Anal Cancer

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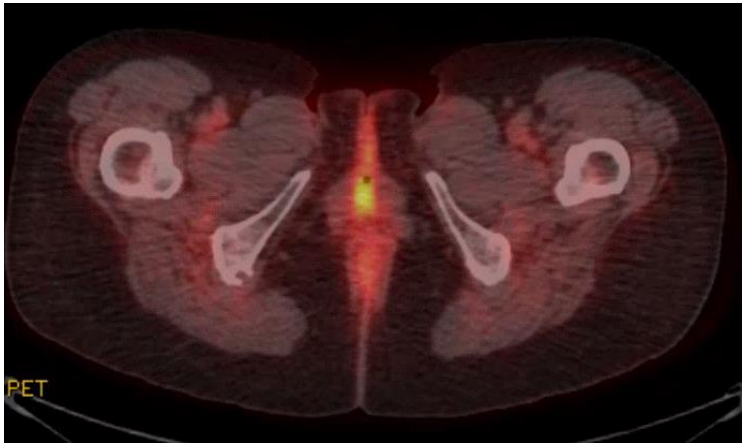
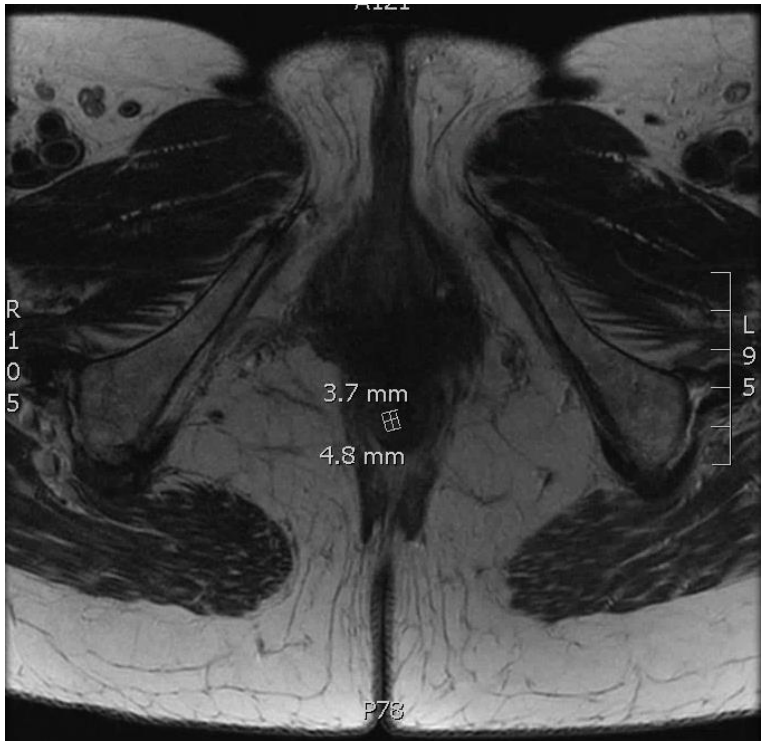
Case presentation

- 65 year old woman who initially presented with perianal discomfort and itching x several weeks
- PMH/PSH: Heart defect - open heart surgery 1962. Genital warts in 1970s
- Family Hx: lung cancer (father, died at 72), cutaneous SCC (mother, age 85)
- Social Hx: works in real estate; no children, smoked ½ ppd x 20 years (quit 15 years ago) E TOH: vodka or white wine (sauvignon blanc) - 2 nightly
- Saw gynecology who noted 1-2 cm perianal lesion on exam
- Referred to colorectal surgery. Planned for exam under anesthesia; performed anoscopy with biopsy which returned 0.6 cm SCC arising from high grade squamous intraepithelial lesion, with less than 1 mm deep and unoriented lateral margins. P16 staining diffusely positive.
- Sought second opinion with medical oncology and colorectal surgery. Reexcision done 10/2/18; pathology returned invasive SCC with positive margins.
- 10/16/18 tumor board discussion; consensus recommendation for chemoradiation

Imaging

- 8/22/18 MRI pelvis 5 mm focus of restricted diffusion along the right aspect of the anal canal likely correlating to the known malignancy.
- 11/7/18 CT C/A/P negative for distant metastases
- 11/7/18 PET/CT focal uptake at the anus (SUV max 4.6)





Background

- 25th most common cancer
- Slightly more common in women than men
- Median age at diagnosis: 62
- Risk factors:
  - HPV-16 (and other high-risk strains: 18, 31, 33, 35)
  - History of cervical, vaginal or vulvar cancer (HPV related)
  - Smoking
  - Anal-receptive intercourse
  - Immunodeficiency (HIV) or immunosuppression (organ transplant)

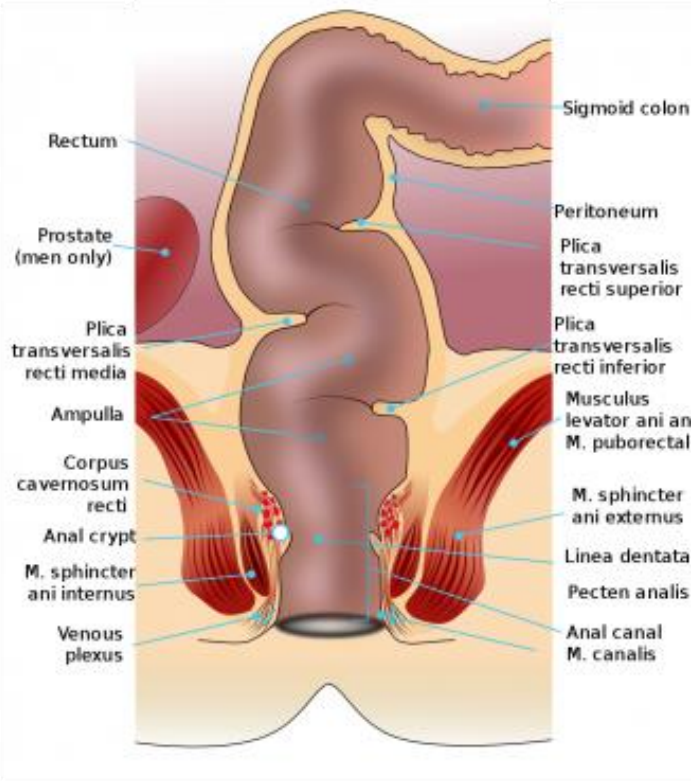
Estimated New Cases in 2018	8,580
% of All New Cancer Cases	0.5%

Estimated Deaths in 2018	1,160
% of All Cancer Deaths	0.2%

Percent Surviving 5 Years
67.4%
2008-2014

SEER 18 2008-2014

Anatomy



Rectum and anal canal anatomy. Courtesy of Wikimedia Commons

Anal canal

- Length: ~4 cm (from anal verge to anorectal ring)
- Dentate (pectinate) line
  - Transition from glandular to squamous cells
  - Middle of anal canal (2 cm)
- Anal verge
  - Transition from anal squamous mucosa to the epidermis-lined perianal skin (hair-bearing)

Perianal skin (anal margin)

- Within 5 cm radius of anus

Lymphatic drainage

- Proximal to dentate
  - Internal iliac and perirectal nodes
- Distal to dentate
  - Inguinal nodes

Diagnostic work-up

- H&P
  - Symptoms, anal continence
  - DRE – check sphincter tone
  - Inguinal lymph node evaluation
- Biopsy
  - Primary
  - FNA of suspicious nodes
- CT or MRI of pelvis with contrast
- CT chest/abdomen
- PET/CT (optional per NCCN)
  - Should not replace diagnostic CT (NCCN)
- Anoscopy
- Gynecological exam for women
  - Cervical cancer screening
- HIV testing (if status unknown)
  - If HIV+ then CD4 count

NCCN Guidelines V 2.2018

STAGING

Primary tumor (T)	
T1	≤ 2cm
T2	>2cm, ≤5cm
T3	>5cm
T4	Invades vagina, urethra, or bladder (but not rectal wall, perirectal skin, or sphincter muscles)

Regional lymph nodes (N)	
N1a	Inguinal, mesorectal, or internal iliac lymph nodes
N1b	External iliac lymph nodes
N1c	External iliac *and* any N1a nodes

Distant metastases (M)	
M0	No
M1	Yes

AJCC 8th edition Stage Grouping	
I	T1 N0
II A	T2 N0
II B	T3 N0
IIIA	T1-T2 N1
IIIB	T4 N0
IIIC	T3-T4 N1
IV	Any T, Any N, M1

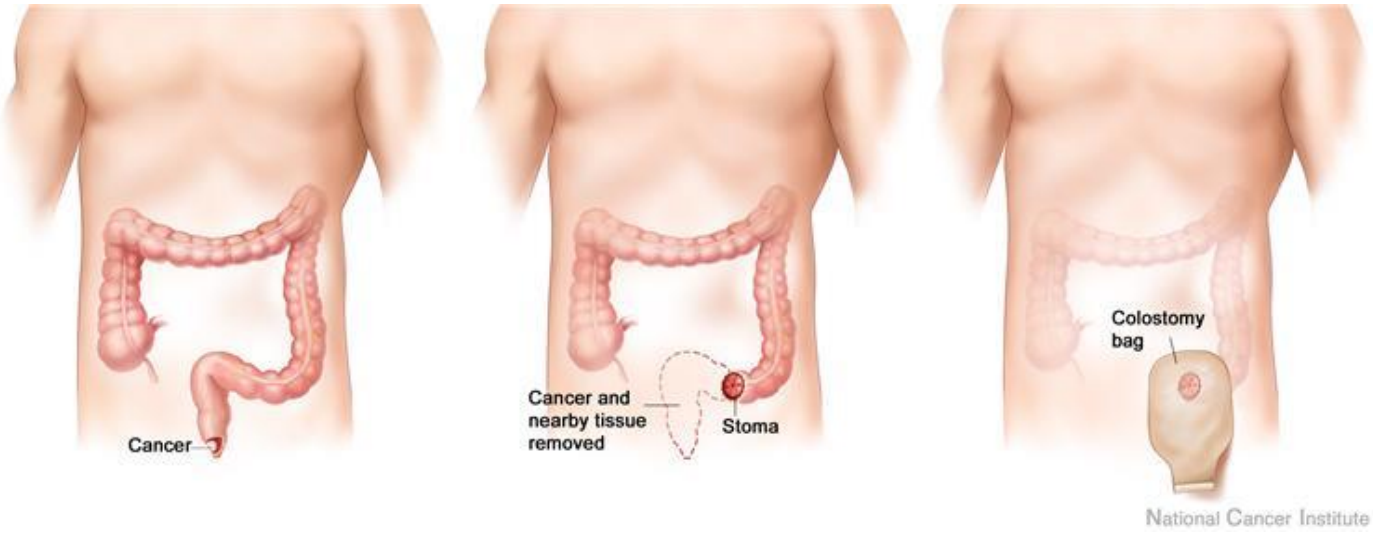
	N0	N+
T2	82% OS, 17% LRF	70% OS, 26% LRF
T3	74% OS, 18% LRF	57% OS, 44% LRF
T4	57% OS, 37% LRF	42% OS, 60% LRF

Treatment options

- Surgery alone
- Radiation alone
- Chemoradiation
  - Nigro Protocol
- Chemo RT vs. RT alone
  - UKCCCR ACT I
  - EORTC
- Different chemotherapy regimens
  - RTOG 87-04
  - RTOG 98-11
  - UKCCCR ACT II
- RT dose escalation
  - ACCORD 03
- IMRT
  - RTOG 05-29

Surgery Alone

- Historically (before 1970s), standard treatment consisted of APR and permanent colostomy
- Local recurrence rate ranged from 27-47%
- 5 year survival rates 40-70%, worse with nodal involvement (<20%)



Boman BM, et al. Cancer. 1984;54(1):114–25.

Radiation Alone

- Effective, but high local recurrence with larger tumors, or nodal involvement

Author	Radiation	T1	T2	T3/T4	Serious complications/ colostomy	5 year survival
Newman, 1992	50 Gy/20fx	8/9 (≤2cm)	42/52 (81%) (≤5cm)	13/20 (65%) (>5 cm or T4)	2	66%
Cummings, 1991	50 Gy/20fx	6/6 (≤2cm)	19/29 (66%) (≤5cm)	13/28 (46%) (>5 cm or T4)	6	61%
Martenson and Gunderson, 1993	45-50Gy/25-28 fx (+boost 55-67Gy)	9/9 (≤2cm)	17/17 (100%) (≤5cm)	--	2 temp	94% (actuarial)
Otim-Oyet, 1990	60-65 Gy/30-33fx (+/- boost)	2/2 (≤2cm)	16/22 (73%) (≤4cm)	8/17 (47%) (>4 cm)	1	56% (cause-specific)
Papillon & Montbarbon, 1987	42 Gy/10fx + 20 Gy at 8 wk	Not given	29/39 (74%) (≤4cm)	27/64 (42%) (>4 cm)	6	60%

Chemoradiation→ Surgery

- Nigro protocol (1974)
  - 3 patients given pre-op 5-FU + MMC + RT (30 Gy in 15 fractions, AP/PA, to pelvis and inguinal LNs)
  - All then had surgery and each demonstrated a complete pathologic response
- 1984 update
  - 104 cases of SCC of anal canal, 97/104 (93%) with complete pathologic response
  - Of those with complete response, 89% OS at 50 months

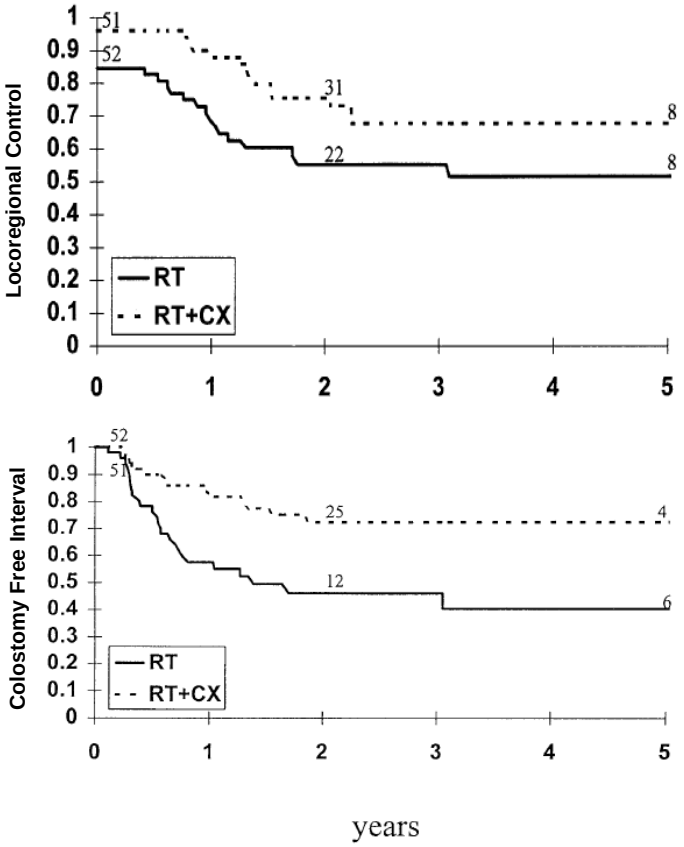
- Pioneered chemo-RT as viable alternative to avoiding APR

Cancer. 1983 May 15;51(10):1826-9.

ChemoRT vs. RT alone

EORTC

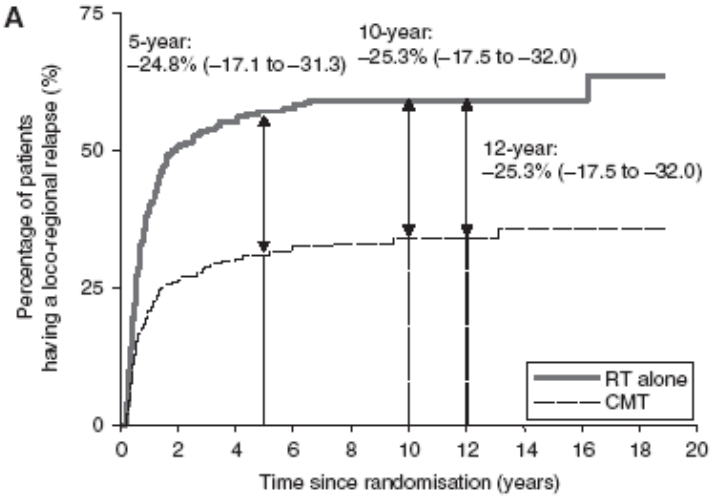
- 110 patients Randomized
- T1-T4 tumors, any N (excluded T1N0 and T2N0)
- Arm 1: RT alone (45 Gy) then assess at 6 weeks
  - Complete response -> 15 Gy boost (EBRT)
  - Partial response -> 20 Gy boost (EBRT)
  - Stable disease or progression -> APR
- Arm 2: RT + 5-FU (daily for first and last week) + MMC (first day only)
- Chemo-RT arm demonstrated:
  - Higher complete response rate (80% vs. 54%)
  - Better 5 year local control (68% vs. 50% p=0.02)
  - Higher 5 year colostomy-free survival (72% vs. 40% p= 0.002)
  - More toxicity (anal ulcers more frequent)
  - No OS benefit



Bartelink H, et al. J Clin Oncol. 1997;15(5):2040.

ChemoRT vs. RT alone

- **UKCCCR ACT I**
  - 585 patients with anal SCC
  - T1-T4 tumors, any N (excluded T1N0)
  - Randomized
    - Arm 1: RT alone (45 Gy) then re-assessed at 6 weeks
      - If <50% response (<50% of original size) -> APR
      - If >50% then RT boost (15 Gy (EBRT) or 25 Gy (brachy boost))
    - Arm 2: RT (same as above) + 5-FU (first and last week) + MMC (on first day only)
  - Better colostomy free survival in chemo-RT arm
  - Better 3 year local control rates 61% vs. 36% (p<0.001)
  - Acute toxicity worse with chemo-RT; no difference in late toxicity



Lancet. 1996;348(9034):1049.
Northover J, et al. Br J Cancer. 2010;102(7):1123.

- ACT I and EORTC showed adding chemotherapy to radiation improved local control and colostomy free survival (no difference in overall survival)
- UKCCR did 45 Gy with a 6 week break followed by a boost to 60 Gy. local control with RT alone was lower than prior studies because of a 6 week break

The merits of MMC: RTOG 87-04

- 310 patients
- Randomized
  - Arm 1: RT (45-50.4 Gy) + 5-FU + MMC, then assess with biopsy 6 weeks later
    - Biopsy positive -> 9 Gy + 5-FU + cisplatin
    - Biopsy negative -> no treatment
    - Assess with second biopsy 3-4 weeks later
      - Biopsy positive -> APR
      - Biopsy negative -> APR
  - Arm 2: Same as arm 1, without MMC

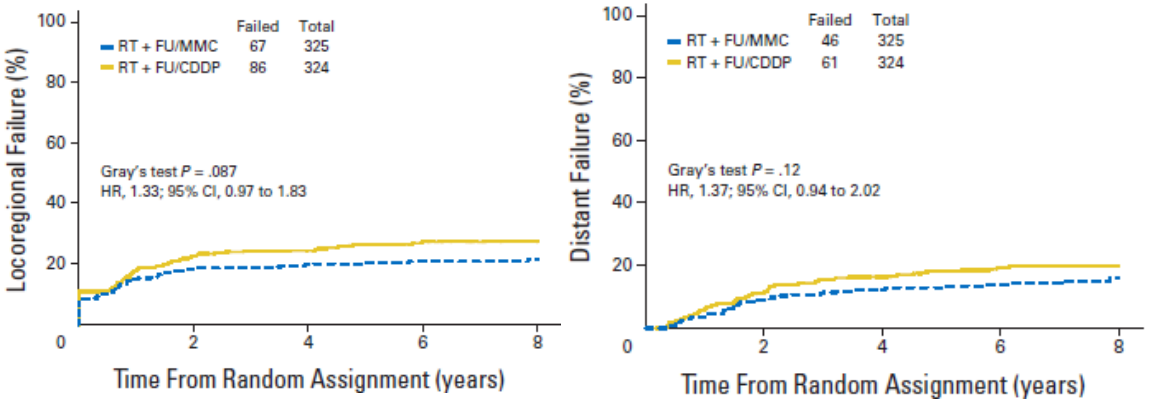
- Chemo-RT with MMC arm demonstrated:
  - Higher toxicity rates (23% vs. 7% grade 4; 4% vs. 1% grade 5)
  - Trend towards more negative post-tx biopsies (92% vs 86%, p=0.135)
  - Lower colostomy rates (4-yr rate 9% vs. 22%)
  - Better colostomy-free survival (4-yr rate 71% vs. 59%)
  - Better disease-free survival (4-yr rate 73% vs. 51%)
- No difference in overall survival
- Conclusion
  - MMC adds toxicity but improves local control

Flam M, et al. J Clin Oncol. 1996;14(9):2527.

Looking at chemo further: RTOG 98-11

- 682 patients
- T2-T4, any N (excluded T1)
- Randomized
  - Arm 1: 5-FU + MMC + RT (45 Gy + boost (10-14 Gy for T3/T4 or residual disease after 45 Gy)
  - Arm 2: Induction 5-FU + cisplatin followed by 5-FU + cisplatin + RT

- Cisplatin arm
  - Lower hematologic toxicity (G3/4 42% vs 61%)
  - No difference in non-hematologic toxicity
  - Trend towards more locoregional failures (5-yr: 26% vs. 20% p=0.087)
  - Trend towards more distant failures (5-yr: 18% vs. 13%, p=0.12)
  - Trend towards higher colostomy rates (5-yr: 17% vs. 12%, p=0.074)
  - Worse DFS (5-yr DFS 58% vs. 68%, p=0.006)
  - Worse OS (5-yr OS 78% vs. 71%, p=0.026)



- Conclusion
  - Induction cisplatin followed by cisplatin + 5-FU + RT worse than MMC + 5-FU + RT
  - Is the induction bad or is the cisplatin bad?
  - Concern for accelerated repopulation with longer treatment duration?

Ajani JA, et al. JAMA. 2008;299(16):1914.
Gunderson LL, et al. J Clin Oncol. 2012 Dec;30(35):4344-51.

UKCCCR ACT II

- To determine if replacing MMC with cisplatin in chemo-RT improves response, and whether maintenance chemo after chemo-RT improved OS
- Primary end point: complete response rate
- 940 patients
- 2 x 2 randomization
- 1st randomization
  - 5-FU + MMC + RT (50.4 Gy)
  - 5-FU + cisplatin + RT (50.4 Gy)
- 2nd randomization
  - Maintenance 5-FU + cisplatin (2 cycles)
  - Observation

- Efficacy for MMC vs cisplatin

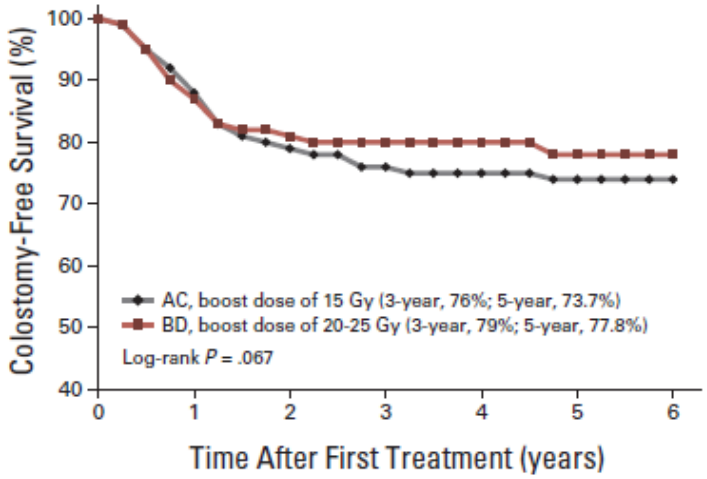
  Complete response rate at 6 months equivalent (95% in both arms)
  - Colostomy rates equivalent
  - Relapse-free survival equivalent
  - Overall survival equivalent
- Toxicity
  - MMC with worse hematologic toxicity (Grade 3/4 26% vs. 16%)
  - Similar non-hematologic toxicity
- MMC remains standard of care
- Maintenance chemo does not decrease rate of disease recurrence following primary treatment

James R, et al. Lancet Oncol. 2013;14(6):516-24.

RT Dose Escalation: ACCORD 03

- 307 patients
- Tumors ≥ 4cm, or <4cm and LN+
- 2 x 2 randomization
- Primary end point: colostomy-free survival (CFS)
- 1st randomization
  - Concurrent chemo (5-FU + cisplatin)
  - Induction chemo (5-FU + cisplatin) then concurrent chemo
- 2nd randomization
  - SD RT: 45 Gy to pelvis, 3 week break, then 15 Gy boost (EBRT or brachy)
  - HD RT: 45 Gy to pelvis, 3 week break, then 20-25 Gy based on response

- No difference in induction vs. no induction chemo with tumor complete response, tumor partial response, 3 year CFS
- High RT dose with trend towards better CFS
  - 5-yr colostomy-free survival 78% vs. 74% (p=0.067)



- No difference in local control, tumor-free survival with higher RT dose

Peiffert D, et al. J Clin Oncol. 2012 Jun;30(16):1941-8.

IMRT vs 3D: RTOG 05-29

- Evaluation of Dose-Painted IMRT in Combination with 5-FU and MMC for Reduction of Acute Morbidity in Carcinoma of the Anal Canal
- Phase II study with 63 patients
- Primary goal:
  - To determine if the combined rate of ≥ grade 2 GI and GU adverse events from IMRT + 5-FU/MMC is decreased by at least 15% in the first 90 days following the start of treatment as compared to RT + 5-FU/MMC from RTOG 9811
- T2-T4, N0-N3 (no T1N0)
- Compared to historical controls (RTOG 98-11)
  - No difference in acute grade 2+ GI/GU toxicity (77% in both)
  - IMRT with reduced grade 2+ hematologic toxicity (73% vs. 85%)
  - IMRT with reduced grade 3+ GI toxicity (21% vs. 36%)
  - IMRT with reduced grade 3+ skin toxicity (23% vs. 49%)

- Radiation dose
  - T2N0
    - Primary tumor 50.4/1.8
    - Elective nodes 42/1.5
  - T3-T4N0
    - Primary tumor 54/1.8
    - Elective nodes 45/1.5
  - N+ disease
    - Primary tumor 54/1.8
    - Nodes ≤3cm – 50.4/1.68
    - Nodes >3cm – 54/1.8

Kachnic L. Int J Radiat Oncol Biol Phys. 2013 May 1;86(1):27-33.

Radiation planning

- Simulation
  - Supine with alpha cradle and frog-legged
  - Anal marker and wire on distal edge of tumor

- Radiation dose per RTOG 0529
  - T2N0 (28 fx)
    - Primary tumor 50.4 Gy (1.8 Gy/fx)
    - Elective nodes 42 Gy (1.5 Gy/fx)
  - T3-T4N0 (30 fx)
    - Primary tumor 54 Gy (1.8 Gy/fx)
    - Elective nodes 45 Gy (1.5 Gy/fx)
  - N+ disease
    - Primary tumor 54 Gy (1.8 Gy/fx)
    - Nodes ≤3cm – 50.4 Gy (1.68 Gy/fx)
    - Nodes >3cm – 54 Gy (1.8 Gy/fx)

Treatment planning

- GTV
  - GTVA = gross primary anal tumor volume (exam, scope and radiology)
  - GTV50.4 = involved nodal regions macroscopic disease < 3 cm
  - GTV54 = all nodal regions containing macroscopic disease > 3 cm
- CTV
  - CTVA = GTVA with a 2.5 cm superior-inferior expansion and 1.5 cm radial expansion (except into bone or air)
  - CTV54, CTV50.4 = involved nodal regions containing > 3 cm or < 3cm, respectively + 1 cm radial expansion
  - CTV45, CTV42 = uninvolved nodal coverage (mesorectum, pre-sacral, inguinal, internal & external iliac to common bifurcation) + 1 cm radial expansion
- PTV
  - 1 cm around the CTV in all directions to define each respective PTV; pull back under inguinal skin
  - 95% of PTV must receive 95% of dose; and only 2% of PTV can receive 115% of Rx dose

Normal Tissue Constraint Guidelines

DP-IMRT Dose Constraints for Normal Tissues Listed in Order of Descending Priority			
Organ	**< 5% exceed (Gy)**	**< 35% exceed (Gy)**	**< 50% exceed (Gy)**
Small bowel*^	**45 < 20cc**	**35 < 150cc**	**30 < 200cc**
Femoral heads*	**44**	**40**	**30**
Iliac crest	**50**	**40**	**30**
External genitalia	**40**	**30**	**20**
Bladder	**50**	**40**	**35**
Large bowel^	**45 < 20cc**	**35 < 150cc**	**30 < 200cc**

*assigned criteria for major and minor violations on the RTOG 0529 trial;
^dose constraints based on cubic centimeters

Miscellaneous facts

- T1N0 tumors excluded from randomized chemo-RT vs. RT trials (UKCCCR ACT I and EORTC)
- Retrospective cohort study using 2014 SEER-Medicare database showed IMRT associated with higher total costs than 3D CRT (median total cost, $35,890 vs. $27,262 p <0.001) but unplanned health care utilization costs (hospitalizations, ER visits) higher for 3DCRT pts (median $711 vs. $4,957 at 1 year; p= 0.02)
- How long does treatment response take?
  - If at first follow up mass is still present?
  - If mass is stable or decreasing, continue observation since regression can take up to 12 months to achieve
  - No benefit to biopsy before six months if stable or regressing (ACT II data)
  - If mass enlarging at any time, biopsy
  - If biopsy (+) → APR

Schlienger et al IJROBP 1989
Chin et al J Oncol Pract. 2017 Dec;13(12):e992-e1001.

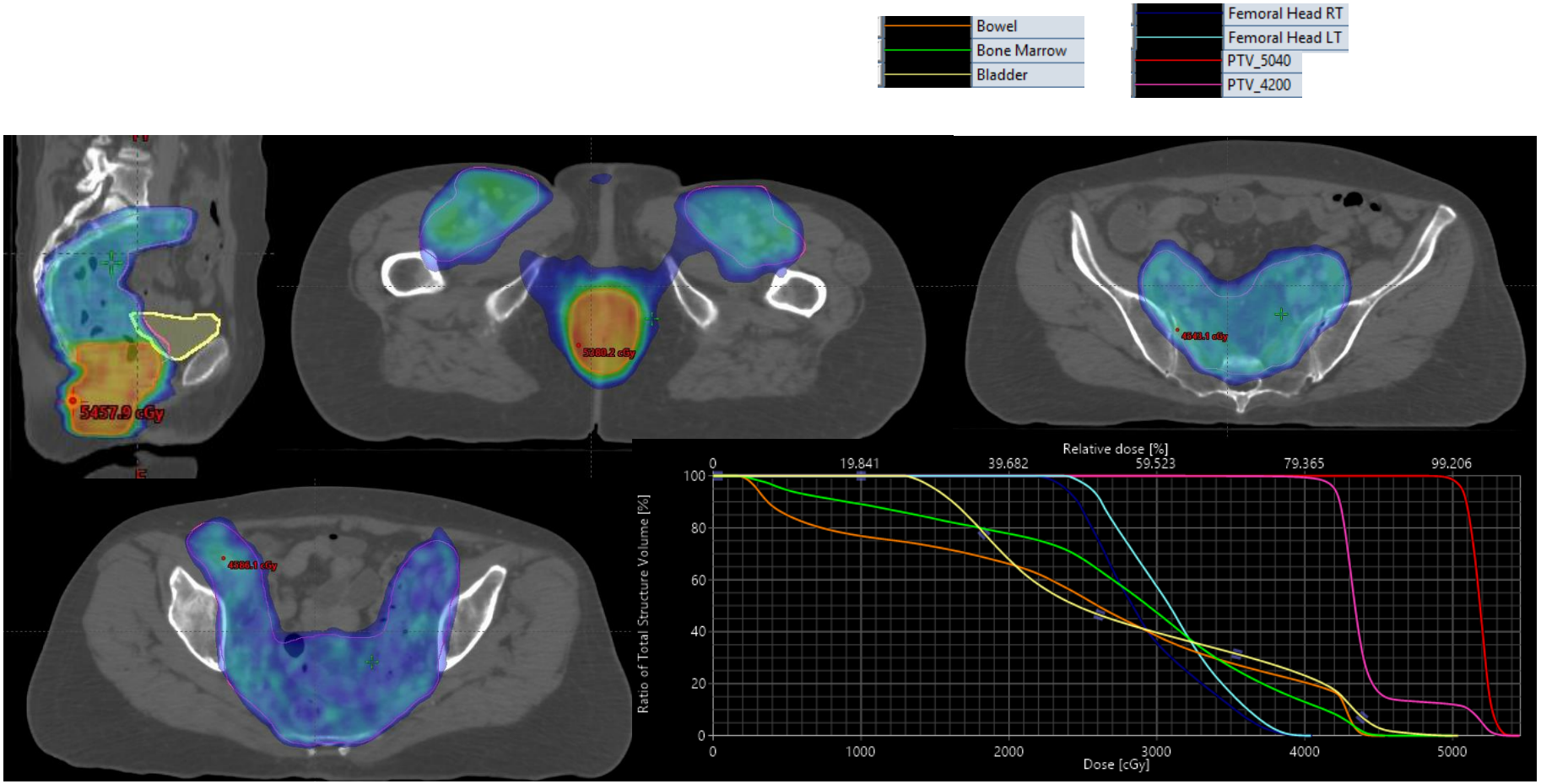
Treating our patient

- T1N0 perianal SCC, HPV positive s/p local excision with positive margin
- 11/13/2018 C1D1 Mitomycin-C/Capecitabine + concurrent radiation
- 12/11/2018 C1D29 Mitomycin-C - chemotherapy canceled due to low ANC
- 12/21/2018 Completed RT 50.4 Gy in 28 fractions with 42 Gy in 28 fractions to elective nodal volume

- Please note the capecitabine is often substituted for 5-FU for convenience; supported by retrospective and phase II evidence (EXTRA)

Glynne-Jones et al. IJROBP. 2008 Sep 1;72(1):119-26
Thind et al. Radiat Oncol. 2014; 9: 124..

Treating our patient



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