Risk of Radiation-Induced Cardiotoxicity and Secondary Cancers in Hodgkin's Lymphoma Patients

Purpose: This project investigates the potential impact of increased normal-structure sparing achieved with intensity modulated proton therapy (IMPT) as compared to 3D conformal photon therapy.

Methods and Materials: Patients selected for the study received photon therapy for Hodgkin's Lymphoma in 2010 from one of ten hospitals participating in the province of Quebec. Patients who were under thirty years of age at the time of treatment were selected to emphasize the maximum long-term impact of proton therapy. Critical late secondary effects were specified as premature death due to radiation-induced cardiotoxicity, induction of lung cancer, and induction of breast cancer (for female patients only).

The CT simulation images and dose file for each patient's original photon treatment plan were anonymized and imported into Eclipse v. 10.0 treatment planning software (Varian Medical Systems, Palo Alto, CA). Contouring of heart and lung volumes was checked for consistency of inferior and superior limits as well as tissue differentiation and modified when necessary. Breast volume was contoured for all female patients. Patients were then re-planned (Figure 1) using the proton beam data supplied by Varian, and the dose distribution was calculated using the proton convolution superposition algorithm v. 8.9.08.

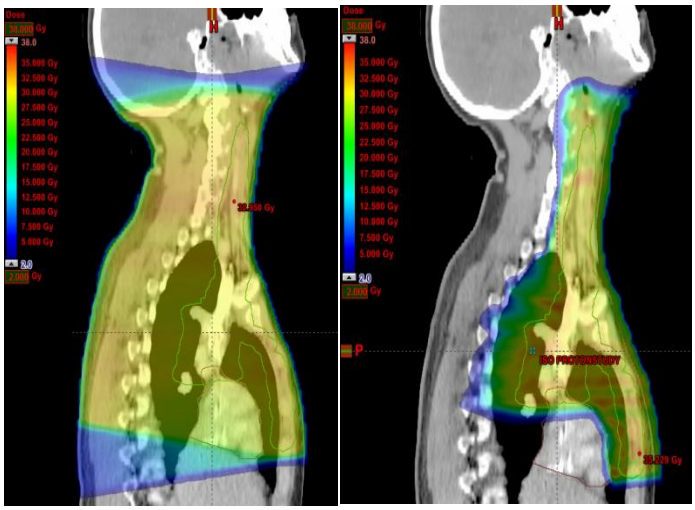

Figure 1: Plan comparison illustrating significant sparing of heart (left: 3DCRT, right: IMPT; PTV contour: green, heart contour: brown)

Radiotherapy treatment plans were exported in DICOM format, and the CERR 4.0 Beta 4 platform was used to import and convert the dose-volume matrix information into a MATLAB matrix file. The subsequent analysis for risks of secondary effects was performed in MATLAB. Models were selected from literature to evaluate the risks of cardiotoxicity and induction of lung and breast cancer implementing patient-specific dose-volume information from the treatment plans. This allowed for a calculation of the reduction of risk for each effect if proton therapy were to be used.

The relative seriality model was used to predict the excess risk of fatal radiation-induced cardiotoxicity using dose-volume information (Equations 1a and 1b). This model incorporates a seriality term, *s,* describing the ratio of the number of serial subunits to all subunits, and it is set to 1 for the heart. Other parameters are D_{50}, which represents the dose at which the probability for the given complication is 50%, and γ, which is the maximum slope of the dose-response curve. The values for these parameters were derived from long-term, post-radiotherapy cardiac mortality studies by Gagliardi[i] and by Eriksson[ii] on breast cancer and Hodgkin's lymphoma patient populations.

$$P = \left[1 - \prod_{1}^{n}\left[1 - P(D_i)^s\right]^{\Delta v_i}\right]^{1/s} \quad \text{(1a)}, \qquad P(D) = 2^{-e^{e\gamma(1-D/D_{50})}} \quad \text{(1b)}$$

The organ equivalent dose concept was used in conjunction with a risk model based on a modified linear quadratic model[iii] developed by Schneider to predict the excess absolute risk for organ-specific cancer induction using dose-volume information (Equations 2a, 2b, and 2c). The parameter α' incorporates the parameters α and β from the linear quadratic model to account for the number of cells killed after irradiation. The ability of the cells to repopulate and repair is represented by the parameter R, and μ is the slope of the cancer induction curve from the linear no-threshold model. The parameters used for this evaluation were derived from model-fitting studies by Schneider based on Hodgkin's disease patients and Japanese atomic bomb survivors.

$$EAR^{\,\mathrm{mod}} = \mu \frac{e^{-\alpha' D}}{\alpha' R}\left(1 - 2R + R^2 e^{\alpha' D} - (1-R)^2 e^{-\frac{\alpha' R}{1-R} D}\right) \equiv \mu RED \quad \text{(2a)} \qquad \alpha' = \alpha + \beta d \quad \text{(2b)}$$

$$EAR_{organ} = \mu \frac{1}{V_{organ}} \sum_i V_i RED_i \equiv \mu OED_{organ} \quad \text{(2c)}$$

Results: The risks for each patient are summarized in Table 1. Proton treatment plans were able to reduce the risks of fatal cardiotoxicity and lung and breast cancer induction for all patients. The mean excess risk of fatal cardiotoxicity was 0.9% for photon plans and 0.6% for proton plans. These results are in agreement with studies by Gagliardi where the excess risk of cardiac mortality varied from 0% to 8.8% (mean 1.8%). The mean excess absolute risk (EAR) for lung cancer was at thirty years post-irradiation was 11.6 per 10,000 persons per year (PY) for photons and 6.9 PY for protons. The photon risks correlate well with findings of Schneider and others where EAR for lung cancer induction varied between 9.7 PY and 21.5 PY. The mean EAR for breast cancer induction was 5.6 PY for photons and 2.1 PY for protons.

Table 1: *Summary of Risks of Radiation-Induced Late Effects for photon (PH) and proton (P+) plans (per 10^3 PY).*

Patient	Excess Risk of Fatal Cardiotoxicity (%)		Excess Absolute Risk of Lung Cancer at Thirty Years Post-Irradiation (*per 10^3 PY)*				Excess Absolute Risk of Breast Cancer at Thirty Years Post-Irradiation (*per 10^3 PY)*			
			Left Lung		*Right Lung*		*Left Breast*		*Right Breast*	
	PH	P+	PH	P+	PH	P+	PH	P+	PH	P+
1	0.96	0.66	19.0	13.2	12.9	9.7	-	-	-	-
2	0.06	0.03	9.0	3.4	9.1	2.9	-	-	-	-
3	0.33	0.28	6.5	5.1	5.5	4.1	2.6	1.0	2.1	0.6
4	0.66	0.34	10.9	4.5	13.5	6.8	-	-	-	-
5	1.02	0.95	8.7	6.1	9.2	6.3	3.0	0.7	3.5	0.8
6	0.01	0.00	15.8	9.4	1.0	0.00	-	-	-	-
7	0.38	0.36	8.4	5.9	6.1	3.8	-	-	-	-
8	2.15	0.79	14.2	8.1	17.0	9.4	6.1	1.2	6.9	1.5
9	1.90	1.38	7.5	3.8	17.4	10.7	3.7	0.1	12.8	7.8
10	1.82	1.59	17.0	9.2	24.2	16.0	5.5	1.6	14.2	5.4
11	0.82	0.75	13.9	8.0	7.7	5.6	-	-	-	-
Mean	**0.92**	**0.65**	**11.9**	**7.0**	**11.2**	**6.8**	**4.2**	**0.9**	**7.9**	**3.2**

Potential Impact & Future Work: The results of this study provide a quantitative method of comparison for radiotherapy modalities by examining risks of potentially lethal radiation-induced effects. The advantages of intensity modulated proton therapy over modern photon radiotherapy techniques can now be evaluated for a specific patient, and this work may be used as a tool for selecting patients for proton therapy on a case-by-case basis. Future work will include expanding the patient cohort to reduce uncertainties. It is the goal of this study to research the potential impact of building a proton therapy facility in Quebec.

i Gagliardi et al. Radiotherapy and Oncology 55, 63-71 (1998)
ii Eriksson et al., Radiotherapy and Oncology 55, 153-162 (2000)
iii Schneider et al., International Journal of Radiation Oncology Biology Physics 61(5), 1510-1515 (2005)

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