

Supplementary material: Life years lost attributable to late effects after radiotherapy for early stage Hodgkin lymphoma: the impact of proton therapy and/or deep inspiration breath hold

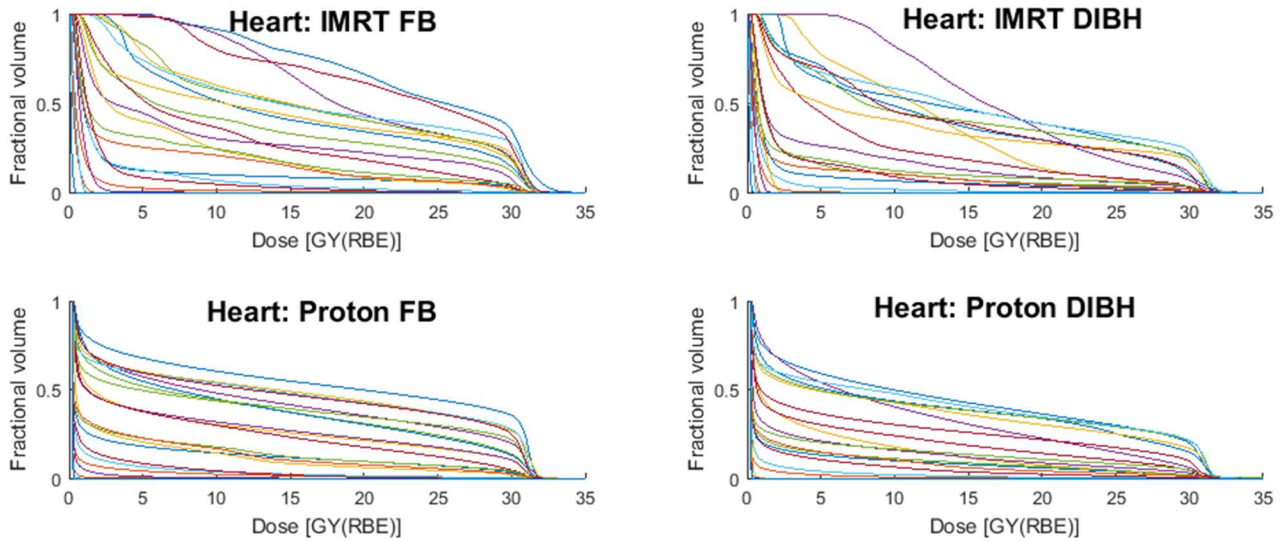


Figure S1: Cumulative dose volume histograms (DVHs) for each treatment technique for each patient for the heart. Abbreviations: Intensity modulated radiation therapy (IMRT), free breathing (FB), deep inspiration breath hold (DIBH).

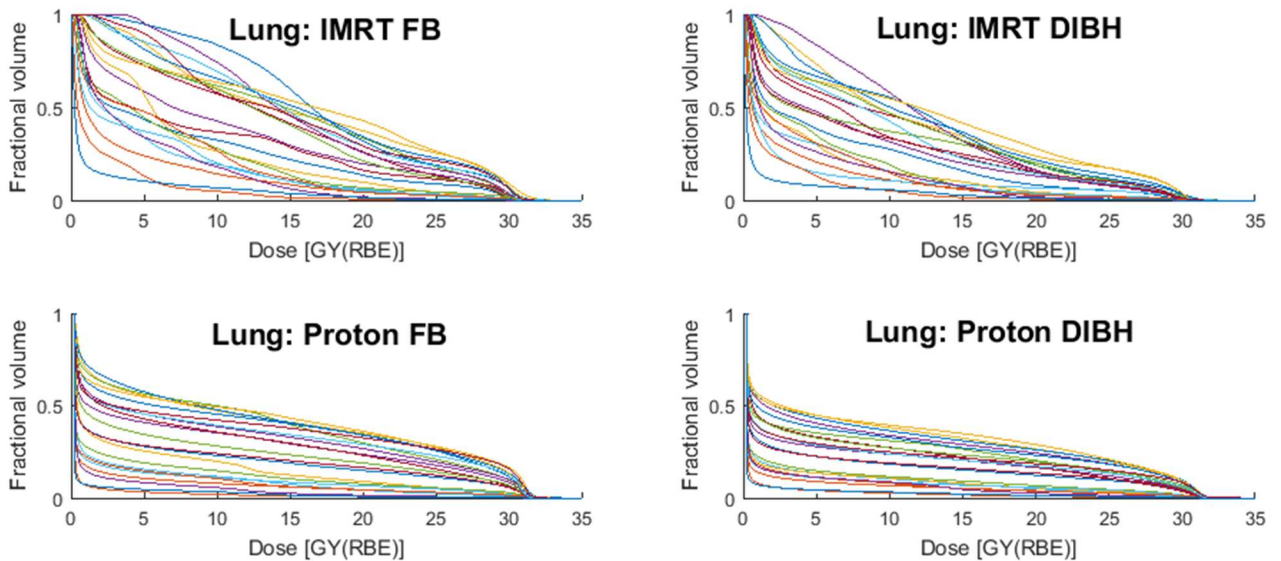


Figure S2: Cumulative dose volume histograms (DVHs) for each treatment technique for each patient for the lung. Abbreviations: Intensity modulated radiation therapy (IMRT), free breathing (FB), deep inspiration breath hold (DIBH).

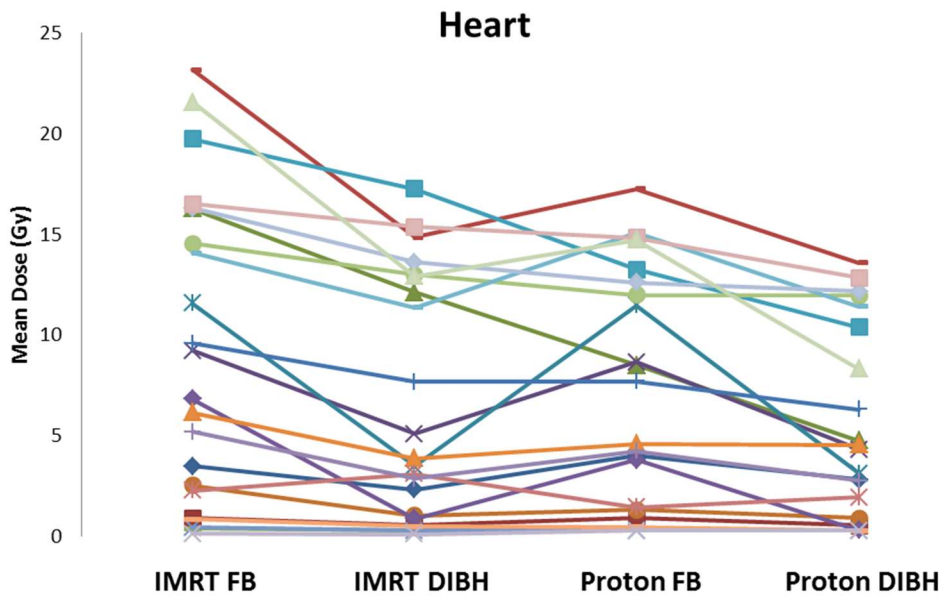


Figure S3: Spaghetti plot of mean dose to the heart for the 22 patients for each technique. Abbreviations: Intensity modulated radiation therapy (IMRT), free breathing (FB), deep inspiration breath hold (DIBH).

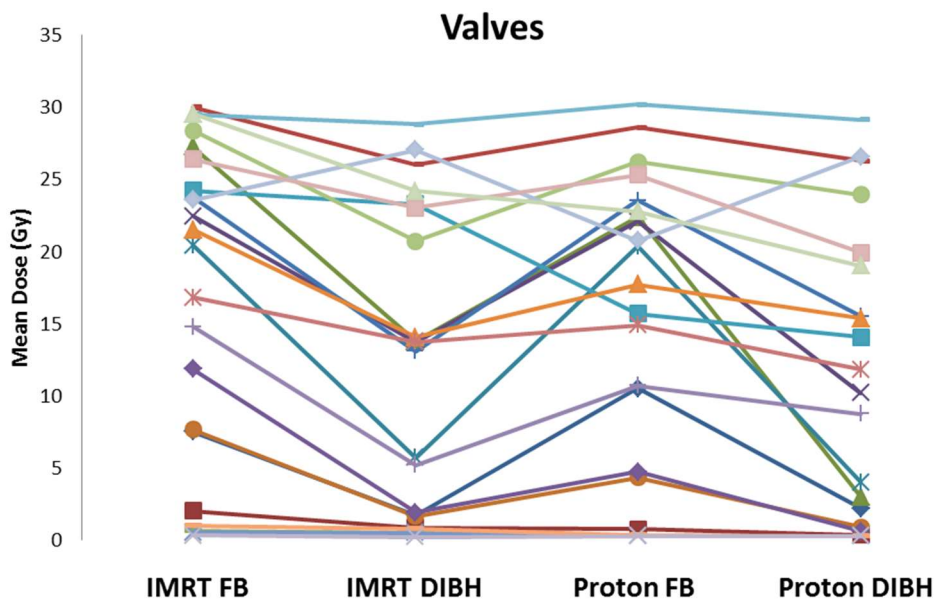


Figure S4: Spaghetti plot of mean dose to the valves for the 22 patients for each technique. Abbreviations: Intensity modulated radiation therapy (IMRT), free breathing (FB), deep inspiration breath hold (DIBH).

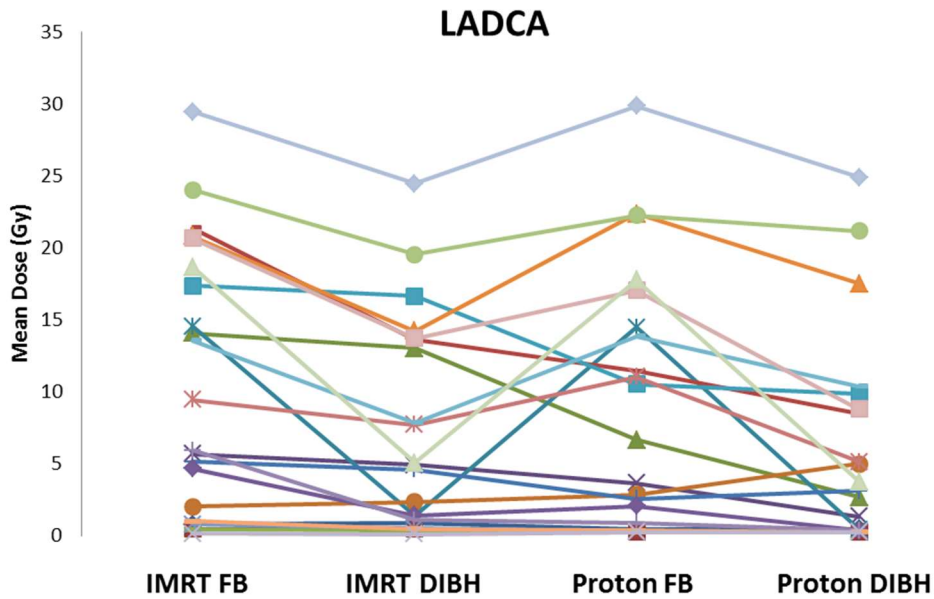


Figure S5: Spaghetti plot of mean dose to the left anterior descending coronary artery (LADCA) for the 22 patients for each technique. Abbreviations: Intensity modulated radiation therapy (IMRT), free breathing (FB), deep inspiration breath hold (DIBH).

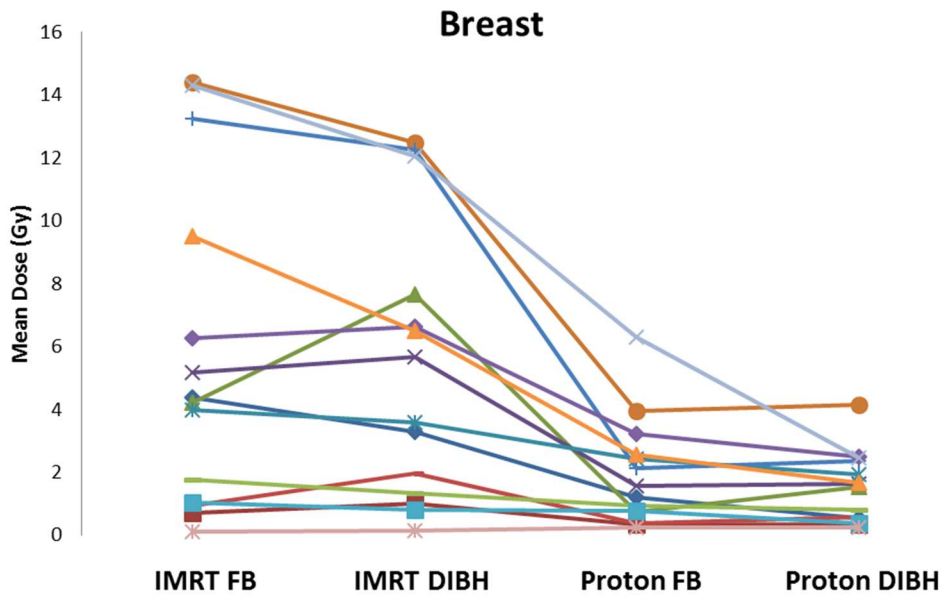


Figure S6: Spaghetti plot of mean dose to the breast for the 14 female patients for each technique. Abbreviations: Intensity modulated radiation therapy (IMRT), free breathing (FB), deep inspiration breath hold (DIBH).

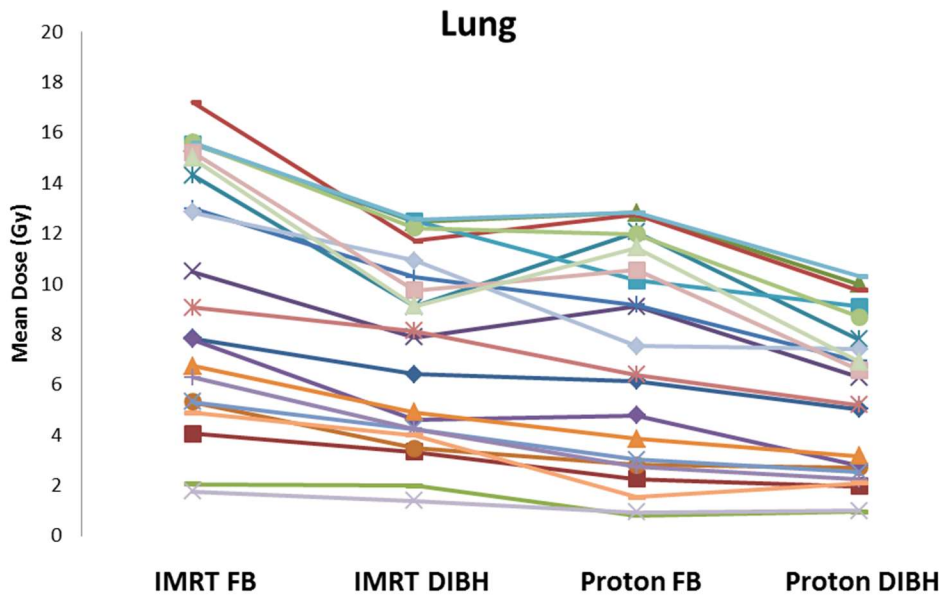


Figure S7: Spaghetti plot of mean dose to the lung for the 22 patients for each technique. Abbreviations: Intensity modulated radiation therapy (IMRT), free breathing (FB), deep inspiration breath hold (DIBH).

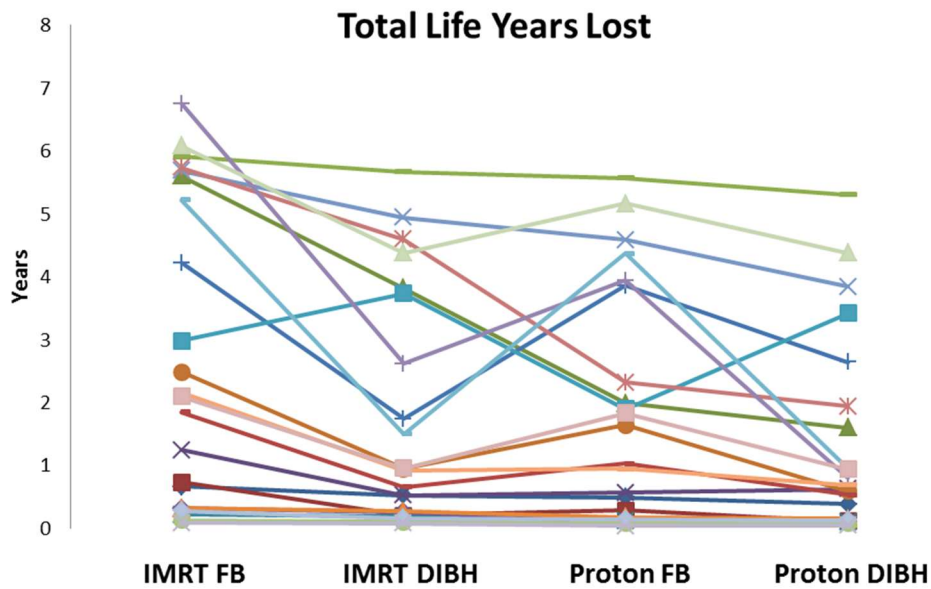


Figure S8: Spaghetti plot of total life years lost (LYL) for the 22 patients for each technique. Abbreviations: Intensity modulated radiation therapy (IMRT), free breathing (FB), deep inspiration breath hold (DIBH).

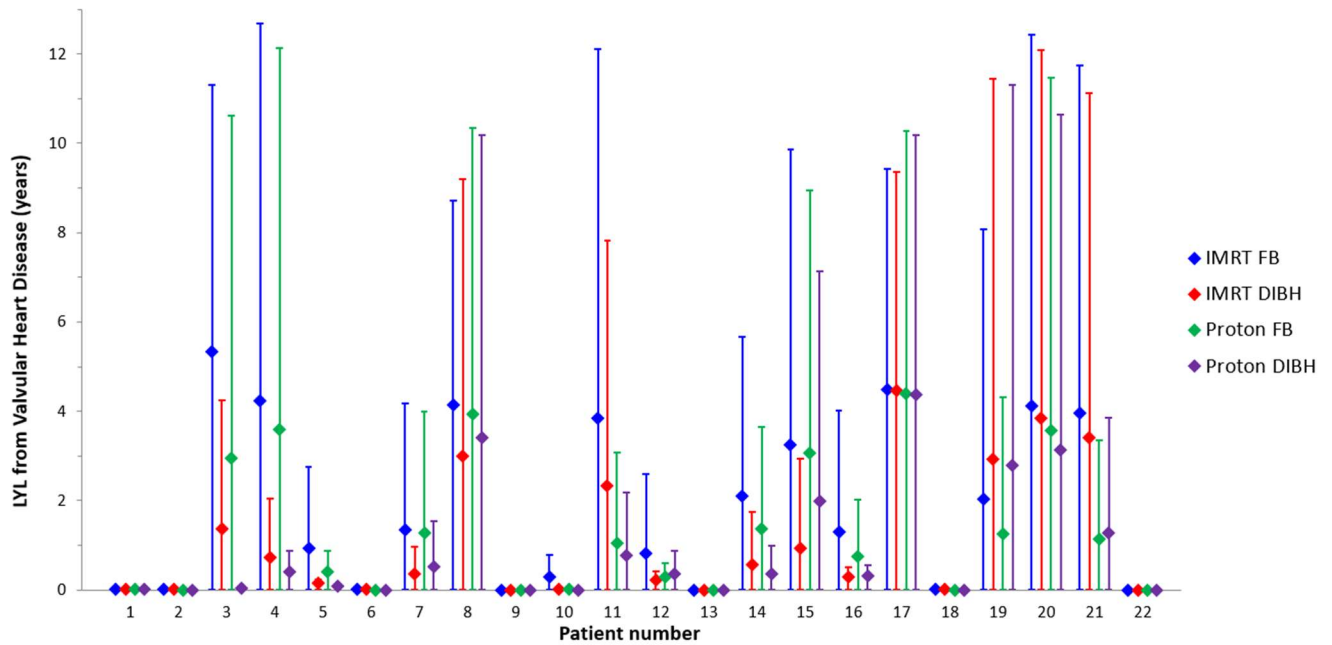


Figure S9: Life years lost (LYL) from valvular heart disease for the 22 patients for each technique. Error bars represent the 95% confidence interval, calculated by using the confidence interval for excess hazard ratio for each risk model (see Table S1 description). Abbreviations: Intensity modulated radiation therapy (IMRT), free breathing (FB), deep inspiration breath hold (DIBH).

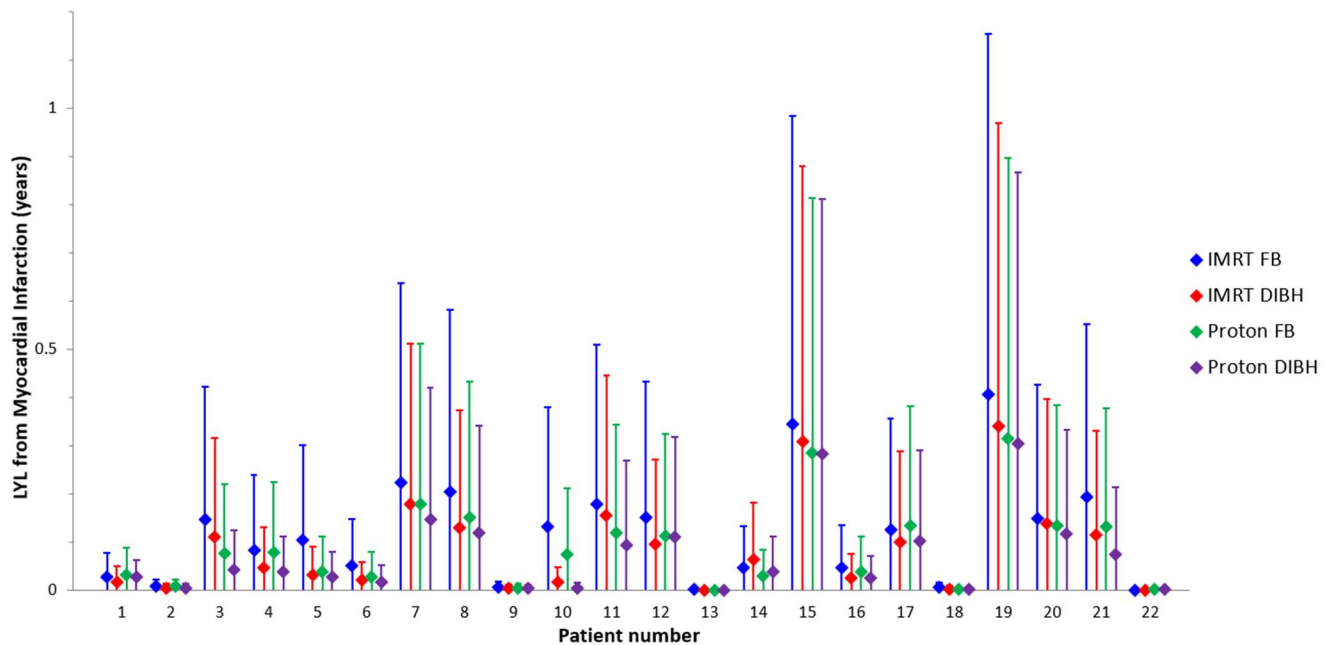


Figure S10: Life years lost (LYL) from myocardial infarction for the 22 patients for each technique. Error bars represent the 95% confidence interval, calculated by using the confidence interval for excess hazard ratio for each risk model (see Table S1 description). Abbreviations: Intensity modulated radiation therapy (IMRT), free breathing (FB), deep inspiration breath hold (DIBH).

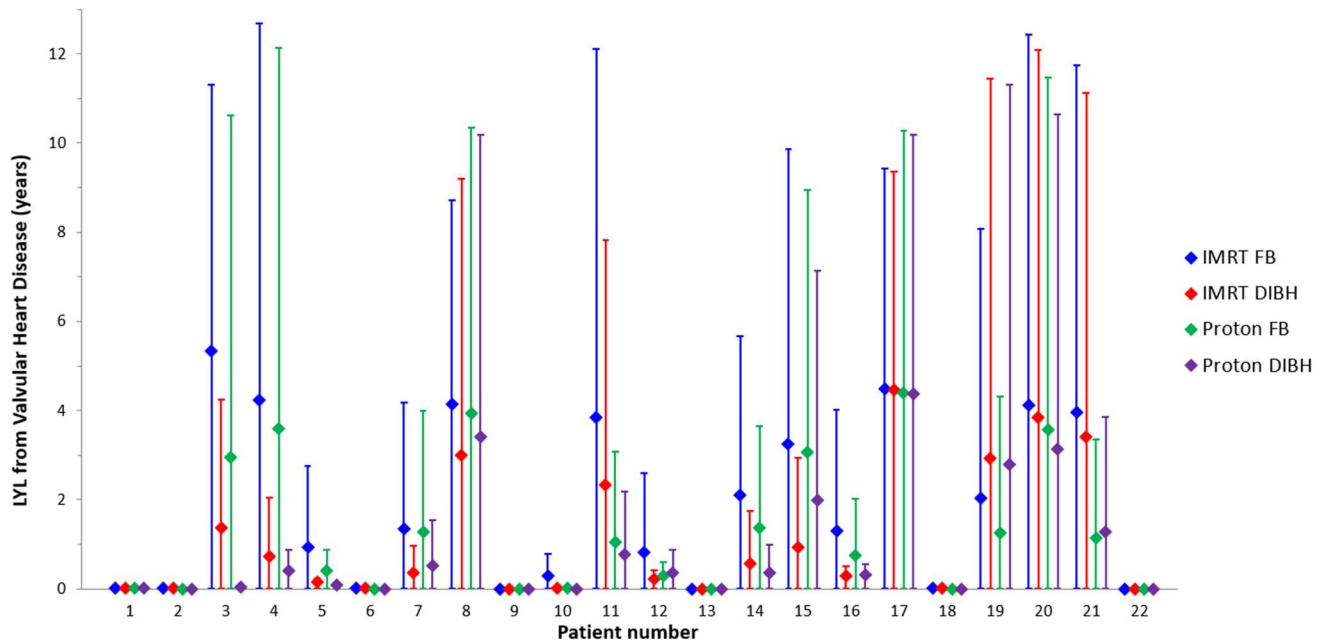


Figure S11: Life years lost (LYL) from valvular heart disease for the 22 patients for each technique. Error bars represent the 95% confidence interval, calculated by using the confidence interval for excess hazard ratio for each risk model (see Table S1 description). Abbreviations: Intensity modulated radiation therapy (IMRT), free breathing (FB), deep inspiration breath hold (DIBH).

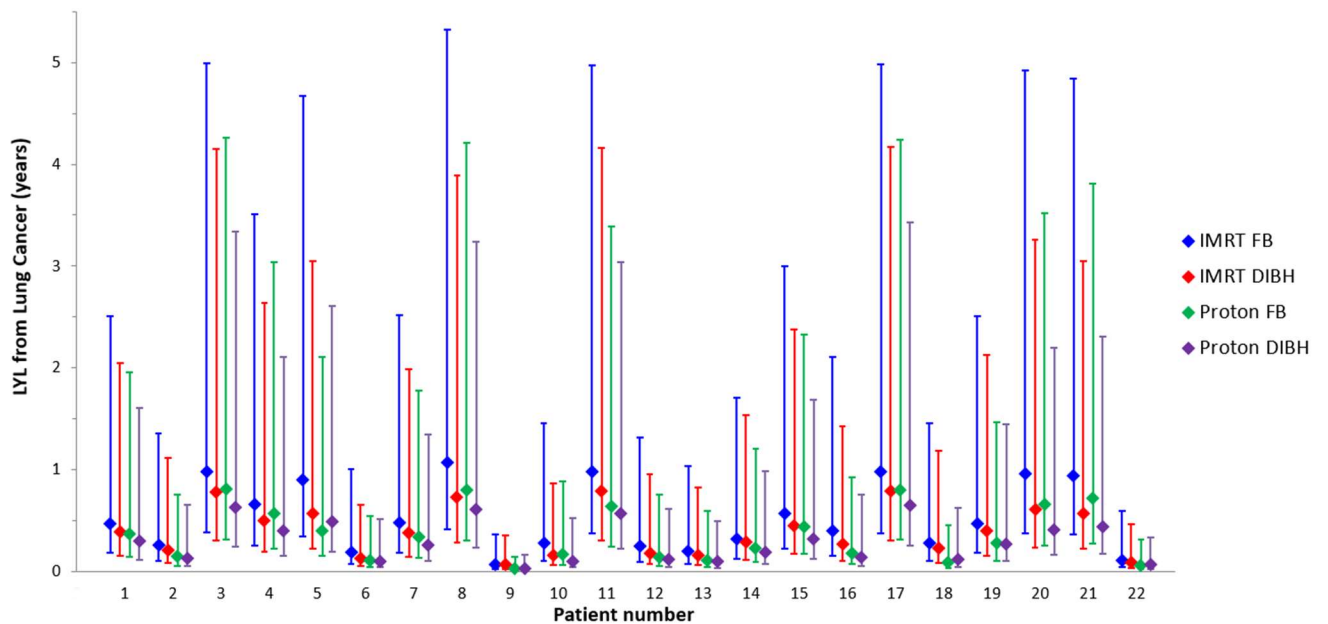


Figure S12: Life years lost (LYL) from lung cancer for the 22 patients for each technique. Error bars represent the 95% confidence interval, calculated by using the confidence interval for excess hazard ratio for each risk model (see Table S1 description). Abbreviations: Intensity modulated radiation therapy (IMRT), free breathing (FB), deep inspiration breath hold (DIBH).

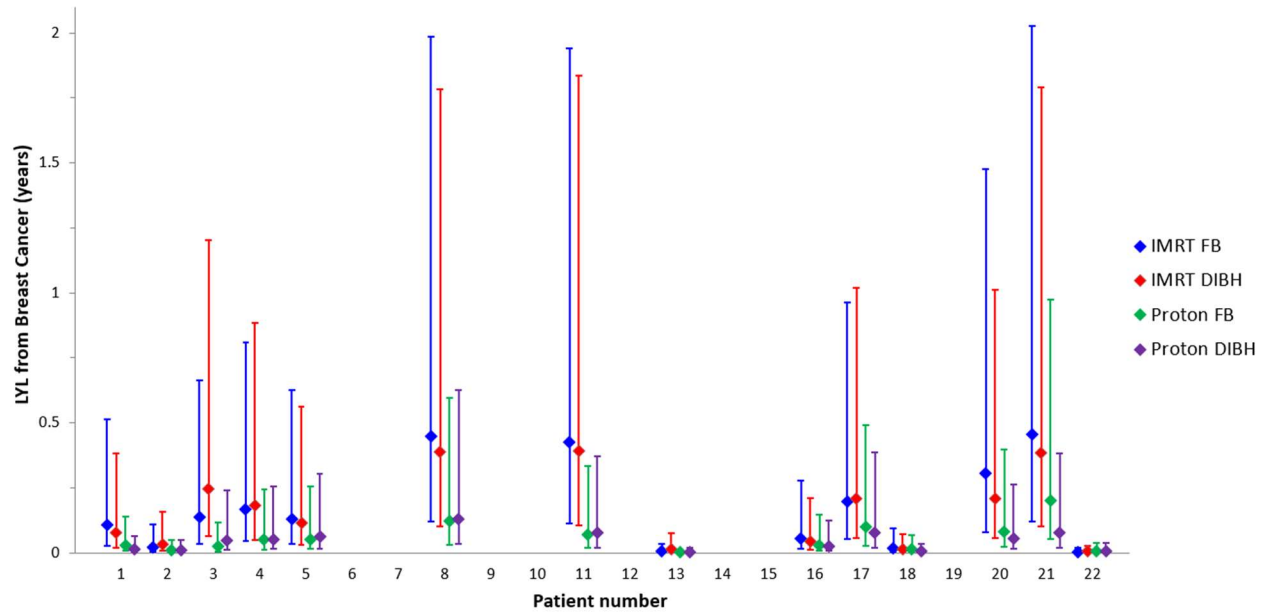


Figure S13: Life years lost (LYL) from breast cancer for the 14 female patients for each technique. Error bars represent the 95% confidence interval, calculated by using the confidence interval for excess hazard ratio for each risk model (see Table S1 description). Abbreviations: Intensity modulated radiation therapy (IMRT), free breathing (FB), deep inspiration breath hold (DIBH).

Late Effect	Equation for HR_{excess}	Reference
Heart Failure	$0.061 * (\text{Mean Heart Dose (Gy)})$	Mulrooney et al. 2009 [19]
Myocardial Infarction	$0.045 * (\text{Mean Heart Dose (Gy)})$	Mulrooney et al. 2009 [19]
Valvular Heart Disease	$e^{-5.015 * (\text{Valve EQD2 (Gy)})} * e^{0.07531 * (\text{Valve EQD2 (Gy)})}$	Cutter et al. 2015 [20]
Lung Cancer	$0.141 * (\text{Mean Lung Dose (Gy)})$	Travis et al. 2002 [21]
Breast Cancer	$0.15 * (\text{Mean Breast Dose (Gy)})$	Travis et al. 2003 [22]

Table S1: Risk models used in this study, where $HR = HR_{\text{excess}} + 1$. (HR: hazard ratio). Valve EQD2 is the equivalent dose in 2 Gy fractions to the aortic or mitral valve, whichever was higher, calculated from the differential dose-volume histogram. In most cases, the aortic valve had the highest EQD2. 95% confidence intervals for each value used in the risk models are as follows: heart failure (0.0213 to 0.0999), myocardial infarction (0.00 to 0.1285), valvular heart disease (-9.867 to -1.915, and 0.007243 to 0.1774), lung cancer (0.0545 to 0.752), and breast cancer (0.04 to 0.73) [13,20]. Survival and background incidence data were from SEER [23] for lung cancer and breast cancer, the Centers for Disease Control [24] for myocardial infarction and heart failure, and Nkomo et al. [25] for valvular heart disease.

Metric	IMRT FB (1)	IMRT DIBH (2)	Proton FB (3)	Proton DIBH (4)	Median of Pairwise Differences					
	Median (Range)	Median (Range)	Median (Range)	Median (Range)	1-2	1-3	1-4	2-3	2-4	3-4
CI	1.19 (1.05-1.61)	1.16 (0.99-1.92)	1.14 (1.05-1.24)	1.17 (1.08-1.38)	0.04 (-0.57-0.41)	0.08 (-0.07-0.47)	-0.01 (-0.24-0.47)	0.06 (-0.17-0.80)	-0.04 (-0.39-0.80)	-0.03 (-0.25-0.03)
HI	1.08 (1.05-1.12)	1.08 (1.04-1.11)	1.07 (1.05-1.12)	1.09 (1.05-1.18)	0.00 (-0.03-0.05)	0.01 (-0.03-0.04)	-0.01 (-0.10-0.03)	0.01 (-0.05-0.06)	-0.01 (-0.08-0.04)	-0.02* (-0.11-0.01)

Table S2: Medians and ranges of conformity index (CI) and heterogeneity index (HI) values and their pairwise differences for intensity modulated radiation therapy (IMRT) in free breathing (FB) and deep inspiration breath hold (DIBH) and proton therapy in FB and DIBH for the 22 patients in this study. The Friedman test and post-hoc analysis with Bonferroni correction were used, values significant at the < 0.05 level are marked with*.

Volume	Technique	Median (UD)	Min/Max (UD)
CTV	IMRT FB	30.8 (30.6)	30.4 (30.0)
	IMRT DIBH	30.9 (30.7)	30.7 (30.5)
	Proton FB	30.8 (30.5)	30.4 (29.9)
	Proton DIBH	30.8 (30.3)	30.4 (28.9)
Heart	IMRT FB	8.0 (9.6)	23.2 (24.2)
	IMRT DIBH	3.6 (4.7)	17.3 (17.9)
	Proton FB	5.9 (7.3)	17.0 (18.5)
	Proton DIBH	3.4 (4.5)	13.3 (14.8)
Valves	IMRT FB	21.0 (23.1)	30.0 (30.3)
	IMRT DIBH	13.4 (16.1)	28.8 (29.3)
	Proton FB	16.4 (19.0)	29.9 (30.4)
	Proton DIBH	9.2 (13.3)	28.9 (29.2)
LADCA	IMRT FB	7.7 (11.0)	29.5 (30.1)
	IMRT DIBH	4.7 (6.1)	24.5 (25.4)
	Proton FB	4.9 (6.7)	29.6 (30.2)
	Proton DIBH	2.7 (4.0)	24.6 (25.7)
Lung	IMRT FB	9.8 (10.5)	17.2 (17.8)
	IMRT DIBH	8.0 (8.5)	12.6 (13.1)
	Proton FB	6.7 (7.0)	12.6 (13.2)
	Proton DIBH	5.5 (5.9)	10.1 (10.5)
Breast	IMRT FB	4.3 (4.8)	14.4 (15.2)
	IMRT DIBH	4.6 (5.1)	12.5 (13.0)
	Proton FB	1.1 (1.4)	6.0 (6.3)
	Proton DIBH	1.3 (1.6)	3.9 (4.3)

Table S3: Doses (Gy) from the original plans and uncertainty doses (UDs) given in parentheses that were calculated with the built-in tool in the treatment planning system. UD were calculated assuming 5 mm positional shifts for both IMRT and proton therapy and a 3.5% uncertainty in HU for proton therapy (independently). The first column shows the median of mean doses for all patients. The UD in the first column are the medians of the minimum UD of all patients for the CTV and the medians of the

maximum UD of all patients for the organs at risk (OARs). The second column shows the minimum dose to the CTV of all patients or the maximum dose to the OARs of all patients. The UD in the second column are the minimums of the minimum UD of all patients for the CTV and the maximums of the maximum UD of all patients for the organs at risk (OARs). In summary, the first column displays the median doses and the median of the extreme UD. The second column displays the extreme doses and the corresponding extreme UD. Neutron doses were not added to proton plans for this analysis. Abbreviations: LADCA: left anterior descending coronary artery, IMRT: intensity modulated radiation therapy, FB: free breathing, DIBH: deep inspiration breath hold.

Organ	Technique	Patient 4		Patient 10	
		Dose (Gy)	LYL	Dose (Gy)	LYL
Heart	IMRT FB	9.2	0.16	6.8	0.16
	IMRT DIBH	5.1	0.09	0.9	0.02
	Proton FB	8.4	0.15	3.5	0.09
	Proton DIBH	4.0	0.08	0.0	0.01
Valve	IMRT FB	22.5	4.23	11.8	0.30
	IMRT DIBH	13.7	0.73	1.9	0.02
	Proton FB	21.8	3.59	4.5	0.03
	Proton DIBH	9.9	0.42	0.3	0.00
LADCA	IMRT FB	5.7	-	4.7	-
	IMRT DIBH	4.9	-	1.4	-
	Proton FB	3.4	-	1.8	-
	Proton DIBH	1.1	-	0.1	-
Lung	IMRT FB	10.5	0.66	7.8	0.27
	IMRT DIBH	7.9	0.49	4.6	0.16
	Proton FB	8.8	0.57	4.5	0.17
	Proton DIBH	6.0	0.39	2.6	0.10
Breast	IMRT FB	5.2	0.17	-	-
	IMRT DIBH	5.7	0.18	-	-
	Proton FB	1.3	0.05	-	-
	Proton DIBH	1.4	0.05	-	-

Table S4: Mean doses to organs at risk and corresponding life years lost (LYL) for patients 4 (female) and 10 (male), for which life years lost data is shown in Figure 4. LYL for the heart includes myocardial infarction and heart failure. No LYL data is given for the LADCA because it was not used during risk calculation. Abbreviations: LADCA: left anterior descending coronary artery, IMRT: intensity modulated radiation therapy, FB: free breathing, DIBH: deep inspiration breath hold.