Lower GI Malignancies

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Disclosure

- Employment: The University of Texas MD Anderson Cancer Center
- Grant Funding: Merck
- Scientific Advisory Board/Safety Monitoring Committee: Adlai Nortye

Learning Objectives

- To choose between appropriate total neoadjuvant therapy options for a patient with locally advanced rectal adenocarcinoma

- To assess controversial topics such as omission of surgery and omission of radiation for patients with locally advanced rectal adenocarcinoma

- To implement modern definitive chemoradiation for patients with anal squamous cell carcinoma.

Outline

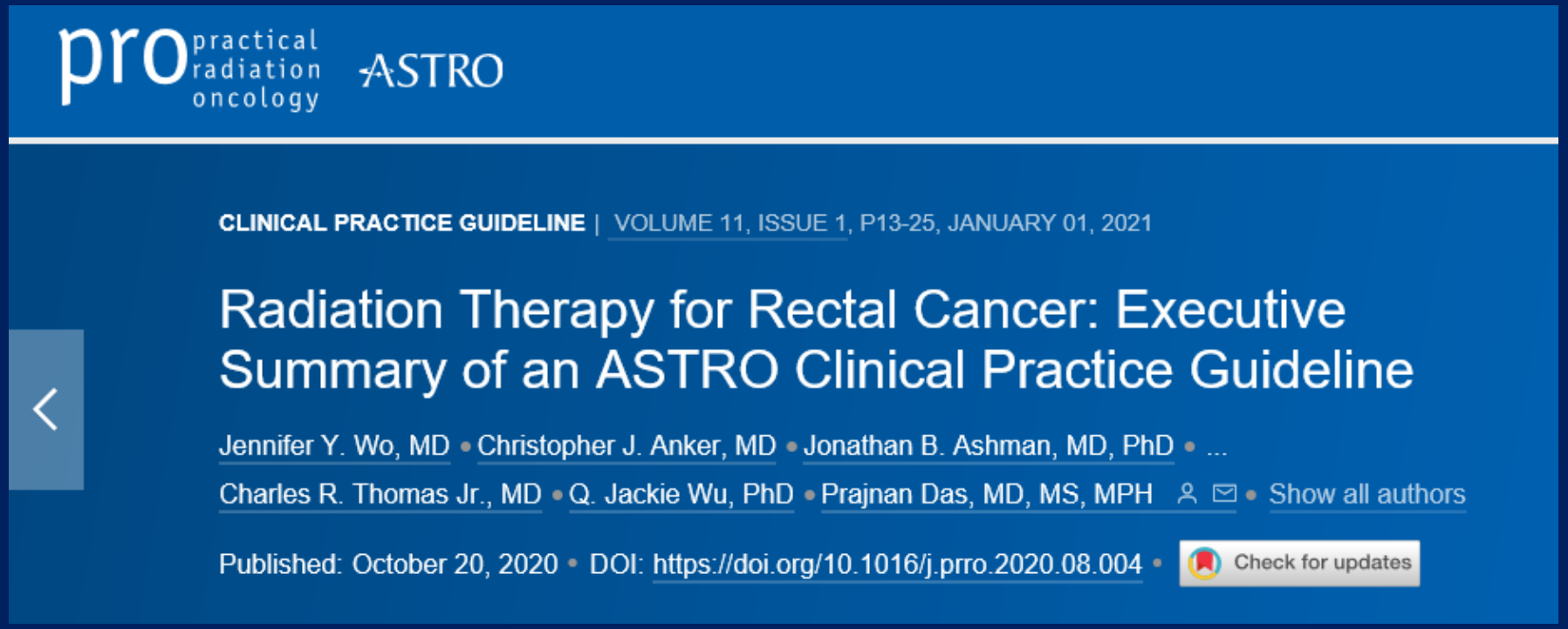
Rectal Cancer

- Background
- Total neoadjuvant therapy
- Short course vs long course
- Nonoperative management
- Selective omission of radiation?

Anal Cancer

- Current standard of care
- Treatment escalation
- Treatment deescalation

Rectal Cancer



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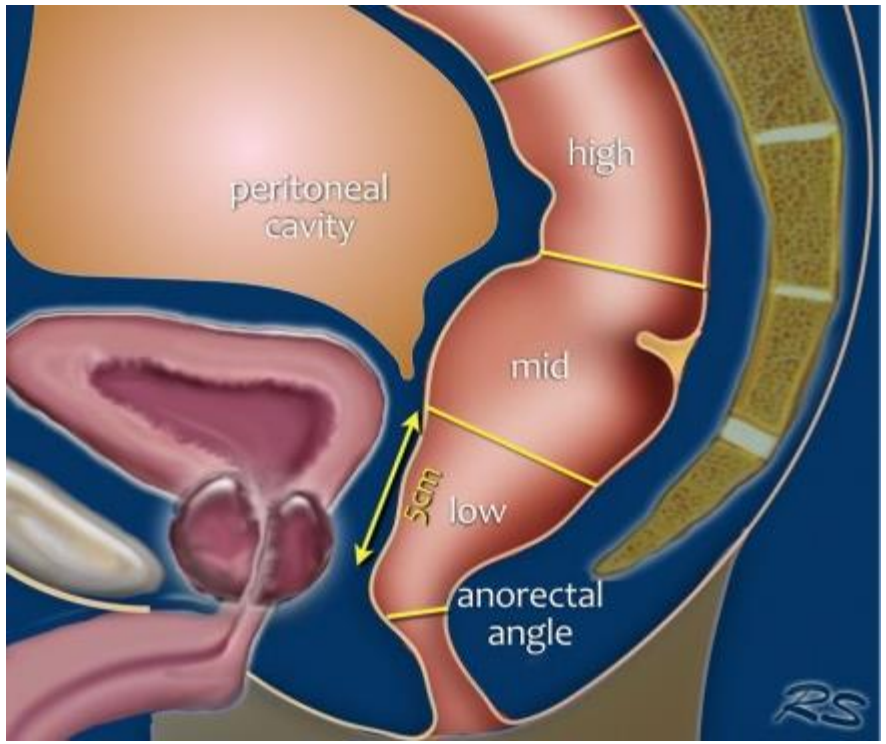
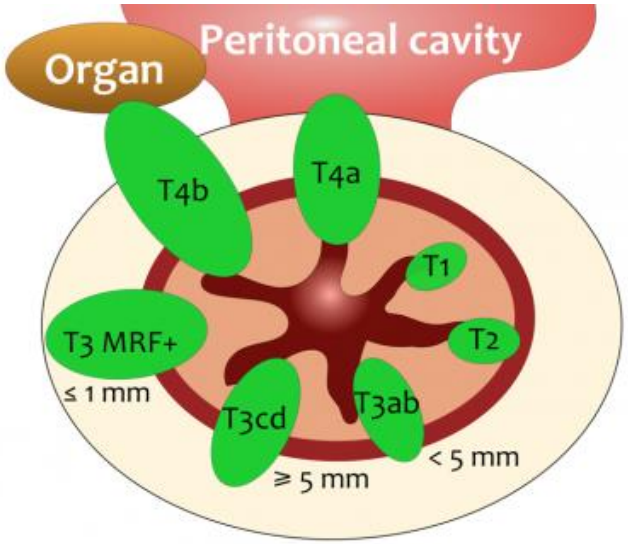
Rectal Cancer Anatomy & Staging



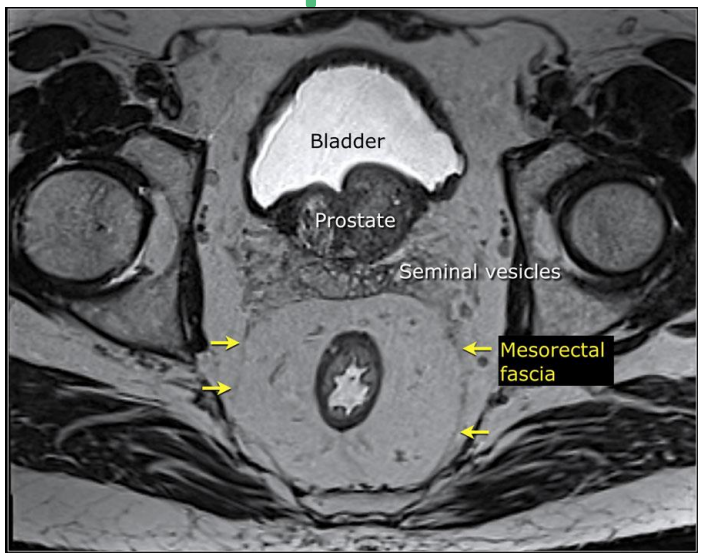


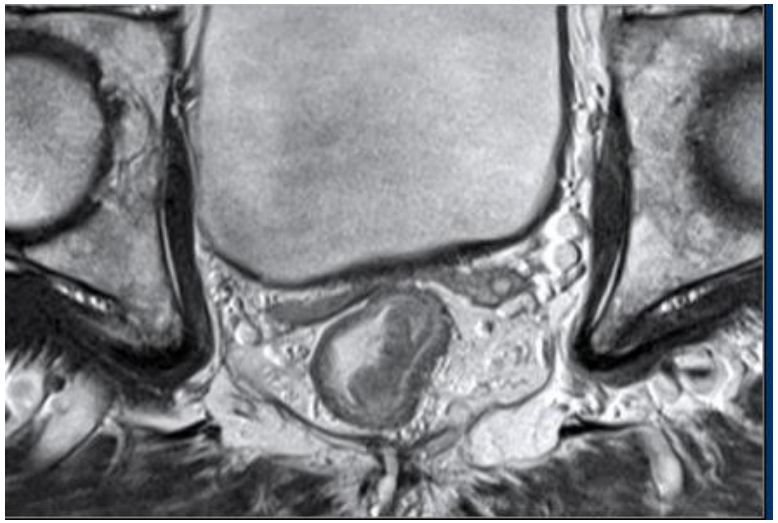
N-stage - suspicious nodes			
	Indistinct	Heterogeneous	Round
Malignant characteristics			
Short axis	- < 5mm : needs 3 malignant characteristics - 5 -9mm : needs 2 malignant characteristic - > 9mm : always suspicious		
cN-stage	- N0 : ***no*** *suspicious* lymph nodes - N1 : 1-3 *suspicious* lymph nodes - N2 : ≥ 4 *suspicious* lymph nodes		

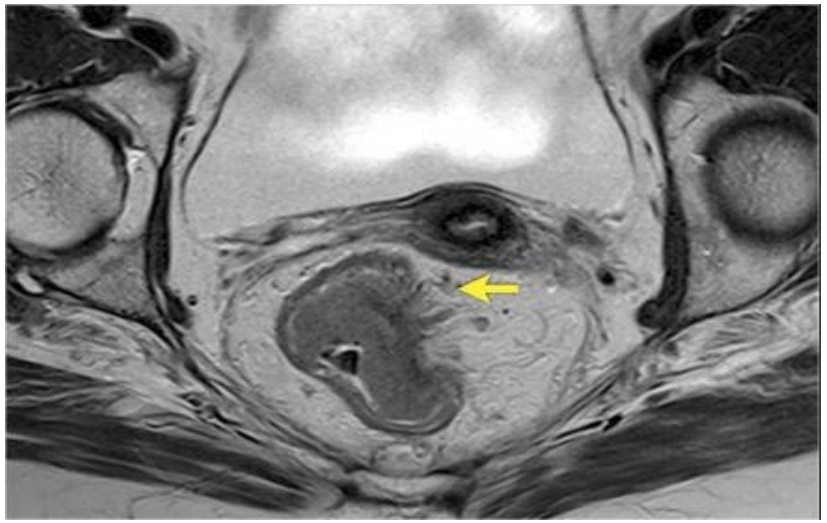
Van Loenhout et al. Radiology Assistant

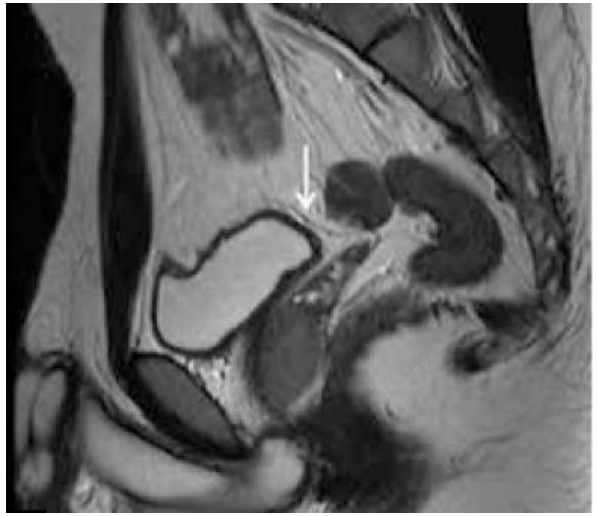
Van Loenhout et al. Radiology Assistant

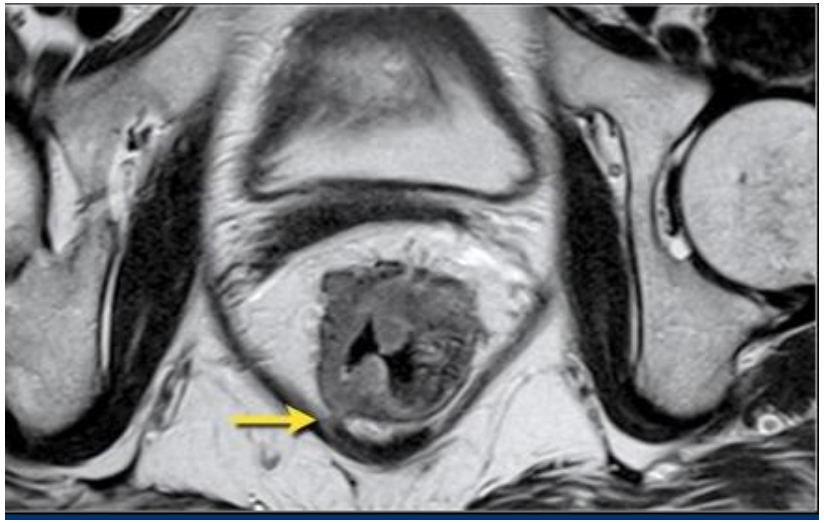
Importance of MRI

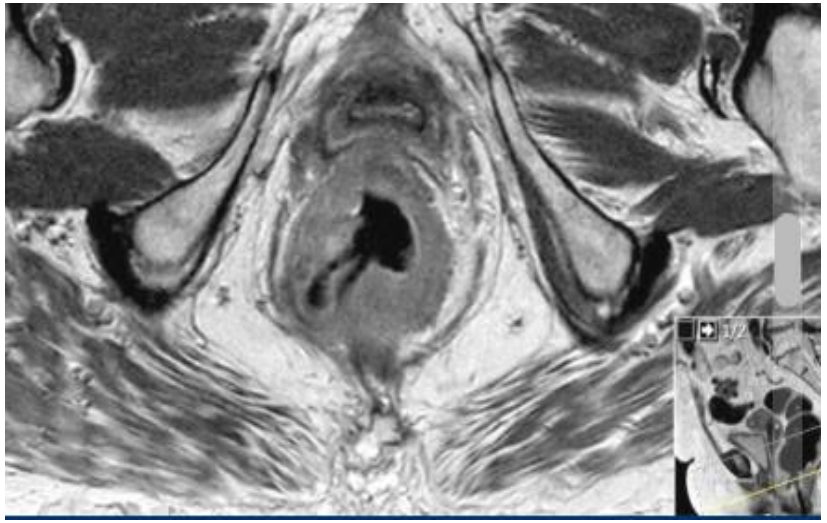












Rectal Cancer Work-up

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Rectal Cancer

CLINICAL PRESENTATION[a,b]	WORKUP
Rectal cancer appropriate for resection[j,k]	• Biopsy • MMR/MSI testing[f] • Pathology review • Colonoscopy • Consider proctoscopy[i] • Chest CT and abdominal CT or MRI[c] • CBC, chemistry profile, CEA • Pelvic MRI with or without contrast[c] • Endorectal ultrasound (if MRI is contraindicated, inconclusive, or for superficial lesions)[c] • Enterostomal therapist as indicated fo preoperative marking of site, teaching • PET/CT scan is not indicated[c] • Multidisciplinary team evaluation, including formal surgical evaluation • Fertility risk discussion/counseling in appropriate patients

~15% CRC are MSI-high

Best done by the treating surgeon

"rectal protocol" = specific sequences including a small FOV T2 perpendicular to the plane of the rectum

EUS can't tell CRM or EMVI but is better for distinguishing T1 vs T2

Historic Role of RT for Rectal Cancer

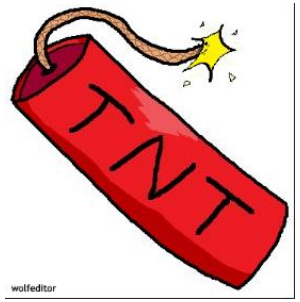
- Preop (SC) radiation decreases 10yr LF over TME surgery alone: 11% → 5%

Dutch Trial
Lancet Onc 2011

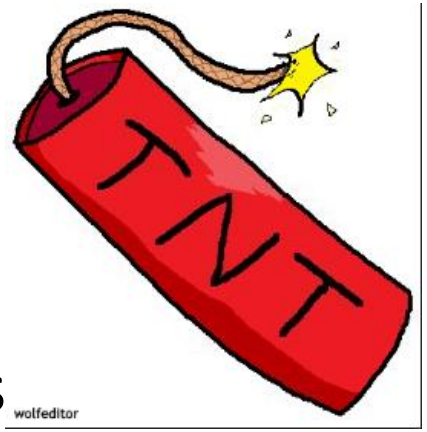
- Preop (LC) CRT improves 10yr LC over postop: 10.1% → 7.1%.
  - pCR rate w/ 50.4Gy/28 was **8%**

German Rectal Ca Trial
JCO 2012

- **No improvement in DFS or OS.**
  - ***How do we improve DFS?***



Rationale for TNT



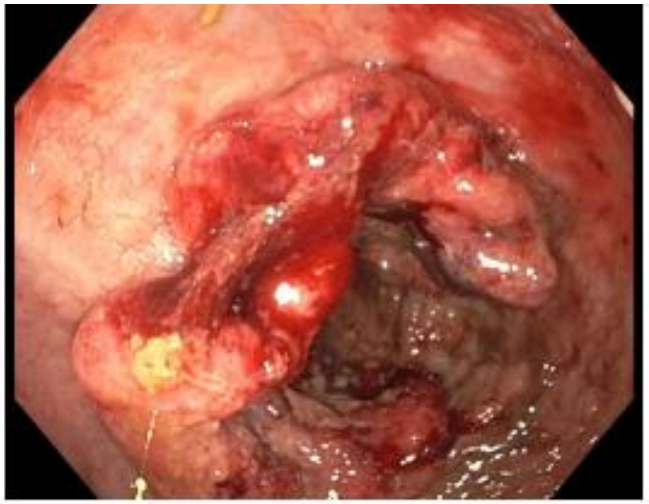
- With *preop CRT*: LR from >25% → ~5% but distant failure is still 25-30% & is the leading cause of cancer related death.

- **6 months adj chemo historically recommended even after RCT failed to show benefit**
  - Only 40-70% of patients complete adj chemo b/c of toxicity.
  - Moving systemic therapy preop improves tolerability & pCR/downstaging

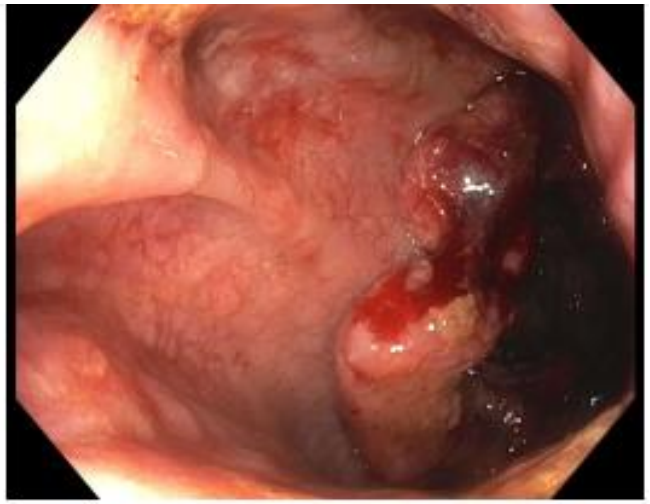
Brændengen et al
JCO 2008
EORTC 22921

High-risk locally advanced rectal cancer

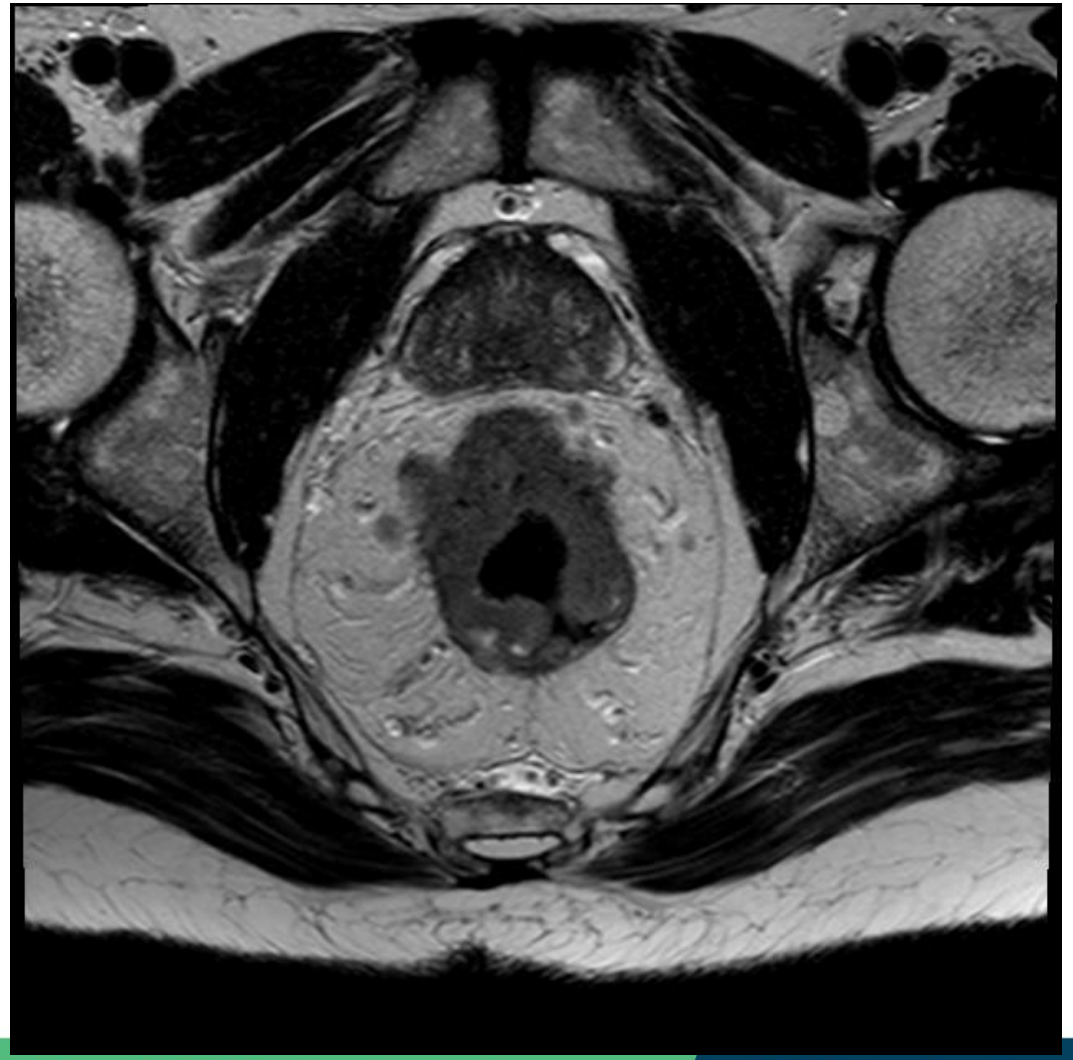
- 45 y/o M with mid-rectal mod diff adenoCA.



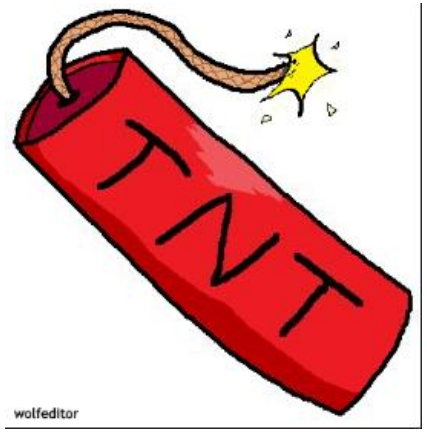
8 Rectum : Mass



9 Rectum : Mass



Treatment Options:



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Rectal Cancer

CLINICAL STAGE

T3, N any with involved or threatened CRM (by MRI);[n] T4, N any or Locally unresectable or medically inoperable

TOTAL NEOADJUVANT THERAPY

- **Long-course chemo/RT[q,r]**
  - **Capecitabine or infusional 5-FU[p]**
  - **or**
  - **Short-course RT[r,u]**

  → **Chemotherapy (12–16 weeks)**
  - **FOLFOX or CAPEOX**
  - **Consider FOLFOXIRI (for T4, N+)**

  → **Restaging[c]**
  - **Transabdominal resection[i,v,x]** → **Surveillance (See REC-11)**
  - **Resection contraindicated** → **Systemic therapy[w] (See REC-F)**

- **or**

- **Chemotherapy (12–16 weeks)**
  - **FOLFOX or CAPEOX**
  - **Consider FOLFOXIRI (for T4 N+)**

  → **Long-course chemo/RT[q,r]**
  - **Capecitabine or infusional 5-FU[p]**
  - **or**
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  → **Restaging[c]**
  - **Transabdominal resection[i,v,x]** → **Surveillance (See REC-11)**
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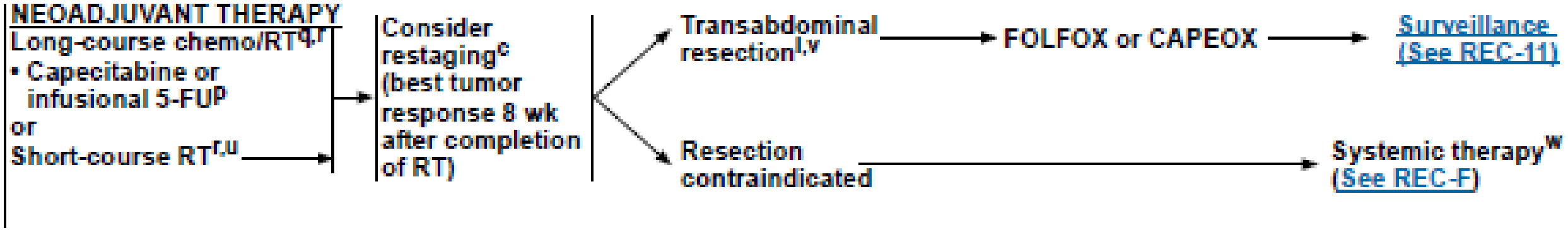
What treatment option is missing?

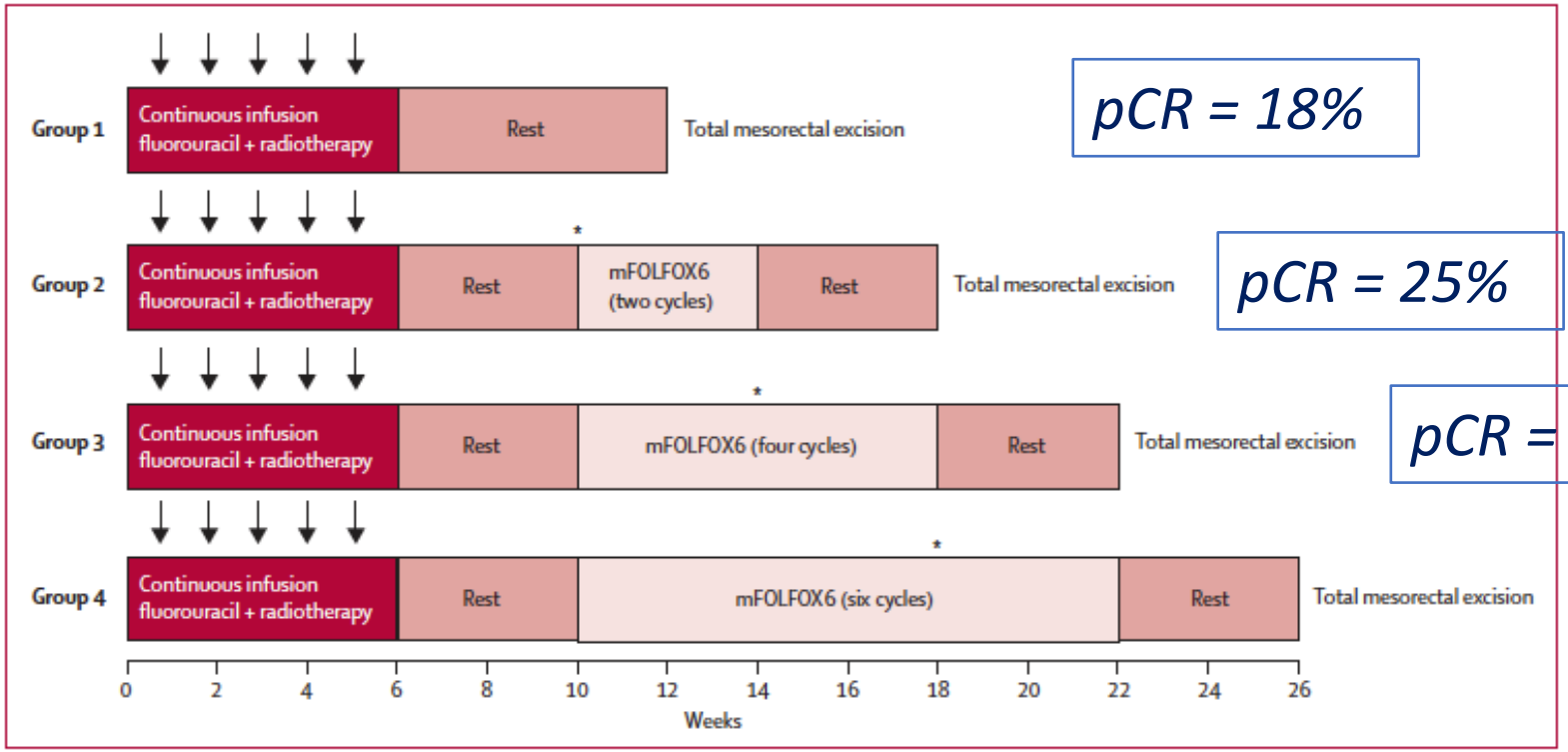


- *The German Rectal Cancer Trial standard was **removed** as SOC option from NCCN v1.2021 unless the tumor is T3 and/or N+ **with a clear CRM** by MRI*

Phase II Data Supporting TNT

- Giving chemo after LC-CRT but before TME improves pCR

Garcia-Aguilar
Lancet Onc 2015



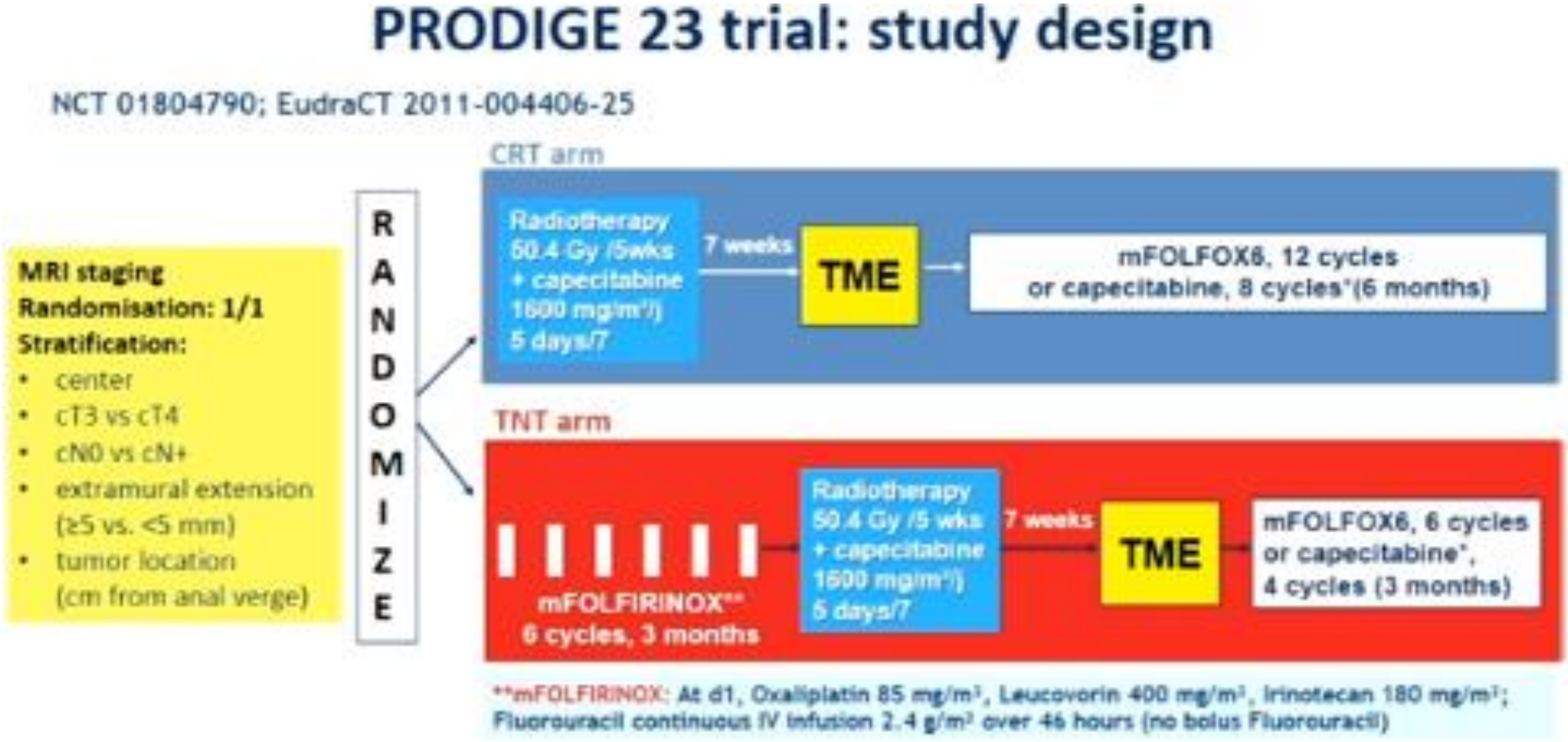
pCR = 18%

pCR = 25%

pCR = 30%

pCR = 38%

PRODIGE-23

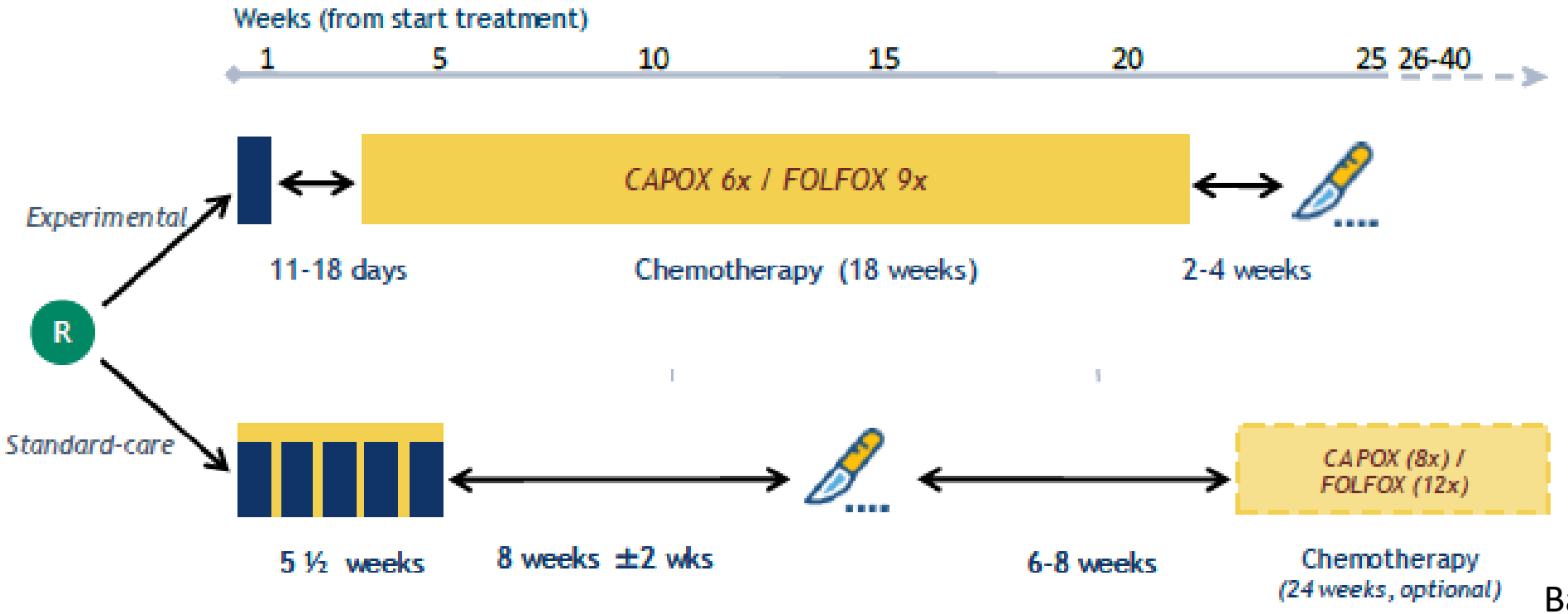


Conroy et al ASCO 2020

RAPIDO: Study Design

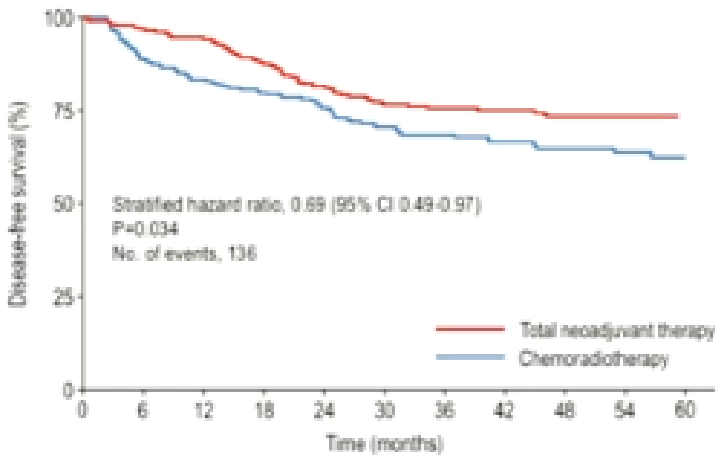
Inclusion criteria: rectal adenoCA w/ >/=1 of the following:

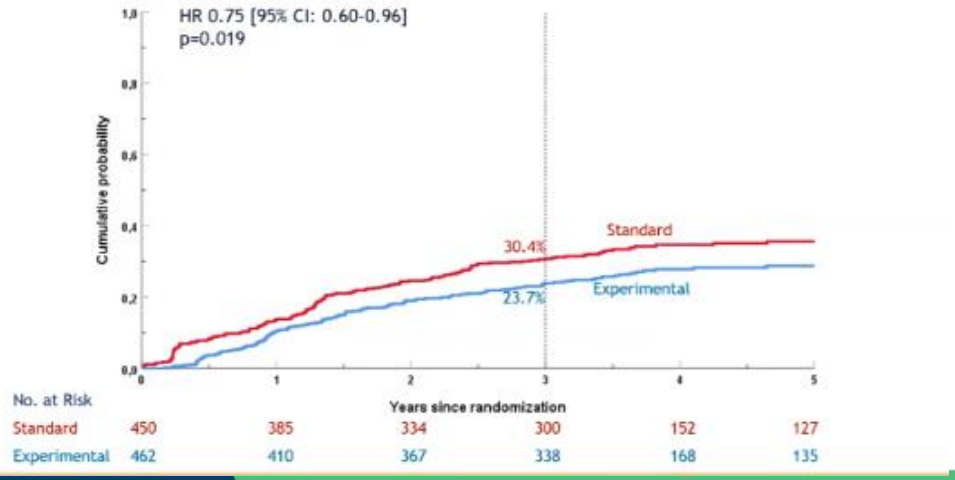
- *T4a/b*
- *EMVI+*
- *N2+*
- *MRF+*
- *Enlarged lateral LNs*



Bahadoer et al
Lancet Oncol 2021

PRODIGE-23 & RAPIDO Results





PRODIGE:

DFS better w/ TNT: 75.7% vs 68.5% (HR 0.69; P=.034)

pCR = 27.8% in TNT arm vs 12.1% in CRT arm (p<.001)

RAPIDO:

DR-TF better w/ TNT: 23.7% vs 30.4% (HR 0.75; P=.019)

pCR = 28.4% in TNT arm vs with 14.3% in CRT arm (p<.001)

Applying PRODIGE-23 & RAPIDO

- TNT was the clear winner for high-risk locally advanced disease.
  - Should we do chemo 1st or RT 1st?
  - Should we escalate to triplet chemo for patients who can tolerate it?
  - Should we use SC or LC?

Evolution of Short-Course RT Trials

- Older trials did surgery w/in 1 week of SCRT
  - Concerns of less downstaging, pCR essentially 0%

Dutch Trial, TROG Trial

- Newer trials waited 4-8wks from SCRT to TME
  - **pCR 11%,** no increased postop complications or toxicity

Stockholm III

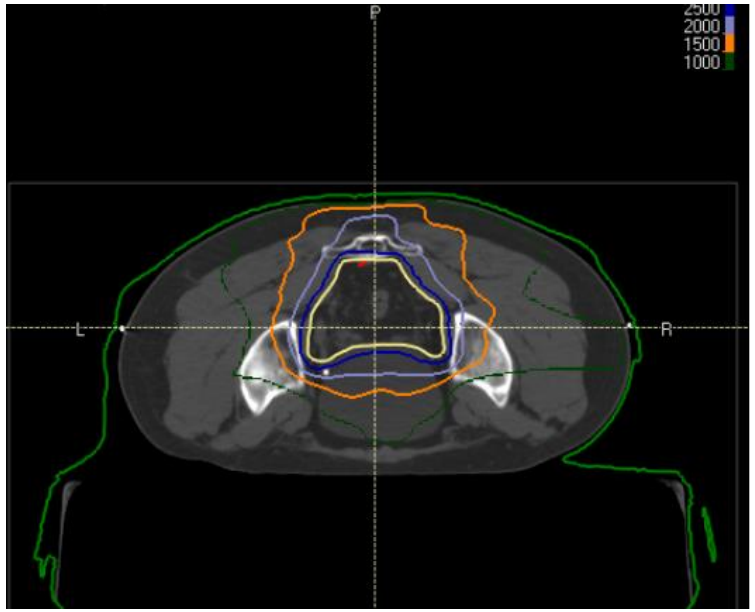
- Most recent trials gave chemo in the interval btwn SCRT and TME
  - **pCR 28%** on RAPIDO

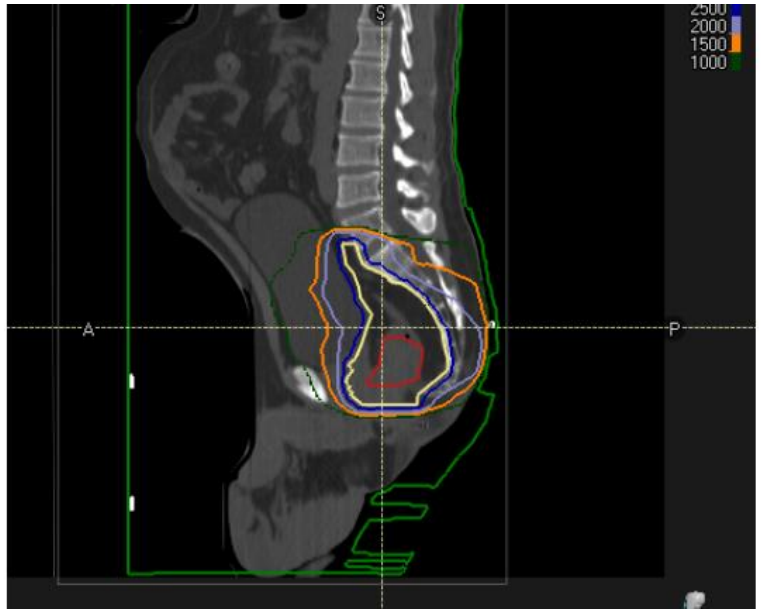
Polish Trial, RAPIDO

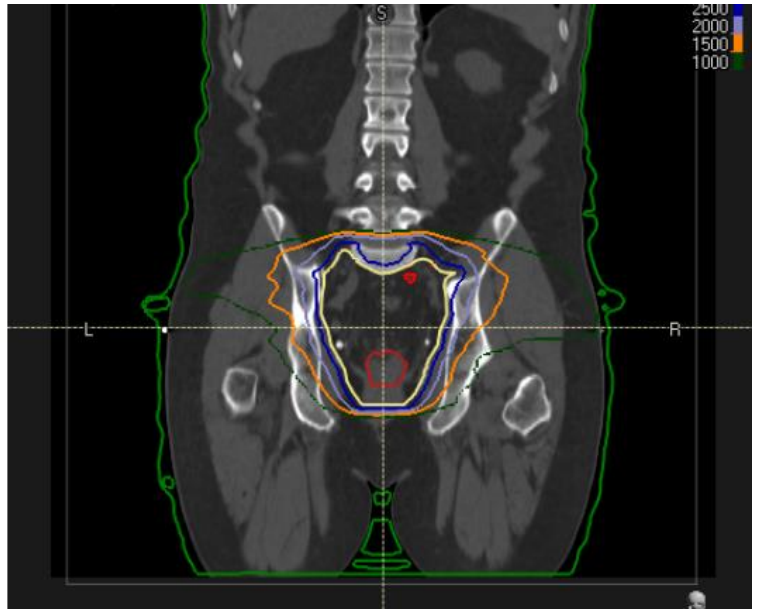
- SCRT is less costly, more convenient.

SCRT Treatment Logistics:

Volume: Whole pelvis.
RX dose: 25Gy in 5 fxns to standard pelvic field.
OK to include EIs for T4b disease.
Treat prone on BB w/ full bladder.
3D or VMAT. Daily IGRT = CBCT.

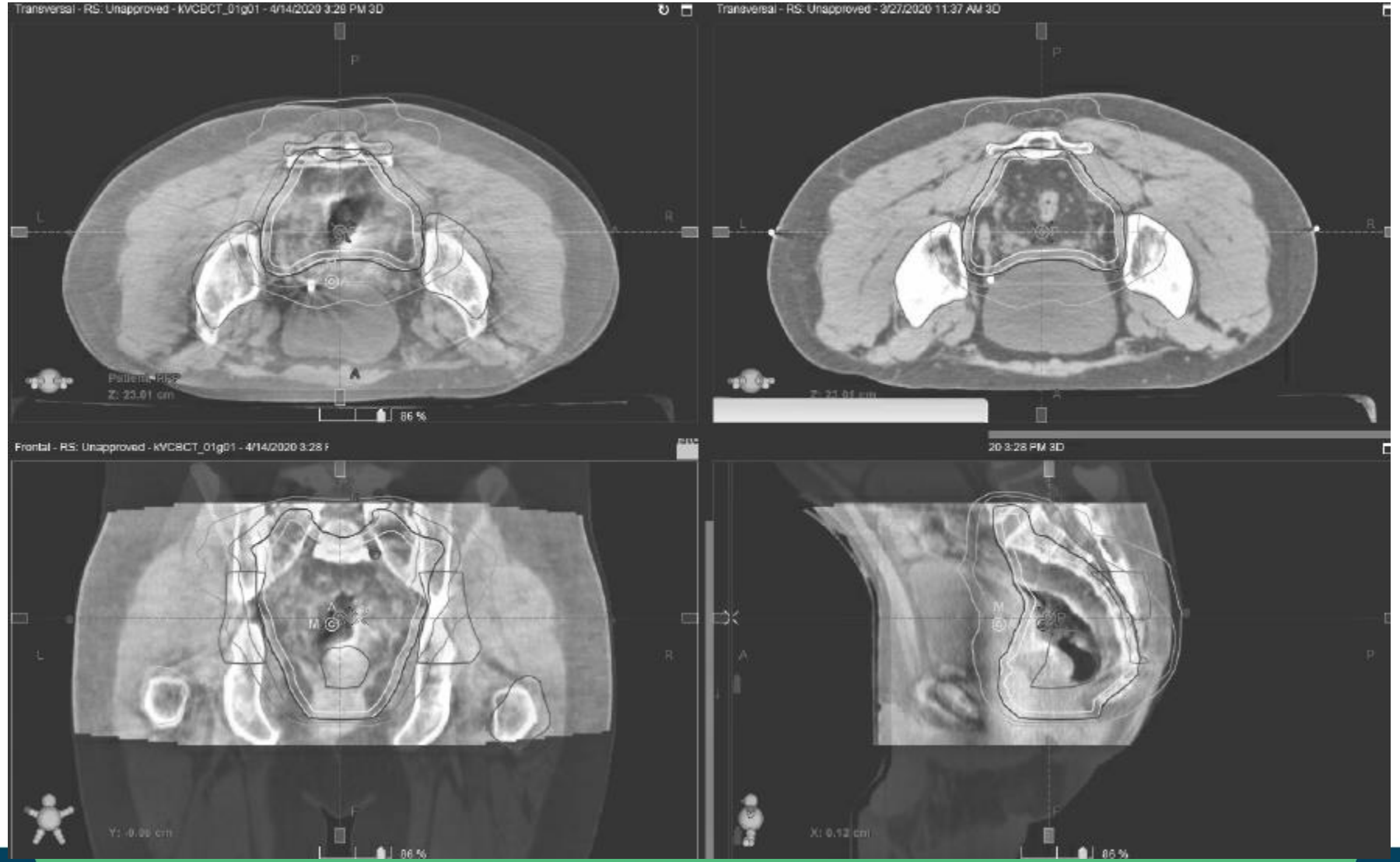






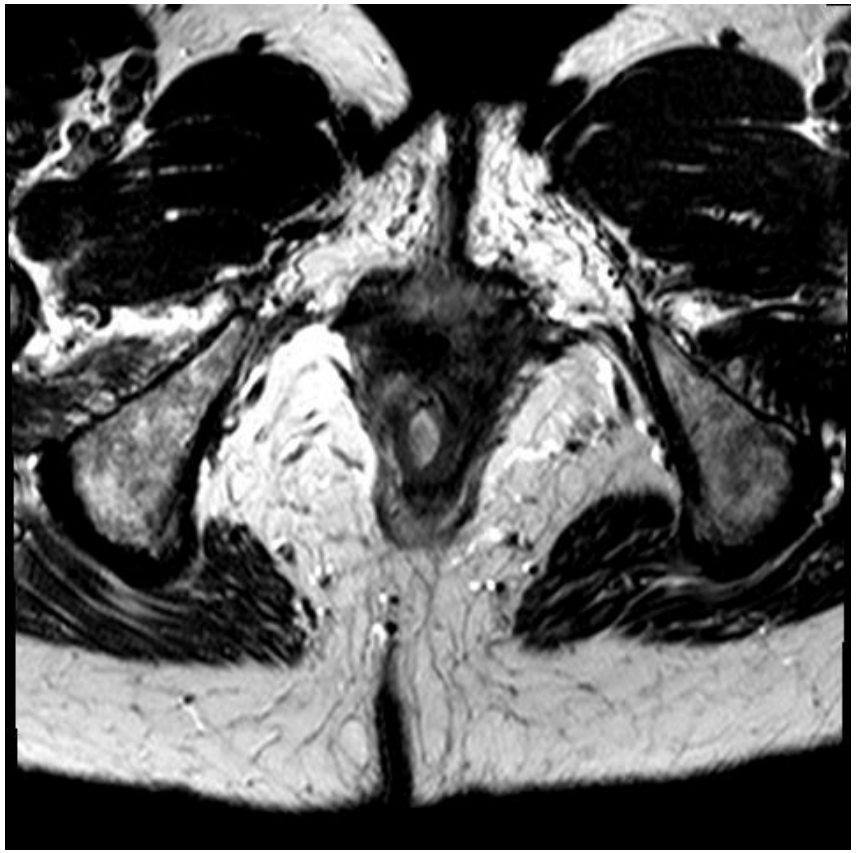
- Dose Constraints (VCU Phase I study Fields et al):
  - Small bowel: Dmax<27.8, V25Gy<65cc, V22.2Gy<100cc, V19.5Gy<180cc
  - Bladder: Dmax<27.8Gy, V25Gy<15%, V22.2Gy<40%
  - Fem Heads: Dmax<27.8Gy, V25Gy<25%, V22.2Gy<40%
- *Chemo can start 11-18 days after last day of SCRT per RAPIDO*

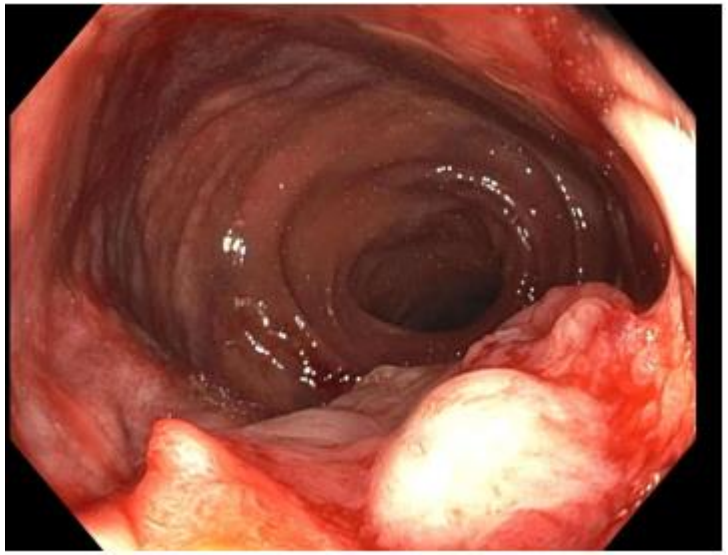
Potential interfraction problems to watch for:



Early Stage Rectal Cancer

- 74 y/o F with Parkinsons was diagnosed with T2N0 very low rectal adenoCA, poorly differentiated. 4cm tumor invading into the anal canal. No EMVI, 2mm from the MRF.





Treatment Options?

Candidates for TAE: cT1N0 tumors, <30% circumference, <3cm size,
Margin >3mm, mobile, not fixed, w/in 8cm of the AV
No LVSI, No PNI, No G3 disease.

- T2 tumor, poor diff: not optimal candidate for TAE

CALGB 8984

- Oncologic surgery would require APR.
- Indications for RT?
  - CRT to improve chances of sphincter-sparing operation
  - CRT to facilitate a non-operative approach

OPRA

GRECCAR-2
Sauer et al JCO 2012

TAE → Chemoradiation

- **CALGB 8984**:
  - Greenberg et al 2008

- Prospective single arm trial for cT1/T2 low to mid rectal cancer, <4cm, <40% circumference.
  - T1 patients were observed after TAE
  - T2 patients received 54Gy/30fxns chemoradiation.

	T1:	*T2:*
10yr LR	*8%*	*18%*
10yr DM	*5%*	*12%*
10yr OS	*84%*	*66%*
10yr DFS	*75%*	*64%*

- **SOC operation for T2N0 remains TME surgery.**

Chemoradiation → TAE

- **GRECCAR-2**: 5 year update
  - Rullier et al Lancet Gastroenterol Hepatol. 2020

- RCT for cT2/T3 N0-1 <4cm low rectal cancer comparing CRT → TAE vs TME
  - If ypT2-3 or R1 TAE → completion TME.

- No difference in LR, DM or OS at 5yrs, *but not powered for non-inferiority.*

- **SOC operation for T2/T3 remains TME,** *though preop CRT may facilitate:*
  - *Sphincter sparing by downgrading APR → LAR*
  - *Non-operative management.*

Watch & Wait/Non-operative Management

- **Rationale**: Studies show a 20-25% pCR rate after TNT. If this subset can be identified, could surgery be omitted for this low risk population?

- *IW&W Database:* cCR in 880pts, 2-yr local regrowth 25%, DM 8%, 5-yr OS 85%, DSS 94%

- *MSKCC Retrospective*: 113 cCR/WW vs 136 pCR/TME, local regrowth in 19.5%, 82% rectal preservation, **higher rate of DM in pts with local regrowth (36% vs 1%),** 5-yr OS 73% vs 94%, DFS 75% vs 92%

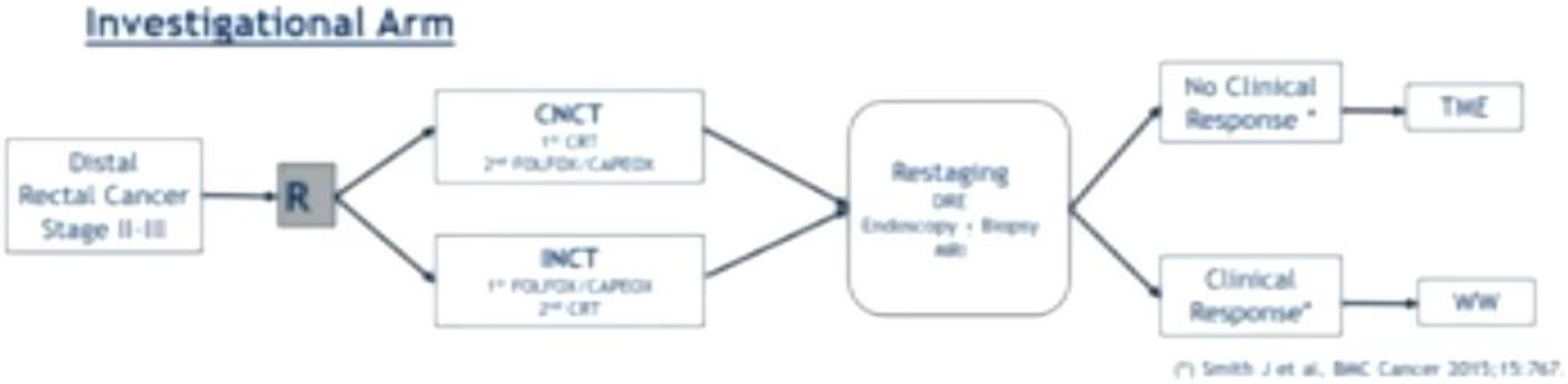
Van der Valk, Lancet, 2018
Smith, JAMA Oncol, 2019

OPRA: Study Design

Inclusion Criteria:
Stage II/III Rectal adenoCA
Must be a distal rectal cancer requiring either APR or coloanal anastomosis at baseline to achieve TME.

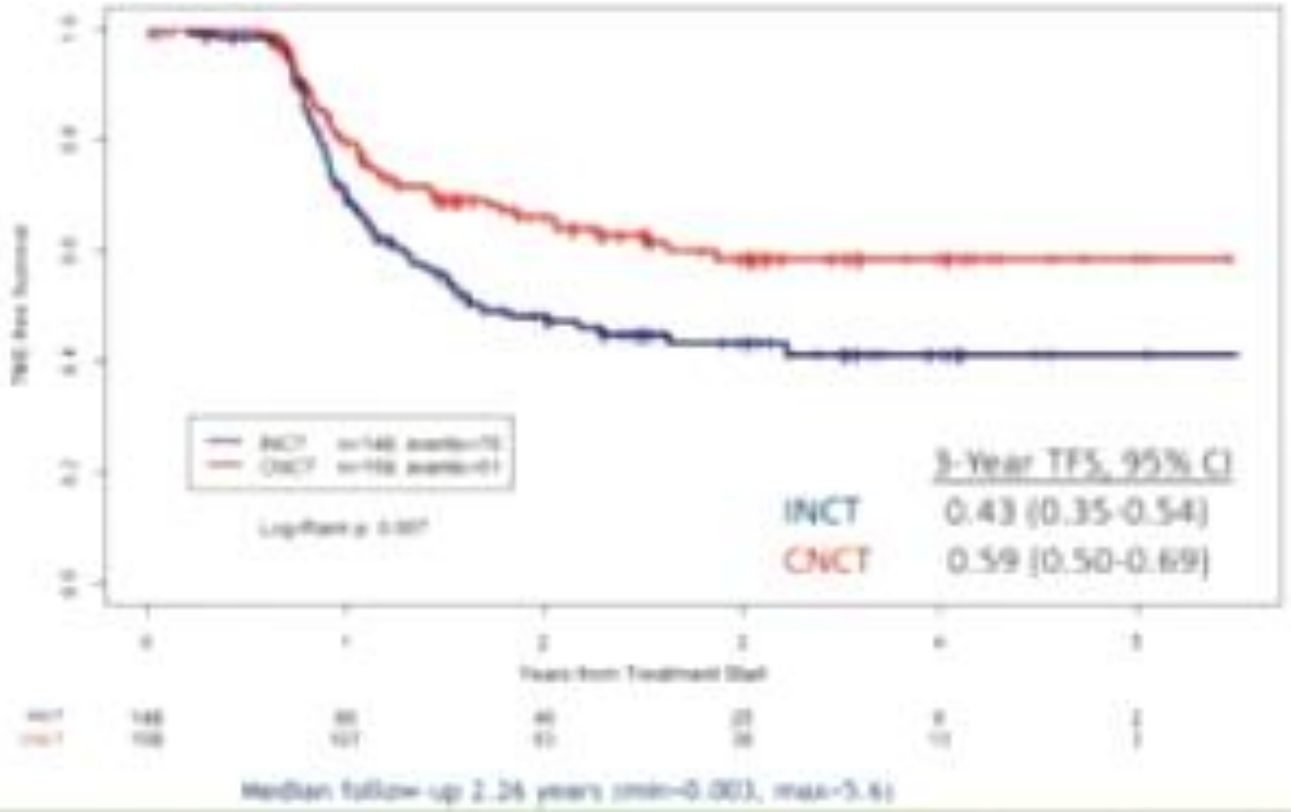
Protocol Schema

NCI trial registration: NCT02008656
NIH-funded (R01): 1R01CA182551-01



TME-Free Survival

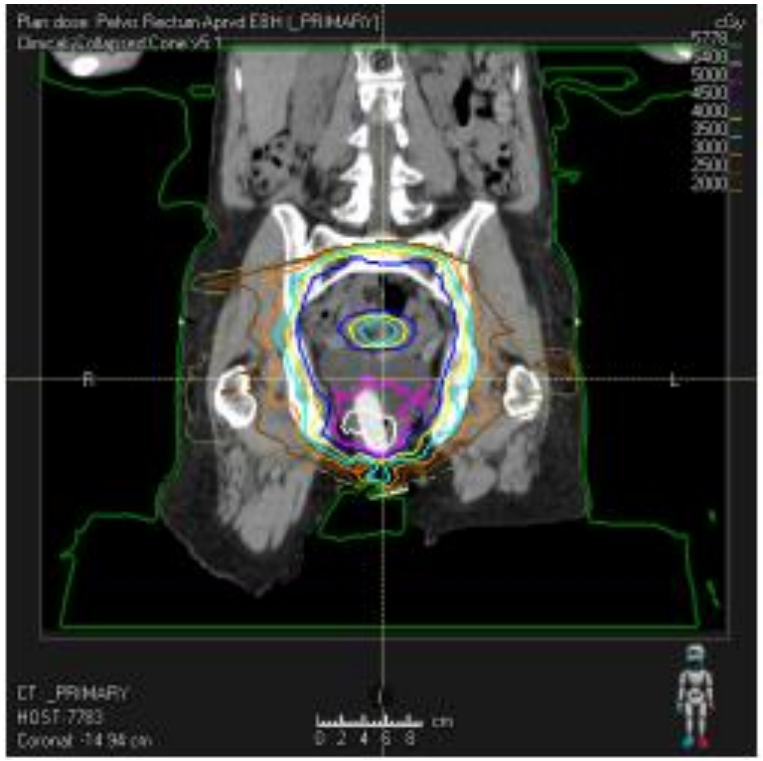
Results: TME-Free by Treatment Group



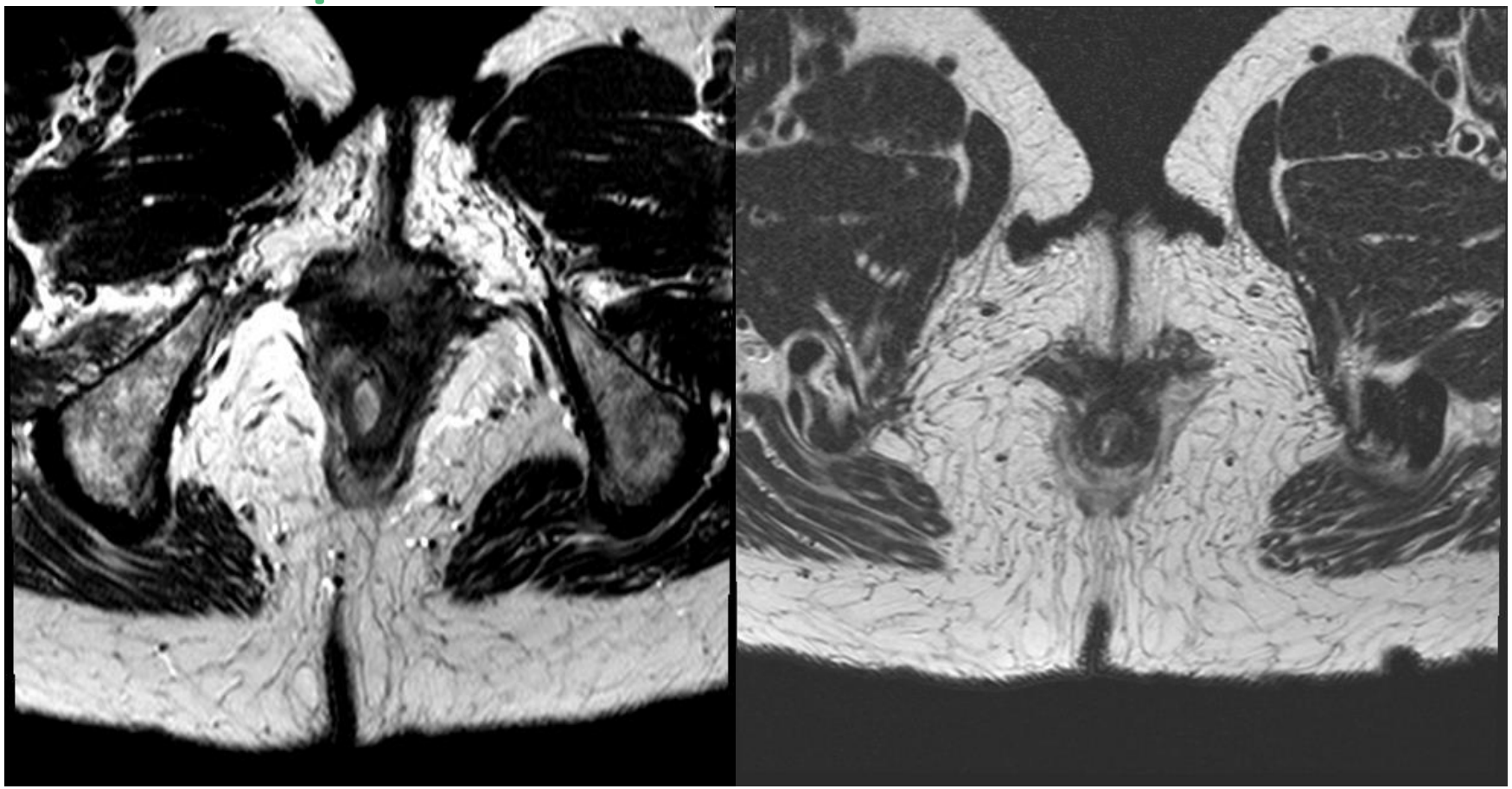
**German trial (Foksas et al JCO 2019) also showed higher pCR rates w/ RT-first TNT compared with chemo-first TNT.

Back to the Case:

- Dose/Fractionation: 54Gy in 27 fractions
  - 45Gy in 25 fraction pelvis w/ SIB 50Gy in 25 to tumor + margin
  - Sequential 4Gy boost to the tumor + margin to total 54Gy
- Volumes: Standard elective pelvis (Myerson et al RTOG atlas)
  - Internal iliacs, perirectal, presacral, obturator
  - **elective inguinal coverage is controversial for low rectal tumors**
- 3D vs IMRT/VMAT depending on ability to meet constaints. (I use VMAT when I go to 54Gy)
- Chemo can begin ~2 weeks after chemoradiation



Response Assessment:



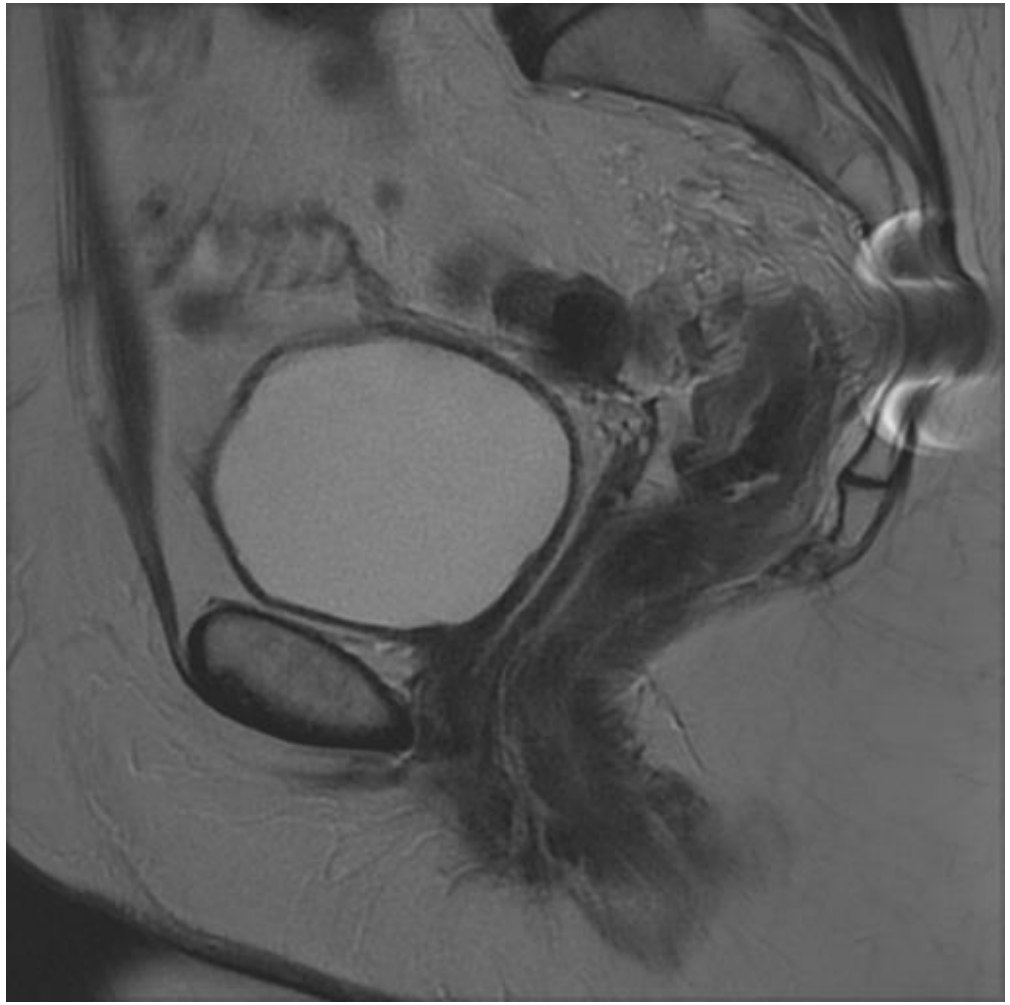
	Complete Response
Endoscopy	Flat, white scar Telangiectasia No ulcer No nodularity
Digital Rectal Exam	Normal
MRI-T2W	Only dark T2 signal, no intermediate T2 signal
	AND
	No visible lymph nodes
MRI-DW	No visible tumor on B800-B1000 signal
	AND/OR
	Lack of or low signal on ADC map Uniform, linear signal in wall above tumor is ok

- ***W&W follow up protocol***: flex sig q4m x 2yrs and q6m x 3 years, MRI q6m x 2 years and q12m x 3 years. CT CAP q12mo x 5 years.

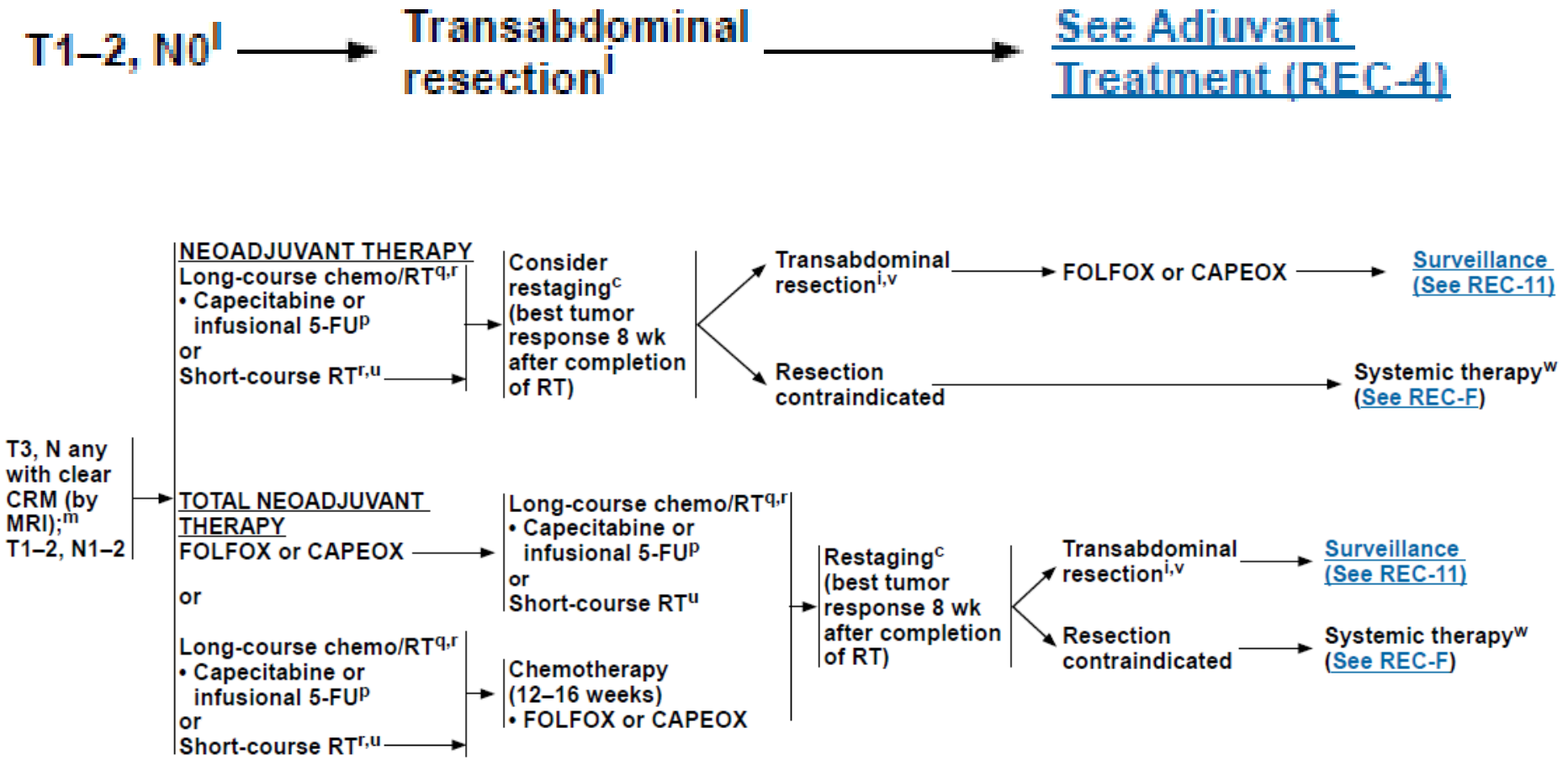
Early Stage Rectal Cancer- *Case Variation*

- 68 y/o F with diagnosed with mod diff mrT2 vs T3a N0 adenoCA 10-13cm from the anal verge, 3.5cm in craniocaudal length.

- No EMVI, *MRF is clear.*



Treatment Options?



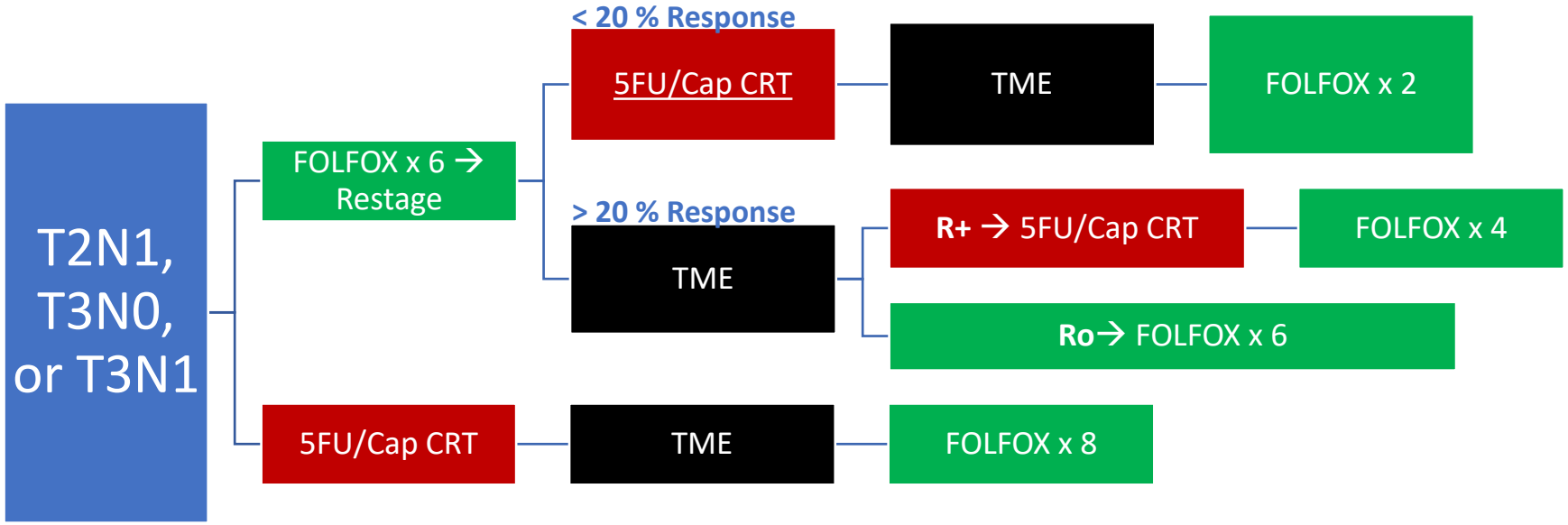
Can some T3 and/or N+ patients safely omit RT?

- UK MERCURY: **Straight to surgery**
  - MRI can define "low risk" = T1-T3b with <5mm extramural spread, *any nodal stage*, CRM >1mm, no EMVI.
  - The local control rate for these patients who then underwent good quality TME surgery was 97%

- MSKCC Phase 2 Trial: **Preop chemo alone**.
  - 6 cycles of chemo → restaging. If any response, proceed to surgery.
  - All patients had R0 resection, 25% had pCR.

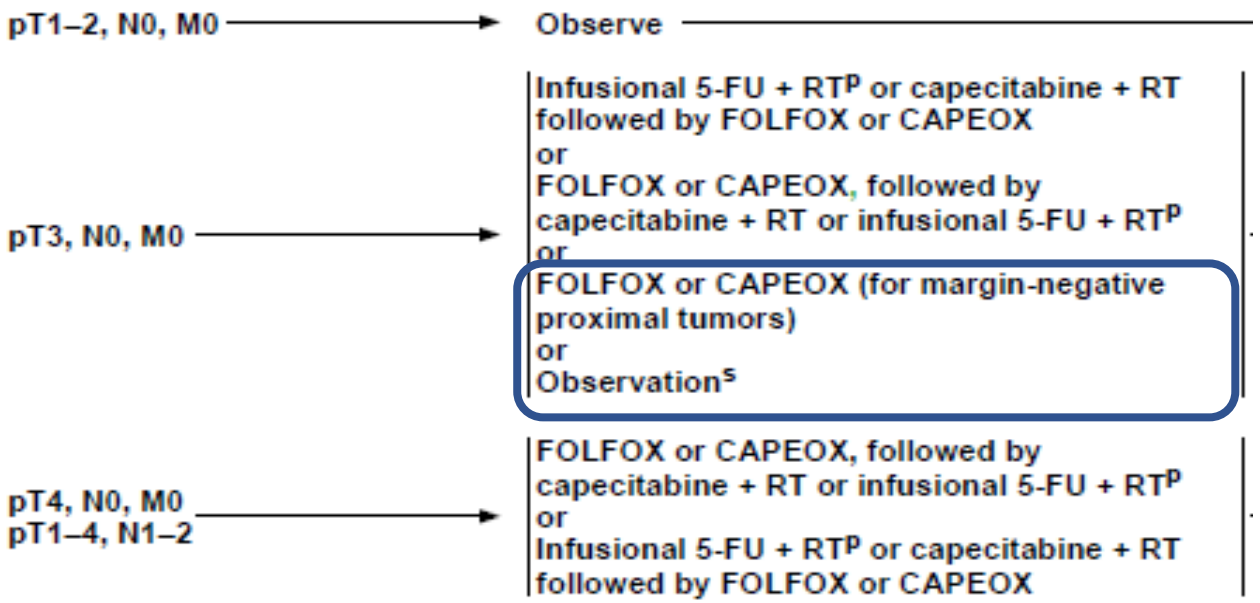
PROSPECT Trial

Hypothesis: Treatment with neoadjuvant FOLFOX and selective use of preop 5FU-CRT for LARCs with curative intent sphincter sparing TME is non-inferior to 5FU-CRT followed by surgery and FOLFOX



Back to the Case:

- Given the T2 vs T3 staging and the widely clear distance to the CRM, the patient was taken to the OR for an LAR.
- Surgical pathology showed pT3N0 mod diff adenoCA.



Per *Willett et al 1999*- 10yr LC was **95%** for favorable T3N0 patients with **surgery alone**

- G1-2, no LVSI, <2mm mesorectal invasion
- Upper rectum (>10cm)

Anal Cancer

Type in your twitter handle here

Anal Cancer Staging- AJCC 8th edition

- T1: </=2cm
- T2: >2-5cm
- T3: >5cm
- T4: invades vagina, urethra, bladder

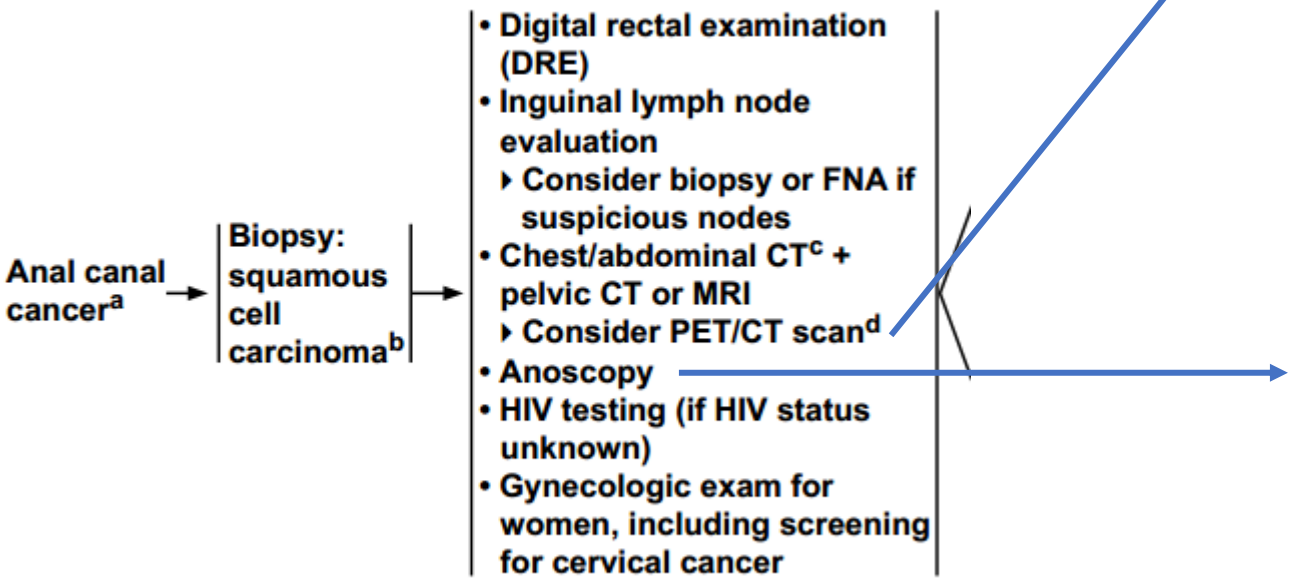
- N1a- inguinal, mesorectal, II
- N1b- external iliac nodes
- N1c- N1a + N1b

- I: T1N0
- IIA: T2N0
- IIB: T3N0
- IIIA: T1-2 N1
- IIIB: T4N0
- IIIC: T3-4N1
- IV: M1

*Skin cancer staging applied to perianal tumors, 5cm radius around the anus

Anal Cancer Work-up

WORK UP- Per NCCN 1.2021



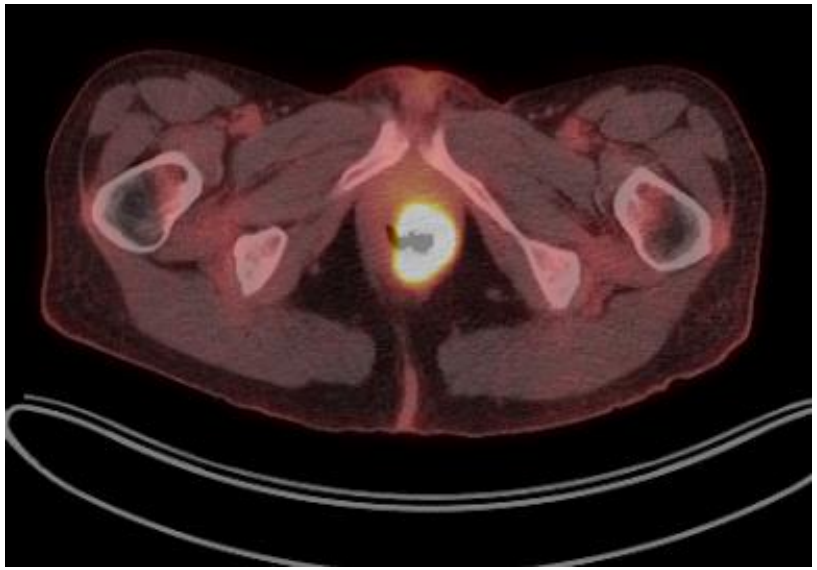
PET is more sensitive for primary anal tumor but also for occult nodes (can result in upstaging and RT plan modification.

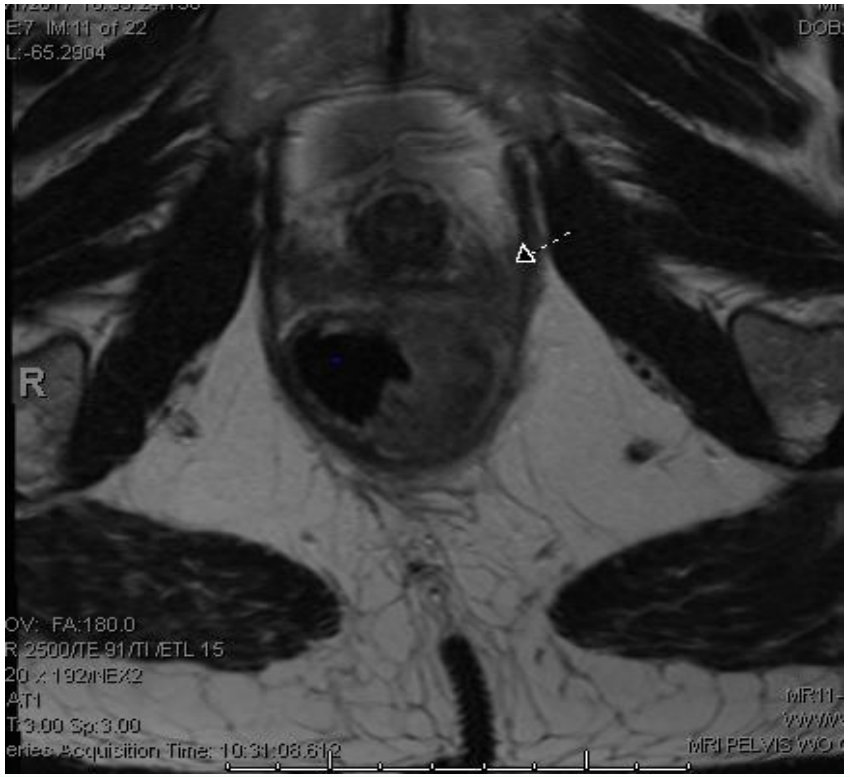
- Sensitivity ~60%, specificity ~90%
- Changed nodal stage of 28%, ½ upstage, ½ downstage

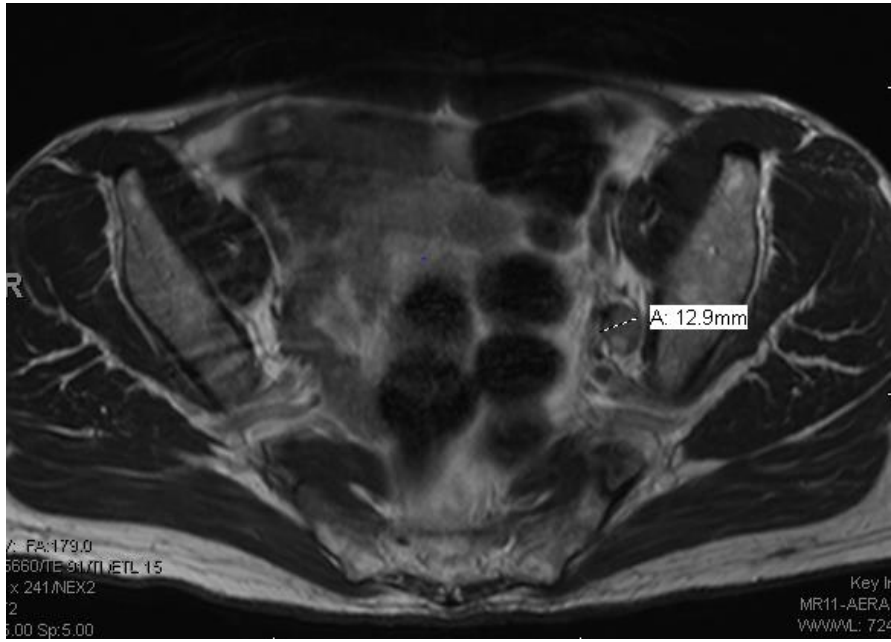
Important to have the colorectal surgeon or other doc who will follow the patient do this baseline scope for comparison.

Locally Advanced Anal Cancer

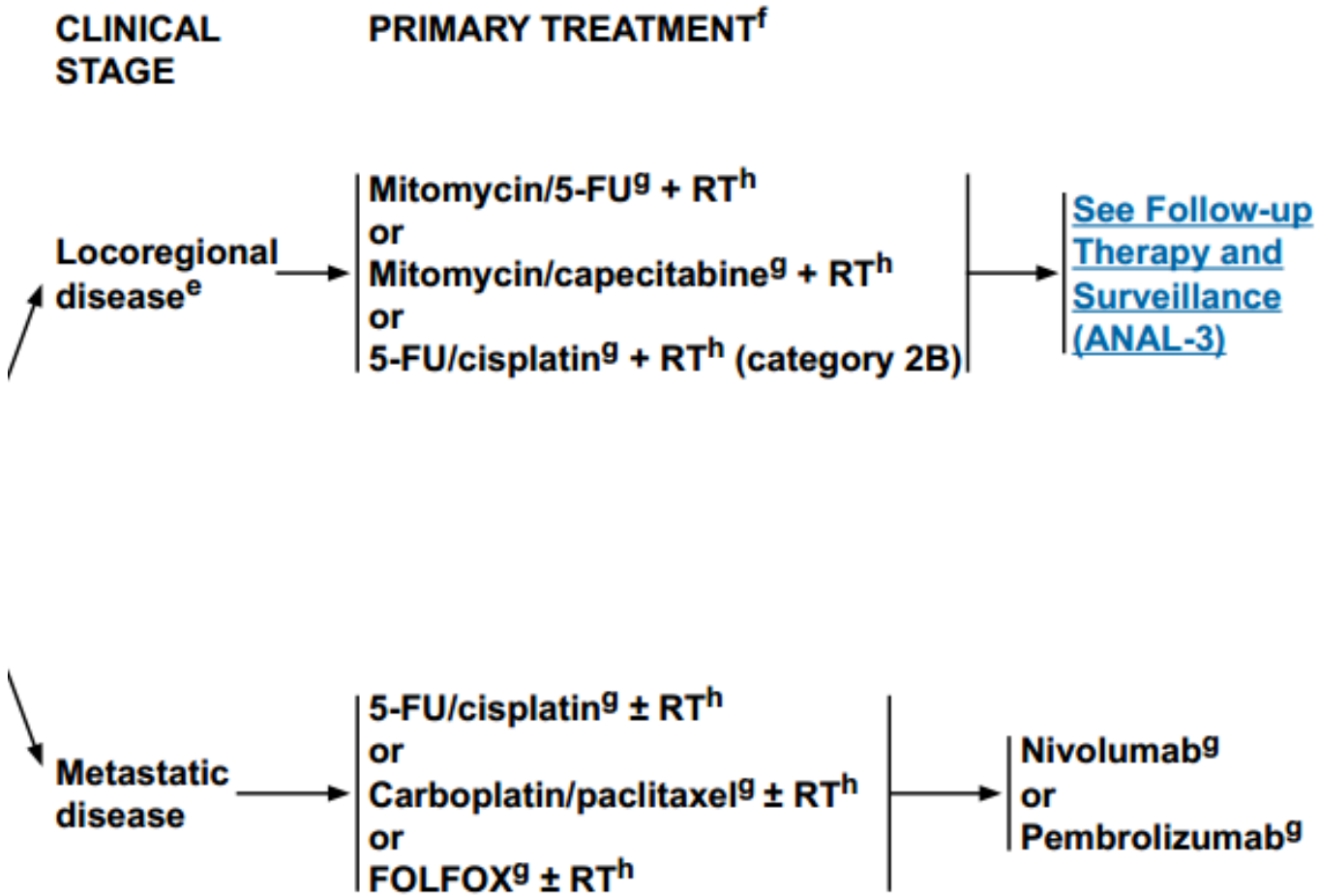
- A 55 year-old woman presents with a 5.5cm tumor in the L anterior anal canal. Biopsy shows poorly differentiated squamous cell carcinoma.







Anal Cancer- Treatment paradigm



Dose to the primary tumor is 50-59.4Gy in 1.8-2Gy per fraction
Dose to pelvis is 42-47Gy in 1.5-1.7Gy per fraction

*Preferred modality is **IMRT/VMAT** given improved G3+ tox on RTOG 0529 compared with historic 9811 control.*

Treatment Planning: RTOG Standard

Dose/Frac:

- T1N0- weren't included:
- T2N0- **50.4Gy** in 28 fractions (1.8Gy) w/ 42Gy in 28 fractions to PTV2 (1.5Gy)
- T3/T4 or N+- **54Gy** in 30 fractions (1.8Gy) w/ 45Gy in 30 fractions to PTV2 (1.5Gy).
- Nodes based on size: <3cm 50.4 (1.68Gy) and >3cm 54 (1.8Gy)

- Volumes:
  - CTVp = GTV + 2.5cm including anal canal, presacral space and mesorectum at involved levels. Keep w/in 3mm of levator ani
  - CTVel= 7mm on EI and II vessels carved out of muscle, bone & bowel, covering inguinals mesorectum and presacral space.

Concurrent Chemotherapy- RTOG Standard

- **SOC:**
  - mitomycin C 10mg/m2 IV bolus days 1 and 29
  - 5FU continuous infusion 1000mg/m2m/d x 5 days on weeks 1 and 4

Chemoradiation is better than RT alone

Trial	Eligible Pts	Primary Endpoint	Arms	RT Details	LC	CFS	DFS	OS
ACT I (1987-1994)	577 pts T2-T4M0	LC	1.) RT 2.) CRT w/ 5FU/MMC	45Gy in 20-25fxns → reassess @ 6 weeks, if >50% response, boost w/ 15Gy EBRT or 25Gy Ir 192. OTW → APR	12yr 41% 66% (SS)	12yr 20% 30% (SS)	12yr 18% 30% (SS)	12yr 28% 33% (trend)
EORTC 22861 (1987-1994)	103 pts T3-T4, N1-N3	LC	1.) RT 2.) CRT w/ 5FU/MMC	45Gy in 25fxns → reassess @ 6 weeks, if CR, boost 15Gy, if PR, boost 20Gy, if no response → APR	5yr 50% 68% (SS)	5yr 40% 68% (SS)	5yr 42% 58% (NS)	5yr 54% 58% (NS)

Why MMC/5FU?

Trial	Eligible Pts	Primary Endpoint	Arms	RT Details	LC	CFS	DFS	OS
RTOG 8704 (1988-1991)	291 pts M0	LC (6wk bx)	1.) CRT 5FU/MMC 2.) CRT 5FU alone	45Gy in 20-25fxns → bx @ 4-6wks, if +, boost 9Gy w/ 5FU/cis. If -, observe	6wk 92% 86% (NS)	4yr 71% 59% (SS)	4yr 73% 51% (SS)	4yr 75% 70% (NS)
RTOG 9811 (1998-2005)	649 pts T2-T4, M0	DFS	1.) CRT 5FU/MMC 2.) cis/5FU x 2 → CRT cis/5FU	45Gy in 25fxns → if T3/T4, N+ or residual T2 disease → boost 10-14Gy	5yr 80% 74% (NS)	5yr 72% 65% (NS)	5yr 68% 58% (SS)	5yr 78% 71% (SS)
ACT II (2001-2008)	940 pts M0	CR at 26wks DFS	1.) CRT 5FU/MMC 2.) CRT cis/5FU 3.) CRT 5FU/MMC → maint cis/5FU 4.) CRT cis/5FU → maint cis/5FU	50.4Gy in 28fxns	26wk MMC: 91% Cis: 90% (NS)	3yr 75% 72% 73% 75% (NS)	3yr 73% 72% 73% 74% (NS)	3yr 86% 84% 82% 83% (NS)

Anal Cancer- Prognosis

Per the Gunderson analysis of RTOG 9811 (IJROBP 2013)

- T2N0- 5yr OS 82%, LRF 17%
- T3N0- 5yr OS 74%, LRF 18%
- T2N+ 5yr OS 70%, LRF 26%
- **T4N0 5yr OS 57%, LRF 40%**
- **T3N+ 5yr OS 57%, LRF 44%**
- **T4N+ 5yr OS 42%, LRF 60%**

Local control for early stage disease is excellent

Local failure for T3/T4 N+ disease is unacceptably high.

Is there a role of treatment escalation?

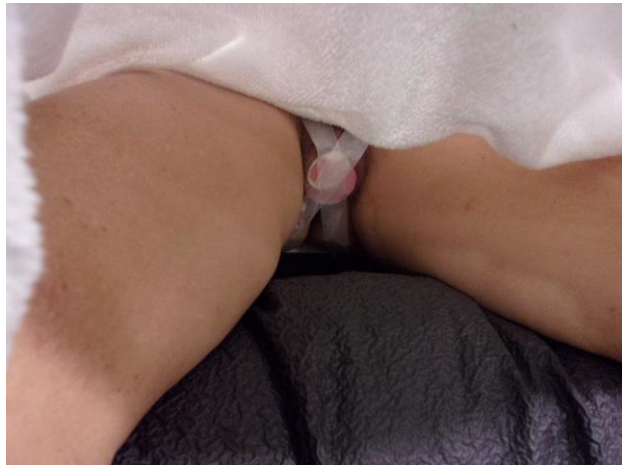
Trial	Eligible Pts	Primary Endpt	Arms	RT Details	LC	CFS	DFS	OS
ACCORD 03 1999-2005	307 pts T >4cm or N+, M0	CFS	1.) CRT cis/5FU 15Gy boost 2.) CRT cis/5FU 20-25Gy boost 3.) cis/5FU → CRT cis/5FU 15Gy boost 4.) cis/5FU → CRT cis/5FU + 20-25Gy boost	45Gy in 20-25fxns → reassess @ 3rd week, if any response, boost w/ 15Gy vs 20-25Gy based on randomization. OTW → APR	5yr 84% 78% 72% 88% (NS)	5yr 77% 73% 70% 82% (NS)	5yr 67% 62% 64% 78% (NS)	With neoadj: 75% w/o 71% (NS)

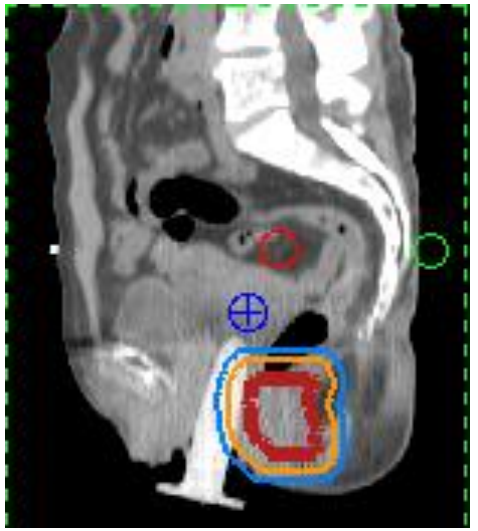
Simulation- Positioning

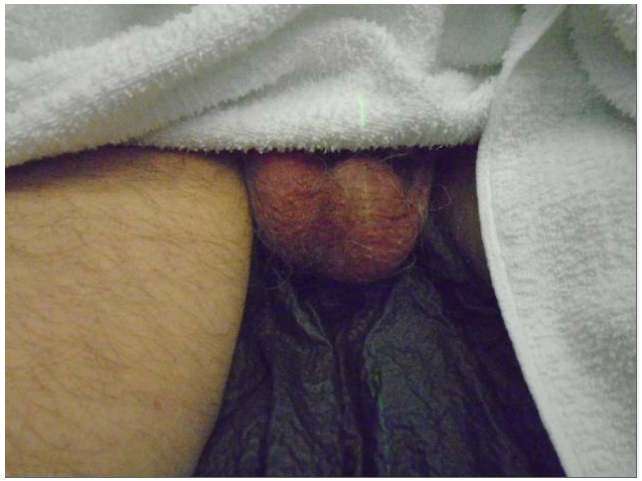
- Supine, frog leg, full bladder.
  BB @ the anal verge

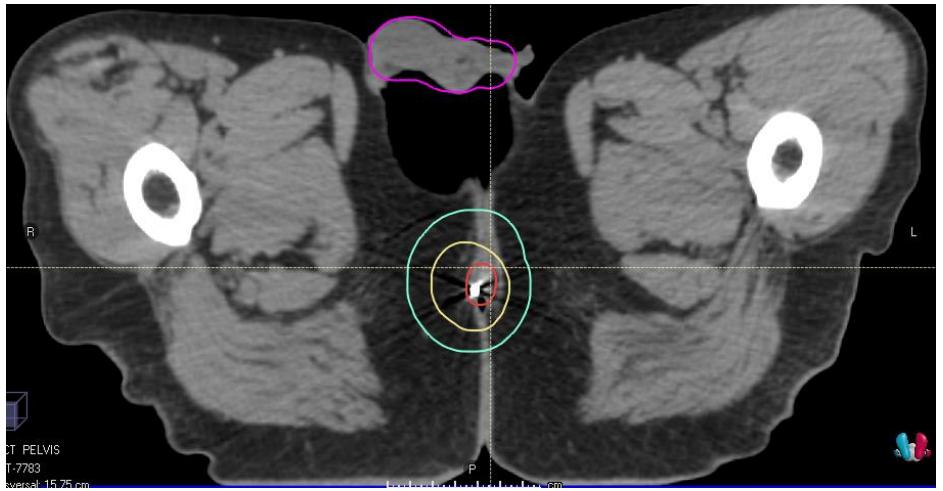
- Women – *vaginal dilator*

- Men – scrotal shelf

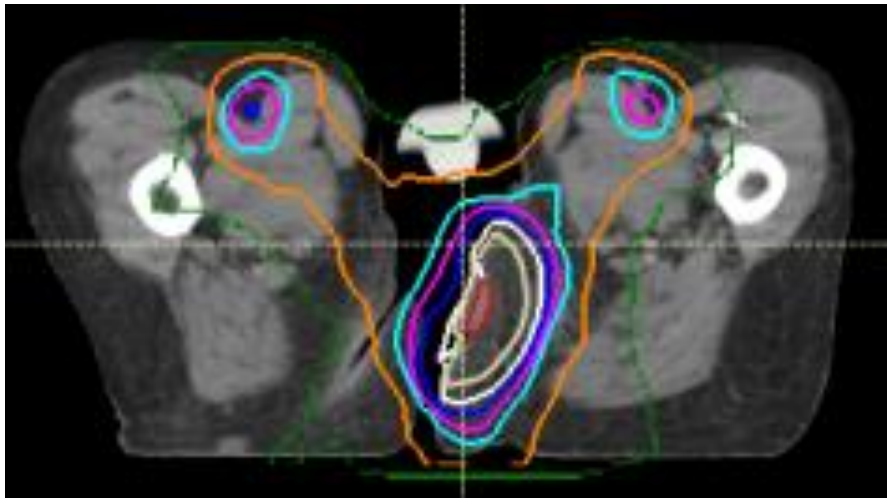


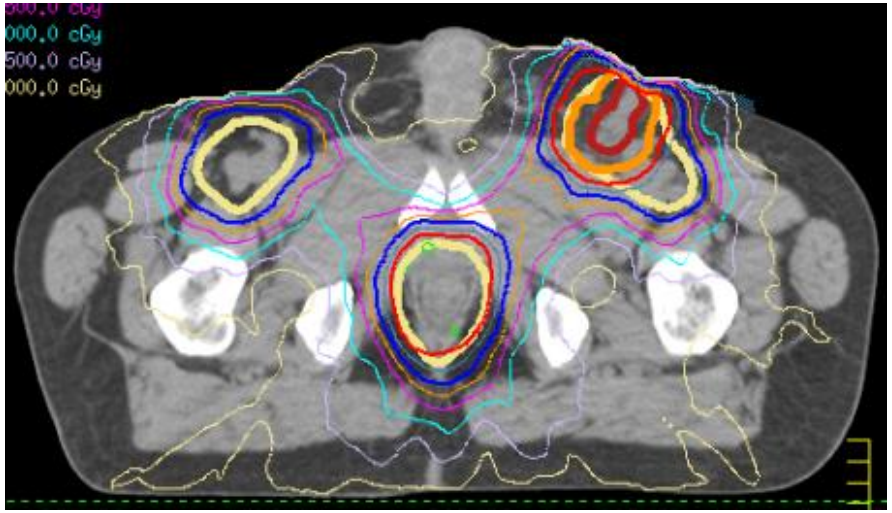


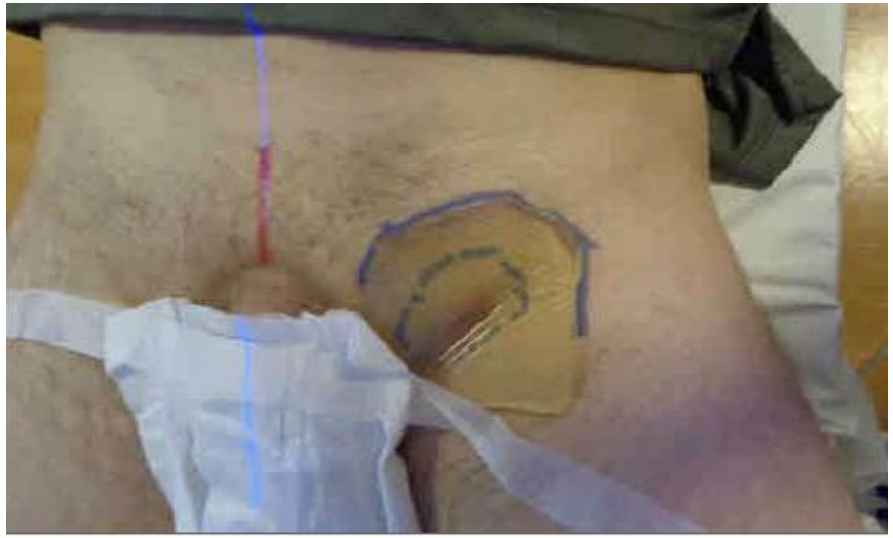




Use of Bolus?



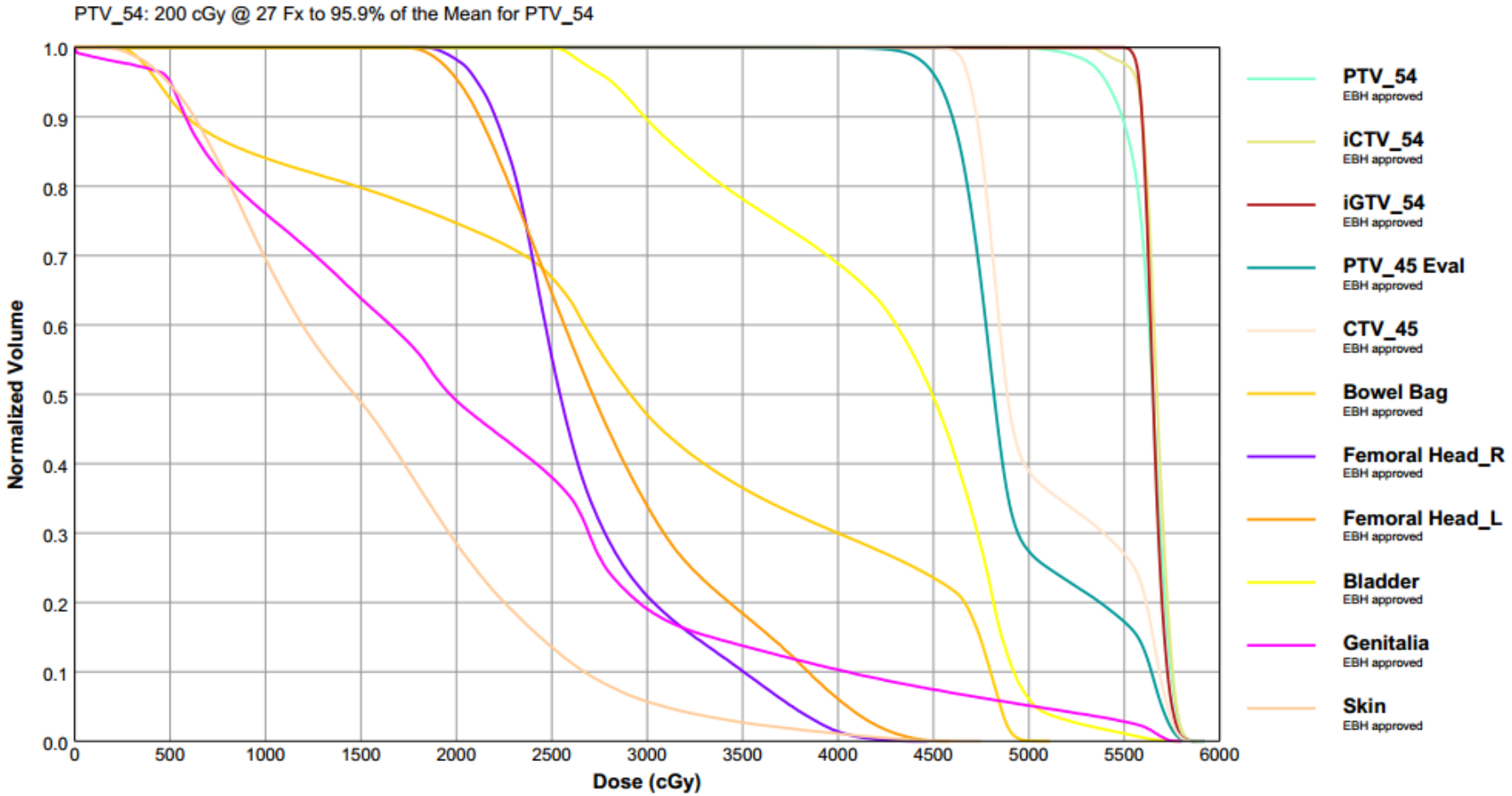




Bolus:

- Not necessary unless there is skin involvement or gross node very close to the skin.
  - Patients often auto-bolus in perianal area.
- False structures can be used during planning to increase PTV coverage inferiorly

Anal Cancer- Dose Constraints

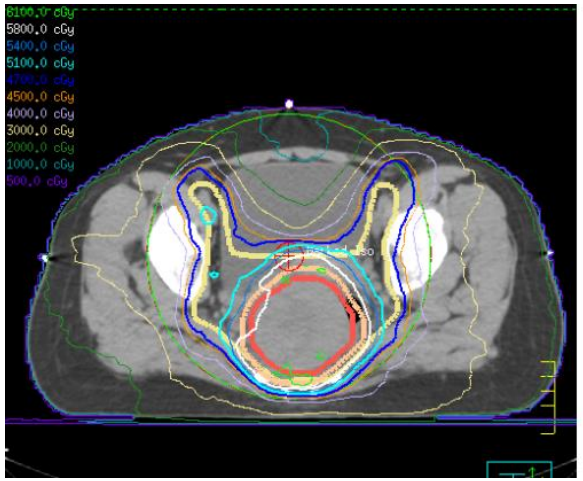


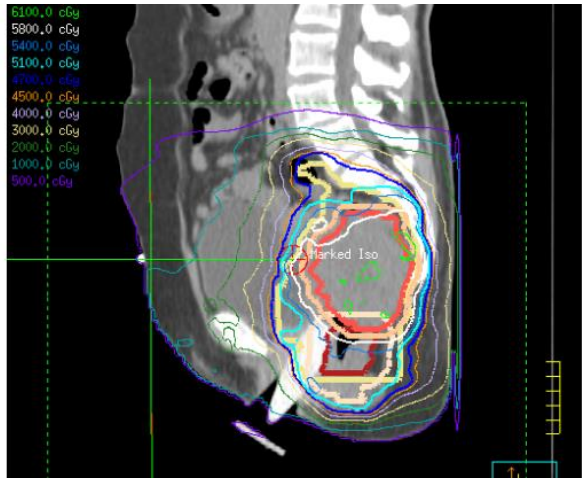
Small bowel- Max <54Gy,
V35<150ccs, V30<200ccs
Bladder- V50<30%
Fem Heads- V45<20%
Genitalia- V30<20%, v20<67%

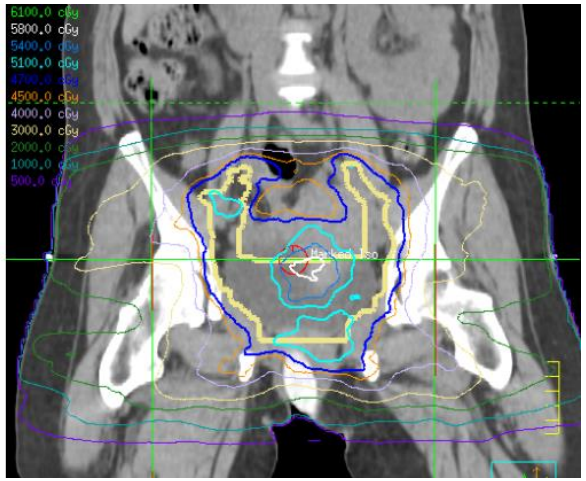
Bowel bag- V45<195ccs, Max <54Gy
(Kavanaugh et al IJROBP 2010)

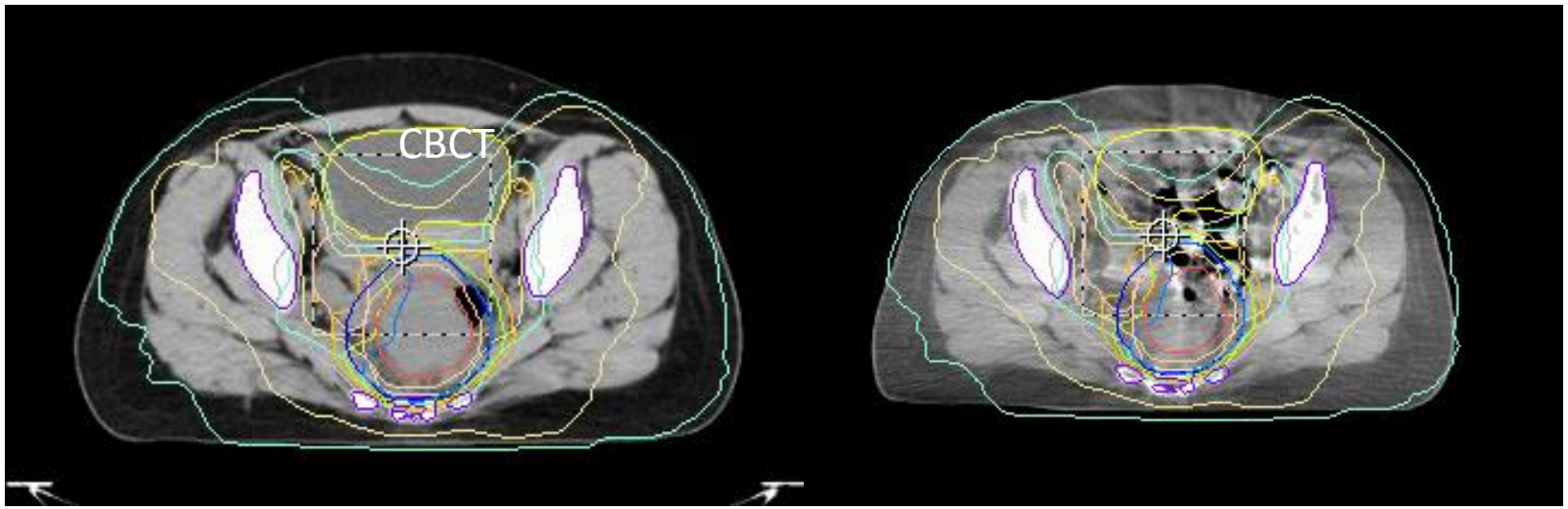
Daily Image Guidance

- I prefer CBCT if treating to a dose =/>54Gy, particularly bowel is nearby.







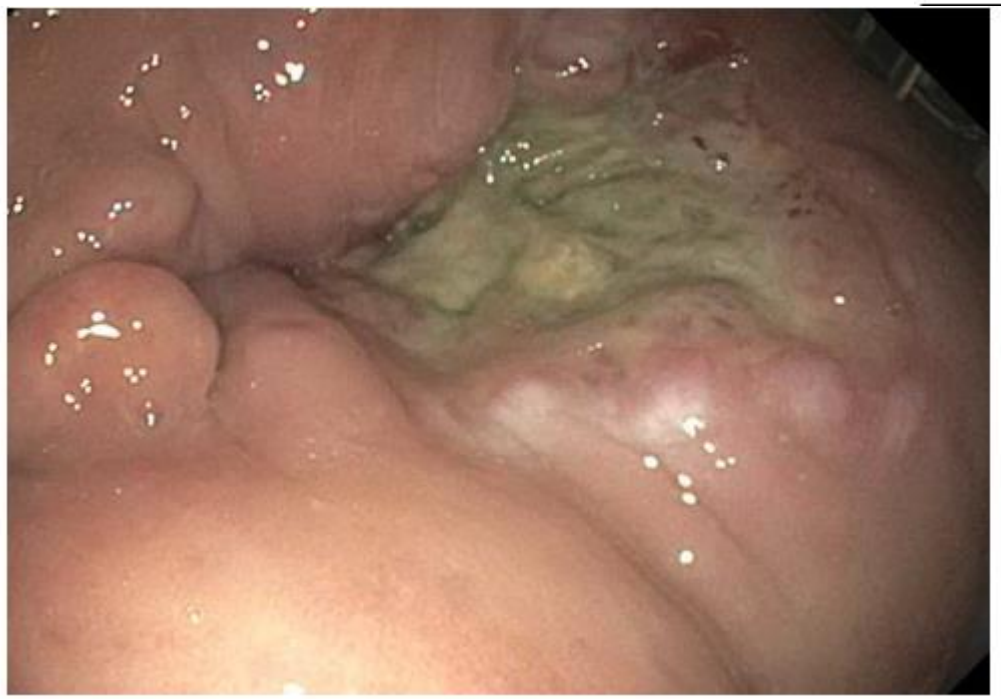


Anal Cancer- Follow up

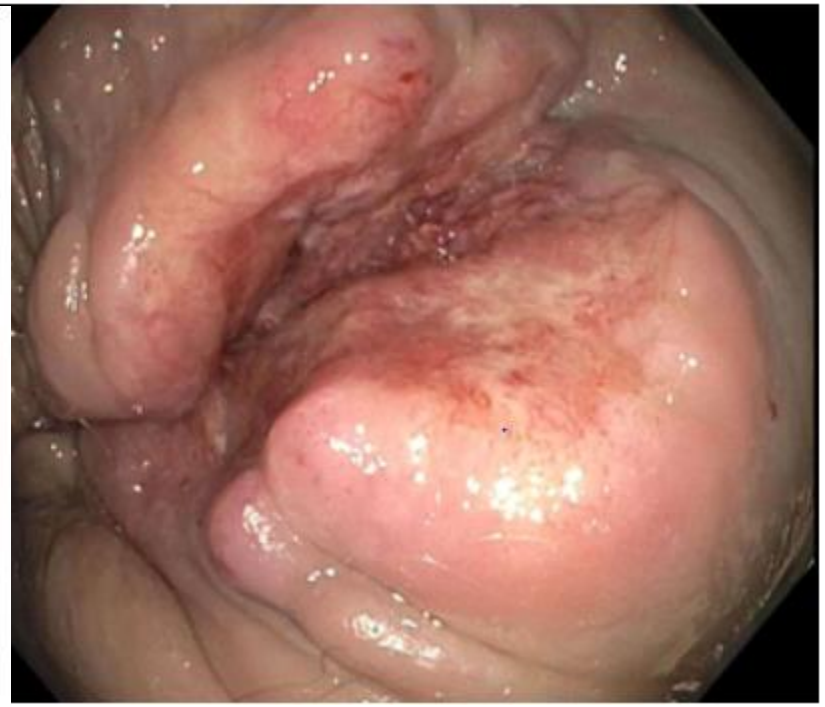
- Exam/DRE Q 6 wks until CR (or ~6mo)
  - NO BIOPSY unless enlarging mass or ulcerated mucosa
    - Can cause ulcer or fistula
- H&P q3-6 mo for 5y
  - DRE
  - Anoscopy q3-6 mon until CR then yearly
  - Inguinal node palpation
  - CT C/A/P annually x3-5 yrs

Follow up

The patient returns for follow up at 12 weeks. She has persistent pain with BMs and some occasional bleeding



Scope shows this



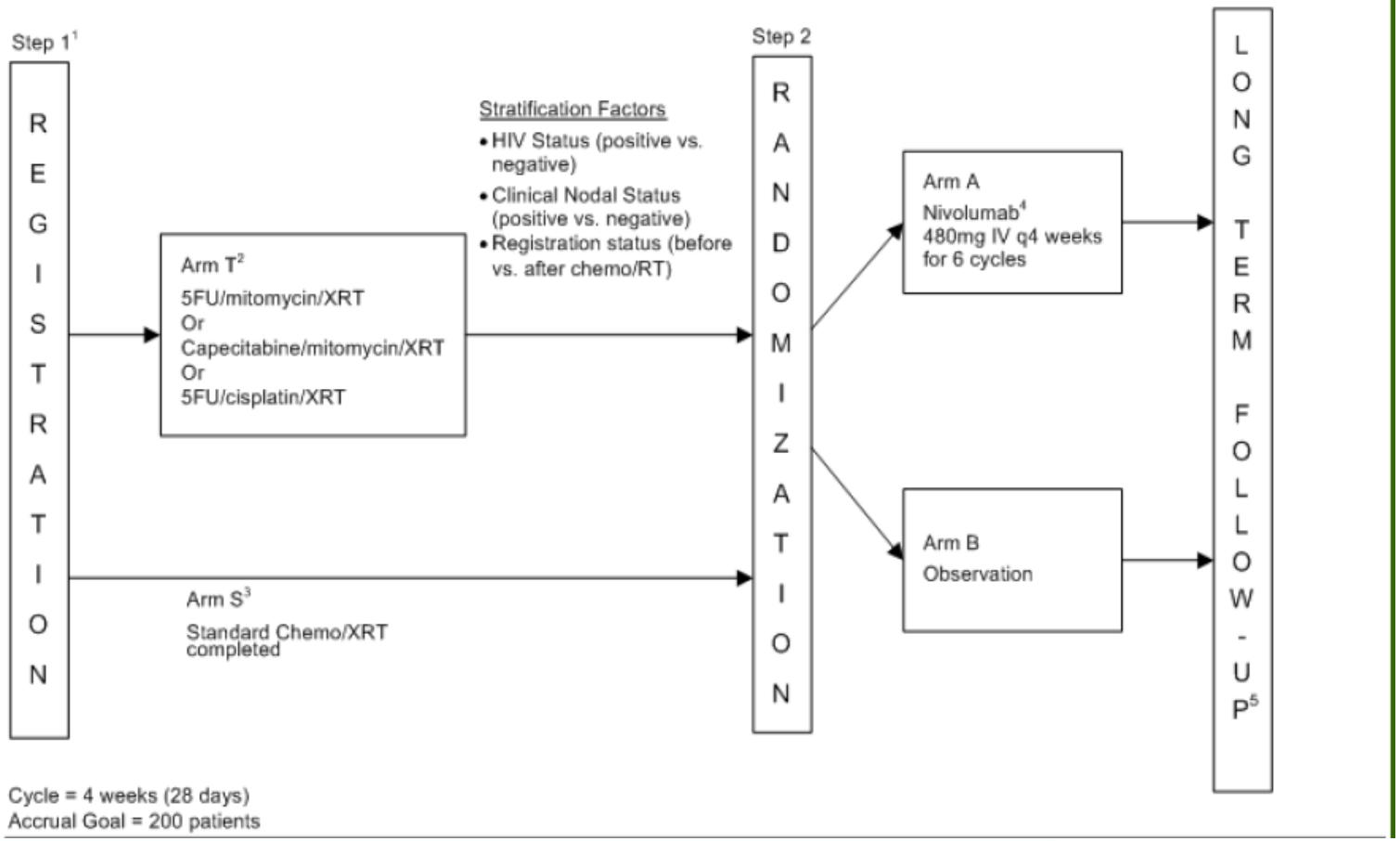
Compared to this pretreatment

Ongoing Trial- EA 2165

EA2165 Available Through ECOG-ACRIN Cancer Research Group

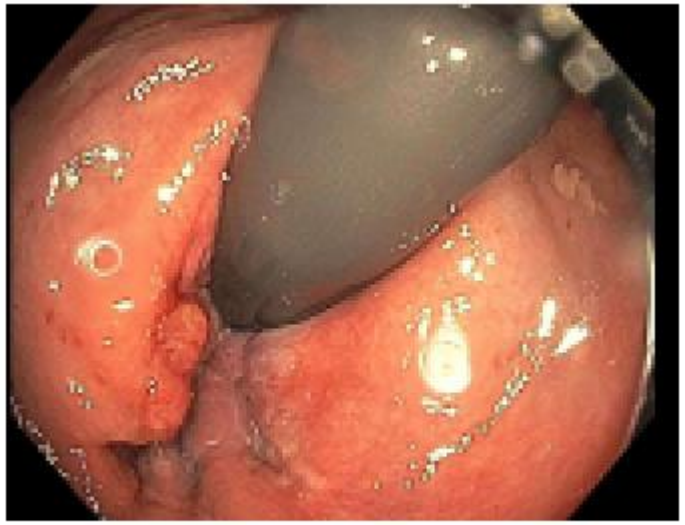
A Randomized Phase II Study of Nivolumab After Combined Modality Therapy (CMT) in High Risk Anal Cancer

Schema

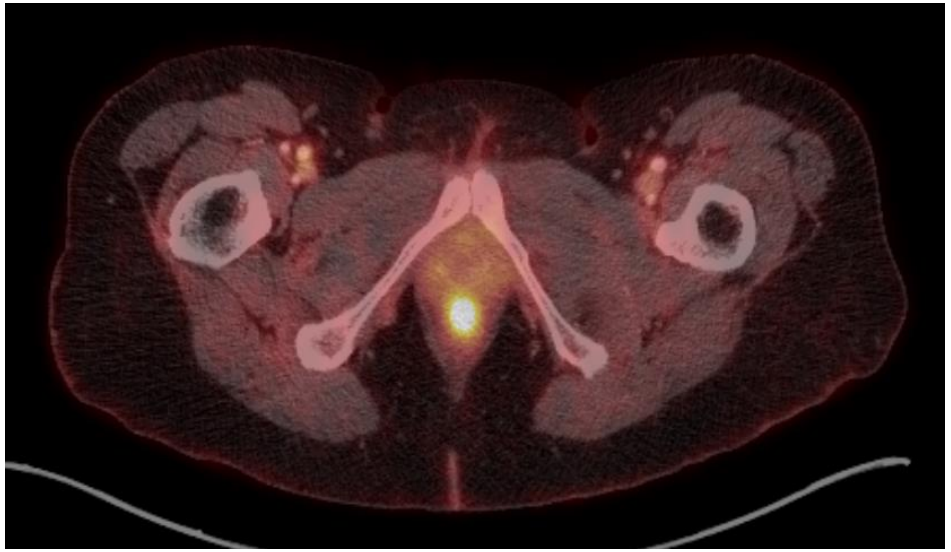


Early Anal Cancer Case-

- A 67 year-old woman presents with rectal bleeding. EUA shows a 8mm mass. Biopsy shows poorly differentiated squamous cell carcinoma. PET shows no regional or distant disease.



3 : Mass



Treatment options for T1N0 Anal SCCa

- T1N0 were not included in RTOG 9811 or 0529 (though were included in UK ACT II).

- NCCN recommends WLE for *perianal* T1N0 (select T2N0) assuming they are not poorly differentiated and margins >1cm can be achieved.

- Superficially invasive SCCa can be removed with excision:
  - </=3mm basement membrane invasion & max horizontal spread </=7m

PLATO trial- ACTS 3, 4 & 5

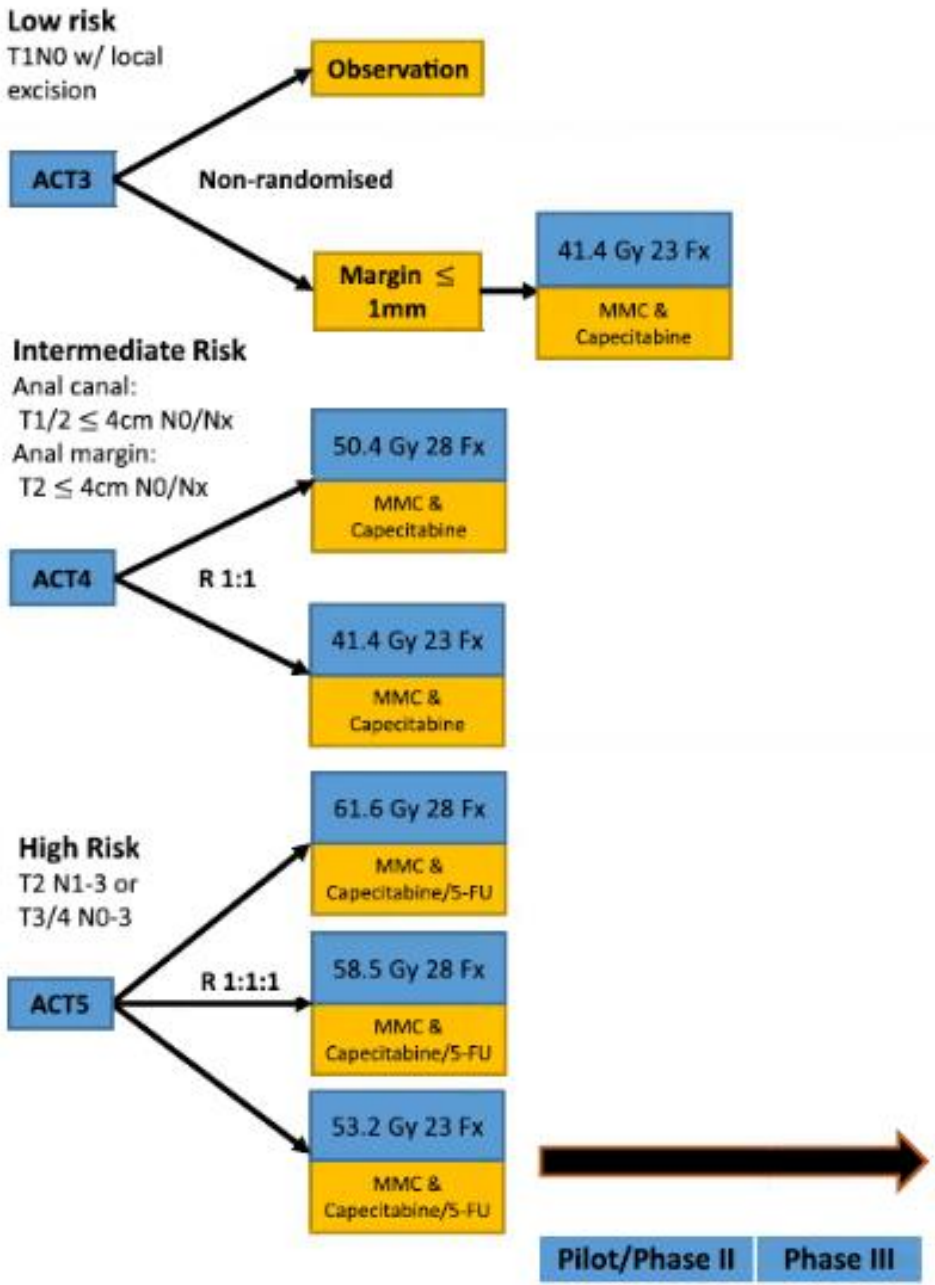
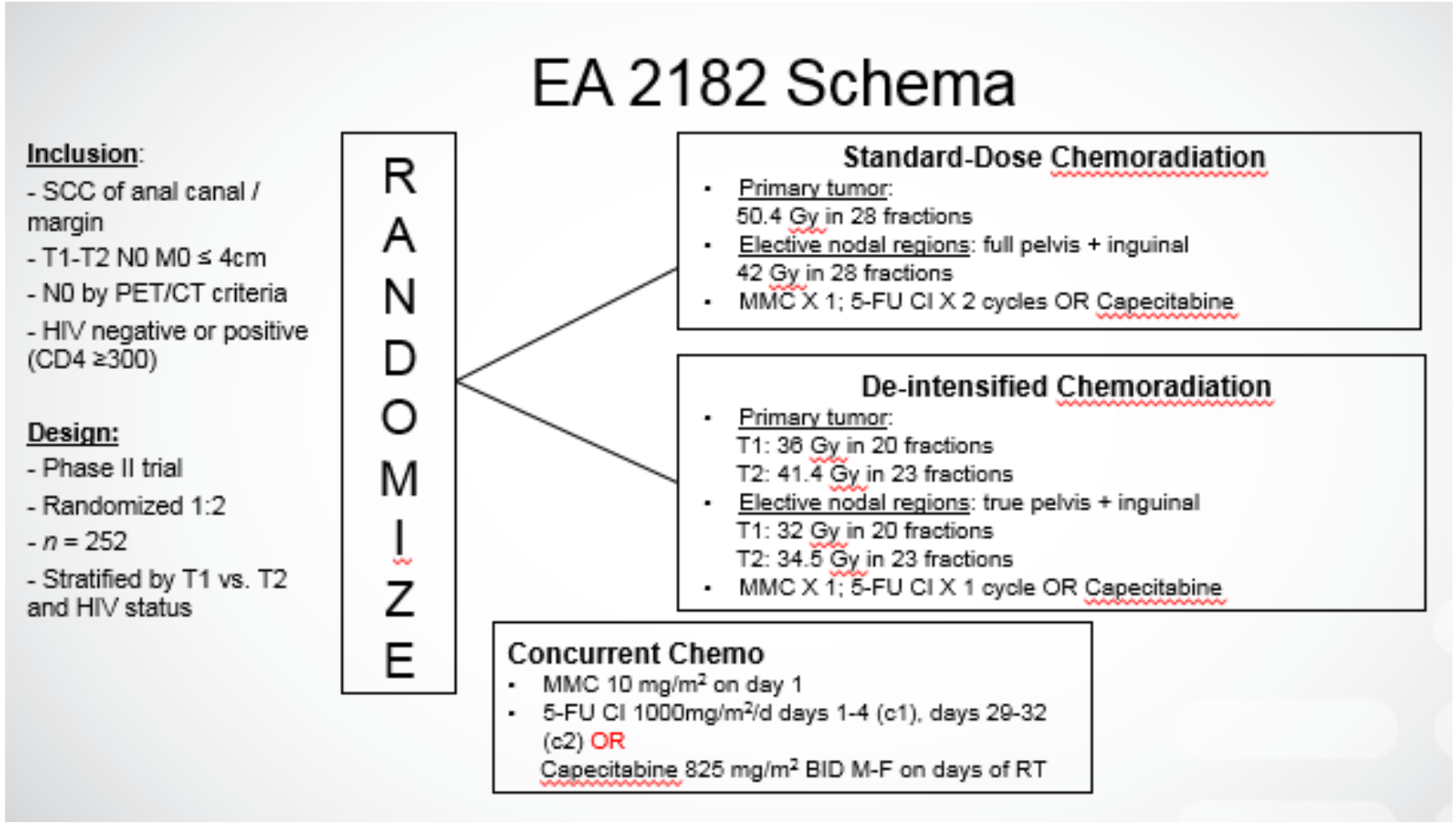


Fig. 1. Overview of the currently ongoing PLATO trial. ACT3 is a non-randomized phase II trial for patients with T1N0 tumors after local resection. Depending on resection margins patients either receive no adjuvant therapy (margins >1 mm) or receive CRT with 41.4 Gy, MMC and capecitabine. ACT4 is a randomized phase II trial in patients with T1/2 (up to 4 cm) N0 tumors. Patients in the standard arm receive CRT with 50.4 Gy to tumor and 40 Gy to the elective nodal region. In the experimental arm, radiotherapy is given with 41.4 Gy and 34.5 Gy to the different PTVs. ACT5 recruits patients with T2N1-3 or T3/4Nany. There are three arms in this trial, the standard arm consists of CRT up to 53.2 Gy, while patients in both experimental arms are treated to a dose of either 58.8 or 61.6 Gy. For the pilot and phase II part of the study patients are randomized 1:1:1, while for the phase III trial randomization is planned 1:1 for the standard arm versus the most acceptable of the experimental arms in order to see if dose escalation can lead to better outcomes (black arrow).

ChemoRadiation for Early-stage Anal Squamous Cell Cancer (DECREASE)



Conclusion/Summary

1. TNT is the standard of care for high-risk LARC
   - *Best TNT regimen still up for debate*

2. SCRT is a SOC option as long as 6-8wk+ interval to surgery
   - *Potential exception is the patient strongly desiring NOM*

3. Omission of RT for low-risk LARC may be acceptable for low-risk high rectal T3N0 (*or more pending PROSPECT results*).

4. Chemoradiation is the SOC for SCCA
   - *Treatment escalation w/ dose & w/ nivo under investigation for T3/T4, N+*
   - *Treatment de-escalation w/ dose & volume under investigation for T1/T2 N0*