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FULL PAPER

Target volume motion during anal cancer image guided radiotherapy using cone-beam computed tomography

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Objective: Literature regarding image-guidance and inter-fractional motion of the anal canal (AC) during anal cancer radiotherapy is sparse. This study investigates interfractional AC motion during anal cancer radiotherapy.

Methods: Bone matched cone beam CT (CBCT) images were acquired for 20 patients receiving anal cancer radiotherapy allowing population systematic and random error calculations. 12 were selected to investigate interfractional AC motion. Primary anal gross tumour volume and clinical target volume (CTV) were contoured on each CBCT. CBCT CTV volumes were compared to planning CTV. CBCT CTV volumes were combined into a CBCT-CTV envelope for each patient. Maximum distortion between each orthogonal border of the planning CTV and CBCT-CTV envelope was measured. Frequency, volume and location of CBCT-CTV envelope beyond the planning target volume (PTV) was analysed.

Results: Population systematic and random errors were 1 and 3mm respectively. 112 CBCTs were analysed in the interfractional motion study. CTV varied between each imaging session particularly T location patients of anorectal origin. CTV border expansions ≥ 1 cm were seen inferiorly, anteriorly, posteriorly and left direction. The CBCT-CTV envelope fell beyond the PTV $\geq 50\%$ imaging sessions ($n = 5$). Of these CBCT CTV distortions beyond PTV, 44% and 32% were in the upper and lower thirds of PTV respectively.

Conclusion: The AC is susceptible to volume changes and shape deformations. Care must be taken when calculating or considering reducing the PTV margin to the anus.

Advances in knowledge: Within a limited field of research, this study provides further knowledge of how the AC deforms during anal cancer radiotherapy.

INTRODUCTION

The ACT2 trial determined the national standard of care for anal canal carcinoma (ACC) comprising of mitomycin and fluorouracil with radical radiotherapy of 50.4 Gy.¹ Since the completion of ACT2, technological advances have been achieved and widely implemented in the UK in the form of intensity-modulated radiotherapy (IMRT), both in the form of static beam IMRT and volumetric modulated arc therapy (VMAT).^{2,3} IMRT has the ability to deliver highly conformal radiotherapy, thus reducing toxicity to normal tissues and promoting tolerability of treatment for ACC.⁴ Furthermore, IMRT provides a technological solution to increase dose to the primary tumour by simultaneous integrated boost (SIB), whilst maintaining acceptable toxicity rates.

The high conformity achieved with IMRT delivery requires image guidance techniques during treatment to prevent geographical miss of the clinical target volume (CTV) and

unnecessary irradiation of normal tissues. Image-guided radiotherapy (IGRT) allows visualisation of the tissues to be treated and can provide the means to correct for anatomic variations. As per the definition from ICRU 50, 62 and 83 the planning target volume (PTV) is comprised of a gross tumour volume (GTV), which is expanded to create the CTV to include microscopic clinical disease.⁵⁻⁷ The CTV is then expanded again to create the PTV. This margin should allow for "set up error" and internal target volume motion. In ACC, only two studies are published that investigate the required CTV to PTV margins or describe the internal motion of the anus during anal cancer radiotherapy.^{8,9} Despite high uptake of IGRT, there is a paucity of literature regarding the optimum IGRT protocol in ACC, in terms of imaging modality, normal tissue matching or frequency of data acquisition.¹⁰

In preparation for the next UK anal cancer trial (PLATO ISRCTN88455282), the consensus document *National*

Guidance for IMRT in Anal Cancer was published in 2014.¹¹ This guidance provides an evidence-based IMRT solution for anal cancer based on the ACT2 fractionation and forms the basis of the standard arm in the PLATO trial.¹² The guidance describes the planning margins required for early and advanced stage anal tumours planned with IMRT. These margins are smaller compared to previous protocol and the guidance recommends accompanying daily online imaging. At a minimum, it is recommended that cone beam CTy (CBCT) is performed for the first five fractions followed by a weekly CBCT. Online paired kV/MV images should be performed on other treatment days.

We currently use CBCT with a bone match to acquire on-treatment verification images, however; it is widely accepted that a bone match is a poor surrogate for soft tissue.¹³ Therefore, we prospectively audited the set up error for a cohort of anal cancer patients receiving radical radiotherapy using CBCT with a bone match. In view of the new national guidance with respect to smaller planning margins, this study investigates the interfractional motion and deformation of the AC for a subset of eligible patients.

METHODS AND MATERIALS

This study was approved by the institutional review board (reference number SE 245).

Patient population

20 consecutive patients were consented to radical chemoradiation for anal cancer treatment between October 2013 and April 2016. Patient characteristics are described in Table 1.

Radiotherapy technique

Patients were immobilised supine using the indexed Combi-fixTM system for knee and ankle support with hands on chest. All patients had a comfortably full bladder, following departmental drinking protocol of 700 ml of water 1 h prior to CT scanning. The same drinking protocol was followed prior to treatment. All patients were scanned from L2/L3 to 10 cm below anal marker. Contrast enhanced CT scans were acquired using a Philips large-bore CT scanner with a 2.5 mm slice reconstruction interval.

Prior to November 2014, 13 patients were treated with a 7-field IMRT step-and-shoot plan for Phase 1; prescription dose 30.6 Gy in 17 fractions followed by a conformal Phase 2 plan of 19.8 Gy in 11 fractions. Target volumes were defined as follows according to institutional protocol; primary anal GTV (as defined by digital exam and multimodality imaging) was outlined as GTVa. Nodal GTV (GTVn) included all involved nodes (as documented by biopsy and imaging). CTVa included GTVa and a uniform 20 mm expansion. CTVn included GTVn with a 10 mm uniform expansion and elective nodal groups (CTV was edited to exclude uninvolved bone, genitourinary structures, muscles, or bowel). Elective nodes (CTVe) included mesorectal, bilateral inguinal, internal and external iliac nodes and presacral space as described in the RTOG consensus contouring atlas for anorectal cancer.¹⁴ PTV1 was defined as CTVa and CTVn with a 10 mm margin circumferentially. PTV2 was defined as the CTVa and CTVn with a 10 mm circumferential margin (CTVn = GTVn + 10 mm).

Table 1. Patient characteristics and radiotherapy dose

Characteristics	All patients (n = 20)	Substudy (n = 12)
Gender		
Male	2	1
Female	18	11
Age (years), median (range)	61 (33–82)	63.5 (33–82)
T stage (from MRI)		
T ₁	3	1
T ₂	8	5
T ₃	4	4
T ₄	4	1
TX	1	1
N stage (from MRI)		
N0	13	7
N1	1	1
N2	2	0
N3	4	3
T-location for substudy		
Anal verge		1
Anal canal		8
Anorectal		2
Low rectum		1
RT dose to primary tumour		
46.6 Gy	1	1
50.4 Gy	15	8
53.2 Gy	4	3

From November 2014, seven patients were treated and target volumes delineated as per The National Guidance for IMRT in Anal Cancer (NG) (v2.0).¹¹ To summarise, GTV and CTVe volumes were defined as above (with the additional inclusion of the obturator nodes in CTVe). For tumour stage T2-4 or node positive tumours, CTVa was comprised of a 15 mm expansion on a revised GTVa volume to include the anorectal junction to the anal verge and internal and external sphincters. CTVn included a 10 mm expansion from GTVn. CTVa and CTVn were edited offbone. All CTVs were then combined to create CTV_{all}. Finally, three PTV volumes were created; PTVa (GTVa + 25 mm), PTVn (CTVn + 10 mm) and PTVe (CTV_{all} + 10 mm). These patients were treated with a 7-field IMRT plan with a SIB. Dose prescriptions were tumour stage dependent. For tumour stage T₁/T₂N0, PTVa and PTVe were prescribed 50.4 and 40 Gy respectively in 28 fractions. For tumour stage T4N0/TAny node positive PTVa, PTVn and PTVe were prescribed 53.2, 50.4 and 40 Gy respectively in 28 fractions. For tumour stage T₃N0, the dose prescription was at the clinician's discretion, however, no T3N0 patients were treated post-November 2014.

Treatment verification

Treatment verification images were acquired using CBCT for at least the first three fractions, then weekly, thereafter. An offline correction strategy with a no action level imaging protocol was applied. Weekly images were reviewed with a tolerance of 3 mm. Images were registered to bony anatomy.

Quantifying set up errors

For all patients, translational displacement data based on a bone match were collected in the anteroposterior (AP), superior-inferior (SI) and left-right (LR) directions. A total 196 CBCT images were acquired for 20 patients. The population systematic and random set up errors were calculated and analysed. The population systematic error (Σ) is defined as the standard deviation of the individual mean set up errors about the overall population mean. The individual random error is defined as the standard deviation of the individual systematic set up error. The population random error (σ) is the mean of all the individual random errors.¹⁵

Quantifying motion and deformation of the anus

We identified a subset of 12 patients, who had adequate clinical and radiological data in order to carry out a retrospective quantification of anal motion and deformation. These 12 patients were categorised as “early” or “advanced” according to the NG classification (v3.0). Early stage included stage $T_1/2$ N0 ($n = 5$). Advanced stage included stages $T_3/4$ N_{any} and T_{any} N2/3 ($n = 7$). T_2 N1 patients were categorised at the clinicians discretion based on prognostic factors, however, we had no T2N1 patients included in this substudy. Following the guidance, the GTVa, CTVa and PTVa were retrospectively contoured on the planning CT as well as the GTVa for all available CBCTs for each patient included in the substudy. To reduce interobserver error, the same clinician contoured each of the patient volumes in one session. The CBCT CTVa for each corresponding CBCT GTVa was then expanded and edited following the NG (v3.0) by the study dosimetrist under the supervision of the same clinician delineating the retrospective contours for the substudy.

To quantify and describe the motion and deformation of the anus, volume data for all CBCT-based CTVa volumes were collected. For each patient, the CBCT CTVa volumes were encompassed into a single contour called the CBCT CTVa envelope. Using the co-ordinates of the treatment planning system, the distance between the most anterior point of the CBCT CTVa envelope and the most anterior point of the planning CTVa at any slice was calculated and described as the maximum anterior distortion. Thus, the anterior distortion could occur at different slice levels. The maximum distortion was measured for all orthogonal directions. Figure 1 describes this method.

The volume of the CBCT CTVa envelope outside of the planning PTVa was calculated to assess if any anal motion resulted in any part of the CBCT CTVa falling beyond the planning PTVa and, therefore susceptible to suboptimal dose coverage. Frequency data of distortion beyond the planning PTVa and location data of distortion within the anorectal complex were also collected.

RESULTS

Quantification of set up error

For the whole group ($n = 20$ and CBCT = 196), the population systematic set up error was 1 mm in each of the lateral, longitudinal and vertical directions, indicating small systematic error between CT and treatment. The population random set up errors was 3 mm for all directions, indicating reproducible setup. However, these set up errors are based on bony anatomy and not on the target volume.

Quantification of motion and deformation of the anus

Volume changes in CBCT CTVa

112 CBCT images were available for the 12 patients included in the anal motion and deformation substudy. Large differences were observed between the planning CTVa volume and between each of the individual CBCT CTVa imaging sessions. The minimum and maximum volume changes were between -22.1 and 66.5%. Table 2 and Figure 2 shows the difference between planning CTVa and mean CBCT CTVa for individual patients. % standard deviation (σ) > 10% were all observed in patients with a T location of anorectal or low rectum. We found that the anus is susceptible to large volume changes that do not appear to reduce or stabilise over time.

During treatment, all borders of the CBCT CTVa envelope showed anal distortion from the original position of the planning CTVa. These distortions were most commonly a result of anal expansion. For 9/12 patients, the anterior, posterior, superior, inferior and lateral borders of the CBCT CTVa envelope moved more anteriorly, posteriorly, inferiorly, superiorly and laterally respectively. Furthermore, three of these nine patients exhibited anal distension ≥ 1 cm in the anterior, posterior and left directions over the 6 weeks of treatment. Inferior anal border movement ≥ 1 cm was observed in 4/12 patients. It should be noted that maximum distensions of 1.7 cm and 2 cm were observed in the anterior and inferior directions respectively. These distensions did not appear to be related with T location.

Relationship of CBCT CTVa to planning PTVa

Data regarding the volume of CBCT CTVa envelope geographically outside of the planning PTVa were collected and analysed. Individual case data are shown in Table 2, as a percentage of CBCT CTVa envelope outside of the planning PTVa. Whilst motion was observed, the volume of CBCT CTVa envelope outside of PTVa was less than 3% for 11/12 patients. However, for case no. 12, 9.7% of the CBCT CTVa envelope fell outside of PTVa (as shown in Figure 3c,d). This particular patient was stage TXN3 with an unknown primary thought to arise from the anorectum region. Because the CTVa included anus as well as the lower rectum, this patient was particularly prone to rectal gas causing extreme motion and deformation of CBCT CTVa. To assess, if this motion was a single event, frequency data were collected regarding the number of times the individual CBCT CTVa fell outside of PTVa for each imaging fraction per patient (Figure 4). Although the volume of CBCT CTVa outside of the planning PTVa was found to be small, 5/12 patients had $\geq 50\%$ of

Figure 1. Diagram (a, b) describe the maximum distortion between the borders of the CBCT CTVa envelope (red contour) and the planning CTVa (blue contour). The corresponding CT contours are shown in (c, d). Planning CTVa (light green contour), CBCT CTVa envelope (orange contour) and planning PTV (pink contour) are presented. CBCT, cone beam CT; CTV, clinical target volume; PTV, planning target volume.

Table 2. Volume changes between planning CTVa and CBCT CTVa

Case	Planning CTVa (cm ³)	CBCT CTVa (cm ³)			Difference between planning CTVa and mean CBCT CTVa (%)	CBCT CTVa envelope outside of planning PTVa (%)
		Mean	σ	% σ		
1	195.4	202.8	22.1	10.9	3.6	1.7
2	86	106.8	10.4	9.7	19.5	0.4
3	95.5	99.1	5.7	5.8	3.7	0.2
4	90.7	104.4	5.2	5.0	13.1	0.3
5	623.1	580.1	66.8	11.5	-7.4	1.5
6	339.9	331.2	19.5	5.9	-2.6	0.2
7	321.6	335.1	13.3	4.0	4	0
8	90.6	96.8	5.1	5.3	6.5	1.3
9	299.1	295	18.3	6.2	-1.4	0
10	362	353.5	27.8	7.9	-2.4	2.8
11	154.4	176.8	17.3	9.8	12.6	1.2
12	338.4	374.9	76.9	20.5	9.8	9.7

Volume of CBCT CTVa envelope outside of planning PTVa.

CBCT, cone beam CT; CTV, clinical target volume; PTV, planning target volume.

Figure 2. Observed change in CBCT CTVa volume compared to the planning CTVa for each patient for each fraction. Difference is shown as a percentage. CBCT, cone beam CT; CTV, clinical target volume.

their imaging sessions, where the CBCT CTVa was outside of the planning PTVa.

Of the 112 CBCT images reviewed, individual distortions of CBCT CTVa outside of the planning PTVa were observed 21, 18 and 11 times in the anterior, posterior and inferior directions respectively. These distortions also correlate with, where the largest anal distensions were seen. To assess if these distortions occurred in one particular location within the anorectal complex, the planning PTVa was divided into upper, middle and lower thirds. 44% of distortions occurred in the upper third followed by 32% in the lower third and 24% in the middle third. Figure 3 shows the variation seen in the CTVa at the inferior border.

DISCUSSION

The main emphasis of this study was to investigate the interfractional motion and deformation of the AC and associated structures. To date, this is not discussed in the literature beyond Chen's conclusion that a bony match is sufficient for IGRT as the anus is a midline structure. However, there are data demonstrating GTVa movement independent of bony anatomy.⁹

We observed large volume changes in CTVa, which varied from the planning CT and between sequential CBCT images.

This volume change did not appear to follow a trend, however, the greatest changes in CTVa were present in patients with a T-location involving the anorectum junction. A small number of studies have shown that rectal motion and deformation is present in rectal cancer, however, it may not be possible to generalise these findings to the anus in anal cancer.¹⁶ Structures included in a rectal CTV include the GTV, rectum, mesorectum and lymph nodes. These structures are more superior to the CTVa in anal cancer and presumed liable to more deformation. Chong et al¹⁷ investigated the interfractional motion of the rectum for 16 patients with rectal cancer. Similar to our findings, they did not observe rectal volume changes that followed a trend. In contrast to this, Yamashita et al¹⁸ observed a statistically significant shrinking of the rectal volume in rectal cancer as radiotherapy progressed with a larger sample of 32 patients.

With respect to the anus and rectum as target organs, there is an obvious difference between the two anatomically. The former is a muscular organ, unlikely to distend and deform circumferentially but is prone to adjustment superiorly/inferiorly depending on the surrounding normal tissue muscular/fascia structures such as the pelvic floor. The rectum on the other hand is a reservoir organ prone to distension and variation depending on bowel, bladder and gas status.

Figure 3. Images (a, b) show the planning CT with the planning CTVa (red) and CBCT CTVa (blue). Images (c, d) show the corresponding CBCT for the derived CBCT CTVa (blue). *N.B* These images were matched on bone. CBCT, cone beam CT; CTV, clinical target volume.

Figure 4. Frequency (%) of CBCT CTVa outside of planning PTVa in one or more directions for individual cases. CBCT, cone beam CT; CTV, clinical target volume; PTV, clinical planning target volume.

Whilst anal distortions ≥ 1 cm were observed in the anterior, posterior, inferior and left directions for 4/12 patients, the volume of CBCT CTVa envelope geographically outside of planning PTVa was less than 3% for 11/12 patients, except for case 12, where 9.7% of the CBCT CTVa envelope was outside the planning PTVa. Our finding is consistent with Yamashita et al,¹⁸ who found that with a 10 mm PTV margin, a mean (SD) of rectum outside of the target was 0.7% (1.8%). The potential impact of large distortions is a geographical miss of the target. It is beyond the scope of this study to report if the minimum dose to CTVa was $\geq 95\%$ dose for 90% of patients. This is the parameter that the commonly used PTV margin formula by van-Herk et al¹⁹ uses, and is considered the lower safety level. The van-Herk et al¹⁹ formula does not assume patient rotations and target shape deformations. A 10 mm CTVa to PTVa margin is the current standard margin as recommended by the NG. Durrant et al⁹ thought that PTVa margins could potentially be reduced, but it was safer to keep the 10 mm margin to account for other sources of error. Currently, literature and experience regarding an imaging protocol that considers the soft tissue match of the anus in anal cancer is sparse. The increasing use of VMAT techniques means that the 95% isodose is extremely conformed and sharp dose gradients exist at the edge of PTVa. In view of these factors, a dosimetric assessment of coverage to all CTVs for patients undergoing radical radiotherapy for anal cancer using IMRT/VMAT is warranted.

To assess if motion and deformation occurred at a particular anatomical level, we divided the PTVa into upper-, middle- and lower-thirds. 44% of distortions occurred in the upper-third, most likely due to the presence of rectal gas within the low rectum. 32% of distortions, then occurred in the lower-third, which we believe could be due to daily variations in patient positioning and placement of the buttocks upon the treatment couch, which can potentially move the inferior border of the anus.

A further aim of this study was to prospectively audit our set up errors for a cohort of anal cancer patients receiving radical radiotherapy using CBCT. We report a population systematic and random set up error of 1 and 3 mm respectively for all orthogonal directions, suggesting our immobilisation is reproducible and of a high standard. Chen et al,⁸ the only other investigators to report set up errors in anal cancer using daily MVCT imaging data report population systematic errors of 1.1, 3.6, 3.2 mm and random set up errors of 3.8, 5.5 mm and 2.9 mm in the AP, LR and SI directions respectively.

As with most imaging studies which include CBCT images, we found that the image quality for soft tissue delineation was a limitation in this study. Identifying CBCT-based GTVa and CTVa was at times challenging. The other limitation of the study was the sample size consisting of 12 patients, which was linked to the challenge of soft tissue identification acknowledged above.

Having identified that deformation occurs during treatment, as per the NG, daily IGRT will increase our understanding of interfraction motion and provide a more detailed analysis of on-treatment verification. A future challenge for anal cancer, IGRT will be to include a soft tissue match in addition to the daily bone match at treatment verification. A soft tissue match should ensure a good match of the planning CTVa with the acquired treatment CBCT CTVa, however, empirical evidence from our experience has shown that a soft tissue match based on CTVa only potentially results in large rotations superiorly. Therefore, there is potential to miss the superior nodal CTVs which have a 5 mm CTV to PTV margin.

CONCLUSION

This study has shown that the anus is susceptible to volume changes and shape deformations. Care must be taken when calculating or considering reducing the PTV margin to the anus.

REFERENCES

- James RD, Glynne-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 × 2 factorial trial. *Lancet Oncol* 2013; **14**: 516–24. doi: [https://doi.org/10.1016/S1470-2045\(13\)70086-X](https://doi.org/10.1016/S1470-2045(13)70086-X)
- Muirhead R, Drinkwater K, O'Cathail SM, Adams R, Glynne-Jones R, Harrison M, et al. Initial results from the royal college of radiologists' UK national audit of anal cancer radiotherapy 2015. *Clin Oncol* 2017; **29**: 188–97. doi: <https://doi.org/10.1016/j.clon.2016.10.005>
- Gilbert DC, Drinkwater K, O'Cathail SM, Adams R, Glynne-Jones R, Harrison M, et al. Stepwise multicenter introduction of intensity modulated radiation therapy for anal cancer in the United Kingdom: from consensus guidance to large-scale prospective audit, prior to future clinical trials. *Int J Radiat Oncol Biol Phys* 2016; **96**: S105–S106. doi: <https://doi.org/10.1016/j.ijrobp.2016.06.260>
- Kachnic LA, Winter K, Myerson RJ, Goodyear MD, Willins J, Esthappan J, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. *Int J Radiat Oncol Biol Phys* 2013; **86**: 27–33. doi: <https://doi.org/10.1016/j.ijrobp.2012.09.023>
- International Commission on Radiation Units and Measurements. Prescribing, recording and reporting beam therapy Report No.: 50.. 1993. doi: <https://doi.org/10.1118/1.597396>
- International Commission on Radiation Units and Measurements. Prescribing, recording and reporting beam therapy (supplement to ICRU Report 50) Report No.: 62.. 1999.
- International Commission on Radiation Units and Measurements. Prescribing, recording and reporting photon beam therapy Report No.: 83.. 2010.
- Chen YJ, Suh S, Nelson RA, Liu A, Pezner RD, Wong JY. Setup variations in radiotherapy of anal cancer: advantages of target volume reduction using image-guided

- radiation treatment. *Int J Radiat Oncol Biol Phys* 2012; **84**: 289–95. doi: <https://doi.org/10.1016/j.ijrobp.2011.10.068>
9. Durrant L, Robinson M, Hawkins MA, Van den Heuvel F, Muirhead R. Quantifying target-specific motion in anal cancer patients treated with intensity modulated radiotherapy (IMRT). *Radiother Oncol* 2016; **121**: 92–7. doi: <https://doi.org/10.1016/j.radonc.2016.08.011>
 10. Nabavizadeh N, Elliott DA, Chen Y, Kusano AS, Mitin T, Thomas CR, et al. Image guided radiation therapy (IGRT) practice patterns and IGRT's impact on workflow and treatment planning: results from a national survey of American society for radiation oncology members. *Int J Radiat Oncol Biol Phys* 2016; **94**: 850–7. doi: <https://doi.org/10.1016/j.ijrobp.2015.09.035>
 11. Muirhead R, Adams RA, Gilbert DC, Harrison M, Glynne-Jones R, Sebag-Montefiore D. *National guidance for IMRT in anal cancer*. 2016. Available from: <http://analimrtguidance.co.uk/National-Guidance-IMRT-Anal-Cancer-V4-Jan17.pdf> [accessed 22 February 2017].
 12. Muirhead R, Adams RA, Gilbert DC, Glynne-Jones R, Harrison M, Sebag-Montefiore D, et al. Anal cancer: developing an intensity-modulated radiotherapy solution for ACT2 fractionation. *Clin Oncol* 2014; **26**: 720–1. doi: <https://doi.org/10.1016/j.clon.2014.08.001>
 13. Nederveen AJ, Dehnad H, van der Heide UA, van Moorselaar RJ, Hofman P, Lagendijk JJ. Comparison of megavoltage position verification for prostate irradiation based on bony anatomy and implanted fiducials. *Radiother Oncol* 2003; **68**: 81–8. doi: [https://doi.org/10.1016/S0167-8140\(03\)00129-4](https://doi.org/10.1016/S0167-8140(03)00129-4)
 14. Radiation Therapy Oncology Group. Elective clinical target volumes in anorectal cancer: an RTOG consensus panel contouring atlas. 2011. Available from: <http://www.rtog.org/LinkClick.aspx?fileticket=DgflROvKQ6w%3d&tabid=231> [Accessed 15th March, 2011].
 15. The Royal College of Radiologists, Institute of Physics and Engineering in Medicine, Society and College of Radiographers. *On target: ensuring geometric accuracy in radiotherapy*. London: The Royal College of Radiologists; 2008.
 16. Gwynne S, Webster R, Adams R, Mukherjee S, Coles B, Staffurth J. Image-guided radiotherapy for rectal cancer — a systematic review. *Clin Oncol* 2012; **24**: 250–60. doi: <https://doi.org/10.1016/j.clon.2011.07.012>
 17. Chong I, Hawkins M, Hansen V, Thomas K, McNair H, O'Neill B, et al. Quantification of organ motion during chemoradiotherapy of rectal cancer using cone-beam computed tomography. *Int J Radiat Oncol Biol Phys* 2011; **81**: e431–e438. doi: <https://doi.org/10.1016/j.ijrobp.2011.04.060>
 18. Yamashita H, Takenaka R, Sakumi A, Haga A, Otomo K, Nakagawa K. Analysis of motion of the rectum during preoperative intensity modulated radiation therapy for rectal cancer using cone-beam computed tomography. *Radiat Oncol* 2015; **10**: 2. doi: <https://doi.org/10.1186/s13014-014-0311-6>
 19. van Herk M, Remeijer P, Lebesque JV. Inclusion of geometric uncertainties in treatment plan evaluation. *Int J Radiat Oncol Biol Phys* 2002; **52**: 1407–22. doi: [https://doi.org/10.1016/S0360-3016\(01\)02805-X](https://doi.org/10.1016/S0360-3016(01)02805-X)