Evidence Based Radiation Oncology Fact Sheets
Anal Cancer 2023

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Overview

- SCC of the anal canal is a relative rare but curable cancer. Standard of care is concurrent CRT with 5-FU and mitomycin C.
- Select T1N0 patients with well-differentiated anal margin cancers may be treated with WLE with 1-cm margins.
- Acute treatment-related toxicities are often severe, but treatment breaks should be avoided as prolonged treatment times has been associated with increase failure rates.
- IMRT has been shown to reduce hematologic, GI, and skin toxicities but expertise is required with this approach.

Epidemiology

- 2023 U.S. incidence: 9,760 new cases (3,180 in men and 6,580 in women)
  death rate: 1,870 deaths (860 in women and 1,010 in men).[1]
  - Lifetime risk is 1 in 500.
  - This has been INCREASING in the previous years. Incidence 8000 and deaths 1000 in 2016.
- 2.5% of GI malignancies (whereas rectal cancer is 25%).
- **Almost exclusively an HPV driven disease** and incidence increasing despite HAART.
- Average age of diagnosis is 60s and 66% are males and 3% females.
- **SCC 80%**, AC 15%, Other 5%.

- Lymph node drainage: perirectal (N1), inguinal (N2), internal illiac (N2)
  - LN positive ~30% (ACT II)
-
- 5-year survival

T2N0 5-year OS 87%, LRF 17%	T2N+ 5-year OS 70%, LRF 26%
T3N0 5-year OS 74%, LRF 18%	T2N+ 5-year OS 57%, LRF 44%
T4N0 5-year OS 57%, LRF 40%	T2N+ 5-year OS 42%, LRF 60%

Risk Factors

- **HPV infection (anal-genital warts) (75%)**
  - **HPV-16 (most common) and HPV-18, 31, 33, 45.**
- History of cervical, vulvar, or vaginal cancer
- Receptive anal intercourse
- HIV infection
- Immunosuppression, ie. after transplant
- Hematologic malignancies or certain autoimmune disorders
- Smoking

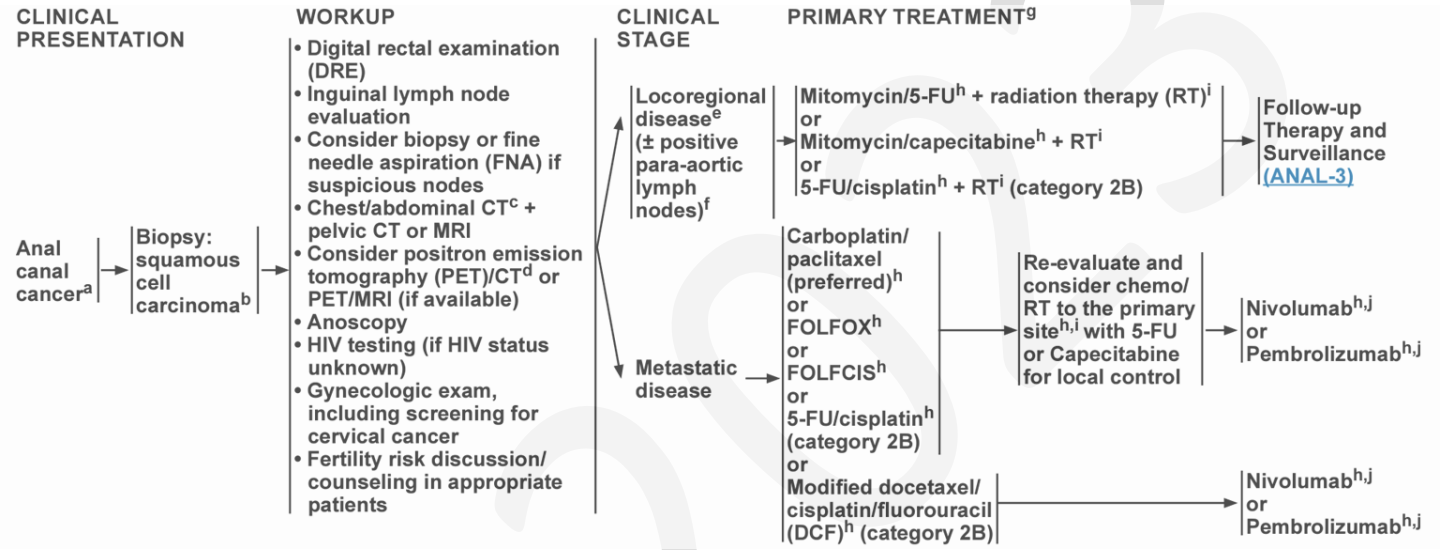
Presentation

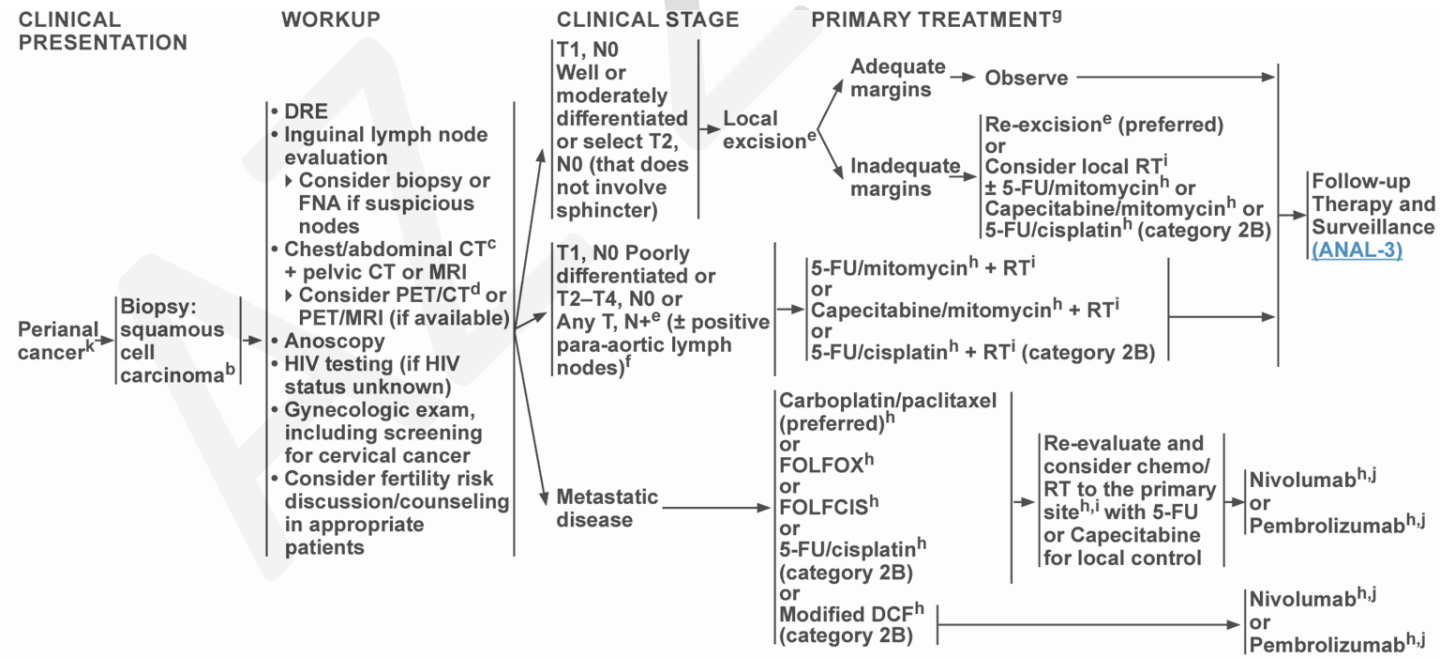
- Mean age 55-65
- Rectal bleeding
- Pain or sensation of mass
- Change in bowel habits (constipation or urgency)
- Pruritis
- Nearly 33% of patients may prolong telling physician for 6 months

[1] https://www.cancer.org/cancer/types/anal-cancer/about/what-is-key-statistics.html

Workup

- All Cases
    - H&P (Rectal and inguinal node exam) – **sexual history and HPV/HIV risk**.
        - **CD4 count**
        - Females: pelvic exam with PAP.
        - Males: full GU exam.
    - Labs: LFT, Renal Fx, HIV, CBC (bleeding)
    - Invasive exam: Flex sig or colonoscopy.
    - Imaging: CT C/A/PP and PET/CT.
    - Biopsy
        - Primary
        - FNA suspicious LN.





Anatomy

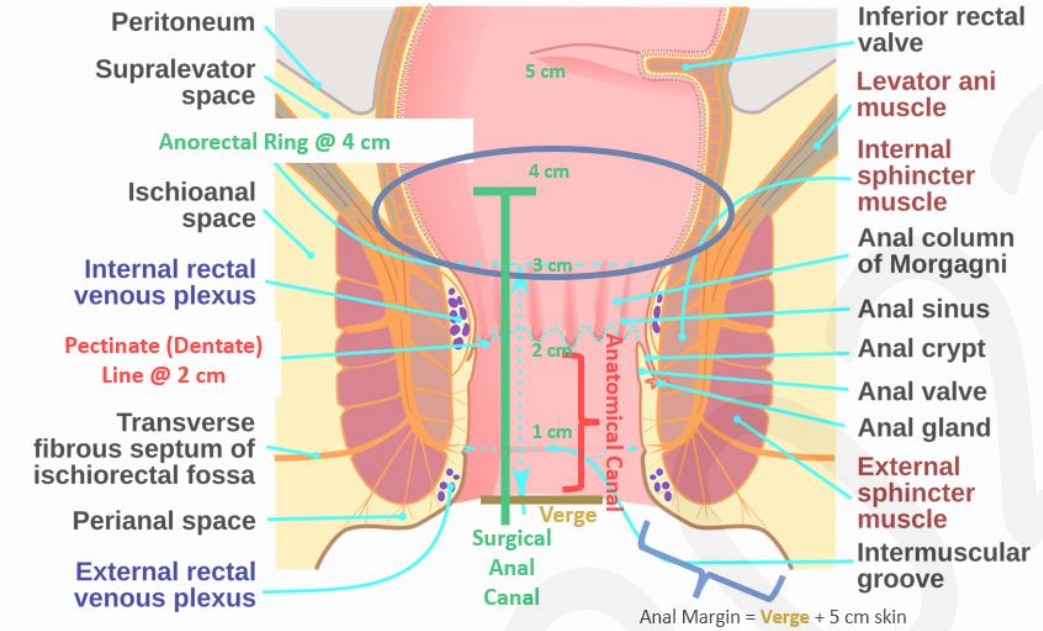
If cancer above surgical anal canal = rectal cancer.
Anal Canal Measurements =
Avg surgical was 4.2 cm (range 3.0–5.3 cm).
Avg anatomic was 2.2 cm (range 1.0–3.8 cm).
https://link.springer.com/article/10.1007/BF02605754

SURGICAL ANATOMY OF THE ANAL CANAL

THE ANATOMICAL AND SURGICAL ANAL CANALS

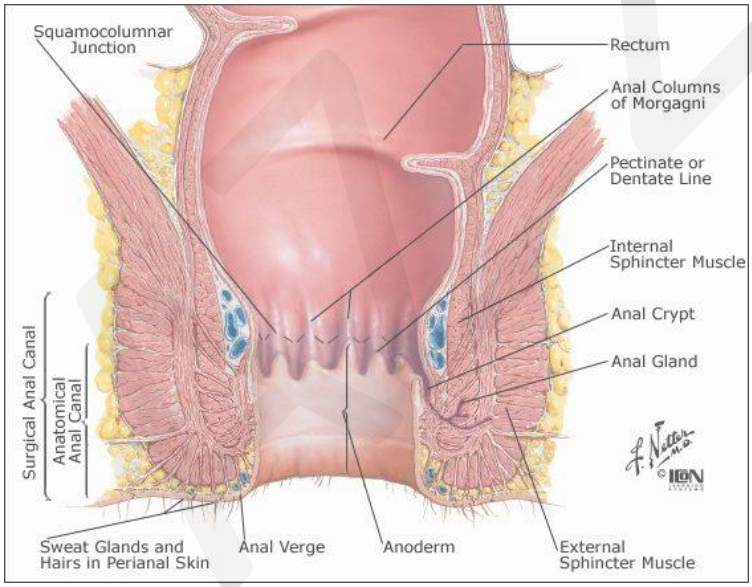
The anatomical anal canal extends from the level of the valves of Morgagni (dentate line) to the anal margin.

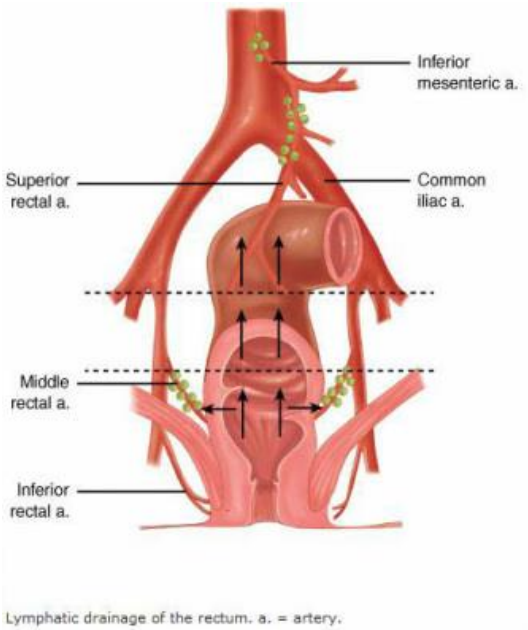
For surgical purposes, the anal canal may be regarded as that portion of the terminal intestine which extends from the level where the rectum passes through the pelvic visceral aperture— the anorectal ring—to the the anal margin. This concept of the anal canal is more apposite for surgical purposes and as the anorectal ring is above the valves of Morgagni, the surgical anal canal is longer than its anatomical counterpart (Fig. 1).



Anal Margin = Verge + 5 cm skin

Anorectal ring = Muscle ring (fusion of Puborectalis sling + int. + ext. anal sphincters).



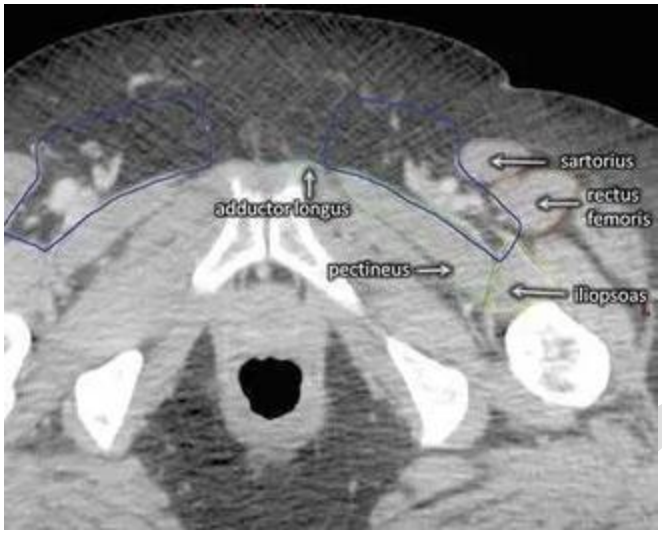


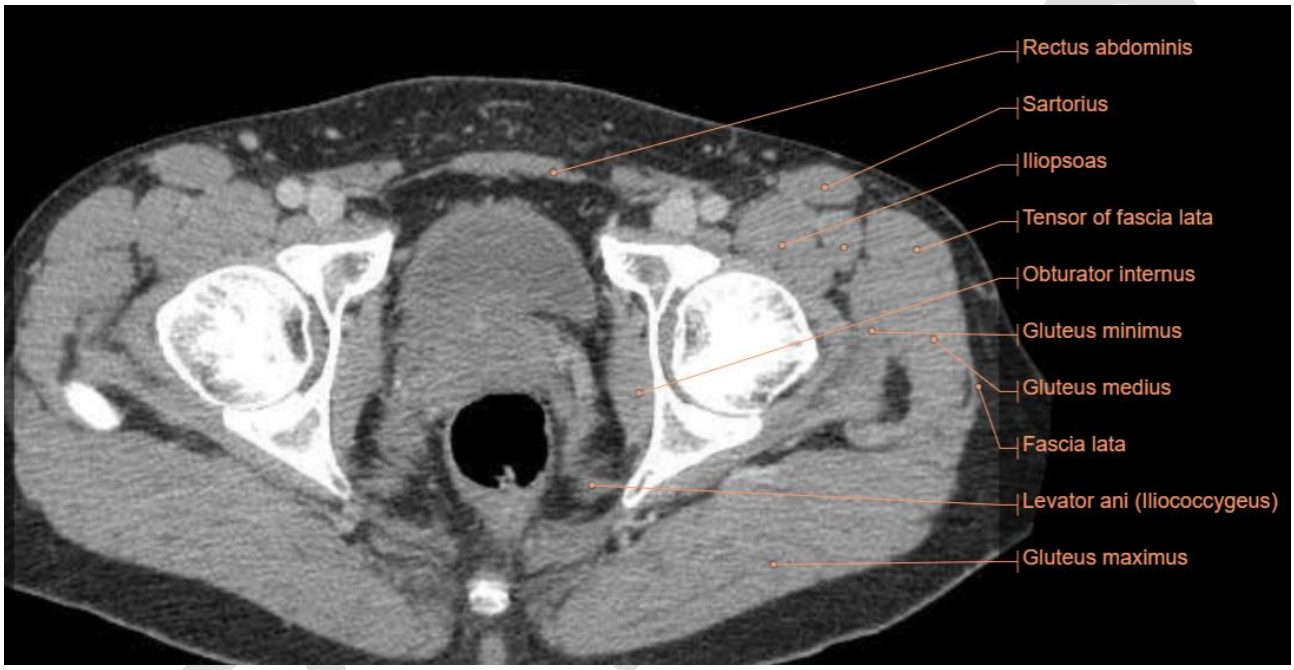
Lymphatic drainage of the rectum. a. = artery.

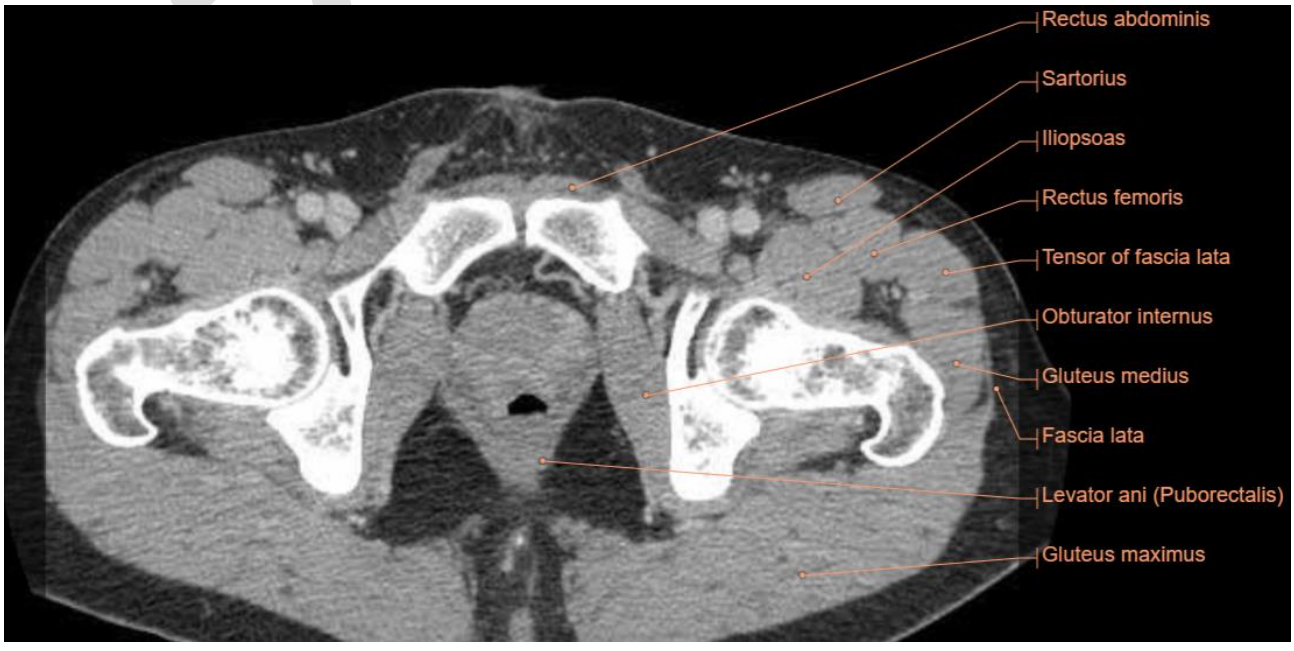
- Nodal Drainage
  - Rectum — Mesorectum/pararectal, Internal iliac, presacral
  - Anterior organs — External iliac
    - Bladder, cervix, prostate, vagina
  - Below dentate (anal) — Inguinal iliac

- The anal sphincter is composed of two muscles. The *internal sphincter* is involuntary and is a continuation of the circular smooth muscle of the rectum. The *external sphincter* is a continuation of the striated muscle of the puborectalis muscle.
- The anorectal ring is a muscular structure at the junction of the anal canal and the rectum. It includes the puborectalis sling and upper portions of the internal and external sphincter (Fig. 2). Division of the anorectal ring results in incontinence.

A **StRIP** of muscle.







MRI anatomy: Excellent resource
https://wiki.radiology.wisc.edu/images/1/1e/Rectal_MR_initial_staging_interpretation_guide_-_Dr._Kim.pdf

HIV Summary

HIV+ patients tend to be male and present at a younger age.
No apparent difference in OS or CSS between HIV+ and HIV-patients treated with concurrent chemoRT.
Controversial, but reports describe decreased LC in HIV+ patients and increased acute toxicity.
IMRT appears to provide improved toxicity with excellent LC.
Control HIV and treat the same as non-HIV with 5FU/MMC and IMRT unless CD4 count < 200; then consider 5FU/CDDP/RT.

Staging

	Esophageal	Stomach	Rectum	Anal	Pancreas
T1a	Lamina propria, muscular mucosae		Tis = in situ = Stage 0s T1 = Submucosa	Tis = in situ = Stage 0 T1 < 2 cm (Breast!)	Tis = in situ (G3 PIN) T1a-c = **BREAST!**
T1b	Submucosa				
T2	**Muscularis propria**			2-5 cm (Breast!)	2-4 cm
T3	Adventitia	Serosa	Pericolorectal soft tissue	> 5 cm (Breast!)	> 4 cm
T4a	Resectable*	Visceral peritoneum		Invade vagina, urethra, bladder	Involve CA, SMA, ComHep
T4b	Unresectable**	Adjacent organs			
M1	Distant Mets		M1a Just 1 single organ M1b ≥ 2 organs M1c Peritoneal Surface	Distant Mets	Distant Mets
N1	1-2		N1a 1 N1b 2-3 N1c only tumor deposits	N1a ing, meso, int N1b external iliac N1c (N1a+N1b)	1-3
N2	3-6		N2a 4-6 N2b ≥ 7		≥ 4
N3	≥ 7	N3a 7-15 N3b ≥ 16			

Prognostic Stage Groups				5 Yr OS
0	Tis	N0	M0	
I	T1	N0	M0	82%
IIA	T2	N0	M0	
IIB	T3	N0	M0	
IIIA	T1-2	N1	M0	62%
IIIB	T4	N0	M0	
IIIC	T3-4	N1	M0	
IV	Any T	Any N	M1	30%

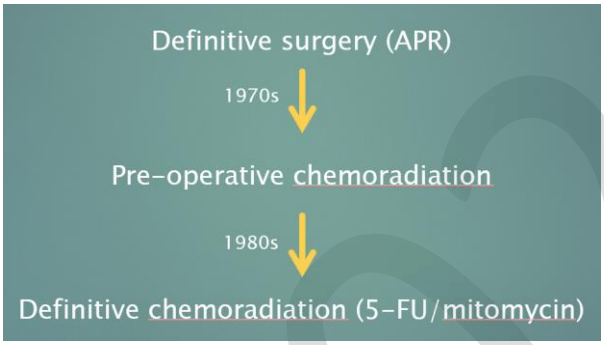
Prognostic Factors (RTOG 98-11)

	Disease-free Survival			Time to Colostomy		
	Adjusted HR	95% CI	P	Adjusted HR	95% CI	P
Male	1.38	1.05-1.81	0.02	0.97	0.60-1.58	0.92
cLN+	2.66	2.04-3.46	<.0001	1.03	0.63-1.69	0.92
> 5 cm	1.5	1.14-1.97	0.004	1.85	1.17-2.91	0.008

Treatment Paradigm

General

Anal margin **(not canal)** T1N0 well differentiated (TREAT AS ANAL CANCER, NOT SKIN CANCER)	WLE ± RT ± C (adjuvant depending on surgical findings)
Localized anal **CANAL** (any T, any N, M0)	ChemoRT with 5-fluorouracil (FU)/mitomycin **or** capecitabine/mitomycin
Metastatic	Systemic therapy ± palliative RT
Local recurrence after chemoRT	Abdominoperineal resection



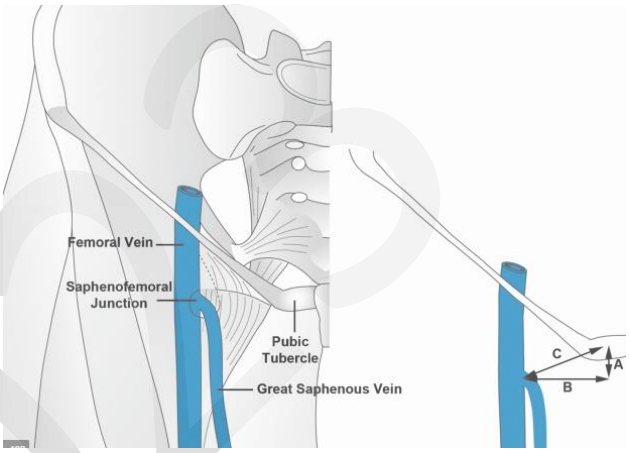
Localized Cancer	Metastatic Cancer
5-FU + Mitomycin + RT Continuous-infusion 5-FU 1000 mg/m^2/d IV days 1–4 and 29–32 Mitomycin 10 mg/m^2/d IV bolus days 1 and 29 Concurrent radiotherapy (now IMRT)	**5-FU + Cisplatin** Continuous-infusion 5-FU 1000 mg/m^2/d IV days 1–5 Cisplatin 100 mg/m^2 IV day 2 Repeat every 4 weeks
+/– Capecitabine + Mitomycin + RT Capecitabine 825 mg/m^2 PO BID, Monday – Friday, on each day that RT is given, throughout the duration of RT (typically 28 treatment days) Mitomycin 10 mg/m^2 days 1 and 29 Concurrent radiotherapy (IMRT) **or** Capecitabine 825 mg/m^2 PO BID days 1–5 weekly × 6 weeks Mitomycin 12 mg/m^2 IV bolus day 1 Concurrent radiotherapy (IMRT)	

Radiation Therapy

Per RTOG 05-29

	PTV 1^{o}	PTV A+B+C	PTV LN
T2 N0	5040 (180 x 28)	4200 (150 x 28)	NA
T3-4 N0	5400 (180 x 30)	4500 (150 x 30)	
T2-4 N+ (LN < 3 cm)	5400 (180 x 30)	4500 (150 x 30)	5040 (**168** x 30)
T2-4 N+ (LN > 3 cm)	5400 (180 x 30)	4500 (150 x 30)	5400 (180 x 30)

IMRT Planning



CT simulation:

- Vac Loc, supine, IV contrast, full bladder, empty rectum, arms on chest.
- Anal marker.
- Consider:
  - Vaginal dilator ↓ G3 derm toxicity from 40 % → 0%.
  - Anterior Vaginal Wall (AVW) D50% >48Gy = ↑ risk of sexual dysfunction.
- Men: Clamshell or sperm banking prior.
- Consider bolus.

Volumes: (According to AnoRectal Contour Guidelines)

- GTV tumor GTV LN
-
- CTV A = Whole pelvis (uninvolved LN) + 0.7 vessel expansion cm.
  - Internal iliac, pre-sacral, peri-rectal
- CTV B = + external iliac
- CTV C = + inguinal nodal region.

- Anal = CTV A+B+C
  - Elective nodal region should extend at least **2 cm inferior to anorectal GTV** **and** include the entire mesorectum to the pelvic floor in ALL high vs. low anorectal cancers.
  - Nodal areas include inguinal, perirectal, presacral, interal iliac, externail iliac and STOP at bifurcation of the common iliac (L5/S1).
  - Inguinal superiorly "somewhat arbitrary" (inguinal ligament or superior pubic rami) and inferiorly (stop at lesser trochanter).
  - **PER CONTOURING ATLAS Caudad extent of elective target volumes**: The group recommended that the caudad extent of the inguinal region (CTVC) should be 2 cm caudad to the saphenous/femoral junction. The transition between inguinal and external iliac regions (CTVC to CTVB) is somewhat arbitrary, but the group recommended the level of the bottom of the internal obturator vessels (approximate boney landmark: upper edge of the superior pubic rami).
-
- CTV P = GTV tumor + 2 cm and (MDACC 1cm)
- CTV N = GTV LN + 1 cm. (MDACC 0.5 cm)

Ng, Australian
Primary tumor
GTV: The GTV should be delineated as a separate structure based on all available clinical and imaging information.
CTV: This volume must encompass (1) the GTV, (2) the entire anal canal from the ano-rectal junction to the anal verge, and (3) the internal and external anal sphincters. A further 20-mm isotropic margin should be added to items (1), (2), and (3) above, to account for microscopic disease, while respecting anatomical boundaries. Attention must be given, especially for anal verge and perianal lesions, that a 20-mm radial and caudal margin is used to ensure coverage of perianal skin.

Involved nodes
GTV: The involved node(s).
CTV: The involved node(s) or nodal region(s) with a 10- to 20-mm margin, respecting anatomical boundaries.

NOTES:

- For anal, MUST extend 2.5 cm around perianal skin involvement or anal verge (RTOG 05-29). Contour atlas says 2.0 cm OK.
- IF adenocarcinoma rectal = treat with TNT rectal regimen.
- IF HIV+, consider ↓ MMC dose to avoid diarrhea and skin toxicity

Dose Constraints

Bowel (Bag) V45 < 195 cc (Kavanaugh paper).
Duodenum / Small Bowel: Max 54, V45 < 10%, V50 < 10cc.
Bladder V50 < 30%, V40 < 40%
Genitalia V30 < 20% (30 Gy line OFF genitalia).
Femoral heads: V45 < 20%

Table 2: DP-IMRT Dose Constraints for Normal Tissues[8]

Organ	Dose (Gy) at <5% Volume	Dose (Gy) at <35% Volume	Dose (Gy) at <50% Volume
Small bowel†	45 (<20 cc)	35 (<150 cc)	30 (<200 cc)
Femoral heads	44	40	30
Iliac crest	50	40	30
External genitalia	40	30	20
Bladder	50	40	35
Large bowel†	45 (<20 cc)	35 (<150 cc)	30 (<200 cc)
Organs are listed in order of decreasing priority. †Dose constraints are based on absolute volume instead of % volume.			

- **Quality Assurance and Image-Guided Treatment Delivery**
  - **Due to the sophistication and complexity of IMRT planning for anal cancer, comprehensive quality assurance measures must be implemented to ensure minimal variability between the designed and delivered treatment plans. Each institution should have a quality assurance program in place for the treatment of patients with anal cancer.**
  - **The use of image guidance for radiation treatment delivery has significantly improved confidence in daily treatment setup. This has allowed for shrinking CTV to PTV expansions during the treatment planning process, which in turn further minimizes dose to OARs.**
  - **If it is not possible to achieve the dosimetric goals in Table 2, small bowel max point dose should be limited to 50 Gy, V45 should be <195 cc for a bowel bag avoidance structure, and V15 should be <120cc for individual small bowel loops.[9]**
- **Supportive Care**
  - **Patients should be considered for vaginal dilators and instructed on the symptoms of vaginal stenosis.**
  - **Patients of childbearing potential should be counseled about the effects of premature menopause and consideration should be given to referral for discussion of hormone replacement strategies.**
  - **Patients of childbearing potential should be counseled that an irradiated uterus cannot carry a fetus to term.**
  - **Patients should be counseled on sexual dysfunction, potential for future low testosterone levels, and infertility risks and given information regarding sperm banking or oocyte, egg, or ovarian tissue banking, as appropriate, prior to treatment.**

General Principles

- The consensus of the panel is that intensity-modulated RT (IMRT) is preferred over 3D conformal RT (3D-CRT) in the treatment of anal carcinoma.[2] IMRT requires expertise and careful target design to avoid reduction in local control by so-called "marginal-miss."[3] The clinical target volumes (CTVs) for anal cancer used in the RTOG-0529 trial have been described in detail.[2] The outcome results of RTOG-0529 have been reported.[4] Also see The RTOG Consensus Panel Contouring Atlas for more details of the contouring atlas defined by RTOG. The information below provides details regarding simulation, target volume definition, dose prescription, organs at risk (OARs), IMRT constraints, quality assurance, and image guidance delivery.
- Image-guided RT (IGRT) with kilovoltage (kV) imaging or cone beam CT imaging should be routinely used during the course of treatment with IMRT and stereotactic body RT (SBRT).
- Consider SBRT for patients with oligometastatic disease.

Treatment Information

- Simulation
  - After clinical and radiologic staging, CT-based simulation is performed for radiation treatment planning. If available, PET/CT, MRI pelvis, or PET/MRI (if available) at the time of simulation may be helpful to define local and regional target structures. Patients can be simulated in the supine or prone position and there are benefits to each approach in the appropriate clinical setting. Prone setup with a false tabletop allows for improved small bowel avoidance and may be useful in individuals with a large pannus and pelvic node involvement. Supine setup is usually more reproducible with less setup variability, potentially allowing for reduced planning target volume (PTV) margins and smaller treatment fields. Patients are typically simulated for anal cancer IMRT planning in the supine position with legs slightly abducted (frog-legged) with semi-rigid immobilization in vacuum-locked bag or alpha-cradle. Patients are instructed to maintain a full bladder for simulation and treatment.
  - In males,* the external genitalia are typically positioned inferiorly such that setup is reproducible. In females,* a vaginal dilator can be placed to help delineate the genitalia and move the vulva and lower vagina away from the primary tumor. A radiopaque marker should be placed at the anal verge and perianal skin involvement can be outlined with radio-opaque catheters. It may be helpful to place a catheter with rectal contrast in the anal canal at the time of simulation for tumor delineation.
  - In patients with adequate renal function, IV contrast facilitates identification of the pelvic and groin vasculature (which approximates at-risk nodal regions). Oral contrast identifies small bowel as an avoidance structure during treatment planning. For tumors involving the perianal skin or superficial inguinal nodes, bolus should be placed as necessary for adequate dosing of gross disease in these areas. Routine use of bolus may not be necessary as the tangential effect of IMRT may minimize skin sparing. In situations where adequate dosing of superficial targets is uncertain, in vivo diode dosimetry with the first treatment fraction can ensure appropriate dose at the skin surface.

Treatment Information (continued)

- Target Volume Definition
  - Target volume definition should be performed per ICRU 50 recommendations. Gross tumor volume (GTV) should include all primary tumor and involved lymph nodes, using information from physical examination, endoscopic findings, diagnostic imaging, and simulation planning study for delineation. CTV should include the GTV plus areas at risk for microscopic spread from the primary tumor and at-risk nodal areas. If the primary tumor cannot be determined with available information (such as after local excision), the anal canal may be used as a surrogate target.
  - The pelvic and inguinal nodes should be routinely treated in all patients.
  - When using IMRT, a separate CTV volume for each planned treatment dose tier is contoured. One approach has been to define three tiers: a gross disease only volume, a high-risk elective nodal volume (including gross disease), and low-risk elective nodal volume (including gross disease). These volumes are determined by the presence or absence of tumor based on physical examination, biopsy, diagnostic and planning studies, and risk of nodal spread depending on tumor stage at presentation. The rationale for this approach is based on the shrinking fields technique. In RTOG-0529, a gross disease volume with a single elective nodal volume are used to deliver the prescribed course (dose-painting).
  - In defining the gross disease CTV around the primary tumor, an approximately 1- to 2-cm margin around GTV should be used with manual editing to avoid muscle or bone at low risk for tumor infiltration. To define the gross disease CTV around involved nodes, a 1-cm expansion should be made beyond the contoured involved lymph node with manual editing to exclude areas at low risk for tumor infiltration.
  - At-risk nodal regions include mesorectal, presacral, internal and external iliac, and inguinal nodes. The mesorectal volume encompasses the rectum and surrounding lymphatic tissue. The presacral nodal volume is typically defined as an approximately 1-cm strip over the anterior sacral prominence. To contour the internal and external iliac nodes, it is recommended to generally contour the iliac arteries and veins with approximately 0.7-cm margin (1- to 1.5-cm anteriorly on external iliac vessels) to include adjacent lymph nodes. In order to include the obturator lymph nodes, external and internal iliac volume contours should be joined parallel to the pelvic sidewall. The inguinal node volume extends beyond the external iliac contour along the femoral artery from approximately the upper edge of the superior pubic rami to approximately 2 cm caudad to saphenous/femoral artery junction. The inguinal node volume should be contoured as a compartment with general margins. The medial and lateral borders may be defined by adductor longus and sartorius muscles, respectively. Several recently published atlases are helpful to review when defining elective nodal CTVs.[5,6] The above descriptions are generalizations and each plan should be individualized based on the anatomy of each patient and tumor distribution.

Treatment Information (continued)

- **Target Volume Definition**
  - **The high-risk elective nodal volume typically includes the gross disease CTV plus the entire mesorectum, presacral nodes, and bilateral internal and external iliac lymph nodes inferior to the sacroiliac joint. In patients with gross inguinal nodal involvement, the bilateral or unilateral inguinal nodes may be included in the high-risk elective nodal volume. The low-risk elective nodal volume should include the gross disease CTV, high-risk elective nodal CTV, and presacral, bilateral internal, and external iliac nodes above the inferior border of the sacroiliac joint to the bifurcation of the internal and external iliac vessels at approximately L5/S1 vertebral body junction. If there is no obvious involvement of the bilateral inguinal nodes, these are included in the low-risk elective nodal volume.**
  - **PTV should account for effects of organ and patient movement and inaccuracies in beam and patient setup. PTV expansions should typically be approximately 0.5- to 1.0-cm depending on use of image guidance and physician practice with treatment setup for each defined CTV. To account for differences in bladder and rectal filling, a more generous CTV to PTV margin is applied in these regions. These volumes may be manually edited to limit the borders to the skin surface for treatment planning purposes.**
- **Dose Prescription**
  - **With IMRT treatment planning, doses are typically prescribed to PTVs. The dose of radiation required to control disease is extrapolated from historical studies that show excellent rates of control with concurrent radiation and chemotherapy. Typically prescribed dose varies by size of the tumor and risk of microscopic spread in elective nodal areas. One approach with "shrinking field technique" is that the low-risk elective nodal PTV volume is typically prescribed to 30.6 Gy in 1.8 Gy daily fractions. The high-risk elective nodal PTV is sequentially prescribed an additional 14.4 Gy in 1.8 Gy daily fractions for a total prescribed dose of 45 Gy. Finally, for T1–2 lesions with residual disease after 45 Gy, T3–4 lesions, or N1 lesions, an additional 5.4–14.4 Gy in 1.8–2 Gy daily fractions is again sequentially prescribed to the gross disease PTV volume (total dose, 50.4–59.4 Gy).**
  - **In RTOG-0529, the prescription parameters are different due to the use of only a single elective nodal volume and slightly different dose prescriptions depending on tumor stage. Furthermore, delivery of escalating dose to different target volumes was performed using a simultaneous integrated boost (SIB) dose painting technique with a maximum dose of 1.8 Gy per fraction to the primary tumor and large volume gross nodal involvement and 1.5 Gy per daily fraction to elective nodal areas. Table 1 outlines dose prescriptions by TNM stage according to the RTOG-0529 protocol. The SIB approach offers the convenience of developing a single treatment plan with reduced planning complexity, albeit with a lower biological dose delivered to the elective nodal areas.**
  - **For untreated patients presenting with synchronous local and metastatic disease, a platinum-based regimen is standard practice, and radiation can be considered for local control. The approach to radiation depends on the patient's performance status and extent of metastatic disease. If performance status is good and metastatic disease is limited, treat involved fields, 45–54 Gy to the primary tumor and involved sites in the pelvis, in coordination with plans for a platinum-based regimen. If there is low-volume liver oligometastasis, an SBRT dosing schema after systemic therapy may be appropriate depending on response. If metastatic disease is extensive and life expectancy is limited, a different schedule and dose of radiation should be considered, again in coordination with plans for 5-FU/cisplatin or a platinum-based regimen.**

Table 1: Dose Specification of Primary and Nodal Planning Target Volumes: RTOG-0529[4]

TNM Stage	Primary Tumor PTV Dose	Involved Nodal PTV Dose	Nodal PTV Dose
T1, N0	50.4 Gy (28 fxs at 1.8 Gy/fx)	N/A	42 Gy (28 fxs at 1.5 Gy/fx)
T2, N0	50.4 Gy (28 fxs at 1.8 Gy/fx)	N/A	42 Gy (28 fxs at 1.5 Gy/fx)
T3–4, N0	54 Gy (30 fxs at 1.8 Gy/fx)	N/A	45 Gy (30 fxs at 1.5 Gy/fx)
T any, N+ (≤3 cm)	54 Gy (30 fxs at 1.8 Gy/fx)	50.4 Gy (30 fxs at 1.68 Gy/fx)	45 Gy (30 fxs at 1.5 Gy/fx)
T any, N+ (>3 cm)	54 Gy (30 fxs at 1.8 Gy/fx)	54 Gy (30 fxs at 1.8 Gy/fx)	45 Gy (30 fxs at 1.5 Gy/fx)

- **Dose Prescription**
  - **The usual scenario of recurrent disease is recurrence in the primary site or nodes after previous RT and chemotherapy. In this setting, surgery should be performed if possible, and, if not, palliative RT and chemotherapy can be considered based on symptoms, extent of recurrence, and prior treatment. RT technique and doses are dependent on dosing and technique of prior treatment. In the setting of pure palliation, doses of 20–25 Gy in 5 fractions to 30 Gy in 10 fractions can be considered. SBRT can also be considered for treatment of primary and nodal recurrence in the setting of low-volume metastatic disease.**
- **OARs and IMRT Constraints**
  - **It is important to accurately define OARs so that dose to these structures can be minimized during treatment. In anal cancer, 2D and 3D treatment planning techniques are limited in their ability to spare most pelvic normal tissues due to the location of the target. With IMRT, dose to small bowel, bladder, pelvic/femoral bones, and external genitalia can be sculpted and minimized despite close proximity of these organs to target volumes. When contouring these structures, it is typically best to demarcate normal tissues on axial CT at least 2 cm above and below the PTV. Oral contrast is helpful to delineate the small bowel. While there is significant variability in how to contour the small bowel, one approach entails contouring the entire volume of peritoneal space in which the small bowel can move. As with elective nodal volume delineation, contouring atlases offer excellent guidance on defining OARs.[7] Once the OARs have been identified, the chief aim of IMRT planning is to limit the dose to these structures without compromising PTV coverage. The extent to which OARs can be avoided largely depends on the location and extent of tumor involvement at presentation as well as the extent to which the bowel extends into the lower pelvis and a given individual's anatomy.**
  - **Given patient variation with respect to OAR position and areas of tumor involvement, practical dose constraint guidelines are challenging. In tumors without gross nodal involvement it is often possible to limit OAR doses even further. Alternatively, in tumors with gross nodal involvement within the pelvis, compromise of PTV coverage may be necessary to limit doses to normal tissues, such as small bowel. Table 2 outlines dose constraints in RTOG-0529.**

Chemotherapy

PRINCIPLES OF SYSTEMIC THERAPY – LOCALIZED CANCER

Chemo/RT for Localized Cancer	
Preferred Regimens	**Other Recommended Regimens**
• 5-FU + mitomycin + RT • Capecitabine + mitomycin + RT	• 5-FU + cisplatin + RT

Systemic Therapy Regimens and Dosing – Localized Cancer

- 5-FU + mitomycin + RT[1,2]
  - Continuous infusion 5-FU 1000 mg/m²/day IV days 1–4 and 29–32
    Mitomycin 10 mg/m² IV bolus days 1 and 29 (capped at 20 mg) with RT
    or
  - Continuous infusion 5-FU 1000 mg/m²/day IV days 1–4 and 29–32
    Mitomycin 12 mg/m² on day 1 (capped at 20 mg) with RT

- Capecitabine + mitomycin + RT[3,4]
  - Capecitabine 825 mg/m² PO BID[a]
    Mitomycin 10 mg/m² days 1 and 29 (capped at 20 mg) with RT
    or
  - Capecitabine 825 mg/m² PO BID days 1–5[a]
    Mitomycin 12 mg/m² IV bolus day 1 (capped at 20 mg) with RT

- 5-FU + cisplatin + RT[5]
  - Cisplatin 75 mg/m² day 1
    Continuous infusion 5-FU 1000 mg/m²/day IV days 1–4
    Repeat every 4 weeks with RT

Recent Studies ≥ 2023

French FFCD-ANABASE Real World Data
Prospective Observational 1015 patients (male: 24.4 %; female: 75.6 %; median age: 65 years), 43.3% (T1-2, N0) and 56.7% (T3-4 or N +).
IMRT 815 (80.3 %) and a concurrent CT (781 patients), consisting of mitomycin-based CT for 80%.
Radiation = median total dose primary tumor = 60Gy (> 1/3 patients in both group >60Gy).

Vendrely, Radiother Oncol 2023
Early Stage 3-year DFS 84.3% CFS 85.6% OS 91.7% 4-6 mo CR 84.3%
Advanced 3-year DFS 64.4% CFS 66.9% OS 78.2% (p < 0.001). 4-6 mo CR 68.1%
MVA = male gender, locally-advanced stage, and ECOG PS ≥ 1 were associated with poorer DFS, CFS, and OS.
IMRT was significantly associated with a better CFS in the whole cohort and almost reached significance in the locally-advanced group.

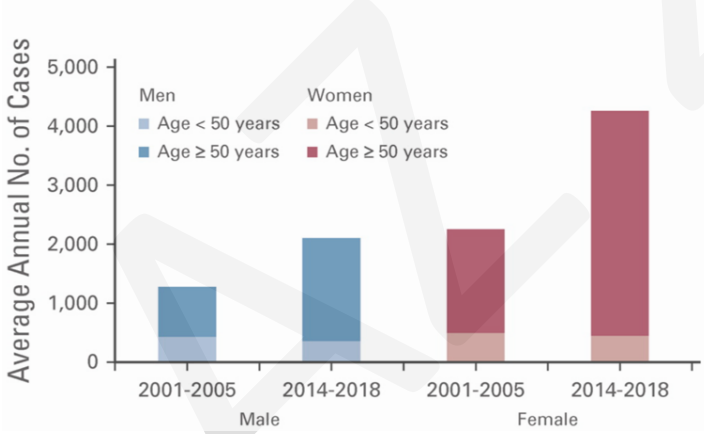
Conclusion: Treatment of SCCA patients showed good respect for current guidelines. Significant differences in outcomes advocate for personalized strategies by either de-escalation for early-stage tumors or treatment intensification for locally-advanced tumors.

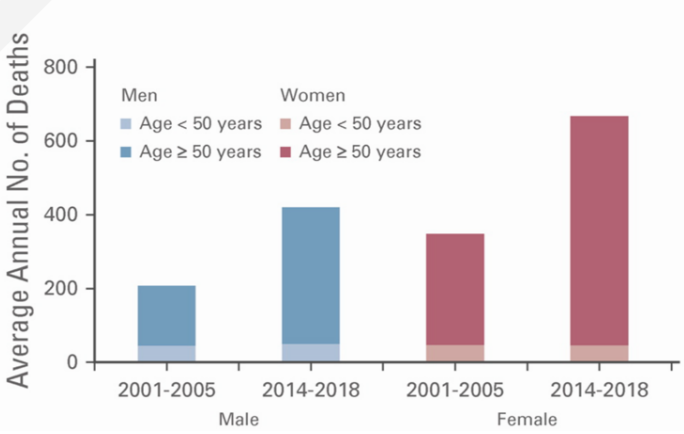
US State Level AIDS + Anal Cancer Study (2014-2018 vs. 2001-2005)
PURPOSE: Squamous cell carcinoma of the anus (SCCA) incidence and mortality rates are rising in the United States. Understanding state-level incidence and mortality patterns and associations with smoking and AIDS prevalence (key risk factors) could help unravel disparities and provide etiologic clues.

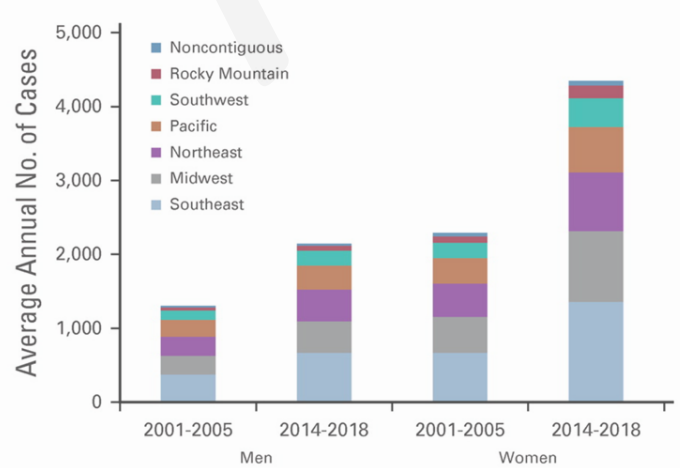
US Cancer Statistics and the National Center for Health Statistics data sets

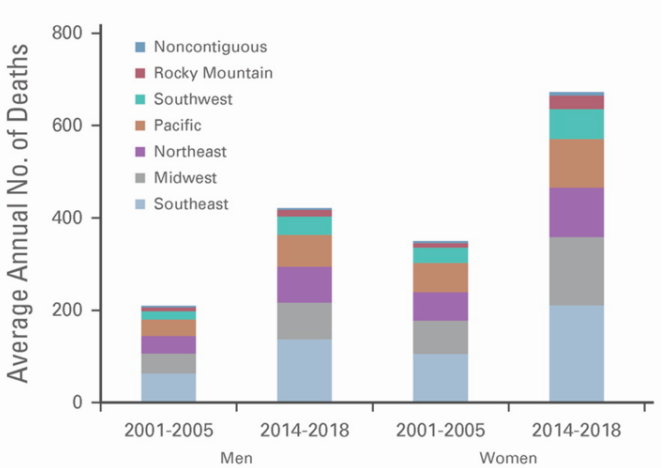
Damgacioglu, JCO 2023
SCCA incidence and mortality rates (per 100,000) ↑ among men (incidence, 2.29-3.36, mortality, 0.46-0.74) and women (incidence, 3.88-6.30, mortality, 0.65-1.02) age ≥ 50 years, but decreased among men age < 50 years and were stable among similar-aged women.
In state-level analysis, a marked increase in incidence (≥ 1.5-fold for men and ≥ two-fold for women) and mortality (≥ two-fold) for persons age ≥ 50 years was largely concentrated in the Midwestern and Southeastern states.
State-level SCCA incidence rates in recent years (2014-2018) among men were correlated (r = 0.47, P < .001) with state-level AIDS prevalence patterns. For women, a correlation was observed between state-level SCCA incidence rates and smoking prevalence (r = 0.49, P < .001).
CONCLUSION
During 2001-2005 to 2014-2018, SCCA incidence and mortality nearly doubled among men and women age ≥ 50 years living in Midwest and Southeast. State variation in AIDS and smoking patterns may explain variation in SCCA incidence. Improved and targeted prevention is needed to combat the rise in SCCA incidence and mitigate magnifying geographic disparities.

Commentary: https://ascopubs.org/doi/full/10.1200/JCO.22.02584









Localized Treatment

How do you manage early stage anal or anal margin cancer that is locally excised with negative but close margins when going back for wider margins would require an APR?

- **Argument for adjuvant CRT.**
- Situation A: patient has an excisional biopsy (ie. the surgeon doesn't think it is cancer) and leaves behind a positive or close margin.
- Recommendation: Full staging the patient with pelvic MRI PET/CT → generally adjuvant chemoradiation (due to risk for recurrence).
    - **Caveats:**
    - W.W. is case by case. CRT is very effective, and patients can be easily salvaged.
    - Unclear if CRT > RT alone (limited data for Stage I cancers). RT alone may be best for poor ECOG or elderly patients.
    - Regarding RT dosing, RT alone may require only 45-50.4 Gy ± boost primary to 55.8 Gy.
    - Conclusion: Need PLATO ACT 3
        - "ACT3: a prospective non-randomised phase II trial which will evaluate a treatment plan in patients with early, small tumours who have undergone surgery (local excision). Patients with no tumour cells close to the cut edge of the removed tissue (margins >1mm) have no further treatment, and those with tumour cells close to the cut edge (margins ≤1mm) receive additional lower-dose CRT (41.4Gy in 23 fractions). We aim to determine whether this treatment strategy results in acceptably low rates of the cancer coming back."

Historical CRT

Nigro Regimen: Wayne State

- **Nigro et al, 1974**
  - First report of 3 patients' s/p **neoadjuvant RT 30 Gy (15 fx) AP/PA** + concurrent 5-FU/mitomycin, who showed pathologically complete response at time of surgery.

- **Nigro et al, 1983**
  - 28 patients treated with neoadjuvant chemoRT, 30 Gy (200 cGy/fx, 3 weeks) AP/PA to pelvis and inguinals and 5-FU/mitomycin followed by surgery **(PLANNED APR)** or biopsy 4-6 weeks later
    - Note: APR was initially planned, but after 5/6 initial pts had no residual tumor at APR, surgery was then reserved as salvage.
  - **Nigro regimen**: 5-FU 1000 mg/m^2 continuous infusion on days 1-4, 29-32; mitomycin 15 mg/m^2 single bolus on day 1
  - **BUT IN AMERICA RTOG 05-29 you do mitomycin 10mg/m2 twice on day 1 and then day 29**.
  - **Results:** 86% (24/28) clinical CR to chemoRT

- **Leichman et al, 1985**
  - 45 patients T2+ treated with above regimen, initially APR (5/6 pCR), remaining avoided APR if negative biopsy at 4-6 weeks (84% negative biopsy)
  - 38/45 with negative biopsies (84%); none had cancer recurrence; 89% survival at 50 months (4 years).
  - All 7 patients (15%) with positive biopsies had distant recurrence and died of cancer
  - **Takeaway:** APR is not necessary in patients with complete response after chemoradiation. CRT is definitive treatment. RT avoids colostomy while maintaining survival.

Primary RT vs. Chemo-RT

EORTC (1987-1994) -- RT vs chemo-RT

Randomized. 110 patients, epidermoid ca of the anal canal or anal margin. T3-4N0-3 or T1-2N1-3. Treated with Arm 1) RT 45/25, if CR/PR then RT boost 15-20 Gy after 6 weeks or 2) RT 45/25 + CI 5-FU 750 mg/m2 + Mitomycin 15 mg/m2 single bolus. Surgical resection as part of primary treatment for those who did not respond after 6 weeks from start or with residual palpable disease after completion.

Bartelink, JCO 1997

Outcome: **Local control RT 50% vs. CRT 68% (SS)** **colostomy-free survival RT 40% vs. CRT 72% (SS)**

5-year OS: 56% (NS)

Toxicity: no difference in severe side effects, but anal ulcers more frequent in CRT

Conclusion: Chemo-RT improves local control and colostomy-free survival, **no impact on overall survival (effective salvage** surgery), with comparable toxicity

UKCCCR (ACT I) (1987-1994) -- RT vs chemo-RT

←R→ 585 patients. 40% with large T3 or T4, 20% N+.

1) RT 45/20 or 45/25 institutional preference 2) same RT + CI 5-FU 1000 mg/m2 + Mitomycin 12 mg bolus.

At 6 weeks A) if clinical response → RT 15 or 25 Gy boost via Ir-192 BT B) if non-respond → salvage surgery.

Primary endpoint local failure.

No Authors, Lancet 1996. Median F/U 3.5 years

Outcome: **Local control RT alone 41% vs. chemo-RT 64% (SS)** for 46% risk reduction.

3-year CSS 72% vs 61% (SS) 3-year OS 58% vs 65% (NS).

65% died with locoregional disease, 40% with mets

Toxicity: Acute worse with chemo-RT, but late similar

Conclusion: Combined chemo-RT should be standard treatment

Northover, British Journal of Cancer 2010.

Outcome: Absolute reduction of 25% in LRR (SS). Anal cancer death was reduced by 12.5% (SS).

9.1% increase in non-anal cancer deaths in the first 5 years of chemoradiation, which disappeared by 10 years.

Conclusion: The clear benefit of chemoradiation outweighs an early excess risk of non-anal cancer deaths **and can still be seen 12 years after treatment**.

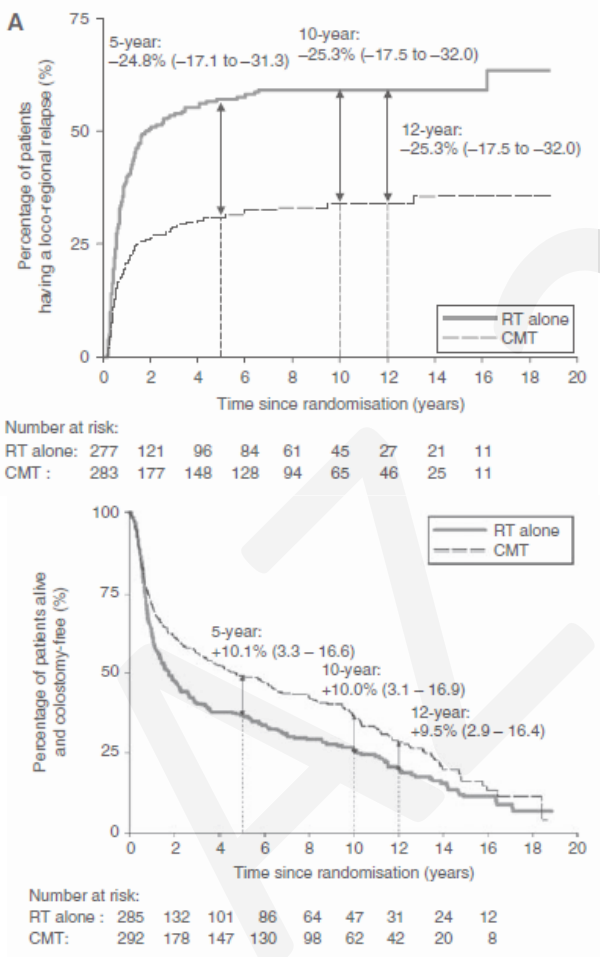


Figure A1 Colostomy-free survival, by treatment. Estimates shown are the absolute risk differences: combined modality therapy (CMT) minus RT alone (95% confidence interval (CI)). Median: RT alone: 1.8 years; CMT: 4.7 years. Hazard ratio (HR): 0.76 (95% CI: 0.63–0.91).

	Radiotherapy	CMT	p*
Early morbidity	110/285	140/292	0·03
Haematological†			
WBC×10⁹/L			
<2·0	0	13	
<1·0	0	6	
Platelets ×10⁹/L			
<50	0	7	
<25	0	7	
Skin			
Overall	76	93	
Severe	39	50	
Gastrointestinal			
Overall	39	46	
Severe	5	14	
Genitourinary			
Overall	13	20	
Severe	1	3	
Late morbidity‡	108/285	122/292	0·39
Skin	47	59	
Gastrointestinal	77	84	
Genitourinary	19	18	
Other	14	23	
Morbidity after surgical salvage	63/114	37/67	1·00
Wound§	22 (35%)	12 (32%)	
Colostomy	6 (10%)	2 (5%)	
Other	51 (81%)	27 (73%)	

*χ^2 with Yate's correction, 1 degree of freedom. †No reduced haemoglobin concentrations were recorded. ‡Excludes reports after residual/recurrent disease. §Includes abdominal and perineal wounds. WBC=white blood cells.

Table 7: **Morbidity**

Problem: CRT Side Effects

- Acute:
    - Anorectal dysfunction (frequency & urgency)
    - GU
    - Dermatitis (grade ¾ > 50%)
    - Hememorbidity (grade ¾ > 50%), neutropenicsepsis
        - 6 chemotherapy-related deaths in UKCCCR study
        - 4 deaths in the RTOG/ECOG study

- Chronic:
    - Anal incontinence/fibrosis (5-15%)
    - Vaginal stenosis (30-80%)
    - Small bowel obstruction (5-10%, but increases over time)
    - Hip fracture (10-15%; more common in women)
    - Sexual dysfunction

Q: How to ↓ Side Effects?

Δ MMC (RTOG 84-07, **98-11**, ACT II)

GET RID OF MMC

RTOG 87-04 (1988-1991) -- RT + 5-FU +/- Mitomycin
Randomized. 291/310 patients. Treated with 1) RT 45-50.4 Gy + 5-FU + Mitomycin or 2) RT + 5-FU. Residual tumor on post-treatment bx salvaged with pelvic RT 9 Gy + 5-FU + cisplatin

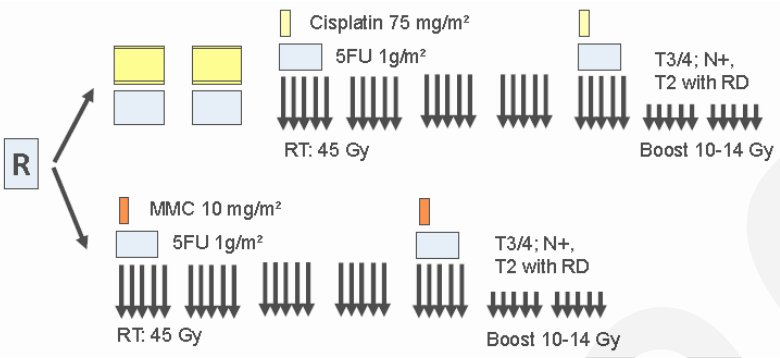
Flam, JCO 1996
Local control: post-treatment bx RT/5-FU 15% vs. RT/5-FU/MMC 8% (NS)
4-year colostomy rate 22% vs. 9% (SS),
DFS 51% vs. 73% (SS).
71 vs 59 % colostomy free survival (SS).
4-year OS 76% vs. 67% (NS).
Toxicity: MMC arm 23% vs. 7% (SS)
Conclusion: Despite greater toxicity, use of Mitomycin is justified

SUBSTITUTE MMC (THE FIRST TRIAL WITH OS!!!!)

RTOG 98-11 : Concurrent 5-FU/Mitomycin C vs. Induction/concurrent cisplatin/5-FU
INCLUDED anal margin.
←R→. 644 patients. Anal canal (squamous, basaloid, or cloacogenic), **T2-T4, any N** (by clinical, imaging, or biopsy). AIDS patients excluded.

Arm 1) **Concurrent** 5-FU 1000 mg/m2 + Mitomycin C 10 mg/m2 **+ RT**.
Arm 2) **Induction** cisplatin 75 mg/m2 + 5-FU C.I. 1000 mg/m2 x2 cycles → **Concurrent** cisplatin/5-FU (same doses) **+ RT**.

RT: large pelvic field (top border at L5/S1) to 30.6 Gy, with field reduction to bottom of SI joints for additional 14.4 Gy (to 45 Gy). Boost tumor + LN for T3, T4, or N+, or residual after 45 Gy for additional 10-14 Gy (2 Gy/fx) for total of 55-59 Gy. Use 2-2.5 cm margin for boost.
Note: the boost 2 Gy/fx was not 1.8 Gy/fraction due to potentially since these are residual disease, they are the bad cells that are still left.
Field Sizes: Inferior field includes anus and tumor with margin of 2.5 cm. AP/PA or 4 field box. AP field includes inguinals. PA field extends laterally to 2cm beyond sciatic notch. Inguinal field: electrons to divergence of PA field; 36 Gy if N0, or 45 Gy if N+; depth measured by CT but at least 3cm depth. Inguinal boost with electrons. They guys may have 10-day break as needed.

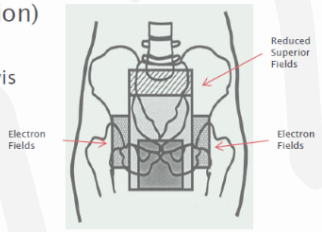


5-Year Rates	CDDP/5FU – RT/CDDP/5FU n=320 (%)	RT+MMC/5FU n=324 (%)	*p*-Value
Disease-free Survival	57.8	67.8	0.006
Local Relapse	26.4	20	0.087
Colostomy	17.3	11.9	0.074
Distant Mets	18.1	13.1	0.12
Overall Survival	70.7	78.3	0.026

5-years; Ajani, JAMA. 2008
Toxicity: Equal G3-4 NONHEME TOXICITY.
Higher severe hematologic toxicity with MMC (61% vs. 42% p<0.001).
PREDOMINANT FAILURE PATTERN: LOCAL REGIONAL.

Conformational Radiation Therapy (3D-CRT)

- 45 Gy in 25 fractions (180cGy/fraction)
- Initial Field (AP-PA) to 3060 cGy
  - Include anus, perineum, inguinal LNs, pelvis
  - Superior border - L5-S1
  - Inferior border - 2.5cm below tumor
  - Lateral - inguinal LNs
- Reduced Field (AP-PA) to 4500 cGy
  - Superior border - SI Joints (at 3060 cGy)
  - Lateral - Reduced fields to come off the inguinal LNs (at 3600 cGy)



CONCLUSIONS: Not a direct comparison between arms
Gunderson JCO, 2012. Long term outcomes.
Of 682 patients accrued, 649 were analyzable for outcomes.
OUTCOME: DFS and OS were statistically better for RT + FU/MMC.
5-year DFS, 67.8% v 57.8%; P = .006, **5-year OS, 78.3% v 70.7%; P=0.026**.
There was a trend toward statistical significance for CFS (P = .05), LRF (P = .087), and CF (P = .074).

BTW, T4N+ LF = 60%, 5-year OS 40% (basically those who do NOT fail).

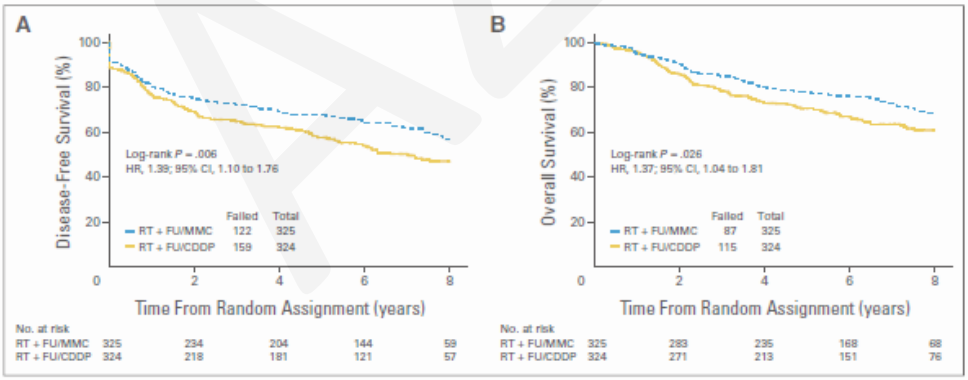


Fig 2. Impact of radiation therapy plus fluorouracil/mitomycin (RT + FU/MMC) *v* radiation therapy plus fluorouracil/cisplatin (RT + FU/CDDP) on (A) disease-free survival (*P* = .006) and (B) overall survival (*P* = .026). HR, hazard ratio.

T2N0 – DFS 80%, OS 86%, CF 9%
T3N0 – DFS 60%, OS 74%, CF 12%
T4N0 – DFS 65%, OS 77%, CF 20%
T2N+ – DFS 68%, OS 83%, CF 4%
T3N+ – DFS 43%, OS 57%, CF 19%
T4N+ – DFS 27%, OS 37%, CF 28%

Table 2. Multivariate Analysis for DFS and OS

		DFS			OS		
Variable	Comparison	Adjusted HR	95% CI	*P*	Adjusted HR	95% CI	*P*
Treatment	RT + FU/MMC *v* RT + FU/CDDP	1.40	1.11 to 1.78	.005	1.39	1.05 to 1.83	.022
Sex	Female *v* male	1.27	0.99 to 1.63	.06	1.38	1.03 to 1.85	.031
Tumor diameter	> 2-5 cm *v* > 5 cm	1.51	1.17 to 1.93	.0012	1.30	0.97 to 1.75	.079
Clinical node status	Negative *v* positive	1.82	1.42 to 2.34	< .001	1.88	1.41 to 2.51	< .001

Abbreviations: DFS, disease-free survival; HR, hazard ratio; OS, overall survival; RT + FU/CDDP, radiation therapy plus fluorouracil/cisplatin; RT + FU/MMC, RT plus fluorouracil/mitomycin.

UK ACT II (2001-2008) -- 2x2: RT + 5-FU + mitomycin vs cisplatin; observation vs maintenance cisplatin + 5-FU

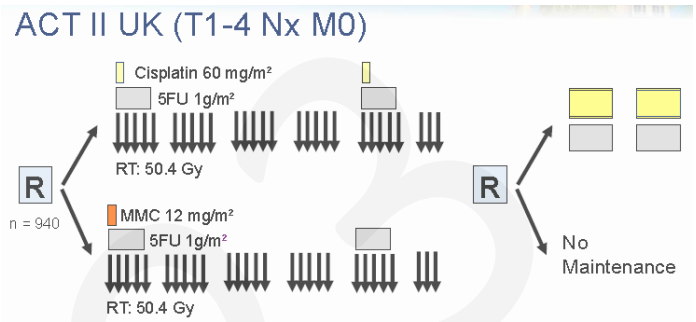
PRETTY MUCH COMPLETE NEGATIVE TRIAL **NOT DESIGNED AS Non-Inferiority**

Randomized, 2x2. 940 patients, 15% anal margin, LN+ 30%. Included T1 10%

Arm 1) RT	5-FU	Cisplatin	RT 50.4/28 + 5-FU 1000 mg/m2 D1-4 and D29-32 + cisplatin 60 mg/m2 D1 and D29
Arm 2) RT	5-FU	Mitomycin	MMC 12 mg/m2 D1.

Then randomized for maintenance chemo.

Arm 1) cisplatin + 5-FU x2 cycles. Arm 2) observation.



ACT II 1st Randomization	RT+CDDP/5FU n=468 (%)	RT+MMC/5FU n=472 (%)	P-value
6 mo. cCR	89.6	90.5	0.64
Colostomy Rate 3Y	11.3	13.7	NS
G 3/4 Heme AE	16	26	0.001
G 3/4 Non-Heme AE	68	62	0.22
2nd Randomization	**CRT + CT n=448**	**CRT alone n=446**	**P-value**
Progression-free Survival 3Y (73%/74% CDDP/MMC arm)	HR 0.95, 95% CI 0.75-1.21		0.70

James, JCO 2009. Median F/U 3 years
Outcome:
Mitomycin vs cisplatin ←R→: **NS in colostomy rate**.
Maintenance ←R→: **NS RFS (3-years 75%) or OS**.
CR identified 90% at 26 weeks after start CRT.
Toxicity: Acute Grade 3-4 hematologic MMC 25% vs cisplatin 13% (SS); non-hematologic no difference
Conclusion: No difference. 5-FU and MMC with RT remains the standard of care

Modern way of assessing response: Resist criteria. Biopsy is not recommended.

Update

Post-Hoc Glynne-Jones, Lancet 2017. pCR evaluation by time.
cCR assessment at **11 weeks, 18 weeks, 26 weeks** from the start of chemoradiotherapy.
FINDINGS:
All Comers cCR 52% → 71% → 78%.
N=691 attended all 3 assessments cCR 64% → 80% → 85%.
N=209 < CR at 11 weeks → 72% converted to cCR at 26 weeks.
N=691 5-year OS ~85% vs. 75%/61%/48% if < CR at 11, 18, and 26 weeks.
INTERPRETATION:
Many patients who do not have a complete clinical response when assessed at 11 weeks after commencing chemoradiotherapy do in fact respond by 26 weeks, and the earlier assessment could lead to some patients having unnecessary surgery. Our data suggests that the optimum time for assessment of complete clinical response after chemoradiotherapy for patients with squamous cell carcinoma of the anus is 26 wee

Δ Induction C or + ↑ RT

ACCORD 03 (Peiffert, JCO 2012) **2 x 2**

FAILED TRIAL (tried to increase RT doses to LC)

←R→ 307 patients with anal SCC (tumor either ≥ 3cm or LN+).
Arm 1) **Induction** chemo → CRT → RT boost (std)
Arm 2) **Induction** chemo → CRT → RT boost (high)
Arm 3) **CRT → RT boost (std) REFERENCE ARM**
Arm 4) CRT → RT boost (high)

* Induction chemo was 2 cycles 5-FU 800 mg/m² IV infuction days 1-4 and 29-32; cisplatin 80mg/m² days 1 and 29.
* CRT was 45 Gy in 25 fractions with 5-FU and cisplatin during weeks 1 and 5.
* Boost std 15 Gy, high 20-25 Gy)

Results: The 5-year colostomy free survival S rates were 69.6%, **82.4%**, 77.1%, and 72.7% in arms A, B, C, and D, respectively.
Conclusion: No benefit for induction C or ↑RT boost.
Trend for ↑ RT boost to improved CFS.

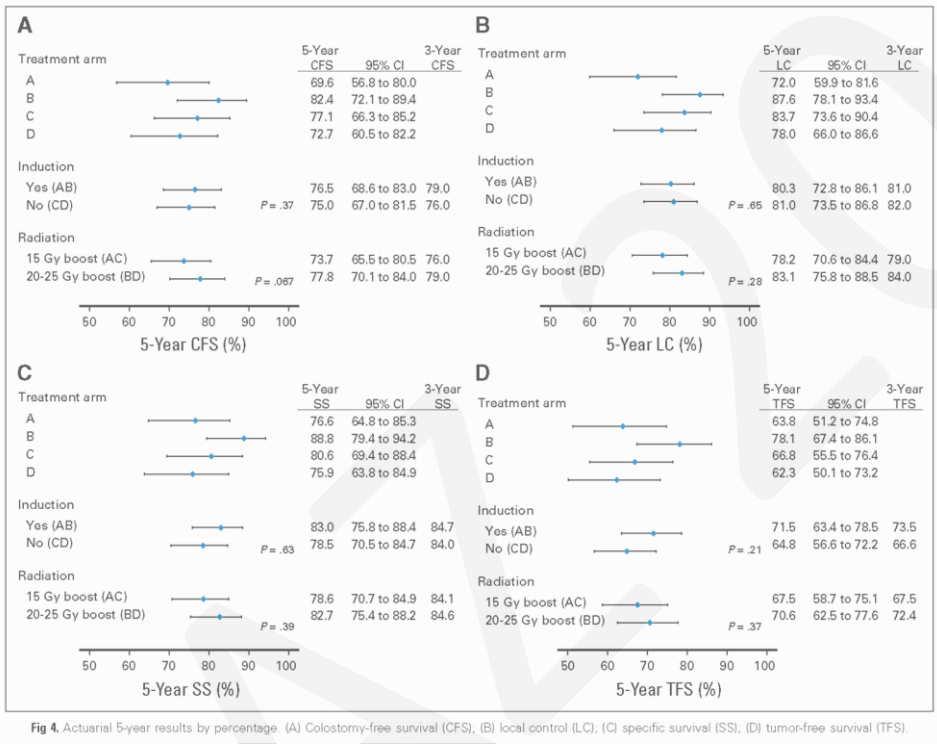
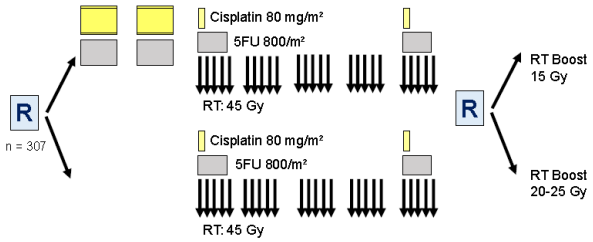


Fig 4. Actuarial 5-year results by percentage. (A) Colostomy-free survival (CFS), (B) local control (LC), (C) specific survival (SS), (D) tumor-free survival (TFS).

ACCORD 03 (T2>4cm-4 Nx M0)



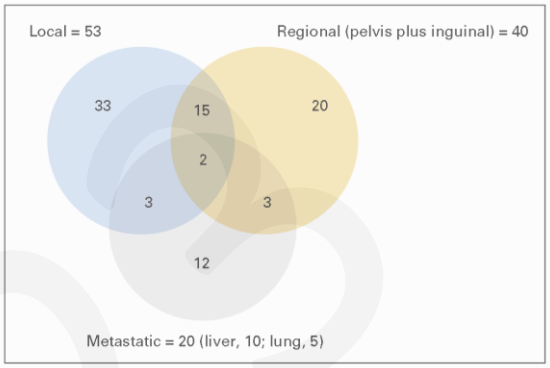
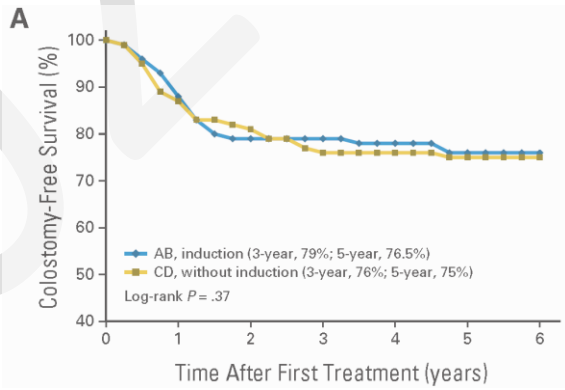
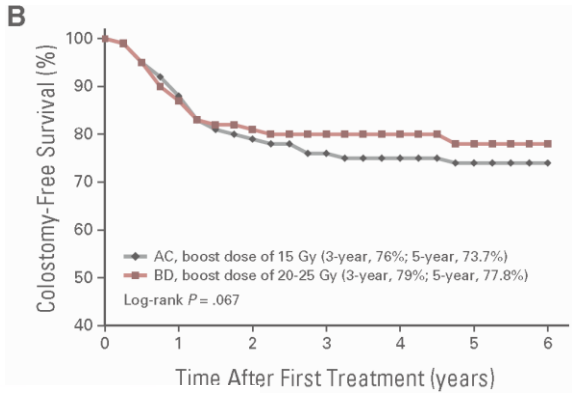


Fig 2. Distribution of the sites of treatment failure (n = 88).





Five Year Outcomes

	CDDP/5FU/ CRT low RT dose	CDDP/5FU/ CRT high RT dose	CRT low RT dose	CRT high RT dose
Complete Response	78%	86%	74%	74%
Colostomy-free Survival	70%	82%	77%	73%

- No survival benefit of adjuvant CT or higher dose RT

E3205 Cetuximab + CRT

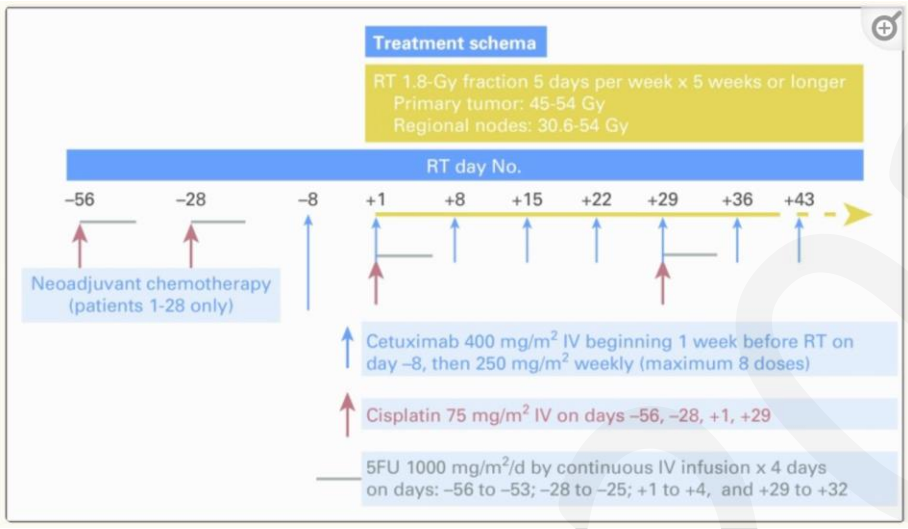
Background: Squamous cell carcinoma of the anal canal (SCCAC) is characterized by high locoregional failure (LRF) rates after sphincter-preserving definitive chemoradiation (CRT) and is typically associated with anogenital human papilloma virus infection. Because cetuximab enhances the effect of radiation therapy in human papilloma virus–associated oropharyngeal squamous cell carcinoma, we hypothesized that adding cetuximab to CRT would reduce LRF in SCCAC.

Prospective 61 patients stage I to III SCCAC → CRT (cisplatin, fluorouracil, + RT) primary tumor and regional lymph nodes (45 to 54 Gy) plus 8x once-weekly doses of concurrent cetuximab.

The study was designed to detect at least a 50% reduction in 3-year LRF rate (one-sided α, 0.10; power 90%), assuming a 35% LRF rate from historical data.

Poor risk features included male sex in 20%, T3 to 4 lesions in 54%, and positive regional nodes in 54%.

Comparison of the characteristics between the first 28 patients treated with neoadjuvant chemotherapy (arm A) and the remaining 33 patients treated without neoadjuvant chemotherapy (arm B) revealed that patients in arm B were more likely to have advanced-stage disease (P = .006).



Garg, JCO 2017

3-year LRF 23%. vs. 31% (ACT I) vs. 33% (RTOG 98-11 5-year results)

3-year PFS 68%.

3-year OS 83%.

Grade 4 toxicity occurred in 32%, and 5% had treatment-associated deaths.

ORR 65% both arms combined (A 63%; B 67%)

cCR A 59%; B 35%.

Conclusion

Although the addition of cetuximab to chemoradiation for SCCAC was associated with lower LRF rates than historical data with CRT alone, toxicity was substantial, and LRF still occurs in approximately 20%, indicating the continued need for more effective and less toxic therapies.

Patient Characteristic or Outcome	RTOG9811[4,5]	RTOG9811[4,5]	ACT1[1,2]	ACT2[6]	AMC045[29]	E3205 (this report)
Systemic therapy	MMC/FU	CP/FU	MMC/FU	MMC/FU or CP/FU	Cetuximab plus CP/FU	Cetuximab plus CP/FU
RT dose to primary tumor	45-59 Gy IMRT, 0%		45-60 Gy IMRT, 0%	50.4 Gy IMRT, 0%	45-54 Gy IMRT, 62%	45-54 Gy IMRT, 84%
No. of patients	324	320	295	940	45	61
Male sex, %	31	30	43	38	91	20
T stage, %						
1	0	0	12	10	29	12
2	63	66	29	42	44	35
3	27	26	41	31	27	37
4	10	7	15	14	0	16
Node-positive, %	26	26	23	32	35	54
Median follow-up, years	2.5		13.1	5.9	4.7	7.0
Range or IQR	Range, 0.1-7.4[4]			IQR, 3.6-6.9	Range, 0-5.7	Range, 2.1-8.1
3-year PFS rate, %	67†	61†	NS	72*	72	68%
95% CI	62 to 72	55 to 66		66 to 78	56 to 84	55 to 79
3-year OS rate, %	84	76	82	83	79	83
95% CI	78 to 88	70 to 81	NS	N.S.	63 to 89	71 to 91
3-year LRF‡ rate, %	25	31	39	N.S	20	21
95% CI	NS	NS	NS		10 to 37	7 to 26
Interruptions in CRT			NS			
No. (%)	200 (62)	163 (51)		126 (15)	19 (44)	22 (36%)
Median No. days	7	6		NS	5	12
Range, days	4-33	4-34			1-21	2-32
Adverse events, grade 3, 4, %	53, 24	63, 20	48§	63, 13	46, 26	61, 32
Treatment-associated deaths	NS	NS	6 (2%)	8 (< 1%)	2 (4%)	3 (5%)

Δ 3D → IMRT (RTOG 05-29)

RTOG 05-29: PHASE 2 DOSE PAINTING TRIAL. *Can we reduce the acute toxicity of chemoradiation with IMRT?*
Prospective phase II trial. 52 patients. 1^O = determine if dose-painted IMRT can reduce the combined rate of grade 2+ GI and GU acute adverse events by at least 15% compared to RTOG 9811. 2^O = potential reduction of all AEs and assessment of ability to perform DP-IMRT within the radiation planning guidelines delineated.
Eligibility criteria T2-4, N0-3, M0, Age ≥ 18, ECOG ≤ 1, Adequate organ function, AIDS exclusion criteria
Of 52 patients, 54% were stage II, 25% were stage IIIA, and 21% were stage IIIB.

Primary: Reduce combined grade 2+ GI/GU toxicities by 15%, as compared to 98-11 5FU/MMC arm (n=59 pts)
Secondary: all AEs vs. 98-11
Secondary: feasibility (< 5 cases with major deviations)
Secondary: two year outcomes

Chemotherapy: 5-FU 1000 mg/m^2 continuous infusion days 1-5, 29-33, Mitomycin 10mg/m^2 bolus days 1 and 29

GTVA includes the gross primary anal tumor volume (as documented by digital exam, and as seen on CT, and PET or MRI if performed).
GTVN50, including all involved nodal regions (as documented by biopsy or radiograph) containing macroscopic disease < 3 cm in greatest dimension (which will receive 50.4 Gy).
6.4.1.3 GTVN54, including all nodal regions (as documented by biopsy or radiograph) containing macroscopic disease > 3 cm in greatest dimension (which will receive 54 Gy).

CTVA includes the gross primary anal tumor volume, the anal canal, and a 2.5 cm expansion (except into bone or air).
6.4.2.2 CTV45, CTV50, CTV54 includes the nodal regions (respectively uninvolved, involved with nodes < 3 cm, and involved with nodes > 3 cm) and a 1.0 cm expansion (except into uninvolved bone, genitourinary structures, muscles, or bowel).
6.4.2.3 Nodal regions include:

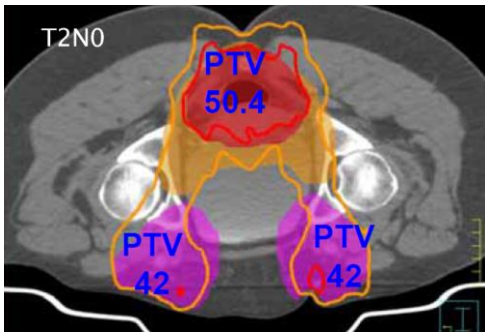
a) Mesorectal (including peri-rectal and presacral)
b) Right and left inguinal
c) Right and left external iliac
d) Right and left internal iliac

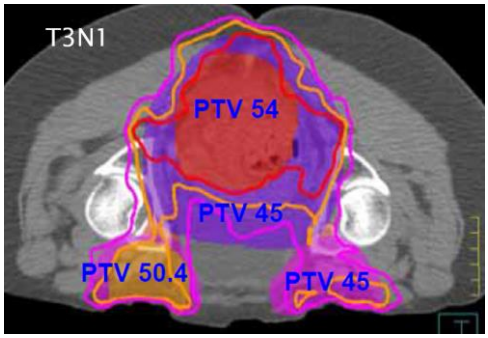
	PTVA	Uninvolved Nodes	LN < 3 cm	LN > 3 cm
T2 N0	5040 (180 x 28)	4200 (150 x 28)		
T3-4 N0	5400 (180 x 30)	4500 (150 x 30)		
T2-4 N+	5400 (180 x 30)	4500 (150 x 30)	5040 (**168** x 30)	5400 (180 x 30)

Kachnic, IJROBP 2021 **Long Term 05-29** Median follow-up was 7.9 years (min-max, 0.02-9.2 years).
Eight patients experienced local-regional failure, with 5 patients having persistent disease at 12 weeks.
No isolated nodal failures occurred in the microscopic elective nodal volumes.
Six patients required colostomy—5 for local-regional salvage and 1 for a temporary ostomy for anorectal dysfunction.
Rates of late adverse events included: 28 patients (55%) with grade 2, 8 patients (16%) with grade 3, 0 patients with grade 4, and 2 patients (4%) with grade 5 events (sinus bradycardia and myelodysplasia, possibly owing to chemotherapy). Only 11 patients reported grade 1 to 3 sexual dysfunction.
Conclusions Dose-painted IMRT with 5FU/MMC for the treatment of anal canal cancer yields comparable long-term efficacy as conventional radiation cohorts. Enhanced normal tissue protection lowered rates of grade 3 and higher late effects without compromising pelvic tumor control.

	RTOG 0529 (n=52)			RTOG 9811-MMC Arm (n=325)		
Endpoint	**Total Events**	**5y-% (95% C.I.)**	**8y-% (95% C.I.)**	**Total Events**	**5y-% (95% C.I.)**	**8y-% (95% C.I.)**
Local-regional Failure	8	16 (7, 27)	16 (7, 27)	67	20 (16, 25)	22 (17, 27)
Colostomy Failure*	6	10 (4, 20)	12 (5, 23)	38	12 (9, 16)	12 (9, 16)
Distant Failure	11	16 (7, 27)	22 (12, 34)	46	13 (10, 17)	16 (12, 21)
Disease-free Survival	19	70 (56, 81)	62 (47, 74)	122	68 (62, 73)	57 (50, 63)
Colostomy-free Survival	17	74 (59, 84)	66 (51, 77)	106	72 (67, 77)	63 (57, 69)
Overall Survival	16	76 (61, 86)	68 (53, 79)	87	78 (73, 83)	69 (62, 74)

- *In 0529, 5 out of 6 colostomies were performed for local-regional failures
- In 9811, colostomies were performed for:
  - Disease - 26/38; Treatment complications - 10/38; Both - 2/38

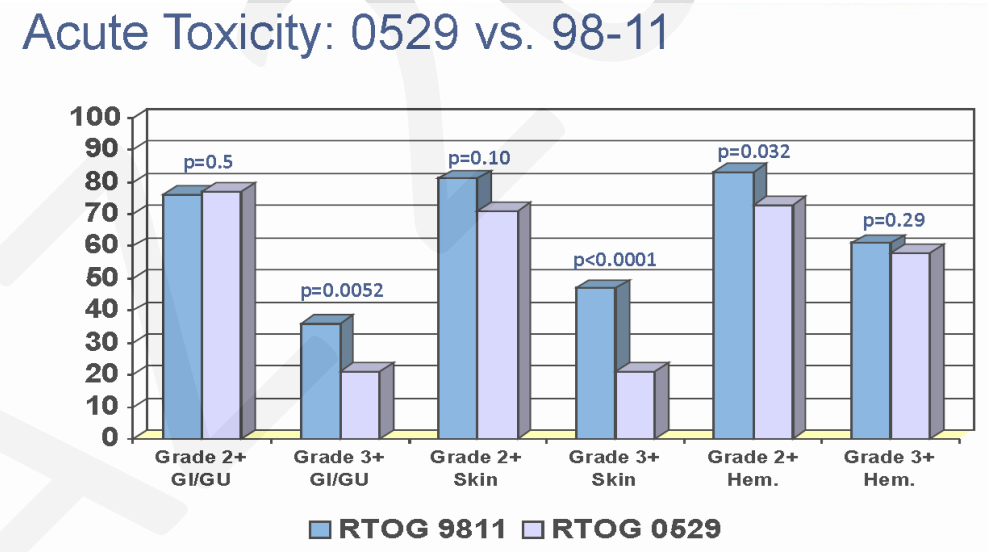




	0529 (n=52)	9811-MMC-arm (n=324)
Endpoint[&]	2y-%	2y-%
Local-Regional Failure	20	23
Colostomy Failure	8	10
Overall Survival	88	91
Disease-Free Survival	77	71
Colostomy-Free Survival	86	84
Distant Failure	15	10

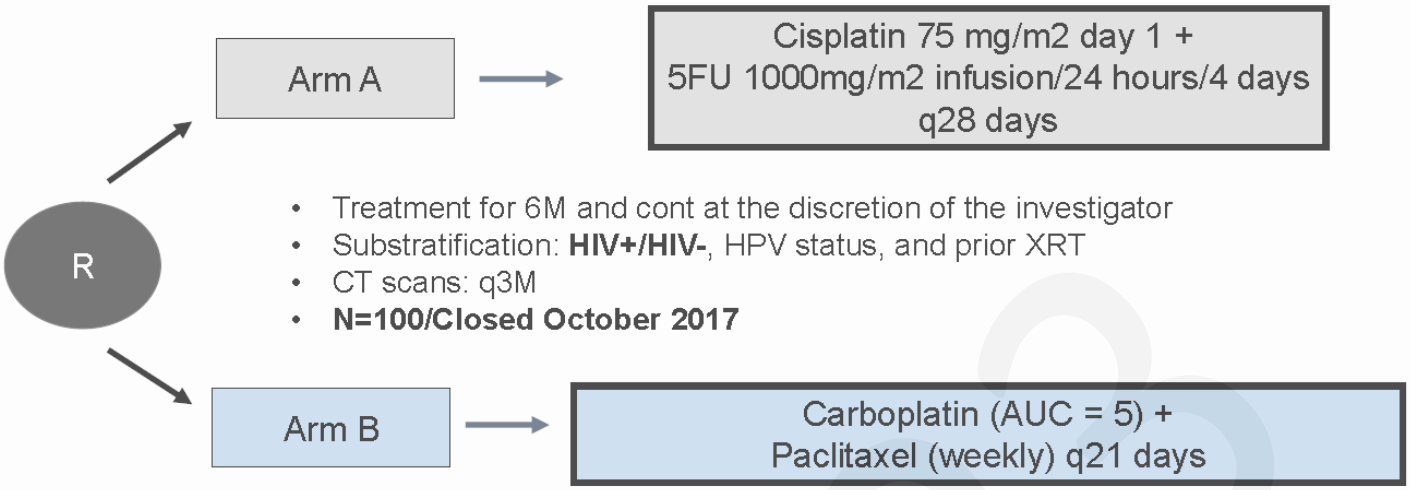
Table 5 Comparisons of acute treatment-related adverse events*

Adverse events	0529 (n=52)	98-11 (Arm 1[†]) (n=325)	*P* value (1-sided proportions test[§])
Grade 2+			
GI/GU[‡]	40 (77%)	249 (77%)	.50
Derm	39 (75%)	271 (83%)	.10
GI	38 (73%)	237 (73%)	.50
GU	8 (15%)	66 (20%)	.18
Heme	38 (73%)	275 (85%)	.032
Overall	49 (94%)	318 (98%)	.12
Grade 3+			
GI/GU	11 (21%)	120 (37%)	.0052
Derm	12 (23%)	159 (49%)	<.0001
GI	11 (21%)	117 (36%)	.0082
GU	1 (2%)	11 (3%)	.32
Heme	30 (58%)	201 (62%)	.29
Overall	43 (83%)	283 (87%)	.23



Constraints.

6.5.1.1 Small bowel:	V 30 Gy ≤ 200 cc	V 35 Gy ≤ 150 cc,	V 45 Gy < 20 cc	Dmax 50 Gy.
6.5.1.2 Femoral heads:	V 30 Gy ≤ 50%	V 50 Gy < 35%	V 44 Gy ≤ 5%	
6.5.1.3 Iliac crests:	V 30 Gy ≤ 50%	V 40 Gy ≤ 35%	V 50 Gy ≤ 5%	
6.5.1.4 External genitalia:	V 20 Gy ≤ 50%	V 30 Gy ≤ 35%	V 40 Gy ≤ 5%	
6.5.1.5 Bladder:	V 35 Gy ≤ 50%	V 40 Gy ≤ 35%	V 50 Gy ≤ 5%	
6.5.1.6 Large bowel:	V 30 Gy ≤ 200 cc	V 35 Gy ≤ 150 cc	V 45 Gy ≤ 20 cc	



Study PIs UK - Rao, US - Eng

Objective: Identify best chemotherapy backbone to build for biologic development

1) Primary endpoint: RR
2) Secondary endpoints: PFS, OS, correlatives, and QOL, etc.

Metastatic Disease

Currently Updating

Paraaortic LNs: https://pubmed.ncbi.nlm.nih.gov/19231109/

Technical Considerations

Vaginal Dilator Use Toxicity Study
RR 339 women → 285 (84.1%) were treated with a daily VD.
Of 184 women alive without disease, ninety patients (49%) completed the FSFI, and 51 (56.7%) were sexually active with valid FSFI scores. All received therapy with a daily VD.

Arzola, PRO 2023
Forty-one women (80%) had sexual dysfunction.
Univariate analysis showed higher dose to 50% (D50%) of the AVW correlated with worse FSFI (β -0.262; p=.043), worse desire FSFI subscore (β -.056; p=.003) and worse pain FSFI subscore (β -.084; p=.009).
Younger age correlated with worse pain FSFI subscale (β .067; p=.026). Age (β 0.070; p=.013) and AVW D50% (β -0.087; p=.009) were significant on multivariable analysis.
Anterior Vaginal Wall (AVW) D50% >48Gy predicted increased risk of sexual dysfunction.
Conclusion
Daily VD use is safe and well tolerated during CRT for SCCA. Using a VD during treatment to displace the AVW may reduce the risk for sexual dysfunction. Limiting the AVW D50% <48Gy may further reduce the risk but additional data are needed to validate this constraint.

1.) **Patient Selection**- Daily VD should not be used for women with T4 disease from vaginal involvement due to the risk of increased pain with VD insertion as well as potential displacement of areas at risk outside standard clinical target volume expansions. Almost all other women should be considered for daily VD.
2.) **Patient Education**- Eligible female patients with SCCA should be informed about the rationale for daily VD use prior to simulation and the logistics of VD insertion and immobilization should be discussed in detail prior to simulation. Women should always be empowered to decline daily VD use if they are uncomfortable with it after discussion of the risks and benefits.
3.) **Dilator Selection**- We recommend use of a silicone vaginal dilator. The largest size that fits comfortably for the patient should be selected. One of the goals is maximal separation of the anterior vaginal wall from the posterior vaginal wall, particularly at the introitus.
4.) **Insertion and Immobilization**- Ideally, daily VD should be utilized in a supine, frog-leg position. Daily VD is more difficult and uncomfortable to insert and immobilize in the prone position with a belly board. Lubricating jelly should be applied to the dilator prior to insertion, and the patient should be given the option to place the dilator herself, or have the therapist insert it for her. The dilator should be inserted so the hub is flush with the introitus. The dilator should be immobilized either by building up a "shelf" in the lower body custom cradle and/or using paper tape in an x-pattern across the perineum.
5.) **Vaginal Wall Delineation**- The vaginal wall should be contoured as per ECOG EA2182 DECREASE atlas guidelines[9]: contour the dilator, expand by 5mm, delete contours that are outside the body, and delete the dilator itself. The anterior vaginal wall contour can be generated by deleting the posterior 180 degrees of the vaginal wall contour. We recommend at least 1cm of margin should be given anteriorly anywhere the gross tumor volume is in contact with the vagina to take into account minor day to day differences in VD insertion.
6.) **Radiation Dose Constraints**- We recommend using ECOG decrease constraints (vaginal wall-PTV D50%</=30Gy). While awaiting validation from a larger cohort, we recommend considering adding AVW D50%<48Gy as an additional constraint if it can be met without compromising tumor target coverage.
7.) **Daily Image Guidance**- We recommend the use of daily cone beam CT whenever daily VD is used in order to verify VD insertion and appropriate target coverage with the prescription isodose line.
8.) **Long-Term Vaginal Dilator Use**- Even with daily VD use, we still recommend women participate in long-term use of a vaginal dilator starting approximately six weeks after completion of pelvic radiation, following healing of acute mucositis. Directions are to use the VD approximately three times per week, 10 minutes per session to reduce the risk of long-term vaginal stenosis.
9.) **Questions to Ask at Follow-up**- i.) are you using your vaginal dilator? ii.) are you currently sexually active? ii.) iii.) would you like to discuss strategies to improve sexual function during our visit today?
10.) **Other Interventions**- For patients experiencing dyspareunia after pelvic radiation, we recommend consideration of vaginal estrogen therapy if no contraindications as well as consultation with a trained pelvic floor physical therapist.

Dose Prescription

Target Delineation

Contour using soft tissue windows as per the RTOG anorectal contouring atlas
Contouring Atlas (Myerson, *Int J Radiat Oncol Biol Phys* 2009; DOI: 10.1016/j.ijrobp.2008.08.070)
Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring

GTVA = primary tumor based on exam, CT, MRI, and/or PET
GTV54 = involved nodes >3 cm
GTV50 = involved nodes ≤3 cm

CTVA = GTVA + 2.5 cm, not extending into bone or air

CTV54: = GTV54 + 1 cm
CTV50 = GTV50 + 1 cm
CTV45 or CTV42 = elective nodes

7 to 8 mm around iliac vessels, carving out of muscle and bone
Consider 10-mm expansion if nodes identified
Inguinal nodes may be farther from vessels and may need greater expansion

CTVA (Perirectal, Presacral, Internal Iliac)

Low Pelvis
- Includes CTVA
- Entire mesorectum to the pelvic floor
- Few mm into levator muscles unless extension into ischiorectal fossa
- **2 cm** below gross disease; **2 cm** around anal verge
- 1 to 2 cm up to bone around any areas of invasion

Mid Pelvis
- Rectum and mesentery
- Internal iliacs with margin for bladder variability
- Posterior and lateral margins to pelvic sidewall musculature or where absent, bone
- Anteriorly, 1 cm into the posterior bladder
- Include at least the posterior internal obturator vessels

Upper Pelvis
- Superior extent of perirectal component is the rectosigmoid junction or at least 2 cm proximal to macroscopic disease
- Nodal volume extends up to bifurcation of common iliacs (boney landmark is sacral promontory).

CTVB (External Iliac)
- Transition from external iliacs to inguinals is at the level of the inferior extent of the internal obturator vessels (boney landmark is upper edge of the superior pubic rami)

CTVC (Inguinal)
- Contour entire compartment down to **2 cm** caudal to the saphenous/femoral junction
- PTV: CTV + 0.5 to 0.7 cm with daily image-guided radiation therapy (IGRT)

Treatment Planning
- Intensity-modulated radiation therapy
- Usually 6-MV photons
- Use heterogeneity corrections

Follow-Up

Exam at 4 weeks…

If still + then reexam at 8 weeks.

Exam at 8 weeks…

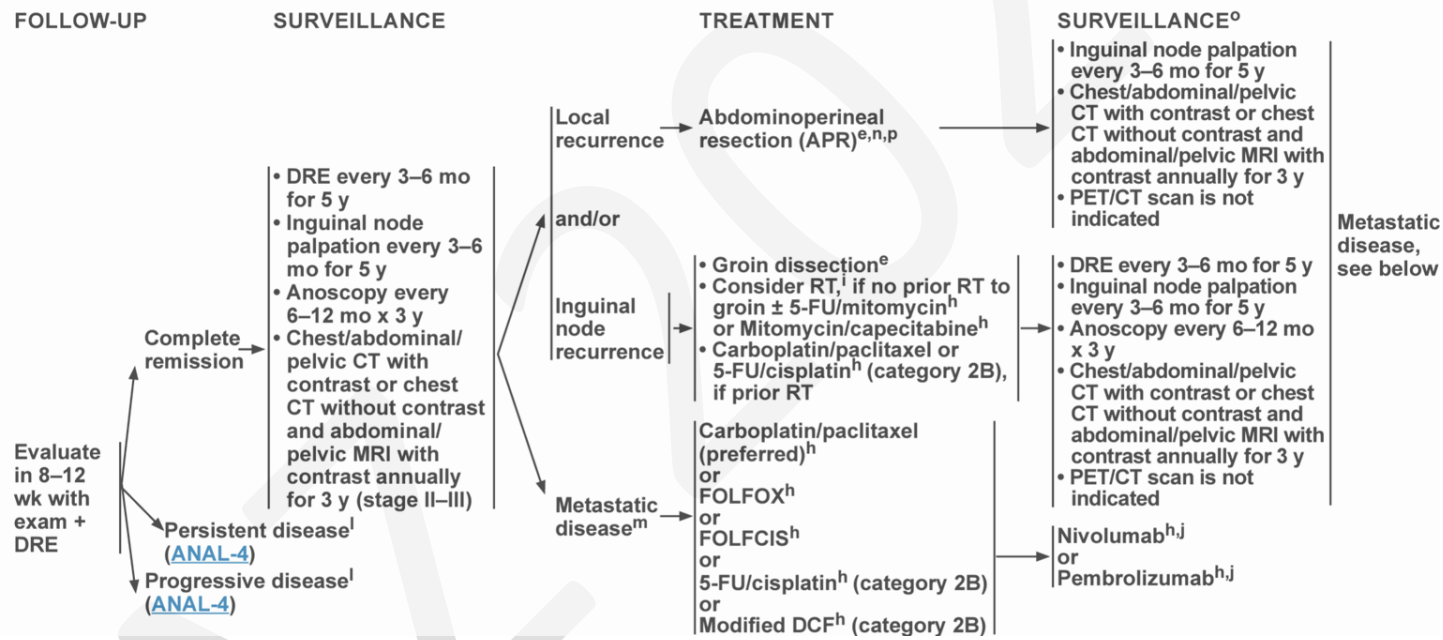
If persistent **but regressing** – monitor monthly; **biopsy NOT indicated at this time.**

Exam at 12 weeks

If clinical suspicion of non-responding disease – can still watch if moving in the right direction **until 6 months** per ACT II.
Aka 26 weeks!!!!

Biopsy for persistent disease OK to do between 3-6 months; if still disease at 6 months, restage and if no met disease, consider APR
Progressive disease at any time = immediate biopsy and re-staging
PET at 3 months post CRT completion is good biomarker of response if insurance will allow
Vaginal dilator for women at one month post CRT

Once complete regression achieved:
H&P, digital rectal exam, and anoscopy q3 to 6 months for 5 years
CT C/A/P annually for 3 years if T3-4 or N2-3
Consider surveillance MRIs



Post-Treatment PET Study
Prospective 94 patients from 2014-2019

Bailleux, Radiother Oncol 2023 Median follow-up was 51 months.
2-month complete radiological response 47.4% 2 month cCR 84.6%.
For disease free survival, the prognostic value of complete response was statistically significant (p=0.02) with 18F-FDG PET/CT and with clinical examination (p<0.001). For local recurrence free survival, the prognostic value with 18F-FDG PET/CT was lower (p=0.04) than clinical examination (p < 0.007).
Conclusion While clinical examination remains the gold standard for post treatment evaluation in anal cancer, 18F-FDG PET/CT has a statistically significant prognostic value. These two assessments could be combined to improve early evaluation.