

Radiation Therapy for Rectal Cancer: When & How Long?



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No disclosures related to this talk





Outline and Objectives

1. Pelvic Radiation Toxicity
2. SCRT vs LCRT
3. MRI defined risk stratification
4. RT technique, volume and the future



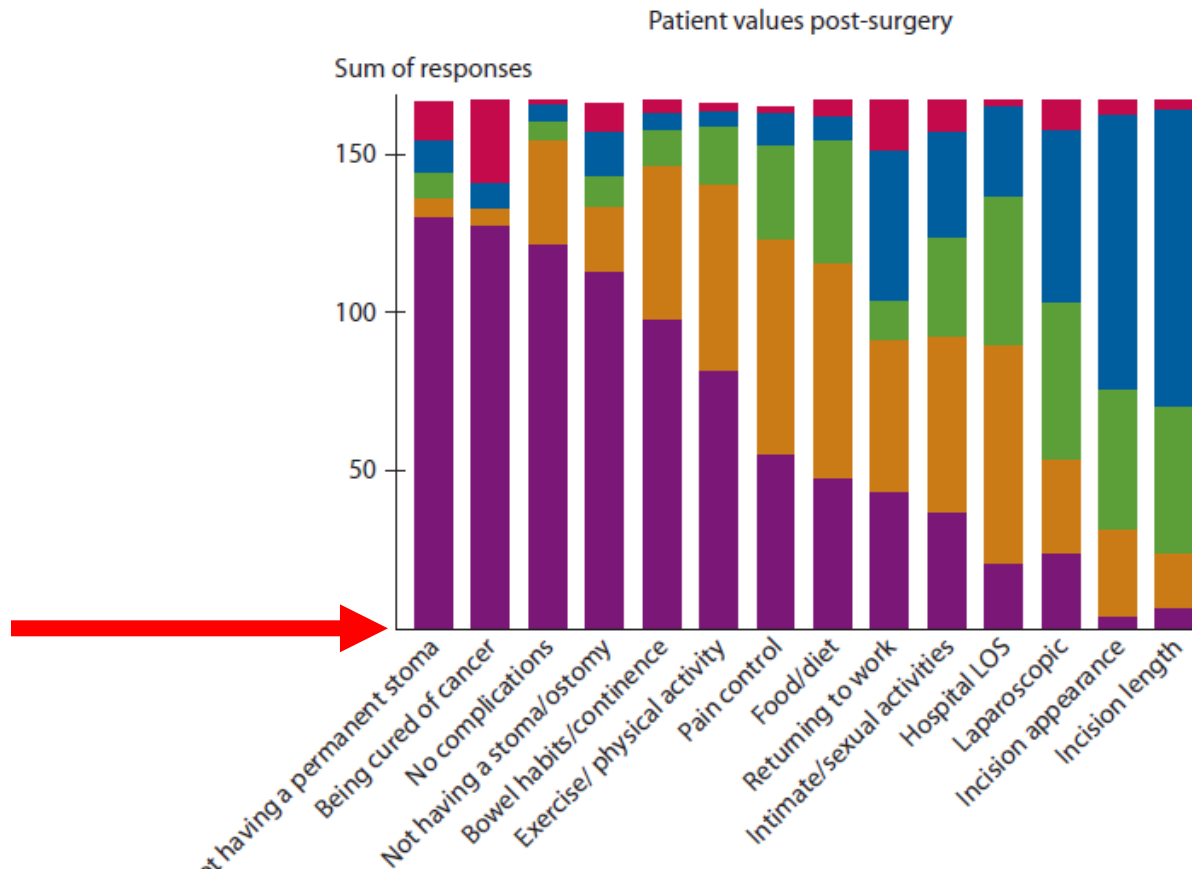
The Role of Modern CRC Radiotherapy?

- *RT can improve local control*
 - But for who? Who doesn't need it?
- *What do our patients prefer?*
 - What are their goals of care?
- *Who is a candidate for NOM and will they be compliant?*
- *When should we consider SCRT?*



Patient Preferences & Surgical Shared Decision Making

- Surgery associated with negative function and quality of life effects
 - Low anterior resection syndrome, rectal urgency predominates
 - Risk of overtreatment of some patients



Cure as important as ostomy/continence?

1. No Permanent Stoma
2. Cancer Cure
3. No Complications
4. No stoma/ostomy
5. Bowel habits and continence



Patient Preferences & Pelvic RT

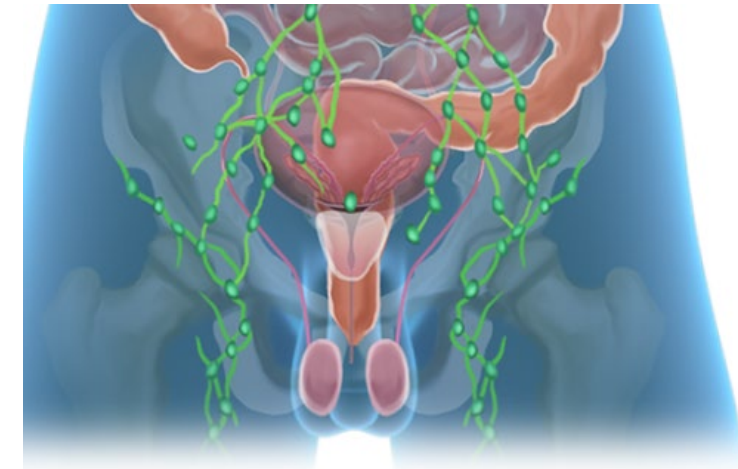
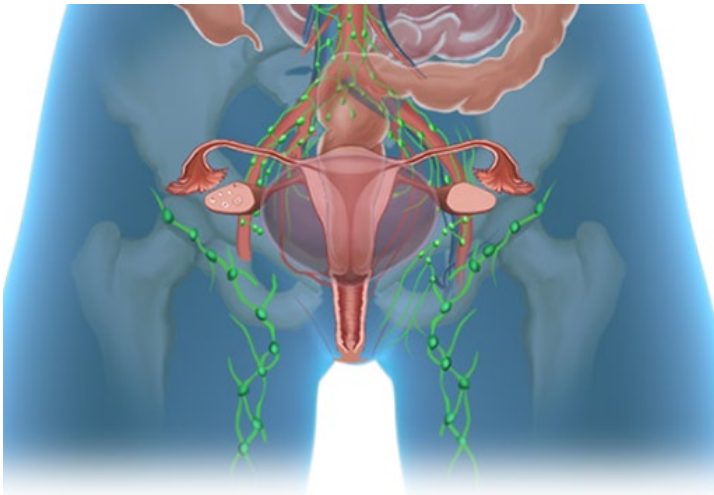
Pelvic Radiation Therapy associated with **negative** bowel/sexual/bladder side effects

Age of the patient? What is their life situation and their goals?

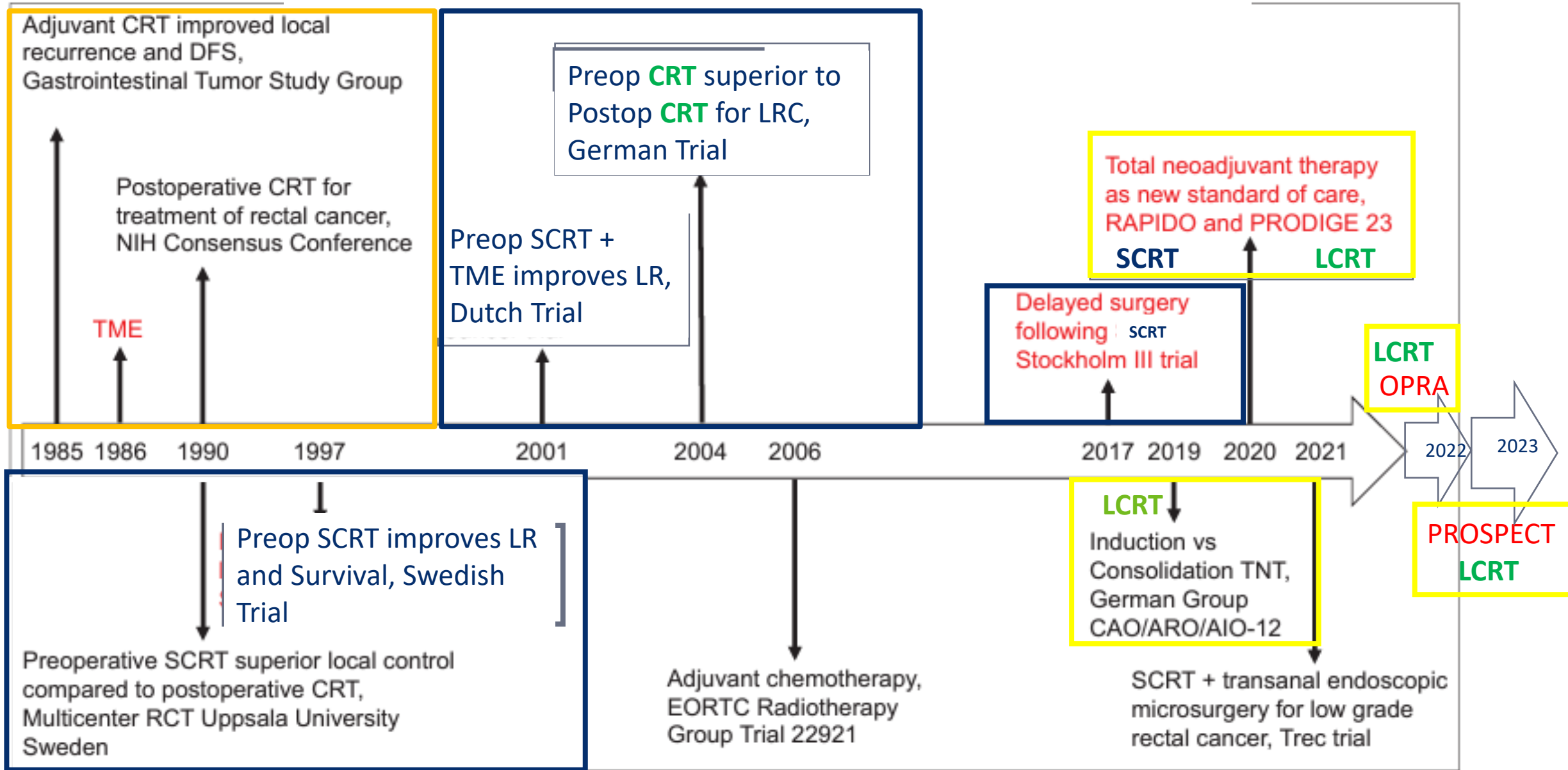
Fertility plans?

Menopausal status?

Sexual health at
baseline



Treatment Landscape Evolution to TNT: From Postop to Preop to TNT





Pre-TNT lessons: SCRT vs LCRT

Preoperative SCRT surgery 1-week later vs LCRT → surgery 4-6 weeks no significant differences in:

Rates of LRR, DFS, OSbut 25-30% risk of distant mets by year 5

Polish Trial long term results, Bujko K, Br J Surg 2006; 93: 1215-1223
TROG 01.04 trial: Ngan S, J Clin Oncol 2012; 30: 3827-3833

SCRT with delayed surgery is associated with better pCR and less complications than SCRT immediate surgery

Stockholm III: Erlandsson J, Lancet Oncol 2017; 18: 336-46 and
Erlandsson J, Radiother Oncol 2019; 135: 178-86

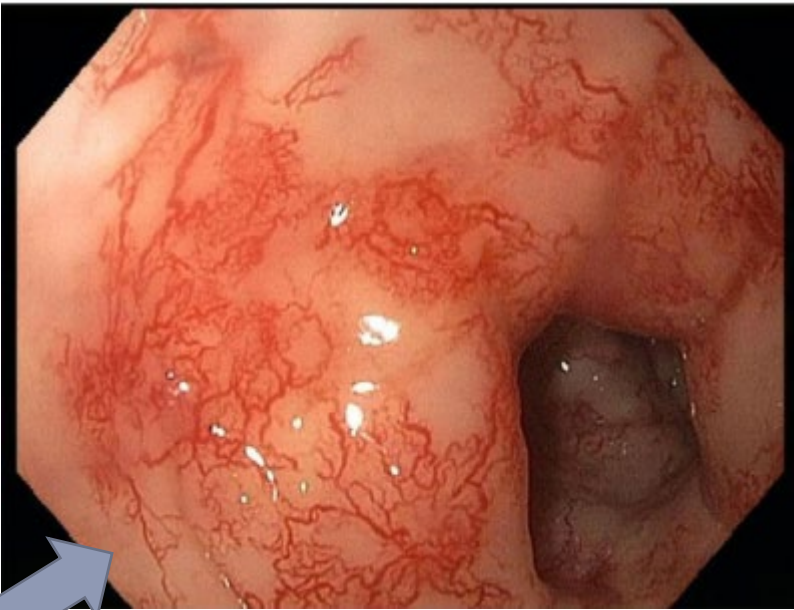
LCRT better for distal tumors?

No, meta-analysis does not support LCRT with better local control for distal tumors < 5cm from anus

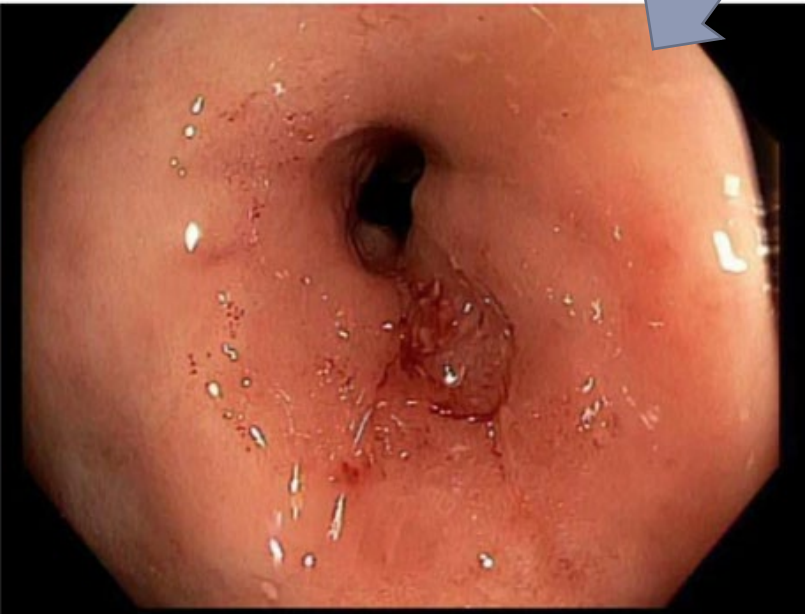
Socha J, Int J Radiat Oncol Biol Phys 2020; 108(5): 1257-64

Preoperative SCRT vs LCRT has similar HRQOL, sexual and anorectal function, late toxicity, & surg complications

Pietrak L, Radiother Oncol 2007; 84: 217-225



Radiation Proctitis & Stricture



Genitourinary		
	Fistula	Surgical evaluation
	Cystitis	Cystoscopy for diagnosis; to start, hydration, transfusion, and bladder irrigation. If severe, consider embolization, endoscopic bladder procedures, or hyperbaric oxygen.
	Urethral stricture	Dilation/stent
	Ureteral stricture	Dilation/stent
	Bladder dysfunction	Antispasmodics
Pelvic Arteries		
	Peripheral vascular disease	Advise smoking cessation, maintain lipids in normal range, and educate about signs of peripheral vascular disease. Treat aggressively if hypertension or diabetes.
Pelvic Bone		
	Insufficiency fracture	First: osteoporosis prevention, calcium, vitamin D, weight-bearing exercise, and bisphosphonates. If fracture, consider sacroplasty.
	Necrosis	Surgical evaluation for fixation
Gastrointestinal		
	Chronic diarrhea	Loperamide or diphenoxylate/atropine, modify diet to avoid raw vegetables, and add stool-bulking agents
	Fecal incontinence	Pelvic rehabilitation consult for Kegel exercises; consider sacral stimulator if pelvic rehabilitation fails
	Malabsorption	Support nutrition, may need low-fat diet or cholestyramine for bile salt deficiency

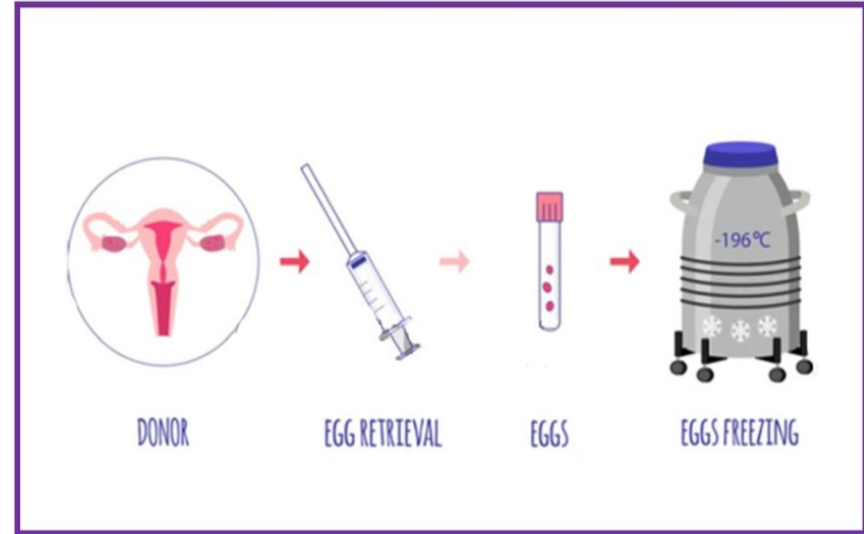
Strategies to Minimize Late Effects From Pelvic Radiotherapy

[Ammoren Dohm](#), MD¹; [Julian Sanchez](#), MD¹; [Eden Stotsky-Himelfarb](#), BSN, RN, ONN-CG²; [Field F. Willingham](#), MD, MPH, FASGE³; and [Sarah Hoffe](#), MD¹ ✉ ASCO Educational Book 2021

Sexual: Female	
Vaginal stenosis	Vaginal dilator insertion three times per week starting 1-month postradiotherapy; some data to suggest insertion daily during radiotherapy
Ovarian failure/infertility	Fertility consult for ovarian preservation, possible ovarian transposition, or oophorexy
Uterine dysfunction	Not possible to carry fetus to term
Vaginal dryness	Water-based lubricant early when healing, then can use oil- or silicone-based lubricant; hormone replacement/intravaginal estrogen, if appropriate
Premature menopause	Hormone replacement/intravaginal estrogen, if appropriate
Dyspareunia	Vaginal dilator, lubricant, or hormone replacement therapy/intravaginal estrogen, if appropriate
Sexual dissatisfaction	Referral to psychologist with expertise in postradiotherapy sexual dysfunction

Female Sexual Health

Egg Cryopreservation



Vaginal Stenosis

Use of vaginal dilators for at least 1 year post rx:

82% of women achieved pre-treatment size

Law E, Radiother Oncol 2015; 116(1): 149-55

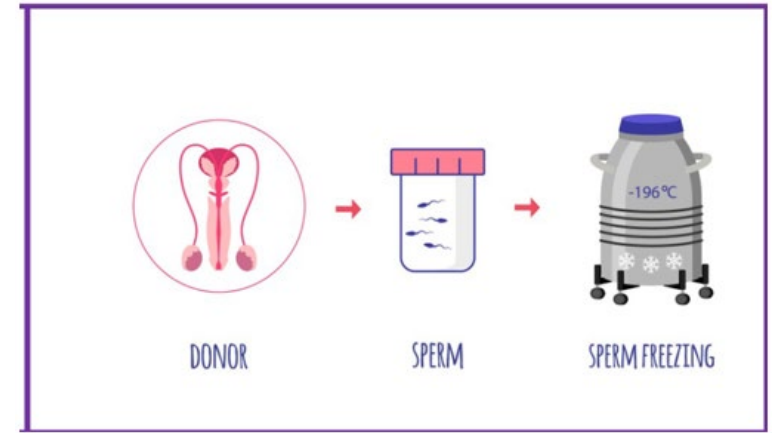


Male Sexual Health

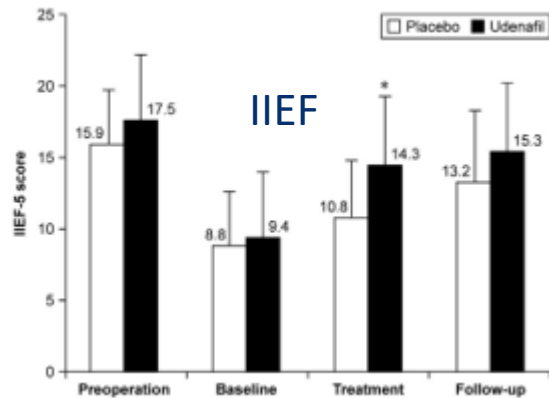
Sexual: Male	
Erectile dysfunction	Prevent, if possible, with vessel-sparing radiotherapy; treat with phosphodiesterase-5 inhibitor. If unresponsive, consider penile implant, vacuum erection device, or intracavernosal injections.
Low testosterone	Consider hormone replacement, if appropriate.
Infertility	Fertility consult for sperm banking
Ejaculatory issues	Prevent as much as possible during radiotherapy planning with avoidance of dose to vessels, penile bulb/bodies, and neurovascular bundles.
Sexual dissatisfaction	Referral to psychologist with expertise in postradiotherapy sexual dysfunction

Dohm, ASCO Ed Book 2021

Sperm Cryopreservation

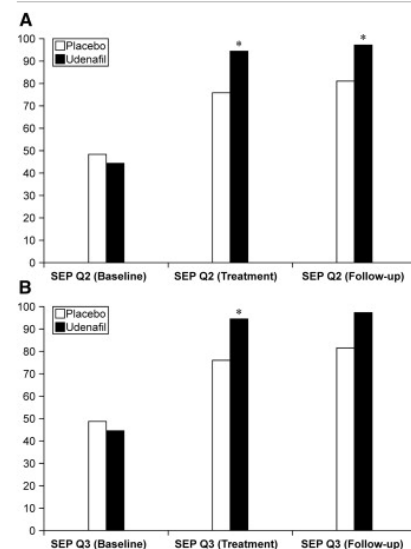


Efficacy of Udenafil after ED post TME



Park, S, Surgery 2015; 157(1): 64-71

SEP



PDE-5i Management of Erectile Dysfunction After Rectal Surgery: A Systematic Review Focusing on Treatment Efficacy

PDE-5i sig better at 3 mos

Margherita Notarnicola, MD¹, Valerio Celentano, MD, PhD², Paschalis Gavriliadis, MD, PhD³, Bilal Abdi, MD¹, Nassiba Beghdadi, MD¹, Daniele Sommacale, MD, PhD¹, Francesco Brunetti, MD¹, Federico Coccolini, MD, PhD⁴, and Nicola de'Angelis, MD, PhD¹

Amer J Men's Health 2020: 1-11

Where We Started 20 Years Ago Pre-MRI Staging...

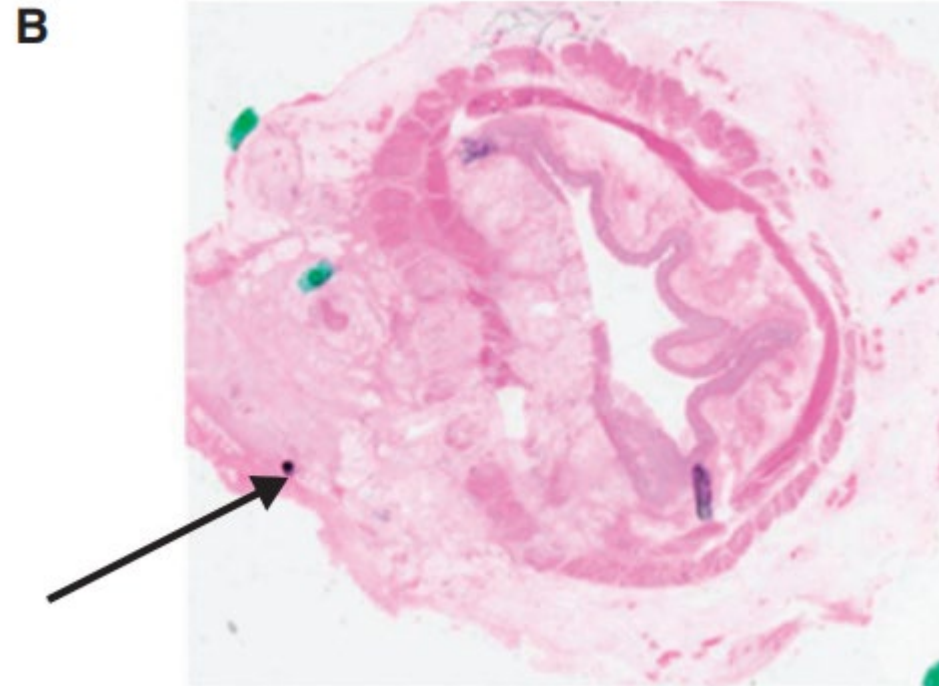
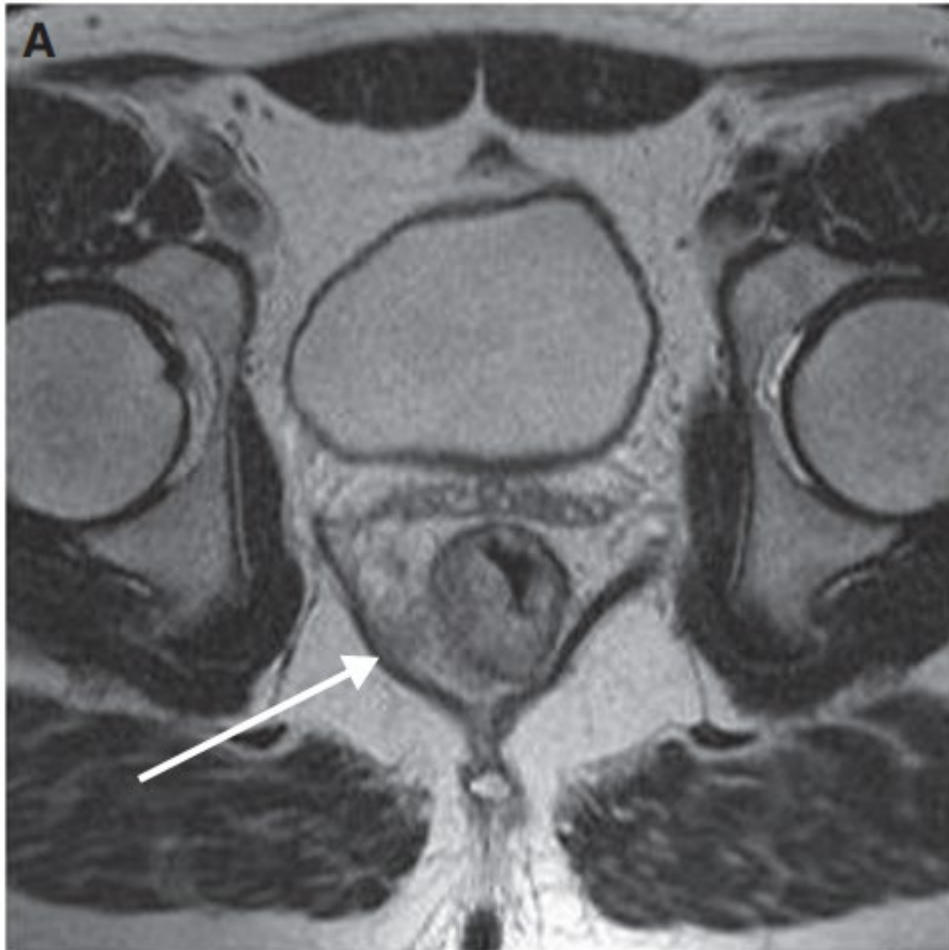


German Rectal Trial

Table 3 German colorectal study group trial

Parameter	Preoperative chemoradiotherapy n=415	Postoperative chemoradiotherapy n=384	P-value
Local recurrence	6%	13%	0.006
Distant recurrence	36%	38%	0.84
Toxicity			
Acute side-effects	27%	40%	0.001
Long-term side-effects	14%	24%	0.01
Sphincter-preserving surgery performed	45/116 (39%)	15/78 (19%)	0.004
Disease-free survival	68%	65%	0.32
Overall survival	74%	76%	0.80

MRI Era: Importance of CRM (MERCURY) for risk



Evaluated CRM in n=374 on high quality pelvic MRI

5 yr OS: 62.2% CRM- vs 42.2% CRM+ P<0.01

5 yr DFS: 67.2% CRM- vs 47.3% CRM +, P<0.05

5 yr LR: 7.1% CRM- vs 20% CRM+

MRI involved CRM was the only preop parameter independently associated with OS, DFS, LR on MVA



MERCURY II: Beyond CRM to Low Rectal Plane

- Prospective multicenter trial to validate MRI staging for tumors (<6 cm AV)
 - Assessment of the tumor-mesorectal fascia relationship (pCRM) and low rectal plane (mrLRP)
- **At surgery, patients with no MRI risk factors had a pCRM positive rate 2%**
- Tumors <4 cm from anal verge AND unsafe mrLRP had a pCRM rate 13%
 - + anterior tumor pCRM 13% → 29%
- **MRI risk factors on MVA:**
 1. “unsafe” Low Resection Plane (OR 3.5)
 2. EMVI (OR 3.8)
 3. Tumor <4 cm from anal verge (OR 3.4)
 4. Anterior tumor (OR 2.0)

QuickSilver – Phase II

Prospective, non randomized phase II in HVC across Canada

MRI criteria for “Good Prognosis” for primary surgery

- MRF >1 mm, T2-3 <5 mm invasion; absent or equivocal EMVI; allow NO-2
- NO planned APR allowed – (No distal rectal)

82 patients enrolled; 65% mid-rectal, 63% cNO

Results:

1. Quality of TME complete or near complete in 98%
2. Pathologic 91% were T2 or greater, 29% pN+
3. Positive CRM rate 5%
4. 30% adjuvant treatment (with 6 patients adj CRT)
5. 88% avoided any RT

Kennedy, *JAMA Onc*, 2019; 5: 961-66

Table 1. Magnetic Resonance Imaging (MRI) Results Among 82 Patients

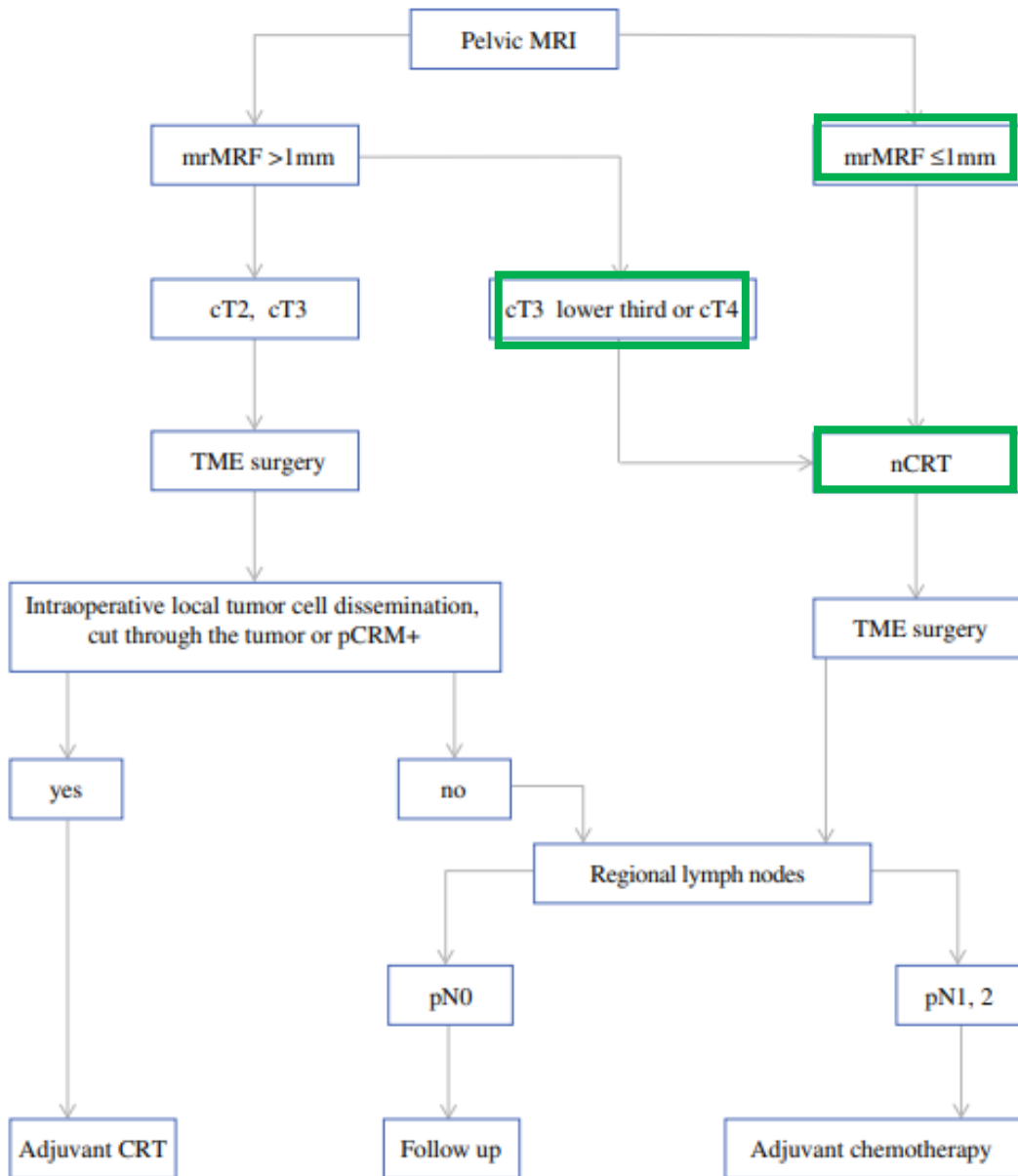
Variable	No. (%)
MRI tumor height	
Low, 0-5 cm	6 (7)
Mid, 5.1-10 cm	53 (65)
High, 10.1-15 cm	23 (28)
MRI T category	
Definite T2	16 (20)
T2/early T3	49 (60)
Definite T3 with <5 mm of EMD	17 (21)
MRI lymph node status	
Not suspicious	52 (63)
Suspicious	30 (37)

Abbreviation: EMD, extramural depth of invasion.

Table 2. Pathology Results Among 82 Patients

Variable	No. (%)
Quality of the TME	
Complete	67 (82)
Near complete	13 (16)
Incomplete	2 (2)
pCRM status	
Negative	78 (95)
Positive	4 (5)
pT category	
T1	7 (9)
T2	33 (40)
T3	40 (49)
T4	2 (2)
pN category	
N0	58 (71)
N1	18 (22)
N2	6 (7)
pStage, AJCC 7th ed	
Stage I, T1-T2, N0	34 (41)
Stage II, T3-T4, N0	24 (29)
Stage III, any T, N1-N2	24 (29)
EMVI	
Absent	69 (84)
Present	13 (16)

Flow Chart "Rectal carcinoma of the middle and lower third"



OCUM Trial

254 patients underwent TME alone (59.3%)

174 underwent nCRT & TME (40.7%)

3-year LR: 1.3%

5-year LR: 2.7%

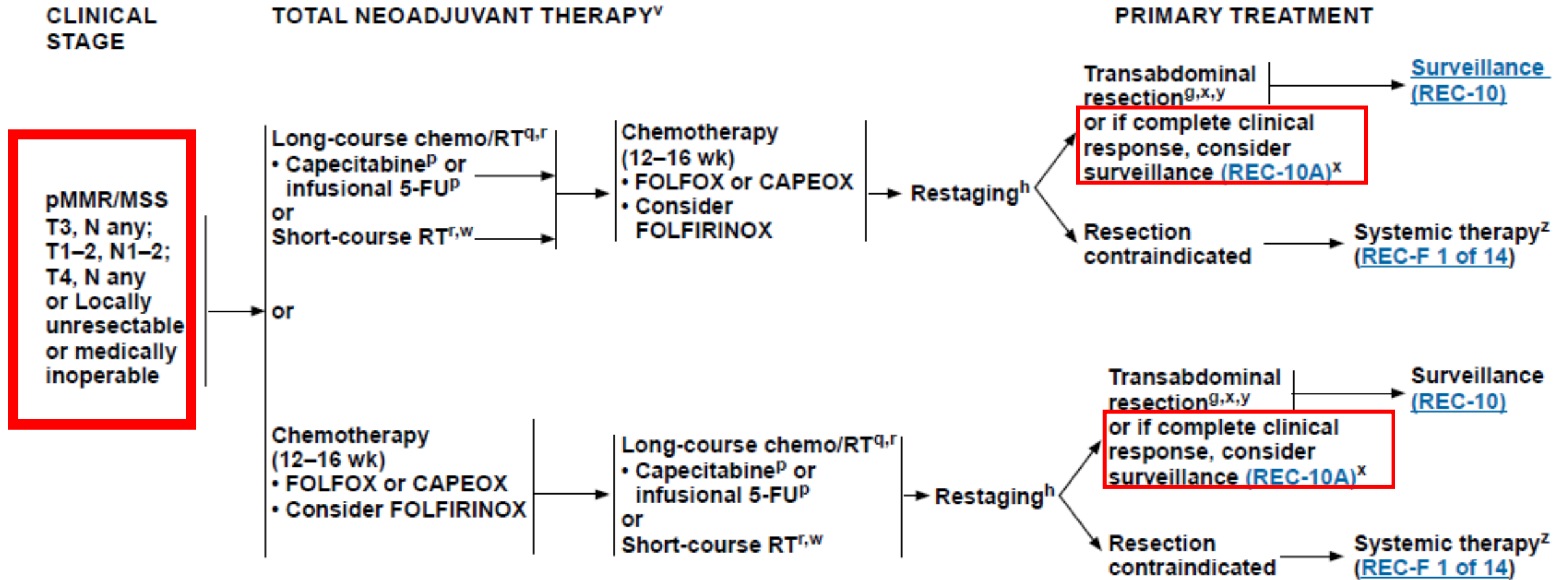


No difference

	nCRT	TME	P value
3-year DM	17.3%	8.9%	
5-year DM	24.9%	14.4%	P=.005
3-year DFS	76.7%	84.9%	
5-year DFS	66.7%	76.0%	P=.016



NCCN: TNT is the SOC but no risk categorization



When and If RT: Add Sx & Risk to SDM

How *symptomatic* is the patient and what is their risk of obstructing?

Will RT associated edema worsen obstruction? (avoid diversion?)

How do we think about their risk for systemic and local recurrence?



MRI Risk Stratification Schema

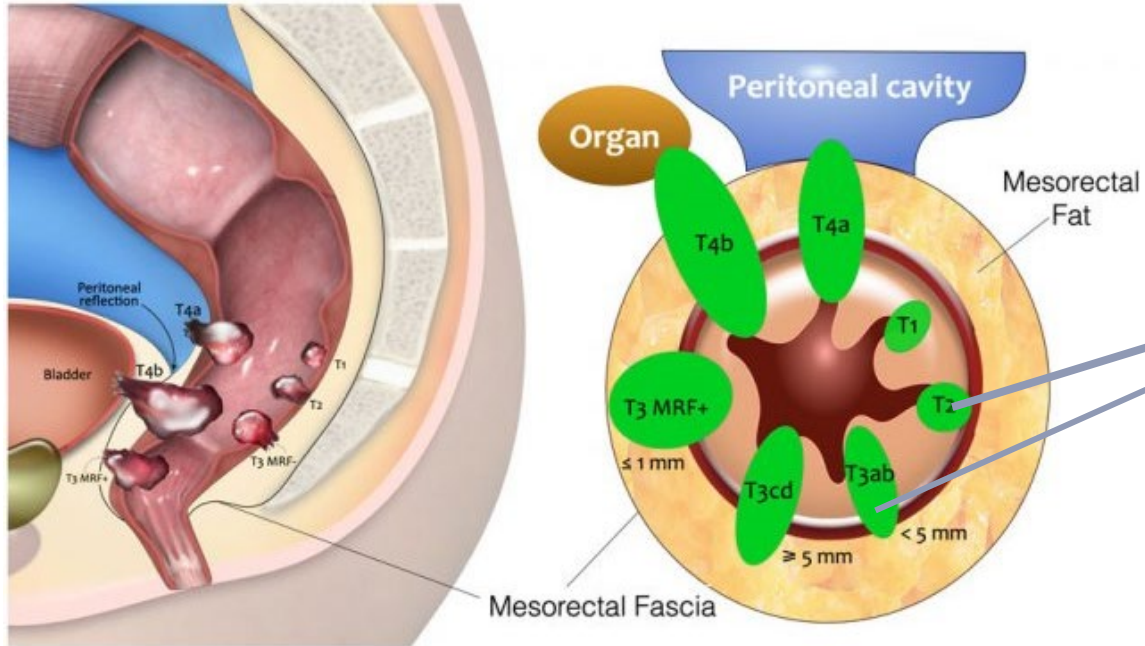
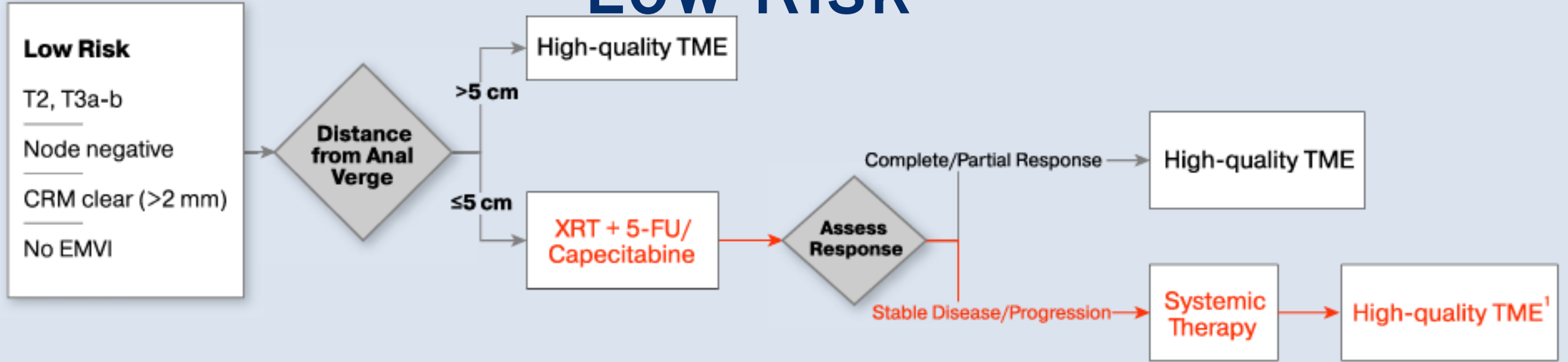


TABLE 1. Risk Stratification Schema

	Low Risk	Intermediate Risk	High Risk
Clinical T category	T2, T3a-b	T3c-d	T3c-d or greater
Clinical nodal status	Negative	Positive	Positive
Circumferential resection margin	Clear	Clear	Threatened or positive
Extramural vascular invasion	Negative	Negative	Positive
Lateral pelvic lymph nodes	Negative	Negative	Positive

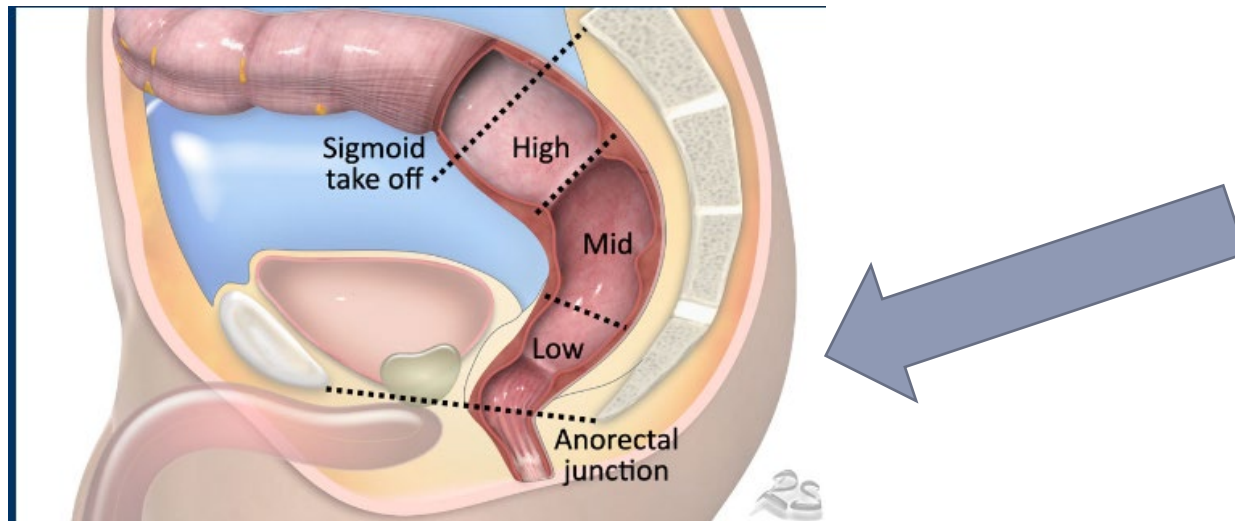
Low Risk



¹ If complete response achieved, organ preservation with deferral of surgery may be considered.

Low Risk

Bhutiani N, Cancer 2022;128: 2064-2072



Lambregts, D, Rectal Cancer MR Staging 3.0



What about SCRT for NOM and toxicity?

25Gy/5 fractions to the pelvis, single arm Wash U
then FOLFOX x 8
or CAPEOX x 5

Kim H, Clinical Colorectal Cancer 2021;20 (3): e185-193

If cCR, surveillance protocol

Stage 1: 21%; Stage 2: 32%; stage 3: 47%

1-year cCR: 68%

Patients with cCR had improved DFS, DMFS, and OS

Anorectal function at 1 year same as baseline

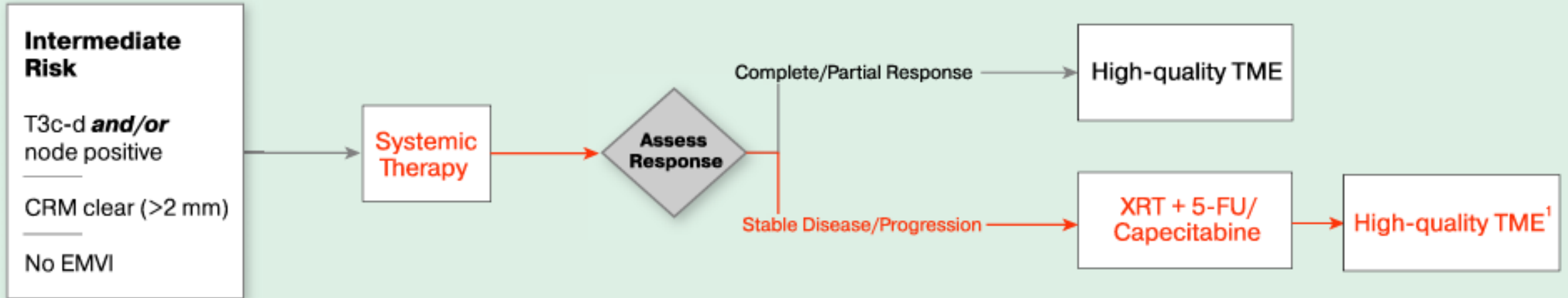
Not significant data yet for long term
bowel function in a NOM approach
using SCRT first

Late Toxicity Studies after SCRT TNT

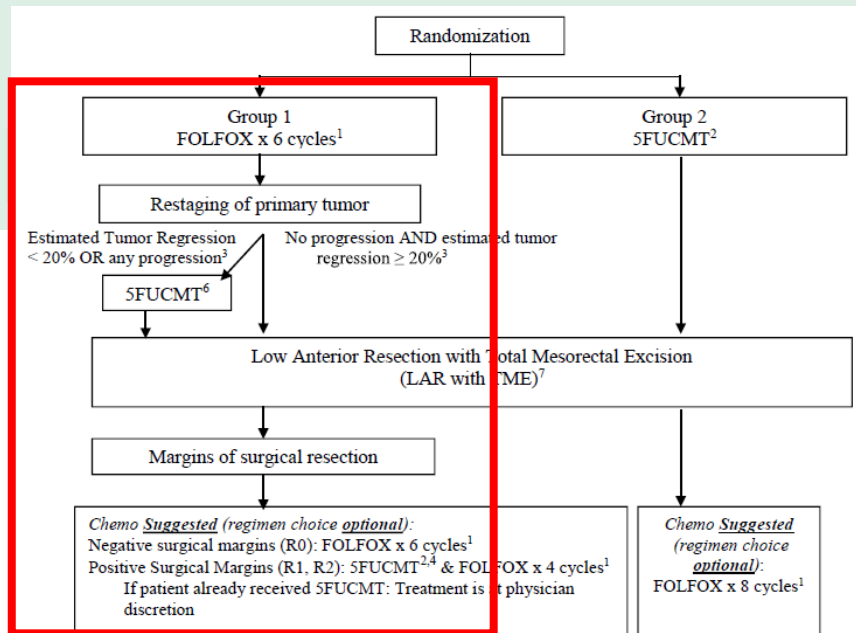
RAPIDO: At 3 years post surgery, no
difference in HRQL, bowel function
or more grade 3+ toxicity compared
with long course

Dijkstra E, Radioth & Oncol 2022; 171: 69-76

Intermediate risk: Prefer to avoid RT



¹ If complete response achieved, organ preservation with deferral of surgery may be considered.



Bhutiani N, Cancer 2022;128: 2064-2072

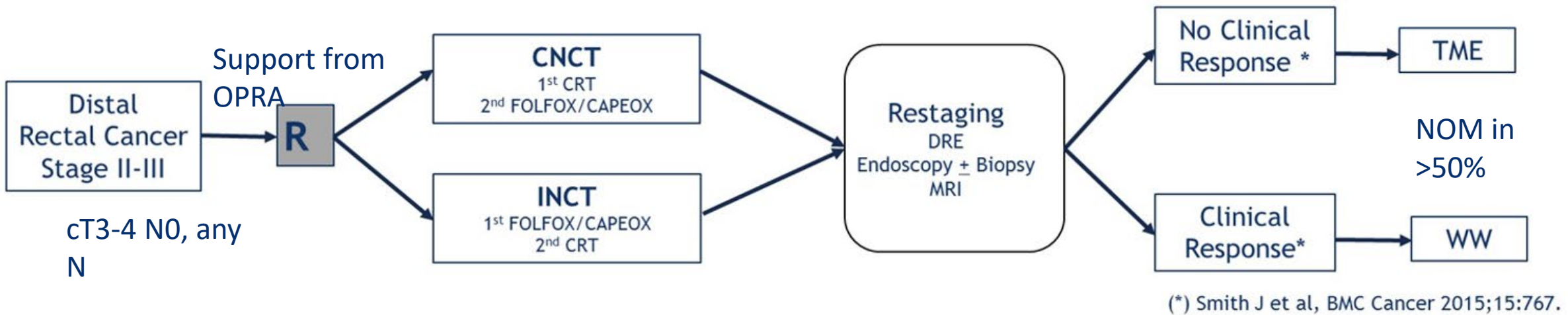
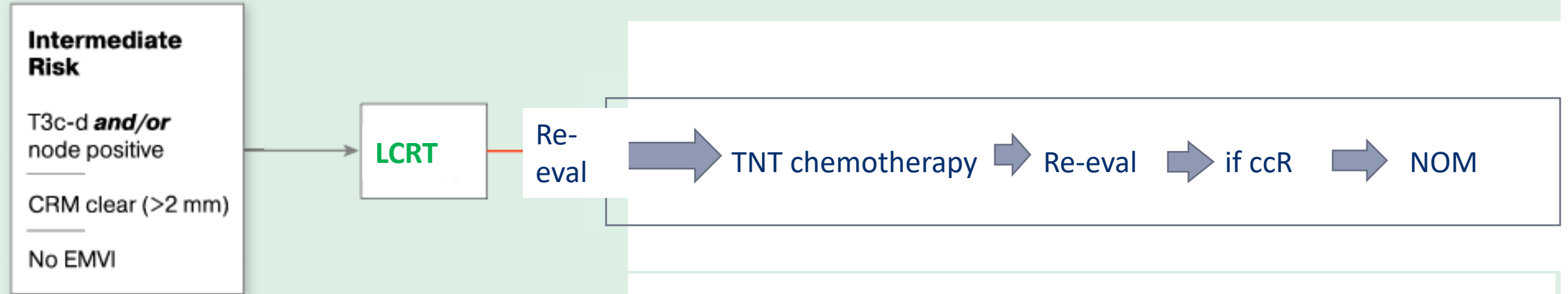
58-month DFS FOLFOX 80.8% vs. 78.6% CRT

- R0 resection rate and non-inferior time to LR

PROSPECT included T2N+, T3N-, T3N+ sphincter preserving candidates

PROSPECT: Schrag D, NEJM 2023; 389: 322-34

Intermediate risk: Prefer to avoid TME



Garcia Aguilar ASCO 2020

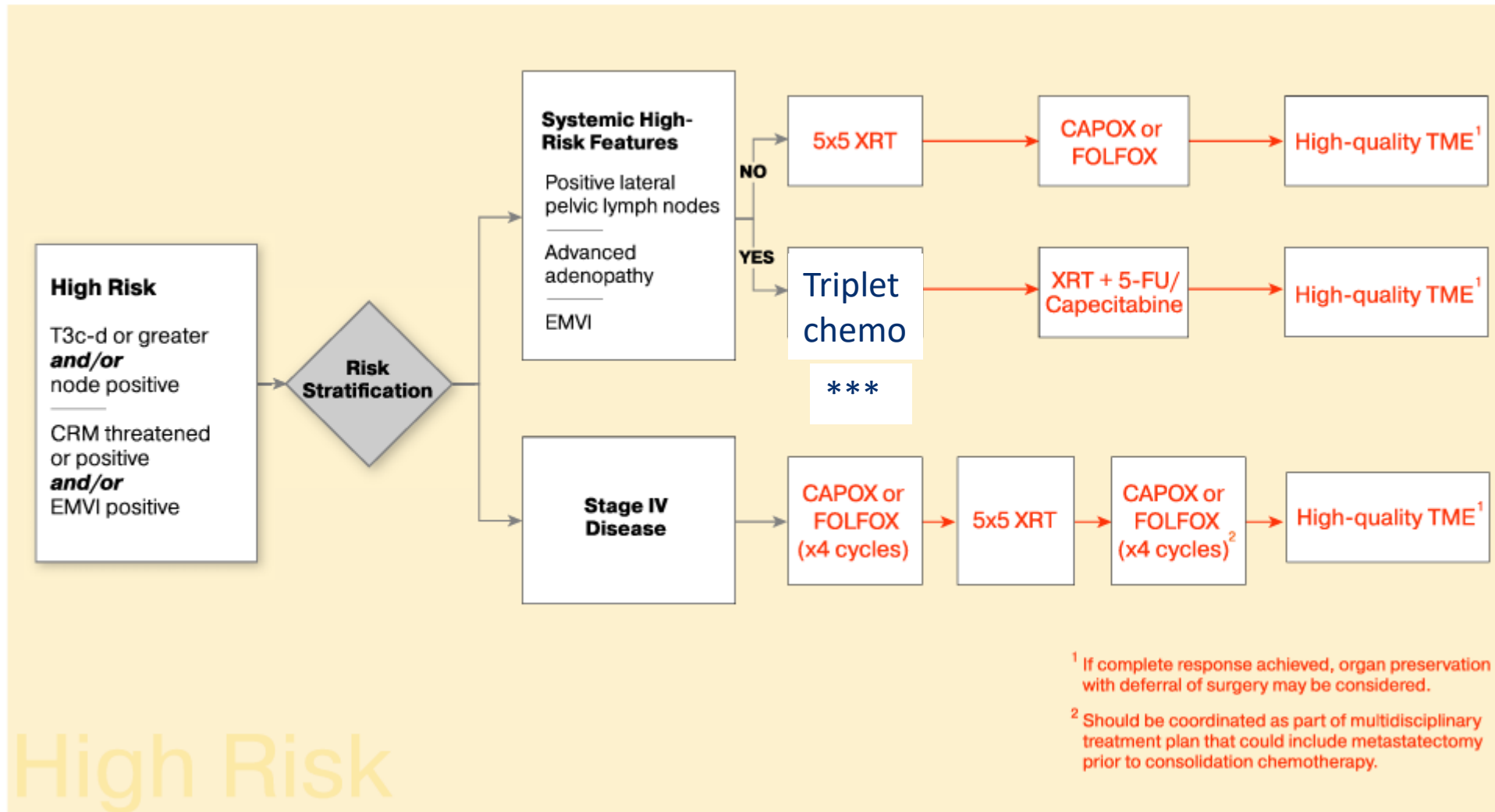
Support from TME trials LCRT first:

Pick the Winner trial, Fokas E

JCO 2019; 37: 3212-22; 25% pCR with consolidation chemo vs 17% with induction

TIMING trial pCR 38% with LCRT then 8 cycles: Garcia Aguilar, Lancet Oncol 2015; 16: 957-66

High Risk





RAPIDO – 5-year update***

- **HIGH RISK PATIENT POPULATION:** cT4a/b, N2, EMVI+, MRF+, Involved lateral nodes

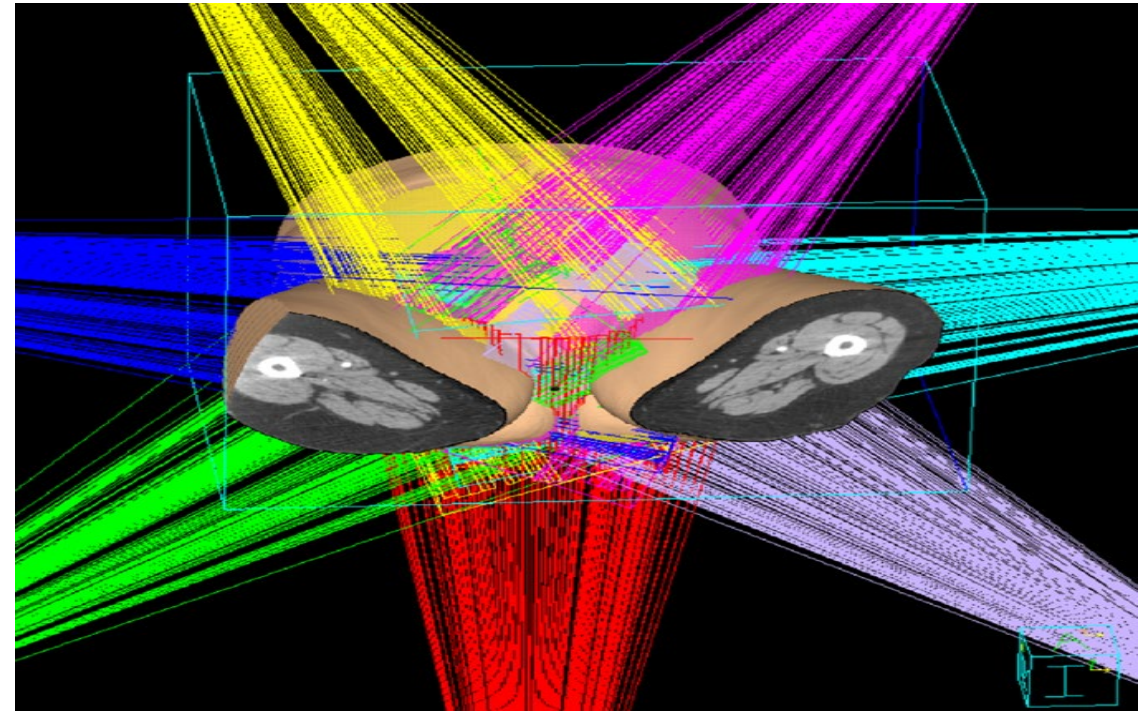
- Short course radiation + CHT TNT associated with **WORSE:**
 - Overall cohort: Higher locoregional failure 12% vs 8 but (p=0.07)
 - Subset with R0& R1: Higher locoregional recurrence 10% vs 6%, (p=0.027) with higher breached mesorectum 21% vs 4%, P=0.048
- However:
 - OS after LRF was comparable (HR 0.76, p=0.3)
 - Reduction in disease-related treatment failure 34% → 28% and distant metastasis 30% → 23%
 - pCR rate improved 14% → 28%

How can we ↓ toxicity?

Prone Bellyboard Technique

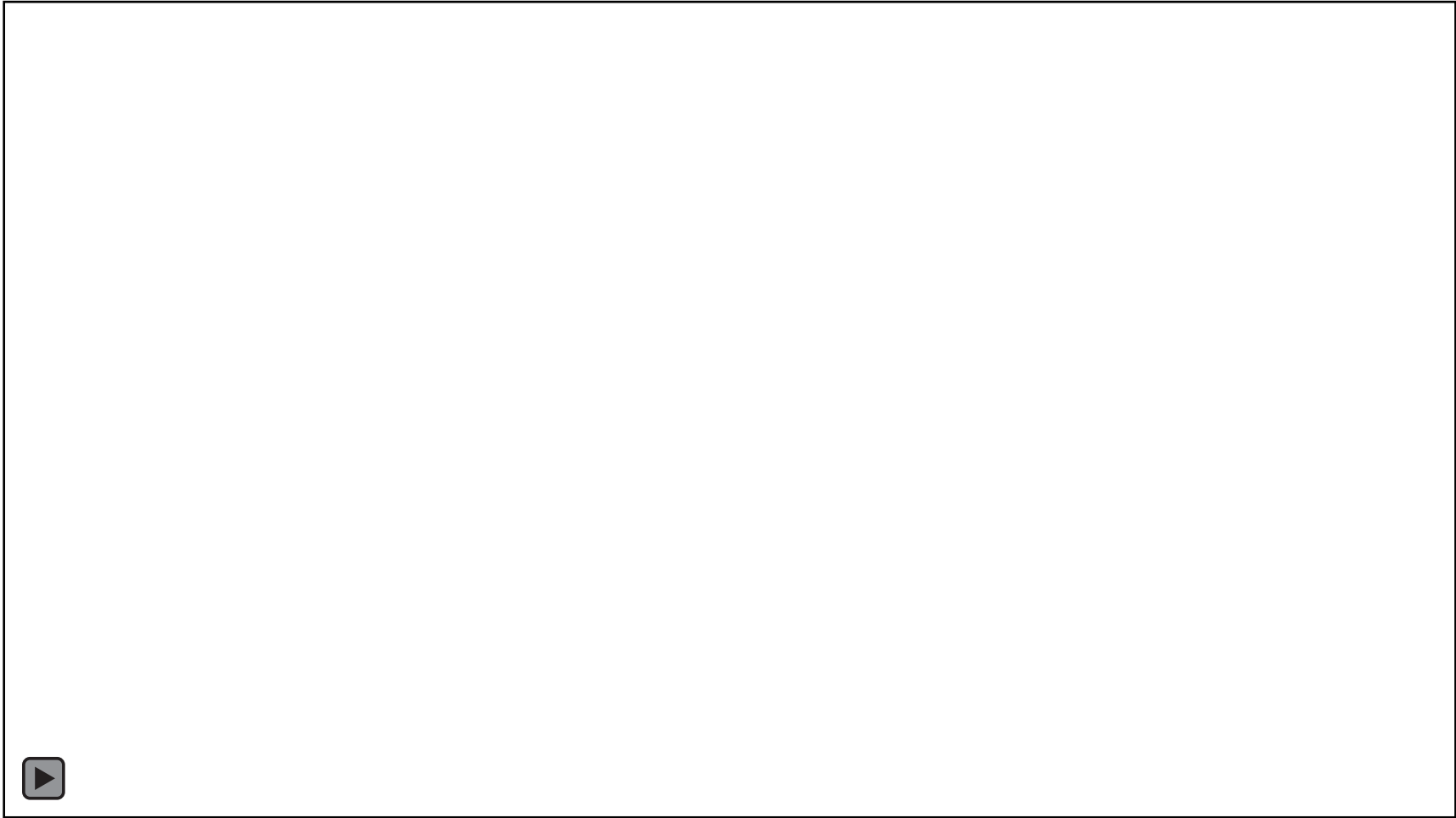


Supine, multiple beams

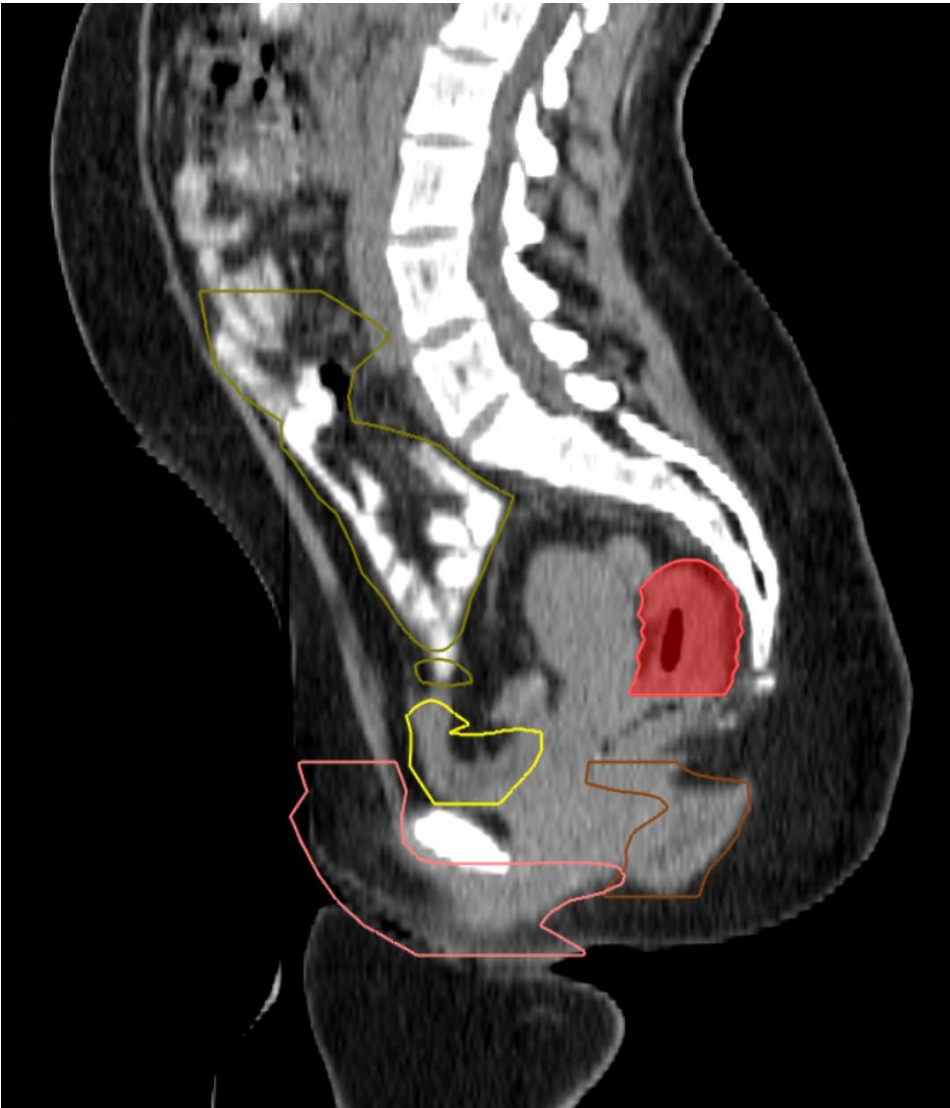


Standard SCRT 25 Gy in 5 fractions of 500 cGy;
Standard **LCRT** 45 Gy to the pelvis + 5.4 Gy boost in 28 fractions of 180 cGy;
Consider boost to 54 Gy if goal is non-operative

Radiation Technique: Minimize Small Bowel

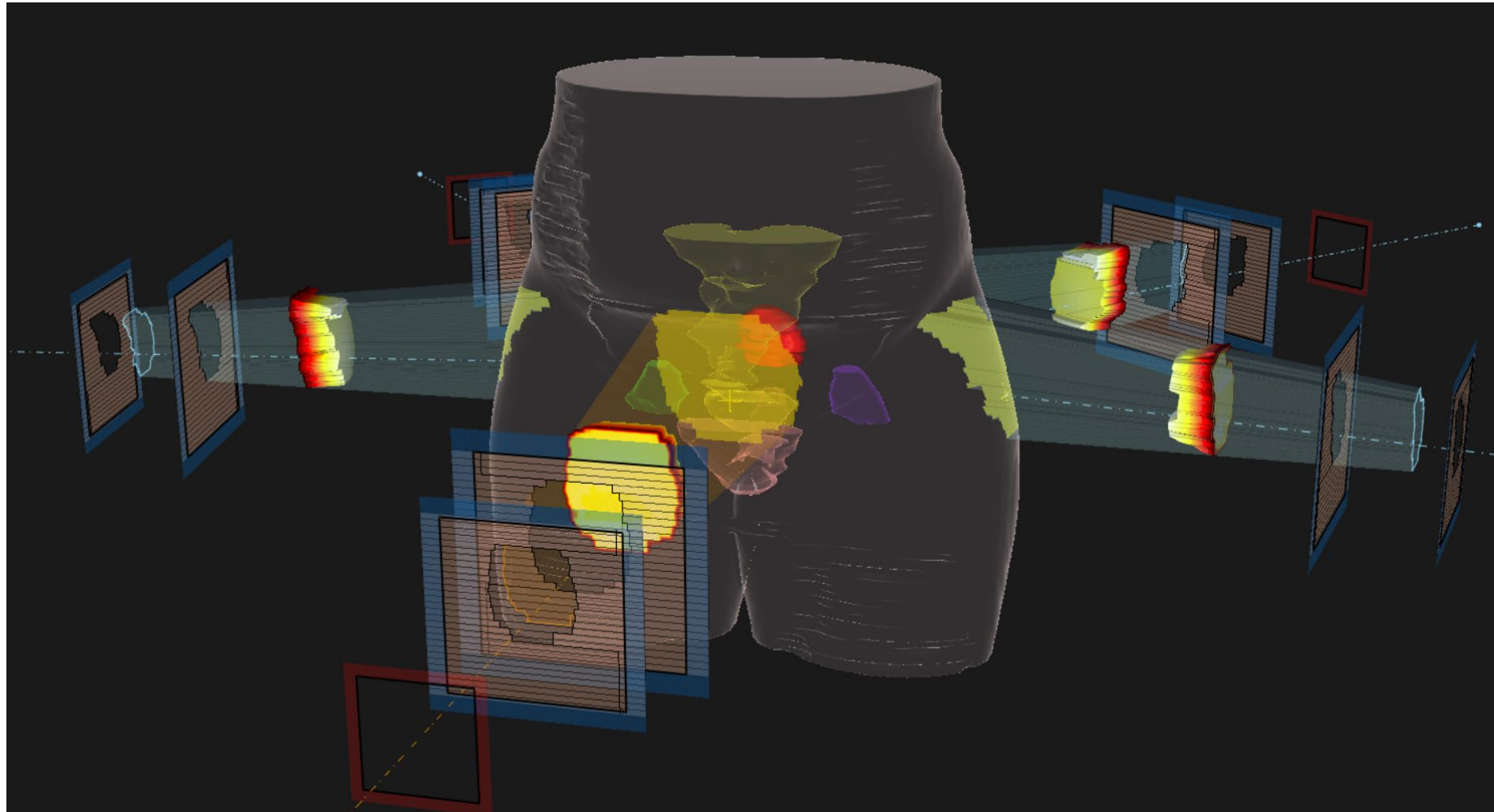


Spare Small Bowel: Empty vs. Full Bladder



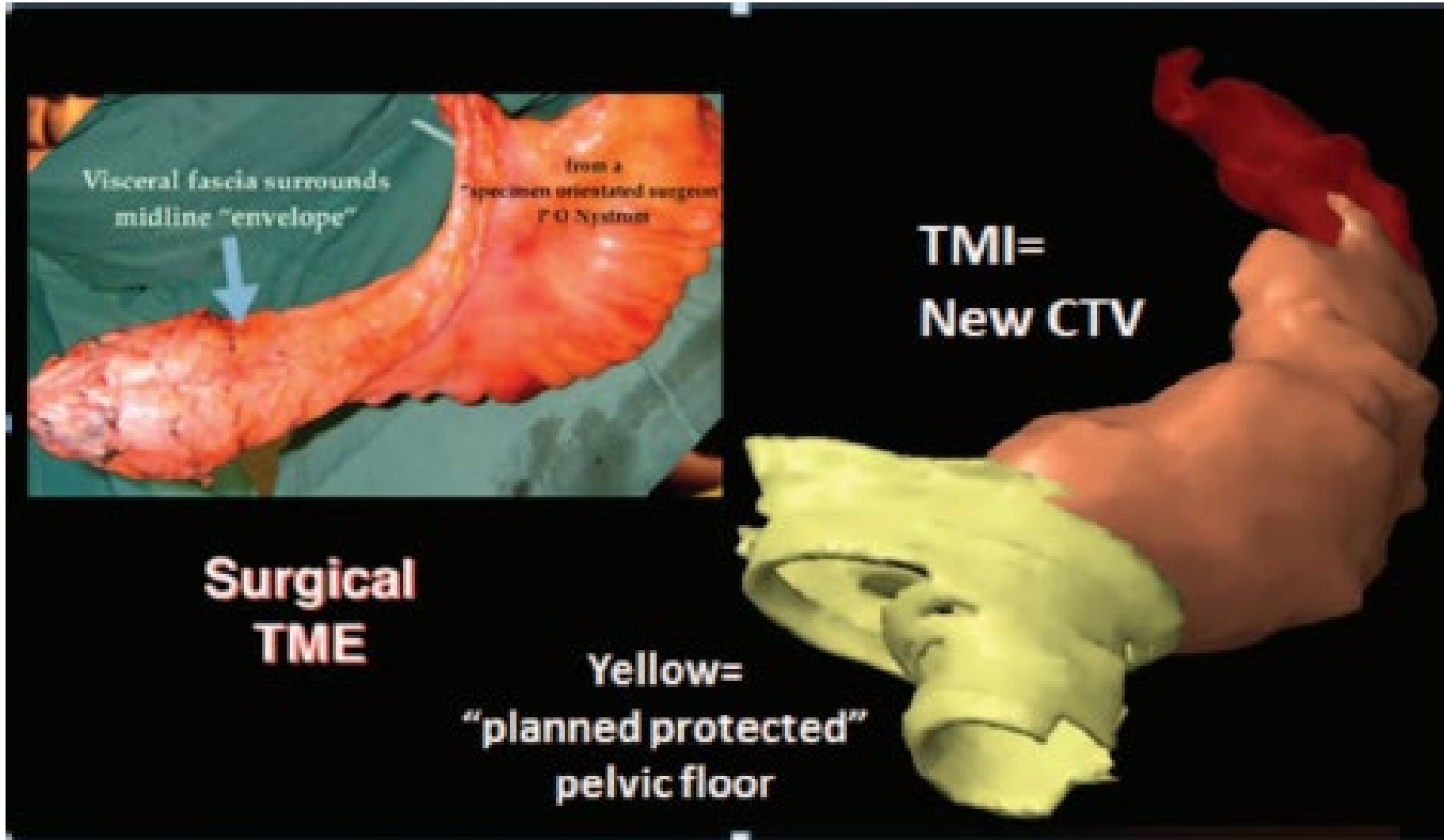


Technique: 3D is the SOC unless T4 or Postop, then IMRT



3Dimensional conformal radiation therapy vs Intensity Modulated Radiation Therapy

Future: Irradiate less with TMI via EBRT?

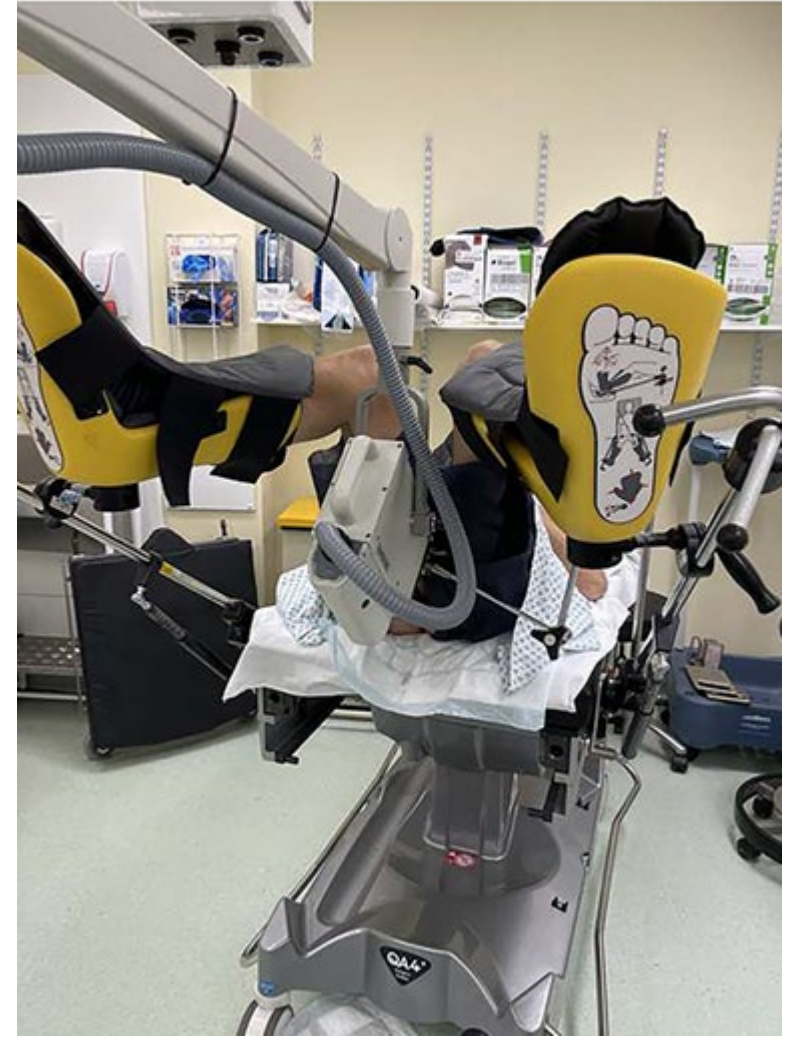
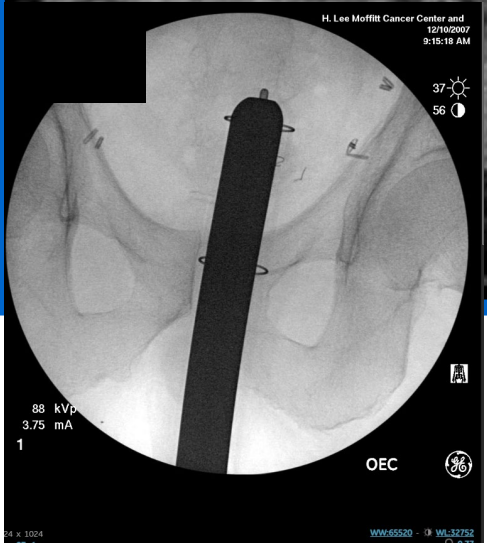
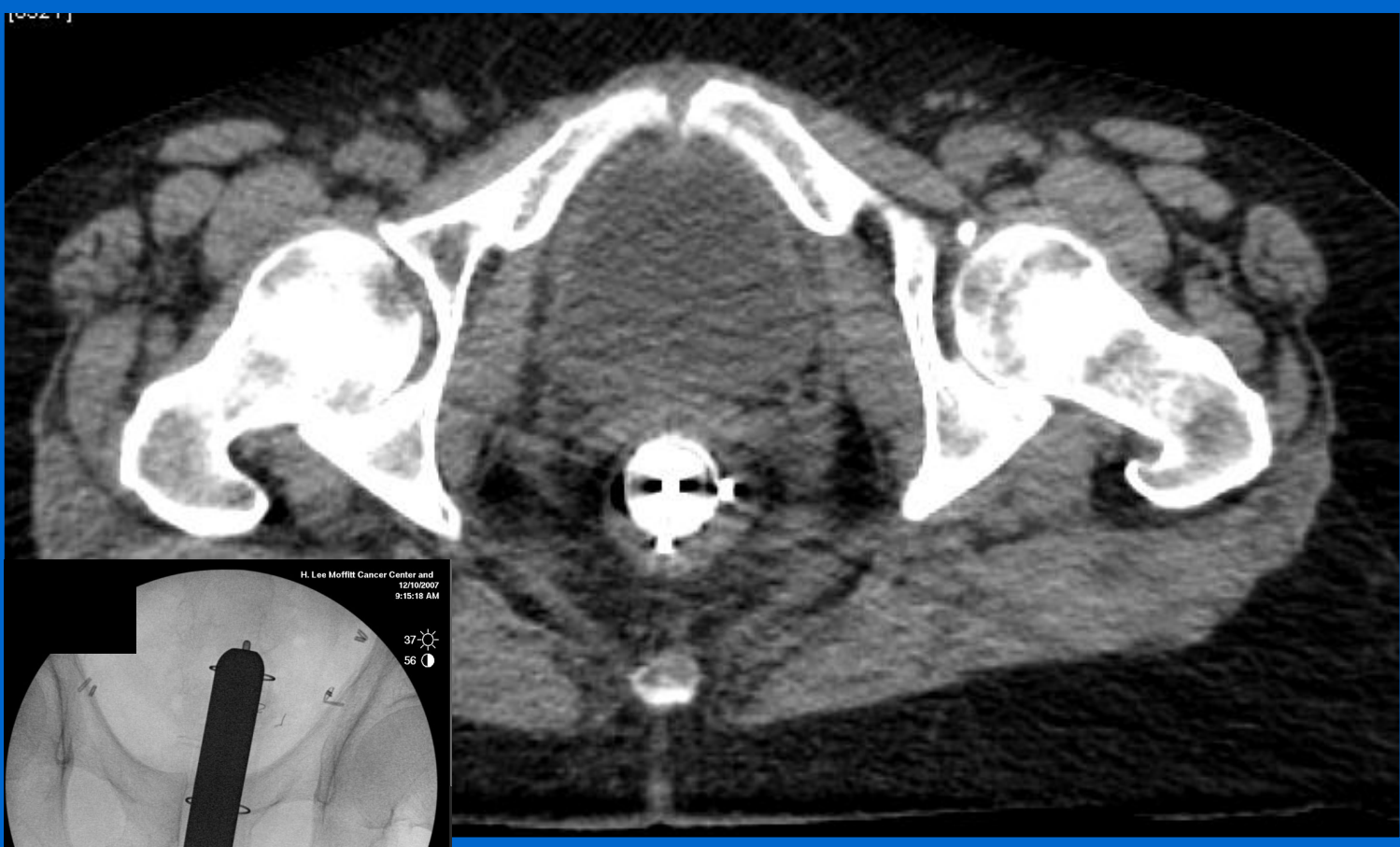


Lessons from OR:
Intramural spread beyond visible margin is rare; 1cm or less is acceptable

All the side effects of pre-op RT come from RT to the *surrounding* tissues

Can we spare the anal canal, nerves? and more small bowel by decreasing superior border to S2-3?

Future: Irradiate Less with Endorectal Brachytherapy?



Vuong TE, J Contemp Brachy 2015; 7: 183-88; Stewart A, Clin Trans Rad Onc 2022; 33: 15-22



Conclusions

- Explore patient preferences and goals
- High quality MRI improves risk stratification
- SCRT vs **LCRT** no differences pre -TNT; SCRT RAPIDO associated with **increased LF**
- *Few data* on long term outcomes with SCRT TNT for NOM; for LCRT, data stronger for consolidation chemotherapy following starting with **LCRT**
- Patients with low and intermediate risk cancers may be candidates to *avoid pelvic RT*
- *Future RT strategies needed to decrease late effects!!!*