ARRO*Case*
Rectal Cancer

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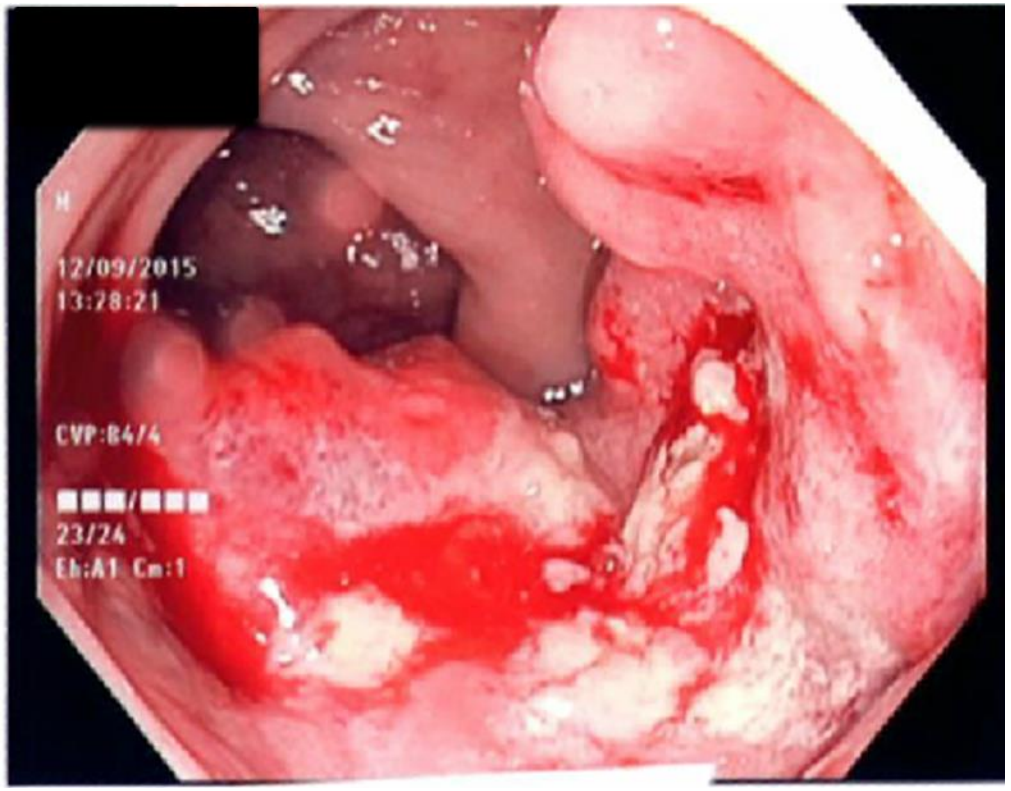
Case: Clinical Presentation

- 57 y/o male with a 2 month history of hematochezia, mainly with bowel movements
- Decrease in stool caliber over last 2 months
- Tenesmus
- Good appetite; weight stable
- KPS 90

Work-up: Colonoscopy

- Near circumferential, partially obstructing, malignant appearing mass 10cm from the anal verge, measuring 4cm in size
- Remainder of the colon was normal
- Biopsy was performed, revealing moderately differentiated invasive adenocarcinoma

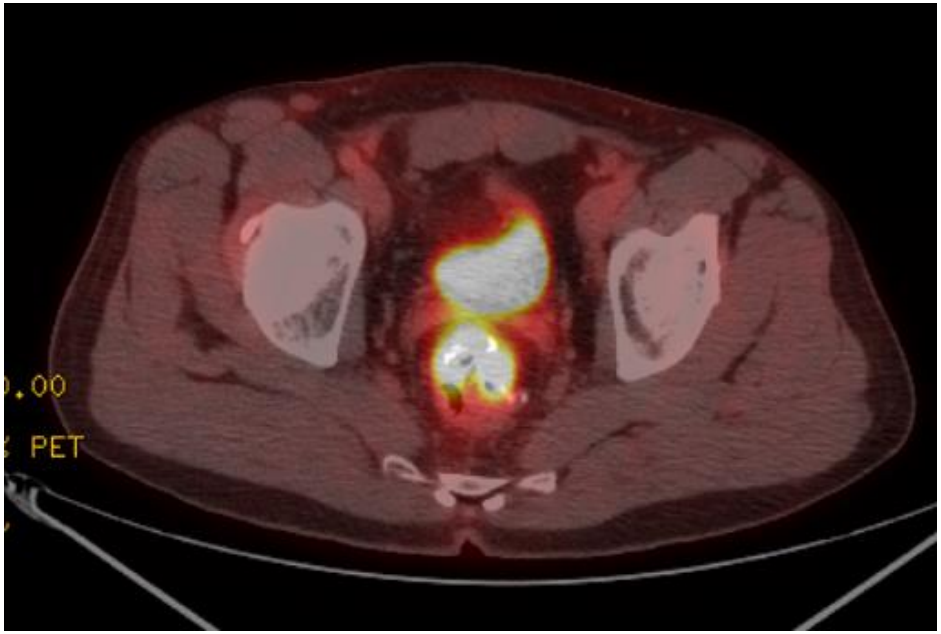


Work-Up: Endoscopic Ultrasound

- Hypoechoic lesion extending through the muscularis propria into pericolorectal tissues
- No abnormal lymphadenopathy was noted, confirming the lesion to be **T3 N0**
- No gross invasion into surrounding structures was noted

Work-Up: PET/CT Scan

- Focal area of FDG uptake is demonstrated in the rectum, measuring 3.9 x 4.2 cm, with maximal SUV of 11.4
- Few subcentimeter lymph nodes in the pelvis bilaterally which demonstrate faint FDG uptake
- No evidence of distal metastases



Epidemiology

- Colorectal cancer: 3rd most common cancer and 2nd leading cause of cancer-related death in men and women in the United States
- Estimated number of cases in the U.S. in 2016
  - 95,270 new cases of colon cancer
  - 39,220 new cases of rectal cancer
  - 49,190 expected deaths
- Lifetime risk is 1 in 21 (4.7%) for men and 1 in 23 (4.4%) for women

[1]American Cancer Society

Risk Factors

- Modifiable
  - Obesity
  - Sedentary lifestyle
  - Diet high in red meat or processed meat
  - Smoking
  - Alcohol
- Non-modifiable
  - Age >50
  - Inflammatory bowel disease (IBD)
  - Family history
  - Inherited syndromes (FAP, HNPCC, Turcot & Peutz-Jeghers syndromes)
  - Type II diabetes mellitus

[1]American Cancer Society

Screening

- Malignant transformation takes several years
- Screening – detection/treatment of benign, premalignant, and curable-stage cancers
- Average-risk population: Start at 50 years old with one of the following:
  - Colonoscopy every 10 years (preferably)
  - Flexible sigmoidoscopy every 5 years
  - Fecal occult blood test (FOBT) or fecal immunochemical testing (FIT) every year

[2]NCCN Clinical Practice Guidelines in Oncology. Colorectal Cancer Screening. Version 1.2015

Anatomy

- The rectum is about 15 cm long (anorectal ring to peritoneal reflection)
- Reference point (anal verge or the dentate line/anorectal ring) should be stated
  - Anal verge - lowermost portion of the anal canal
  - Anorectal ring - is at the level of the puborectalis sling and levators, representing the pelvic floor
- Anterior peritoneal reflexion represents the point at which the rectum exits the peritoneal cavity (~12-15 cm from the anal verge)

[3]Bruce D. Minsky, Claus M. Rödel and Vincenzo Valentini. Clinical Radiation Oncology, Chapter 51, 992-1018.e6.

Histology

- Adenocarcinoma >90% of colorectal cancers
  - Poorly differentiated tumors - worse prognosis
  - Signet-ring cell subtype (1-2%) - poor prognosis

- Other histologic types are rare
  - Carcinoid tumors
  - Leiomyosarcomas
  - Lymphomas
  - Squamous cell cancers

[3]Bruce D. Minsky, Claus M. Rödel and Vincenzo Valentini. Clinical Radiation Oncology, Chapter 51, 992-1018.e6.

Clinical Presentation

- Hematochezia
- Change in bowel habits
  - Constipation
  - Diarrhea
  - Decreased stool caliber
- Urgency, inadequate emptying, and tenesmus may occur in cases with extensive transmural penetration
- Urinary symptoms and/or perineal pain from posterior extension are grave signs

[3]Bruce D. Minsky, Claus M. Rödel and Vincenzo Valentini. Clinical Radiation Oncology, Chapter 51, 992-1018.e6.

Diagnosis/Work-Up

- H&P
  - DRE – evaluate for sphincter function
- Rigid Proctoscopy – assess primary tumor and biopsy
- Colonoscopy – detect possible synchronous primaries
- CT (chest, abdomen, and pelvis)
- Endorectal ultrasound (ERUS)
- MRI
  - Both ERUS and MRI are accurate in predicting T stage
  - PET scan is accurate in identifying nodal disease, though not routinely indicated
- CBC, CEA

[3]Bruce D. Minsky, Claus M. Rödel and Vincenzo Valentini. Clinical Radiation Oncology, Chapter 51, 992-1018.e6.

TNM Staging, AJCC 7th Edition

Primary Tumor	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures

Regional Lymph Nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 2–3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4–6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes

Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

[4]AJCC cancer staging handbook, 7th ed. New York: Springer, 2010, published by Springer Science and Business Media LLC

Group Staging, AJCC 7th Edition

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

[4]AJCC cancer staging handbook, 7th ed. New York: Springer, 2010, published by Springer Science and Business Media LLC

Treatment: T1-2, N0

- cT1 N0 – Transanal excision (if appropriate*)
  - *<30% circumference of bowel; <3cm in size; margin clear >3mm, mobile, non-fixed, within 8cm of anal verge, no LVSI or PNI; well to moderately differentiated; no lymphadenopathy
- cT1-2 N0 – Transabdominal resection
- Advantage of upfront surgery is complete pathologic staging and avoiding overtreatment with preoperative therapy
  - 18% in post-op arm of German Rectal Cancer Trial were overstaged preoperatively and found to have pT1-2, N0 disease at surgery

[2]NCCN Clinical Practice Guidelines in Oncology. Rectal Cancer. Version 1.2016

Adjuvant Treatment

- ChemoRT for pT3-4 N0 or N+

- GITSG 7175 – 227 patients (pT3-4 or N+) randomized to: surgery vs. post-op chemo vs. post-op RT vs. post-op chemoRT
  - Compared to surgery alone, postop ChemoRT improved 10-year OS (45% vs. 27%) and LF (10% vs. 25%)
  - **Underpowered to show benefit, unequal randomization, and not analyzed by intent to treat*
- Intergroup/NCCTG 79-47-51 – 204 patients (pT3-4 or N+) randomized to post-op RT vs. post-op chemoRT
  - Post-op ChemoRT improved 5-year OS (55% vs. 45%) and LR (14% vs. 25%)

[5]Thomas PR et al. Radiother Oncol. 1988 Dec;13(4):245-52.
[6]Krook JE et al. N Engl J Med. 1991 Mar 14;324(11):709-15.

Treatment: T3 N0 or N+

- Neoadjuvant
  - Capecitabine/long-course RT (category 1/preferred) or
  - Infusional 5-FU/long-course RT (category 1/preferred) or
  - Bolus 5-FU/Leucovorin/long-course RT or
  - Short course RT (not recommended for T4 tumors)

- Primary Treatment
  - Transabdominal resection

- Adjuvant Chemotherapy
  - FOLFOX (preferred) or
  - CapeOx (preferred) or
  - FLOX or 5-FU/Leucovorin or Capecitabine

[2]NCCN Clinical Practice Guidelines in Oncology. Rectal Cancer. Version 1.2016

Swedish Rectal Cancer Trial

- 1168 patients randomized to:
  - Pre-op RT (25 Gy in 5 fx) followed by surgery vs.
  - Surgery alone
- Pre-op RT improved 13-year OS: (38% vs. 30%), CSS (72% vs. 62%), and LR (9% vs. 26%)
- *Criticism: high recurrence rate in surgery-alone arm (26%) since total mesorectal excision (TME) surgery not used*
- TME - entire specimen removed by sharp dissection along the mesorectal plane

[7]Folkesson J et al. J Clin Oncol. 2005 Aug 20;23(24):5644-50.

Dutch CKVO 95-04 TME Trial

- 1805 patients randomized to:
  - Pre-op RT (25 Gy in 5 fx) followed by surgery vs.
  - TME alone (post-op RT if positive margins)

- RT improved 10-year LR (5% vs. 11%)
- No difference in OS
  - Unplanned subgroup analysis: RT significantly improved 10-year OS (50% vs. 40%) in stage III patients with a negative circumferential margin

[8]van Gijn W, Lancet Oncol. 2011 Jun;12(6):575-82.

German Rectal Cancer Study CAO/ARO/AIO-94

- 823 patients cT3-4 or N+ randomized to:
  - Pre-op chemoRT: ChemoRT (50.4 Gy/5-FU) followed by TME vs.
  - Post-op chemoRT: TME followed by chemoRT (55.8 Gy/5-FU)
    - Both arms received 4 additional cycles of bolus 5-FU after 4 weeks
- pCR rate in the pre-op group 8%
- No difference in 10-yr OS (59.6% vs. 59.9%)
- Pre-op RT improved 10-yr LR (7.1% vs. 10.1%)
- Increased rate of sphincter-preserving surgery (39% vs. 19%) in pre-op group

[9]Sauer R, N Engl J Med. 2004 Oct 21;351(17):1731-40.
[10]Sauer R, J Clin Oncol. 2012 Jun 1;30(16):1926-33.

Treatment Planning

- CT Simulation
  - IV contrast may be used to delineate GTV and pelvic blood vessels
  - Supine with body immobilizaton or
  - Prone with use of a belly board for anterior displacement of bowel

[11]N.Y. Lee, J.J. Lu (eds.), Target Volume Delineation and Field Setup, DOI 10.1007/978-3-642-28860-9_17 © Springer-Verlag Berlin Heidelberg 2013.00

Target Volumes

- CTVA: always treated for rectal cancer: internal iliac, pre-sacral, and peri-rectal
- CTVB: external iliac nodal region
- CTVC: inguinal nodal region
- For rectal cancer, in most cases, CTVA would be the only volume to receive elective RT
  - For certain presentations (e.g. extension into GU structures, extension to the peri-anal skin) one could consider adding the external iliac (CTVB) and even the inguinal regions (CTVC)

[12]https://www.nrgoncology.org/Portals/0/Resources/Atlases/AnorectalContouringGuidelines.pdf

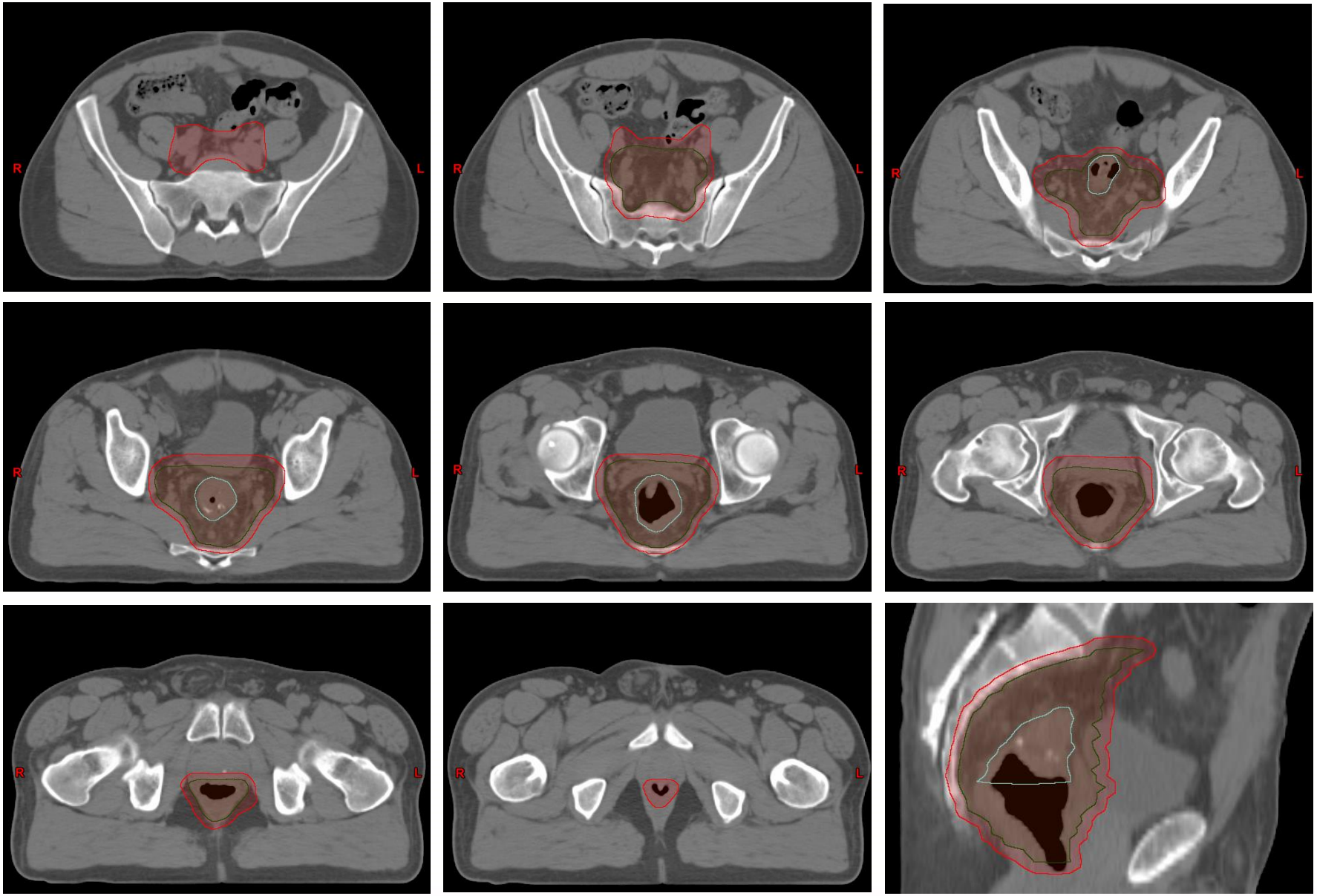
Target Volumes: CTVA

- Inferior
  - At least 2 cm caudad to gross disease, including coverage of the entire mesorectum to the pelvic floor
- Posterior and lateral
  - Lateral pelvic sidewall musculature or, where absent, the bone
- Anterior
  - ~1 cm into the posterior bladder and the posterior portion of the internal obturator vessels
- Superior
  - Primary: the rectosigmoid junction or 2 cm proximal to the superior extent of macroscopic disease
  - LN: where the common iliac vessels bifurcate into external/internal iliacs (approximate boney landmark: sacral promontory)

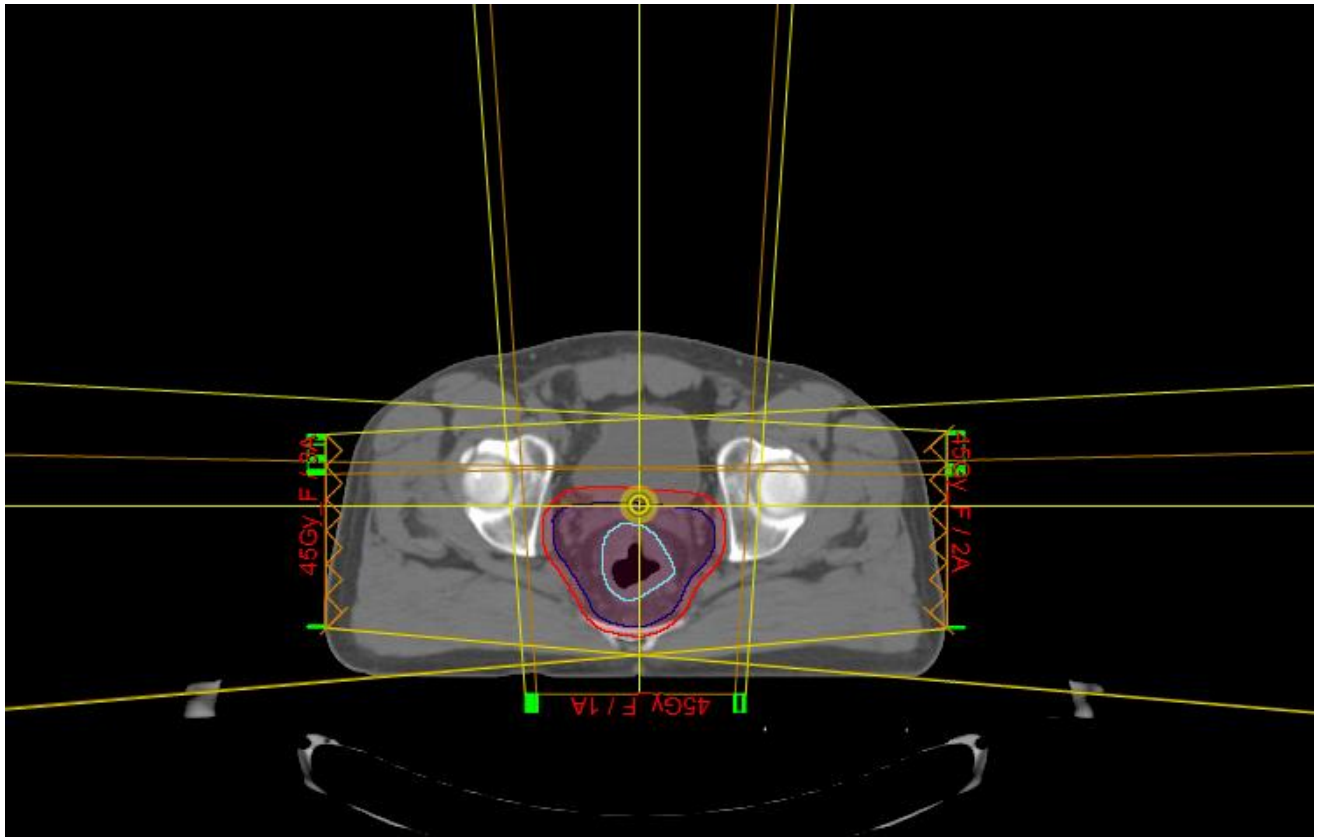
- PTV margin should be ~0.7 to 1.0 cm, except at skin.

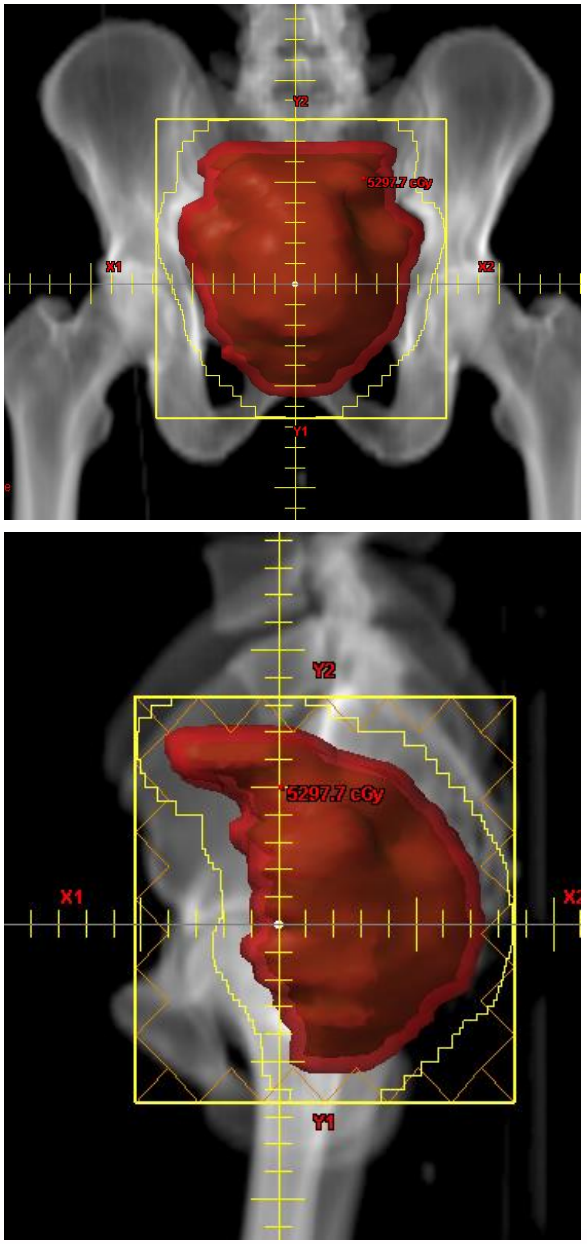
[12]https://www.nrgoncology.org/Portals/0/Resources/Atlases/AnorectalContouringGuidelines.pdf

Contours (See accompanying ARRO*Contour*)

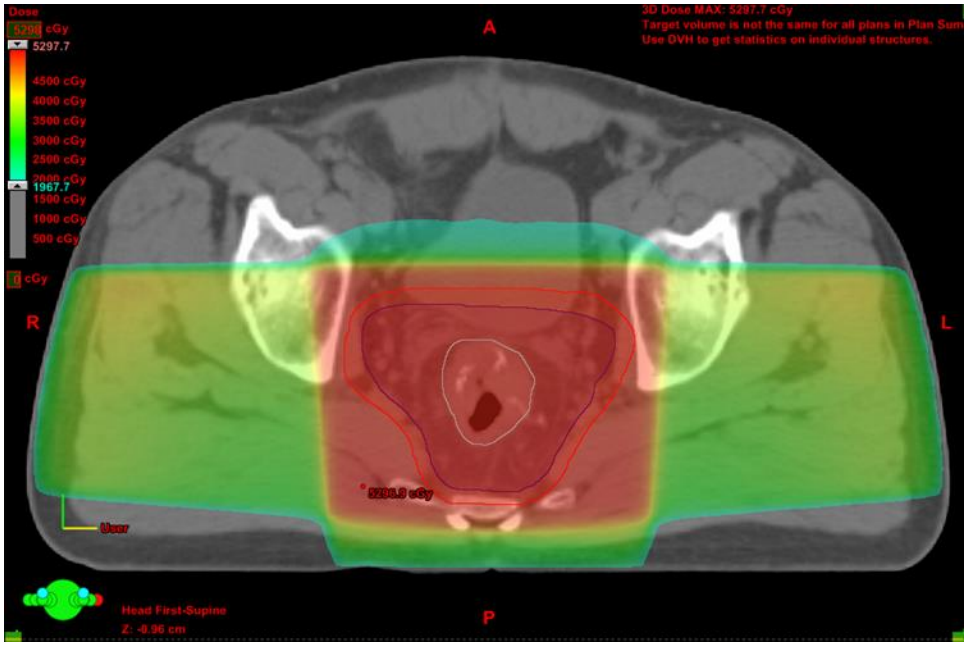


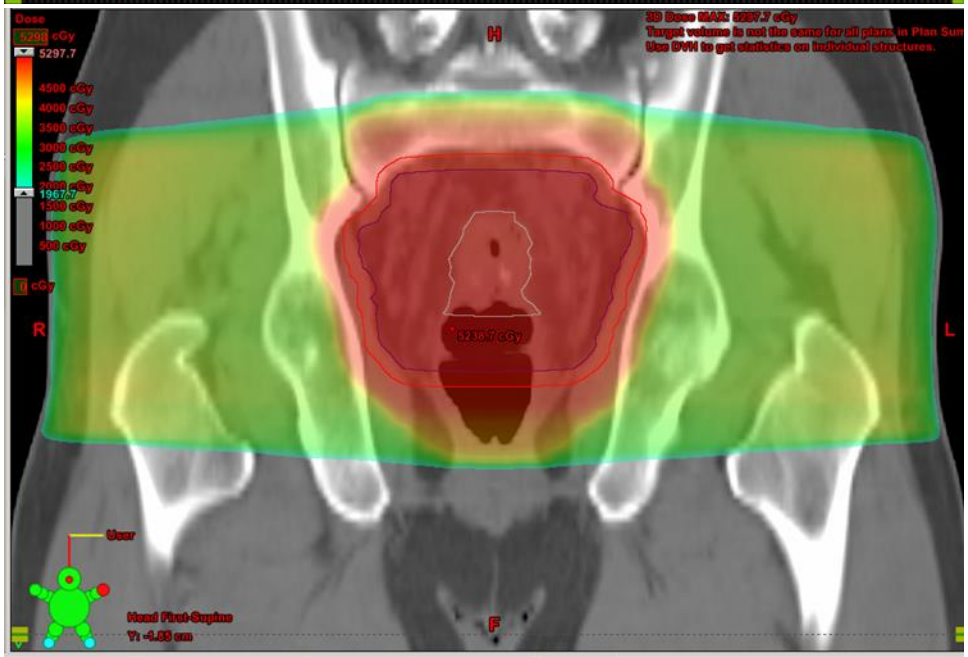
3-field plan: PA and opposed lateral fields

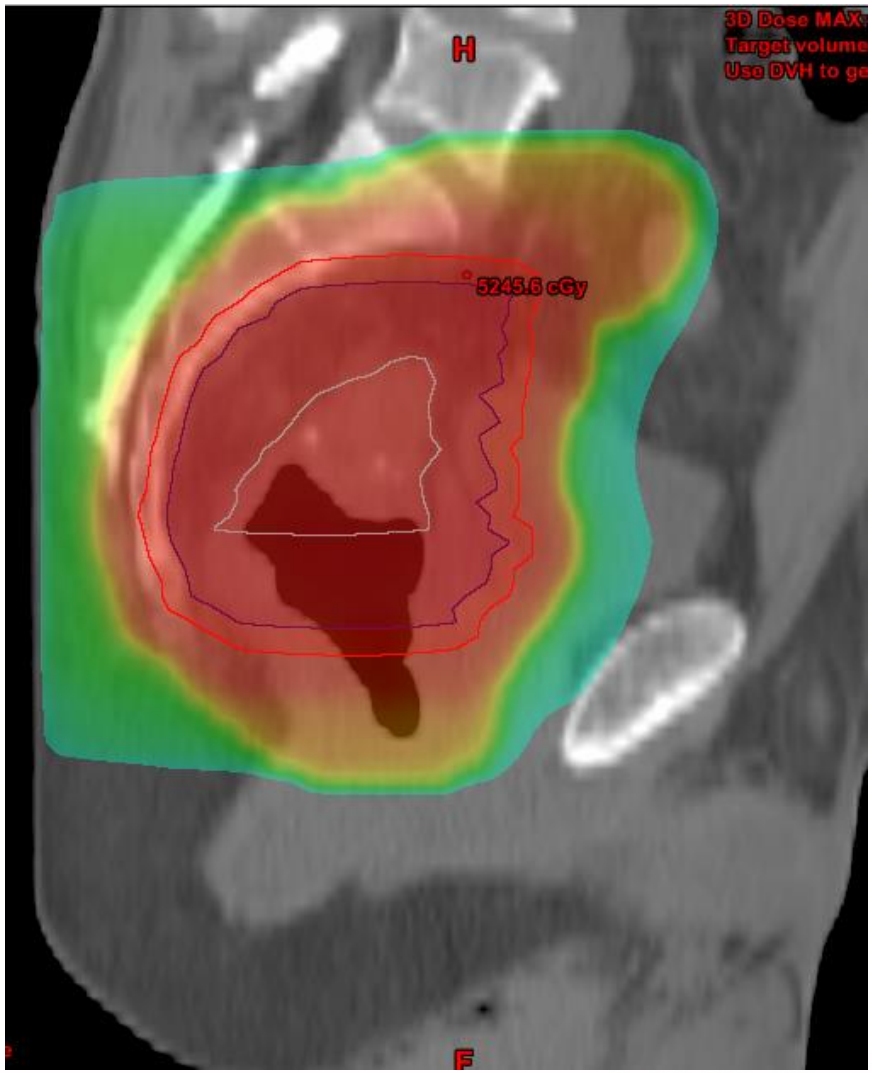




3-field Plan: dose color wash





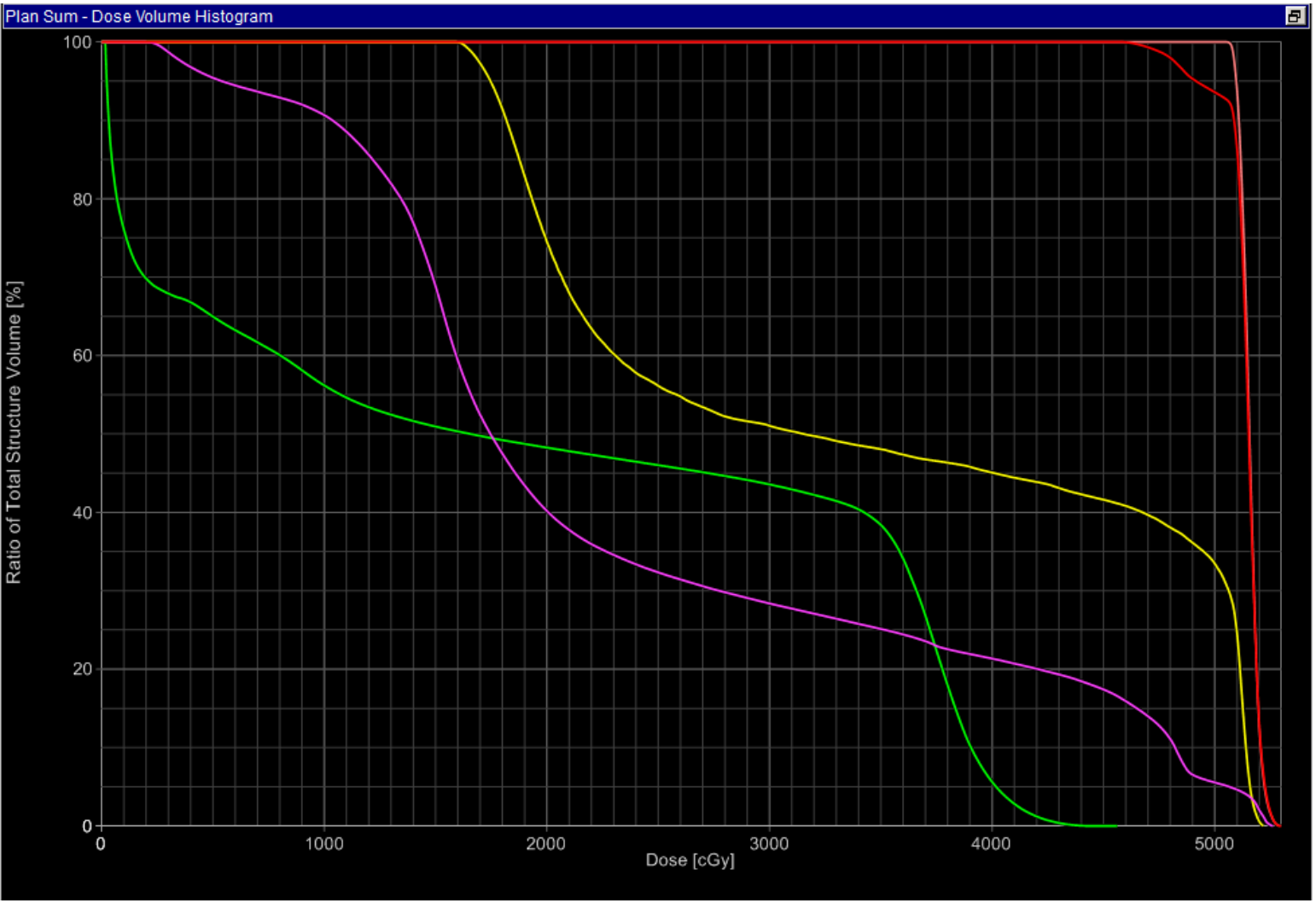


Dose Constraints

Small Bowel	**QUANTEC** V15Gy <120cc (Individual loops) V45Gy <195cc (potential space within peritoneal cavity) **RTOG 0822 (IMRT)** V35Gy <180cc V40Gy <100cc V45Gy <65cc Dmax <50Gy
Bladder	**QUANTEC** Dmax <65 Gy V65Gy <50% **RTOG 0822 (IMRT)** V40Gy <40% V45Gy <15% Dmax <50Gy
Femoral Heads	**RTOG 0822 (IMRT)** V40Gy <40% V45Gy <25% Dmax <50Gy

[13]Marks LB, Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl):S10-9.
[14]RTOG 0822. http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileID=4663

Cumulative DVH

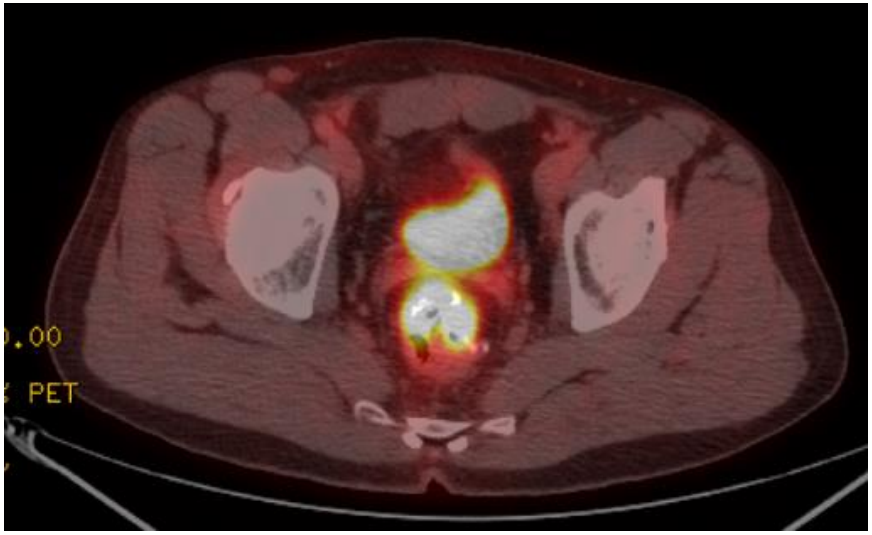


DVH Line	Structure
	Bladder
	Fem Heads
	PTV45
	PTV50.4
	Small bowel

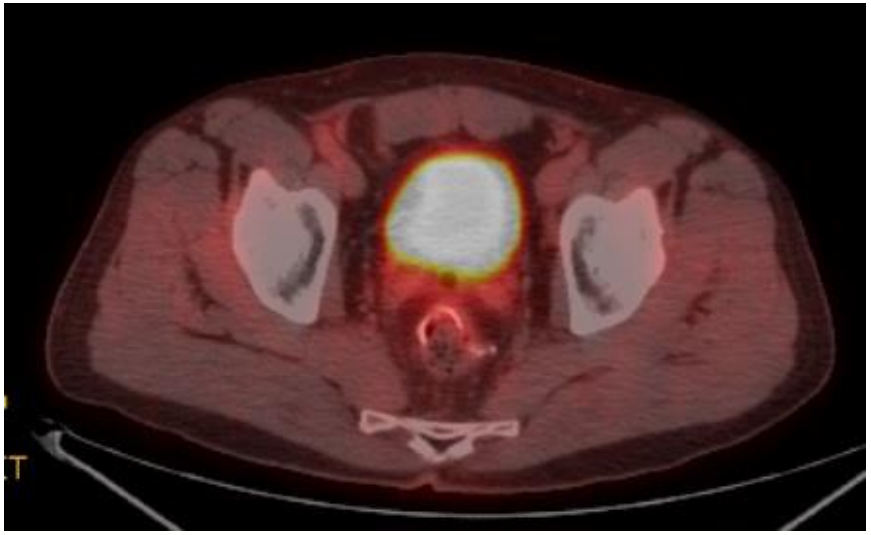
Cumulative DVH (Structure Volumes)

DVH Line	Structure
	Bladder
	Fem Heads
	PTV45
	PTV50.4
	Small bowel

Post-treatment Assessment: PET Scan



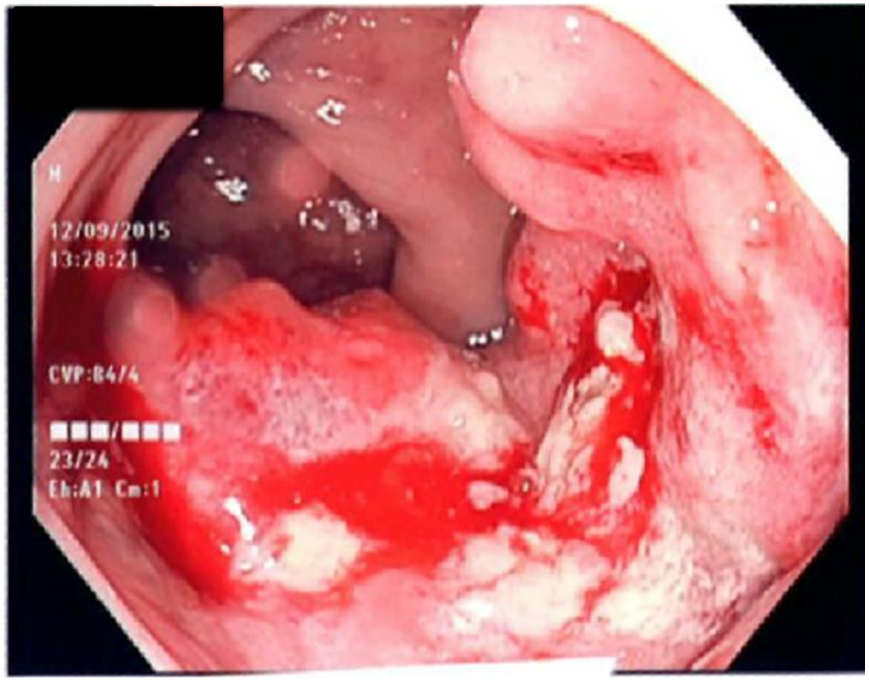
Before neoadjuvant therapy



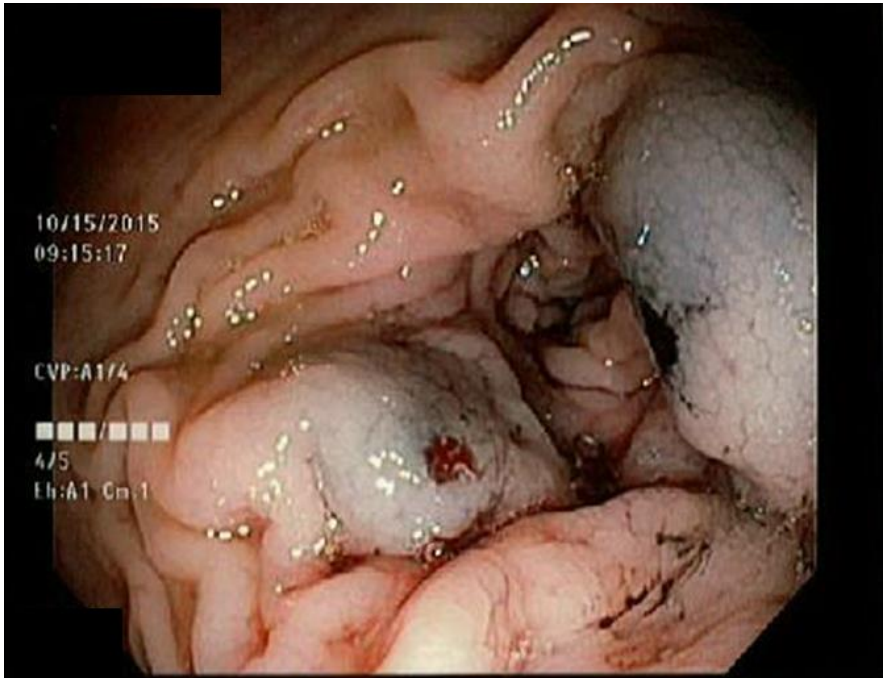
3 weeks after neoadjuvant therapy

- Complete resolution of the previously demonstrated FDG uptake in the rectum and small FDG avid lymph nodes in the pelvis
- No suspicious findings to suggest active malignant process

Post-treatment Assessment: Flexible Sigmoidoscopy



Before neoadjuvant therapy



5 weeks after neoadjuvant therapy

- Minimal residual erythema and granularity at the site of malignancy without any evidence of gross residual malignant tissue
- The rest of the examination was unremarkable

Surgery

- Low anterior resection (TME)
  - 8 weeks after completion of neoadjuvant chemoRT
  - Operative report: “No obviously palpable mass was noted. The tumor apparently had an excellent response to the preoperative radiation and there appeared to be no gross residual tumor”
- Pathology - pCR
  - Benign colonic mucosa with acute hemorrhage and fibrosis of submucosa
  - Seventeen benign lymph nodes (0/17)

Surveillance

	First 2 years	Years 3-5
H&P	Q 3-6 mo	Q 6 mo
CEA	Q 3-6 mo	Q 6 mo
CT Chest/Abd/Pelvis	Q 3-6 mo	Q 6-12 mo

- Colonoscopy in 1 y
  - Except if no preoperative colonoscopy due to obstructing lesion, then colonoscopy in 3-6 mo
- PET/CT not routinely recommended

[2]NCCN Clinical Practice Guidelines in Oncology. Rectal Cancer. Version 1.2016

References

1. American Cancer Society. http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-key-statistics. Accessed 3 March 2016.
2. NCCN clinical practice guidelines in oncology. Colorectal cancer screening. Version 1.2015. Accessed 3 March 2016.
3. Bruce D. Minsky, Claus M. Rödel and Vincenzo Valentini. Clinical Radiation Oncology, Chapter 51, 992-1018.e6.
4. AJCC cancer staging handbook, 7th ed. New York: Springer, 2010, published by Springer Science and Business Media LLC
5. Thomas PR et al. Adjuvant postoperative radiotherapy and chemotherapy in rectal carcinoma: a review of the Gastrointestinal Tumor Study Group experience. *Radiother Oncol*. 1988 Dec;13(4):245-52.
6. Krook JE et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med*. 1991 Mar 14;324(11):709-15.
7. Folkesson J et al. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate.. *J Clin Oncol.* 2005 Aug 20;23(24):5644-50.
8. van Gijn W et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol.* 2011 Jun;12(6):575-82.
9. Sauer R et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med.* 2004 Oct 21;351(17):1731-40.
10. Sauer R et al. Preoperative Versus Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial After a Median Follow-Up of 11 Years. *J Clin Oncol*. 2012 Jun 1;30(16):1926-33.
11. N.Y. Lee, J.J. Lu (eds.), Target Volume Delineation and Field Setup, DOI 10.1007/978-3-642-28860-9_17 © Springer-Verlag Berlin Heidelberg 2013
12. Myerson et al. Elective Clinical Target Volumes in Anorectal Cancer: An RTOG Consensus Panel Contouring Atlas. https://www.nrgoncology.org/Portals/0/Resources/Atlases/AnorectalContouringGuidelines.pdf
13. Marks LB et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys*. 2010 Mar 1;76(3 Suppl):S10-9.
14. RTOG 0822. A Phase II Evaluation of Preoperative Chemoradiotherapy Utilizing Intensity Modulated Radiation Therapy (IMRT) in Combination with Capecitabine and Oxaliplatin for Patients with Locally Advanced Rectal Cancer http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileID=4663. Accessed 3 March 2016.