

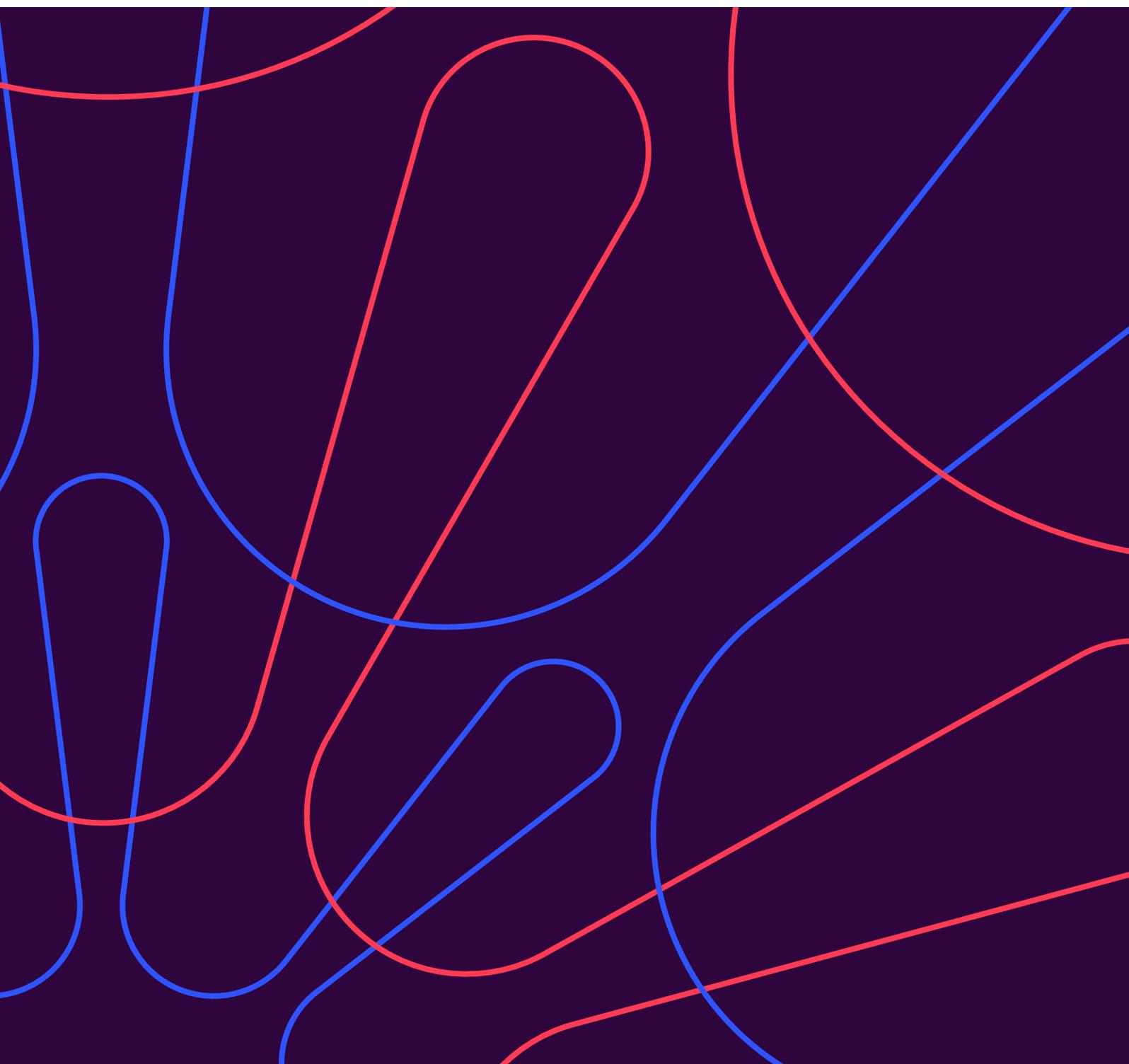
# Clinical Oncology

## National guidance for volumetric-modulated arc therapy (VMAT) or intensity-modulated radiotherapy (IMRT) in anal cancer

MAY 2024



The Royal College of Radiologists



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# 01

## Introduction

This document provides a practical and evidence-based consensus guideline for planning and treatment of patients receiving volumetric-modulated arc therapy (VMAT) or intensity-modulated radiotherapy (IMRT) to a full radiotherapy dose for anal cancer in the UK. The guidance illustrates the consensus reached among the authors and collaborative groups.

This guidance was initially written in 2012 and has undergone a number of iterations over the years until being adopted and published as the current Royal College of Radiologists (RCR) guidance document in 2024. It has formed the basis of the PLATO trial (Personalising Anal cancer radioTherapy dOse, ISRCTN88455282). It is acknowledged that some aspects of the guidance are outdated, such as the lack of a multidisciplinary team on the author list and lack of use of American Association of Physicists in Medicine (AAPM) nomenclature.<sup>1</sup> However, it is felt appropriate to leave the guidance as we currently practise, and as results from the PLATO trial are published, the guidance will evolve accordingly.

This document provides guidance for VMAT/IMRT treatment in anal cancer and the interpretation, local implementation and use remain the responsibility of the treating clinician.

Further discussion on the background to these guidelines is offered in the original 2014 and planned 2024 editorials published in *Clinical Oncology*.<sup>2</sup>

# 02

## Pre-radiotherapy investigations

- History and clinical examination, performance status (PS), document HIV status.
- Computed tomography (CT) scan of chest / abdomen / pelvis.
- Whole body positron emission tomography CT (PET/CT) in  $\geq T2$  tumours is recommended.
- For nodes identified on PET/CT a multidisciplinary team (MDT) discussion is recommended to determine which nodes should be included in the high-dose volume.
- Consider biopsy or fine-needle aspiration (FNA) of any suspicious inguinal nodes depending on likelihood of definitive result and time delay to treatment.
- All female patients should have a per vaginal (PV) exam by the treating oncologist and be up to date with cervical smear screening (or referred for up-to-date smear prior to starting treatment).

Indications for a defunctioning stoma: tumours infiltrating into the posterior vagina.

In centres managing significant faecal incontinence with defunctioning colostomy an awareness of the local reversal rate is recommended, in view of the ACT II data describing a poor reversal rate once a stoma has been formed.<sup>3</sup>

Due to the rarity of HIV and immunocompromised patients in this patient group, clinicians should decide management for HIV-positive patients on a case-by-case basis in collaboration with the infectious disease clinicians. In addition, close liaison with an infectious disease specialist is appropriate during radiotherapy as CD4 counts will need monitoring on chemoradiotherapy (CRT) and management of antiretrovirals may be required. Performance status, presenting CD4 count, co-morbidities, size and stage of the tumour should be taken into account. If there is low viral load, the patient is on HAART (highly active antiretroviral therapy), CD4 is  $>200$  cells/mm<sup>3</sup> and there are no other co-morbidities then the standard CRT regime is indicated.

# 03

## Therapeutic schema

### Dose prescription T1 /T2 N0

- Elective (PTV\_Elec) = 40 Gy in 28 fractions (#) (1.43 Gy per #) in 5.5 weeks.
- Gross anal disease (PTV\_Anal) = 50.4 Gy in 28# (1.8 Gy per #) in 5.5 weeks.

### Dose prescription T3/4N0 or Tany N1–3

- Elective (PTV\_Elec) = 40 Gy in 28# (1.43 Gy per #) in 5.5 weeks.
- Gross nodal disease <3 cm (PTV\_Nodes) = 50.4 Gy in 28# (1.8 Gy per #) in 5.5 weeks.
- Gross nodal disease >3 cm (PTV\_Nodes) = 53.2 Gy in 28# (1.9 Gy per #) in 5.5 weeks.
- Gross anal disease (PTV\_Anal) = 53.2 Gy in 28# (1.9 Gy per #) in 5.5 weeks.

### Concurrent chemotherapy

Concurrent chemotherapy should be prescribed in all patients that are considered fit for standard treatment.

Acceptable regimens are:

- Mitomycin 12 mg/m<sup>2</sup> day 1 with 5FU 1,000 mg/m<sup>2</sup> days 1–4 and days 29–32.
- Mitomycin 12 mg/m<sup>2</sup> day 1 with capecitabine 825 mg/m<sup>2</sup> twice daily on days of external beam radiotherapy (XRT).

Dose reductions due to patient co-morbidities, dihydropyrimidine dehydrogenase (DPD) status, performance status and/or age are at the discretion of the treating team.

### Review on treatment

Patients must be reviewed weekly by a member of the MDT.

### Category

Anal cancer is a Category 1 tumour type.

# 04

## Pre-treatment

### Patient simulation and immobilisation

- Standard position is supine with immobilisation for popliteal fossa and feet.
- Prior to pre-treatment scan, the clinician should assess the diagnostic imaging and ascertain whether the tumour is adequately bolused by the surrounding buttocks – 5 mm of tissue surrounding gross tumour volume (GTV). If there is not 5 mm of tissue around the whole GTV consider lying the patient on tailored wax or sheet bolus. It is suggested to avoid treating patients prone.
- In inguinal nodes, bolus should only be used if there is visible skin infiltration.
- The distal point of macroscopic disease or anal verge can be delineated with a radio-opaque marker prior to imaging, whichever is more inferior (optional).
- Following excision, a radio-opaque marker must be placed at the excision scar or anal verge.
- All patients must be scanned with a comfortably full bladder (>250 ml).
- The use of IV contrast to aid delineation of pelvic vessels is strongly recommended.
- The use of oral contrast is at the discretion of the site but may aid in delineation of small bowel.
- Once the patient is scanned, tattoo and document as per local protocol.

# 05

## Delineation

- Local practice may be followed in relation to fusion of CT simulation and magnetic resonance imaging (MRI) or PET imaging.
- The primary GTV should be determined by the treating clinician using the planning CT, clinical data, MRI and PET/CT.
- The nodal GTV should be determined by the treating clinician using the planning CT, clinical data, MRI and PET/CT.
- We define skin involvement as visible changes to skin such as erythema or ulceration; if skin is normal visually but on palpation feels thickened and/or oedematous, it should be considered involved.
- Principles of microscopic disease extent in the vicinity of gross disease: There are no surgical data regarding the microscopic extent of anal cancer tumours. One study investigating a small number of squamous cell carcinomas (SCC) skin recommends clinical target volume (CTV) 11 mm for SCC <2 cm and 14 mm for SCC >2 cm.<sup>1</sup> We have therefore elected to use a 10 mm GTV to CTV margin for early cancers and 15 mm for locally advanced primary tumours.

# 06

## Volume definitions

### Good prognosis T1N0 tumours

In small, good prognosis tumours it may be appropriate to offer CRT to the primary tumour plus a margin rather than deliver elective nodal irradiation. In these cases:

- **GTV\_A** = Includes the gross primary anal tumour volume OR the site of the primary tumour and excision scar if resected.
- **CTV\_A** = GTV\_A + 10 mm. Following this, manually enlarge to ensure coverage of entire anal canal including outer border, from the anorectal junction (approximately 4 cm superiorly from anal verge identified by the radio-opaque marker) to the anal verge including the internal and external anal sphincters. Edit to exclude bone and muscle. (See Figure 1)
- **PTV\_Anus** = CTV\_A + 10 mm.

Figure 1. Example of a case with tumour extending into lower rectum aiming to demonstrate the steps to produce CTV\_A

1. To create GTV\_A: ■

Draw the GTV\_A using clinical findings, planning CT and diagnostic MRI.



2. To create GTV + margin: ■

Enlarge the GTV\_A by the suggested margin (10 mm for early tumours, 15 mm for locally advanced).



3. To create CTV\_A: ■

Enlarge the GTV + margin to incorporate the entire outer border of anal or rectal lumen around GTV, anal canal and anal verge including internal and external sphincters.



# 06

## Volume definitions

## Early tumours

Early tumours include T1N0 which require prophylactic nodal irradiation due to poor prognostic factors or T2N0 tumours.

For the delineation of the elective nodal regions (CTV\_E) there are detailed directions in Appendix 1. Elective nodal areas should include bilateral inguinal femoral, external iliac, internal iliac, obturators and presacral lymph nodes. For the mesorectal nodal area, if there is no gross disease, either primary tumour or nodal disease, within the mesorectum, only the lower 50 mm of the mesorectum is included in the CTV\_E.

Note: In the unusual event of gross tumour infiltration into the ischiorectal fossa (defined by cancer >5 mm outside the levators, puborectalis muscles, external anal sphincter or anal verge clinically or by diagnostic imaging) please follow the guidance used for inclusion of the ischiorectal fossa as per locally advanced tumours below.

Please follow the nomenclature described below. All the expansions are in three dimensions unless stated otherwise.

- **GTV\_A** = Includes the gross primary anal tumour volume. The volume should be limited to the gross tumour and not include the whole lumen.
- **CTV\_A** = GTV\_A + 10 mm. Following this, manually enlarge to ensure coverage of entire anal canal including outer border from the anorectal junction (approximately 4 cm superiorly from anal verge identified by the radio-opaque marker) to the anal verge including the internal and external anal sphincters. Edit to exclude bone and muscle. (See Figure 1)
- **CTV\_E** = Elective nodal regions. (See Appendix 2)
- **PTV\_A** = CTV\_A + 10 mm.
- **PTV\_E** = CTV\_E + 5 mm.

### Early tumours

<b>GTV_A</b> = primary tumour	<b>GTV_N</b> = involved nodes	
<b>CTV_A</b> = GTV_A + 10 mm	<b>CTV_N</b> = GTV_N + 5 mm	<b>CTV_E</b>
<b>PTV_A</b> = GTV_A + 10 mm*	<b>PTV_N</b> = GTV_N + 5 mm*	<b>PTV_E</b> = CTV_E + 5 mm

\*These margins are appropriate for patients treated with daily online imaging. We recommend centres audit their local set-up regularly.

# 06

## Volume definitions

## Locally advanced tumours

Locally advanced tumours include T3/4Nany or Tany N1–3.

For the delineation of the elective nodal regions (CTV\_E) there are detailed directions in Appendix 1. Elective nodal areas should include bilateral inguinal femoral, external iliac, internal iliac, obturators and presacral lymph nodes. For the mesorectal nodal group, if there is no gross disease, either primary tumour or nodal disease, within the mesorectum, only the lower 50 mm of the mesorectum is included in the CTV\_E; if the primary tumour or mesorectal nodes lie within the mesorectum, the whole mesorectum is included in the CTV\_E. Ischiorectal fossa should not be routinely included in CTV\_E; however, if there is gross tumour infiltration into the ischiorectal fossa (defined by cancer >5 mm outside the levators, puborectalis muscles, external anal sphincter or anal verge clinically or by diagnostic imaging) please follow the guidance in Appendix 1.

Please follow the nomenclature described below. All the expansions are in three dimensions unless stated otherwise.

- **GTV\_A** = Includes the gross primary anal tumour volume. The volume should be limited to the gross tumour and not include the whole lumen.
- **GTV\_N** = Includes all involved nodes.
- **CTV\_A** = GTV\_A + 15 mm. Following this, manually enlarge to ensure coverage of entire anal canal including outer border from the anorectal junction (approximately 4 cm superiorly from anal verge identified by the radio-opaque marker) to the anal verge including the internal and external anal sphincters (see Figure 1). If there is no bone or muscle involvement, edit to exclude bone and muscle; if there is bone or muscle involvement, only edit the structure free from infiltration.
- **CTV\_N** = GTV\_N + 5 mm.
- **CTV\_E** = Elective nodal regions. (See Appendix 1)
- **PTV\_A** = CTV\_A + 10 mm.
- **PTV\_N** = CTV\_N + 5 mm.
- **PTV\_E** = CTV\_E + 5 mm.

### Locally advanced tumours

<b>GTV_A</b> = primary tumour	<b>GTV_N</b> = involved nodes	
<b>CTV_A</b> = GTV + 15 mm	<b>CTV_N</b> = GTV_N + 5 mm	<b>CTV_E</b>
<b>PTV_A</b> = CTV_A + 10 mm*	<b>PTV_N</b> = CTV_N + 5 mm*	<b>PTV_E</b> = CTV_E + 5 mm*

\*These margins are appropriate for patients treated with daily online imaging. We recommend centres audit their local set up regularly.

# 06

## Volume definitions

## Organs at risk

The Radiation Therapy Oncology Group (RTOG) guidance on pelvic normal tissue contouring can offer some direction,<sup>4</sup> although there are some slight differences to what is suggested below. The following organs at risk (OAR) must be delineated by the radiographer, dosimetrist, physicist or consultant:

- **Small bowel:** Contouring should include all individual small bowel loops to at least 20 mm above the superior extent of both planning target volumes (PTVs). It may be helpful to initially delineate the large bowel ± endometrium to exclude these from subsequent delineation of the small bowel.
- **External genitalia:** Delineation of the male genitalia should include the penis and scrotum out laterally to the inguinal creases. In women it should include the clitoris, labia majora and minora out to the inguinal creases. The superior border in both sexes should lie midway through the symphysis pubis. See Appendix 3 for pictorial guidance.
- **Bladder:** The entire bladder including outer bladder wall.
- **Right and left femoral heads:** To be contoured separately on each side. To include the ball of the femur, trochanters and proximal shaft to the level of the bottom of the ischial tuberosities.

All PTVs, other than those where skin is involved with tumour, should be edited to lie 5 mm inside the body contour.

# 07

## Treatment modality

### Good prognosis T1N0 tumours

- If tumour plus margin is treated, it is at the discretion of the treating oncologist whether an inverse plan or 3D conformal plan is used. If IMRT is used, all efforts to reduce dose to OARs to the minimum should be undertaken, as objectives are likely to be easily met.
- For 3D conformal treatment, delivery with 6 MV photons using gantry angles of 90°, 180° and 270° is suggested.

### All other tumours

- Inverse plan using simultaneous integrated boost technique delivered with coplanar beams or arc delivery.
- An advanced convolution superposition algorithm should be used for calculation, for example AAA (Eclipse), CCCS (Pinnacle), CC (Oncentra).

For IMRT:

- Suggested beam positions if supine: 0°; 310°; 275°; 210°; 150°; 85°; 50°.
- Suggested beam positions if prone: 180°; 130°; 95°; 30°; 330°; 265°; 230°.

# 08

## Planning parameters

- Prescription point: 100% to the median dose in PTV (ICRU 83).
- Target coverage and OAR requirements, both objectives and mandatory constraints, are documented on the Anal VMAT/IMRT planning sheet (Appendix 4).
- Standard VMAT/IMRT practice of editing lower dose levels off higher dose levels following contouring. Constraints applicable for edited volume only.

Preferred priority of structures in planning:

1. PTVs – these will always take priority over any OAR constraint
2. Small bowel
3. Femoral heads
4. Genitalia
5. Bladder.

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# 09

## Treatment delivery

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In view of the reduction in CTV to PTV margins, we suggest daily online imaging. We suggest cone beam CT performed on days 1–5 and weekly thereafter as a minimum. Online paired kV/MV images should be performed on other treatment days.

Any deviation from this and 5 mm CTV to PTV margins may not be appropriate.

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# 10

## Follow-up

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Follow-up as per local protocol.

## References

1. Mayo CS, Moran JM, Bosch W *et al*. American Association of Physicists in Medicine Task Group 263: standardizing nomenclatures in radiation oncology. *Int J Radiat Oncol Biol Phys* 2018; **100**(4): 1057–1066.
2. Muirhead R, Adams RA, Gilbert DC *et al*. Anal cancer: developing an intensity-modulated radiotherapy solution for ACT2 fractionation. *Clin Oncol (R Coll Radiol)* 2014; **26**(11): 720–1.
3. James RD, Glynne-Jones R, Meadows HM *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**(6): 516–524.
4. Gay HA *et al*. Pelvic normal tissue contouring guidelines for radiation therapy: a Radiation Therapy Oncology Group consensus panel atlas. *Int J Radiat Oncol Biol Phys* 2012; **83**(3): e353–62.

# Appendices

APPENDIX 1. Instructions for the delineation of CTV\_E

APPENDIX 2. Borders of lymph node compartments

APPENDIX 3. Delineation of the genitalia

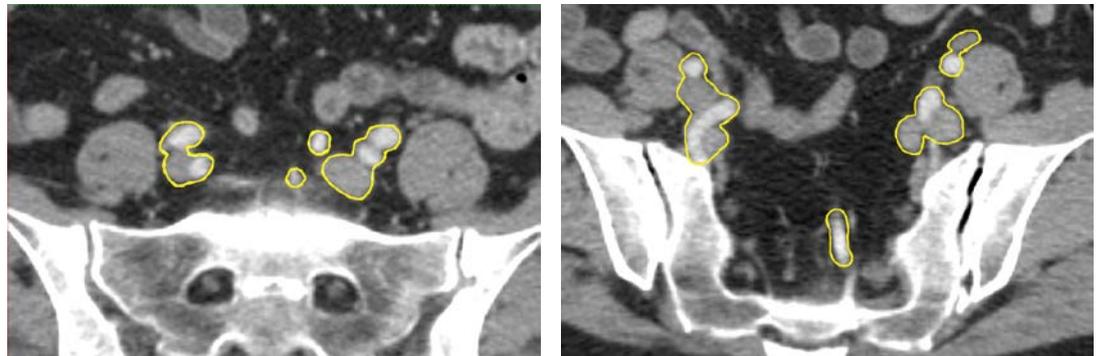
APPENDIX 4: Anal VMAT/IMRT planning sheet

# A1

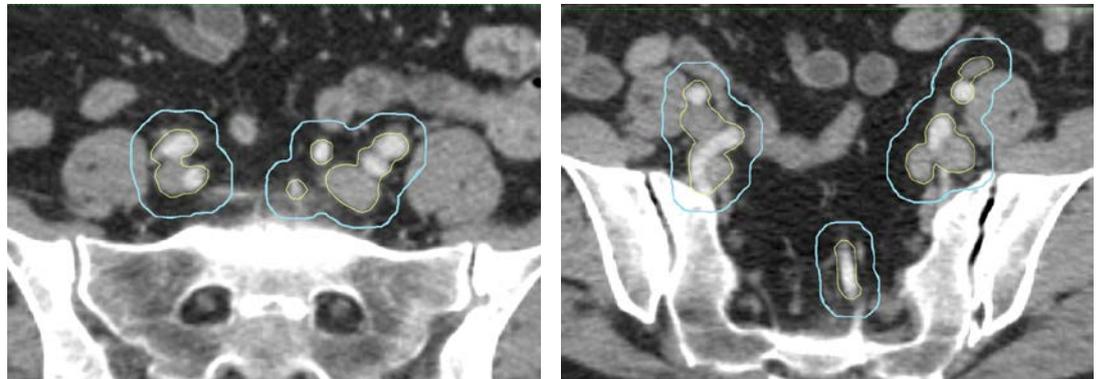
## Instructions for the delineation of CTV\_E

CTV\_E includes the nodal groups internal iliac, external iliac, obturator, inguinal, presacral and mesorectum (lower 50 mm in patients with no mesorectal nodes, whole mesorectum in those with mesorectal nodes present).

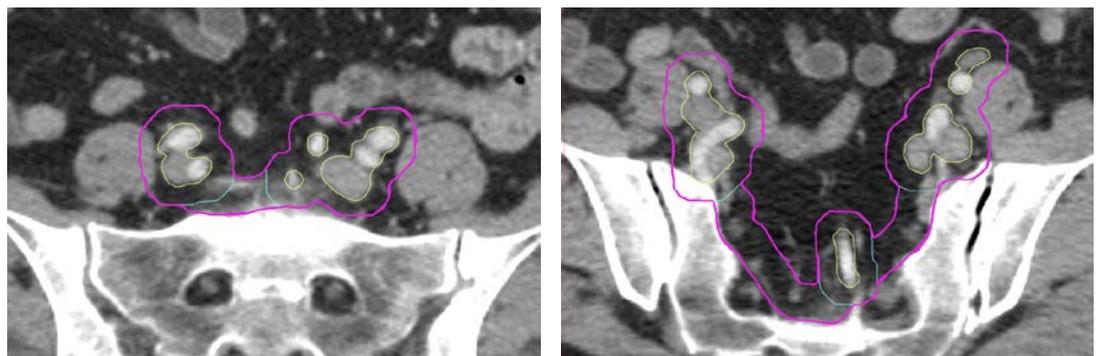
1. To draw the internal iliac, external iliac and sacral nodal groups: draw the internal and external iliac vessels from 20 mm above the inferior aspect of the sacroiliac joints or 15 mm above the most superior aspect of the gross tumour, whichever is most superior.



2. Expand the vessels by 7 mm in all directions except superiorly.



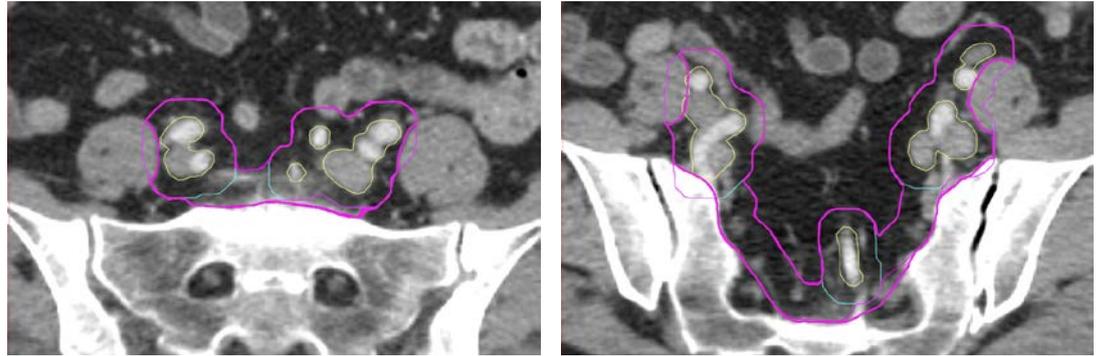
3. Copy the above volumes into CTV\_E and join the volumes together with a 10 mm 'rollerball' along the medial edges of the iliopsoas or obturator internus muscle and anterior to the sacrum.



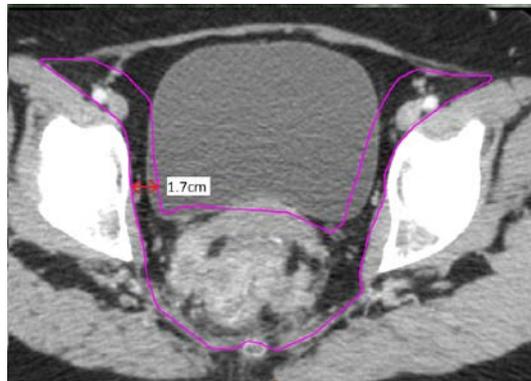
# A1

## Delineation of CTV\_E

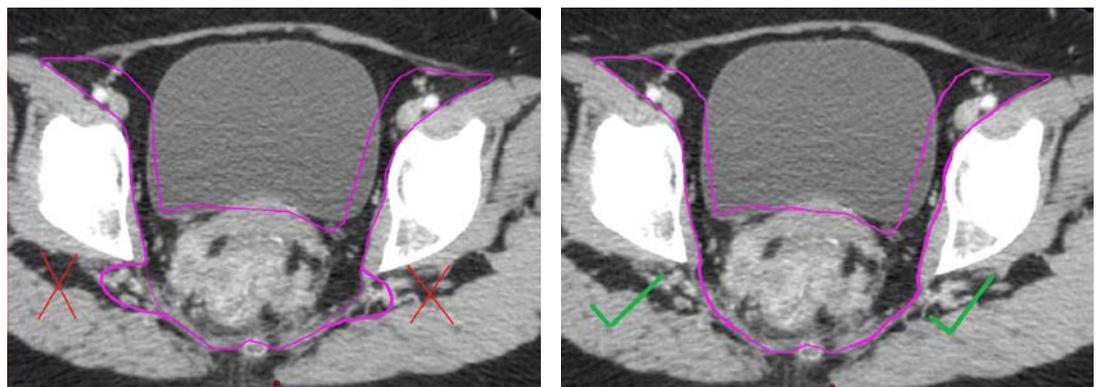
4. Edit the volume off obturator internus muscle or iliopsoas muscle and off bone. Edit out of sacral hollows as no lymph nodes in these.



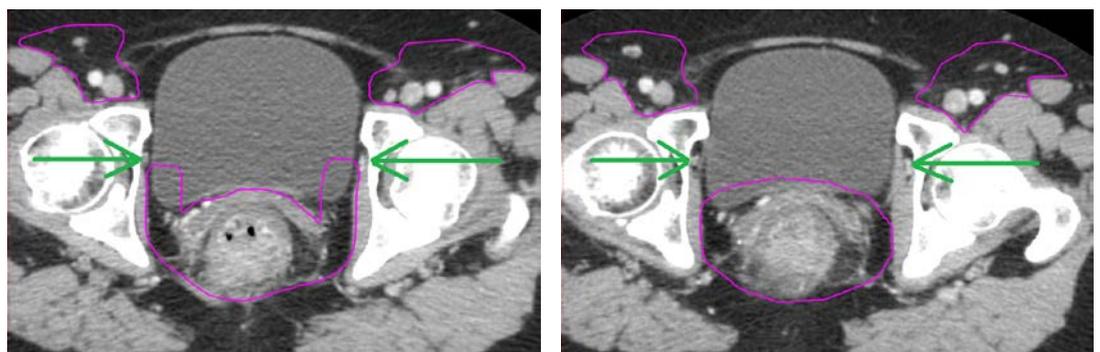
5. The volume is continued inferiorly to encompass the obturators. The obturator nodes should be created by running a 1.7 cm rollerball medial to the obturator muscles. The inner borders can extend into the adjacent organ (eg bladder or small bowel).



6. **Avoid** extending the volume laterally past the lateral border of the obturator internus. There is no need to include the gluteal artery/nerve and sciatic nerve.



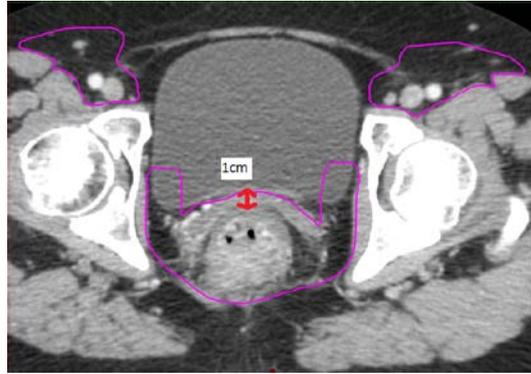
7. The obturator nodes stop inferiorly when the obturator artery exits the pelvis.



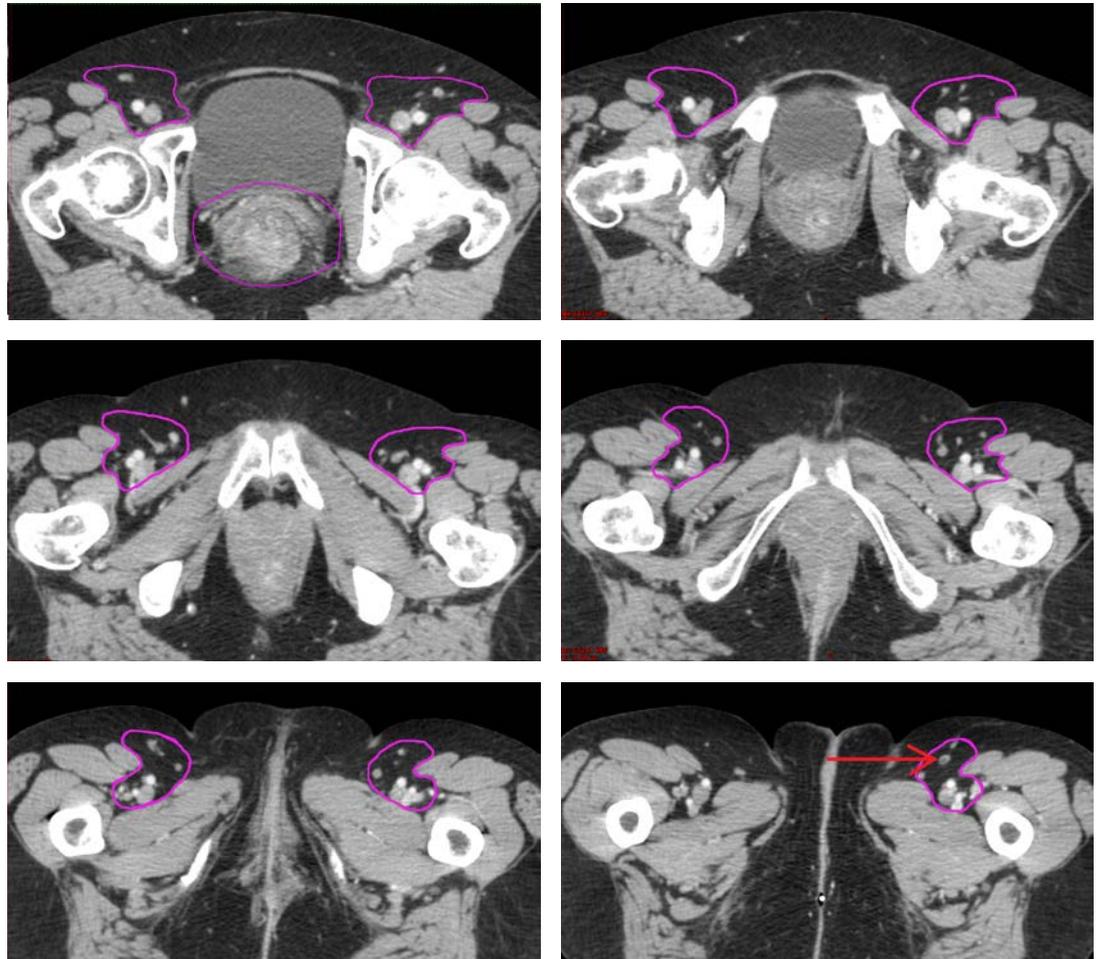
# A1

## Delineation of CTV\_E

8. As the volume extends inferiorly, the mesorectum must be incorporated. For the superior border, if the primary tumour or involved lymph nodes lie within the mesorectum, the whole mesorectum should be delineated. If the primary tumour does not enter the mesorectum and there are no involved mesorectal nodes, the lower 50 mm of the mesorectum should be encompassed (from the anorectal junction). The anterior border should extend 10 mm into the anterior organ (eg bladder, vaginal, endometrium, prostate, seminal vesicles).



9. The inguinal nodes should be added as a compartment. The volumes must cover superficial and deep inguinal lymph nodes of the femoral triangle. All visible nodes and lymphoceles should be included. The lateral borders are the medial edge of sartorius or iliopsoas, medial border is the spermatic cord in men, or the medial third to half of the pectineus or adductor longus muscle in women. Posterior border is defined by pectineus, adductor longus and iliopsoas. Anterior border is 5 mm from skin.

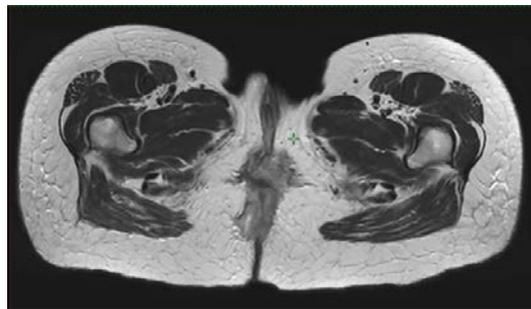


# A1

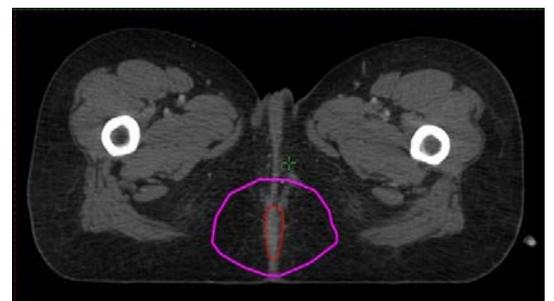
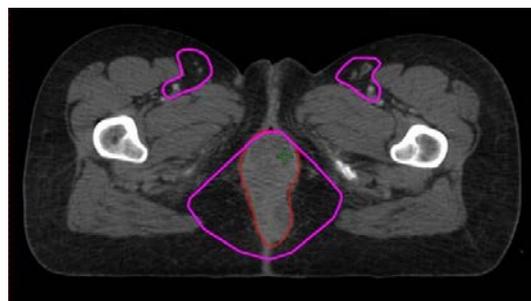
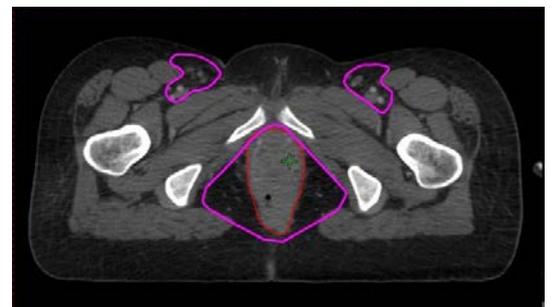
## Delineation of CTV\_E

10. The ischiorectal fossa should only be delineated if there is visible infiltration >5 mm outside the levators, puborectalis muscles, external anal sphincter or anal verge into the ischiorectal fossa, clinically or on diagnostic imaging. Otherwise, it should not be included. The superior border of the ischiorectal fossa is the levator ani, gluteus maximus and obturator internus; the lateral borders are formed by the ischial tuberosity, obturator internus and gluteus maximus muscles; the anterior border is the level where the obturator internus muscle, levator ani and anal sphincter muscles fuse or more inferiorly at least 10–20 mm anterior to the sphincter muscles; there exists no anatomical structure that delineates the most inferior level of the ischiorectal fossa but the level of the anal verge is appropriate; lastly, the posterior border is the transverse plane joining the anterior border of the medial walls of the gluteus maximus.

Below is a diagnostic MRI demonstrating infiltration beyond the anal verge into the right ischiorectal fossa.



Below is an illustration of anal tumour extending beyond the anal verge into the ischiorectal fossa. The purple volume is the CTV\_E encompassing the ischiorectal fossa with the GTV in red.



# A2

## Borders of lymph node compartments

	<b>Superior</b>	<b>Inferior</b>	<b>Lateral</b>	<b>Medial</b>	<b>Anterior</b>	<b>Posterior</b>
<b>Internal iliac nodes</b>	20 mm above the inferior aspect of sacroiliac joint or 15 mm above the most anterior site of gross tumour, whichever is most superior.	The point of levator ani insertion into the obturator fascia and obturator internus.	In the upper pelvis, the iliopsoas muscle. In the lower pelvis, the obturator internus muscle.	In the upper pelvis, 7 mm medial to internal iliac vessels. In the lower pelvis, the mesorectum and presacral space.	In the upper pelvis, 7 mm anterior to the internal iliac vessels. In the lower pelvis, the obturator internus muscle or bone.	The bony pelvis.
<b>External iliac nodes</b>	See superior border of internal iliac.	The inguinal lymph nodes.	The iliopsoas muscle.	In the upper pelvis, 7 mm medial to the external iliac vessels. In the lower pelvis 10 mm inside the bladder or small bowel.	7 mm anterior to the external iliac vessels encompassing all visible benign lymph nodes.	The internal iliac lymph node group.
<b>Inguinal nodes</b>	The external iliac nodal group.	At the inferior slice demonstrating the lesser trochanter.	The medial edge of sartorius or iliopsoas.	To include all visible lymph nodes or lymphoceles. The spermatic cord in men. The medial third to half of the pectineus or adductor longus muscle in women.	Approximately 5 mm in from the skin surface.	The pectineus, adductor longus and iliopsoas.
<b>Mesorectal nodes</b>	If there are no mesorectal nodes: the lower 50 mm of the mesorectum. If the primary tumour or involved nodes lie within the mesorectum: the level of the rectosigmoid junction, best identified where the superior rectal artery turns anteriorly.	The anorectal junction approximately where the levator ani inserts into the sphincter complex.	The medial edges of the mesorectal fascia and levator ani.		10 mm anterior to the mesorectum into the anterior organs (penile bulb/prostate and seminal vesicles/ bladder in males; bladder/vagina/ cervix and uterus in females).	The sacrum or coccyx.

# A2

## Lymph node compartments

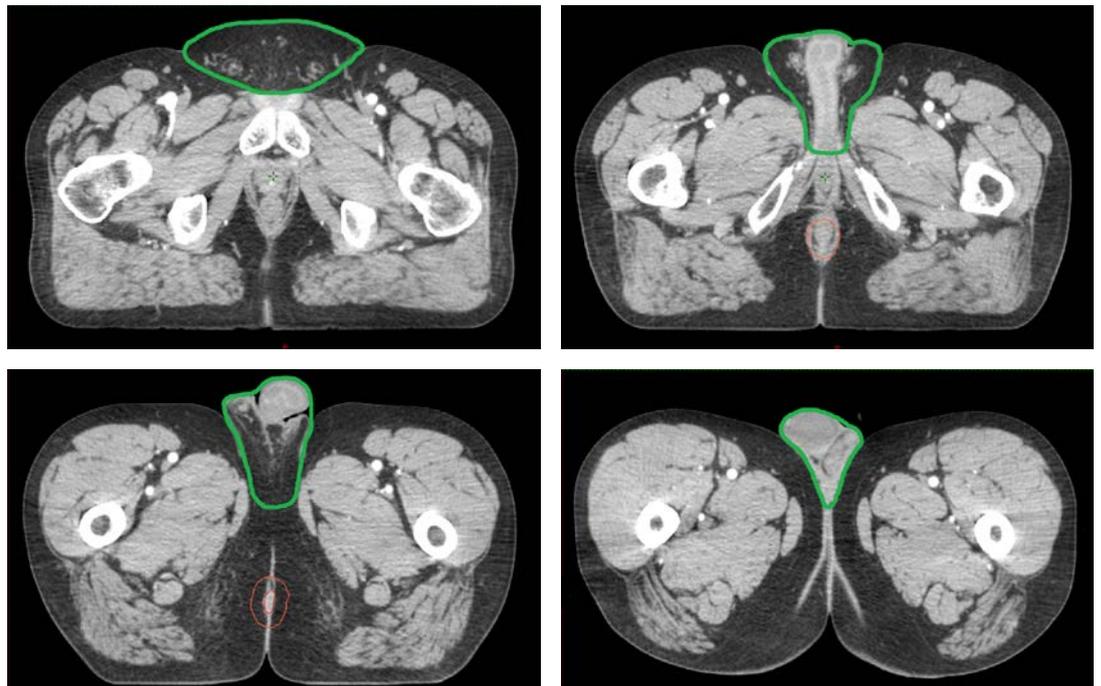
	<b>Superior</b>	<b>Inferior</b>	<b>Lateral</b>	<b>Medial</b>	<b>Anterior</b>	<b>Posterior</b>
<b>Presacral nodes</b>	See superior border of internal iliac.	The edge of the coccyx.	Sacroiliac joints.		10 mm anterior to the anterior sacral border encompassing any lymph nodes or presacral vessels.	The sacrum.
<b>Obturator nodes</b>	Superiorly 3–5 mm above the obturator canal where the obturator artery is sometimes visible.	The obturator canal where the obturator artery has exited the pelvis.	The obturator internus muscle.	Medial: maximum 10 mm into the bladder.	The anterior extent of the obturator internus muscle.	The internal iliac lymph node group.

# A3

## Delineation of the genitalia

### Male

Delineation of the male genitalia should include the penis and scrotum out laterally to the inguinal creases starting superiorly mid-way through the symphysis pubis.



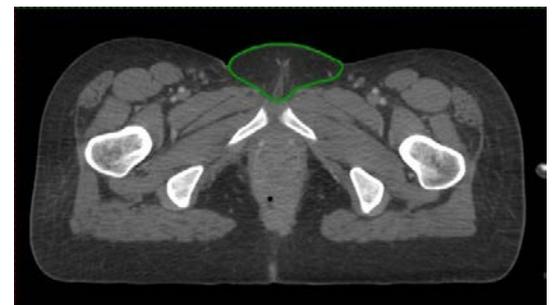
# A3

## Delineation of the genitalia

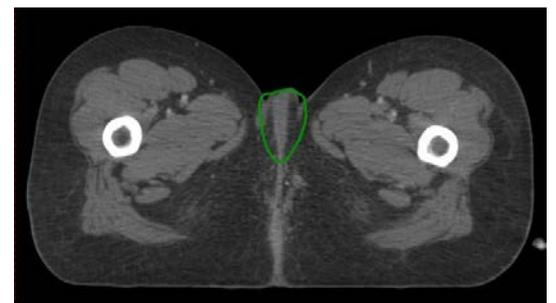
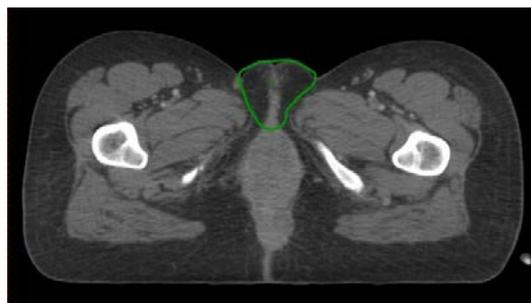
### Female

In women it should include the clitoris, labia majora and minora out to the inguinal creases.

The **superior slice** should be halfway through the symphysis pubis.



**Inferior slice:** Last slice where the vulva is visible.



# A4

## Anal VMAT/IMRT planning sheet

Organ	OAR / target	Optimal constraint	Mandatory constraints
<b>PTV</b>	D99%	>90%	>90%
	D95%	>95%	>95%
	D50%	Between 99% and 101%	Between 97% and 101%
	D5%	<105%	<107%
	D2%	<107%	<110%
<b>Lower-dose PTVs</b>	D99%	>90% of prescribed dose	>90% of prescribed dose
	D95%	>95% of prescribed dose	>95% of prescribed dose
	D50%	<110%	<125%
<b>Small bowel</b>	D200 cc	<30 Gy	<35 Gy
	D150 cc	<35 Gy	<40 Gy
	D20 cc	<45 Gy	<50 Gy
	D5 cc	<50 Gy	<55 Gy
<b>Femoral heads</b>	D50%	<30 Gy	<45 Gy
	D35%	<40 Gy	<50 Gy
	D5%	<50 Gy	<55 Gy
<b>Genitalia</b>	D50%	<20 Gy	<35 Gy
	D35%	<30 Gy	<40 Gy
	D5%	<40 Gy	<55 Gy
<b>Bladder</b>	D50%	<35 Gy	<45 Gy
	D35%	<40 Gy	<50 Gy
	D5%	<50 Gy	<58 Gy

If mandatory constraints cannot be met, please discuss with the trial team. In principle the PTV takes priority, but in advanced cases, especially in the dose escalation arm, there might be difficulties depending on patient anatomy and tumour location.

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# Acknowledgements

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