Derivation of dose/volume constraints for the anorectum from clinician and patient-reported outcomes in the CHHiP trial of radiotherapy fractionation.

Short title: Dose/volume constraints in the CHHiP trial

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Conflicts of Interest

Dr. Wilkins reports a Clinical Research Fellowship from Cancer Research UK, during the conduct of the study. Dr. Brand reports a Clinical Research Fellowship from Cancer Research UK, during the conduct of the study. Prof. Hall reports grants from Cancer Research UK, during the conduct of the study; grants from Accuray Inc., outside the submitted work. Prof. Dearnaley reports grants from NIHR Biomedical Research Centre at the Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, grants from Cancer Research UK Programme Grants C46/A10588 and C33589/A19727, during the conduct of the study; personal fees from Janssen, personal fees from The Institute of Cancer Research, outside the submitted work. In addition, Prof. Dearnaley has a patent EP1933709B1 issued.

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Abstract

Background: The CHHiP trial randomised 3216 men with localised prostate cancer (1:1:1) to three radiotherapy fractionation schedules: 74Gy/37 fractions (f) over 7.4 weeks, 60Gy/20f/4 weeks and 57Gy/19f/3.8 weeks. Literature-based dose constraints were applied with arithmetic adjustment for the hypofractionated arms. This study aimed to derive anorectal dose constraints using prospectively-collected clinician-reported outcomes (CRO) and patient-reported outcomes (PRO) and to assess the added predictive value of spatial dose metrics.

Methods: A case-control study design was used, seven CRO and five PRO bowel symptoms were evaluated. Cases experienced a moderate or worse symptom 1-5 years post-radiotherapy, and did not have the symptom pre-radiotherapy. Controls did not experience the symptom at baseline, or between 1-5 years post-radiotherapy. The anorectum was re-contoured from the anal verge to the recto-sigmoid junction; dose/volume parameters were extracted. Univariate logistic regression, atlases of complication indices and bootstrapped receiver-operating-characteristic (ROC) analysis (1000 replicates, balanced outcomes) were used to derive dose constraints for the whole cohort (hypofractionated schedules were converted to 2Gy equivalent schedules using $\alpha/\beta=3$Gy) and separate hypofractionated/conventional fractionation cohorts. Only areas under the curve (AUC) with 95% confidence interval lower limits >0.5 were considered statistically significant. Any constraint derived in <95-99% of bootstraps was excluded.

Results: Statistically significant dose constraints were derived for CRO, but not PRO. Intermediate to high doses were important for rectal bleeding whereas intermediate doses were important for increased bowel frequency, faecal incontinence and rectal

pain. Spatial dose metrics did not improve prediction of CRO or PRO. A new panel of dose constraints for hypofractionated schedules to 60Gy or 57Gy are $V20_{Gy}$<85%, $V30_{Gy}$<57%, $V40_{Gy}$<38%, $V50_{Gy}$<22% and $V60_{Gy}$<0.01%.

Conclusions: Dose constraints differed between symptoms, indicating potentially different pathogenesis of radiation-induced side effects. Derived dose constraints were stricter than those used in CHHiP and may reduce bowel symptoms post-radiotherapy.

Introduction

Prostate cancer is the most commonly diagnosed non-cutaneous malignancy in the western world, with over 1.3 million cases diagnosed in 2018 (1). For patients with localised disease, external beam radiotherapy (EBRT), brachytherapy and radical prostatectomy are established radical treatments. The CHHiP (Conventional or Hypofractionated High dose intensity-modulated radiotherapy in Prostate cancer) trial (ISRCTN97182923, CRUK/06/016) randomly assigned 3216 men to conventional fractionation (74Gy in 37 fractions (f) over 7.4 weeks) or one of two hypofractionated schedules (60Gy/20f/4 weeks or 57Gy/19f/3.8 weeks). The trial demonstrated that the hypofractionated schedule of 60Gy/20f was non-inferior to conventional fractionation for the rate of biochemical or clinical recurrence up to five years following radiotherapy (2).

There was a low incidence of late bowel and bladder side effects for all radiotherapy schedules in CHHiP. Estimated five year cumulative grade two or worse Radiation Therapy Oncology Group (RTOG) bowel side effects occurred in 11.3-13.7% of men

(2). In addition, patient-reported outcomes (PRO) in CHHiP showed substantially lower rates of bowel bother and distress to those reported in historical trials using equivalent radiotherapy schedules (3). This reduction in side effects may be due to improved dose conformity using intensity-modulated radiotherapy (IMRT) in CHHiP, and the application of dose constraints. The toxicity outcomes of earlier studies using conventional fractionation were used to design the CHHiP dose constraints (table S1) (4-6); dose constraints were not typically used in earlier studies.

An important question is whether further tightening of the CHHiP dose constraints would enable further reduction in toxicity. It is possible that existing constraints are optimal. The low incidence of toxicity seen in CHHiP may be explained by radiogenomic variation (7), pre-existing co-morbidity (8), microbiota (9) or other factors unrelated to radiotherapy dose. However, it is also possible that tighter dose constraints would reduce toxicity. Data-derived constraints for the hypofractionated schedules are particularly important for two reasons. Firstly, the arithmetic conversion to obtain dose constraints for hypofractionated schedules in CHHiP was based on the difference in total dose - no radiobiological correction for changing the fraction size from 2Gy to 3Gy occurred (10). Consequently, the validity of these constraints needs to be established. Secondly, as the 60Gy/20f schedule is increasingly used as a new standard of care for radical radiotherapy for prostate cancer, optimal dose constraints are a clinical priority.

Most dose-volume studies use the RTOG criteria or other clinician-reported outcomes (CRO) to describe toxicity; only more recent studies have evaluated PRO (5, 11). The QUANTEC reviews recommend using PRO to assess dose-volume relationships (12), because PRO may be more sensitive than CRO (13). This study aims to determine

anorectal dosimetric predictors of toxicity using both CRO and PRO in CHHiP, and to assess the added predictive value of spatial dose metrics.

Methods

Study design and patient selection

A case/control methodology was used for the dosimetric analysis of late-onset radiotherapy toxicity because ≥moderate side effects were uncommon in CHHiP. “Cases” with ≥moderate late toxicity were defined using PRO and CRO endpoints 1-5 years post-radiotherapy. Moderate or worse was chosen to represent clinically-important morbidity. Toxicity data at six months after radiotherapy start were excluded as residual acute toxicity may have been present. Specific thresholds for toxicity (table S2) were determined for each CRO and PRO endpoint, according to clinical impact. Thresholds included a maximum permitted level of each symptom prior to radiotherapy, so as to avoid erroneously attributing pre-existing symptoms to radiation damage. For the control group, patients experiencing no toxicity for the relevant endpoint over the 1-5 years post-radiotherapy were identified. Only patients with ≤2 from a possible 6 timepoints with missing data were included as controls to minimise bias from missing data.

Delineation of anorectum and collation of Dose Volume Histograms (DVH)

Dose cube data from relevant patients in the CHHiP trial were imported into VODCA (Visualisation and Organisation of Data for Cancer Analysis v5.4.1, Medical Software Solutions, Switzerland) and the anorectum was checked for outlining consistency. The

superior extent of the anorectum was defined as the recto-sigmoid junction, and the inferior extent was defined as the anal verge (12, 14) (see appendix). The anorectum was then split into the anal canal, (lower 3cm), and the rectum (remaining upper portion) (14, 15) to validate dose constraints reported by Buettner et al. (15).

Dose-volume parameters were extracted from VODCA as a relative cumulative volume. For analysis of the whole cohort, hypofractionated dose schedules were converted to 2Gy equivalent schedules (EQD2) using the Withers formula and α/β=3Gy (10). This conversion included a bin-by-bin correction on the original DVH since the relevant normal tissue structure did not receive the full prescribed dose.

Analysis of DVH data

Univariate logistic regression: DVH

Univariate logistic regression assessed the relationship between the anorectal volume (as a continuous variable) receiving specific doses (using 1Gy dose bins) and toxicity outcomes. Multivariate logistic regression was not performed because of non-independence of dosimetric variables. Three separate cohorts were evaluated: firstly, the full CHHiP cohort (with EQD2 conversion for patients receiving hypofractionated radiotherapy); secondly, all patients receiving hypofractionated radiotherapy (60Gy or 57Gy); and thirdly, all patients receiving conventional radiotherapy (74Gy). For the conventional fractionation analysis, univariate logistic regression evaluated the change in odds of toxicity given a 1% relative increase in volume receiving 20Gy, 30Gy, 40Gy, 50Gy, 60Gy, 65Gy and 70Gy, and for the hypofractionation analysis the volume receiving 20Gy, 30Gy, 40Gy, 50Gy, 55Gy and 60Gy. Both CRO and PRO were evaluated for the anorectum, anal canal and rectum. In view of multiple testing,

a modified Bonferroni adjustment, in which p-values of less than 0.005 were considered statistically significant, was made.

Atlases of complication indices (ACI): DVH

ACI are an established method of visualising the whole DVH for a cohort of patients and relating it to toxicity outcomes (16). The overall spread of colour across the atlas gives a good visual impression of how dose and irradiated volume relate to toxicity, hence, ACI are complementary to formal statistical modelling. Construction of the ACI is explained in the supplementary appendix (page 2).

Receiver Operating Characteristic (ROC) analysis

Area under the ROC curve (AUC) was used to derive dose-volume constraints. As above, three separate cohorts were evaluated, and toxicity outcomes were dichotomised (1=toxicity present, 0=toxicity absent). The test variable was the volume receiving a specific dose, e.g. $V20_{Gy,}$ and 1Gy dose intervals were tested. A ROC curve plotting 1-specificity against sensitivity was constructed for each 1Gy interval. AUC with a 95% confidence interval lower limit >0.5 were considered statistically significant.

Both the Youden index (17) and the Closest Top Left (CtL) index (18) determined the volume constraint that best discriminated between volumes predicting for toxicity. As these gave very similar outcomes (table 1 and figure S3), the mean of the two indices was used as the final dose constraint. To increase the rigour of derived dose constraints, bootstrapping with replacement was used, with 1000 replicates. Outcomes were balanced for the bootstraps, i.e. 50% cases and 50% controls were selected to improve machine learning performance. A pragmatically-selected

threshold for the bootstraps was chosen: if the AUC 95% confidence interval lower limit was <0.5 in >1% of the replicates, the constraint was excluded. For the separate analyses of the smaller hypofractionated and 74Gy cohorts, this 1% threshold was relaxed to 5% due to reduced statistical power.

Analysis of Dose Surface Maps (DSM)

DSM were obtained for the anorectum for all patients with DVH. Methods used to construct DSM are described in the appendix (pages 1-2) and match those used in the analysis of RT01 (15, 19). Metrics extracted from each DSM included the Dose Surface Histogram (DSH), the longitudinal and lateral extent of dose, and eccentricity.

As above, univariate logistic regression was used to analyse the relationship between each CRO and PRO and the four DSM metrics using the dose thresholds and EQD2 conversion described earlier.

Results

Patients and dosimetric data

The cumulative DVH for the anorectum obtained for the 1150 patients (from 40 centres) qualifying as a case or control across each CRO and PRO evaluated are shown in figures S1 and S2 (the latter according to treatment arm with CHHiP dose constraints). A wide variation in DVH shape is seen and some DVH exceed the relevant CHHiP dose constraints, especially at intermediate doses of 30-50Gy.

The numbers of patients who qualified as either “cases” or “controls” for each CRO or PRO is shown in figures 1A and B. Numbers vary considerably because of the different incidence of radiation-induced side effects.

Univariate logistic regression for DVH

Figure 1A summarises the results of univariate logistic regression to assess the relationship between the anorectum, rectum and anal canal DVH and each CRO or PRO for all available patients (with an EQD2 correction using α/β=3Gy). For CRO, several statistically significant dose parameters were derived. There was a significant association between the anorectal volumes receiving intermediate and high doses and rectal bleeding. Odds ratios per 1% relative increase in volume increased steadily from 1.03 (95%CI:1.00-1.03, p<0.001) at 30Gy to 1.09 (95%CI:1.03-1.15, p<0.001) at 70Gy. In addition, there was a significant association between the anorectal volume receiving intermediate doses and increased bowel frequency, faecal incontinence and rectal ulceration (table S3). Here, the volume receiving 30Gy was the strongest predictor of outcome. Overall, dose-volume relationships were weaker for PRO with only rectal urgency showing a significant association with the anorectal volume receiving 30Gy (OR 1.02 (95% CI:1.01-1.03, p=0.003) (table S4).

When the anorectum was split into the rectum and anal canal, results for the rectum were very similar to the whole anorectum (figure 1A), which is unsurprising as the dose-volume parameters are comparable. For the anal canal, similar significant dose-volume associations with rectal bleeding and increased bowel frequency were seen to those for the anorectum and rectum. However, for other endpoints, including faecal incontinence, relationships between dose-volume and toxicity were weaker (table S5).

Figure 1B shows the results of univariate logistic regression modelling with the original cohort split into patients receiving 3Gy or 2Gy per fraction. The smaller cohorts means statistical power is reduced. For the 3Gy cohort, significant relationships between intermediate to high doses and rectal bleeding are seen, as well as between intermediate doses and increased bowel frequency and faecal incontinence. The 2Gy per fraction cohort is the smallest cohort assessed. Here, the only significant relationship is between high doses and rectal bleeding. As above, no significant relationships are seen between dose and PRO.

Atlases of complication indices for DVH

A summary of ACI for the anorectum are shown in figure 2. Collectively, the ACI corroborate findings from univariate logistic regression that higher volumes at intermediate to high doses predict side effects for rectal bleeding and higher volumes at intermediate doses predict side effects for faecal incontinence (figures 2A, 2B). CRO-based increased bowel frequency shows a much stronger association with dose-volume metrics than PRO-based loose stools where little association is seen (figure 2C, 2D).

Derivation of dose constraints for DVH

ROC analysis was used to derive anorectal dose constraints for the three cohorts evaluated. Table 1 shows all derived dose constraints including AUC with 95% confidence intervals. The odds ratios and associated p-values for Youden and CtL represent the increased odds of toxicity if the relevant constraint is not met. Figures S3-S4 demonstrate the separate anorectal constraints for Youden and CtL after ROC analysis with 1000 bootstraps for four CRO in the complete cohort following EQD2 conversion. The values for Youden and CtL are similar which was consistently seen

throughout the analysis. As above, the ROC analysis indicates that intermediate and high doses are important for rectal bleeding, whereas the intermediate dose range is more relevant for increased bowel frequency, faecal incontinence and rectal pain. No dose constraints were derived for PRO.

Figure 3 shows anorectal dose constraints for all symptoms evaluated in relation to the CHHiP dose constraints. The derived dose constraints are considerably tighter than those used in CHHiP. Figures 4 and S5 demonstrate application of the newly-derived dose constraints to the anorectal DVH of patients in CHHiP, where a substantial proportion of patients fail these new dose constraints.

Analysis of DSM

Results of the univariate logistic regression to assess the relationship between toxicity and the four DSM parameters are shown in figure 5. The clearest DSM-based predictors are for rectal bleeding where both the lateral extent of dose and the DSH are associated with toxicity at intermediate to high doses. For all other symptoms, there are very few significant relationships, except for mucosal loss where lateral extent of dose is important at intermediate doses. As few predictive relationships emerged from the univariate logistic regression, ROC analysis was not performed for DSM.

Discussion

This case/control analysis of DVH and DSM according to the presence or absence of moderate or worse side effects has identified new dose constraints for several toxicity endpoints. To our knowledge, this is the first study to derive dose constraints for

moderately hypofractionated radiotherapy. In the United Kingdom, 60Gy/20f/4 weeks is a new standard of care, with 57Gy/19f/3.8 weeks showing comparative efficacy in patients older than 75 years (20). Modest hypofractionation is recommended in recent UK and North American guidelines (21, 22) indicating that the dose constraints derived in this study (figure 4) are clinically relevant and widely applicable to contemporary practice. Modern image-guided radiotherapy strategies permit tighter margins than those used for the majority of patients in CHHiP, as has recently been reported in the experimental arms of the CHHiP-IGRT study (23). These tighter margins mean that meeting the target constraints we present is feasible and the proposed new anorectal constraints have recently been introduced as target (i.e. non-mandatory) constraints in both PACE-C and PIVOTALboost trials.

The specific dose levels for which constraints were derived for different symptoms are broadly consistent with the published literature. Dose constraints for rectal bleeding have been particularly well-studied and indicate that the maximum dose is the most important factor contributing to bleeding (11, 24-26). However, as shown in our study, considerably lower doses have been shown to be important for other symptoms including bowel frequency, faecal incontinence and rectal urgency (11, 24, 27). Historically, the dose range of 20-40Gy has been considered less important than higher doses and one of the dosimetric trade-offs of IMRT is an increased low dose bath. Our findings indicate that meeting all dose constraints between 20Gy to 70Gy is clinically important. It is also possible that some dose constraints are conditionally relevant i.e. a dose constraint at V20 may matter less if the volume receiving high dose falls low enough.

The different dose ranges thought to be important for different side effects points to differing pathophysiology underlying side effects. Further insight is provided by the

analysis of surface dose metrics. The analysis of DSM did not produce as many significant dosimetric predictors of toxicity as DVH. The most significant association was between the lateral extent of dose and rectal bleeding, which externally validates findings from the RT01 trial (19). It has been postulated that migration of healthy cells (stem cells) from nearby regions may aid repair. This concept is reiterated with the inverse relation between eccentricity and outcome where a more eccentric shape is inversely related to toxicity. A more eccentric shape would mean a shorter distance to healthy cells in one axis. Other DSM-based correlations from RT01, including the longitudinal extent of dose and loose stools, were not observed in our study. Possible reasons include the reduced toxicity in CHHiP versus RT01 (3), and the improved conformality of radiotherapy in CHHiP causing different spatial dose patterns.

This study does not support separation of the anorectum into the anal canal and rectum in clinical practice. We found that the dose to the entire anorectum or rectum was a stronger predictor of faecal incontinence than the dose to the anal canal. The published literature with respect to the pathogenesis of radiation-induced faecal incontinence has not reached a consensus; the dose to sub-structures including the external anal sphincter and puborectalis have been suggested as important factors for incontinence (28). Manometry studies identified both rectal and anal wall pressures as relevant (28). Elsewhere, anal surface dose and lateral extent of anal canal dose have correlated with subjective sphincter control (15). Finally, a recent study identified mean rectal dose and prior abdominal surgery as leading factors contributing to incontinence (29). Overall, these data suggest that anal canal dose should not be considered in isolation as a predictor of faecal incontinence.

We found that CRO consistently identified more dosimetric predictive factors than PRO. This finding was unexpected as PRO have been shown to detect more side

effects than CRO (13, 27) but may be due to the increased subjectivity of PRO. Additionally, PRO of overall bowel bother or distress encompass a range of clinical syndromes. The EPIC questionnaire was only used by a minority of patients - this captures more radiotherapy-related bowel symptoms than the UCLA-PCI instrument used by more patients. In addition, the time period assessed in PRO questions i.e. “during the last four weeks” is typically much shorter than in CRO.

Dose cube data used to derive DVH from this analysis were derived from the planning radiotherapy scan – accumulated dose was not measured. The anorectum moves during and between radiotherapy fractions (30); the planning scan DVH may be a better surrogate of the true anorectal DVH during treatment than the planning scan DSH or DSM. Measurement of accumulated dose using deformable image registration of images taken during treatment should enable more precise evaluation of predictive metrics from DSM than just using the planning scan DSM (31).

A statistically significant dose constraint does not inevitably mean it is clinically significant. Youden and CtL indices weight specificity and sensitivity equally (32), yet the sensitivity may be more important provided Clinical Target Volume coverage is not compromised. Other limitations include use of the same α/β ratio of 3Gy across symptoms. This may be overly simplistic - other studies have used α/β=5Gy for faecal incontinence (29). Presently we do not know how α/β ratios differ between anorectal symptoms. The uncertainty in α/β ratio might also account for the differences in constraints derived between the 2Gy cohort and the entire EQD2-corrected cohort.

For rectal pain and rectal ulceration, the number of cases (symptom events) was particularly low, which means derived constraints for rectal pain may be less robust than for other symptoms. We carefully incorporated baseline symptoms into the

modelling process and our missing data analysis did not identify differences in baseline characteristics between patients included versus not included (table S7). However, our dosimetric modelling did not include radiogenomic variation (33), bowel microbiota patterns (9, 34) or co-morbidities such as diabetes, hypertension, previous pelvic surgery, and inflammatory bowel disease. Finally, we acknowledge that we have not included the impact of endorectal balloons or hydrogel spacers on bowel symptoms, which provide an opportunity for further dosimetric improvements (35).

Conclusions

Despite the low incidence of radiation-induced side effects in CHHiP, we have identified new tighter dose constraints for conventional fractionation and hypofractionated schedules than those currently in clinical use. The new constraints differ widely per symptom and extend from 20Gy to 70Gy, indicating that low to intermediate doses are important in the aetiology of radiation-induced damage. Application of these new dose constraints may enable further reduction in gastro-intestinal side effects from EBRT for prostate cancer.

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Legends for figures

Figure 1A Results of univariate logistic regression for dose bins from 20-70Gy using Dose Volume Histogram data for the whole cohort, including a correction to 2Gy per fraction equivalent schedules using $\alpha/\beta=3$. Odds ratios are for a relative increase in rectal volume of 1%.

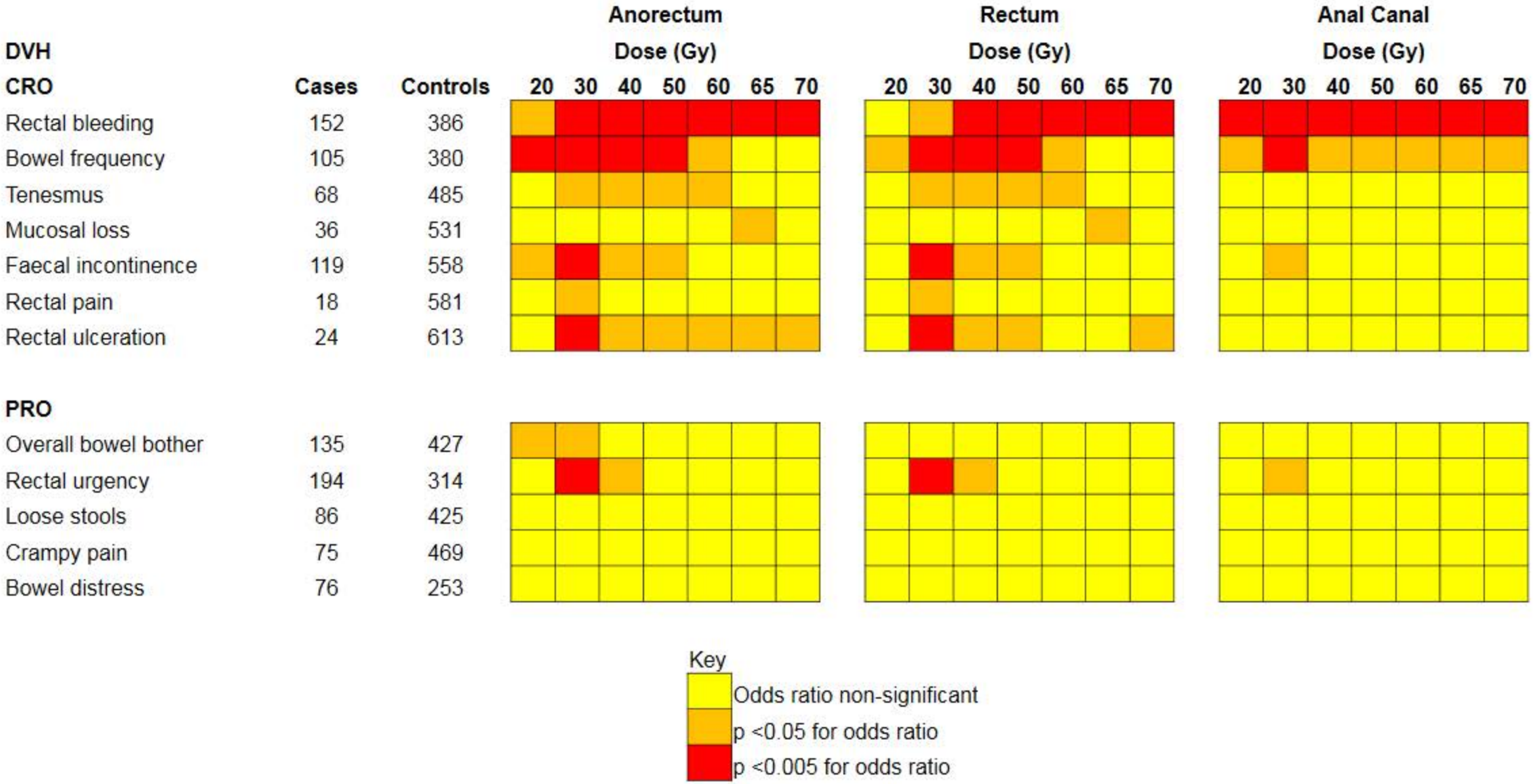
Figure 1B: Results of univariate logistic regression for dose bins from 20Gy to 60-70Gy using Dose Volume Histogram data for separate 2Gy (left) or 3Gy (right) per fraction cohorts, without a correction to 2Gy per fraction equivalent schedules.

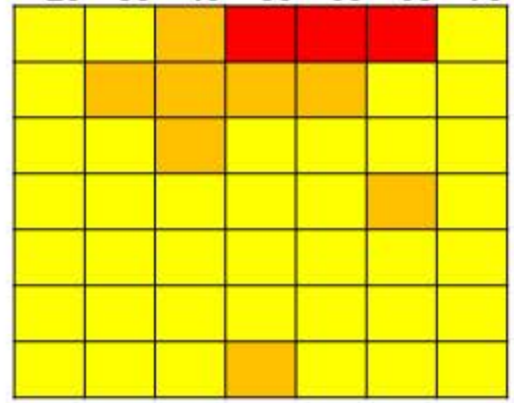
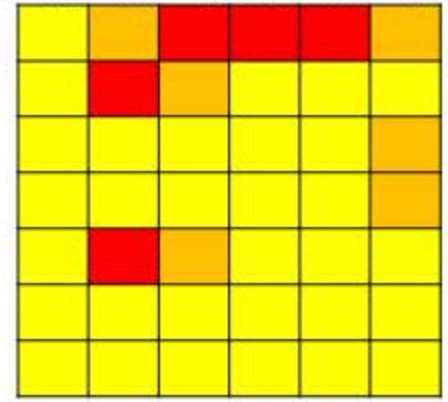
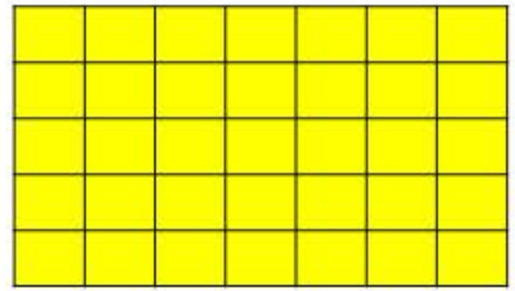
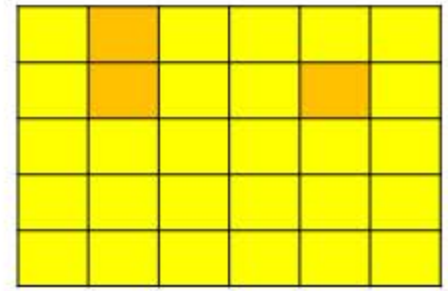
Figure 2: Atlas of Complication Indices to visualise dose/volume relationships for rectal bleeding (A), faecal incontinence (B), increased bowel frequency (C) and increased loose stools (D). Atlases are adjusted for symptom incidence.

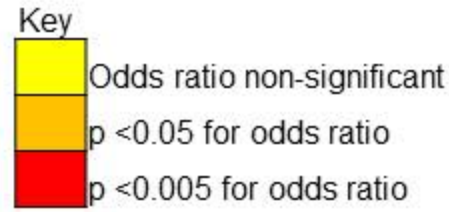
Figure 3. A: Anorectal dose constraints with a correction to 2Gy per fraction equivalent schedules for all patients, in relation to the dose constraints used in CHHiP. B: Anorectal dose constraints for patients receiving hypofractionated radiotherapy, in relation to the absolute dose constraints used in CHHiP. C: Anorectal dose constraints for patients receiving standard fractionation, in relation to the absolute dose constraints used in CHHiP.

Figure 4: A: Recommended anorectal dose constraints for hypofractionated radiotherapy to 60Gy or 57Gy, B: Application of new dose constraints to Dose Volume Histograms of patients treated with hypofractionated schedules within CHHiP.

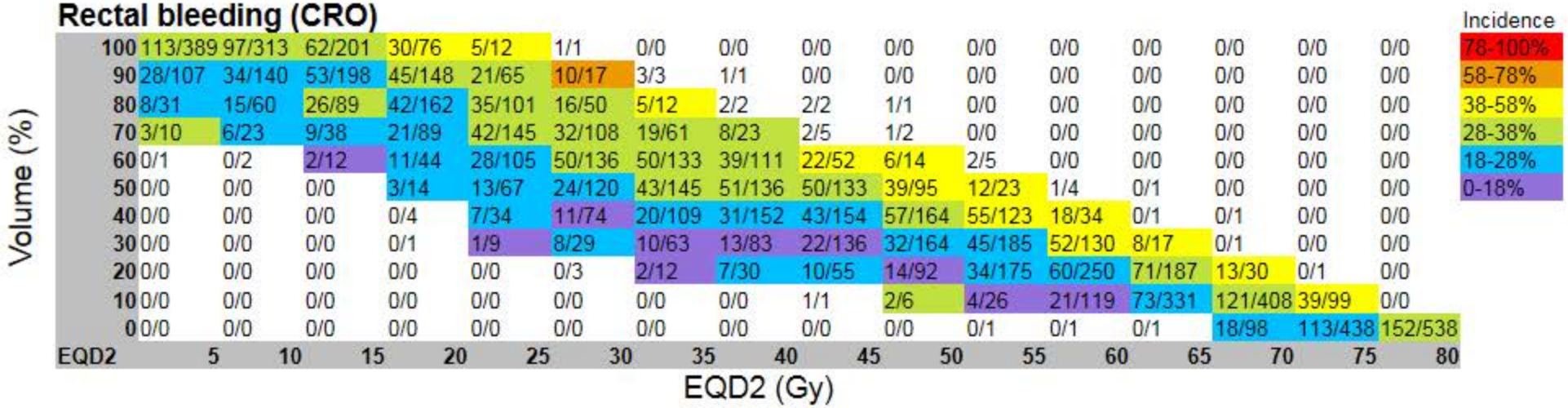
Figure 5: Results of univariate logistic regression for dose bins 20-70Gy for Dose Surface Map data for the anorectum following a correction to 2Gy per fraction equivalent schedules.


Anorectum
Dose (Gy)
Rectum
Dose (Gy)
Anal Canal
Dose (Gy)
20 30 40 50 60 65 70
DVH
CRO
Cases
Controls
Rectal bleeding 152 386
Bowel frequency 105 380
Tenesmus 68 485
Mucosal loss 36 531
Faecal incontinence 119 558
Rectal pain 18 581
Rectal ulceration 24 613
PRO
Overall bowel bother 135 427
Rectal urgency 194 314
Loose stools 86 425
Crampy pain 75 469
Bowel distress 76 253
Key
Odds ratio non-significant
p <0.05 for odds ratio
p <0.005 for odds ratio

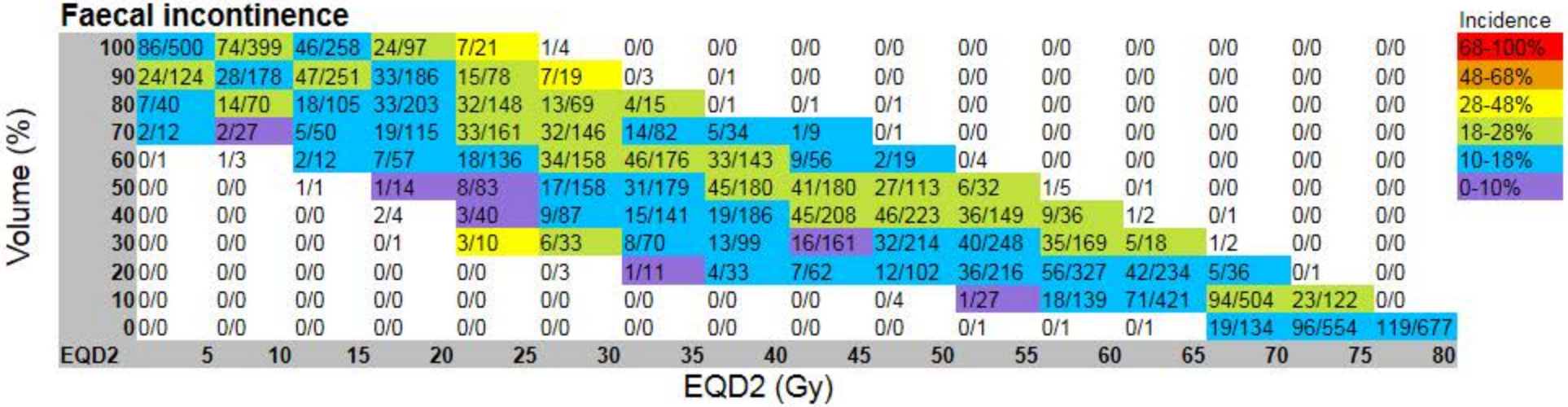
	2Gy per fraction DVH		Anorectum Dose (Gy)	3Gy per fraction DVH		Anorectum Dose (Gy)
CRO	**Cases**	**Controls**	20 30 40 50 60 65 70	**Cases**	**Controls**	20 30 40 50 55 60
Rectal bleeding	55	118		97	268	
Bowel frequency	37	116		68	264	
Tenesmus	31	139		37	346	
Mucosal loss	14	150		22	381	
Faecal incontinence	47	166		72	392	
Rectal pain	7	173		11	408	
Rectal ulceration	12	184		12	429	
PRO						
Overall bowel bother	50	136		85	291	
Rectal urgency	57	104		137	210	
Loose stools	20	122		64	303	
Crampy pain	23	151		52	318	
Bowel distress	31	83		45	170	

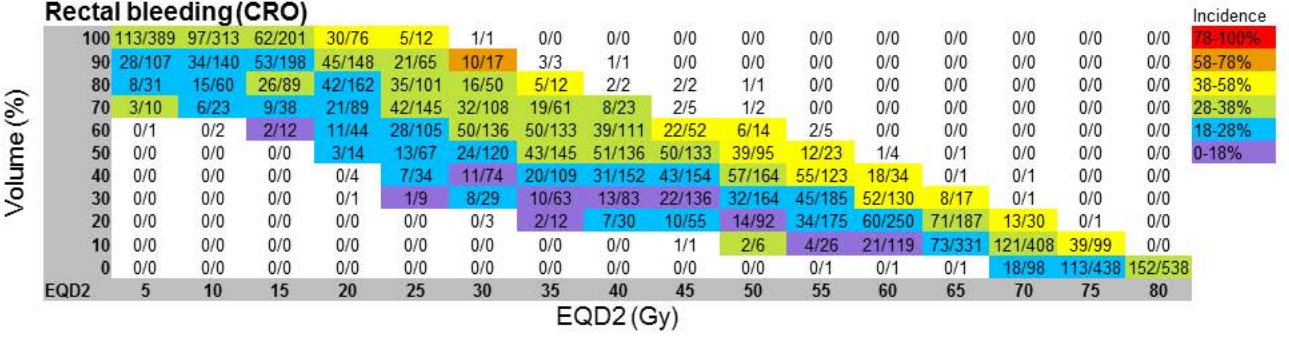


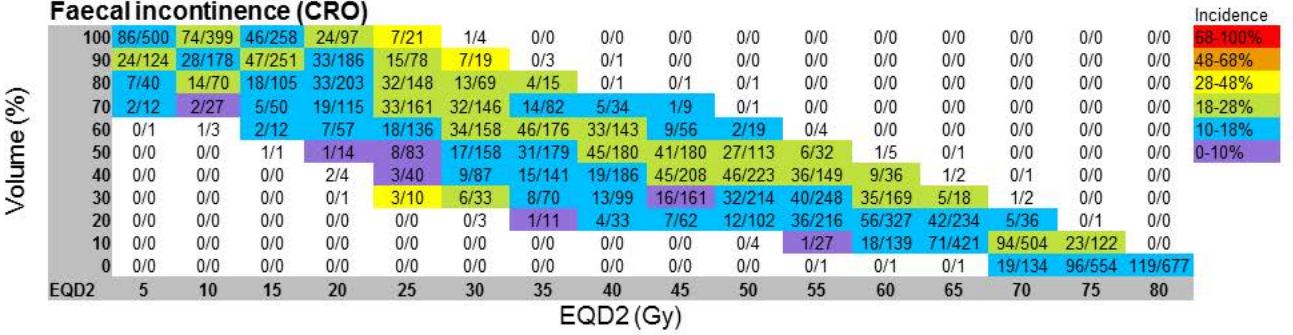
Rectal bleeding (CRO)

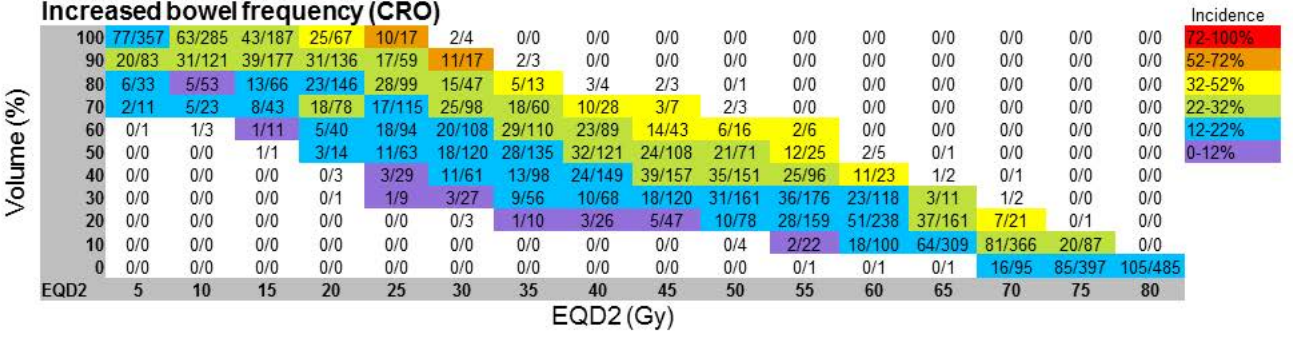


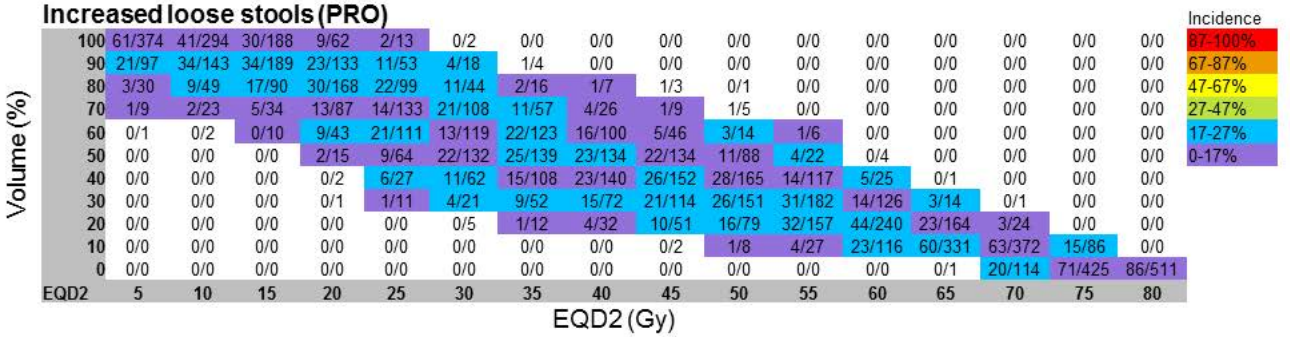
Faecal incontinence



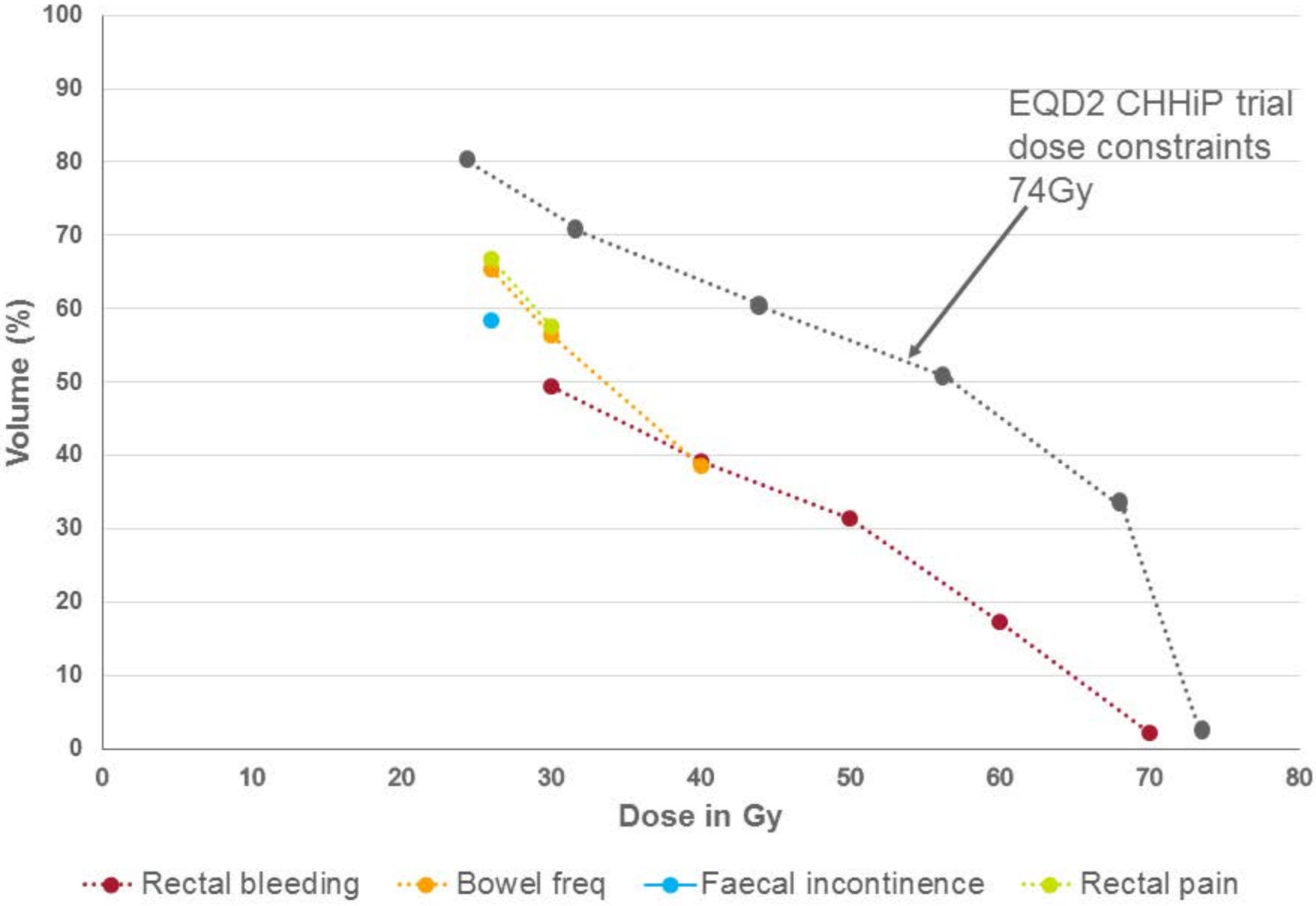

Rectal bleeding (CRO)
Incidence
78-100%
58-78%
38-58%
28-38%
18-28%
0-18%
Volume (%)
EQD2 (Gy)
100 113/389 97/313 62/201 30/76 5/12 1/1 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0
90 28/107 34/140 53/198 45/148 21/65 10/17 3/3 1/1 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0
80 8/31 15/60 26/89 42/162 35/101 16/50 5/12 2/2 2/2 1/1 0/0 0/0 0/0 0/0 0/0 0/0
70 3/10 6/23 9/38 21/89 42/145 32/108 19/61 8/23 2/5 1/2 0/0 0/0 0/0 0/0 0/0 0/0
60 0/1 0/2 2/12 11/44 28/105 50/136 50/133 39/111 22/52 6/14 2/5 0/0 0/0 0/0 0/0 0/0
50 0/0 0/0 0/0 3/14 13/67 24/120 43/145 51/136 50/133 39/95 12/23 1/4 0/1 0/0 0/0 0/0
40 0/0 0/0 0/0 0/4 7/34 11/74 20/109 31/152 43/154 57/164 55/123 18/34 0/1 0/1 0/0 0/0
30 0/0 0/0 0/0 0/1 1/9 8/29 10/63 13/83 22/136 32/164 45/185 52/130 8/17 0/1 0/0 0/0
20 0/0 0/0 0/0 0/0 0/0 0/3 2/12 7/30 10/55 14/92 34/175 60/250 71/187 13/30 0/1 0/0
10 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 1/1 2/6 4/26 21/119 73/331 121/408 39/99 0/0
0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/1 0/1 0/1 18/98 113/438 152/538
EQD2 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80


Faecal incontinence (CRO)
Incidence
68-100%
48-68%
28-48%
18-28%
10-18%
0-10%
Volume (%)
EQD2 (Gy)
100 86/500 74/399 46/258 24/97 7/21 1/4 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0
90 24/124 28/178 47/251 33/186 15/78 7/19 0/3 0/1 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0
80 7/40 14/70 18/105 33/203 32/148 13/69 4/15 0/1 0/1 0/1 0/0 0/0 0/0 0/0 0/0 0/0
70 2/12 2/27 5/50 19/115 33/161 32/146 14/82 5/34 1/9 0/1 0/0 0/0 0/0 0/0 0/0 0/0
60 0/1 1/3 2/12 7/57 18/136 34/158 46/176 33/143 9/56 2/19 0/4 0/0 0/0 0/0 0/0 0/0
50 0/0 0/0 1/1 1/14 8/83 17/158 31/179 45/180 41/180 27/113 6/32 1/5 0/1 0/0 0/0 0/0
40 0/0 0/0 0/0 2/4 3/40 9/87 15/141 19/186 45/208 46/223 36/149 9/36 1/2 0/1 0/0 0/0
30 0/0 0/0 0/0 0/1 3/10 6/33 8/70 13/99 16/161 32/214 40/248 35/169 5/18 1/2 0/0 0/0
20 0/0 0/0 0/0 0/0 0/0 0/3 1/11 4/33 7/62 12/102 36/216 56/327 42/234 5/36 0/1 0/0
10 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/4 1/27 18/139 71/421 94/504 23/122 0/0
0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/1 0/1 0/1 19/134 96/554 119/677
EQD2 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80

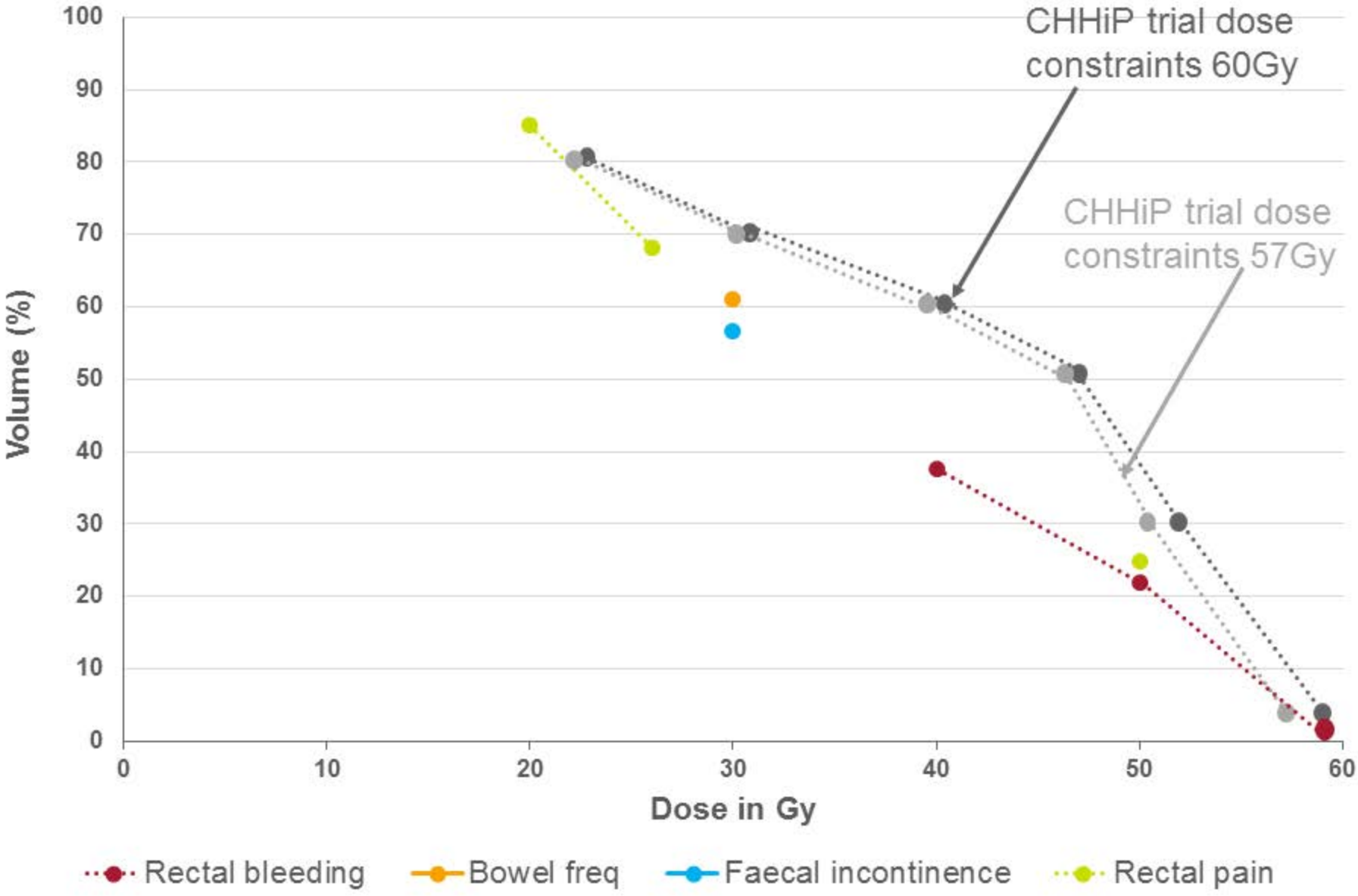

Increased bowel frequency (CRO)
Incidence
72-100%
52-72%
32-52%
22-32%
12-22%
0-12%
Volume (%)
EQD2 (Gy)
100 77/357 63/285 43/187 25/67 10/17 2/4 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0
90 20/83 31/121 39/177 31/136 17/59 11/17 2/3 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0
80 6/33 5/53 13/66 23/146 28/99 15/47 5/13 3/4 2/3 0/1 0/0 0/0 0/0 0/0 0/0 0/0
70 2/11 5/23 8/43 18/78 17/115 25/98 18/60 10/28 3/7 2/3 0/0 0/0 0/0 0/0 0/0 0/0
60 0/1 1/3 1/11 5/40 18/94 20/108 29/110 23/89 14/43 6/16 2/6 0/0 0/0 0/0 0/0 0/0
50 0/0 0/0 1/1 3/14 11/63 18/120 28/135 32/121 24/108 21/71 12/25 2/5 0/1 0/0 0/0 0/0
40 0/0 0/0 0/0 0/3 3/29 11/61 13/98 24/149 39/157 35/151 25/96 11/23 1/2 0/1 0/0 0/0
30 0/0 0/0 0/0 0/1 1/9 3/27 9/56 10/68 18/120 31/161 36/176 23/118 3/11 1/2 0/0 0/0
20 0/0 0/0 0/0 0/0 0/0 0/3 1/10 3/26 5/47 10/78 28/159 51/238 37/161 7/21 0/1 0/0
10 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/4 2/22 18/100 64/309 81/366 20/87 0/0
0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/1 0/1 0/1 16/95 85/397 105/485
EQD2 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80

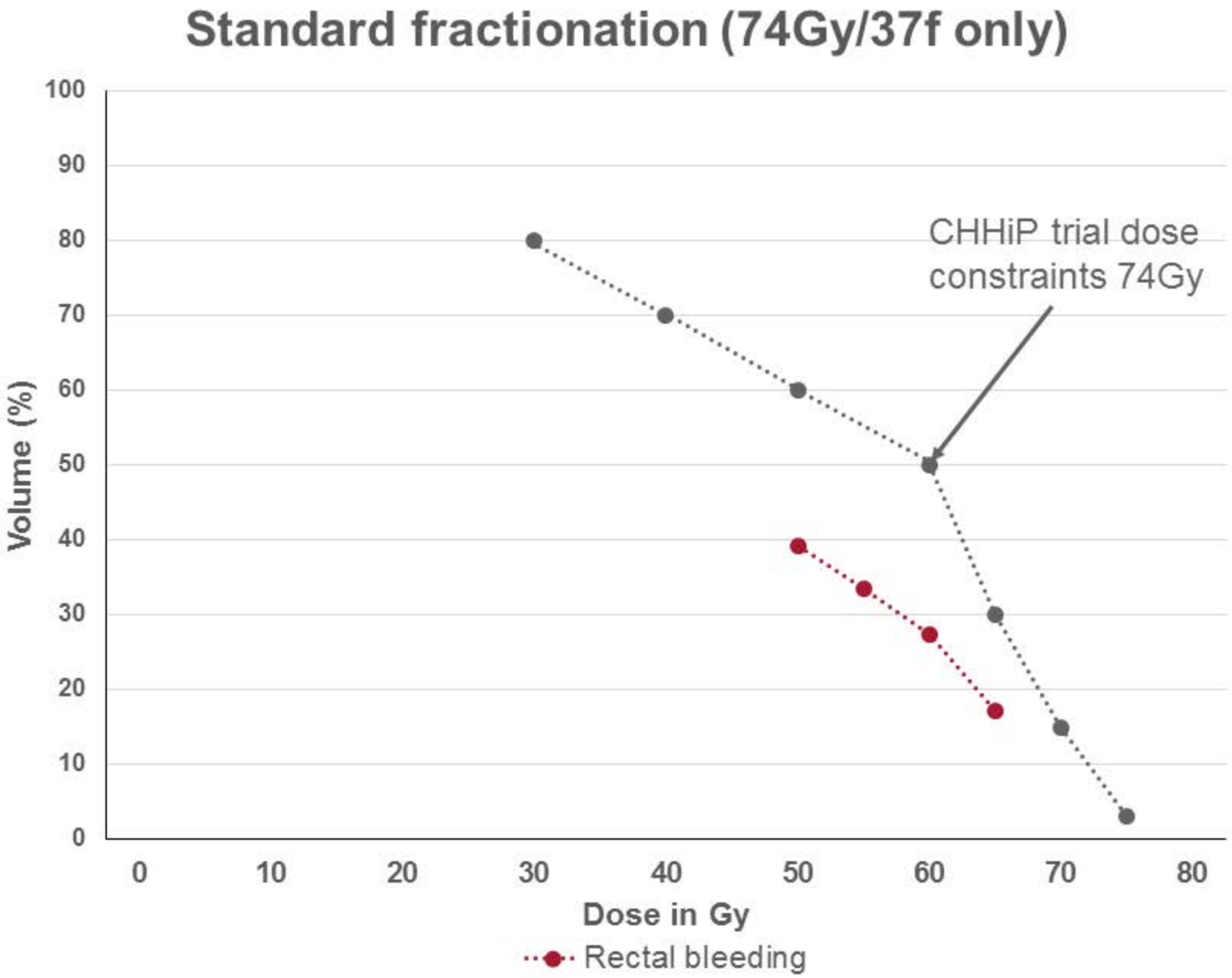

Increased loose stools (PRO)
Incidence
87-100%
67-87%
47-67%
27-47%
17-27%
0-17%
Volume (%)
100 61/374 41/294 30/188 9/62 2/13 0/2 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0
90 21/97 34/143 34/189 23/133 11/53 4/18 1/4 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0
80 3/30 9/49 17/90 30/168 22/99 11/44 2/16 1/7 1/3 0/1 0/0 0/0 0/0 0/0 0/0 0/0
70 1/9 2/23 5/34 13/87 14/133 21/108 11/57 4/26 1/9 1/5 0/0 0/0 0/0 0/0 0/0 0/0
60 0/1 0/2 0/10 9/43 21/111 13/119 22/123 16/100 5/46 3/14 1/6 0/0 0/0 0/0 0/0 0/0
50 0/0 0/0 0/0 2/15 9/64 22/132 25/139 23/134 22/134 11/88 4/22 0/4 0/0 0/0 0/0 0/0
40 0/0 0/0 0/0 0/2 6/27 11/62 15/108 23/140 26/152 28/165 14/117 5/25 0/1 0/0 0/0 0/0
30 0/0 0/0 0/0 0/1 1/11 4/21 9/52 15/72 21/114 26/151 31/182 14/126 3/14 0/1 0/0 0/0
20 0/0 0/0 0/0 0/0 0/0 0/5 1/12 4/32 10/51 16/79 32/157 44/240 23/164 3/24 0/0 0/0
10 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/2 1/8 4/27 23/116 60/331 63/372 15/86 0/0
0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/1 20/114 71/425 86/511
EQD2 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80
EQD2 (Gy)

All patients (with EQD2 conversion)

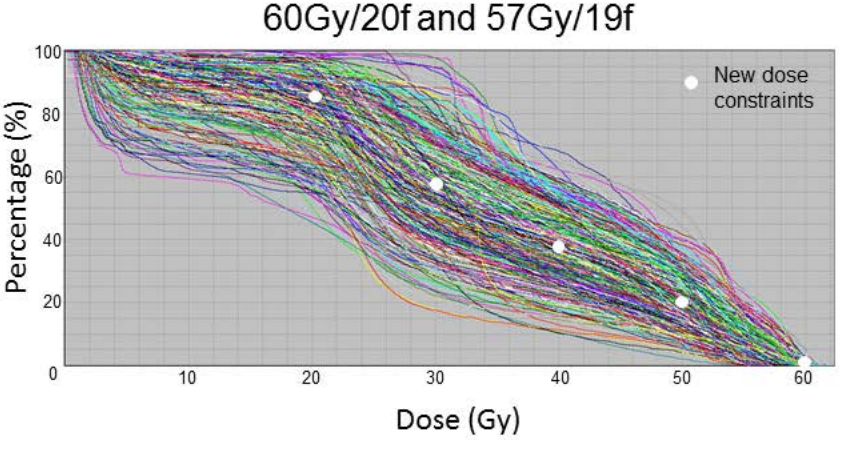


Hypofractionated schedules




Standard fractionation (74Gy/37f only)
100
90
80
70
60
50
40
30
20
10
0
Volume (%)
CHHiP trial dose constraints 74Gy
0
10
20
30
40
50
60
70
80
Dose in Gy
Rectal bleeding

Recommended anorectal dose constraints for hypofractionated radiotherapy to 60Gy or 57Gy	
$V20_{Gy}$	85%
$V30_{Gy}$	57%
$V40_{Gy}$	38%
$V50_{Gy}$	22%
$V60_{Gy}$	<0.01%


60Gy/20f and 57Gy/19f
New dose constraints
Percentage (%)
Dose (Gy)
0
20
40
60
80
100
10
20
30
40
50
60

DSM All anorectum

CRO	Cases	Controls
Rectal bleeding	143	424
Bowel frequency	90	436
Tenesmus	61	521
Mucosal loss	30	574
Faecal incontinence	103	615
Rectal pain	13	629
Rectal ulceration	13	655
PRO		
Overall bowel bother	66	487
Rectal urgency	106	373
Loose stools	36	467
Crampy pain	46	488
Bowel distress	37	275

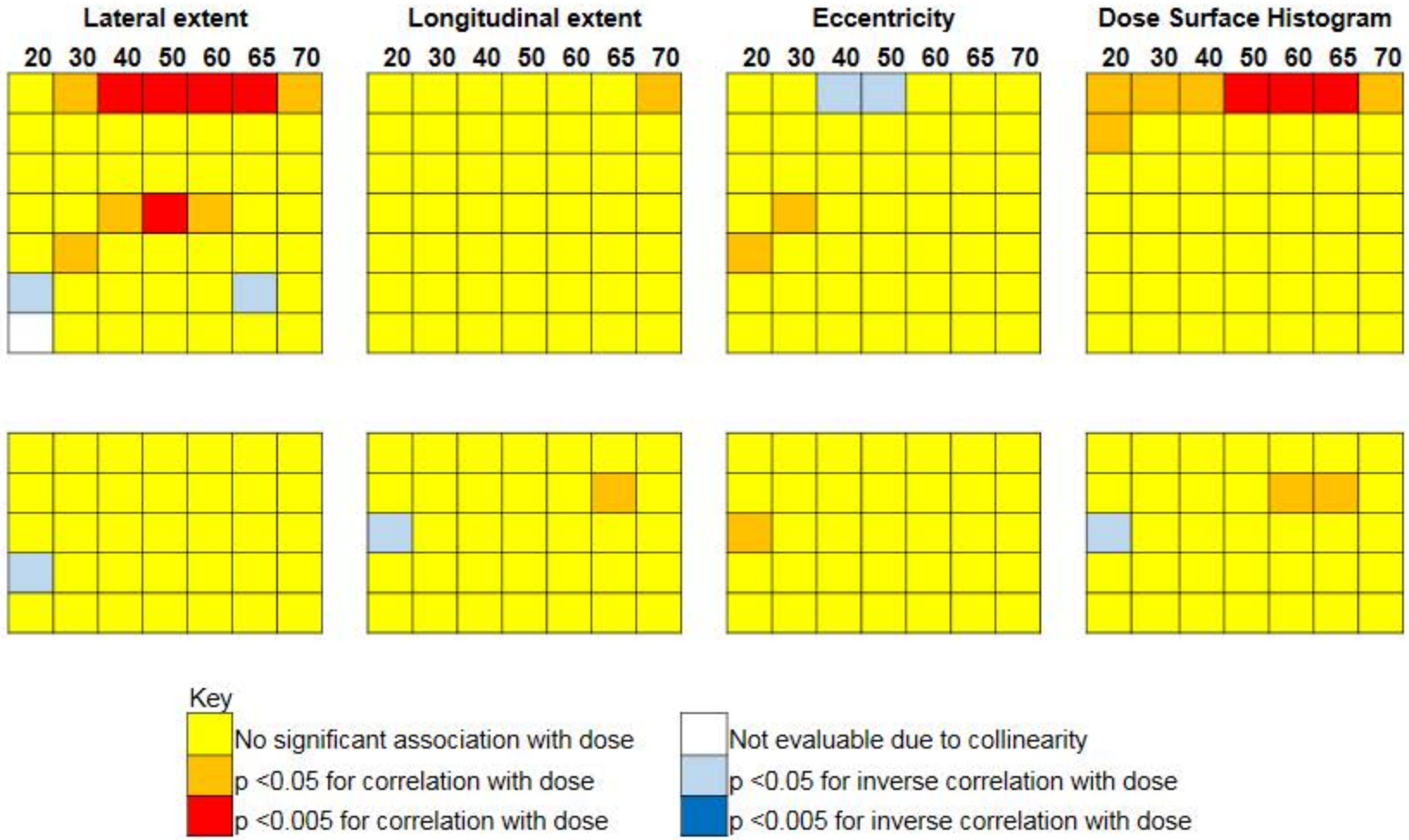


Table 1: Anorectal dose constraints including Area under the Curve (AUC) with 95% confidence intervals (CI). Odds ratios (OR) and associated p values for Youden (Y) and Closest to Left (CtL) represent the increased odds of toxicity if the constraint is not met.

Symptom	Dose level	Percent*	AUC	95%CI AUC	Percent CtL	OR CtL	p-value CtL	Percent Y	OR Y	p-value Y
All patients with EQD2 conversion of hypofractionated patients using α/β=3										
Rectal bleeding	$V30_{Gy}$	49.5	0.60	0.55-0.65	50.5	2.42	0.0004	48.5	2.63	<0.0001
	$V40_{Gy}$	39.3	0.63	0.58-0.67	39.9	2.87	<0.0001	38.7	3.02	<0.0001
	$V50_{Gy}$	31.5	0.65	0.60-0.70	31.4	3.50	<0.0001	31.7	3.58	<0.0001
	$V60_{Gy}$	17.5	0.64	0.59-0.68	15.9	2.66	<0.0001	19.0	3.37	<0.0001
	$V70_{Gy}$	2.3	0.60	0.55-0.65	1.9	2.19	0.0007	2.7	2.55	<0.0001
↑ Bowel frequency	$V26_{Gy}$ $^{\$}$	65.4	0.63	0.58-0.68	63.2	2.76	<0.0001	67.5	3.34	<0.0001
	$V30_{Gy}$	56.5	0.63	0.58-0.68	54.2	2.58	0.0003	58.8	3.13	<0.0001
	$V40_{Gy}$	38.6	0.61	0.56-0.66	39.4	2.38	0.0008	37.7	2.70	<0.0001
Faecal incontinence	$V26_{Gy}$ $^{\$}$	58.5	0.60	0.56-0.64	60.3	2.09	0.0007	56.7	2.52	<0.0001
Rectal pain	$V26_{Gy}$ $^{\$}$	66.9	0.66	0.62-0.70	67.5	3.92	<0.0001	66.2	4.36	<0.0001
	$V30_{Gy}$	57.7	0.65	0.61-0.70	59.0	3.66	<0.0001	56.4	4.34	<0.0001
Patients receiving 3Gy per fraction to total dose of 57Gy or 60Gy No EQD2 conversion										
Rectal bleeding	$V40_{Gy}$	37.7	0.61	0.55-0.67	38.1	2.98	<0.0001	37.2	3.15	<0.0001
	$V50_{Gy}$	22.2	0.63	0.58-0.69	20.5	2.76	0.0005	23.5	3.47	<0.0001
	$V60_{Gy}$	0.01	0.59	0.54-0.63	0.0	2.70	0.0018	0.02	3.08	0.0008
↑ Bowel frequency	$V30_{Gy}$	61.0	0.62	0.56-0.68	58.8	2.52	0.0022	63.3	3.20	0.0003
Faecal incontinence	$V30_{Gy}$	56.7	0.61	0.55-0.66	56.3	2.33	0.0011	57.2	2.74	<0.0001
Rectal pain	$V20_{Gy}$	85.2	0.67	0.61-0.72	86.1	4.56	<0.0001	84.4	6.18	<0.0001
	$V26_{Gy}$ $^{\$}$	68.2	0.63	0.57-0.68	68.6	2.90	0.0002	67.9	4.95	<0.0001
	$V50_{Gy}$	24.9	0.62	0.57-0.68	23.0	3.12	<0.0001	26.8	4.20	<0.0001
Patients receiving 2Gy per fraction to total dose of 74Gy No EQD2 conversion										
Rectal bleeding	$V50_{Gy}$	39.1	0.66	0.58-0.74	38.3	4.52	0.0003	39.4	4.75	0.0002
	$V55_{Gy}$	33.5	0.67	0.58-0.75	33.5	5.09	0.0001	33.5	5.17	<0.0001
	$V60_{Gy}$	27.3	0.67	0.59-0.75	27.1	4.43	0.0004	27.4	4.66	0.0002
	$V65_{Gy}$	17.2	0.66	0.57-0.74	16.8	3.65	0.0016	17.6	3.65	0.0005

*Percent dose constraint is the mean of CtL and Youden constraints (CtL and Youden constraints are also shown in the table and figure S3)
Note AUC, 95% CI values, OR CtL, p-value CtL, OR Youden and p-value Youden are the mean values across 1000 bootstraps, pts: patients.
$: $V26_{Gy}$ is included as dose constraints for faecal incontinence (faecal incont) ranged from V26 to V30 across different cohorts