th>
<th>CTV</th>
<th>Photon Beam Characteristics</th>
<th>Proton Beam Characteristics</th>
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<tr>
<td></td>
<td>Volume - Left Breast (cc)</td>
<td>Volume - Right Breast (cc)</td>
<td>Volume - Total Breast (cc)</td>
<td>Total Breast % within 50% line of photons IMRT plan (%)</td>
<td>Volume - Left Lung (cc)</td>
<td>Volume - Right Lung (cc)</td>
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<tr>
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<td>138.8</td>
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<td>1.00</td>
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</tr>
</tbody>
</table>

| Average             | 493.3  | 391.6 | 884.9   | 100.0 | 100.0                       | 100.0                     | 200.0                  | 200.0                     | 200.0                     | 200.0                     | 200.0                  | 200.0 | 5                              | 0.49, 1.00, 1.00, 2.00, 2.00 |
| Standard Deviation  | 9.6    | 10.2  | 39.6    | 14.8  | 14.8                        | 14.8                      | 28.7                   | 28.7                      | 28.7                      | 28.7                      | 28.7                   | 28.7 | 5                              | 0.49, 1.00, 1.00, 2.00, 2.00 |
Table 2: Sign test results, LNT dose response model, exposed age (e) = 26, attained age (a) = 46, neutron \( \bar{w}_N \) = 20. Table showing the sign test results for each individual OAR tested (RRR<sub>j,k</sub>). In order to show significance (P < 0.05) for the proton plan, at least 8 of the 9 patients had to have a RRR<sub>j,k</sub> value < 1. Columns with just the OAR name (i.e. Breast, Lung, and Thyroid) indicate the nominal RRR<sub>j,k</sub> values. Columns with the OAR name plus the calculated uncertainty (i.e. Breast w/ + Error, Breast w/- Error, etc.) indicates the nominal RRR<sub>j,k</sub> plus its corresponding error (+ or −, respectively).

<table>
<thead>
<tr>
<th>Treatment Type Compared to</th>
<th>Parameters</th>
<th>Breast w/ Error</th>
<th>Breast</th>
<th>Breast w/- Error</th>
<th>Lung w/- Error</th>
<th>Lung</th>
<th>Lung w/+ Error</th>
<th>Thyroid w/- Error</th>
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<td>8</td>
<td>6</td>
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<tr>
<td></td>
<td># of Patients with Mean RRR &lt; 1</td>
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<td></td>
<td>Protons</td>
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<td>Protons</td>
<td>None</td>
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<tr>
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<td>Treatment Modality Significantly Better?</td>
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<td></td>
<td></td>
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<td></td>
<td>Protons</td>
<td>None</td>
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<td></td>
<td># of Patients with Mean RRR &lt; 1</td>
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<td></td>
<td>Treatment Modality Significantly Better?</td>
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<td>Protons</td>
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<td>Protons</td>
<td>None</td>
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</tbody>
</table>
Figure 1: Mean equivalent dose from all sources per patient (cSv / prescribed Gy); neutron $\bar{w}_n = 20$. Graph showing the mean equivalent dose per prescribed Gy to each OAR for the various treatment plans for 3 of the 9 patients. This illustrates the wide variation of results depending on the individual. Averaged over all patients, the mean total neutron equivalent dose contribution for the proton plans was 2.8 cSv/Gy for total breast, 3.1 cSv/Gy for total lung, and 3.0 cSv/Gy for thyroid.
Figure 2: $\frac{R_{RR,LT}}{R_{RR,PT}}$, PSPT vs IMRT, LNT dose response model, exposed age (e) = 26, attained age (a) = 46, neutron $\bar{W}_n = 20$; Each of the three OARs are shown for all 9 patients. The red line is set at 1 and is used to indicate whether the specific OAR for each patient shows a decreased risk of RSC for the proton treatment (< 1) or the photon treatment (> 1).
**Figure 3**: $R_{j,k}$, proton plans vs IMRT, LNT dose response model, exposed age ($e$) = 26, attained age ($a$) = 46, neutron $w_n = 20$; The red line is set at 1 and indicates either a decreased relative risk of RSC for the PSPT or IMPT proton treatment (< 1) or the photon treatment (> 1). Recall that the RRR metric is the ratio of the RR for a given proton plan and the RR for the photon IMRT plan. All OARs (average over all patients) showed a lower relative risk of RSC for their respective proton plan compared to their IMRT photon plan.

### 4. Discussion

We calculated baseline $R_{j,k}$ values (both $R_{j,k}$ and $R_{j}$) for proton PSPT and IMPT treatment plans vs a corresponding photon IMRT plan for the total breast, total lung, and thyroid of nine patients using a representative patient exposed at the age of 26 years and attaining the age of 46 years. Two $R_{j,k}$ endpoints (Equations 4 and 5) were used for the RSC risk calculations. Evaluation of the range of possible $R_{j,k}$ values with the sign test showed that while the majority of patient’s individual OARs ($R_{j,k}$) displayed decreased RSC risk for each proton plan compared to the IMRT plan, significant reductions were only seen when the average of all nine patients for each OAR ($R_{j}$) were compared.

Proton plans with just one field (Patients #3 and #6) had the lowest $R_{j,k}$ of all proton plans. While a single field configuration is likely desirable from a RSC risk perspective, coverage of the tumor volume may be compromised and/or specific OAR dose distributions could increase. Additionally, proton plans of the younger patients (#7-9) showed the highest $R_{j,k}$ in the cohort.

From a public health perspective, the high cure rates and long survival times after HL treatment make plausible reductions of RSC risks a relevant study. Since the turn of the millennium, many epidemiological and radiation exposure studies have examined this topic. Unlike other studies, which have shown clear advantages of protons vs photon treatments\cite{8,9,11,27-31}, our work has a more nuanced conclusion. In the majority of patients considered, the proton plans offered a lower predicted mean RR to the OARs of interest.

This was not the case for all patients, however, and can be attributed to several unique contributions of this work including more comprehensive dose calculations of the stray and out of field dose components than previous studies and the large inter-patient variations of HL tumor size and location within the body. Unlike other treatment sites, such as prostate that have a more fixed position.
relative to their respective normal tissue restraints, the location of the HL tumor can be in close or far proximity to any of the three OARs examined. This greatly changes the approach taken to reduce OAR exposure. These findings indicate that large inter-patient variations necessitate population-based studies as well as personalized dose and risk assessments to support clinical decision making.

Several studies have indicated a clear advantage for proton plans versus photon plans for HL, either dosimetrically or with risk calculations included. Comparing the RRR to the literature, the work which most closely resembles ours was that of Cella et al., in it, they benchmarked a similar calculation to the RRR (called the risk ratio), and calculated for an IMPT configuration on a single representative patient with artificially drawn CTVs. Their results favored the IMPT plans and indicated a more significant reduction compared to our results, especially for the total breast. There are several possible reasons for this.

1) The proton beam energies they used ranged from 62-180 MeV. Ours were higher due to an increased nominal spread out Bragg Peak (SOBP) compared to their work, which increased the neutron dose and which they only accounted for in-field. Additionally, they prescribed a dose of 30 Gy instead of 36 Gy as we did, which would also reduce neutron contributions.

2) Their PTV was constructed to be symmetrical in a single patient’s anatomy both laterally and in the superior/inferior direction. Our PTV location varied sometimes dramatically from this centralized setup depending on the patient examined.

3) Their IMRT treatment used seven fields. Ours were five field setups. A reduction in the number of fields and therefore, volume of healthy tissue irradiated, could lower the patient’s risk of RSC using IMRT.

Other results were also in line compared with other published data. Our adjustment of the photon dose to voxels below the 5% isodose line led to an average increase in our OAR mean dose by 14.5% in total breast, 2.6% in total lung, 4.6% for the thyroid. Previous papers reported an under dosage by the commercial TPS to voxels which fell below the 5% isodose line by 40 - 60%. Since voxels with values greater than the 5% isodose line were unchanged, and the majority of OARs for the 9 patients had larger portions of their volume above the 5% isodose line, our adjustments were lower than the values they reported.

Our neutron calculations also match up well with previous studies, including Taddei et al., which is the closest comparison to our work, most closely corresponding to Patient #2 from our work. Adjusting Taddei et al. to equate the neutron $w_N$ value to 20 and to deliver the same prescribed dose, the mean cSv/Gy for their work to the liver is 3.8 cSv/Gy. The mean H/D value for the total breast and total lung together in our work was 5.7 cSv/Gy. The increased value of our calculations can be partially explained by their use of an intermediate snout size. Zheng et al. have shown that a change from the intermediate snout to the larger size for a 250 MeV beam can lead to an increase in neutron equivalent dose by more than 25%. Adjusting the values to account for this brings the values closely in line.

Our study had several limitations. The lack of 4DCT data sets when calculating dose could lead to discrepancies between the dose, and subsequently the RSC risk, calculated compared to what is delivered. Our study was an in-silico trial as opposed to an in-vivo trial. This is a common issue in radiation dosimetry/risk analysis and is difficult to eliminate due to the amount of time required to acquire statistically meaningful results before the treatment technique is rendered technologically obsolete.

Also, while the nine patients in our study were the largest of HL risk analysis involving proton therapy to our knowledge, more patients would help increase power and significance. This is a major concern because our sample revealed pronounced inter-patient differences in tumors and treatments that lead to mixed qualitative findings regarding the superiority of one radiation modality over another. Thus, the inclusion of additional patients would not alter our central finding, which is a cautionary tale regarding the importance of clinically realistic and personalized risk assessment methods.

Additionally, there are still unknowns regarding RSC outcomes for medically irradiated populations, not only compared to the cohort we used from BEIR VII, but also from variations in techniques for medically exposed populations over the last 40 years, which were largely treated with mantle fields. The now more commonly used smaller IFRT field sizes, which reduce the dose to surrounding tissue, have led many epidemiologists to caution against the use of the BEIR VII risk models. By taking the ratio of two plans against each other, many of these confounders have been removed, but when calculating absolute risk as opposed to relative risk as we have, further care should be taken.

Finally, for both photon and proton treatments, there has been substantial interest in moving to even smaller fields than IFRT. To further validate our results, a more comprehensive study of all available treatment techniques, including the increasingly popular involved node radiation therapy (INRT) tumor delineation, should be explored in the future.

5. Conclusion

Individualized PSPT and IMPT proton treatment plans
which included a comprehensive dose calculation were compared for RSC risk to a corresponding photon IMRT plans for nine patients. Calculations of out of field and secondary doses were shown to be important to accurately calculate risk as their absence for both the proton and photon plans resulted in a $R_{\text{RRR}}$ value incorrectly being greater or lesser than 1. Additionally, plans with single proton fields showed the lowest RSC risk for proton plans while the youngest HL patients in our cohort were more likely to show a lower RSC for the photon IMRT treatments. Due to the high variability of each patient’s anatomy, tumor location, treatment angles, and OAR doses, individualized analysis is paramount in order to determine the lowest possible risk of RSC formation.

**Conflict of Interest**

The author declares he has no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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