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Basic Original Report

ECOG-ACRIN Guideline for Contouring and Treatment of Early Stage Anal Cancer Using IMRT/IGRT

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Abstract

Purpose: Previous anal cancer guidelines delineate target volumes similarly for all patients with squamous cell carcinoma of the anal canal and/or perianal skin (SCCA), regardless of disease stage. The purpose of this guideline is to provide customized radiation treatment recommendations for early stage (T1-2 N0 M0) anal cancer treated with intensity modulated and image guided radiation therapy (RT).

Methods and Materials: A contouring atlas and radiation treatment recommendations for the ongoing, randomized phase II trial of deintensified chemoradiation for early stage SCCA (EA2182) was created by an expert panel of radiation oncologists. A literature search was conducted to update and expand these recommendations into a guideline for routine clinical use.

Results: For the majority of cases, we recommend treatment in the supine, frog leg position with the use of a customized immobilization device and daily image guided RT to ensure optimal bone and soft tissue alignment. Vaginal dilators can be used daily during RT to maximize genitalia sparing. We recommend use of a 10-mm margin on the gross tumor plus including the anal complex to create the primary clinical target volume. To define the elective lymph node clinical target volume, we recommend starting with a 7-mm expansion on blood vessels, but then further refining these volumes based on the anatomic location. A 5- to 10-mm planning target volume (PTV) margin is suggested based on institutional setup and patient-specific factors. When using a simultaneous integrated boost

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technique, a dose of 50.4 Gy to primary PTV and 42 Gy to lymph node PTV, both delivered over 28 fractions, with chemotherapy is appropriate for early stage anal cancer.

Conclusions: This guideline provides anatomic, clinical, and technical instructions to guide radiation oncologists in the planning and delivery of intensity modulated and image guided RT for early stage SCCA.

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Introduction

Guidelines from the Radiation Therapy Oncology Group (RTOG)[1] and the Australasian Gastrointestinal Trials Group[2] delineate target volumes for intensity modulated radiation therapy (IMRT) similarly for all patients with squamous cell carcinoma of the anal canal and/or perianal skin (SCCA), regardless of disease stage. However, patients with early stage (T1-2 N0 M0) SCCA have a higher likelihood to be cured by chemoradiation therapy (CRT) (approximately 90%) and have different patterns of failure compared with patients with advanced stage disease.[3-5] Furthermore, the published guidelines haven't incorporated newer approaches to radiation simulation, planning, and treatment delivery, such as the use of image guided RT (IGRT). It is possible that using a customized approach to treating early stage SCCA with more precise targeting of IMRT could reduce common side effects, including leukopenia, dermatitis, fecal incontinence, vaginal stenosis, and/or erectile dysfunction.[6]

The ongoing ECOG-ACRIN ECOG-ACRIN randomized clinical trial EA2182 (DECREASE) is testing the hypothesis that reduced-dose CRT will maintain excellent disease control rates for early-stage anal cancer while reducing side effects, compared with standard-dose CRT (https://clinicaltrials.gov/ct2/show/NCT04166318). Central review of RT plans for the first 40 patients revealed that 35% had major deviations in contours that required plan revisions.[7,49] Although this replanning rate is considerably lower than the 81% rate for the RTOG 0529 trial,[8] it still points to the unmet clinical need for an updated, comprehensive contouring guideline.

Therefore, the RT planning instructions for the DECREASE study were adapted into this guideline intended for the wider radiation oncology community. The purpose of this guideline is to customize radiation treatment recommendations and to provide a comprehensive atlas for routine clinical use for patients who have early stage SCCA and will be treated with IGRT/IMRT.

Methods and Materials

The study was approved by the institutional review board at University Hospitals Cleveland Medical Center (UHC). Radiation treatment recommendations were created for the EA2182 clinical trial by coinvestigators representing radiation oncology, medical physics, and dosimetry. A literature search was performed using PubMed. Publications considered by the group included: (1) existing nodal consensus atlases;[1,2,9,10] (2) pelvic lymph node mapping studies using radiographic or surgical dissection information;[11-14] and (3) patterns of failure studies after CRT.[5,15,16] The final guideline was reviewed and approved by study coinvestigators and the EA2182 Radiation Oncology Committee.

Simulation

Positioning

For the majority of patients, the supine, frog leg position has advantages over the prone and supine, straight leg positions, including: (1) separation of the skin folds in the upper inner thighs, groin, and genitalia to reduce radiation dermatitis, (2) displacement of the male genitalia, and (3) use of a vaginal dilator in females.[17] Although the prone position can displace more bowel outside the pelvis compared with the supine position,[18] it is associated with greater rotational setup variability (potentially requiring larger planning target volume [PTV] margins) and does not result in significantly lower bowel doses in the context of IMRT.[19,20] However, patients with a significant degree of tumor extension into the perianal skin may benefit from prone positioning to ensure accurate bolus positioning.

Immobilization devices

For the supine, frog leg position, custom immobilization of the lower extremities with an appropriate device (ie, Alpha Cradle or VAC-LOCK) is recommended. A wing board can also be used to build a foot stop and knee support, while maintaining the pelvis flat on the table and taking care not to have the bag touch the perineum (Fig 1A-C). Measuring the distance between reference marks (red arrows, Fig 1C) helps to reproduce the angle of the knee. At the time of simulation, it is helpful to place the patient in their immobilization device on the LINAC table to be sure there is no collision at the planned treatment isocenter.

For the prone position (Fig 1D-F), we recommend using a VAC-LOCK bag to abut the lower edge of the belly board and placing reference marks on the patient and belly board (green marks, Fig 1D). A rolled towel provides separation between the thighs to reduce radiation dermatitis.



Figure 1 Computed tomography (CT) simulation techniques. Immobilization in the supine, frog-leg position (A-C) and the prone position (D-F). Optimizing genitala avoidance using a scrotal sling or shelf (G and H, respectively) or vaginal dilator (I,J). Bolus placement in the supine (K) and prone positions (E,L).

Optimizing genitalia positioning

To reduce dose to male genitalia, a scrotal sling (rolled pillowcase in Fig 1G) or scrotal shelf (Fig 1H) can be used in the frog leg position to elevate the genitalia away from the perineum.[21] At the same time, the genitalia should be kept midline so as to not extend laterally toward either inguinal target volume.

For women who use a vaginal dilator, the setup position must be supine in the frog leg position with creation of a backstop to prevent expulsion during treatment (Fig 1I, J). The depth of dilator insertion is reproduced by placing a mark at the vaginal introitus (red arrow, Fig 1I). Consider using a silicone dilator with dimensions of approximately 3 cm in diameter and 11 cm in length or otherwise the maximal dilator diameter that is comfortably tolerated by the patient (Soul Source, North Hollywood, CA).[17]

Male genitalia or vaginal dilators should be contoured and specifically identified on daily image guidance to confirm accurate positioning.

Marking perianal skin

Placement of a radiopaque marker at the anal verge is recommended. All areas of perianal skin involvement

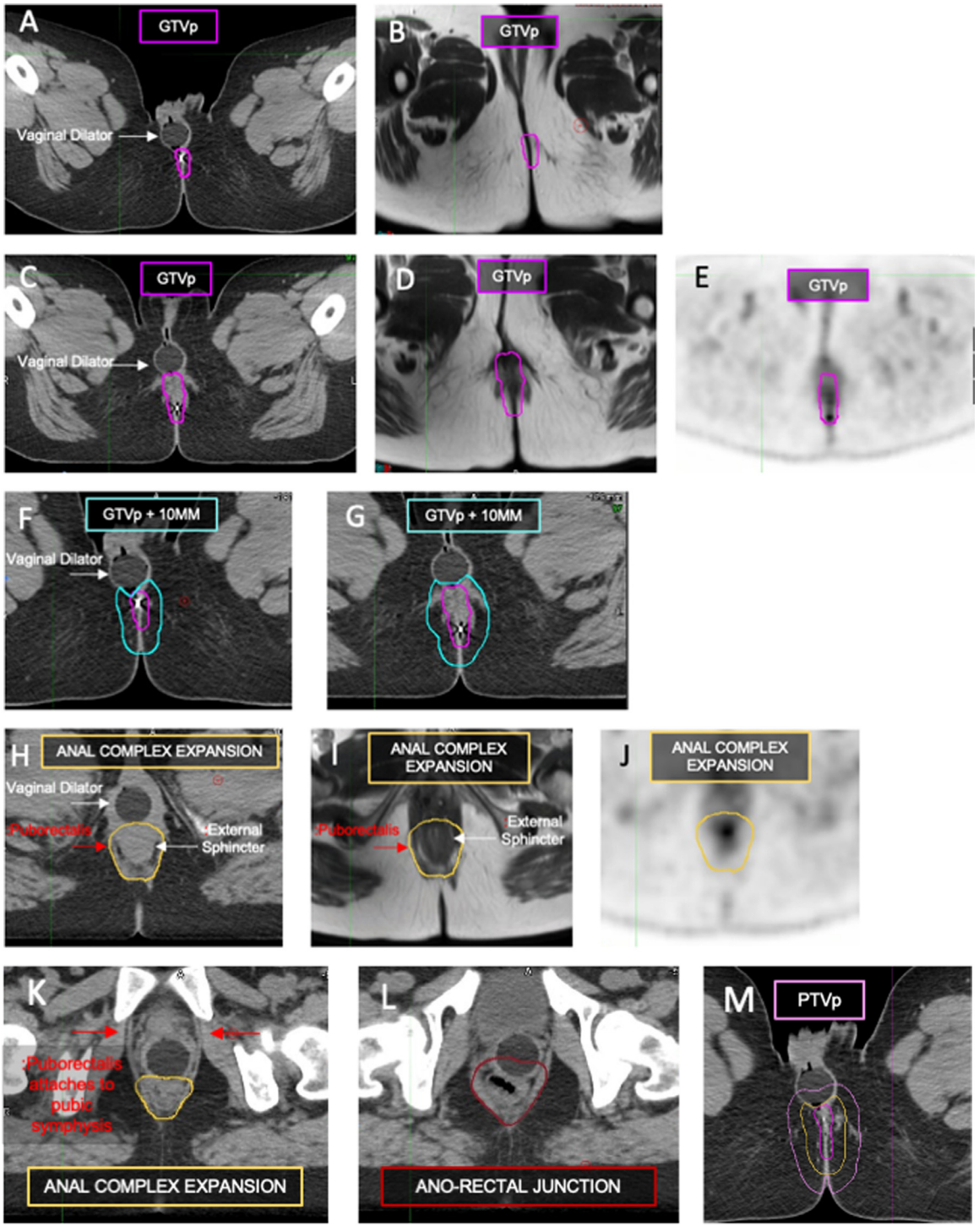


Figure 2 Delineation of the primary clinical target volume (CTVp). Case 1 is a female with multifocal T1N0 squamous cell carcinoma of the anal margin status postexcision of lesions at the perineal body (radiopaque marker in A and F) and anal verge (marker in C and G) with positive margins. Computed tomography (CT) planning scan (A,C,F,G,H,I,K-M) was obtained in the frog leg position with a vaginal dilator (arrow). The magnetic resonance imaging (MRI) and positron emission tomography (PET)/CT fusions (B,D,E,I,J) preferentially focus alignment on the anal canal.

should be marked with radiopaque markers and/or wires, which may include scars from positive biopsy or excision sites, areas with erythema and/or ulceration, as well as thickening, induration, or edema on palpation.

Use of bolus

We recommend that bolus be used if the primary tumor involves the anal margin or perianal skin or if it protrudes through the anal canal and if there is less than

20 mm between gross tumor volume (GTV) in the perianal skin and the end of the buttock tissue (free air). This is because it will be necessary to cover GTV with margins of 15 to 20 mm (depending on the PTV margin selected) with the full prescription dose. Please refer to the Supplementary Materials for examples of customized bolus design in the supine and prone positions.

Computed tomography scan considerations

Comfortable and reproducible bladder filling is encouraged for simulation and treatment, such as instructing patients to void and then drink 300 to 400 mL of water approximately 1 to 2 hours before scanning and daily treatment.[19,20] Intravenous computed tomography (CT) contrast is recommended to define the lymph node target regions. If the rectum is distended at the time of simulation (ie, >4 cm in diameter), the simulation should be repeated after further bowel evacuation.[22]

Steps for primary tumor CTV delineation

Please refer to Fig 2 for patient case description and pictorial representation of steps.

1. **Primary GTV**
   - Draw the GTV to include all known gross disease in the anal and perianal region as determined by clinical examination, endoscopy, biopsy, and radiographic studies (Fig 2A-E, magenta contour).
   - The GTV should include the anal complex on axial slices at the level of the tumor.

     We define the anal complex as the entire circumference and thickness of the anal canal, including the internal/external sphincters and the adherent puborectalis muscle where it surrounds the sphincter muscles (laterally and posteriorly) (Fig 2H, I-K). *Covering the anal complex at the level of the tumor is recommended due to the challenges of confirming the exact degree of circumferential involvement or depth of invasion by tumor based on imaging and physical examination.*
   - The GTV should also include areas of perianal skin involvement marked at the time of CT simulation.
2. **Primary CTV**
   - Expand the primary GTV by 10 mm in all directions, except no expansion into bone, air, or beyond the skin surface (Fig 2F, G, cyan contour).[9]

     If a patient is using a vaginal dilator during RT, trim the contour off the vaginal dilator on axial slices that do not contain the bladder and/or rectum (Fig 2F, G). *On axial slices containing the bladder or rectum, do not trim the contour off the dilator because there could be differences in positioning due to bladder and/or rectal filling* (Fig 2L, *maroon contour).*
   - Manually contour the rest of the anal complex to include its full length from the anal verge (defined by the radio-opaque marker placed at CT simulation) superiorly to the ano-rectal junction.

     Radially, include the puborectalis muscle as part of the anal complex in the region where it surrounds the sphincter muscles (laterally and posteriorly) and continue its coverage superiorly until the point where it attaches to the pubic symphysis (red arrows in Fig 2K*).*

     The ano-rectal junction is defined by where the levator muscles fuse with the external sphincter muscles and where the mesorectal fat/space is no longer seen tapering inferiorly (when moving in the superior to inferior direction on axial images), as seen in Fig 2K and L.[2] *Please see the transition between the anal canal in* Fig 2K *to the rectal junction in* Fig 2L. In Fig 2L, *the maroon contour defines the inferior extent of nodal CTV (CTVn) to cover the mesorectum.*

     Marginal failures outside of the anal canal are uncommon and thus a CTV expansion is not placed on the entirety of the anal canal, only on the GTV.[23,24]
   - The entire mesorectum should also be included in the primary CTV (CTVp) contour at levels containing the rectum.[1]

     Previous guidelines and clinical trials for anorectal cancers required boosting the primary tumor with a 2.5-cm radial margin up to the mesorectal fascia.[24,25]
   - On axial slices containing the bladder, add an additional 10-mm anterior margin to extend into the bladder, seminal vesicles, uterus, and/or bowel to account for differences in bladder and rectal filling (Fig 2L).[1,2]
   - The entire ischiorectal fossa should added to the CTVp described previously in the event that the primary tumor infiltrates > 5 mm outside the external anal sphincter, puborectalis, or other muscles of the levator ani[9] or for tumor that extends into the ischiorectal fossa based on clinical examination or diagnostic imaging.

Rationale for elective nodal CTV definition

The elective nodal CTV (CTVn) includes the elective nodal areas at risk for microscopic regional metastasis, including the internal and external iliac, obturator, inguinal,[26,27] mesorectal, and presacral regions. We recommend that the superior border of CTVn start at the level of the common iliac vessel bifurcation into the external and internal iliac vessels, which is approximately located at the L5-S1 interspace.[1,2] In comparison, the United Kingdom (UK) IMRT Guidance Document recommends that the superior margin of CTVn be located 20 mm above the inferior aspect of the sacroiliac joint.[9] There are

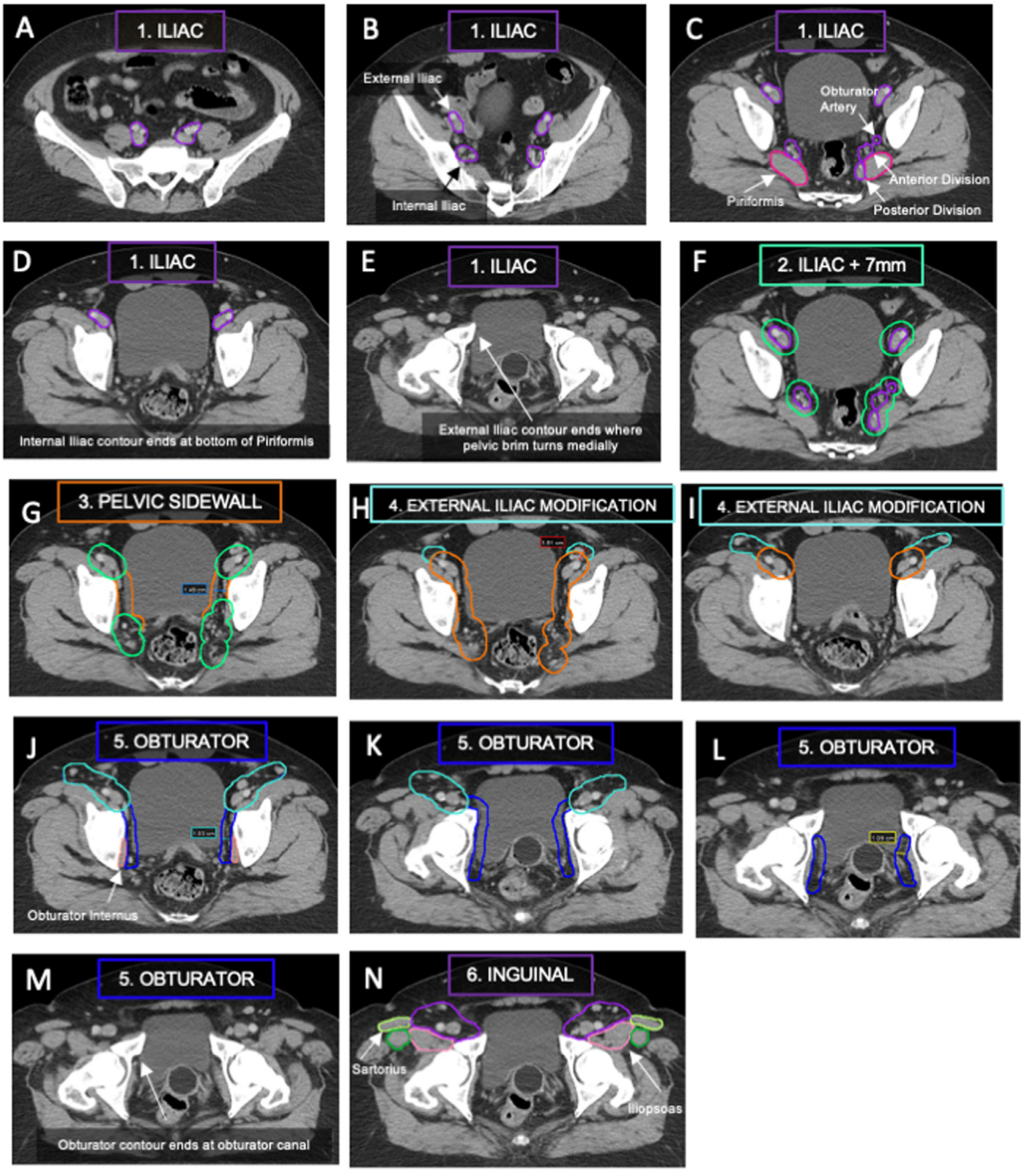


Fig. 3 Delineation of the nodal clinical target volume (CTVn) in steps depicted in A-V.Abbreviations: EI = external iliac vessels; II = internal iliac vessels; SI = sacroiliac.

conflicting data about whether or not this alternative superior border is sufficient.[5,28]

Anal cancer guidelines do not recommend deleting the bowel space from CTVn, which reflects the important role that elective nodal radiation serves in this disease and the uncertainty in daily location of the bowel versus vascular/nodal space.[1,2,9] We recommend following the UK guidelines, which specify that expansions around the pelvic vessels should be made extending into bowel, but that CTVn should not extend more than 10 mm into the adjacent organs, including bowel or bladder.[9] We also recommend including visible lymph nodes or lymphoceles that are located outside of standardized boundary definitions as part of CTVn, especially in the external iliac and inguinal regions, where borders are less well defined.[1,2,11]

Steps for CTVn delineation

Please refer to Fig 3 for pictorial representation of steps.

1. Iliac (internal and external):

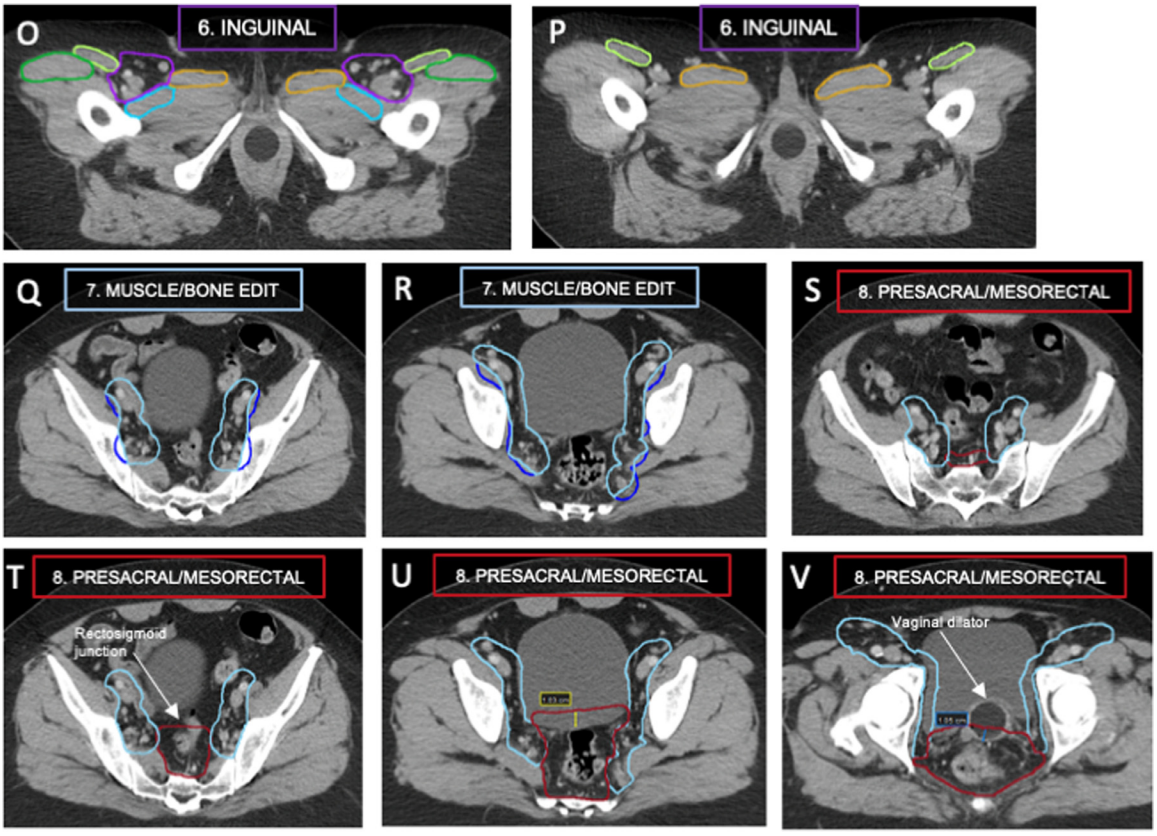


Fig. 3 Continued.

- Contour the internal and external iliac artery and vein, starting superiorly at the level of the bifurcation of the common iliac vessels (Fig 3A-E, purple contour).
  This includes contouring the branches of the internal iliac vessels, such as the anterior/posterior divisions and their branches, such as the obturator artery (Fig 3C).
  The internal iliac contour ends at the bottom of the piriformis muscle (Fig 3C-D), *just above where the inferior gluteal artery exits the pelvis through the greater sciatic foramen. Below this point, the obturator contour described in step 2 will begin in order to cover the obturator vessels and other branches of the internal iliac vessels along the pelvic sidewall.*
  The external iliac contour should continue further inferiorly (Fig 3D) *and end at the point where the pelvic brim begins to turn medially before it joins with the superior pubic rami* (Fig 3E), *near the first slice showing the femoral neck.*
- Add a uniform 7-mm margin around the iliac vessel contour (Fig 3F, green contour).
- Connect the external and internal iliac contours by creating a 15-mm strip along the pelvic sidewall, which is defined as the medial edge of the iliopsoas or obturator internus muscles (Fig 3G, orange contour).[11-13]
  Choose a larger width if necessary to cover small branching vessels and visible lymph nodes in this region. This contour covers the nodes along the anterior branches of the internal iliac vessels, including the obturator vessels.
- At the start of the iliopsoas muscle, extend the external iliac contour in the anterolateral direction such that the final margin on vessels is 15 to 17 mm (Fig 3H-I, aqua contour).[1,11-13,29]
  The iliopsoas muscle is formed by the fusion of the iliacus and psoas muscles, which begins approximately at the bottom of the sacroiliac joint.

2. **Obturator**: Where the internal iliac contour ended in step 1, continue the obturator contour as a 10-mm strip medial to the obturator internus muscle (Fig 3J-M, blue contour) and continue until the obturator artery exits the obturator canal (Fig 3J-M, blue contour).
   Superiorly, the obturator contour (blue contour) should meet the posterior extent of the external iliac contour (aqua contour). When the external iliac contour ends, limit the anterior/posterior extent of the

Table 1 Target volume and normal structure dose constraints

Structure	Definition	Dosimetric parameter	Per protocol	Variation acceptable
PTV_5040-xx*	PTV receiving 5040 cGy	$D_{95\%}$ (%)	≥100	≥97
		$D_{97\%}$ (%)	≥97	≥90
		$D_{99\%}$ (%)	≥90	≥88
		$D_{0.03}$cc [Gy]	≤115	≤120
CTV_5040	CTV receiving 5040 cGy	D_{min} (%)	≥93	≥88
PTV_4200-xx*	PTV receiving 4200 cGy	$D_{95\%}$ (%)	≥100	≥97
		$D_{97\%}$ (%)	≥97	≥90
		$D_{99\%}$ (%)	≥90	≥88
		$D_{30\%}$ (Gy)	≤110	≤115
CTV_4200	CTV receiving 4200 cGy	D_{min} (%)	≥93	≥88
Bowel space - PTV	Small and large bowel beginning 1-cm superior to the PTV through the pelvis minus the PTV	$D_{30\%}$ (Gy)	≤34	≤42
		$D_{0.03}$cc (Gy)	≤52	≤54
		V42Gy (cc)	≤100	≤200
Bone marrow	Entirety of the sacrum, iliac crests, acetabula, and femoral heads, contoured as a continuous structure, inferiorly through the ischial tuberosities	Mean (Gy)	≤25	≤27
		V10Gy (%)	≤80	≤90
		V20Gy (%)	≤66	≤75
Femoral head	Entirety of the bone, contoured as a continuous structure that does not include the femoral neck	$D_{15\%}$ (Gy)	≤30	≤50
		$D_{0.03}$cc (Gy)	≤50	≤55
Bladder	Entirety of the bladder, contoured as a continuous structure	$D_{50\%}$ (Gy)	≤35	≤42
		$D_{0.03}$cc (Gy)	≤54	≤56
External genitalia	The male genitalia include the penis and scrotum. The female genitalia include the entirety of the vulva.	$D_{50\%}$ (Gy)	≤20	≤35
Gluteal cleft - PTV	Superficial 5 mm of skin within the cleft that extends 1-cm laterally minus the PTV	$D_{50\%}$ (Gy)	≤20	≤35
Vaginal wall - PTV	5-mm radial expansion of vaginal dilator minus the PTV and dilator	$D_{50\%}$ (Gy)	≤30	≤40

Abbreviations: CTV = clinical target volume; PTV = planning target volume.
* Where xx is 3-5 mm subtracted from the skin surface.

Table 2 Target volume definitions

	ECOG-ACRIN guideline	RTOG 0529
GTVp	Primary tumor gross disease as defined by clinical examination, endoscopy, and imaging. Include entire thickness and circumference of the anal complex on axial slices at the level of the tumor. Anal complex = anal canal (including internal and external sphincters) + puborectalis muscle where it adheres to the sphincter muscles laterally and posteriorly.	Primary tumor gross disease as defined by clinical examination, endoscopy, and imaging.
CTVp	GTVp + 1 cm + entire anal complex	GTVp + entire anal canal + 2.5 cm
CTVn	Mesorectum, presacral region, inguinal and iliac lymph node regions with customized expansions defined in Table 3	Mesorectum, presacral region, inguinal nodes, and iliac nodal regions + 1,cm
PTV	Combination of CTVp and CTVn with a 0.5-1-cm expansion based on institutional and patient setup uncertainty	Combination of CTVp and CTVn with >= 1-cm expansion

Abbreviations: CTVn = lymph node clinical target volume; CTVp = primary clinical target volume; GTVp = primary gross tumor volume; PTV = planning target volume; RTOG = Radiation Therapy Oncology Group.

contour within the bony pelvis to align with obturator internus muscle (pink contour).

3. **Inguinal**: Superiorly, begin the inguinal contour where the external iliac contour ended and continue inferiorly until the lower edge of the lesser trochanter of the femur is visualized[9] or else where the sartorius and adductor longus muscles meet in Fig 3P[2,10] (Fig 3N-P, purple contour). Anteriorly, include a 15- to 20-mm margin on the vessels and include any visible lymph nodes.
   Both the superficial and deep inguinal lymph nodes of the femoral triangle should be included. The boundaries of this volume are defined by the surrounding muscles (sartorius, iliopsoas, pectineus, adductor longus). The medial border is the spermatic cord in men and in men and women is the medial third to medial half of the pectineus muscle and the medial border of adductor longus muscle.
4. **Muscle/bone exclusion**: Edit the final CTVn contour to exclude muscle and bone.
5. **Presacral/mesorectal:**
   - Starting at the L5-S1 interspace, draw a 10-mm strip anterior to the sacrum to connect the iliac + obturator volumes on each side of the pelvis (Fig 3S, maroon contour).[9]
   - At the level of the rectosigmoid junction, start contouring the mesorectum merging with the presacral region (Fig 3T).
     The rectosigmoid junction is visualized where the sigmoid colon lies approximately horizontal in orientation, while the rectum follows the hollow of the sacrum.[30]
   - In the upper pelvis (above the anterior peritoneal reflection), be sure to cover the rectum with at least a 10-mm margin anteriorly and to abut the iliac + obturator contour laterally and the presacral space posteriorly.
     The anterior peritoneal reflection is best visualized in the sagittal plane on a fat-saturated T2 MRI scan and is typically located at the level of S2 or S3. At this level, there is no mesorectal fascia anteriorly, but there is mesorectal fat surrounding the rectum laterally and posteriorly.[31] *It is important to cover the rectum with at least a 10- mm margin anteriorly in this region because there is a risk of perirectal lymphatic spread along the superior rectal artery and its branches.*[29,30]
   - In the mid to lower pelvis (below the anterior peritoneal reflection), there is mesorectal fat surrounding the rectum in all directions. Be sure to include an additional 10-mm margin anteriorly on the mesorectal fat and fascia extending into bladder, seminal vesicles, uterus, and/or bowel to account for differences in bladder and rectal filling (Fig 3U).[1,2]
     In patients using a vaginal dilator during RT, the contour should include a 10-mm internal margin extending into the vaginal dilator on axial slices containing the bladder and/or rectum (Fig 3V).

PTV margin concepts

In the setting of IGRT with daily cone beam CT (CBCT), expansion margins of 7 to 10 mm are generally preferred for both the primary and nodal planning target volumes (PTVp and PTVn) to account for uncertainty due to treatment setup, rotational error, and bowel or bladder filling.[18,32-34] Additional factors to consider when selecting the PTV margin include institutional experience with daily setup, rotational error associated with prone positioning,[34] and the individual patient's body habitus and comfort in the treatment position. It is allowable to select different expansion margins for PTVp and PTVn based on plans for IGRT. For example, if a daily CBCT with whole pelvis auto match is used for patients positioned with straight legs, there is better reproducibility for PTVn compared with PTVp (5 vs 9 mm).[32]

The final PTVs should be subtracted out of air outside the body contour and can be trimmed away from the skin

Table 3 Anatomic borders of lymph node regions

	Cranial border	Caudal border	Anterior border	Posterior border	Lateral border	Medial border
Mesorectum	Rectosigmoid junction (contour should not extend above L5/S1 interspace)	Anorectal junction (where levator muscles fuse with external sphincter)	1. Upper pelvis (above the anterior peritoneal reflection): at least 10-mm anterior to the rectum, should extend into bowel loops 2. Mid/lower pelvis: interface of mesorectum with anterior pelvic viscera with an additional internal margin of 10 mm into bladder, seminal vesicles, uterus, and/or bowel	Presacral space superiorly and posterior aspect of mesorectum inferiorly	1. Upper/mid pelvis: mesorectal fascia if visible or medial border of the iliac and obturator contours 2. Lower pelvis: medial edge of levator ani where visible	N/A
Presacral space	L5/S1 interspace	Inferior aspect of sacrum	10-mm anterior expansion from posterior border	Anterior border of the sacral bone, excluding the sacral hollows	SI joint	N/A
External iliac	Bifurcation of the common iliac artery into the internal and external iliac arteries	Pelvic brim turns medially, near appearance of femoral neck	7-mm anterior to the vessels in all regions except 15-17- mm anterolaterally along the iliopsoas muscle below the sacroiliac joint	7-mm margin on vessels, excluding muscle/bone of pelvic sidewall	Iliopsoas muscle	7-mm medial to the vessel
Internal iliac	Bifurcation of the common iliac artery into the internal and external iliac arteries	Bottom of piriformis muscle where the inferior gluteal artery exits the pelvis through the sciatic foramen (below this point, the obturator contour will cover the obturator vessels and other branches of the internal iliac artery)	7-mm radial expansion on iliac vessels, then join the expanded internal and external iliac contours with a 15-mm strip along the pelvic sidewall (ie, the medial edges of the iliopsoas/obturator internus muscles)			
Obturator	Inferior extent of the internal iliac volume (above this level, the obturator vessels and other branches of the internal iliac vessels are contained within the internal iliac volume)	Obturator vessels exit pelvis within the obturator canal	1. Superior: join the obturator contour to meet the posterior aspect of the external iliac contour 2. Inferior (once the external iliac contour ends): limit the anterior extent to be even with the anterior aspect of obturator internus muscle and contained within bony pelvis	Posterior aspect of obturator internus muscle (do not include the gluteal vessels or sciatic nerve)	Obturator internus muscle	10-mm strip medial to the obturator internus muscle
Inguinal	Inferior extent of external iliac volume	Lower edge of the lesser trochanter of femur or where the sartorius and adductor longus muscles cross	At least 15-20 mm around any inguinal vessels and including any visible lymph nodes	Pectineus, adductor longus, and iliopsoas muscles	Medial edge of the sartorius muscle or iliopsoas muscle	Spermatic cord in men, medial third to medial half of the pectineus muscle/adductor longus muscle in women, and including any visible lymph nodes

Abbreviation: SI = sacroiliac.

surface by 3 to 5 mm in the perineal and inguinal regions, as long as the volume does not extend inside the CTV and there is not gross perianal skin extension of the tumor. If bolus was used for perianal skin involvement, then PTVp can extend up to the bolus, but not beyond the skin or into the bolus. In the example case, PTVp was not subtracted away from the skin because the primary tumor involved the perianal skin (Fig 2M, pink contour).

Dose and fractionation

We define 50.4 Gy delivered in 1.8 Gy per fraction delivered over 28 fractions to PTVp to be the standard of care for T1-2 N0 M0 SCCA.[35,36] Based on RTOG 9811, an acceptable alternative is 45 Gy; however, a range of doses were used for T2N0 tumors and they did not report a dose-response analysis.[4]

With regards to PTVn, we define 42 Gy delivered in 1.5 Gy per fraction delivered over 28 fractions as the standard of care.[36] Alternatively, if sequential boost RT plans are designed, with all regions receiving 1.8 Gy per fraction, doses of 30.6 to 36 Gy to the upper pelvic and/or inguinal nodal regions are also acceptable.[35,37,38]

Organs at risk

Since the publication of RTOG 0529, additional information has been published regarding the optimal organ-at-risk (OAR) dose constraints, especially related to the pelvic bone marrow[39-44] and vaginal wall for patients who use a dilator during RT.[17,45] For the first 40 patients enrolled in EA2182, all RT plans were able to meet the dose constraints given in Table 1 either per protocol or variation acceptable (Dr T.J. Fitzgerald, personal communication, April, 2021).

Planning details

A strategy to achieve homogeneity across PTVs with dose-painted IMRT is to subtract PTVs with varying doses from one another with a 5- to 7-mm margin to optimize the plan by creating a dose fall-off region. In so doing, it is possible to minimize the volume of each PTV receiving 105% or more of prescription dose outside of the fall-off region. OARs can be spared most efficiently by subtracting them out of the overlapping PTVs with a margin of 5 to 7 mm for plan optimization. This enables reduction of maximum doses within the overlapping OARs and both high and low doses to the nonoverlapping OARs.

Dose verification with thermoluminescent dosimeters

For tumors involving the anal verge and/or perianal skin, thermoluminescent dosimeters should be placed at the distal extent of the tumor to verify the planned dose within 15%, given the accuracy of treatment planning systems to calculate surface dose.[46,47]

IGRT principles

Daily CBCT imaging should be obtained as part of IGRT to allow for bony and soft tissue alignment. We recommend that the isocenter be placed halfway between the anticipated superior and inferior borders, usually near the top of the pubic symphysis. When it is not possible to visualize the entire treatment volume within one CBCT, the isocenter should be placed lower than the halfway point to ensure that the primary tumor is well aligned on a daily basis. A second CBCT scan of the upper aspect of the treatment field should also be obtained on a regular basis.

Discussion

This ECOG-ACRIN guideline refines best practices for contour delineation and treatment delivery for T1-T2 N0 SCCA. Please refer to Table 2 for a summary of the major differences between our guideline and instructions for RTOG 0529.[36] Although previous guidelines recommend creating CTVp using a 20 to 25-mm expansion on the GTV plus the anal canal for all stages of SCCA,[1,2,36] we recommend using a 10-mm expansion on the GTV plus including the adjacent anal complex for early stage disease, which aligns with current UK guidelines.[9] In support, retrospective experiences report excellent outcomes using 10- to 15-mm margins for CTVp for all stages of SCCA.[5,23,48] Across these 3 publications, which include more than 700 patients with early and advanced SCCA, there were only 7 patients who experienced local recurrences in the anal margin/canal that were at the margin or outside of the radiation field, while 44 local recurrences occurred within the field.

Although these current guidelines draw from existing literature, ongoing trials (ECOG-ACRIN 2182 and Personalising Anal Cancer Radiotherapy Dose - Anal Cancer Trial 4) will hopefully serve to further validate our treatment approach. There is still much to learn about early-stage SCCA, including how to define uninvolved lymph nodes using radiologic criteria (Supplementary Materials). Please note that while many of the principles described in this guideline will also apply to advanced-stage disease, further discussion on this topic is beyond the scope of this guideline. Readers are encouraged to reference the related, interactive eContour cases at: https://econtour.org.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.prro.2022.01.015.

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