ACRODeck

Anal Cancer

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Introduction to ACRODeck

ACRODeck

- The goal of ACRODeck is to introduce standard treatments of oncologic malignancies for early radiation oncology residents

- Please note that there is often considerable variation in standard treatment recommendations

- Moreover, the landscape of oncology is ever-changing; for practice changing landmark studies and feedback, please email: resident@acro.org

Table of Contents

ACRODeck

1. Clinical Presentation and Differential Diagnosis
2. Anatomy
3. Initial Workup
4. Staging
5. Treatment Summary
   - Radiation
   - Chemotherapy
   - Surgery
6. Prognosis
7. Review Questions

Clinical Presentation and Differential Diagnosis

HPV exposure is a risk factor for development of anal cancer

- Rectal bleeding is the most common symptom
  - Perineal pain, mass sensation, and altered bowel habits are also common

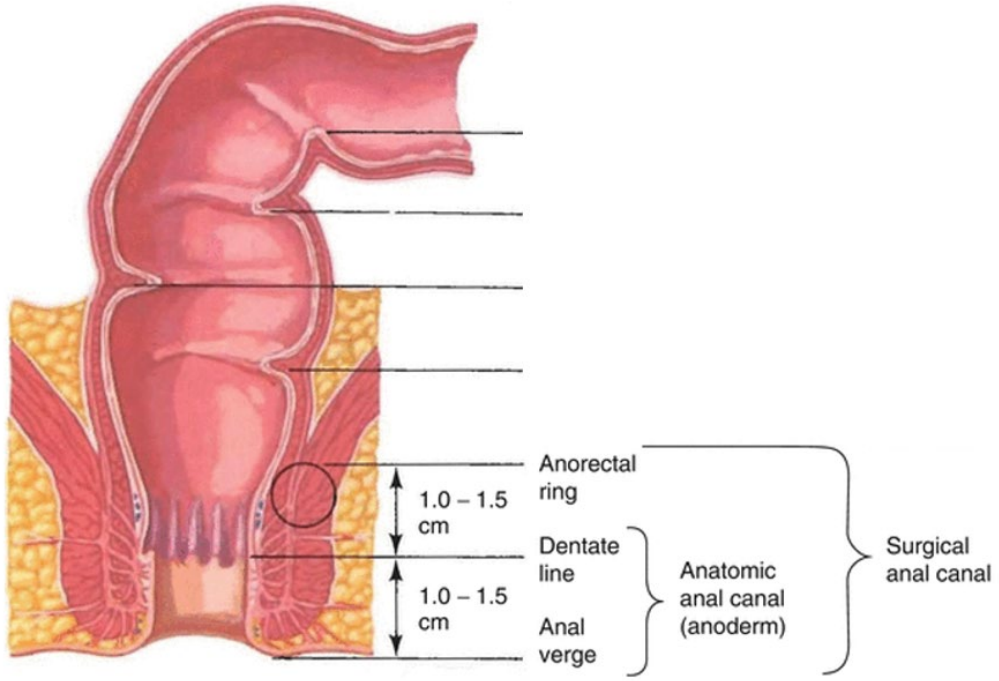
- Differential Diagnosis:
  - Hemorrhoids
  - Anal fissure
  - Anal warts
  - Low rectal cancer
  - Skin cancer
  - Carcinoid tumors

Anal Anatomy

- The anal canal is approximately 3-5 cm in length
  - It extends from **anal verge** (palpable junction between non–hair-bearing and hair-bearing squamous epithelium) to the **dentate line** (the line between simple columnar epithelium and stratified squamous epithelium)

- The **anal margin** refers to the peri-anal skin within 5 cm of anal verge

Above dentate line, lymphatic drainage is via the internal iliac nodes. Below the dentate line, drainage is via the superficial inguinal nodes.

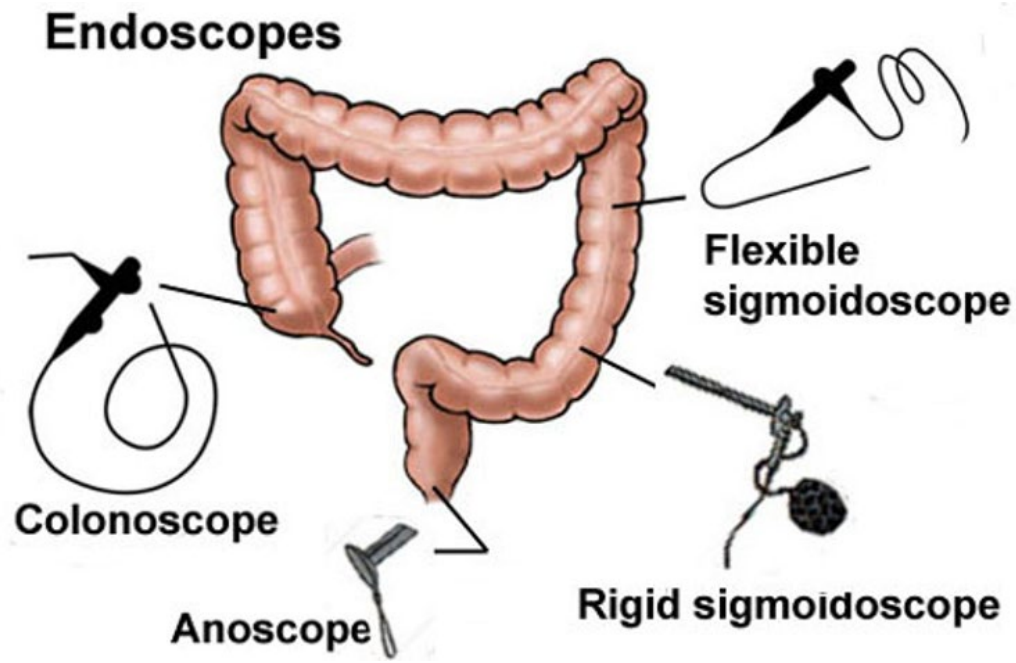


Surgical Anatomy of the Colon, Rectum and Anus

Initial Workup

Squamous cell carcinoma is the most common histology for anal cancers

- H/P with labs
  - DRE, GYN exam, lymph node exam
  - HIV testing
- Imaging
  - CT CAP (with oral and IV contrast)
  - MRI pelvis
    - T2 is often the most helpful sequence
  - Consider PET CT
- Procedures
  - Anoscopy with biopsy



Staging

Note how T4 disease specifies organ invasion

Table 37.2: AJCC 8th ed. (2017): Staging for Anal Cancer

T/M		cN0	cN1a	cN1b	cN1c
T1	• ≤2 cm	I	IIIA		
T2	• 2.1–5 cm	IIA			
T3	• >5 cm	IIB	IIIC		
T4	• Invasion into adjacent organs[1]	IIIB			
M1	• Distant metastasis	IV			

Notes: Organs[1] = Invasion of vagina, urethra, bladder. Invasion of rectal wall, perirectal skin, subcutaneous tissue, or sphincter muscle are not always T4.
cN1a, metastasis in inguinal, mesorectal, or internal iliac nodes; cN1b, metastasis in external iliac nodes; cN1c, metastasis in external iliac node as well as any of inguinal, mesorectal, or internal iliac node involvement.

Essentials of Clinical Radiation Oncology



T2 MRI: Large T2 tumor involving the anal canal (Radiopaedia)

Treatment Summary

ChemoRT
Capecitabine (or 5-FU)

ChemoRT
50.4 – 54 Gy / 28 -30 fx (to the primary)
42 – 45 Gy / 28 - 30 fx (to the nodes)

8 – 12 weeks

Assess for a complete response
Physical Exam, DRE, Anoscopy, CT CAP with MRI Pelvis

- Perianal skin tumors (SCC, BCC, Melanoma) are treated as skin cancers (WLE ± chemoRT)
- T1N0 disease of the anal margin may sometimes be treated with WLE alone (with a 1 cm margin)
- An anal adenocarcinoma would be treated as a rectal carcinoma
- If there is biopsy proven persistent local disease, an abdominal perineal resection ± groin dissection may be warranted

Radiotherapy

RTOG 0529 demonstrated a significant reduction in toxicities when using IMRT for anal cancer (PMID 23154075)

- Organ preservation with chemoradiation is the standard of care for most anal cancers, as established with the pCR rates seen with the Nigro regimen (PMID 3918441)
- RTOG 0529 established IMRT as the standard of care and provides standard doses for anal cancers
  - Simultaneous integrated boost is standard
- Elective nodal coverage is standard and is described by the RTOG contouring atlas
  - PMID: 19117696

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)

NCCN

Radiation Simulation

The prone position (with a belly board) may be beneficial in limiting the amount of small bowel receiving RT dose

- CT (with oral and IV contrast)
  - NPO 3 hours prior
- Fuse MRI
  - T2 MRI is often the most helpful

- Use of an immobilization device is strongly recommended
- Vaginal sparing and intertreatment vaginal dilator use may decrease sexual dysfunction in females (PMID: 35774492)
  - This is not recommended for T4 disease directly invading the vagina
- A radiopaque marker should be placed at the anal verge and any perianal skin involvement should be outlined

Selected Dose Constraints

Anterior Vaginal Wall $D_{50\%}$ < 48 Gy (PMID: 37898354)

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)

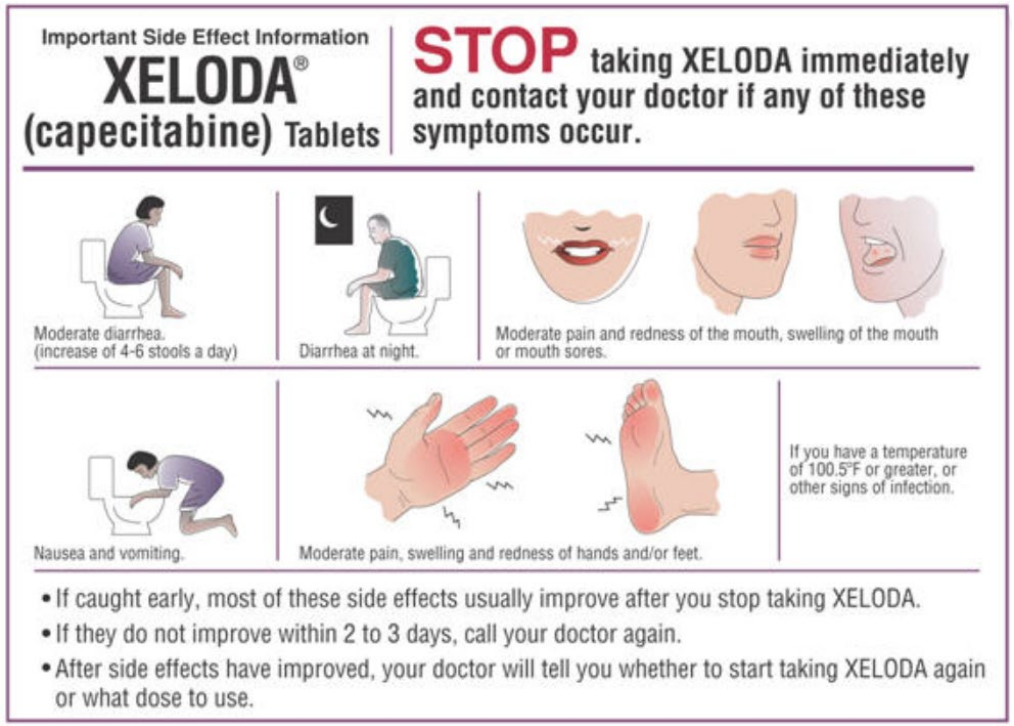
Organs are listed in order of decreasing priority.
†Dose constraints are based on absolute volume instead of % volume.

NCCN

Chemotherapy

The major toxicity of mitomycin is neutropenia

- Organ preservation with chemoradiation is the standard of care for most anal cancers, as established with the pCR rates seen with the Nigro regimen (PMID 3918441)
- Preferred regimens include
  - 5-FU + Mitomycin
  - Capecitabine + Mitomycin
- Capecitabine is take orally BID on the days of radiation (M-F)
- 5-FU infusion is given on days 1-4 and days 29-32
- Mitomycin is given on days 1 and 29 (or as bolus on day 1 alone)



Side effects of capecitabine may include hand/foot syndrome as well as GI effects

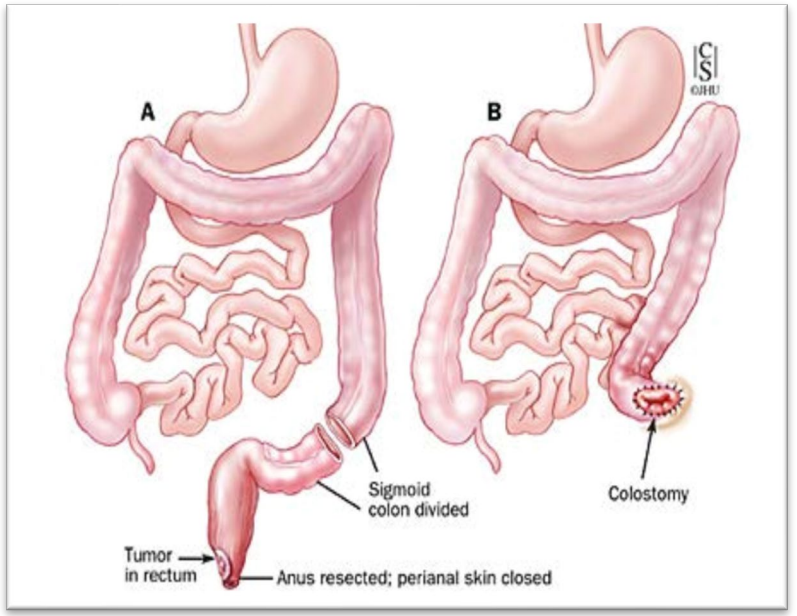
Surgery

- T1N0 (and select T2N0) squamous cell carcinomas of the perianal region / anal margin may be treated by local excision with a 1 cm margin

- Otherwise, the role of surgery is primarily limited to progressive / recurrent disease
  - Abdominal perineal resection (± inguinal node dissection) is the standard of care

For superficially invasive squamous cell carcinomas (SISCCA), local excision alone with surveillance may be appropriate

APR



JHU

Prognosis

The liver and lung are the most common sites of metastases

- Per long term results of RTOG 0529 (PMID 34400269):

Table 1 Two, 5-, and 8-year outcomes for NRG/RTOG 0529 and NRG/RTOG 9811

	NRG/RTOG 0529 (n = 52)				NRG/RTOG 9811 - MMC Arm (n = 325)			
Outcome	No. of events	2 y, % (95% CI)	5 y, % (95% CI)	8 y, % (95% CI)	No. of events	2 y, % (95% CI)	5 y, % (95% CI)	8 y, % (95% CI)
Local-regional failure	8	14 (6-24)	16 (7-27)	16 (7-27)	67	19 (15-23)	20 (16-25)	22 (17-27)
Colostomy failure	6	8 (2-17)	10 (4-20)	12 (5-23)	38	11 (8-15)	12 (9-16)	12 (9-16)
Overall survival	16	86 (73-93)	76 (61-86)	68 (53-79)	87	91 (87-94)	78 (73-83)	69 (62-74)
Disease-free survival	19	76 (62-86)	70 (56-81)	62 (47-74)	122	75 (70-80)	68 (62-73)	57 (50-63)
Colostomy-free survival	17	84 (71-92)	74 (59-84)	66 (51-77)	106	83 (79-87)	72 (67-77)	63 (57-69)
Distant metastases	11	14 (6-25)	16 (7-27)	22 (12-34)	46	9 (6-13)	13 (10-17)	16 (12-21)

Abbreviations: CI = confidence interval; MMC = mitomycin-C.

RTOG 0529 utilized IMRT
RTOG 9811 utilized conventional radiotherapy

Review

Review #1: The Standard of Care

There have been many attempts to change the standard chemoRT regimen

What were the findings of RTOG 9811 (PMID: 23150717), which compared RT + 5-FU/MMC against RT + induction/concurrent cisplatin?

(A) Equivalent OS in the two arms

(B) Improved OS in the 5-FU/MMC arm

(C) Improved hematologic toxicity in the 5-FU/MMC arm

Review #2: Clinical Complete Response

Per ACT II (PMID 23578724), 72% who did not have a complete response at 11 weeks obtained one at 26 weeks

After chemoRT, how many months should pass before performing a biopsy on a persistent but responding lesion?

(A) 1

(B) 6

(C) 12

Review #3: Clinical Complete Response

PMID 23578724

Per ACT II, what was the complete response rate at 26 weeks?

(A) 70%

(B) 80%

(C) 90%

Review #4: MMC

The oncologic benefit of MMC has been proven through multiple randomized controlled trials

What is the most common toxicity of mitomycin?

(A) Hematologic toxicity

(B) Hand Foot Syndrome

(C) Ototoxicity

Review #5: Surveillance

Imaging is done annually after complete remission

Which of the following is recommended (per NCCN) for surveillance of anal cancer after chemoRT?

(A) DRE

(B) Inguinal node exam

(C) Anoscopy

(D) CT CAP or CT Chest with Pelvic MRI

(E) All of the above

Answer Key

1. B
2. B
3. C
4. A
5. E

The PLATO trials (ACT III, IV, V) are exploring dose de-escalation for anal cancers