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Objectives

Proton therapy for breast cancer patients has been demonstrated to be effective with low toxicities and potentially reduce late cardiovascular events. There is limited data in Asian population, hence this study aims to benchmark outcome for proton therapy in our local population and compare toxicity and dose-volume metrics with photon cohorts.

Methods

This retrospective study included Stage 0-4 breast cancer patients with definitive surgery followed by proton therapy to breast or chest wall with or without regional nodal irradiation (RNI), from July 2023 to March 2025 at the Hong Kong Sanatorium & Hospital (HKSH). Patients were treated with intensity modulated proton therapy (IMPT) with pencil-beam scanning with various fractionations (50Gy in 25 fractions, 40.05Gy in 15 fractions, 25Gy in 5 fractions). Propensity score matching was used in 1:1 ratio with conventional radiotherapy patients using tomotherapy or volumetric modulated arc therapy (VMAT) in 2020-2024. The primary endpoint was CTCAE 5.0 acute and late toxicity. Secondary endpoints included matched cohort analysis comparing toxicity and dose-volume metrics.

Results

158 proton therapy patients were analyzed, and 82 patients were matched in 1:1 ratio with photon cohorts. Patients were all Chinese with median age 51 years old (Range 24-84). 63% had left sided breast cancer, and majority (73%) of patients received 40.05Gy in 15 fractions (Table 1). Median-follow up time was 78 days (Range 10-619). Most common acute side effects were dermatitis (76% Grade 1, 19% Grade 2 and 3% Grade 3), fatigue (19% Grade 1, 1% Grade 3) and dysphagia (19% Grade 1, 1% Grade 2) (Table 1). Late side effects were dermatitis (56% Grade 1, 2% Grade 2-3), subcutaneous fibrosis (23% Grade 1) and chest wall pain (18% Grade 1). Proton therapy achieved a low mean heart dose 0.17Gy and V8-20Gy ipsilateral lung dose 4.38% across left and right-sided breast cancer patients, with and without RNI. Compared to photon cohorts, there is less acute Grade 2-3 dermatitis (20% vs. 30%, p=0.04), Grade 1 fatigue (24% vs. 43%, p=0.03) and breast edema (2% vs. 24%, p<0.01) in the proton cohort (Table 2). Significant improvement (p<0.01) in all parameters including mean heart dose (0.14Gy vs. 4.86Gy), V16-20Gy lung (3.52% vs. 17.18%), esophagus and contralateral breast were seen in proton cohort (Table 3).

Conclusions

This study demonstrated low toxicity and significant dosimetric advantage for proton therapy in Chinese breast cancer patients. Longer follow up is warranted for survival and late toxicity analysis.

Table 1. Characteristic and toxicity of proton-treated breast cancer patients at HKSH (n=158)

Age at diagnosis	
- Median (Range)	51 (24-84)
Days of follow-up (from start of radiotherapy)	
- Median (Range)	78 (10-619)
Radiotherapy laterality	
- Unilateral left	100 (63%)
- Unilateral right	50 (32%)
- Bilateral	8 (5%)
Overall stage	
- Stage 0	29 (18%)
- Stage 1	62 (39%)
- Stage 2	42 (26%)
- Stage 3	19 (13%)
- Stage 4	6 (4%)
Histology type	
- Ductal	132 (84%)
- Lobular	10 (6%)
- Others	16 (10%)
Triple negative	
- No	145 (92%)
- Yes	13 (8%)
Total dose (Number of fractions (fr))	
- 25Gy (5 fr)	12 (8%)
- 40.05/40.5Gy (15 fr)	116 (73%)
- 44Gy (22 fr)	1 (1%)
- 50Gy (25 fr)	29 (18%)
Nodal irradiation	
- Nil	99 (63%)
- SCF, AX, IMN	57 (36%)
- AX	2 (1%)
Simultaneous integrated boost	
- No	59 (37%)
- Yes	99 (63%)
Previous radiotherapy	
- No	145 (92%)
- Yes	13 (8%)

Toxicity grading [CTCAE 5.0]	Grade 0	Grade 1	Grade 2	Grade 3
Acute toxicity (n=157)				
Skin reaction / Dermatitis	3 (2%)	119 (76%)	30 (19%)	5 (3%)
Dysphagia	125 (80%)	30 (19%)	2 (1%)	0 (0%)
Breast / Chest wall pain	143 (91%)	14 (9%)	0 (0%)	0 (0%)
Lymphedema	155 (99%)	2 (1%)	0 (0%)	0 (0%)
Fatigue	126 (80%)	30 (19%)	0 (0%)	1 (1%)
Nausea / Vomiting	154 (98%)	3 (2%)	0 (0%)	0 (0%)
Mucositis	155 (99%)	2 (1%)	0 (0%)	0 (0%)
Breast edema	154 (98%)	2 (1%)	1 (1%)	0 (0%)
Anxiety	156 (99%)	1 (1%)	0 (0%)	0 (0%)
Hoarseness	156 (99%)	1 (1%)	0 (0%)	0 (0%)
Late toxicity (n=74)				
Skin reaction / Dermatitis	31 (42%)	41 (56%)	1 (1%)	1 (1%)
Subcutaneous tissue	57 (77%)	17 (23%)	0 (0%)	0 (0%)
Pneumonitis	74 (100%)	0 (0%)	0 (0%)	0 (0%)
Heart	74 (100%)	0 (0%)	0 (0%)	0 (0%)
Esophagus	74 (100%)	0 (0%)	0 (0%)	0 (0%)
Breast / Chest wall pain	61 (82%)	13 (18%)	0 (0%)	0 (0%)
Lymphedema	72 (98%)	1 (1%)	1 (1%)	0 (0%)
Fatigue	72 (98%)	2 (2%)	0 (0%)	0 (0%)
Breast edema	70 (95%)	4 (5%)	0 (0%)	0 (0%)

Table 2. Characteristic and toxicity of matched proton (n=82) and photon (n=82) breast cancer patients

	Proton (n=82)	Photon (n=82)	p-value
Age at diagnosis			
- Mean (SD)	51.7 (9.52)	51.9 (10.79)	0.915
Days of follow-up (from start of RT)			
- Median (Range)	104 (18-521)	224 (5-1706)	
Radiotherapy laterality			
- Left	50 (61%)	51 (62%)	0.775
- Right	29 (35%)	28 (34%)	
- Bilateral	3 (4%)	3 (4%)	
Overall stage			
- Stage 0	18 (22%)	19 (23%)	0.857
- Stage 1	35 (43%)	31 (38%)	
- Stage 2	22 (26%)	26 (32%)	
- Stage 3	7 (9%)	6 (7%)	
Histology type			
- Ductal	75 (92%)	72 (88%)	0.835
- Lobular	2 (2%)	2 (2%)	
- Others	5 (6%)	8 (10%)	
Triple negative			
- No	76 (93%)	78 (95%)	0.746
- Yes	6 (7%)	4 (5%)	
Total dose (Number of fractions (fr))			
- 25/26Gy (5 fr)	1 (1%)	1 (1%)	0.847
- 40Gy (15 fr)	66 (80%)	63 (77%)	
- 50Gy (25 fr)	15 (18%)	18 (22%)	
Nodal irradiation			
- Nil	58 (71%)	57 (70%)	0.896
- SCF, AX, IMN	22 (27%)	24 (29%)	
- AX	2 (2%)	1 (1%)	
Simultaneous integrated boost			
- No	27 (33%)	46 (56%)	0.003**
- Yes	55 (67%)	36 (44%)	
Previous radiotherapy			
- No	78 (95%)	80 (98%)	0.682
- Yes	4 (5%)	2 (2%)	

Toxicity grading [CTCAE 5.0]	Grade 0		Grade 1		Grade 2		Grade 3		p-value
Acute toxicity – Proton (n=82), Photon (n=82)									
Skin reaction / Dermatitis	Proton	Photon	Proton	Photon	Proton	Photon	Proton	Photon	0.04*
	0 (0%)	3 (4%)	66 (80%)	54 (66%)	13 (16%)	23 (28%)	3 (4%)	2 (2%)	
Dysphagia	70 (86%)	70 (85%)	11 (13%)	12 (15%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1
Breast / Chest wall pain	74 (90%)	69 (84%)	8 (10%)	13 (16%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.35
Lymphedema	82 (100%)	80 (98%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.497
Fatigue	61 (75%)	46 (56%)	20 (24%)	35 (43%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	0.03*
Nausea / Vomiting	81 (99%)	79 (96%)	1 (1%)	3 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.62
Mucositis	80 (98%)	81 (99%)	2 (2%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1
Breast edema	79 (97%)	62 (76%)	2 (2%)	20 (24%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.00004***
Hoarseness	81 (99%)	81 (99%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1
Late toxicity – Proton (n=42), Photon (n=53)									
Skin reaction / Dermatitis	14 (33%)	24 (45%)	27 (65%)	28 (53%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)	0.5
	29 (69%)	52 (98%)	13 (31%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	
Subcutaneous tissue	42 (100%)	53 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.00001***
Pneumonitis	42 (100%)	53 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1
Heart	42 (100%)	51 (96%)	0 (0%)	0 (0%)	0 (0%)	2 (4%)	0 (0%)	0 (0%)	0.501
Esophagus	42 (100%)	53 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1
Breast / Chest wall pain	85 (83%)	47 (77%)	6 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.552
Lymphedema	41 (98%)	52 (98%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0.691
Fatigue	41 (98%)	51 (96%)	2 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1
Breast edema	39 (93%)	42 (79%)	3 (7%)	11 (21%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.0827

Table 3a. Organ-at-risk (OAR) dosimetric parameters for proton-treated breast cancer patients (n=149, excluded cases of bilateral disease and partial breast irradiation), and OAR dosimetric comparison of matched photon (n=79) and proton-treated (n=79) breast cancer patients at HKSH (excluded cases with bilateral diseases)

Organ	Parameter		Proton (n=149)		Photon (n=79)		Proton (n=79)	
			Mean (Range)		Mean (Range)		Mean (Range)	p-value
Ipsilateral Lung	V20Gy (for 25fr), V16Gy (for 15fr) V8Gy (for 5fr)	%	4.38 (0-20.35)		17.18 (7.49-25.48)		3.52 (0-20.35)	< .00001****
	V10Gy (for 25fr), V8Gy (for 15fr), V5Gy (for 5fr)	%	9.44 (0.03-33.43)		33.53 (17.62-51.62)		7.74 (0.03-33.38)	< .00001****
	V5Gy (for 25fr), V4Gy (for 15fr)	%	17.04 (0.54-47.56)		61.61 (40.52-89.56)		14.15 (0.62-45.64)	< .00001****
Contralateral Lung	V5Gy (for 25fr), V4Gy (for 15fr), V4Gy (for 5fr)	%	0.58 (0-7.57)		31.73 (0-266.52)		0.34 (0-3.58)	< .00001****
Heart	D _{max}	Gy	18.47 (0.02-54.51)		28.33 (7.42-51.93)		17.10 (0.02-48.83)	< .00001****
	D _{mean}	Gy	0.17 (0-1.08)		4.86 (1.19-8.77)		0.14 (0-0.97)	< .00001****
Contralateral Breast	D _{mean}	Gy	0.51 (0.14-1.46)		7.07 (2.82-24.78)		0.50 (0.14-1.29)	< .00001****
Spinal Cord	D _{0.01cc}	Gy	2.11 (0-21.22)		8.25 (0.48-29.98)		1.59 (0-21.22)	< .00001****
Larynx	D _{mean}	Gy	2.32 (0.04-16.34)		1.65 (0.11-14.39)		1.57 (0.04-10.10)	< .00001****
Esophagus	D _{1cc}	Gy	11.18 (0.01-48.74)		10.11 (0.54-40.93)		8.39 (0.01-48.74)	< .00001****
	D _{0.01cc}	Gy	14.03 (0.08-51.89)		13.06 (0.61-48.03)		10.70 (0.09-51.14)	< .00001****
Rib Cage	D _{0.01cc}	Gy	44.50 (25.7-62.91)		45.88 (27.41-58.46)		45.33 (29.26-56.41)	0.18024
	D _{0.01cc}	Gy	44.82 (25.78-63.07)		46.07 (27.52-58.80)		45.68 (29.86-57.40)	0.29834
	V _{50%}	cc	78.87 (19.77-159.33)		179.34 (88.27-289.76)		73.77 (28.95-159.33)	< .00001****
Ipsilateral Humeral Head	D _{1cc}	Gy	8.21 (0-48.78)		16.02 (0.49-49.22)		6.65 (0-45.97)	< .00001****
	D _{0.01cc}	Gy	11.89 (0-51.19)		19.06 (0.60-50.70)		10.35 (0-50.79)	< .00001****
Skin Breast/Chest wall	D _{1cc}	Gy	43.63 (26.09-54.69)		44.44 (27.41-54.42)		43.63 (26.09-54.69)	0.0006***
Skin Boost	D _{1cc}	Gy	47.13 (29.11-59.92)		46.91 (40.34-61.74)		47.13 (29.11-59.92)	0.12114
Skin SCF	D _{1cc}	Gy	39.82 (31.13-48.92)		40.64 (23.37-51.75)		39.82 (31.13-48.92)	0.22628
Left Anterior Descending Artery (LAD)	D _{max}	Gy	5.53 (0-23.92)		22.82 (1.92-47.8)		5.56 (0-23.92)	< .00001****
	D _{mean}	Gy	0.79 (0-3.84)		9.92 (1.03-25.99)		0.77 (0-3.83)	< .00001****
	V _{15Gy}	%	0.13 (0-7.45)		21.39 (0-93.92)		0.10 (0-7.45)	< .00001****
Right Coronary Artery (RCA)	D _{max}	Gy	0.92 (0-13.6)		10.70 (1.76-23.03)		0.87 (0-13.60)	< .00001****
	D _{mean}	Gy	0.12 (0-1.88)		5.77 (1.25-14.71)		0.1 (0-1.88)	< .00001****
	V _{15Gy}	%	0.00 (0-0.03)		2.41 (0-65.08)		0 (0-0)	0.07508

Table 3b. Comparison of OAR parameters for the matched photon and proton-treated breast cancer patients at HKSH, subdivided into groups receiving 25 and 15 fractions

Organ	Parameter		Photon (25 fr) (n=16)		p-value	Photon (15 fr) (n=62)		p-value
			Mean (Range)	Mean (Range)		Mean (Range)	Mean (Range)	
Ipsilateral Lung	V20Gy (for 25fr), V16Gy (for 15fr)	%	18.49 (13.64-24.84)	7.37 (0.01-18.09)	0.0006***	16.81 (7.49-25.48)	2.72 (0-20.35)	< .00001****
	V10Gy (for 25fr), V8Gy (for 15fr)	%	36.67 (23.63-50.57)	13.41 (0.86-31.04)	< .00001****	32.81 (17.62-51.62)	6.57 (0.03-33.38)	< .00001****
	V5Gy (for 25fr), V4Gy (for 15fr)	%	67.04 (41.72-89.32)	20.61 (3.11-43.74)	< .00001****	60.21 (40.52-89.56)	12.74 (0.62-45.64)	< .00001****
Contralateral Lung	V5Gy (for 25fr), V4Gy (for 15fr)	%	32.69 (14.62-59.18)	0.49 (0-3.06)	< .00001****	31.91 (0-266.52)	0.31 (0-3.58)	< .00001****
Heart	D _{max}	Gy	34.00 (18.51-51.93)	32.30 (6.26-48.83)	0.88076	27.20 (10.13-39.75)	13.97 (0.02-42.03)	< .00001****
	D _{mean}	Gy	5.71 (3.91-8.77)	0.29 (0.02-0.75)	< .00001****	4.70 (1.19-7.17)	0.11 (0-0.97)	< .00001****
Contralateral Breast	D _{mean}	Gy	8.23 (5.34-14.38)	0.70 (0.24-1.29)	< .00001****	6.83 (2.82-24.78)	0.46 (0.14-1.2)	< .00001****
Spinal Cord	D _{0.01cc}	Gy	13.29 (3.29-28.52)	4.06 (0-21.22)	0.00096***	7.07 (0.48-29.98)	1.08 (0-12.73)	< .00001****
Larynx	D _{mean}	Gy	3.53 (0.33-14.39)	3.13 (0.15-9.06)	0.32708	1.16 (0.11-7.98)	1.23 (0.04-10.1)	< .00001****
Esophagus	D _{1cc}	Gy	14.79 (4.46-36.64)	19.00 (0.04-48.74)	0.84930	9.04 (0.54-40.93)	6.19 (0.01-39.47)	< .00001****
	D _{0.01cc}	Gy	21.10 (4.92-48.03)	23.24 (0.33-51.14)	0.78716	11.17 (0.61-42.84)	8.12 (0.09-40.96)	< .00001****
Rib Cage	D _{0.01cc}	Gy	55.03 (52.21-58.46)	52.84 (50.90-56.41)	0.00438**	43.81 (40.24-51.14)	43.94 (40.22-49.92)	0.25014
	D _{0.01cc}	Gy	55.29 (52.46-58.80)	53.15 (51.15-57.40)	0.00652**	43.99 (40.39-51.28)	44.30 (40.44-50.23)	0.45930
	V _{50%}	cc	191.48 (121.69-289.76)	81.64 (48.99-117.42)	< .00001****	175.89 (88.27-275.48)	72.19 (28.95-159.33)	< .00001****
Ipsilateral Humeral Head	D _{1cc}	Gy	28.05 (2.67-49.22)	17.10 (0-45.97)	0.07030	13.11 (0.49-41.77)	4.47 (0-27.52)	< .00001****
	D _{0.01cc}	Gy	31.92 (3.58-50.70)	21.74 (0.01-50.79)	0.27134	15.95 (0.60-43.18)	8.01 (0-34.64)	< .00001****
Skin Breast/Chest wall	D _{1cc}	Gy	52.93 (51.07-54.42)	52.28 (51.30-54.69)	0.02202*	42.53 (40.17-47.39)	42.01 (40.68-45.36)	< .00001****
Skin Boost	D _{1cc}	Gy	57.02 (52.63-61.74)	57.12 (50.91-59.92)	0.81034	44.71 (40.34-51.09)	45.98 (42.06-49.38)	0.00596**
Skin SCF	D _{1cc}	Gy	42.17 (26.83-51.75)	45.70 (41.93-48.92)	0.65994	39.12 (23.37-42.31)	36.87 (31.13-39.32)	0.00452**
LAD	D _{max}	Gy	27.82 (8.08-47.80)	9.57 (0.10-23.92)	0.00032***	21.81 (1.92-38.84)	4.74 (0-17.26)	< .00001****
	D _{mean}	Gy	12.08 (5.53-25.99)	1.48 (0.01-3.83)	< .00001****	9.49 (1.03-20.52)	0.62 (0-3.07)	< .00001****
	V _{15Gy}	%	27.49 (0-93.92)	0.56 (0-7.45)	0.00194**	20.16 (0-61.69)	0.01 (0-0.25)	< .00001****
RCA	D _{max}	Gy	12.72 (4.39-23.03)	1.43 (0.01-13.60)	< .00001****	10.32 (1.81-20.73)	0.76 (0-9.40)	< .00001****
	D _{mean}	Gy	6.39 (2.54-11.63)	0.28 (0-1.88)	< .00001****	5.68 (1.25-14.71)	0.06 (0-0.45)	< .00001****
	V _{15Gy}	%	3.42 (0-26.98)	0 (0-0)	0.25428	2.19 (0-65.08)	0 (0-0)	0.16152