Oncology Updates: Colorectal Cancer

Perspectives from a Radiation Oncologist

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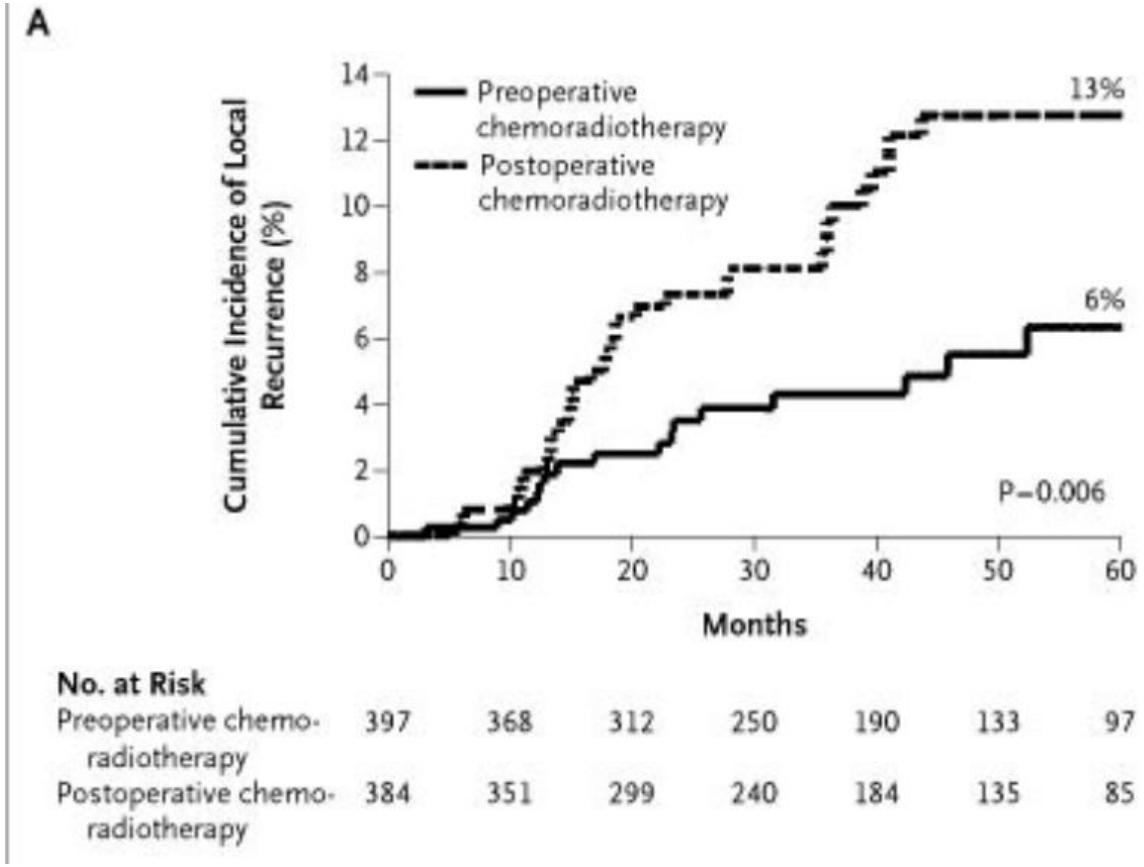
Agenda

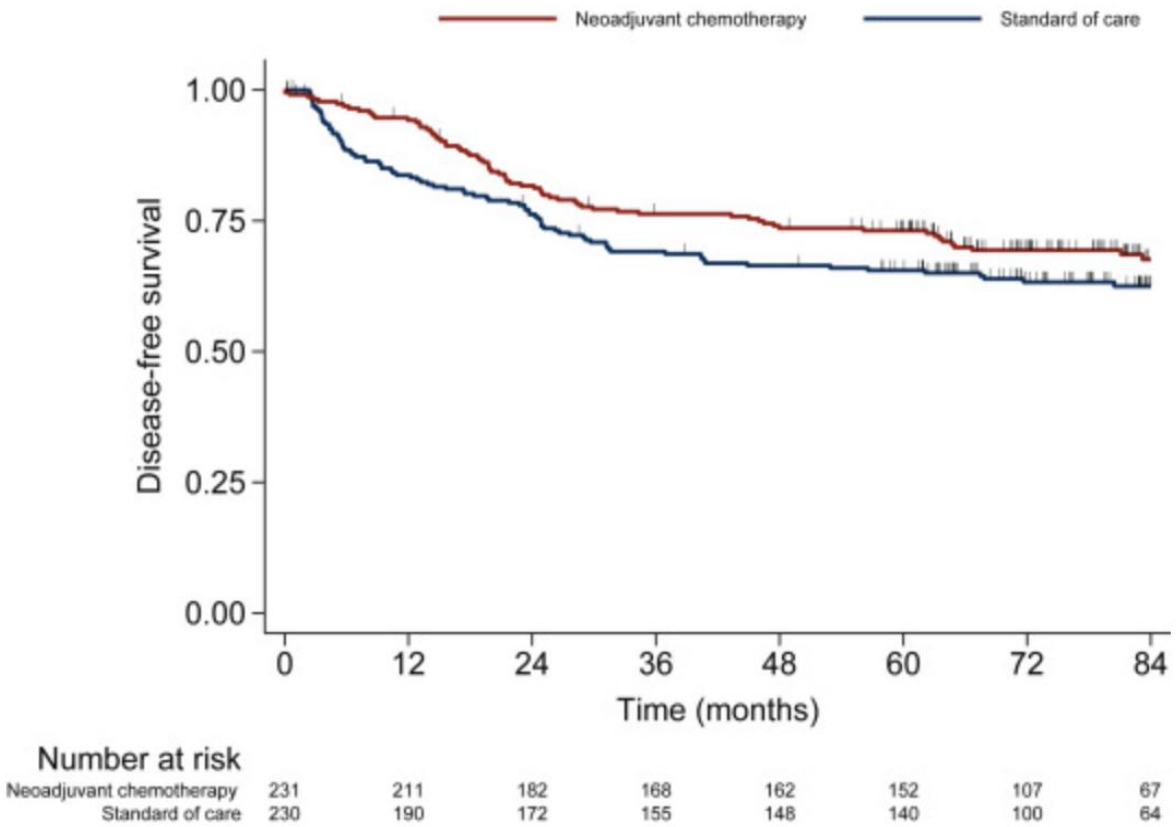
- Localized Rectal Cancer
  - Customizing Total Neoadjuvant Therapy (TNT) to achieve patient goals
- Metastatic CRC
  - New trials to determine role of local therapy in oligometastatic disease

The TNT Era in Rectal Cancer

- Data suggest that delivering both radiation and chemotherapy preoperatively for T3/N+ disease is better tolerated and more effective



Sauer, et al. NEJM (2004)



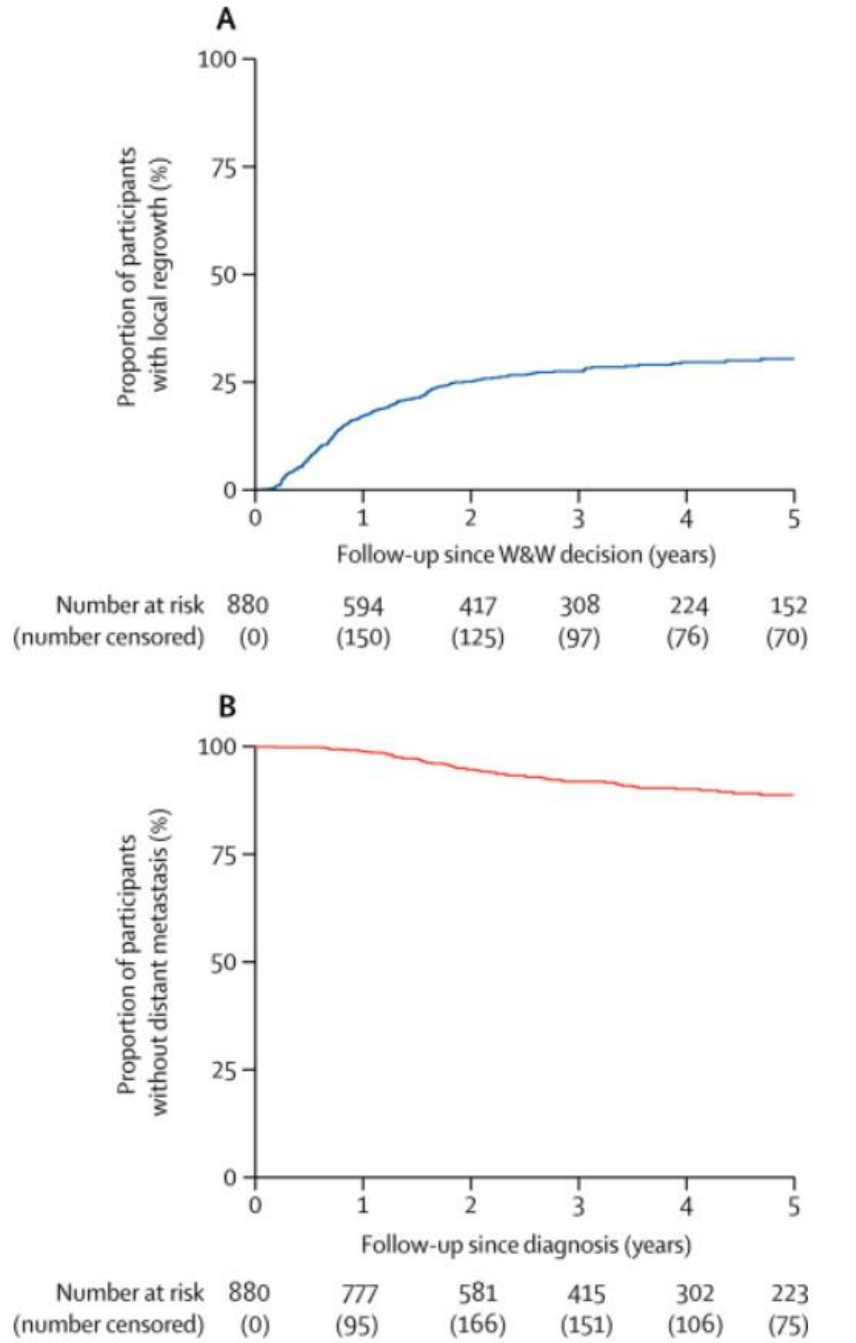
Conroy et al. Ann Onc 2024

Do all patients need chemo, RT and surgery?

- Trimodality therapy may be overtreatment for many patients
- Emerging data suggest that we can customize TNT based on patient's goals and preferences
- Key options include:
  - Nonoperative management AKA "Watch and wait"
  - Omitting RT for selected patients

What happens if we don't resect?

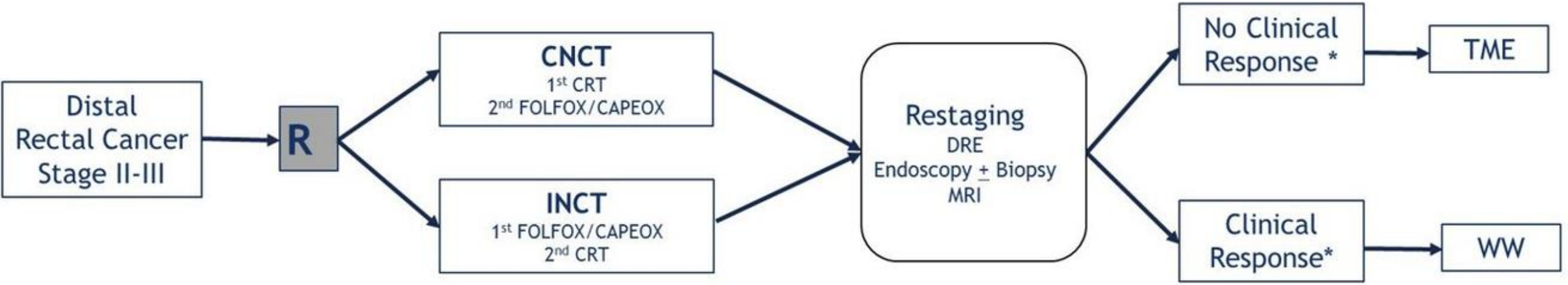
- Observational study of n=880 patients with complete response after neoadjuvant therapy (mostly chemoRT only)
- 25% cumulative local regrowth
- Almost all in first two years
- Most patients with local regrowth underwent successful salvage surgery
- 94% 5 year disease free survival



van der Valk MJM, et al. Lancet (2018)

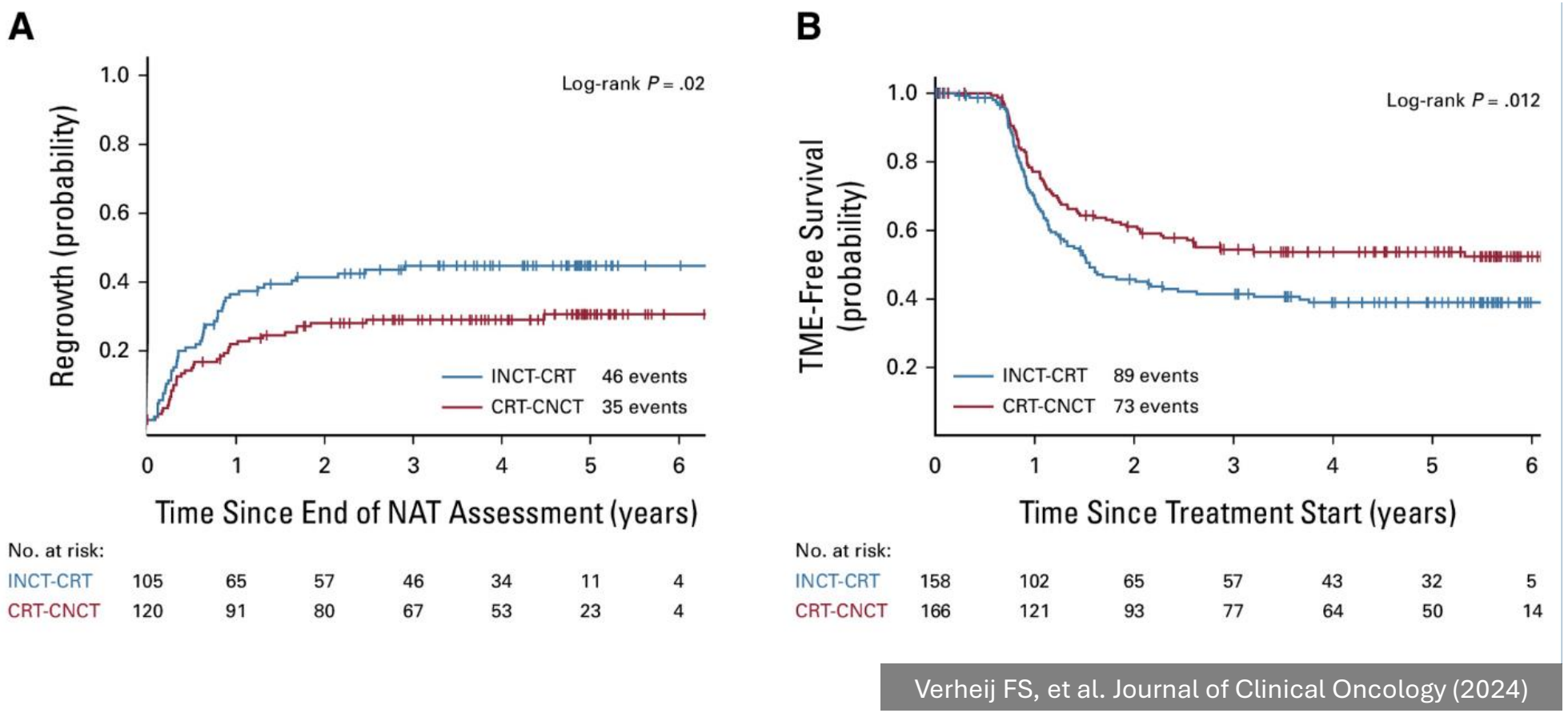
Organ Preservation in Rectal Adenocarcinoma (OPRA) trial

- Randomized phase II trial evaluating sequencing of TNT and effect on organ preservation



- Enrolled n=324 patients from 2014 - 2020

OPRA results

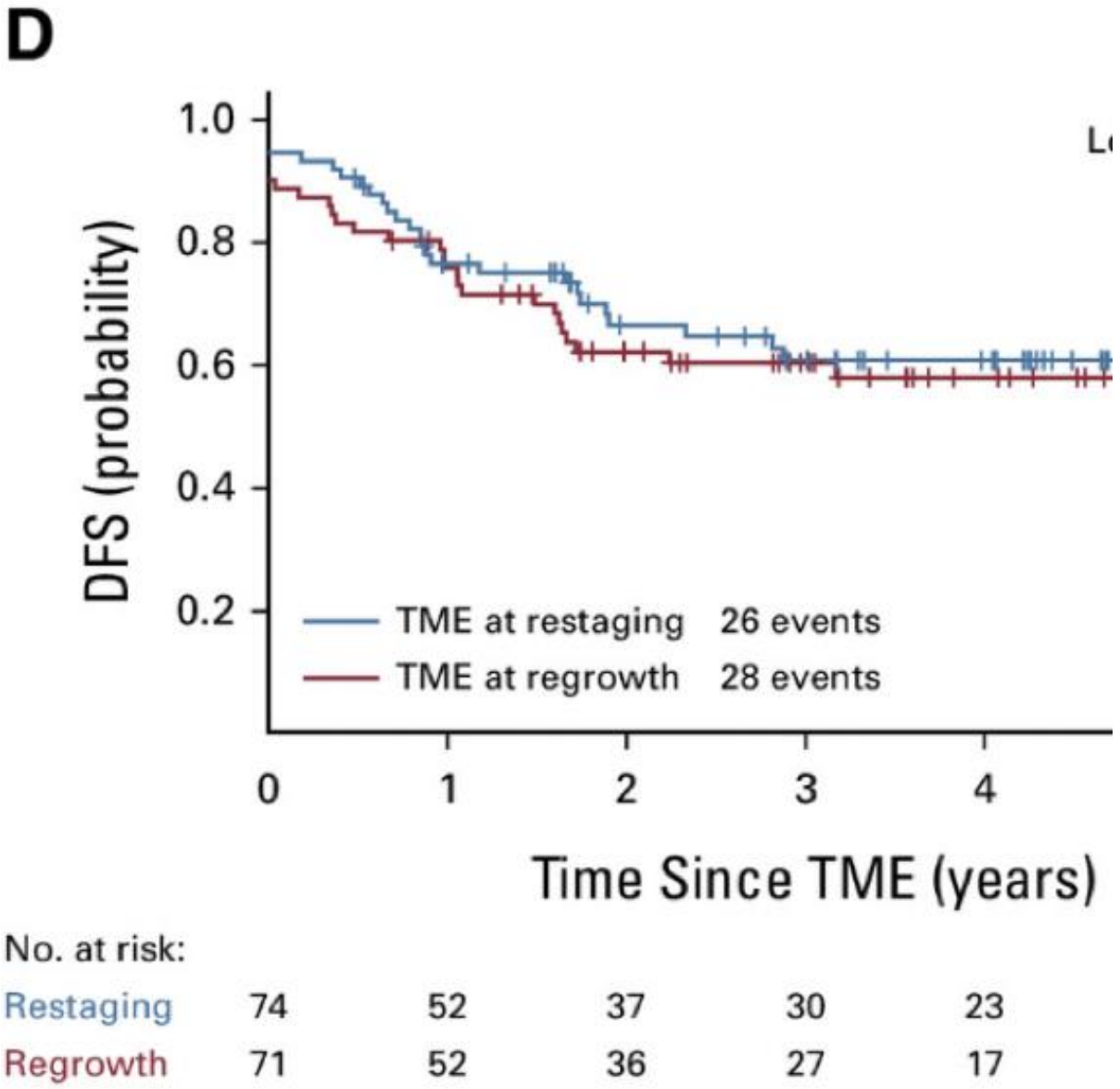


Verheij FS, et al. Journal of Clinical Oncology (2024)

Up to 50% of patients can successfully avoid surgery, especially if RT given before chemo

Is it safe to delay surgery?

- Long term disease free survival outcomes are similar to other studies with TNT and mandatory surgery



How to define clinical complete response

Table 1 Adapted MSKCC criteria of rectal tumor regression schema following neoadjuvant treatment [7]

	Complete clinical response (cCR)	Near complete clinical response (nCR)	Incomplete clinical response (iCR)
Endoscopy	- Flat, white scar - Telangiectasia - Absence of ulcer and mucosal nodularity	- Small mucosal nodules/minor mucosal irregularity - Superficial Ulceration - Mild persisting erythema of the scar	- Visible tumor
MRI-T2W	Only dark T2 signal, no intermediate signal AND No visible lymph nodes	Mostly dark T2 signal, some intermediate signal AND/OR Partial regression of lymph nodes	More intermediate than dark T2 signal, no T2 scar AND/OR No regression of lymph nodes
MRI-DWI	No visible tumor on B800-B1000 signal AND/OR Lack of or low signal on ADC map Uniform linear signal in wall above tumor acceptable	Significant regression of signal on B800-B1000 AND/OR Minimal or low residual signal on ADC map	Insignificant regression of signal on B800-B1000 AND/OR Obvious low signal on ADC map

Smith JJ, et al. BMC Cancer (2015)

Watch and wait surveillance protocol

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Rectal Cancer

NCCN Guidelines Index
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Discussion

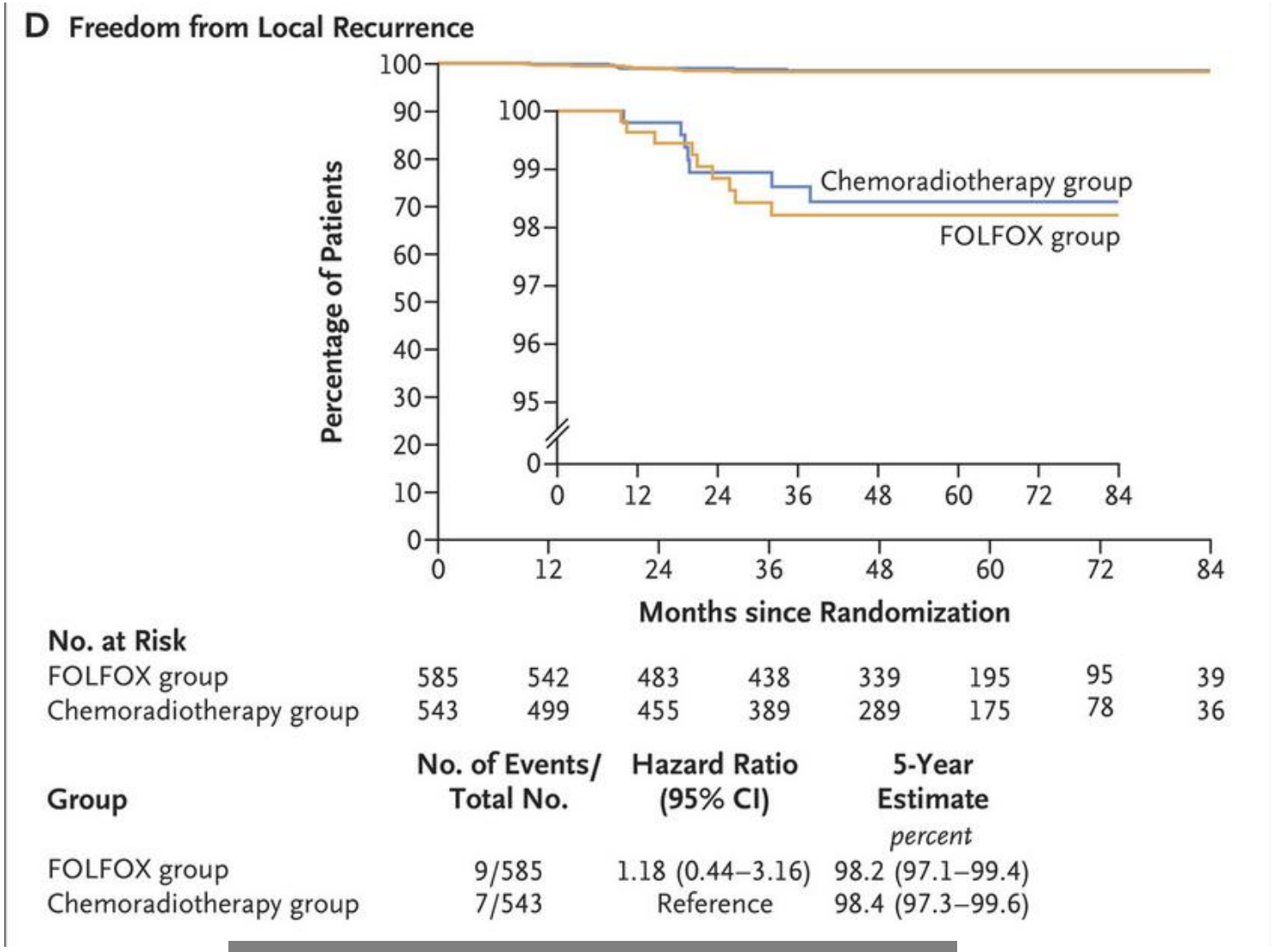
SURVEILLANCE FOLLOWING NONOPERATIVE MANAGEMENT

- **History and physical examination every 3–6 months for 2 years and then every 6 months for a total of 5 years**
- **CEA every 3–6 months for 2 years, then every 6 months for a total of 5 years**
- **DRE and proctoscopy or flexible sigmoidoscopy every 3–4 months for 2 years, then every 6 months for a total of 5 years**
- **MRI rectum every 6 months for up to 3 years**
- **CT chest/abdomen every 6–12 months for a total of 5 years, CT pelvis to be included once no longer doing MRI**
- **Colonoscopy at 1 year following completion of therapy**
  - **If advanced adenoma, repeat in 1 year**
  - **If no advanced adenoma, repeat in 3 years, then every 5 years**

Do all patients need chemo, RT and surgery?

- Trimodality therapy may be overtreatment for many patients
- Emerging data suggest that we can customize TNT based on patient's goals and preferences
- Key options include:
  - Nonoperative management AKA "Watch and wait"
    - ChemoRT followed by Chemotherapy is likely ideal sequence
    - Good for:
      - Low tumors requiring APR
      - Patients who desire to avoid surgery
      - Ok with intensive follow up
  - Omitting RT for selected patients

RT Omission: PROSPECT trial



No. at Risk

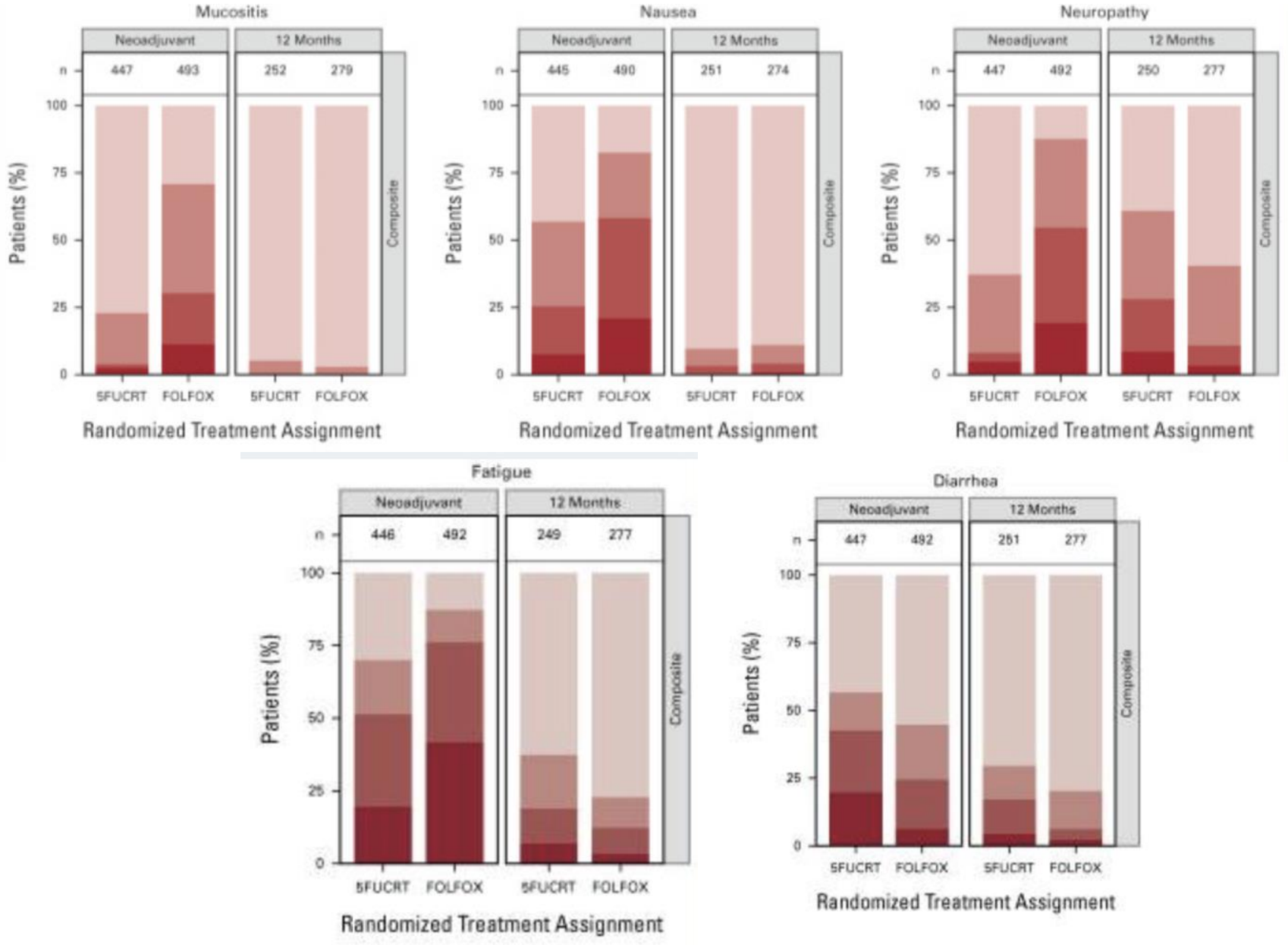
FOLFOX group	585	542	483	438	339	195	95	39
Chemoradiotherapy group	543	499	455	389	289	175	78	36

Group	No. of Events/ Total No.	Hazard Ratio (95% CI)	5-Year Estimate
			percent
FOLFOX group	9/585	1.18 (0.44–3.16)	98.2 (97.1–99.4)
Chemoradiotherapy group	7/543	Reference	98.4 (97.3–99.6)

Schrag, et al. NEJM (2023)

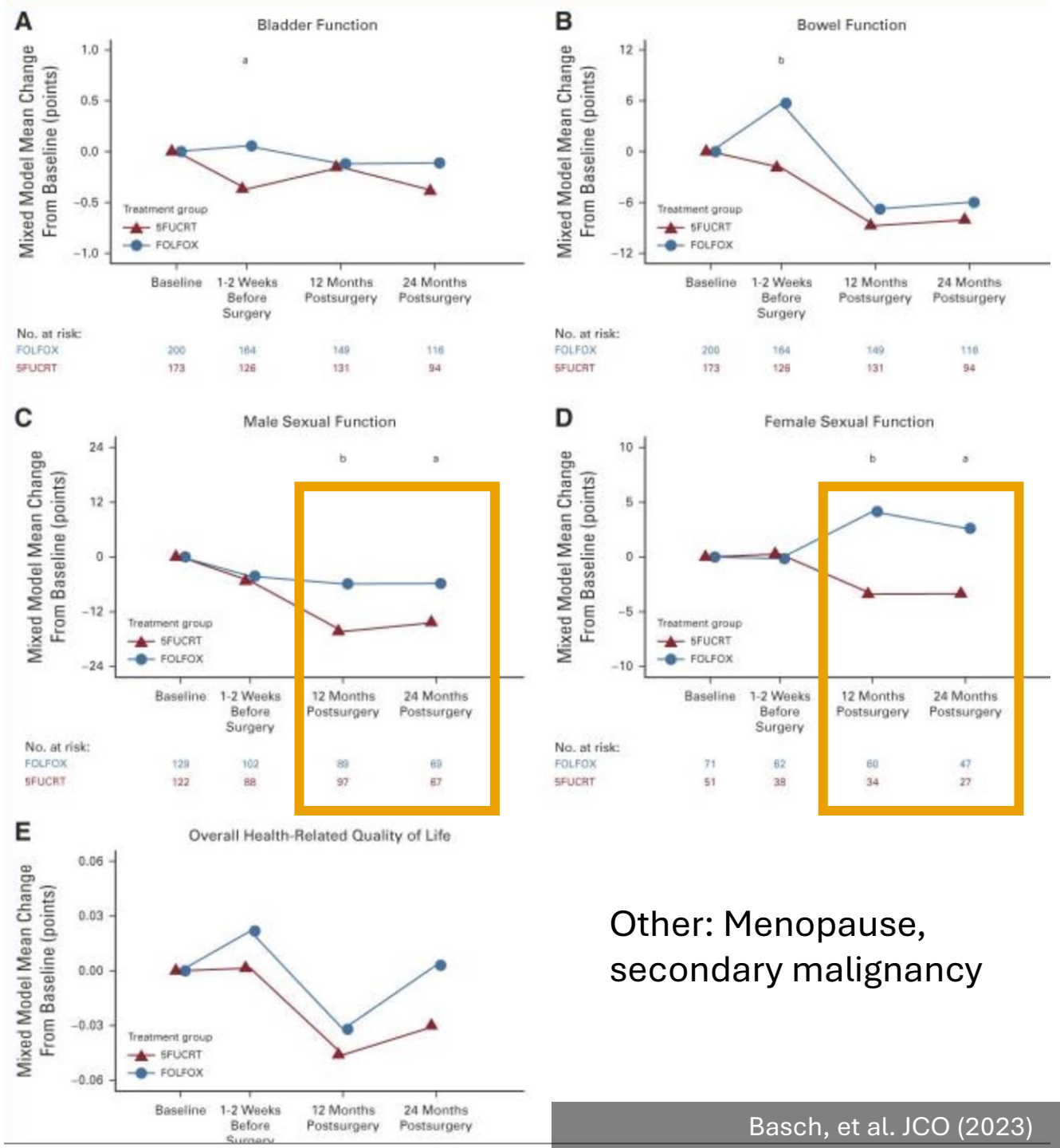
- Alternative strategy is to give neoadjuvant chemotherapy alone followed by surgical resection
- Key is to select a population of tumors at LOW risk for local recurrence -> less benefit from RT
- NOT Eligible:
  - Low tumors (surgeon assed as requiring APR)
  - T4 disease
  - N2 disease
  - Threatened MRF/CRM on MRI
- Patients must get surgery - watch and wait NOT recommended after chemo alone
- ~10% risk of needing chemoRT if poor response to chemo

Chemo vs CRT side effect profile – Short Term



Basch, et al. JCO (2023)

Chemo vs CRT side effect profile – Long Term



Other: Menopause, secondary malignancy

Basch, et al. JCO (2023)

Do all patients need chemo, RT and surgery?

Nonoperative management AKA "Watch and wait"

- ChemoRT followed by Chemotherapy is likely ideal sequence
- Good for:
  - Low tumors requiring APR
  - Patients who desire to avoid surgery
  - Ok with intensive follow up

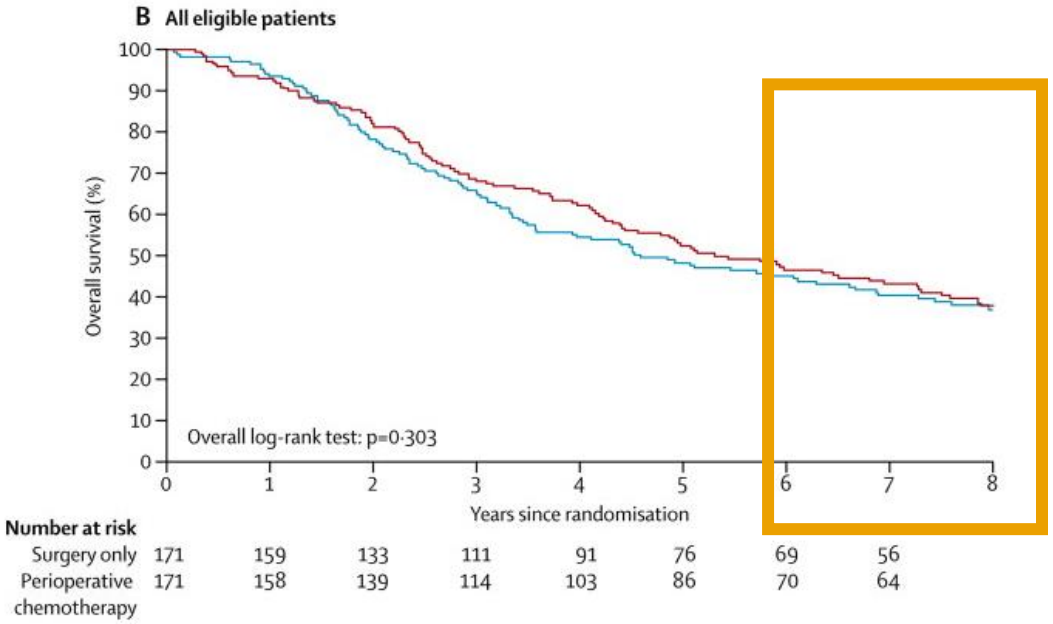
Omitting RT

- Chemo alone followed by surgery does not compromise outcomes for low risk patients
- Good for:
  - Higher tumors
  - Patients OK receiving surgery
  - Concern about RT side effects (menopause, sexual dysfunction, secondary malignancy)
  - Patients with prior pelvic RT

Part 2: Defining and Treating Oligometastatic Disease

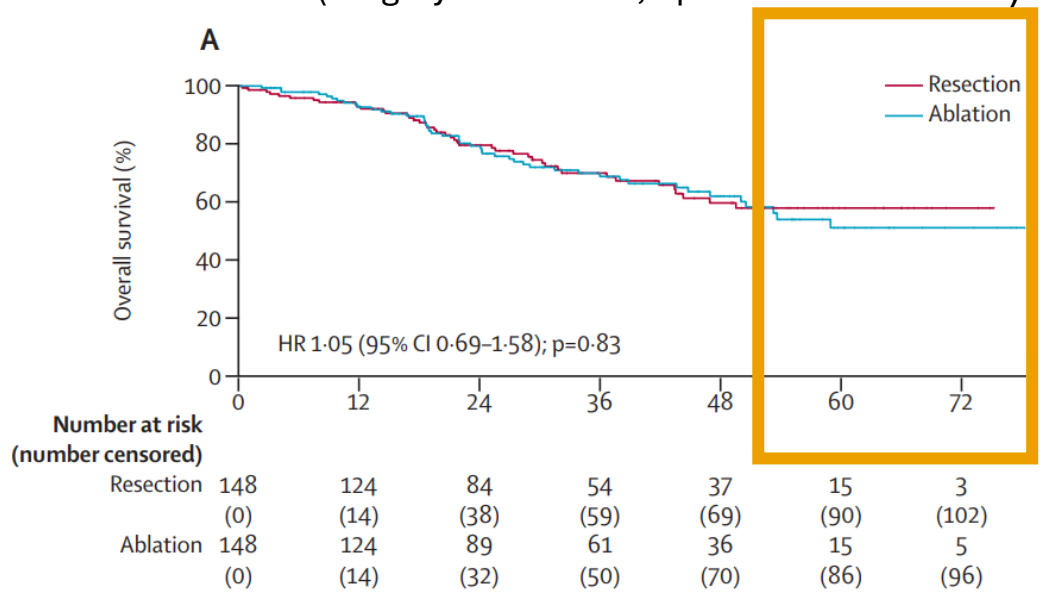
- It has long been recognized that colorectal cancer with liver metastases can be cured in selected patients
- Variety of liver directed therapies used: Surgery, Ablation, SBRT

EORTC 40983: Resection +/- chemotherapy, up to 4 mets:



Nordlinger, et al. Lancet Oncology (2013)

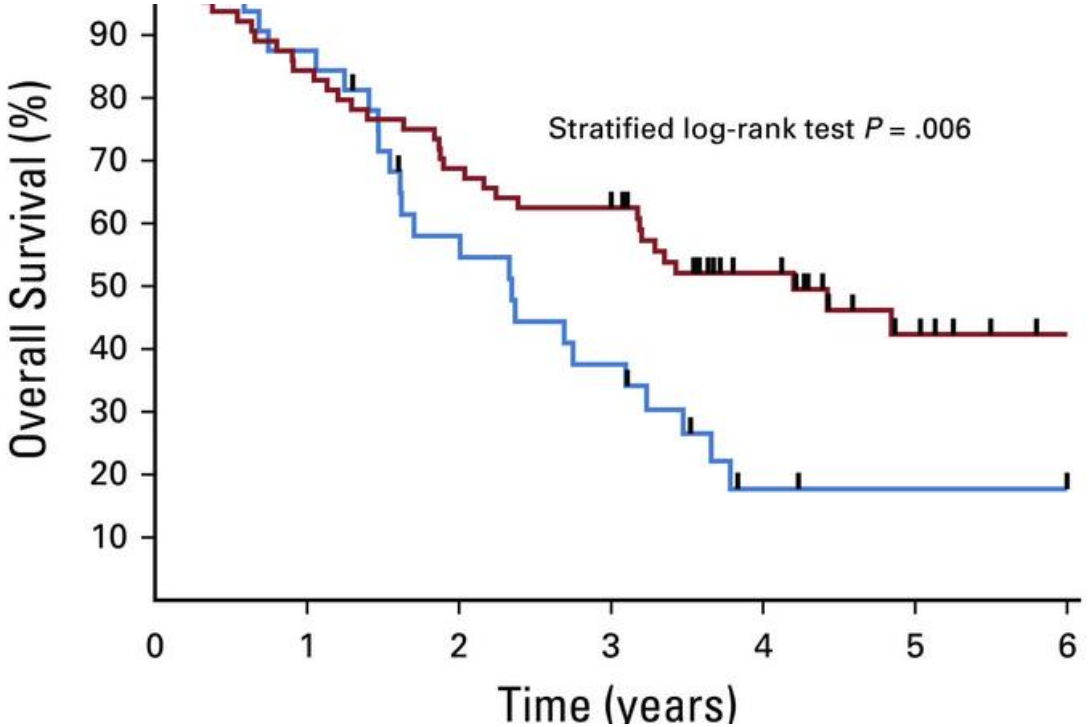
Collision trial (Surgery vs Ablation, up to 10 but median 2):

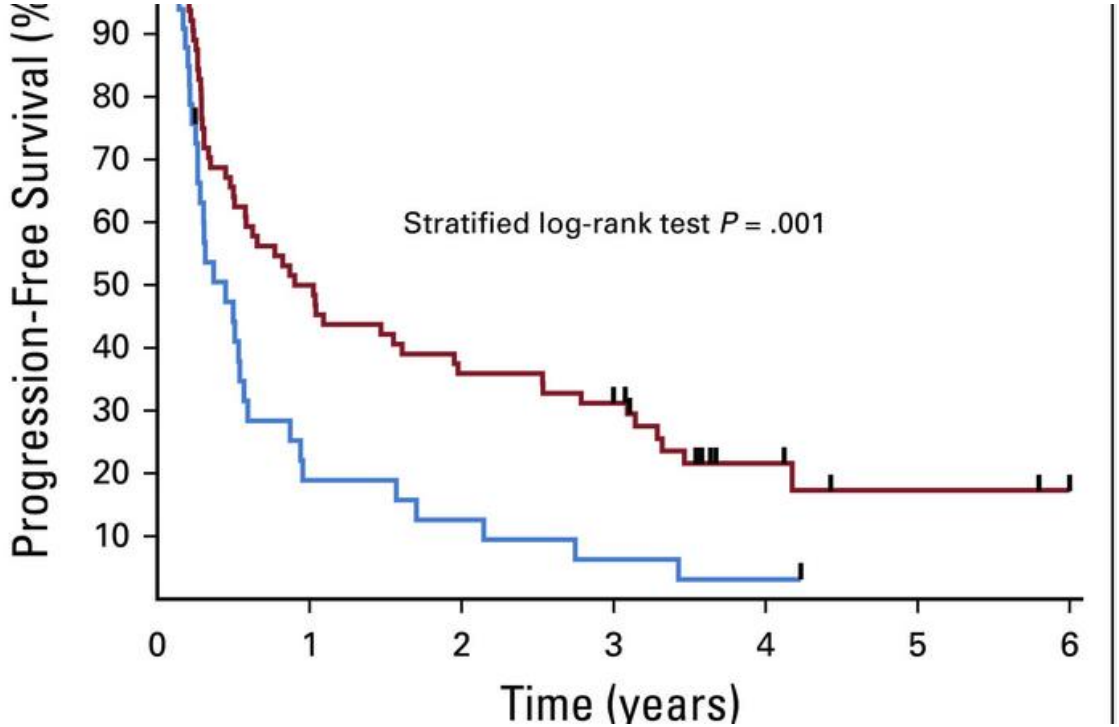


Van der Lei, et al. Lancet (2025)

What about extrahepatic oligometastatic disease?

- SABR is highly effective, often achieving long-term local control
- Phase II SABR-COMET randomized (2:1) 99 patients with 1-5 metastases and a controlled primary to +/- SABR
- Median OS 41 months vs 28 months, p=0.09
- Several other small or nonrandomized studies with mixed results





Palma, et al. JCO (2021)

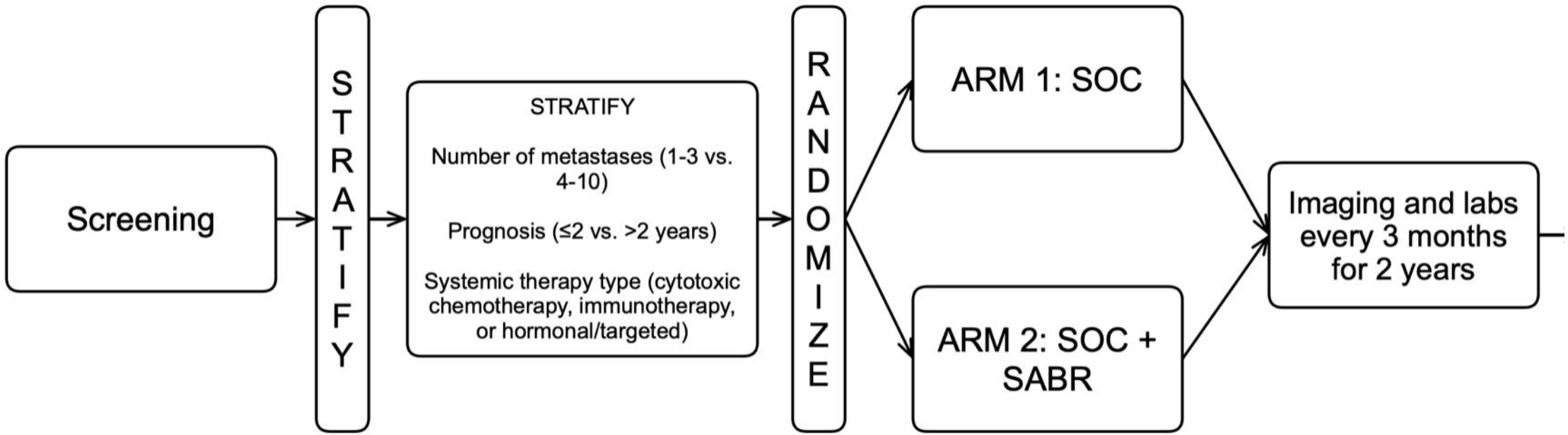
Ongoing Research at UCSD

- Several other small or nonrandomized studies with mixed results
- No published phase III RCT results
- Which patients most likely to benefit?

Total RadIoTherapy of Oligometastatic CaNcerS (TRITONS)

- Phase III, single center, randomized controlled trial of stereotactic ablative radiotherapy (SABR) for oligometastatic cancer
  - PI / Rad Onc: Tyler Seibert
  - Co-Chair / Med Onc: Rana McKay

Total RadIoTherapy of Oligometastatic CaNcerS (TRITONS)



ClinicalTrials.gov: NCT06587490

Target enrollment: N=300

TRITONS Endpoints

- Primary endpoint: PFS at 2 years
- Secondary endpoints:
  - OS at 3 years
  - All-grade and grade ≥3 toxicity
- Key secondary objective:
  - To investigate prognostic biomarkers and biomarkers predictive of benefit to treatment

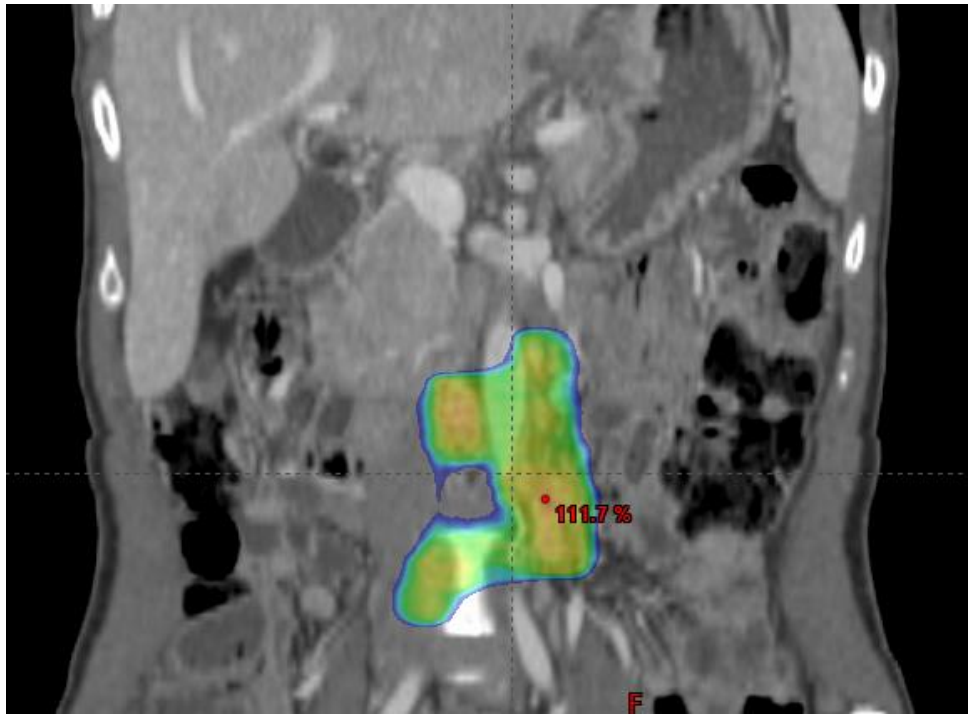
TRITONS Inclusion/Exclusion Criteria

- Key inclusion criteria:
  - 1-10 metastases from any solid malignancy
  - Can be de novo or recurrent, newly metastatic
  - At least 1 metastasis outside the brain parenchyma
- Key exclusion criteria:
  - Leptomeningeal CNS involvement
  - Any unresected metastasis >5 cm anywhere or >3 cm in brain
  - Malignant pleural effusion or ascites

Current Accrual (March 2026): 43/300 patients

TRITONS Example

- 47F with h/o reported early stage sigmoid cancer s/p endoscopic removal in 2017
- Now biopsy proven recurrence to ~9 LNs (supraclav, retroperitoneal)
- Systemic: FOLFOXIRI + Cetuximab
- Randomized to SBRT, received 35Gy/5Fx to all lesions



Conclusions

- We are in an exciting era with many evolving paradigms for treating colorectal cancer

- For patients with localized rectal cancer, customizing TNT with omission of either surgery or RT (in appropriate candidates) offers the potential for improved quality of life without compromising disease control

- The definition of oligometastatic disease is evolving, and the currently enrolling Phase III TRITONS study will help determine whether upfront SBRT in addition to systemic therapy is beneficial for patients with up to 10 metastatic lesions.