UT Southwestern Medical Center

Radiotherapy in Rectal Cancer:
Personalizing Treatment to Improve Quality of Life

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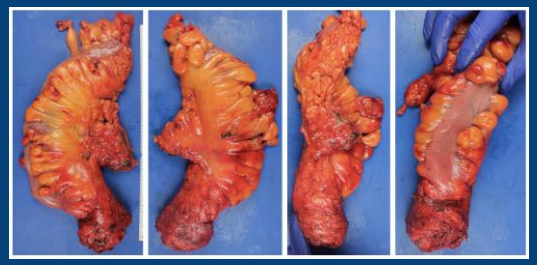
Outline

- Rationale for radiotherapy in rectal cancer

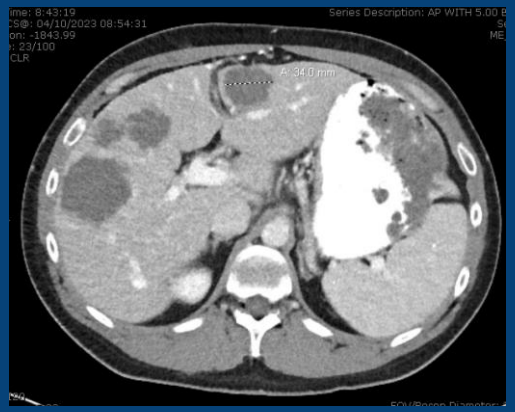
- Choosing the appropriate radiotherapy regimen
  1. Is the intent of treatment surgical or non-operative?
  2. Do we need radiotherapy?
      PROSPECT trial
  3. Short or long course radiotherapy?
  4. Sequencing of radiotherapy in total neoadjuvant therapy

Rationale for RT in locally advanced rectal cancer

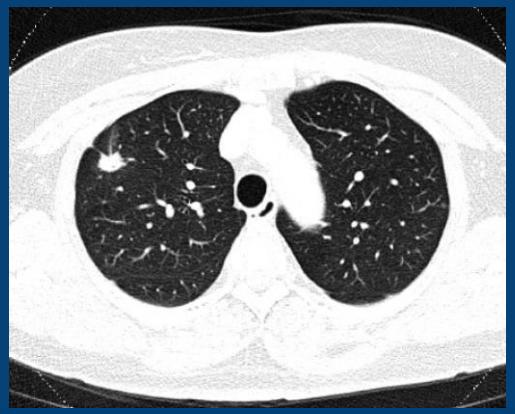


- Historically, to reduce local recurrence

Local Recurrence	No RT	With RT	Reference
Pre-TME	~25-40%	~10-15%	Swedish Trial, 1997
With TME	~10%	~5%	Dutch Trial, 2001



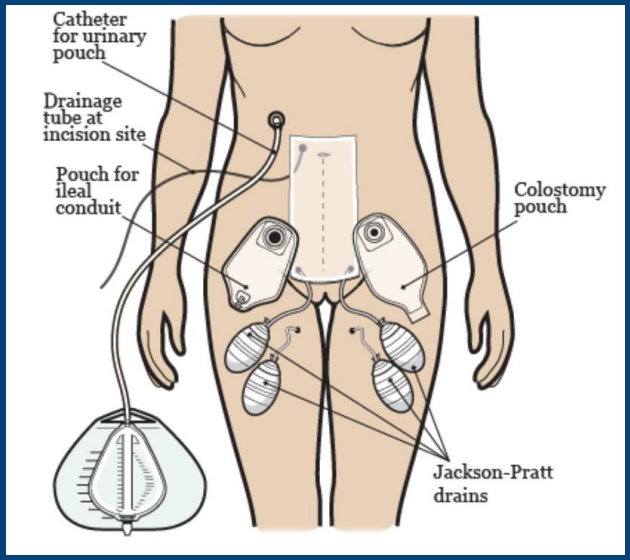
- With TME, most rectal cancers recur distantly (~25-30% for Stage III)



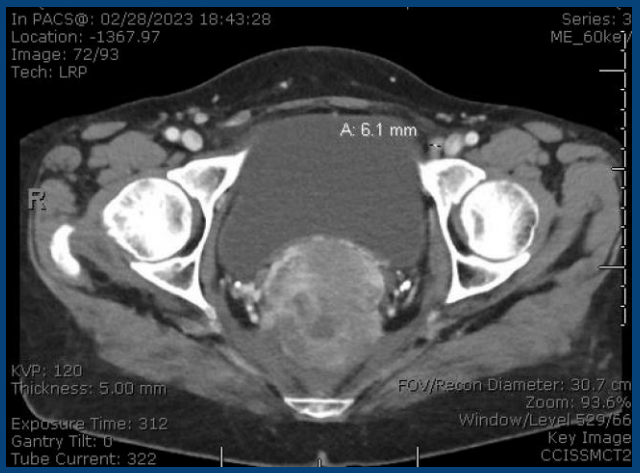
1. Swedish Rectal Cancer Trial, Cedermark B, Dahlberg M, et al. *NEJM,* 1997
2. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. *NEJM,* 2001

Why do we care about local recurrence?

1. Local recurrence associated with:
   - Poor survival: ~30% at 5 years
   - Poor QOL/morbidity: chronic pelvic pain, discharge/bleeding, tenesmus, obstruction, fistula, sexual & urinary dysfunction



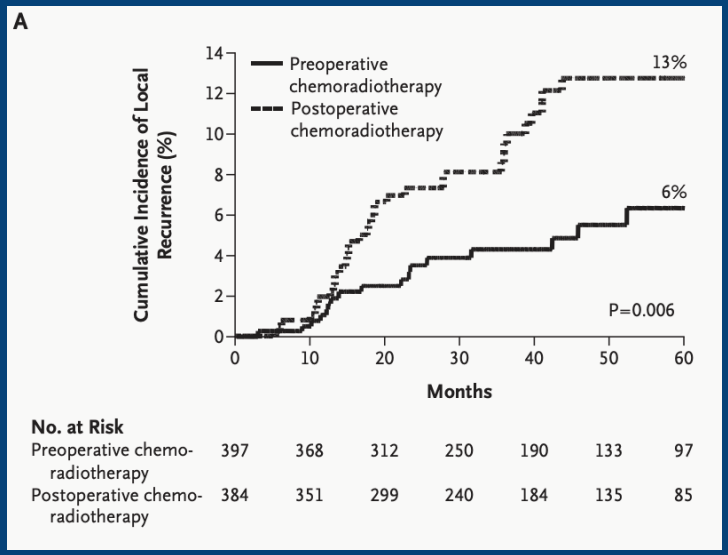
2. For some patients, risk of local recurrence is high
   - Important of risk stratification for RT



1. Glyn T, Frizelle F. *Seminars in Colon & Rectal Surgery,* 2020.

Treatment used to be one-size fits all

- German Rectal Trial showed pre-operative long-course chemoRT (vs post-op chemoRT):
  - Reduced local recurrence rate:
    - 13% vs. 6%
  - Increased sphincter sparing surgery:
    - 19% vs. 39%
  - Decrease acute & late toxicities



Long course chemoRT → surgery → adjuvant chemotherapy

1 standard of care → over- or under-treatment for many, and no organ preservation option

1. Sauer R, Becker H, Hohenberger W, et al. *NEJM,* 2004

Now, there are many more options.

- Chemotherapy:
  - Pre- (total neoadjuvant therapy) or post-op
  - Doublet or triplet
  - Duration
- Immunotherapy
- Surgery:
  - TME
  - Transanal excision
- Radiotherapy:
  - Short or long course
  - Brachytherapy

How do we choose?

- Question 1: is the intent of treatment surgical or non-operative?

- Question 2: if surgical, do we need radiotherapy?

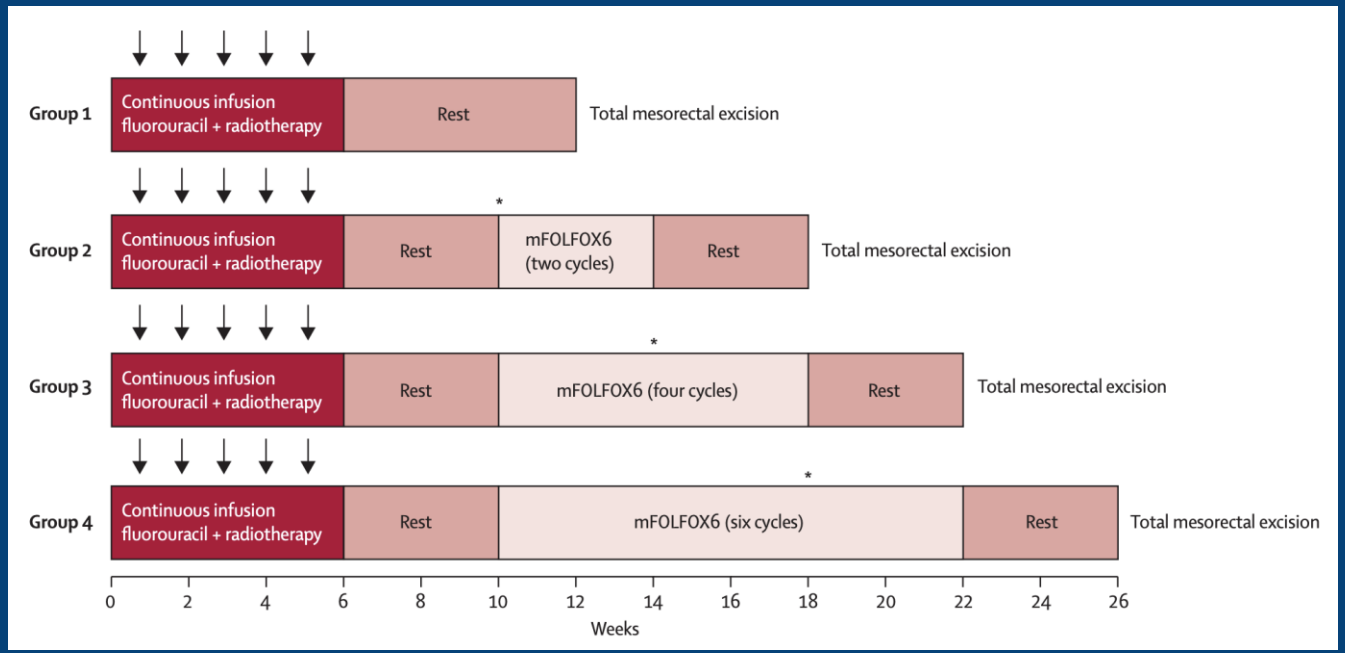
- Question 3: if we need radiotherapy, should we use short or long course?

- Question 4: should radiotherapy come before or after chemotherapy?

Q1: Intent – surgical vs. non-operative

- Total neoadjuvant therapy increases pathologic complete response (pCR) rate
  - Longer interval from RT to assessment
  - More systemic therapy

TIMING trial



pCR: 18%

pCR: 25%

pCR: 30%

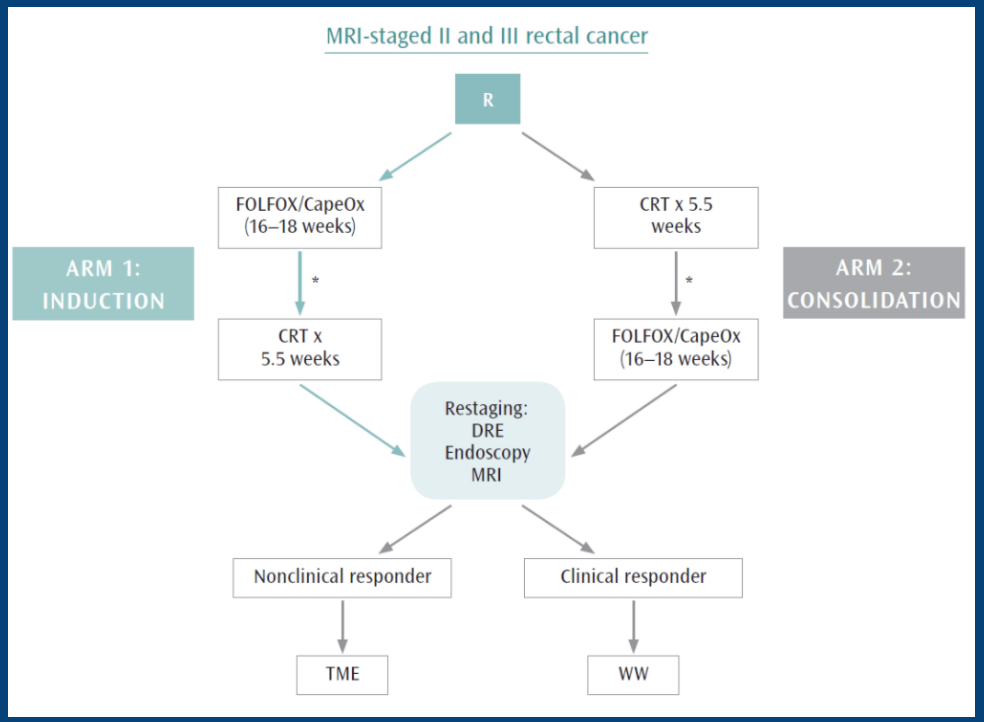
pCR: 38%

1. Garcia-Aguilar J, Chow OS, Smith DD, et al. *Lancet Oncol,* 2015

Q1: Intent – surgical vs. non-operative

- OPRA trial: Phase III multi-institutional RCT

Patients: stage II (T3-4, N0) or stage III (any T, N1-2)

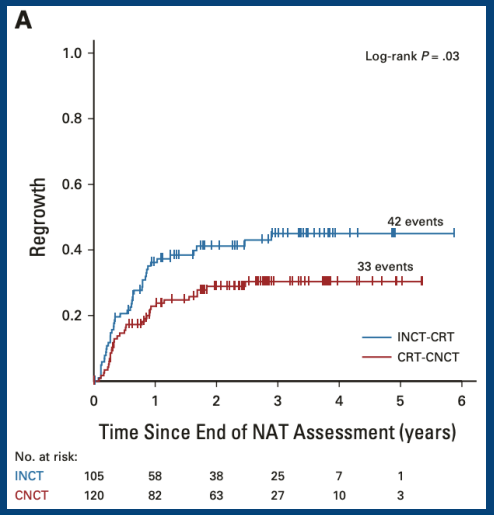


3-year results

3-year rates with 95% CI.

	Induction		Consolidation		p*
DFS	78%	(70%,87%)	77%	(69%,86%)	0.90
DMFS	81%	(74%,90%)	83%	(76%,91%)	0.86
OP	43%	(35%,54%)	58%	(49%,69%)	0.01

*OP=organ preservation



1. Garcia-Aguilar J, Patil S, Gollub M, et al. *JCO,* 2012

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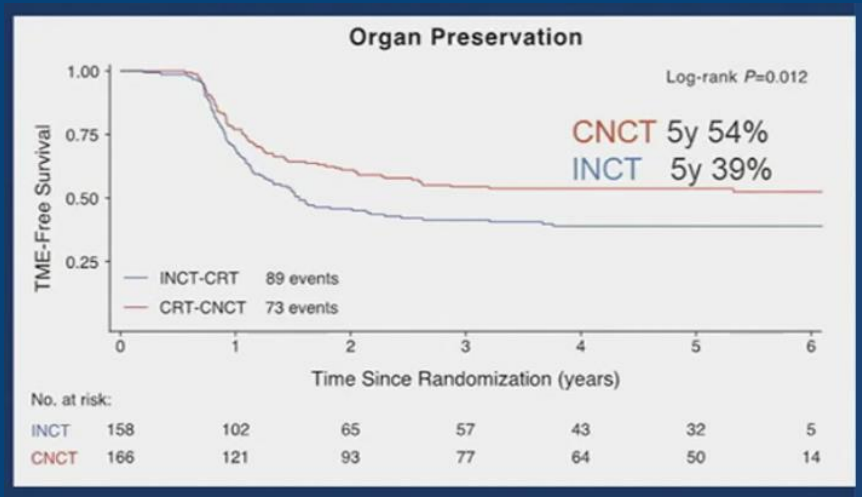
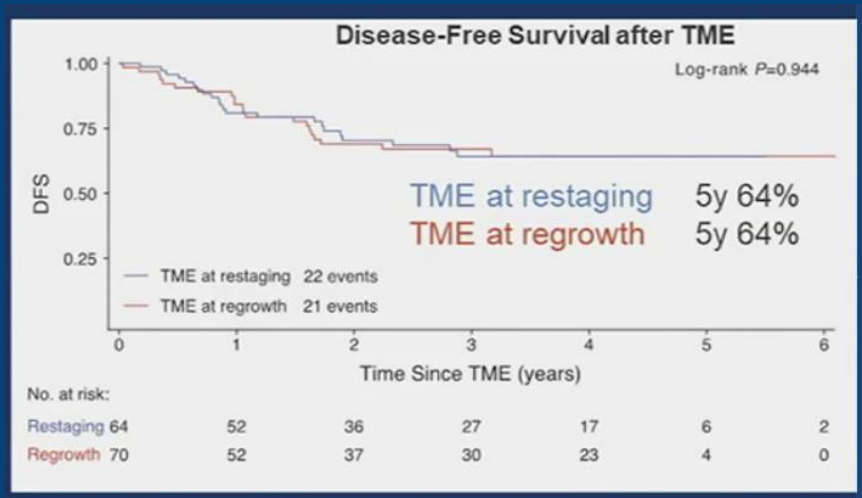
Q1: Intent – surgical vs. non-operative

5-year results





Fewer regrowths for induction chemoRT: 29% vs. 44%

No difference in DFS between TME at restaging vs. regrowth

- 94% regrowth w/in 2 years,
- 99% w/in 3 years

1. Verheji FS, Omer DNR, Williams H, et al. *ASCO,* 2023

Q1: Intent – surgical vs. non-operative

Chemotherapy Completion

	Chemo first	Chemo RT first	p
Completed intended cycles of chemotherapy[†]	129 (83)	127 (77)	.28
FOLFOX[‡]	n = 118[§]	n = 117[§]	
Completed intended FOLFOX cycles[†]	101 (86)	97 (83)	.60
≥90% of planned dose fluorouracil received	81 (69)	86 (74)	.47
≥90% of planned dose oxaliplatin received	73 (62)	73 (62)	>.99
≥75% of planned dose fluorouracil received	106 (90)	109 (93)	.48
≥75% of planned dose oxaliplatin received	104 (88)	100 (85)	.57
CAPEOX[‡]	n = 38[‖]	n = 39[‖]	
Completed intended CAPEOX cycles[†]	28 (74)	30 (77)	.80
≥90% of planned dose capecitabine received	23 (61)	23 (59)	>.99
≥90% of planned dose oxaliplatin received	20 (53)	21 (54)	>.99
≥75% of planned dose capecitabine received	29 (76)	28 (72)	.80
≥75% of planned dose oxaliplatin received	26 (68)	30 (77)	.45

Starting with chemoRT did not reduce ability to complete all cycles of intended chemotherapy

- Winning arm: long course chemoRT → chemotherapy → response assessment
  - Current preferred regimen if intent is non-op

1. Verheji FS, Omer DM, Lin ST, et al. *Red Journal,* 2023

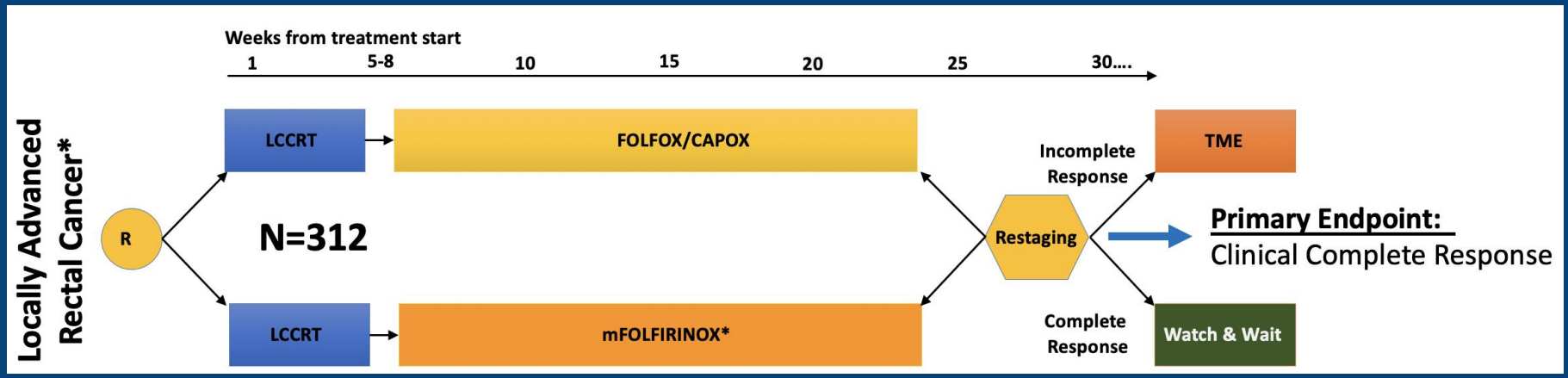
Q1: Intent – surgical vs. non-operative

Ongoing trials assessing other regimens with non-operative intent

JANUS

FOLFOX vs. FOLFIRINOX

(OPRA vs. PRODIGE 23)



* <=12cm, cT4N0, anyT, N+; T3N0 that would require APR or coloanal anastomosis

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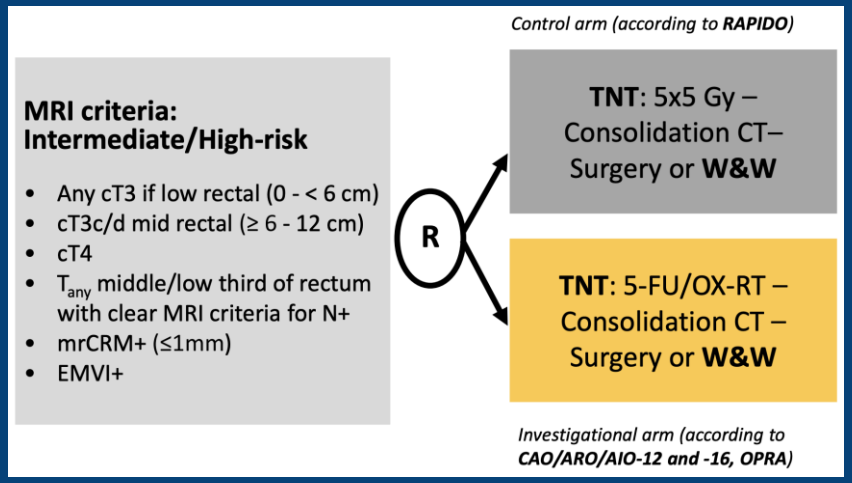
Qian Shi, PhD

Q1: Intent – surgical vs. non-operative

Ongoing trials assessing other regimens with non-operative intent

ACO/ARO/AIO-18.1

Long course vs. short course
(OPRA vs. RAPIDO)



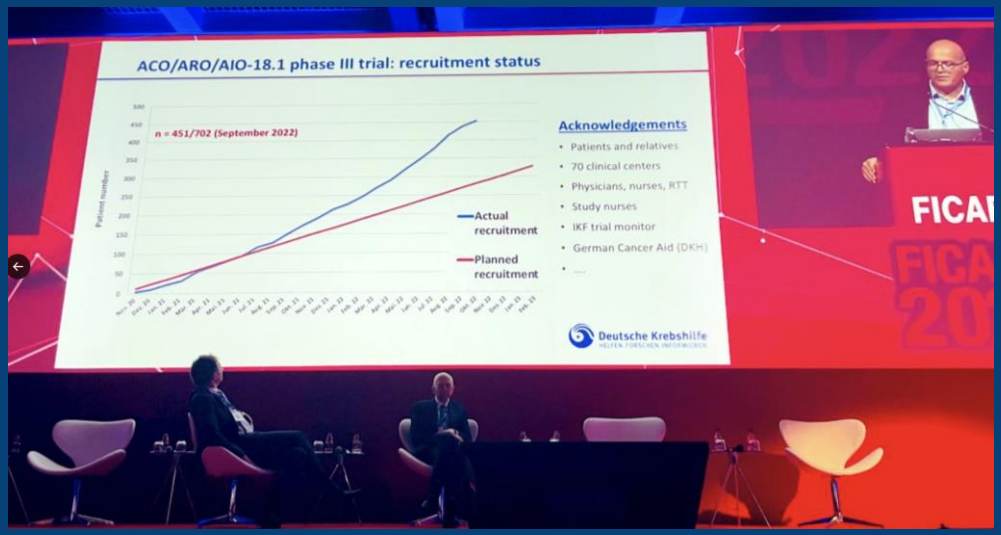
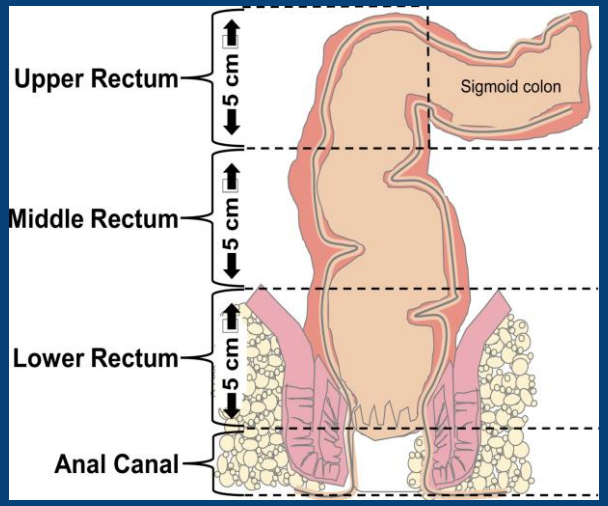
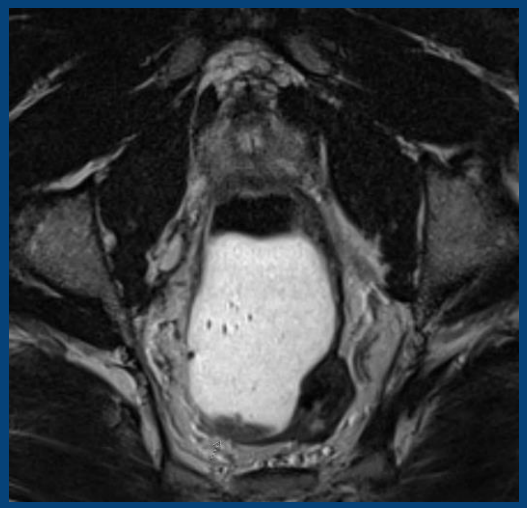


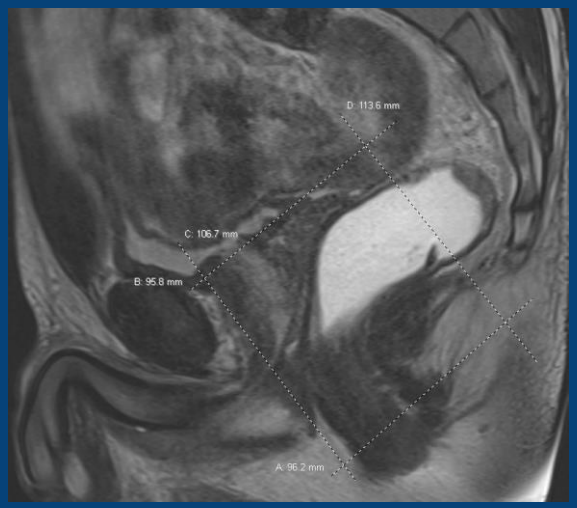
Photo from Dr. Josh Smith

Now > 600 accrued!

Q2: When can we omit RT?







Prospective series assessing omission of RT for MRI-defined good prognosis tumors

Study	N	CRM	T stage	EMVI	Outcome
Mercury (2011)	133	>1 mm	T1/2, T3a, T3b	None	5-year LR 3.3%
OCUM (2018)	254	>1 mm	T1/2, T3 (upper/mid)	None	5-year LR 2.7%
QuickSilver (2019)	82	>1 mm	T2, T3a/b	None	+CRM 4.9%

1. Taylor FGM, Quirke P, Heald RJ, et al. *Ann Surg,* 2011.
2. Ruppert R, Junginger T, Ptok H, et al. *Br J Surg,* 2018.
3. Kennedy ED, Simunovic M, Jhaveri K, et al. *JAMA Oncol,* 2019.

Q2: When can we omit RT?

ASTRO

CLINICAL PRACTICE GUIDELINE | VOLUME 11, ISSUE 1, P13-25, JANUARY 2021 Download Full Issue

Radiation Therapy for Rectal Cancer: Executive Summary of an ASTRO Clinical Practice Guideline

Jennifer Y. Wo, MD • Christopher J. Anker, MD • Jonathan B. Ashman, MD, PhD • Nishin A. Bhadkamkar, MD • Lisa Bradfield, BA • Daniel T. Chang, MD • Jennifer Dorth, MD • Julio Garcia-Aguilar, MD • David Goff • Dustin Jacqmin, PhD • Patrick Kelly, MD • Neil B. Newman, MD, MS • Jeffrey Olsen, MD • Ann C. Raldow, MD, MPH • Erika Ruiz-Garcia, MD • Karyn B. Stitzenberg, MD • Charles R. Thomas Jr., MD • Q. Jackie Wu, PhD • Prajnan Das, MD, MS, MPH • Show less

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

GASTROINTESTINAL CANCERS | VOLUME 28, SUPPLEMENT 4, IV22-IV40, JULY 2017 Download Full Issue

Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

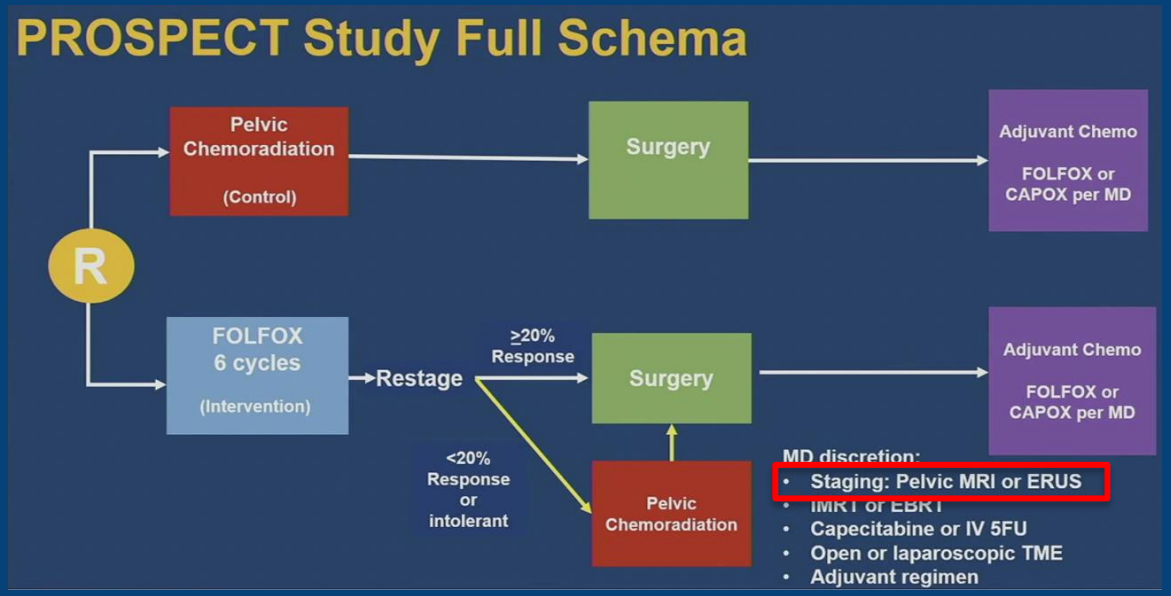
R. Glynne-Jones • L. Wyrwicz • E. Tiret • G. Brown • C. Rödel • A. Cervantes • D. Arnold • on behalf of the ESMO Guidelines Committee • Show less • Show footnotes

	ASTRO	ESMO
Location	Upper	Mid or upper
T stage	T3a/b	T3a/b
N stage	N0	N0 (mid), N0/1 (upper)
CRM	> 2 mm	>0 mm
EMVI	None	None

1. Wo JW, Anker CJ, Ashman J, et al. *Prac Radiat Oncol,* 2019.
2. Glynne-Jones R, Wyrwicz L, Tiret E, et al. *Ann. Onc,* 2017.

Q2: When can we omit RT?

PROSPECT: Chemo Alone or Chemo+RT in LARC Undergoing Surgery (PI Schrag)



Inclusion:

- Clinical Stage T2N+, T3N-, T3N+
- Chemoradiation is indicated
- Candidate for sphincter-sparing surgery

Exclusion:

- Tumor requiring an APR
- cT4 tumor
- ≥ 4 pelvic lymph nodes ≥ 1cm in short axis

1. Schrag D, Shi Q, Weiser M, et al. *ASCO,* 2023.

Q2: When can we omit RT?

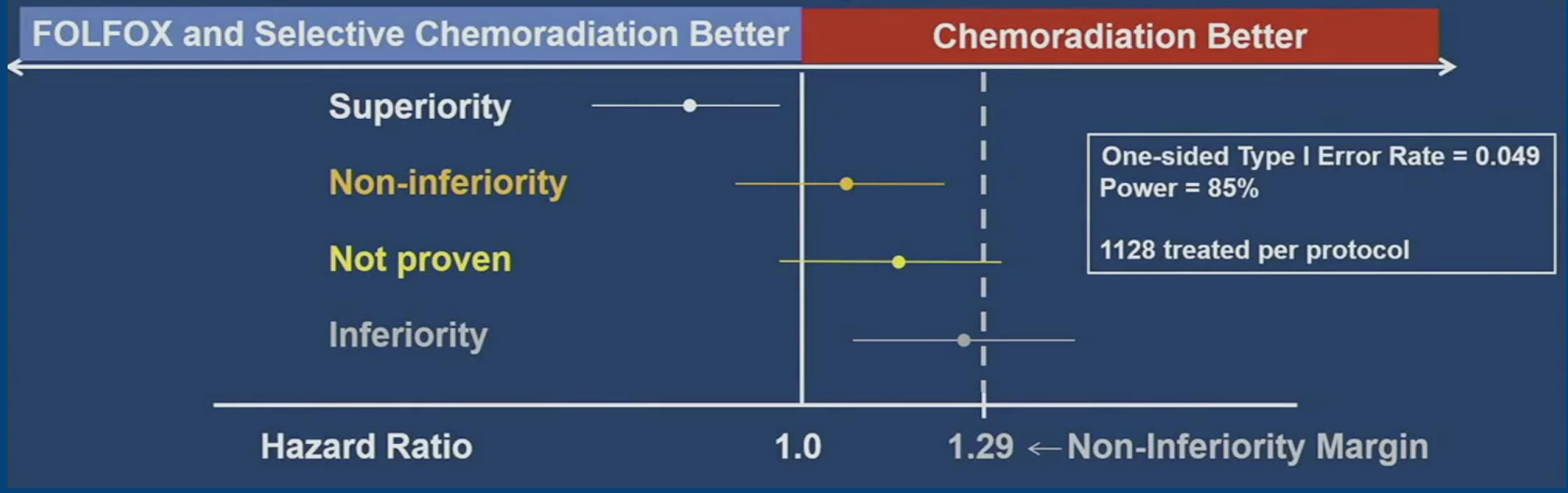
PROSPECT

- Primary Endpoint:
  - Disease Free Survival
- Secondary Endpoints:
  - Local recurrence
  - Overall survival
  - Complete (R0) surgical resection
  - Complete pathologic response
  - Toxicity-CTCAE and PRO-CTCAE
  - Quality of Life

Non-inferiority Hypothesis for Disease Free Survival

Non-inferiority could be claimed if the upper limit of the two-sided 90.2% confidence interval of the hazard ratio (HR) did not exceed 1.29.

This corresponds to an absolute difference in 5-year DFS of <5%



Upper limit of 90% CI cannot exceed **1.29**

1. Schrag D, Shi Q, Weiser M, et al. *ASCO,* 2023.

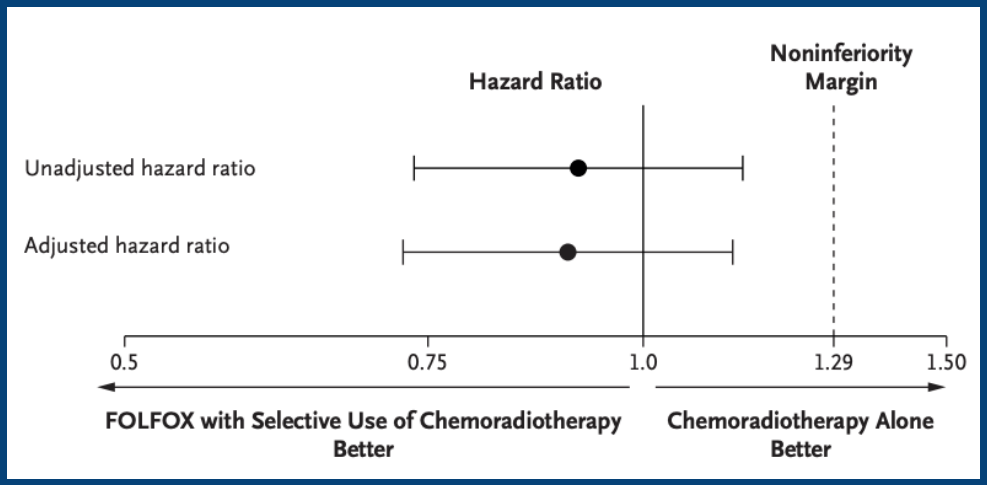
Q2: When can we omit RT?

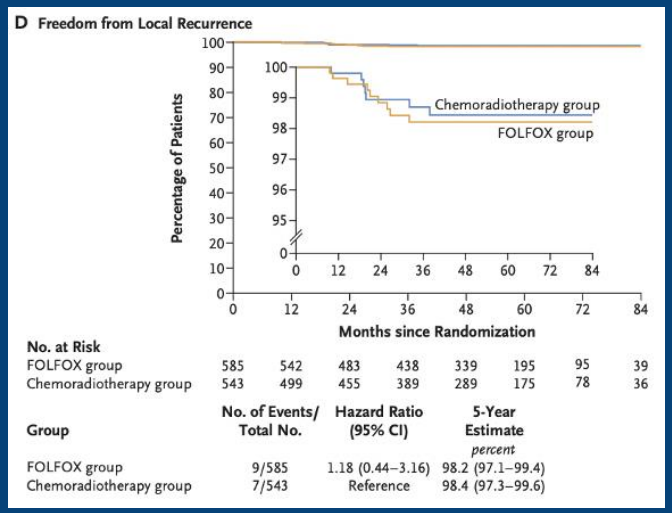
PROSPECT

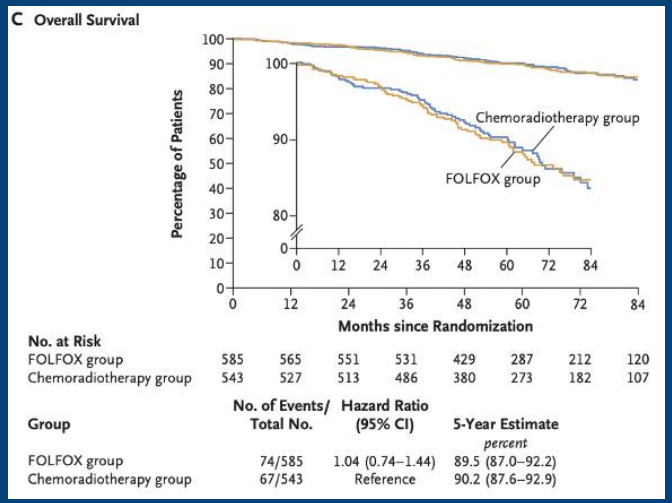

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Preoperative Treatment of Locally Advanced Rectal Cancer







- No differences in oncologic outcomes
- 9% of patients in neoadjuvant FOLFOX arm required chemoRT

1. Schrag D, Shi Q, Weiser M, et al. *NEJM,* 2023.

Q2: When can we omit RT?

PROSPECT

Journal of Clinical Oncology > List of Issues > Newest Content >

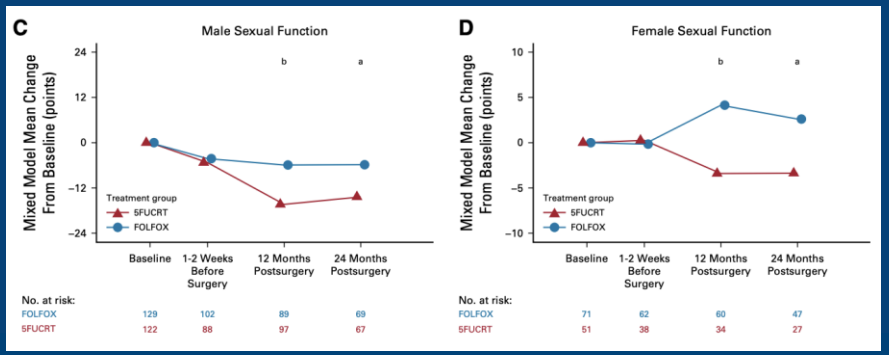
ORIGINAL REPORTS | Supportive Care and Quality of Life

Patient-Reported Outcomes During and After Treatment for Locally Advanced Rectal Cancer in the PROSPECT Trial (Alliance N1048)

- PROs used!
- Toxicity worse w FOLFOX pre-op
- By 12 & 18 months, similar

	Neoadjuvant Treatment			
PRO-CTCAE	FOLFOX	5FUCRT	Raw *P*	Multiplicity-Adjusted *P*
Anxiety	200/493 (41%)	117/446 (26%)	<.001	<.001
Appetite loss	376/492 (76%)	241/446 (54%)	<.001	<.001
Constipation	339/493 (69%)	192/446 (43%)	<.001	<.001
Depression	199/493 (40%)	94/443 (21%)	<.001	<.001
Diarrhea	220/492 (45%)	253/447 (57%)	<.001	.004
Dysphagia	340/493 (69%)	74/447 (17%)	<.001	<.001
Dyspnea	281/492 (57%)	128/447 (29%)	<.001	<.001
Edema	117/492 (24%)	58/445 (13%)	<.001	<.001
Fatigue	429/492 (87%)	312/446 (70%)	<.001	<.001
Mucositis	349/493 (71%)	102/447 (23%)	<.001	<.001
Nausea	404/490 (82%)	253/445 (57%)	<.001	<.001
Neuropathy	431/492 (88%)	166/447 (37%)	<.001	<.001
Pain	283/493 (57%)	267/446 (60%)	.44	.86
Vomiting	187/492 (38%)	88/447 (20%)	<.001	<.001

Any Severe Adverse Event (composite score 3)		
FOLFOX	5FUCRT	Raw *P*
5/236 (2%)	8/203 (4%)	.26
0/237 (0%)	0/205 (0%)	—
4/238 (2%)	8/204 (4%)	.15
3/238 (1%)	1/198 (1%)	.41
6/237 (3%)	8/205 (4%)	.41
0/238 (0%)	0/204 (0%)	—
1/237 (0%)	1/203 (0%)	.91
1/238 (0%)	3/203 (1%)	.24
13/235 (6%)	7/204 (3%)	.29
0/238 (0%)	1/205 (0%)	.28
0/233 (0%)	0/205 (0%)	—
8/237 (3%)	10/205 (5%)	.43
10/237 (4%)	10/205 (5%)	.74
0/237 (0%)	0/205 (0%)	—



- Sexual toxicity worse with RT

1. Basch E, Dueck AC, Mitchell SA, et al. *NEJM,* 2023.

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Q2: When can we omit RT?

Rectal Cancer Patients Could Be Spared the Effects of Radiation

A large "de-escalation" trial suggests that tens of thousands of people annually may be able to rely on only chemotherapy and surgery to treat their illness.

Share full article

Awilda Peña of Boston found out she had rectal cancer when she was 38. "I could not believe it," she said. She agreed to participate in the trial because, she said, "I was motivated by hope." Sophie Park for The New York Times

The ASCO Post COVID-19 ABOUT NEWS MEETINGS TOPICS VIDEOS POD

PROSPECT Trial: Pelvic Radiation Therapy Avoided for Most Patients With Intermediate-Risk, Locally Advanced Rectal Cancer

By Caroline Helwick
July 10, 2023

Radiation May Be Safely Omitted in Select Patients With Locally Advanced Rectal Cancer

By The ASCO Post Staff

Posted: 6/4/2023 11:46:00 AM
Last Updated: 6/19/2023 2:45:36 PM

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Patients with locally advanced rectal cancer with tumors that respond to chemotherapy may safely forgo radiation therapy before surgery, based on the findings of the PROSPECT trial. These data were presented by **Deborah Schrag, MD, FASCO, MPH**, at the 2023 ASCO Annual Meeting (Abstract LBA2) and simultaneously published in *The New England Journal of Medicine* (efficacy data) and the *Journal of Clinical Oncology* (patient-reported outcomes data). Omitting radiation therapy can reduce short- and long-term side effects that impact quality of life, while providing similar outcomes in disease-free survival and overall survival.

Deborah Schrag, MD, FASCO, MPH

About the Study

The phase III PROSPECT trial enrolled 1,194 patients from June 2012 to December 2018 with rectal cancer that had spread to nearby tissue or lymph nodes but had not spread to distant organs. Patients were randomly assigned to the chemoradiation therapy group (control) or to the modified FOLFOX6 (leucovorin, fluorouracil, oxaliplatin) chemotherapy with selective use of chemoradiation therapy group (intervention), and 1,128 patients went on to receive treatment through the study.

Q2: When can we omit RT?

PROSPECT: considerations

	ASTRO	ESMO
Location	Upper	Mid or upper
T stage	T3a/b	T3a/b
N stage	N0	N0 (mid), N0/1 (upper)
CRM	> 2 mm	>0 mm
EMVI	None	None

- Patients had lower risk rectal cancer
  - Many eligible for upfront surgery (w likely de-escalation of adjuvant chemo)
- Experimental arm had intensified chemotherapy

Supplementary Table 3A Adherence to neoadjuvant FOLFOX

	Intervention Group FOLFOX + selective Chemoradiation (N=585)
Total number of preoperative FOLFOX cycles, n (%)	
Received protocol stipulated quantity (≥ 5 cycles) of FOLFOX	555 (94.9%)
Received 3 to 4 cycles of FOLFOX	12 (2.1%)
Received 1 to 2 cycles of FOLFOX	18 (3.1%)

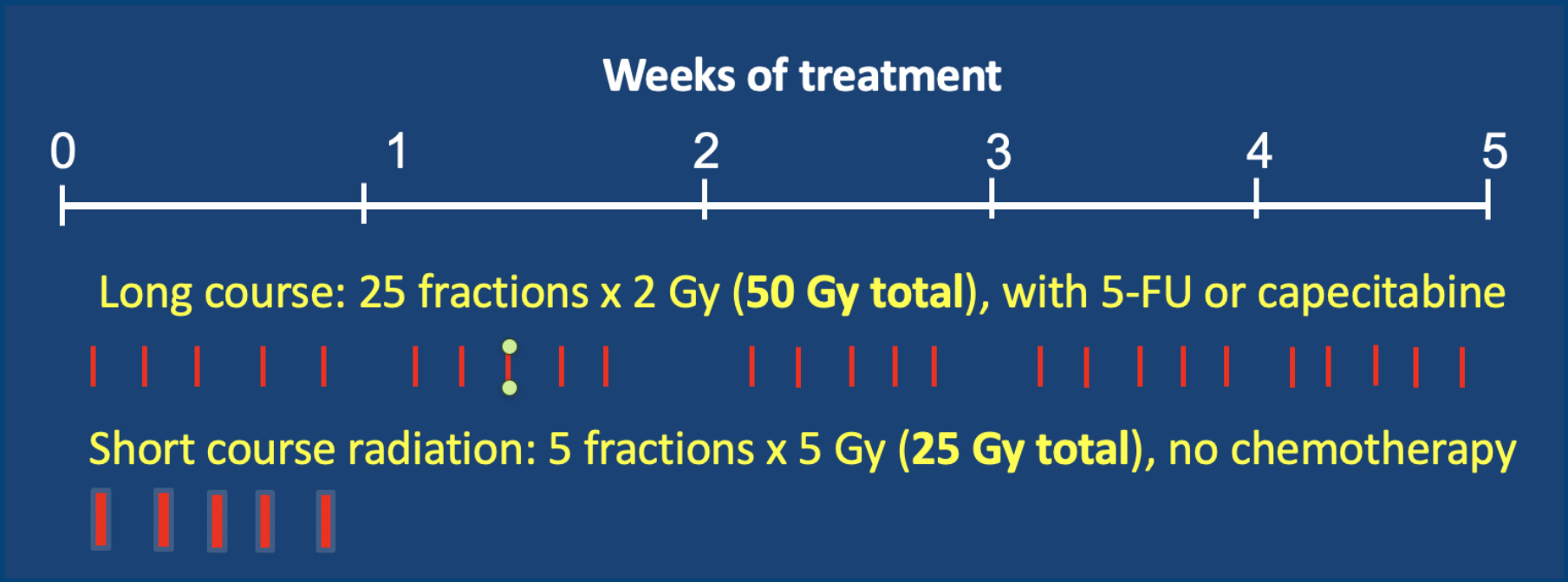
Among patients who had rectal surgery and received post-operative FOLFOX

	N=348	N=281
Number of postoperative FOLFOX cycles administered n (%)		
1-4 cycles of FOLFOX	60 (17.2%)	35 (12.5%)
5-6 cycles of FOLFOX	274 (78.7%)	36 (12.8%)
7-9 cycles of FOLFOX	7 (2.0%)	201 (71.5%)
10-12 cycles of FOLFOX	7 (2.0%)	9 (3.2%)

- No non-operative management option

- PROSPECT provides an OPTION in lower risk rectal cancer
- Toxicity tradeoffs key

Q3: Duration of RT – short versus long

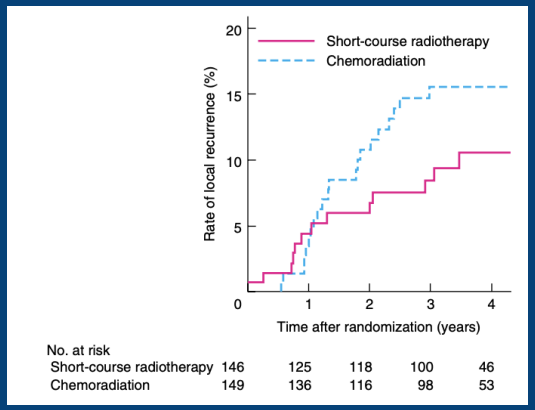


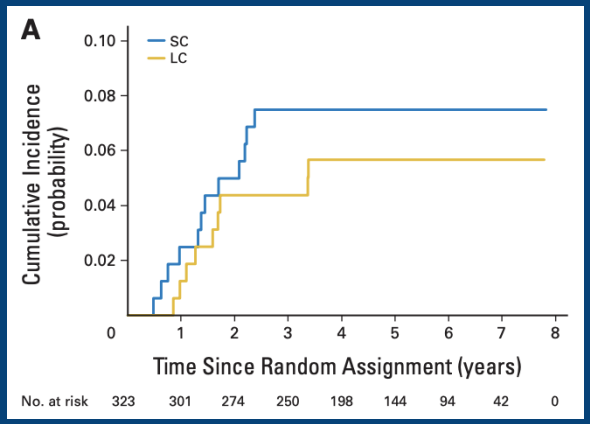
- Biologic effective dose (BED):
  - Bigger fraction sizes more potent – 5 Gy given in 1 fraction vs. 5 Gy in 2 fractions

- BED of short course: **37.5** Gy BED of long course: **50** Gy

Q3: Duration of RT – short versus long

- Two trials showed similar outcomes in the pre-operative setting:





RT	Polish (n=312)	TROG 01.04 (n=326)
Short course LR*	15.6% (4 year)	4.4% (3 year)
Long course LR	10.6% (4 year)	7.5% (3 year)
P	0.21	0.24

*LR=local recurrence

1. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. *Br J Surg,* 2006.
2. Ngan SY, Burmeister B, Fisher RJ, et al. *J Clin Oncol,* 2012.

Q3: Duration of RT – short versus long

PRODIGE 42

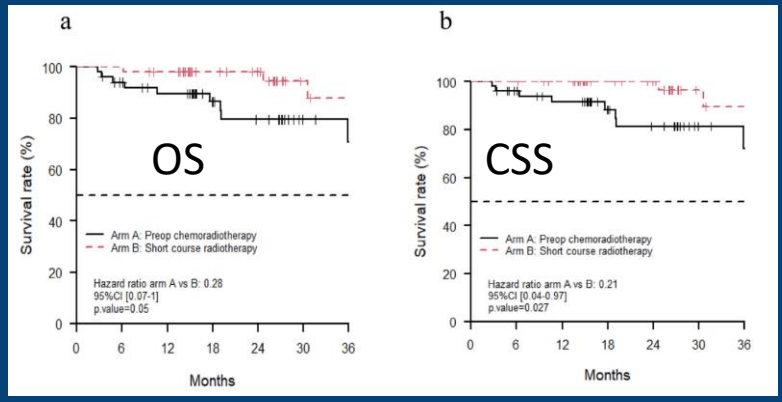
Eligibility:
≥75 years
Resectable
T3-4 <12 cm AV
T2 distal

R

- Long-course chemoRT (50 Gy/25 fractions) → 7+/- 1 week → TME
- Short course RT (25 Gy/5 fractions) → 7+/- 1 week → TME

Co-primary endpoints:
-R0 resection rate
-Degradation of autonomy IADL score

N=103	Short	Long	Significance
R0 resection	84.3%	88%	NS
IADL worsening (3 mo)	14.8%	44.8%	0.03
Serious acute AE	9.8%	22%	NS



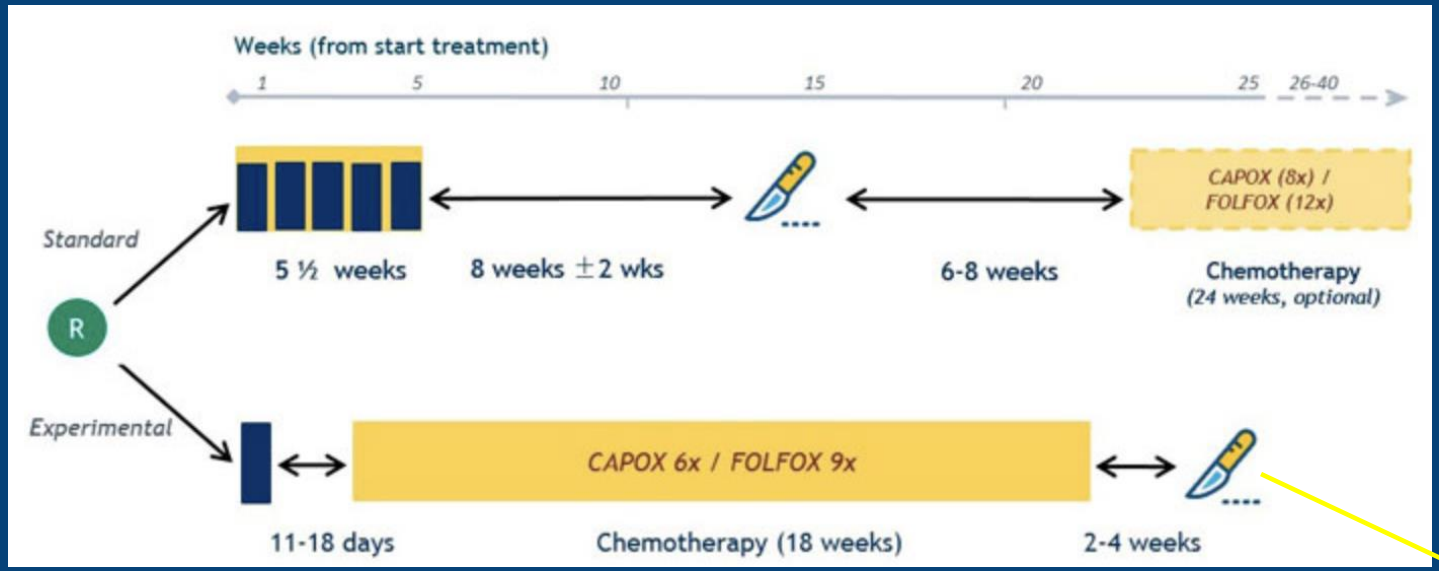
Short course RT may be preferable in elderly patients

1. Francois E, De Bari B, Ronchin, et al. *Eur J Cancer,* 2023.

Q3: Duration of RT – short versus long

RAPIDO

(n=912)



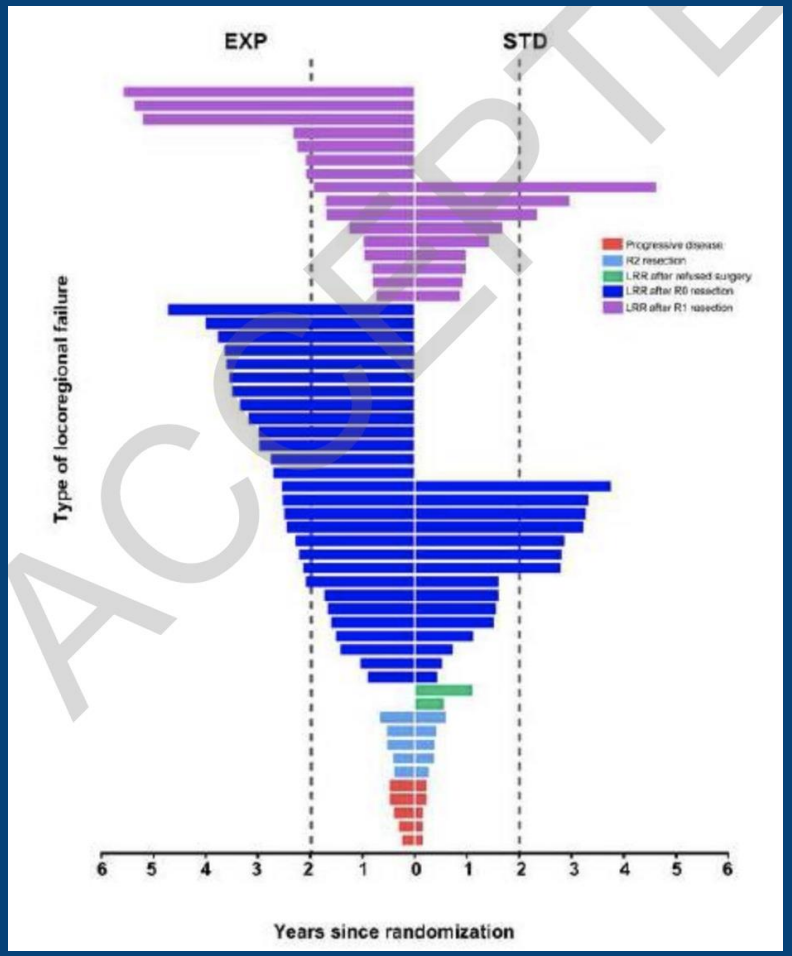
42% adjuvant chemo

- Patients were high risk:
  - cT4, EMVI+, MRF+, lateral LN+
- Primary endpoint: 3-year disease-related treatment failure (DrTF)
  - Distant met, new tumor, treatment-related death, locoregional failure

1. Bahadoer RR, Dijkstra EA, van Etten B, et al. *Lancet Oncol,* 2021.
2. Dijkstra EA, Nilsson PJ, Hospers GAP, et al. *Ann Surg,* 2023

Q3: Duration of RT – short versus long

- **RAPIDO**: 5-year follow-up



- DrTF better with short course:
  - -27.8% vs. 34.0% (p=0.048)
  - -Driven by distant metastases
- LR higher w short course:
  - -10% vs. 6% (p=0.03)

Location of Recurrence	Short course TNT (n=44)	"Standard" (n=26)
Presacral	19	9
Anastomosis	14	9
Anterior	11	3
Lateral	8	7
Perineal	6	3
Other	0	3

1. Bahadoer RR, Dijkstra EA, van Etten B, et al. *Lancet Oncol,* 2021.
2. Dijkstra EA, Nilsson PJ, Hospers GAP, et al. *Ann Surg,* 2023

Q3: Duration of RT – short versus long

- Short course RT:
  - ↓ LR vs. surgery alone
    - Swedish, Dutch trials
  - ~ LR, OS, DFS vs. long course RT
    - Polish I, TROG, Stockholm III Trials
  - ↑ LR with TNT strategy vs. long course RT
    - RAPIDO
- When do I use short course RT?
  - Logistics: patient cannot come for 5 weeks
  - Patients with metastatic cancer
  - Consider in elderly patients
  - No high-risk features per RAPIDO
    - cT4, EMVI+, MRF+, lateral LN+ (obturator, internal iliac)

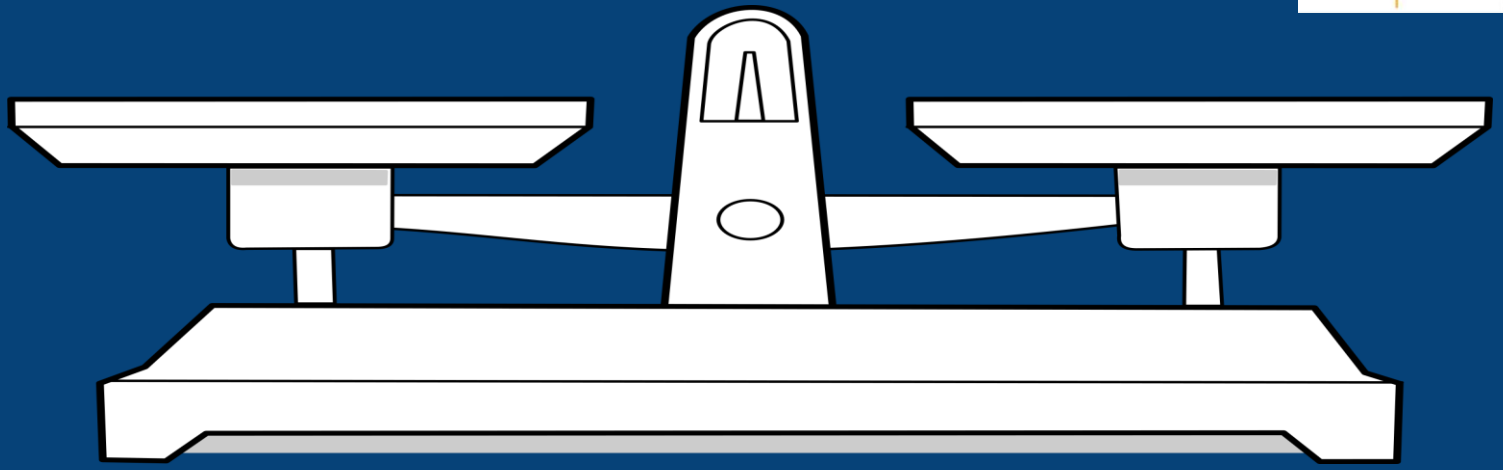
Q4: RT or chemo first?

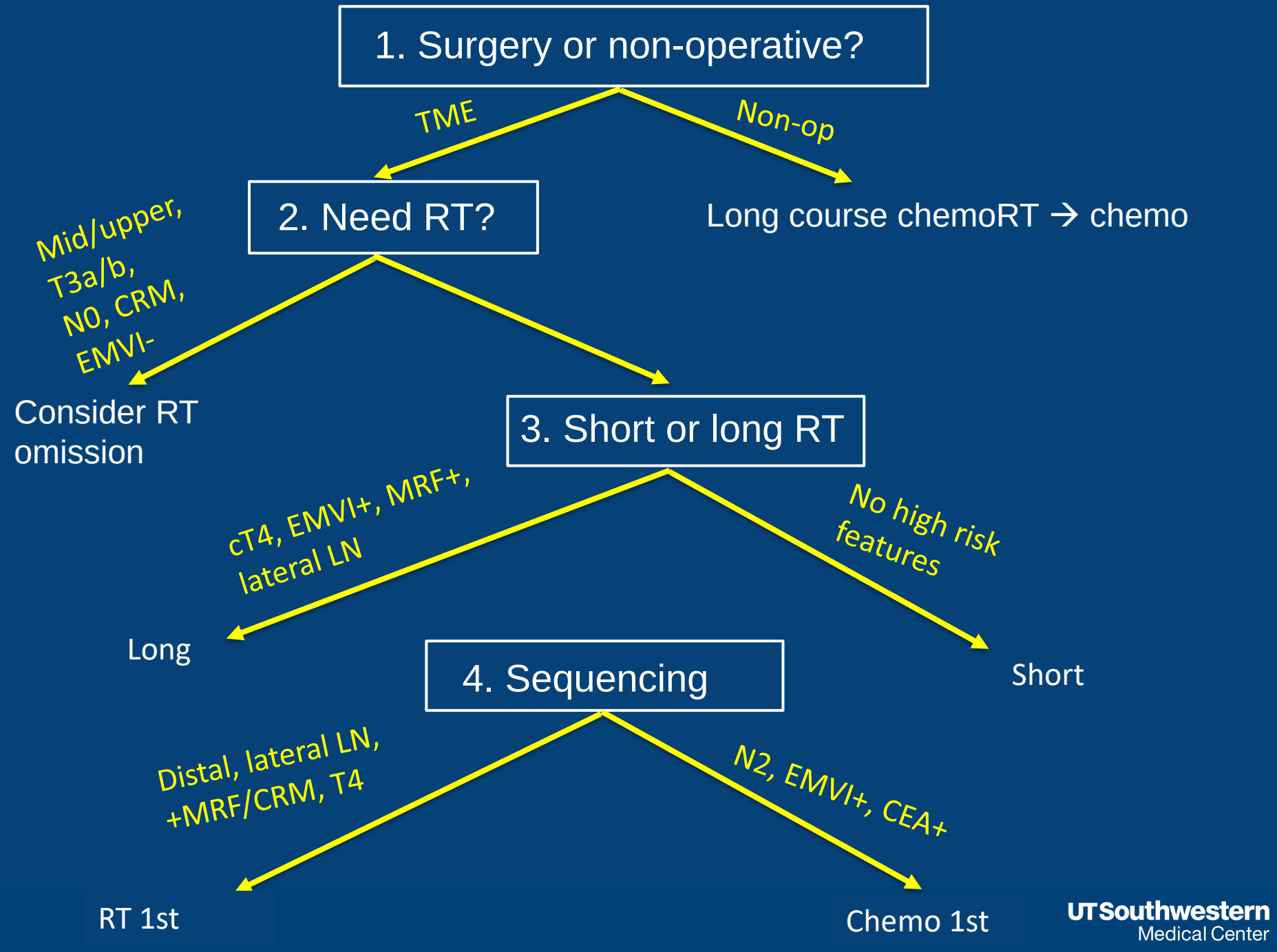
Local recurrence

- Distal tumor requiring APR
- Lateral pelvic nodes
- +MRF/CRM →
- T4 disease

Distant recurrence

- N2
- EMVI+
- Elevated CEA →





Conclusions/Take-Away

- In the pre-operative setting, RT is used to reduce local recurrence.
  -“Definitive” RT is used for organ preservation.
- If treating with non-operative intent, chemoradiation with consolidation chemotherapy is a preferred regimen.
- Upfront surgery with omission of RT an option for subset of “good prognosis” tumors identified on MRI.
- Long (versus short course) RT preferable for high-risk tumors.
- RT sequencing in neoadjuvant setting depends on balance between local and distant recurrence risk factors.

Thank you!

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