Estimating late toxicities based on multivariable NTCP models in patients of high-risk prostate cancer requiring pelvic nodal irradiation: Comparison between Proton beam therapy and helical tomotherapy

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Abstract

Purpose:

To compare the estimated late gastrointestinal (GI) and genitourinary (GU) toxicities between pencil beam scanning proton bream therapy (PBT) and helical Tomotherapy (HT) in patients of high-risk prostate cancers requiring pelvic nodal irradiation (PNI) using moderate hypo-fractionated regimen.

Materials and Methods

Twelve consecutive patients treated with PBT at our centre were re-planned with HT using the same dose prescription and constraints. Late GI and GU toxicities were estimated based on the published NTCP models using clinico-dosimetric parameters. ΔNTCP (difference in absolute NTCP between HT and PBT plans) for each toxicity domains for all patients were calculated. Based on ΔNTCP, model-based selection (MBS) thresholds for PBT were applied on the dataset. One-Sample Kolmogorov-Smirnov test was used to analyze distribution of data and either Paired T-test or Wilcoxon matched-pair signed rank test was used to test statistical significance.

Results

PBT and HT plans achieved adequate target coverage. PBT plans led to significantly better sparing of bladder, rectum and bowel bag especially in the intermediate range of 15-40Gy; whereas doses to penile bulb and femoral heads were higher with PBT plans. The average ΔNTCP for grade(G)2-rectal bleeding, G2-fecal incontinence, G2-stool frequency,

G2-dysuria, G2-urinary incontinence and G1-hematuria were 12.17%, 1.67%, 2%, 5.83%, 2.42% and 3.91% respectively favoring PBT plans. The average cumulative ΔNTCP for GI and GU toxicities (ΣΔNTCP) were 16.58% (8.25-24.95; 95% CI) and 11.41%(6.8-16.05) respectively favoring PBT. On applying the MBS threshold of any G2 ΔNTCP >10%, 8 (67%) patients would have qualified for PBT.

Conclusion:

PBT plans led to superior OAR sparing compared to HT which translated to lower NTCP for late moderate GI and GU toxicities in patients of prostate cancer treated with PNI. For two-thirds of our patients, the difference in estimated absolute NTCP values between PBT and HT, crossed the accepted threshold for minimal clinically important difference.

Introduction

Elective pelvic nodal irradiation (PNI) in high risk prostate cancers has been a long-standing controversy (1). Most international guidelines (2, 3) support this on the basis of the previously reported prospective and retrospective studies, including a recently published randomized controlled trial (RCT) (4). However, PNI has been associated with a mild to moderate increase in late gastrointestinal (GI) and genitourinary

(GU) toxicities as demonstrated by results from the two randomized trials incorporating modern hypofractionation regimens (5, 6). Traditionally, the major focus during prostate radiotherapy planning has been to reduce the higher doses (> 65Gy EQD2) received by normal bladder and rectal mucosa. However, there is now a growing recognition regarding intermediate doses (30-50Gy) received by bladder, rectum, pelvic musculature and other sub-structures impacting the severity of physician reported late GI and GU toxicities (7–9).

Currently, there are no published RCTs comparing protons and IMRT for prostate cancers. Retrospective studies comparing these techniques in prostate only radiation have not shown clinically significant differences either in biochemical control or toxicities (10, 11). However, most proton data comes from studies using passive scattering technique with or without image guidance compared to photon data which mostly incorporates modern image guided IMRT. Although dosimetric studies comparing these techniques, have demonstrated superiority of PBT plans especially with regards to intermediate doses received by bladder, rectum and small bowel, most of them have evaluated patients not receiving PNI (12–14). High risk prostate cancers are also excluded from the two ongoing RCTs comparing PBT with IMRT (15, 16). In the absence of RCTs, model-based approach has been proposed as a modality for patient selection for PBT (17). However, this approach has been not been attempted for patient selection in prostate cancer especially in high-risk setting.

Our study compares the dosimetry between pencil beam scanning PBT with that of helical tomotherapy (HT) in patients of high-risk prostate cancers requiring PNI using a moderately hypofractionated regimen. Dose volume parameters achieved in these comparative plans were used to estimate late toxicities based on normal tissue complication probability (NTCP) models previously published in the literature (8, 9). Using the same, we have also attempted to estimate the percentage of our patients suitable for PBT based on acceptable model based selection thresholds (18).

Methods And Materials

Clinical and dosimetric data of 12 consecutive patients diagnosed and treated with PBT for high-risk prostate cancers and requiring PNI were included in this study. The patient images were used to make rival HT plans.

Simulation

Patients were simulated in supine position with indexed knee and ankle support with a partially filled bladder using institutional bladder protocol. Per rectal examination was performed to determine the level of prostate and a saline filled endorectal balloon (ERB) was inserted up to the base of prostate. A plain CT scan from D12 to mid-thigh with 2mm slice thickness was obtained. Subsequently, volumetric MR imaging of the pelvis was also obtained with the same protocol including the ERB.

Volume definition

The CT and MR images were exported to RayStation Treatment Planning System (TPS), Version 9A (RaySearch Laboratories AB, Stockholm, Sweden) for delineation of targets and organs at risk (OAR). CT and MR images were co-registered before volume definition. The entire prostate gland with or without bilateral seminal vesicles were outlined as high-risk clinical target volume (CTV-HR). Pelvic lymph nodes including bilateral obturator, internal iliac, external iliac, pre-sacral up to S3 level and common iliac lymph nodes were defined as low risk CTV (CTV-LR). OAR defined for dose optimization included rectum, bladder, femoral heads, penile bulb, anal canal and bowel bag. The rectal and bladder wall were defined as the outermost 3mm of rectum and bladder respectively (19). Trigone of urinary bladder, anorectum, external sphincter, ilio-coccygeus and levator ani were contoured (19) (Table 1, Fig. 1) to obtain dosimetric parameters for NTCP estimation.

Treatment planning

All patients were planned to a dose of 50Gy in 25 fractions to CTV-LR with a simultaneous integrated boost of 68Gy to CTV-HR. The planning target volumes (PTV-HR and PTV-LR) for each of the CTV's were generated using a uniform geometric expansion of 5mm except posteriorly for CTV-HR which was expanded to 3mm towards the rectum. This margin recipe was based on our institutional practice of daily on-board image guidance using cone beam CT scans with ERB and bladder protocol. The dose-volume goals to the targets and constraints to OAR's for treatment planning were as per our institutional protocol and were same for HT and PBT plans.

Proton beam therapy plan

Two lateral fields (90° and 270°) were used to generate multi-field optimized plans wherein both fields treated the prostate/seminal vesicles and the relatively central portion of CTVLR (common iliac/pre-sacral nodes) while each individual fields treated lateralized portion of ipsilateral CTVLR. In obese patients with skin folds in the beam path due to abdominal sag, a 5*°/10* posterior gantry angle tilt (95° and 265° degree) was used to avoid skin folds. All doses for PBT plans were expressed as Cobalt Gray equivalent (CGE) assuming a uniform radiobiological equivalence (RBE) of 1.1. The spot spacing was set to 1.06 times the average projected sigma multiplied by scaling doctor of 1. Plans were optimised to cover 100% of CTV with the prescribed dose, except at the CTV-rectum interface (at least 95% of prescribed dose). All CTV's were robustly optimised for 5mm translational errors and 3.5% range uncertainty using minimax robust optimization. Dose calculation was performed for grid size of 3mmx3mmx3mm. Monte Carlo Algorithm (Version 4.4) was used for dose optimization and calculation. For proton planning, PTV's were used solely for dose comparison and reporting.

Helical Tomotherapy plan

The planning CT and the structure set containing the targets and OARs were exported to Precision TPS (V 2.0.1.1, Accuray Inc., Sunnyvale, USA) from Raystation TPS. For the study, HT plans were generated using a field width of 2.5cm, pitch of 0.41 & modulation factor of 2.0 to minimize the thread effect. These were generated using a least squares minimization function for optimization and a convolution-superposition

algorithm for dose calculation. All plans were optimized to achieve similar target coverage as achieved by PBT plans.

NTCP estimation

Bladder and rectal toxicities were estimated based on NTCP models published from University of Groningen (8, 9), using the equation:

$$NTCP = \frac{1}{(1 + e^{-S})}$$

where S is a value defined based on the parameters and their respective regression coefficient mentioned in Table 2 for a specific toxicity. Since the NTCP models were based on conventional dose fractionation, all dose parameters obtained were converted to 2Gy dose equivalents using the BED formula (20). Absolute difference in NTCP values between HT and PBT was represented as ΔNTCP for each of the toxicity domains.

Statistical Analysis

Dosimetric parameters used for comparison were D95, D98, D2 for PTV-HR; D99, D100 for CTV-HR; D95 for PTV-LR and D99 for CTV-LR. For urinary bladder and rectum, incremental doses received by specified volume of each of the structure; and for other OARs, mean dose of penile bulb, V30 of femoral heads and V45 of bowel bag were used for dosimetric comparison. One-Sample Kolmogorov-Smirnov test was used to analyze distribution of data and based on that either a Paired T-test or a Wilcoxon matched-pair signed rank test was used. Statistical analysis was done using IBM SPSS Statistics Version 26.

Results

Target volume dosimetry

Table 3 shows the median dose and standard deviation among the twelve patients for various dosimetric parameters for CTVHR/PTVHR and CTVLR/PTVLR. All PBT and HT plans achieved adequate target coverage satisfying all the pre-treatment coverage goals. The difference in dose coverage parameters between the two modalities was not statistically significant except for CTVD99 ($p = 0.00$) in the low risk region and PTVD95 in the high ($p = 0.016$) and low risk regions ($p = 0.00$).

OAR dosimetry

Figure 2a and 2b show rectal and bladder dosimetry from V15 to V65 with 5Gy increments.

The difference in average doses between PBT and HT plans for each of the dose volume parameters for both bladder and rectum were statistically significant for all dose volume parameters in favor of PBT. The doses received by penile bulb (mean dose) and bilateral femoral heads V30 were significantly higher in PBT plans whereas V45 for the bowel bag was significantly higher in HT plans as shown in Table 3.

NTCP comparison

Among the 12 patients included in this study, 5 patients had cardiovascular ailments, 4 on anti-coagulants and 5 had undergone channel transurethral resection of prostate before the treatment. The average risk for rectal bleeding (grade II), fecal incontinence (grade II) and stool frequency (grade II) for PBT and HT plans were 13.75% vs. 3.25%($p = 0.002$), 2.58% vs. 0.17% ($p = 0.016$) and 2.25% vs. 0.25%($p = 0.007$) respectively. Similarly, the average risk for dysuria (grade II), urinary incontinence (grade II) and hematuria (grade I) for PBT and HT plans were 15.08% vs. 9.25%($p = 0.011$), 12% vs. 10.33% ($p = 0.023$) and 8.41% vs. 4.5%($p = 0.024$) respectively. Figure 3a shows ΔNTCP of each toxicity with mean and distribution with 95% confidence intervals. The average cumulative ΔNTCP for GI and GU toxicities (ΣΔNTCP) were 16.58%(8.25–24.95%) and 11.41%(6.8-16.05%) respectively favoring PBT (Fig. 3b). Based on an eligibility criteria of any G2 ΔNTCP > 10% or a ΣΔNTCP > 15% with each G2 ΔNTCP > 5%, 8 of 12 (67%) patients were found to be eligible (Fig. 4). With a more stringent criteria of cumulative ΔNTCP > 20% and with any G2 ΔNTCP > 10%, 7 of the 12 (58%) patients were eligible for PBT.

Discussion

We compared PBT and HT plans of the initial 12 consecutive patients of high-risk prostate cancers requiring PNI treated at our centre. We found that PBT plans led to better sparing of OAR's such as bladder, rectum and bowel bag. There were large differences in rectal and bladder doses between PBT and HT plans in the intermediate dose range between 15-40Gy. To quantify the impact of dosimetric difference on physician reported toxicity outcomes, we have estimated the NTCP using previously published models (8, 9) based on IMRT treatments. Based on the NTCP models that were used, PBT plans led to a significant reduction in the average risk of G1 hematuria, G2 dysuria and urinary incontinence; G2 rectal bleeding, stool incontinence and frequency. We also found that based on the estimated NTCP values, two thirds of our patients would qualify for PBT if the patients were selected using the Dutch consensus PBT eligibility criteria of any G2 ΔNTCP ≥ 10% or ΣΔNTCP ≥ 15% with each G2 ΔNTCP ≥ 5% (18) .

Most published photon studies reporting toxicity for patients treated with PNI have shown increased acute GI, late GI and GU toxicities (21, 22) with a few studies showing no significant differences (23, 24). The recent randomized studies (PIVOT and POP-RT) incorporating contemporary hypofractionated image-guided IMRT schedules, have also shown either increased late GI or late GU toxicities (5, 6). The authors of the POP-RT study that compared prostate only vs. prostate and pelvic RT, have hypothesized that increased late GU toxicities noted in the pelvic RT arm, could possibly be related to increase in the intermediate doses (volumes receiving 30-50Gy) received by urinary bladder. A similar finding of correlation of G3 GU toxicity with volume of urinary bladder receiving 30-40Gy was observed in a large retrospective study evaluating long term outcomes of dose escalated image guided PBT (25). Intermediate doses of 30-50Gy to rectum have also been associated with increased bowel frequency, rectal pain, tenesmus, and fecal incontinence (7). PBT by reducing the intermediate doses to the OARs, can potentially reduce the above-mentioned late GI and GU toxicities in the setting of PNI.

PBT's potential of reducing the doses to rectum and bladder were evaluated in two other previously reported PBT vs. IMRT dosimetric comparative studies in patients receiving PNI (26, 27). All the three studies including ours noted a significant reduction in the rectal and bladder doses especially at the low to intermediate dose ranges. Unlike our study and the one by Whitaker et al, the study by Chera et al evaluated patients who received phased conventionally fractionated treatments (to pelvis to a dose of 46Gy followed by a boost to prostate to a total dose of 78Gy) and used passive scattering proton therapy plans. Unlike other studies, we have used ERB which improves the setup reproducibility as it ensures stabilization of prostate between the balloon and the pubic bone. Also, in the presence of a rectal balloon, the actual delivered doses are likely to be close to the planned doses to target and OARs (28). Although the doses to rectum and bladder were significantly lower in the PBT plans, the doses to femoral heads were recorded to be higher across the three studies due to the use of lateral or lateral oblique fields. A similar trend was observed for penile bulb doses in our study, probably due to a larger lateral penumbra. However, the dose to penile bulb could potentially be reduced if a different beam arrangement such as posterior or posterior obliques were used. Despite relatively small increase in doses to the femoral heads and penile bulb in PBT plans, they were well within the planned dose constraints.

Our study also recorded doses to pelvic musculature, external anal sphincter, anorectum and trigone of bladder and they were used to estimate NTCP for late rectal and urinary complications. Most published NTCP models have used older dose regimens, older techniques, conventional dose fractionation and have estimated higher grade toxicities based on high doses received by OARs (28). These models are almost exclusively based on prostate only radiotherapy including the recently published "proton only" NTCP model (29). Among the several published NTCP models for estimating late toxicities (28) after radiation for prostate cancer, we have used the models from University of Groningen (8, 9) which were based on patients treated uniformly with contemporary doses (78Gy) and technique (IMRT). Although these models were based on prostate only radiation, they estimated multiple moderate (grade 1–2) toxicity endpoints (G1 hematuria, G2 dysuria, G2 urinary incontinence; and G2 rectal bleeding, G2 stool frequency, G2 fecal incontinence) and have demonstrated the impact of doses to several sub-structures. These models have also incorporated the impact of anticoagulant use and cardiovascular disease which has been shown to impact rectal bleeding and hematuria across several studies (30, 31).

The NTCP estimates of the photon plans reported in our study were similar to the toxicities reported in literature (21–24). However, the incidence of G2 urinary incontinence noted in our study, although was similar to the reported incidence in Schaake, et al (12%), it is higher than that reported in the literature (< 5%). It is possible that the model over-estimated the incidence of this toxicity. Although the average risk of all the estimated toxicity domains were significantly lower in PBT plans, the average absolute ΔNTCP for only G2 rectal bleeding and G2 dysuria were more than 5%. However, it needs to be noted that the average ΔNTCP values can potentially under-estimate the benefit of PBT in certain patients. For example, average ΔNTCP of G2 dysuria and G1 hematuria with PBT were 5.83% and 3.91% respectively, but 42% of patients had a ΔNTCP ≥ 9% for both domains.

The model-based selection for PBT has been proposed as an alternative to the standard RCTs. It has been shown that, validated NTCP models for predicting G2 and G3 toxicities in head neck cancers can be used to select patients for PBT (32) using accepted NTCP thresholds. These thresholds have been based on a consensus of Dutch society of Radiation Oncologists (18) The same is being contemplated for other sites such as lung cancers, left sided breast cancers and prostate cancers using similar NTCP thresholds (33). We have attempted to use the same for our cohort of high-risk prostate cancers. Based on these observed NTCP values, we found that 67% of the patients in our study would be eligible for PBT using a threshold of any G2 $\Delta NTCP \geq 10\%$ or cumulative $\Delta NTCP > 15\%$ with each G2 $\Delta NTCP > 5\%$. Using a more stringent criteria of cumulative $\Delta NTCP > 20\%$ and with any G2 $\Delta NTCP > 10\%$, 58% of patients would still be eligible for PBT.

However, this approach has several limitations. Most NTCP models are based on physician reported toxicities which are known to be under-reported and are based on single institutional experience. Also, most models are also based on patients treated with conventional dose per fraction. Extrapolation of these models to hypofractionation and for proton therapy may introduce inaccuracies. It has also been seen that with use of variable RBE values, there could be a significant under or over estimation of toxicities (34). Since the models used in our study are based on prostate only RT, they may not have captured the impact of reduction in intermediate doses to OARs by PBT. This emphasizes the need for more reliable and long-term prospective or retrospective data of representative cohorts to build robust multivariable NTCP models. These models will also need to be externally validated on separate patient cohorts, to be able to use them for making clinical decisions on a day to day basis (35).

Conclusion

On dosimetric comparison between HT and pencil beam scanning PBT for high risk prostate cancer patients requiring PNI, PBT plans were dosimetrically superior with respect to bladder and rectal doses especially in the range of 15-40Gy. Based on the dose volume parameters achieved in this study, PBT plans predicted lower mild to moderate GU and GI toxicities compared to HT plans. For two-thirds of our patients, the difference in estimated absolute NTCP values between PBT and HT, crossed the accepted threshold for minimal clinically important difference.

Declarations

Ethics approval and consent to participate: We confirm that this study is approved by the institutional ethics committee.

Consent for publication: Yes

Availability of data and material: Yes

Competing interests: None

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Authors' contributions: Conceptualized by SC and SS, data collection by SC,SS, KP, MS, RS,MA,DS,RJ, Manuscript preparation by SC,SS, PP.

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Tables

Table 1

OAR delineation guidance

Organs at risk	Cranial	Caudal	Lateral	Comment
Trigone	Vesico-ureteric junction (VUJ)	Urethra	Area between right and left VUJ	Triangular area
External sphincter	2-3cm above the anal marker	Anal marker	Wraps around the rectum	Cylindrical structure
Ilio-coccygeus	Posterior edge of ischial spine	Merges with levator ani complex	Between ischial spine and wraps around rectum	V shaped sling structure
Levator ani	Inner surface of ischial spine	Upto external sphincter	Inner surface of ishial spine	U shaped sling structure

Table 2

Parameters for NTCP estimation and respective regression coefficients

	Constant	Variables	Regression co-efficient
Rectal bleeding (Grade II)	-8.09	Anorectum V70	0.32
		Anticoagulant use	1.19
Fecal incontinence (Grade II)	-7	External sphincter V15	0.064
		Iliococcygeus V55	0.015
Stool frequency (Grade II)	-7.78	Iliococcygeus V45	0.027
		Levatoranii V40	0.046
Urinary Incontinence (Grade II)	-9.67	Trigone Mean	0.1015
Hematuria (Grade I)	-3.45	Bladder wall V75	0.028
		Anticoagulant use	1.15
Dysuria (Grade II)	-3.87	Trigone V75	0.021
		Transurethral resection of prostate (TURP)	1.06

Table 3

Dosimetric comparison between PBT and HT for targets and OARs

Modality	**Helical Tomotherapy**		**Proton therapy (PBS-IMPT)**		
High risk target volume					
	Median (Gy)	Std. dev. (cGy)	Median (Gy)	Std. dev. (cGy)	p-value
PTV D95	67.52	24.43	67.81	31.13	0.016
PTV D98	67.03	101.75	67.04	107.49	0.315
PTV D2	69.58	50.25	70.21	106.41	0.236
HI	0.05	0.012	0.044	0.027	0.866
CTV D99	67.94	14.25	67.84	13.08	0.196
CTV D100	67.37	19	67.54	19.68	0.191
Low risk target volume					
	Median (Gy)	Std. dev. (cGy)	Median (Gy)	Std. dev. (cGy)	p-value
PTV D95	49.49	6.3	4990	6.5	0.000
CTV D99	49.57	5.8	4994	5.9	0.000
Organs at risk (OAR)					
	Median	Std. dev.	Median	Std. dev.	p-value
Penile bulb Dmean (Gy)	28.46	9.51	40.56	10.18	0.000
Femoral head Left V30 (in %)	7.2	4.94	17.45	9.31	0.004
Femoral head Right V30 (in %)	7.2	5.3	16.9	12.16	0.016
Bowel bag V45 (in cc)	130.65	106.84	106.75	98.27	0.031

Figures

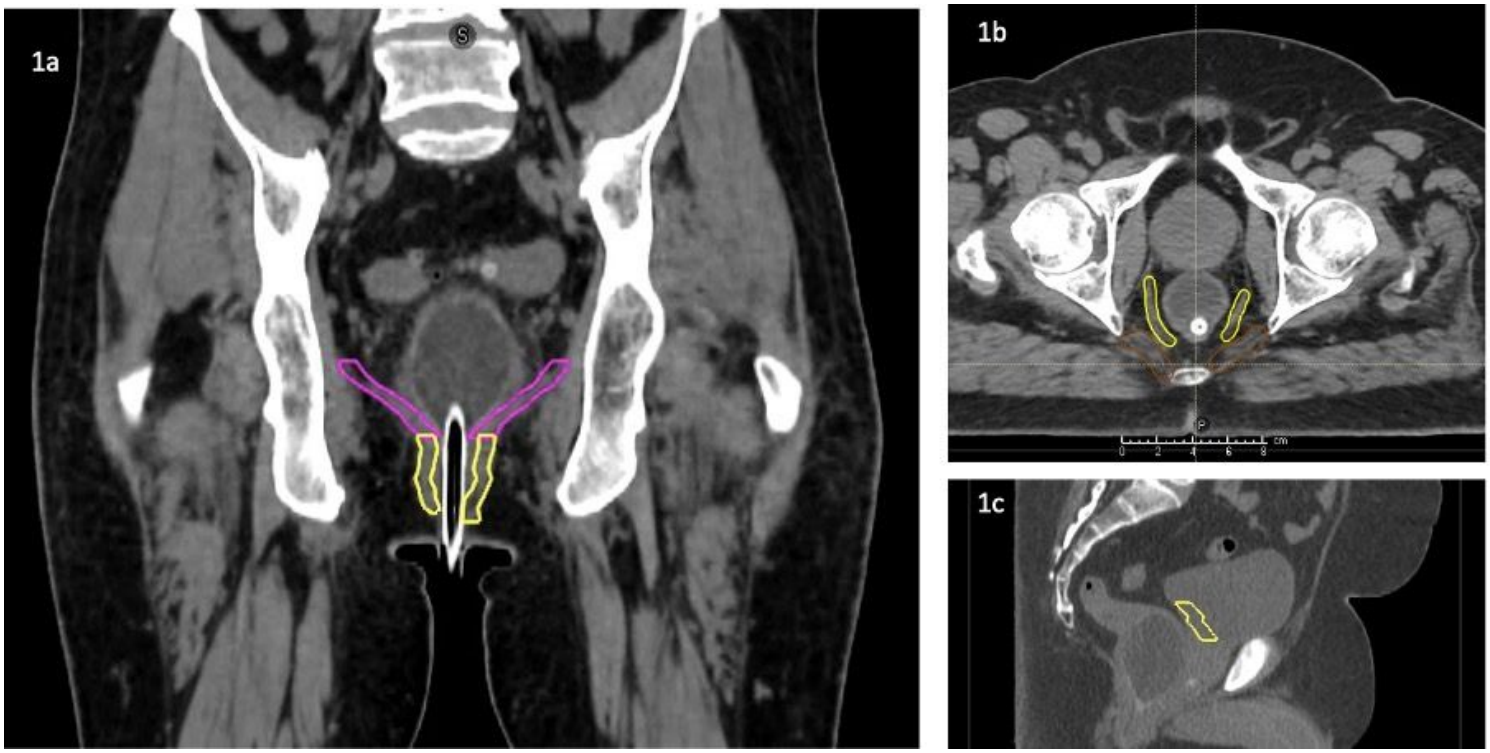

Figure 1

a: Coronal view of the levator ani complex and external anal sphincter b: Axial view showing Levator ani and ilio-coccygeus c: Sagittal view showing trigone of urinary bladder

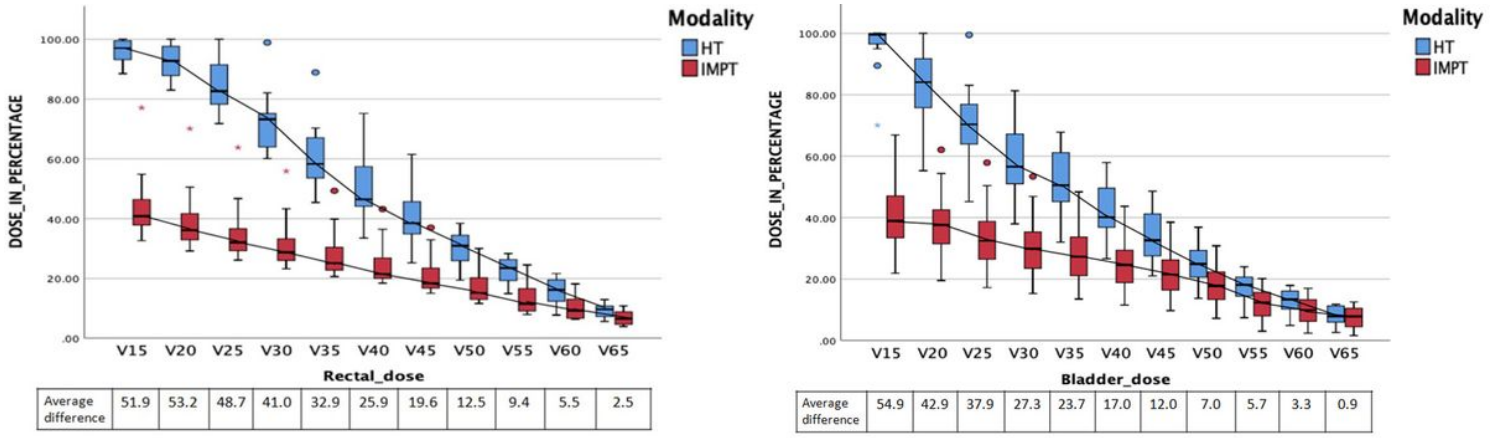

Figure 2

a (left): Rectal dosimetry of 12 patients comparing HT and PBT plan (Boxplot shows median and Interquartile range) b (right): Bladder dosimetry of 12 patients comparing HT and PBT plan (Boxplot shows median and Interquartile range)

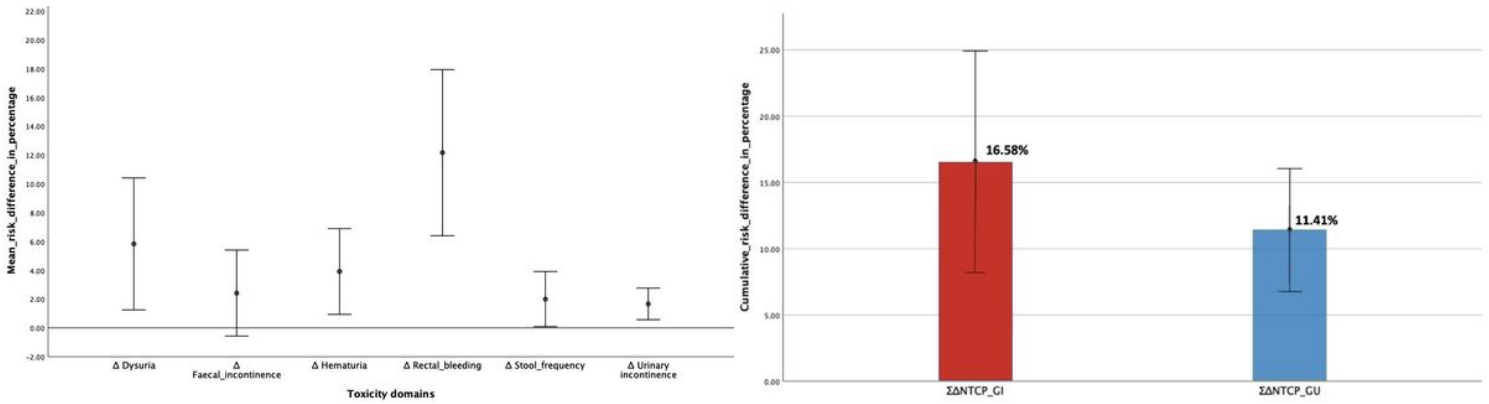

Figure 3

a (left): ΔNTCP of each toxicity with mean and error bars showing 95% confidence interval b (right): ΣΔNTCP of GI and GU toxicity with mean and error bars showing 95% confidence interval

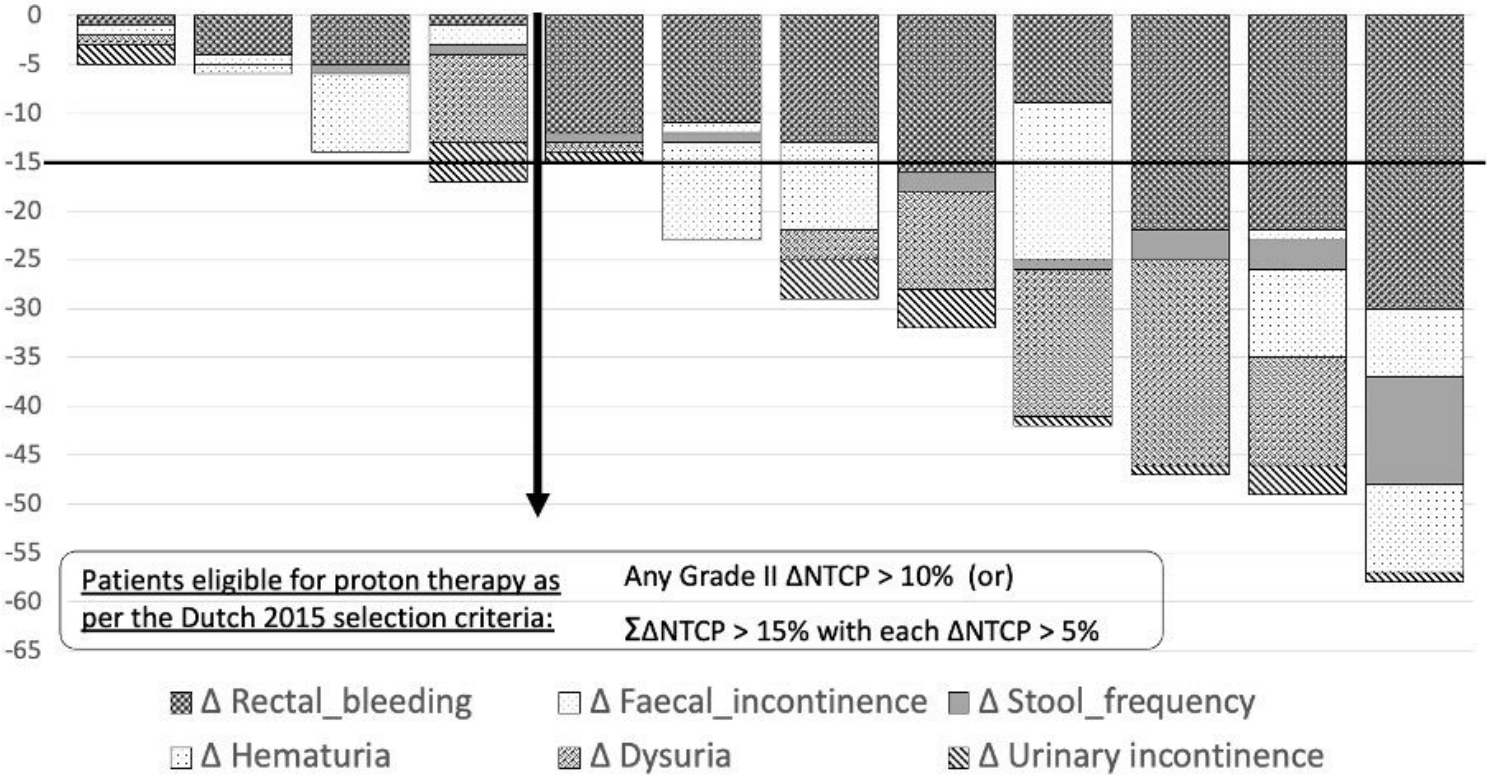

Figure 4

Graph showing ΔNTCP distribution across each patient (Arrow separates patients eligible for proton therapy as per accepted criteria)