Correcting rotational error in rectal cancer radiation therapy: Can planning target volume margins be safely reduced?

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Abstract

Introduction: The magnitude and impact of rotational error is unclear in rectal cancer radiation therapy. This study evaluates rotational errors in rectal cancer patients, and investigates the feasibility of planning target volume (PTV) margin reduction to decrease organs at risk (OAR) irradiation. Methods: In this study, 10 patients with rectal cancer were retrospectively selected. Rotational errors were assessed through image registration of daily cone beam computed tomography (CBCT) and planning CT scans. Two reference treatment plans (TPR) with PTV margins of 5 mm and 10 mm were generated for each patient. Pre-determined rotational errors (±1°, ±3°, ±5°) were simulated to produce six manipulated treatment plans (TPM) from each TPR. Differences in evaluated dose-volume metrics between TPR and TPM of each rotation were compared using Wilcoxon Signed-Rank Test. Clinical compliance was investigated for statistically significant dose-volume metrics. Results: Mean rotational errors in pitch, roll and yaw were −0.72 ± 1.06°, −0.04 ± 1.36° and 0.38 ± 0.96° respectively. Pitch resulted in the largest potential circumferential displacement of clinical target volume (CTV) at 1.42 ± 1.06 mm. Pre-determined rotational errors resulted in statistically significant differences in CTV, small bowel, femoral heads and iliac crests (P < 0.05). Only small bowel and iliac crests failed clinical compliance, with majority in the PTV 10 mm margin group. Conclusion: Rotational errors affected clinical compliance for OAR dose but exerted minimal impact on CTV coverage even with reduced PTV margins. Both PTV margin reduction and rotational correction decreased irradiated volume of OAR. PTV margin reduction to 5 mm is feasible, and rotational corrections are recommended in rectal patients to further minimise OAR irradiation.

Introduction

Rectal cancer is the eighth most common cancer worldwide, accounting for 3.2% of all cancer deaths in 2018. The 5-year survival rate of rectal cancer ranges from approximately 88% for localised disease, 83% for regional disease and 13% for metastatic disease. With increased survivorship, maintaining patients’ quality of life is increasingly important.
life by minimising treatment side effects has become a crucial aspect in rectal cancer management.

While surgery is the primary radical treatment option for rectal cancer, the addition of neoadjuvant radiation therapy in the form of volumetric modulated arc therapy (VMAT) further reduces the risk of local recurrence and improves overall survival. VMAT provides a highly conformal dose distribution through steep dose gradients. This translates to increased organs at risk (OAR) sparing, which may improve patients' quality of life by reducing radiation-induced toxicities. The high dose conformity of VMAT treatments require precise patient positioning to limit geometric uncertainties since compromising target coverage can decrease local tumour control rates. Inter and intra fraction positional variations are accounted for using a planning target volume (PTV) expanded from the clinical target volume (CTV). The Radiation Therapy Oncology Group (RTOG) recommends a uniform PTV margin expansion of 7–10 mm in rectal cancer treatments. Patient positional variations are corrected through image-guided radiation therapy (IGRT) using cone beam computed tomography (CBCT) scans obtained prior to treatment, allowing for accurate target localisation through correction of translational and rotational set up errors. However, current practice in rectal cancer radiation therapy only corrects in three translational planes. Rectal cancer patients can be susceptible to rotational errors due to long treatment fields and the rectal sacral flexure following the concavity of the sacrum. With the introduction of a 6 degrees-of-freedom (6DOF) couch, both translational and rotational errors can be corrected with sub-millimetre and sub-degree accuracy, respectively, without manual repositioning of the patient. PTV margins may potentially be reduced as geometric uncertainties stemming from both translational and rotational errors are eliminated. Reducing PTV margins can decrease the volume of OAR being irradiated, therefore minimising the risk of radiation-induced toxicities.

Current literature evaluating the impact of set up errors in radiation therapy found that correcting rotational errors is clinically important for accurate treatment delivery. Yao et al. concluded that PTV margin reductions by approximately 69% were feasible on 13 gynaecological patients when rotational corrections are implemented, resulting in significantly decreased OAR doses. The importance of rotational errors is supported by Laursen et al.'s cervical study. They concluded that residual rotational errors have a significant impact on target displacement when only translational errors were corrected in 25 patients, as it resulted in CTV target shifts of more than 5 mm at cranio-caudal ends in 8% of treatment fractions. While published literature has evaluated the impact of rotational errors and the potential benefits of rotational corrections in various treatment sites, pelvic studies specific to rectal cancer are lacking. To our knowledge, there is no published literature exploring rectal PTV margin reduction in VMAT treatments through the correction of rotational errors. This study proposes to investigate the feasibility of PTV margin reduction in rectal cancer to minimise radiation-induced side effects through the correction of rotational errors.

Methods

Patient selection and characteristics

Ethics approval was obtained from the South Western Sydney Local Health District Human Research Ethics Committee (HREC number LNR/11/LPOOL/372). A retrospective cohort of 10 patients who had undergone VMAT treatments at Liverpool Cancer Therapy Centre between October 2019 and March 2020 were selected. Eligibility criteria included patients diagnosed with colorectal or anal cancer who were treated in supine positions with a dose prescription of 45 or 50 Gy. Individual patient characteristics are recorded in Table 1. Nodal involvement and location can be found under Table S1.

All 10 patients included in the study had undergone computed tomography (CT) scans in supine position with full bladder preparation. Scans were acquired with a Phillips Big Bore CT scanner (Philips Healthcare, the Netherlands). All treatment target volumes and OAR contours had been delineated by radiation oncologists as per the International Consensus Guidelines on CTV delineation in rectal cancer and RTOG guidelines. Contours were either reviewed during a weekly audit or by at least one other radiation oncologist in the department. Translational errors were corrected for all patients prior to treatment through daily CBCT scans using X-ray Volumetric Imaging (XVI) system on Elekta Synergy or Versa HD (Elekta, Sweden) linear accelerator machines.

CBCT assessment

Rotational error data were obtained through retrospective comparison of 249 daily CBCT and planning CT scans through automatic image fusion in MIM Maestro V6.9 (MIM Software Inc., North America). Image matches were visually assessed using bony anatomy such as the sacrum and pubic symphysis. A manual box-based image match was conducted for unsatisfactory automated image
matches where bony anatomy were misaligned. Rotational error data obtained through this process was termed true rotations. Data analysis was conducted in Microsoft Excel (Microsoft Corporation, USA) to derive mean and standard deviation of true rotations in each patient to represent systematic and random error respectively.

Potential circumferential displacement of CTV was calculated using true rotations (roll, pitch and yaw) and distance measured from treatment isocentre to corresponding CTV edges in the central axis of longitudinal, lateral and vertical planes with the formula shown in Figure 1:

\[ d = r \sin(c) \]

**Plan generation and evaluation**

Original planning CT datasets were used to generate two PTVs from previously defined CTV: PTV05 and PTV10 using 5 and 10 mm PTV margin expansions respectively. New treatment plans were generated in Pinnacle treatment planning system V16.21 (Philips Healthcare, USA). An auto-planning script was used to generate treatment plans with a dose objective of 45Gy in 25 fractions to the PTV, utilising 6MV beams delivered by two 360° dynamic arcs with a dose grid resolution of 0.25 cm in all three planes.

Planning objectives were derived from the International Commission on Radiation Units and Measurements (ICRU) Report 8316 and Kachnic et al’s17 multi-institutional study (Table 2). In cases where OAR doses exceeded constraints due to PTV overlaps, secondary PTV objectives were utilised. All treatment plans were normalised to mean dose covering 95% of PTV volume for consistency. Each patient had two reference treatment plans (TPR) for each PTV margin, resulting in a total of 20 TPR for the cohort. All plans were reviewed by a radiation therapist experienced in rectal cancer planning for quality assurance.

Digital Imaging and Communication in Medicine (DICOM) dose files of PTV05 TPR and PTV10 TPR were exported to MATLAB® 2019 (Matrix Laboratory, New Mexico) for rotation simulation. To assess the impact of rotational error on dose distribution, dose matrix of TPR were rotated using an in-house script to generate
Table 2. Dose-volume parameters for target volumes and organs at risks.

| Structures     | Metric | Primary objective | Secondary objective |
|----------------|--------|-------------------|---------------------|
|                |        | Volume (%)        | Dose (Gy)           | Volume (%)        | Dose (Gy) |
| PTV            | D98, D95 | 98 ≥44.1          | 95 ≥42.75          |                    |           |
|                | D10 cc | 100 ≤48.15        |                    |                    |           |
| CTV            | D98, D95 | 98 ≥44.1          | 95 ≥42.75          |                    |           |
|                | D10 cc | 100 ≤48.15        |                    |                    |           |
| Small bowel    | V45    | <5 45             |                    | NA                 |           |
|                | V35    | <35 35            |                    |                    |           |
|                | V30    | <50 30            |                    |                    |           |
| Femoral heads L/R | V44 | <5 44             |                    | NA                 |           |
|                | V40    | <35 40            |                    |                    |           |
|                | V30    | <50 30            |                    |                    |           |
| Iliac crests L/R | V40 | <35 40            |                    | NA                 |           |
|                | V30    | <50 30            |                    |                    |           |
| External genitalia | V40 | <5 40             |                    | NA                 |           |
|                | V30    | <35 30            |                    |                    |           |
|                | V20    | <50 20            |                    |                    |           |
| Bladder        | V40    | <35 40            |                    | NA                 |           |
|                | V35    | <50 35            |                    |                    |           |

CTV, clinical target volume; Gy, Gray; L, left; PTV, planning target volume; R, right; Vx = volume (%) of structure receiving x dose (Gy); Dxy = dose (Gy) received by y% of the structure.

manipulated treatment plans (TPM). Pre-determined symmetric simulated rotations of ±1°, ±3° and ±5° were applied to all three rotational axes at the isocentre. Evaluated dose-volume metrics for each structure of interest (Table 2) were compared between TP_R and TP_M of each rotation within margin groups using Wilcoxon Signed-Rank Test. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 27 (IBM, Chicago, IL). Statistical significance was considered at P ≤ 0.05. Clinical compliance was investigated for individual dose-volume metrics that were statistically significant for the cohort.

Results

Evaluation of true rotations from CBCT analysis

Mean and standard deviation of true rotations obtained from retrospective CBCT analysis are displayed in Table 3. Directions of positive and negative rotations in each rotational plane (pitch, roll and yaw) are demonstrated in Figure 2. The largest overall systematic and random errors were both observed in pitch at −0.72° and 1.81° respectively. The smallest overall systematic error was observed for roll at −0.04°, while yaw accounted for the smallest overall random error at 0.96°. Overall systematic errors of all three rotational axes were less than ±1°. The single largest rotational error was found in pitch at −6.14° (Fig. 3).

Maximum potential circumferential displacement of CTV in left–right, superior–inferior and anterior–posterior planes caused by true rotations of roll, pitch and yaw, respectively, are displayed in Table 3. The maximum distance from isocentre to CTV edge in our study range from 1.95–5.74 cm, 4.21–7.83 cm and 2.03–6.92 cm for left–right, superior–inferior and anterior–posterior planes respectively. Pitch resulted in the largest overall displacement of CTV in the superior–inferior plane at 1.42 mm, with the single largest displacement occurring in Patient 06 at 3.72 mm.

Clinical compliance for cohort and individual dose-volume metric

Clinical compliance was defined as dose-volume metrics that met primary planning objectives stated in Table 2. Both Figures 4 and 5 compared TP_R against TP_M of symmetric rotations (±1°, ±3° and ±5°) applied to all three rotational axes.

Cohort dose-volume metrics refer to the mean dose-volume of all 10 patients (Fig. 4), while individual dose-volume metrics refer to the dose-volume received by each patient (Fig. 5). All dose-volume metrics of the small bowel are presented on the cohort and individual level, as it is the most important dose-limiting OAR in rectal cancer treatment. Only one cohort dose-volume metric that best demonstrates the differences in irradiated volume are presented for the other OAR (Fig. 4), while the remaining are found under (Table S2).

Across all three CTV cohort dose-volume metrics, it is observed that larger degrees of rotational errors result in bigger decreases in dose received by the CTV. However, these rotations had minimal impact on cohort CTV dose-volume metrics as shown in Figure 4a. The maximum dose difference of only 0.7 Gy is observed for CTV D98 when a rotational error of 5° is introduced to PTV05, with a mean dose of 44.89 Gy, 95% CI [44.67 Gy, 45.12 Gy].

For all OAR, it is observed that larger extent of rotations increases the interquartile range, therefore demonstrating that larger rotations result in greater variability in the difference of irradiated OAR volumes. The influence of rotational directions on irradiated OAR volumes were consistent in both PTV margin groups; Figure 4b shows that negative rotations increase irradiated volume of small bowel. With extreme rotational errors of 5°, the mean irradiated volume of SB V30 was 11.5%, 95% CI [1.6%, 21.4%] in PTV05 and 14%, 95% CI [3.8%, 24.2%] in PTV10. This is similar with rotational errors at the
opposite spectrum of $-5^\circ$, with a mean irradiated volume of 12.8%, 95% CI [3.3%, 22.4%] in PTV05, and 15.6%, 95% CI [5.7%, 25.5%] in PTV10.

Similarly, negative rotations increase the irradiated volume of both left femoral heads (Fig. 4c) and left iliac crest (Fig. 4d). In contrast, negative rotations decrease the irradiated volume of both right femoral heads (Fig. 4e) and right iliac crest (Fig. 4f). Bladder V$_{40}$ of PTV10 was the only cohort dose-volume metric to fail clinical compliance in both TPR and TPM of all rotations due to bladder overlaps in one patient, with a mean irradiated volume of 37.4%, 95% CI [27.5%, 47.3%]. However, no statistical significance was observed.

As for individual dose-volume metrics for the small bowel, it is observed that variations in irradiated volume increases when evaluating higher values of dose received (Fig. 5). The extent of variability caused by rotational errors is also dependent on individual patients.

### Statistical analysis of dose-volume metrics

Statistical pairwise plan comparisons of dose-volume metrics were made between TPR and TPM of each rotation ($\pm 1^\circ$, $\pm 3^\circ$, $\pm 5^\circ$) within each margin group (PTV05 and PTV10). Mean and standard deviation of evaluated dose-volume metrics, p-values and presence of statistical significance are displayed under Table S2. Dose-volume metrics of external genitalia (V$_{20}$, V$_{30}$ and V$_{40}$) and femoral heads V$_{44}$ were excluded due to frequency of near zero values.

### Discussion

The adoption of IGRT into modern radiation therapy has improved the accuracy of treatment through correction of patient positioning. OAR sparing can be achieved through the reduction of PTV margins, but this requires
minimal patient setup errors. While it is clinical practice to correct for translational setup errors, rotational set up errors are not routinely adjusted. In this study, we evaluated the magnitude of rotational errors in rectal cancer patients through retrospective offline CBCT image analysis. To our knowledge, this is the only study that investigated the impact of rotational errors in rectal target volumes and surrounding OAR, and subsequently, the feasibility of PTV margin reduction.

The analysis of retrospective CBCT data in this study revealed that rectal patients have inherent rotational errors in clinical settings. Rotational errors are a subject of interest as they are often considered to have significant influence on dosimetric distributions. Both Zhang et al.\textsuperscript{18} and Laursen et al.\textsuperscript{13} reported that pitch was the most frequent source of error for elongated gynaecological target volumes, and pitch had the largest impact in set up accuracy.\textsuperscript{13} Our results were consistent with the findings of these two gynaecological studies\textsuperscript{13,18} as we also found the largest magnitude and frequency of rotational error to occur in pitch (Table 3). Our evaluation of potential circumferential displacement of the CTV revealed that pitch also caused the largest displacement to occur in the superior–inferior plane; this may be attributed to the nature of elongated cranio-caudal rectal target volumes.

Internal changes from over- or under-filled bladder and bowel, presence of pelvic tilt or patients not lying in the same way they were simulated can also be contributing factors to rotational errors and subsequently, CTV displacement. However, the extent of CTV displacement was minimal in our study as the maximum average displacement observed was only 1.42 mm (Table 3). In contrast, Laursen et al.\textsuperscript{13} reported that pitch resulted in CTV target shifts of more than 5 mm in 6.5% of treatment fractions. These conflicting outcomes were likely due to the difference in target volume lengths, as the maximum isocentre to CTV edge distance was larger in Laursen et al.’s study at 10.5 cm, while the maximum distance in our study was 7.83 cm. Other studies have demonstrated that the impact of pitch is increasingly

![Figure 3. Distribution and frequency of true rotational errors (in degrees) caused by pitch, roll and yaw observed in individual daily CBCT scans.](image-url)

![Figure 4. Dose difference observed in (A) clinical target volume (D1cc, D95, D98), and volume difference observed in (B) small bowel (V30, V35, V40), (C) left femoral head (V30), (D) left iliac crest (V30), (E) right femoral head (V30), (F) right iliac crest (V30) and (G) bladder (V35, V40) between TPR and TPM of all degrees of rotations (±1°, ±3° and ±5°) applied to all three rotational axes.](image-url)
larger with longer target volume extensions in the longitudinal plane.\textsuperscript{13,18,19}

In this study, target displacements caused by rotational errors have minimal impact in terms of CTV target coverage when utilising standard treatment parameters, for example, symmetrical field size, centric isocentre placement and single dose level. We found that CTV dose-volume objectives (Table 2) were not compromised even with rotational errors of ±5°, and the dose differences were negligible. Our findings are consistent with Zhang et al’s\textsuperscript{18}

Figure 5. Variation in volume of small bowel (V_{30}, V_{35} and V_{45}) irradiated within each patient for both PTV05 and PTV10 margins, when comparing TPRs and TPMs of all degrees of rotations (±1°, ±3° and ±5°) applied to all three rotational axes.
study, who reported that gynaecological CTV coverage was not susceptible to clinical rotational errors as CTV dose-volume objective was maintained at 98% of prescribed dose. They found that rotational corrections only improved CTV coverage by 0.08%. Similar results were reported by Yao et al. as they found that CTV D95 were maintained at appropriate dosimetric requirements despite introduction of clinical intra-fractional rotational errors. Since our results showed that CTV dose-volume objectives could be met in all treatment plans regardless of PTV margins and remained unaffected by rotations, it is plausible that the current recommended PTV margin of 7–10 mm may be too generous when compensating for residual rotational errors. Although PTV coverage was not evaluated in our study, existing literature have demonstrated that rotational errors can reduce PTV dose coverage in asymmetrical or elongated targets.

Clinical compliance was still met for cohort dose-volume metrics that displayed statistically significant differences when rotational errors were introduced. Bladder V40 in PTV10 was the only cohort dose-volume metric that breached clinical compliance, but no statistical significance was observed; this was attributed to one of the patients with the majority of their bladder overlapping the PTV. Rotations were unlikely to have significant influence on bladder irradiated volumes, as the initial recorded volume in PTV10 TP_R exceeded constraints by 2.4% and failed clinical compliance even without the introduction of rotational errors.

Further investigation of cohort dose-volume metrics that were statistically significant revealed that individual dose-volume metrics of small bowel and iliac crests breached clinical compliance when rotational errors were introduced. PTV10 margin group accounted for 66.6% and 71.4% of breached small bowel and iliac crests individual dose-volume metrics respectively. Therefore, it is deduced that rotational corrections are required to maintain OAR clinical compliance, especially with larger PTV margins. Although statistical comparisons were not made between PTV margin groups, it was observed that irradiated OAR volumes were lower in PTV05 as compared to PTV10. Yao et al.’s study also demonstrated that reducing PTV margins improve OAR sparing, as smaller PTV margins decreased small bowel maximum and mean dose by 0.9Gy and 2.1Gy, respectively, while small bowel V50 and V40 were reduced by 5% and 4.1% respectively. Doses to other OAR such as femoral heads and bladder also decreased. Both Yao et al. and our study showed that PTV margin reduction has a role in OAR sparing. In addition, our study found that this can be further improved with rotational corrections. Since the small bowel is the most important dose-limiting OAR in pelvic radiation therapy with patients remaining at risk of small bowel toxicities indefinitely, both PTV margin reduction and rotational correction can be implemented to minimise OAR irradiation.

With regards to the assessment of positional variations prior to treatment delivery, current clinical practice of utilising bony structures for image guidance, before verification of soft tissues coverage (e.g. rectum and mesorectum or bladder interface), still remains as the gold standard for image matching regardless of PTV margins. In terms of rotational directions, we observed that negative and positive rotations were correlated with increase and decrease of irradiated volumes, respectively, in both small bowel and bladder. This may be attributed to negative pitch rotations tilting the patient anteriorly and potentially moving the posterior portion of OAR towards the rectal target volume, while positive rotations cause the OAR to move away from the treatment site. Larger variability of irradiated OAR volume differences was observed with increasing magnitude of rotational errors. It was also demonstrated that the impact of rotational errors on the variability of irradiated OAR volumes differs between individual patients, which may have been attributed to the proximity of the OAR to the target volume. Since the external genitalia was distant from the rectal target volume, rotations were not expected to have any impact on the dosimetry of this structure. However, our observations cannot be supported as there is no existing literature evaluating the impacts of rotational directions on pelvic OAR.

Limitations of our study include a small sample size and the investigation of only supine patients. Dosimetric data obtained through symmetric rotational simulation should also be appraised with caution as they do not represent actual clinical data. In addition, our study limited the assessment of geometric variation to the potential impact of rotations on the planned dose to OAR on the planning CT scan. Any potential variations of OAR, which has been shown to change during treatment, were not accounted for. The reduction in PTV margins based on rotational correction using a 6DOF couch should be considered in conjunction with potential OAR intrafraction movement, unless verified with daily imaging. Other factors such as extent of overlapping structures, internal soft tissue motion or deformation, treatment field size and isocentre placement were also not considered.

CTV dose-volume metrics were able to meet clinical compliance regardless of rotational errors or PTV margins, suggesting that rotational corrections are not required since even extreme rotations of up to ±5° did not compromise CTV coverage. As such, current recommended PTV margins may be overly generous in compensating for residual rotational errors. Although rotational correction is not required for maintaining treatment accuracy in our
study, it is still beneficial in limiting irradiated volumes of OAR. Therefore, OAR sparing can be maximised by implementing both rotational corrections and PTV margin reduction where possible. However, due to the limitations and small scope of our study, more research is required to validate our findings.

**Conclusion**

Reduction of PTV margin to 5 mm did not compromise CTV coverage despite rotational errors. Both PTV margin reduction and rotational correction can decrease irradiated OAR volumes. Therefore, reducing PTV margins is feasible in rectal cancer radiation therapy in terms of accounting for geometric uncertainties, and rotational corrections should be implemented for further OAR sparing.

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**Conflict of Interest**

The authors declare no conflict of interest.

**Ethics Approval**

Ethics approval was obtained from the South Western Sydney Local Health District Human Research Ethics Committee (HREC number LNR/11/LPOOL/372).

**Statements**

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**Supporting Information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Tables S1.** Nodal involvement and location in each patient.

**Table S2.** Evaluated cohort dose-volume metrics, $P$-value and $z$-value in 26 plan comparisons between TP R and TP M ($\pm 1^\circ$, $\pm 3^\circ$ and $\pm 5^\circ$) within PTV05 and PTV10.