What can proton beam therapy achieve for patients with pectus excavatum requiring left breast, axilla and internal mammary nodal radiotherapy?

Abstract

Background

Exposure of the heart to radiation increases the risk of ischaemic heart disease, proportionate to mean heart dose (MHD). Radiotherapy techniques including proton beam therapy (PBT) can reduce MHD. The study aims: to quantify the MHD–reduction achievable by PBT compared to volumetric modulated arc therapy in breath hold (VMAT–BH) in patients with pectus excavatum (PEx); to identify an anatomical metric from a CT scan that might indicate which patients will achieve the greatest MHD–reductions from PBT.

Method

Sixteen patients with PEx (Haller Index ≥2.7) were identified from RT-planning CT images. Left breast / chest wall, axilla (I-IV) and internal mammary node (IMN) volumes were delineated. VMAT and PBT plans were prepared, all satisfying target coverage constraints. Signed-rank comparison of techniques were undertaken for mean dose to: heart; ipsilateral lung; contralateral breast. Spearman's rho correlations were calculated for anatomical metrics against MHD–reduction achieved by PBT.

Results

Mean MHD for VMAT-BH plans was 4.1 Gy compared to 0.7 Gy for PBT plans. PBT reduced MHD by an average of 3.4 Gy (range 2.8–4.4 Gy) compared with VMAT–BH ($p<0.001$). PBT significantly reduced mean dose to ipsilateral lung (4.7 Gy, $p<0.001$) and contralateral breast (2.7 Gy, $p<0.001$). The distance (mm) at the most inferomedial extent of IMN volume (IMN to Heart distance) negatively correlated with MHD–reduction achieved by PBT (Spearman rho -0.88 (95% CI -0.96 to -0.67, $p<0.001$).

Conclusion

For patients with PEx requiring left sided breast and IMN radiotherapy, a clinically significant MHD–reduction is achievable using PBT, compared to the optimal photon technique (VMAT–BH). This is a patient group in whom PBT could have the greatest benefit.

Introduction

Radiotherapy is an important part of the multimodality treatment of breast cancer and plays a vital role in maximising local disease control, enabling safe breast conservation and contributing to better survival rates [1,2]. In high risk, early stage patients, the benefit of including internal mammary nodes (IMN) in the target volume has been confirmed, influencing change in radiation oncology practice [3–5]. Delivery of left sided loco-regional radiotherapy poses technical challenges in terms of delivering adequate dose to target tissues whilst minimising the dose to organs at risk (OAR) and therefore risks of late radiotherapy-related effects in heart, lung and contralateral breast [6,7]. Epidemiological data have shown rates of radiation-induced major coronary events increase linearly with mean heart dose (MHD), with no threshold below which patients are not at risk of late cardiac effects [8].

Achieving the balance between target volume coverage and heart-sparing is even more challenging in patients with pectus excavatum (PEx), an internal depression of the lower sternum leading to a reduced anteroposterior chest wall depth. This can cause an anatomical distortion of the heart and is often associated with sternal torsion [9]. The heart position tends to be closer to the ribs, such that the breast and IMN targets form an arch over its anterior surface, making it difficult to achieve a low dose to the heart. PEx has different degrees of severity. Clinically subtle cases are often not apparent until found incidentally on cross-sectional imaging. The Haller Index is a common measure of the degree of deformity in PEx, defined as the ratio of the maximum transverse intra-thoracic diameter divided by the minimum anteroposterior (AP) diameter on the same CT slice (**Figure 1**), taken at the point of maximal sternal depression [9]. A Haller Index (HI) of 2.7 is the upper limit of normal [10]. Estimates for the incidence of PEx range from 0.3% to 3.7% [11,12]. In the UK alone, around 35 000 women per year receive radiotherapy for breast cancer, of whom 13% meet the criteria for IMN treatment [13]. Using the mid-range of PEx incidence, it is estimated that the population requiring left sided IMN treatment will include around 50 PEx patients per year.

Studies demonstrate that the optimal photon technique for covering IMN but minimising heart / lung dose is volumetric modulated arc therapy in breath hold (VMAT–BH) [14,15]. Proton beam therapy (PBT) has the potential to decrease OAR doses further but is a more expensive technology with, as yet, no randomised data to support its use in the locoregional

LN setting. Quantification of dosimetric improvements from PBT versus optimal photons is an important step in identifying the subgroups with the most to gain from PBT. We hypothesised that the reduction in MHD from PBT versus optimal photon therapy would be greater in PEx patients than previously reported for patients with normal chest wall shapes. In the equivalent arm of the dosimetry study by Ranger *et al* comparing radiotherapy techniques in a normal chest wall shaped cohort, PBT achieved an average MHD–reduction of 2 Gy [14]. The minimum reduction was 0.5 Gy and maximum 3.5 Gy. Therefore, for PEx patients only, this study aims to quantify the difference in OAR doses planned using PBT versus VMAT–BH, expecting an average MHD–reduction of >3 Gy. Additionally, the study aimed to determine whether anatomical metrics, such as Haller Index, might predict those patients most likely to achieve the greatest MHD–reduction.

Method

Patient Selection and Target Definition

Twenty patients with PEx (defined for this study as HI ≥2.7), undergoing radiotherapy for breast cancer at a single institution, between August 2017 and October 2019, were contemporaneously identified by their oncologists. The patients had either been referred centrally due to pre-identified PEx on CT imaging at their local hospital, or their radiotherapy planning scans identified incidental PEx. Sixteen patients had provided written, informed consent specific to the use of their radiotherapy medical images for research and were included in the study.

Thirteen patients' radiotherapy planning scans were performed in breath hold (BH). The BH technique was either voluntary or Active Breathing Control (ABC) [16,17]. Three patients' radiotherapy planning scans were undertaken in free breathing (FB). The mix of BH and FB scans reflect their accrual for clinical purposes. The PEx patients represented a mix of breast only and locoregional target volumes, one was bilateral and eight patients were right sided. For the purposes of the study, all patients were planned as left-sided patients. It should be noted that for a left-sided breast and IMN radiotherapy treatment all patients would routinely be offered a breath hold technique [18]. The decision to include the patients with FB scans in the wider study reflects the clinical scenario that some patients cannot manage BH techniques.

__Figure 1__ Three axial radiotherapy planning CT images (BH scans) of patients with different severity of pectus excavatum. Patient A has a Haller Index (HI) of 3.4 (obtained by dividing measurements x/y at level of maximal sternal depression on sagittal reconstruction. Patient B has HI of 4.2, Patient C has HI of 4.9

Clinical target volumes (CTV) of left breast / chest wall, axilla levels I-IV and internal mammary nodes (IMN) were delineated on CT scans according to ESTRO consensus guidelines [19] by two experienced clinical oncologists (SS and AK). OARs contoured were: heart, left anterior descending (LAD) coronary artery, contralateral breast, lungs and humeral head (SS and LM). The mandatory target dose-volume constraints for breast / axilla and contouring of heart aligned with the nodal substudy of the FAST-forward trial [20]. LAD was contoured using Duane *et al*'s cardiac contouring atlas [21]. The prescription was for the moderately hypofractionated schedule of 40.05 Gy in 15 fractions over three weeks, as per UK standard practice [22]. Adjusting for fractionation schedule, but in keeping with IMN trial requirements, the volumetric constraint $V_{17\ Gy}$ was applied instead of $V_{20\ Gy}$ for both heart and ipsilateral lung [18,23]. The constraints and objectives are summarised in **Table 1**.

All patients had a VMAT and a PBT plan designed, optimised and evaluated using the Research Raystation Treatment Planning System (TPS) [RaySearch laboratories, Stockholm, Sweden]. The order of prioritisation was: 1) mandatory target coverage; 2) mandatory OARs 3) optimal target coverage; 4) optimal OARs. Initial optimisation settings for each technique are shown in Supplementary Material, Table S1.For the heart, the maximum equivalent uniform dose (EUD) for VMAT was initially set at 375 cGy, for PBT the maximum EUD was set at 100 cGy.

Table 1: Target volume and organ at risk constraints and objectives

Region of Interest*	Mandatory Constraint	Objective
Breast / Chest Wall Target Volume	$D_{95\%}$ >38 Gy	
Axillary Nodal Target Volume	$D_{90\%}$ >36 Gy	$D_{95\%}$ >38 Gy
IMN Target Volume	$D_{90\%}$ >36 Gy	$D_{95\%}$ >38 Gy
Heart	$V_{17\ Gy}$ <10%	Mean Heart Dose <6 Gy
Left Lung	$V_{17\ Gy}$ <35% Mean Dose <14 Gy	
Right lung	Mean Dose <4 Gy	
Right Breast Dose	Mean Dose <4 Gy	Mean Dose <3.5 Gy

**Target volume refers to PTV for VMAT plans and CTV (robustly optimised) for PBT plans. IMN: Internal Mammary Nodes. V_{17Gy} is Volume receiving 17 Gy. $D_{90\%}$ is Dose to 90% of volume.*

VMAT Planning

Planning Target Volumes (PTVs) were generated from the corresponding CTVs using 5 mm isotropic expansion margins. All target volumes were clipped 5 mm from the surface. To enable online CBCT verification, a single isocentre was chosen at the midpoint of the volume craniocaudally, <7 cm from midline and less than 30 cm from the couch, located in the ipsilateral lung. A two arc 6 MV plan was designed with maximum beam delivery time of 45 seconds per arc to enable breath hold technique. Starting gantry angles were 179^{o} to 310^{o} adjusted manually if necessary to avoid beam entry through the contralateral breast. 4005 cGy in 15 fractions was prescribed to the PTV median dose. Dose calculations used a collapsed cone TPS algorithm [24]. At this point, before clinical delivery at our centre, VMAT plans would undergo further robust optimisation to ensure superficial coverage and simulate breast swelling by creating three additional modified planning CT sets [25]. However, to compare techniques and use an equivalent robustness process for both VMAT and PBT plans, it was the optimised PTV-based VMAT Dose Volume Histogram (DVH) data from the single planning CT that were used in this analysis. Results comparing the robustly optimised VMAT plans for all figures are available in supplementary material.

PBT Treatment Planning

Intensity modulated pencil beam scanning PBT plans were prepared by combining all CTVs, with the isocentre set as the centre of this volume. A two beam plan, to maximise robustness, was designed with one beam anterior and one en face (0^{o} and 45^{o}) [26]. A 3 cm range shifter was used with a minimum air gap of 30 cm. Plans were multiple field optimised (MFO) using Monte Carlo for both optimisation and dose calculations with uncertainty set at 1.5%. Relative Biological Effectiveness (RBE) was applied automatically by TPS at 1.1. The prescription was for 4005 cGy(RBE) in 15 fractions, prescribed to the Median D50%.

Plans were generated using a method previously described for robust optimisation using a range uncertainty of +/-3.5% and set up uncertainty of 5mm [14].

Plan Evaluation and Statistical Analysis

Both VMAT and PBT plans had robust evaluation of the DVHs under uncertainty scenarios. All plans were subjected to 5mm patient shifts isotropically, PBT plans had an additional density uncertainty of +/-3.5% for each scenario (**Figure 2**).

The target and OAR DVH data from a PBT and VMAT plan for each of the 16 patients were analysed in GraphPad Prism™ 8.3.0. The cohort was analysed both as a combined group of breath hold and free breathing patients (n=16) and breath hold only patients (n=13). Normal distribution of the variables was examined visually by QQ-plots, and numerically by D'Agostino and Pearson tests. Wilcoxon signed-rank tests were used for pair-wise comparisons to allow conservative testing between a mix of normal and non-normally distributed variables. OAR doses were compared between the techniques with respect to: heart (mean dose and volume receiving 17 Gy ($V_{17\ Gy}$); ipsilateral lung (mean dose and $V_{17\ Gy}$); LAD coronary artery (maximum dose to 1% of volume, $D_{1\%}$); contralateral breast (mean dose) and humeral head (mean dose).

Anatomical Metrics

The Haller Index (HI) was measured on the planning CT scans at the outset of the study for each patient and defined inclusion in the study. Additionally, a single measurement was recorded for each PEx patient from an axial CT slice of the RT planning scan by a single observer: the distance (mm) from heart to thoracic wall at the medial, craniocaudal surface of the 4th rib (**Figure 3**: IMN to Heart distance). This point on the thoracic wall is the inferior border of the IMN Clinical Target Volume (IMN-CTV) according to the ESTRO consensus guidelines. The Haller Index and IMN to Heart distance were investigated for correlation with the MHD–reduction using PBT via the Spearman rho.

Using G*Power version 3.1 [27], a post hoc power calculation was performed for paired data from a parent normal distribution (approximation), using mean and standard deviation of the differences from the actual data (supplementary material). It showed that a sample size of 13 has power >99% to show a MHD–reduction > 3 Gy using PBT, therefore no further patients were accrued.

Results

Patient Characteristics

From the cohort of sixteen patients with pectus excavatum, eleven patients had undergone breast conservation surgery and five unilateral mastectomy. The patients' median Haller Index was 3.6 (range 2.7 to 6.5) and their median age was 46 years (range 36 to 72 years).

Data confirm satisfactory target coverage for the VMAT and PBT techniques (Table S2, supplementary material), including uncertainty evaluation (**Figure 2**). It is notable that, while minimum coverage for Axilla Target Volume constraint was set at $D_{90\%} > 36$ Gy, both techniques achieved the objective of $D_{95\%} > 38$ Gy in all 16 patients.

The mean MHD for VMAT-BH plans was 4.1 Gy compared to 0.7 Gy for PBT plans. The mean reduction in MHD was 3.4 Gy with PBT, compared to VMAT–BH (p<0.001) (Table 2). The MHD–reduction for PBT ranged from 2.8 Gy to 4.4 Gy. Statistically significant dose reductions for PBT compared to VMAT–BH were reported for all OARs. The number of patients in free breathing (n=3) was too small for separate analysis, however when they were included in the combined analysis of the whole PEx cohort (FB and BH) the dose reductions from PBT are slightly elevated: MHD–reduction 3.5 Gy (p<0.001), (**Figure 4**).

Table 2: Summary of dose statistics

Region of Interest	Dose Statistic	Technique	Dose Reduction* ***Mean***, Median (range)	p-value

Breath Hold patients n=13		VMAT ***Mean*** (range)	PBT ***Mean*** (range)		
Heart	Mean Dose (Gy)	***4.1*** (3.6; 5.4)	***0.7*** *(0.3; 1.0)*	***3.4***, 3.3 (2.8; 4.4)	**0.0002**
LAD	Max Dose (Gy)	***22.4*** *(7.6; 32)*	***14.4*** *(7.4;27.9)*	***8.0,*** 8.8 (-5.5; 19.4)	**0.0081**
Heart	$V_{17\ Gy}$ (%)	***1.4*** *(0.2; 3.4)*	***0.5*** *(0.0; 1.4)*	***0.9***, 0.7 (-0.5; 2.6)	**0.0024**
Lung (Left)	Mean Dose (Gy)	***13.2*** *(12.2; 13.7)*	***8.5*** *(7.7; 12.0)*	***4.7***, 5.0 (1.1; 5.6)	**0.0002**
Lung (Left)	$V_{17\ Gy}$ (%)	***32*** *(29; 34)*	***20*** *(18; 33)*	***12,*** 13 (-1; 16)	**0.0005**
Lungs	$V_{5\ Gy}$ (%)	***39*** *(35; 44)*	***22*** *(18; 31)*	***17**, 18 (7; 24)*	**0.0002**
Breast (Right)	Mean Dose (Gy)	***3.4*** *(3.2; 3.7)*	***0.6*** *(0.2; 1.3)*	***2.8***, 2.9 (2.2;3.1)	**0.0002**
Humeral Head (Left)	Mean Dose (Gy)	***5.8*** *(2.0; 10.1)*	***1.5*** *(0.3; 3.3)*	***4.4***, 4.0 (1.1; 8.9)	**0.0002**
Free Breathing patients, n=3		VMAT ***Mean*** (range)	PBT ***Mean*** (range)		
Heart	Mean Dose (Gy)	***5.0*** *(3.9; 5.8)*	***0.8*** *(0.5; 1.0)*	***4.2*** (3.5; 4.7)	**-**
LAD	Max Dose (Gy)	***18.4*** *(16.9; 20.4)*	***5.7*** *(2.9; 7.9)*	***12.7*** (8.9; 17.5)	**-**
Heart	$V_{17\ Gy}$ (%)	***2.9*** *(1.6; 4.5)*	***1.1*** *(0.3; 1.5)*	***1.9*** (1.2; 3.0)	**-**
Lung (Left)	Mean Dose (Gy)	***13.3*** *(13.3; 13.4)*	***7.8*** *(6.8; 8.5)*	***5.6*** (4.8; 6.5)	**-**
Lung (Left)	$V_{17\ Gy}$ (%)	***32*** *(32; 34)*	***18*** *(15; 20)*	***15*** (13; 18)	**-**
Lungs	$V_{5\ Gy}$ (%)	***43*** *(40;46)*	***19*** *(16;22)*	***24*** *(18; 28)*	**-**
Breast (Right)	Mean Dose (Gy)	***3.8*** *(3.4; 4.0)*	***0.6*** *(0.4; 0.8)*	***3.2*** (2.8; 3.4)	**-**
Humeral Head (Left)	Mean Dose (Gy)	***8.1*** *(6.2; 9.9)*	***1.7*** *(1.0; 2.3)*	***6.4*** (4.0; 9.0)	**-**

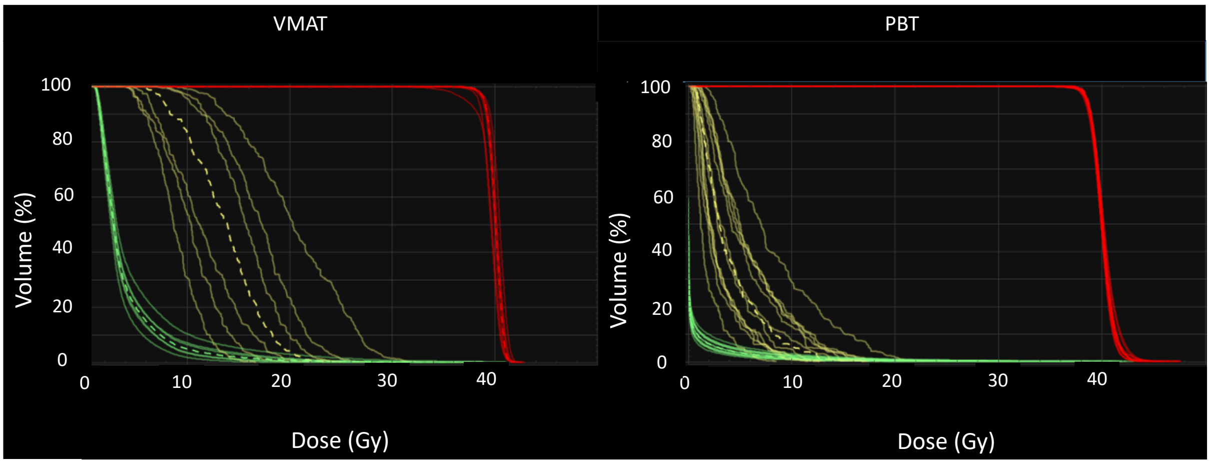

Figure 2*: Representative example showing Robust Evaluation of DVHs under uncertainty: 5mm set up for both (including +/- 3.5% range uncertainty for PBT). Combined CTV structure shown in red, LAD in yellow and heart in green. The nominal DVH is dashed line, each solid line represents a different scenario. Satisfactory coverage is maintained however LAD doses show variability in different scenarios for both techniques.*

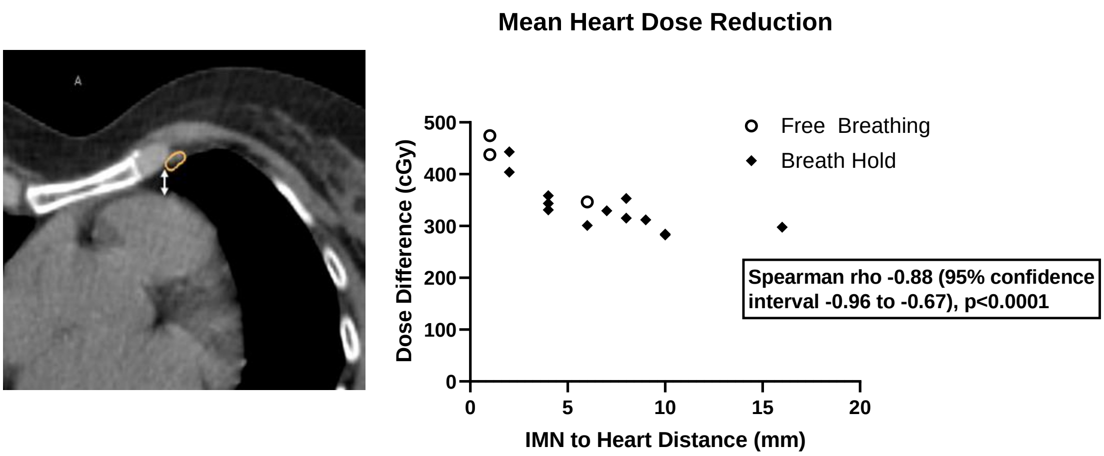

Figure 3: *IMN to Heart Distance indicated by the white arrow. On an axial CT scan this measurement (mm) is taken anteroposterior (AP) from the medial edge of the most inferior slice of CTV-IMN to the anterior surface of the heart. Scatter plot showing relationship between MHD reduction achieved by PBT and IMN to Heart distance.*

IMN: i*nternal mammary nodes;* ***MHD: M****ean Heart Dose;* ***CTV-IMN:*** *Clinical Target Volume of Internal Mammary Nodes;* ***VMAT:*** *Volumetric Modulated Arc Therapy****; PBT: P****roton Beam Therapy*

Anatomical Metrics Results

There was no statistically significant correlation between the Haller index and the magnitude of reduction in MHD using PBT (Spearman's rho 0.12, p=0.65).

For the combined (BH and FB) PEx cohort the distance from heart to thoracic wall at the medial, craniocaudal surface of the 4th rib (IMN to Heart distance) was strongly correlated with MHD–reductions achieved by PBT. Spearman's rho -0.88 (95% confidence interval -0.96 to -0.67, p<0.0001, **Figure 3**)

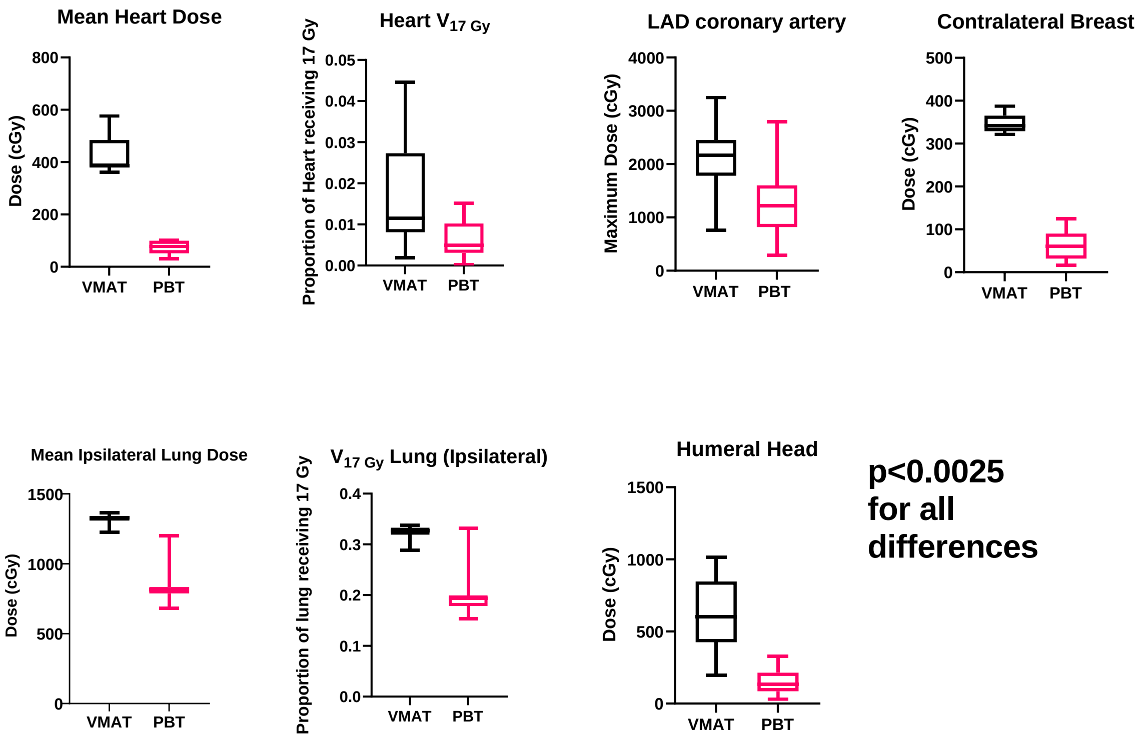

Figure 4: *Organs at risk Dose-Volume Histogram data for whole cohort (Breath Hold and Free Breathing combined), n=16*
$V_{17\ Gy}$: *Volume receiving 17 Gy (expressed as proportion of organ)* ***LAD:*** *Left Anterior Descending* ***VMAT:*** *Volumetric Modulated Arc Therapy;* ***PBT:*** *Proton Beam Therapy*

Discussion

The reduction in MHD achieved using PBT, compared to VMAT, for breast and locoregional radiotherapy for a patient in the breath hold cohort with PEx was on average 3.4 Gy. The minimum reduction in MHD achieved being 2.8 Gy and the maximum 4.4 Gy. Minimising MHD is desirable as the risk of major coronary events in patients irradiated for breast cancer increases by 7.4% per Gy [8]. The reduction in MHD seen with PBT-usage, equates to a clinically meaningful absolute risk reduction for death from ischaemic heart disease (IHD). For example, applying the tables provided by Darby *et al*, when MHD is reduced from approximately 4.1 Gy (with VMAT) to 0.7 Gy (with PBT) for a 50 year old woman. If no pre-existing cardiac risk factors exist, the absolute reduction in risk of death from IHD at 80 years is 0.5%, and for a woman with at least one risk factor, such as diabetes or hypertension, 0.8% [8]. The absolute reduction in risk of radiation related disease by the age of 80 for a 50 year old with no risk factors is 1.2% and with at least one risk factor is 1.9% [8].

Maximum dose to LAD was included in the comparison as cardiac substructure doses are likely to be important in subsequent risk of cardiac event and it has been shown these can be high even in the context of acceptable MHD in photon studies [28]. A maximum dose to LAD exceeding 20 Gy with conventional radiotherapy has been used as one of the indications for entry to a Phase II trial of breast PBT [29]. The cohort study by Van den Bogaard *et al* suggested the volume of left ventricle receiving 5 Gy was a better predictor of acute coronary events in the first decade after treatment [30]. However, their data support the use of MHD as the most validated dose metric for radiation related cardiac disease therefore it was the primary endpoint of this study.

Aside from MHD, PBT achieved statistically significant dose reductions across all OARs with the potential for risk reduction in other late effects of radiotherapy such as lung fibrosis, secondary malignancy or arm / shoulder problems. Taylor et al estimated the Excess Rate Ratio (ERR) for a radiation induced lung malignancy as 0.11 per Gy whole lung dose [6]. For a PEx patient, accounting for the different lung doses between cohorts, this approximates to a relative risk (RR) of 2.5 for VMAT compared to RR of 1.9 for PBT for a lung malignancy induced by radiation. This does not take into account the additional risk from smoking, which substantially elevates both cardiac and second malignancy risks.

There is a higher risk of a second primary breast cancer in young women (< 40 years) following RT if dose to any quadrant of the contralateral breast exceeds 1 Gy [7]. For a left sided VMAT plan, the greatest risk is to the upper inner quadrant of the contralateral breast, where PBT could decrease the risk six fold [31]. This risk is likely to be even higher if applied to the PEx cohort as mean contralateral breast dose is greater and it is a dose-dependent model. It is likely that there is also a dose-response relationship for arm / shoulder toxicity although no validated models are available currently.

VMAT is able to achieve target coverage goals and acceptable OAR doses in PEx patients. A limitation of this study is that OAR doses might represent an underestimate as no tumour bed boost was planned in the conserved breasts. In addition, PBT is not widely delivered in breath hold. Still, OAR dose reductions are likely to be maintained using PBT in free breathing. Patel *et al* compared different PBT techniques with photons (Wide Tangents in BH) with and without breath hold in a group with unfavourable cardiac anatomy, finding no significant difference between the PBT techniques with the addition of BH [32]. Although the number of FB PEx patients in this study was too small for separate statistical analysis, the data support previous findings that MHD results for PBT-FB are similar to PBT-BH. Also, that MHD–reduction increases when VMAT-FB is compared to PBT-FB [14], an important consideration for a patient that cannot manage BH techniques.

In our study Haller Index did not correlate with MHD on a VMAT plan or MHD–reduction with PBT, unlike a previous case series of left sided breast patients (PEx and normal shapes combined) [12]. One possible reason is that the Haller Index measurements are from the point of lowest sternal depression, which may not be relevant to the Breast and IMN clinical target. For example, patient B in **Figure 1** has HI measurements taken at the lowest extent of the breast volume. Additionally, it should be acknowledged that subtle differences in HI may occur if measured on a FB or BH scan, a variable that was not possible to explore without FB and BH scans for each patient.

Lee *et al*'s study of anatomic metrics used the number of axial CT slices in contact with the heart to define unfavourable cardiac anatomy and showed that it was correlated with higher MHD [33]. Lohr *et al* used minimal distance of heart to thoracic wall and/or PEx to define patients as having “unfavourable anatomy” for their dosimetry study comparing photon techniques [34].As a comparison, considering BH patients only, the IMN to Heart distances measured on the HeartSpare Plus normal shaped cohort averaged 14 mm, compared to 7mm in this PEx cohort. Further exploratory analysis of IMN to Heart measurement in this cohort is shown in Figure S5.

In terms of achieving MHD–reduction using PBT, there remains a spectrum of unfavourable anatomy within our cohort of PEx patients, in whom the minimum reduction was 2.8Gy, the smallest IMN to Heart distances correlating with the largest gains.

Conclusion

For patients with PEx requiring left sided breast and nodal radiotherapy that includes IMN, a clinically significant MHD–reduction is achievable using PBT compared to the optimal photon technique (VMAT–BH). This is likely to be a patient group in whom PBT could have the greatest benefit.

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