



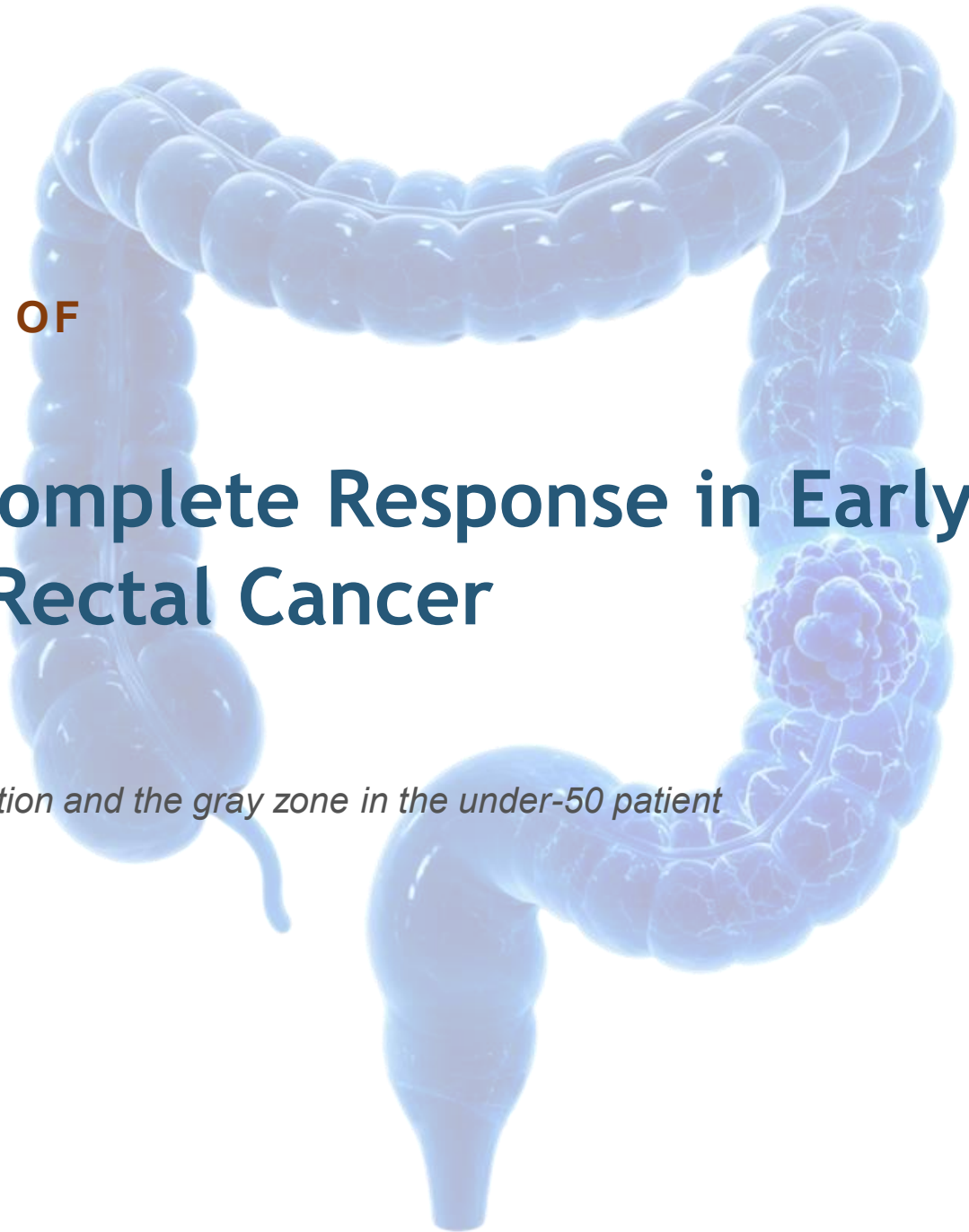
Prof. Isam Juma MD, FACS

Consultant Colorectal & General Surgeon
Associate Professor, RCSI Bahrain
Royal Medical Services, King Hamad
University Hospital – Bahrain.

THE TRAP OF

Near-Complete Response in Early-Onset Rectal Cancer

Organ preservation and the gray zone in the under-50 patient



Agenda

- 01 The near-complete response dilemma in the young patient
- 02 Why early-onset rectal cancer is different
- 03 Defining nCR: endoscopy vs MRI
- 04 Does early-onset disease respond differently?
- 05 Strategy A: nonoperative management and waiting a bit longer
- 06 Strategy B: local excision vs TME
- 07 The red flag: distant metastasis
- 08 Mismatch repair and immunotherapy
- 09 Proposed decision-making algorithm
- 10 Synthesizing the data: the trade-off
- 11 Take-home messages

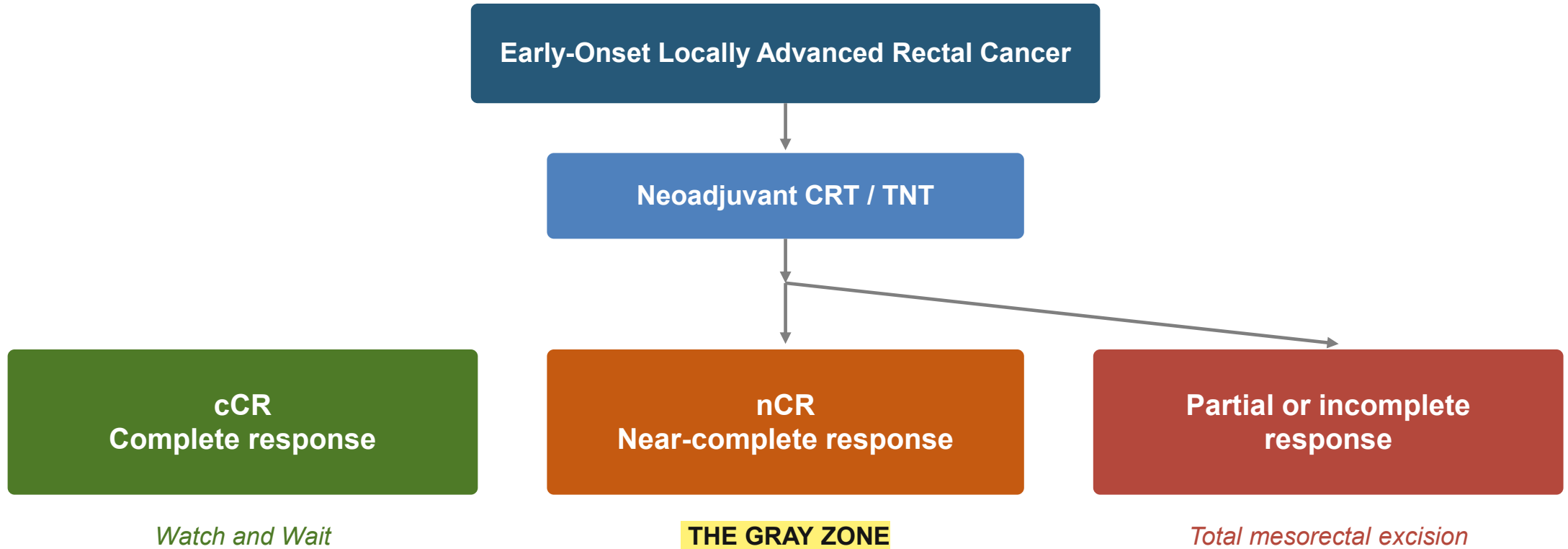
Declaration

Nothing to disclose

The Clinical Dilemma in the Young Patient

- **The Context:** nCRT and TNT have raised response rates and made organ preservation a realistic goal.
- **The Goal:** Avoid the morbidity of TME (stoma, LARS, sexual and urinary dysfunction). In a young patient that burden lasts for decades.
- **The Problem:** cCR has a clear pathway (Watch and Wait). Near-complete response sits in a gray zone, and in the under-50 the evidence is thin.
- **The Core Question:** In the young patient, is it safe to surveil an nCR to maximise organ preservation, or does leaving residual disease raise the risk of regrowth and distant metastasis?

The Response Spectrum, and the Trap



As residual disease increases, organ preservation becomes less likely. This is the difficult group.

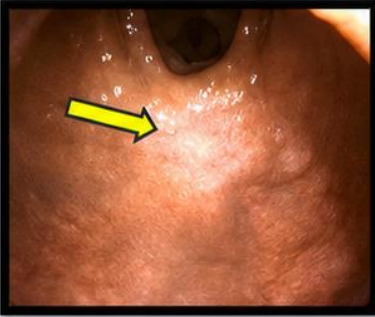
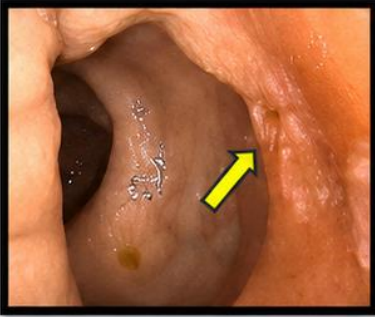
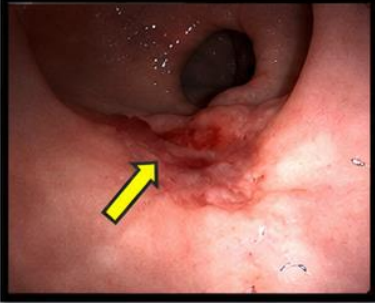
Why Early-Onset Rectal Cancer is Different

- **The Trend:** Overall rectal cancer is falling, but early-onset disease (under 50) is rising by about 2% a year. By 2030 close to **1 in 4** rectal cancers will be early-onset.
- **The Presentation:** Higher T and N stage at diagnosis, so more of these patients receive neoadjuvant therapy.
- **The Stakes:** A young patient lives for decades with a stoma or with LARS. Organ preservation matters most in this group.
- **The Evidence Gap:** The pivotal trials were mostly older patients, and the guidelines are not age-specific.

Defining Near-Complete Response (nCR)

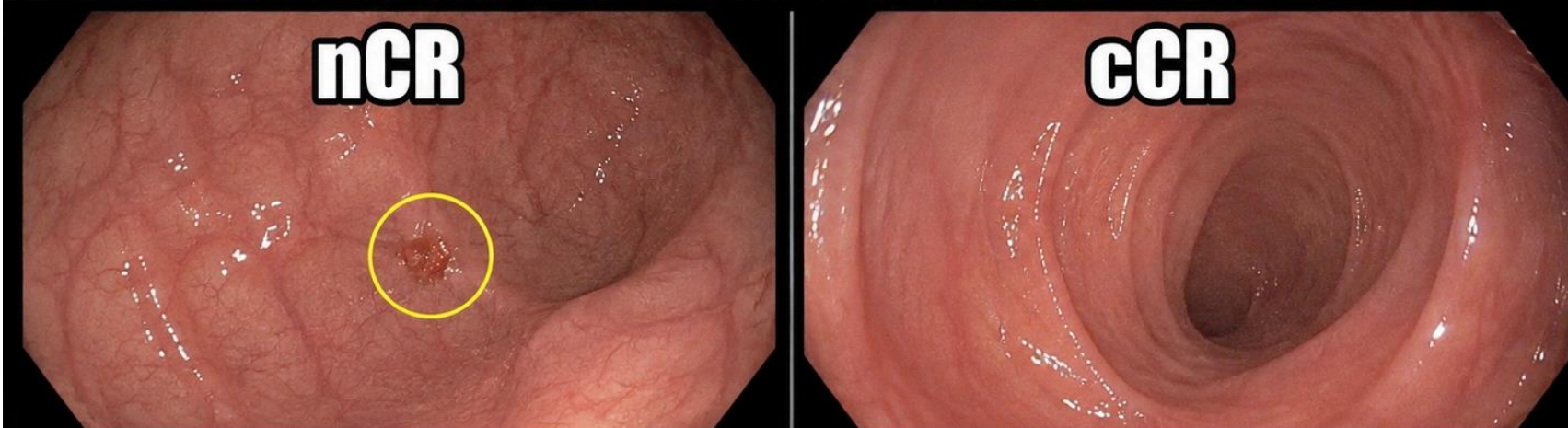
- **Endoscopic Features:** Small superficial ulceration, persistent erythema, minor mucosal irregularity, or nodules. Zivanov et al. (2025) found endoscopic features such as ulceration or nodularity in 91.8% of their nCR cohort.
- **Radiological Features (MRI):** Residual fibrosis, mixed signal intensity, or focal diffusion restriction (mrTRG 2 or higher). Beets (2023) notes that flat ulcers and polypoid tissue are often mistaken for residual tumor.
- **Clinical Findings (DRE):** No palpable tumor, and a smooth rectal wall with mild induration from fibrosis.

The Challenge: Diagnostic accuracy is limited. We cannot reliably separate slow-resolving inflammation from **microscopic residual disease**. A negative biopsy does not rule out active disease.

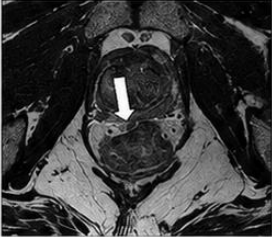
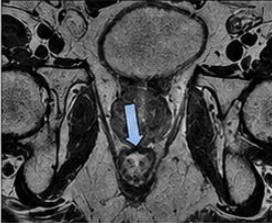
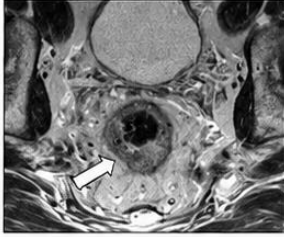
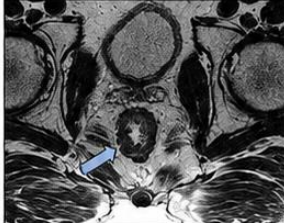
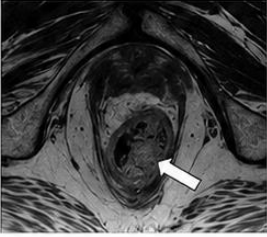
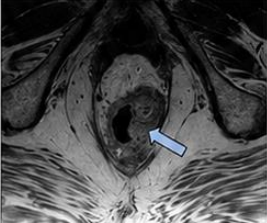
<u>Degree of Response</u>	<u>Pre-treatment</u>	<u>Initial Reassessment</u>	<u>Key Features</u>
Complete Response (cCR)			• Flat, white scar • Small associated telangiectasias • No mucosal irregularities or ulcer
Near Complete Response (nCR)			• Minor mucosal irregularity/nodularity • Associated scar erythema
Incomplete Response (iCR)			• Deep erythematous ulceration, mucosal irregularities

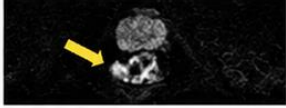
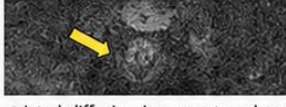
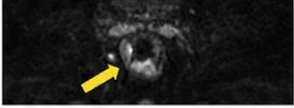
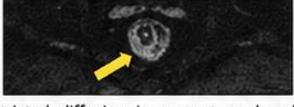
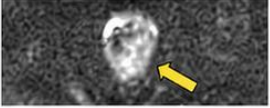
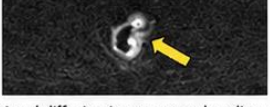
Adapted from: Williams H, et al. Nonoperative management of rectal cancer. 2024.

FIND THE DIFFERENCE



NOT THE SAME.

	MR-Clinical Complete Response (mr-cCR)	MR-Near Complete Clinical Response (mr-nCR)	MR-Incomplete Clinical Response (mr-iCR)
MRI-T2W Criteria	Normal appearing rectal wall or only dark T2 signal	Mostly fibrosis with one or two punctate foci of intermediate T2 signal	More intermediate than dark T2 signal; no T2 scar
	Baseline  Restaging  Baseline: Axial oblique T2WI shows a partially circumferential low rectal mass with slight extension into mesorectal fat (white arrow). At restaging, only fibrosis (dark T2 signal) and no intermediate signal intensity at the site of the tumor (blue arrow).	Baseline  Restaging  Partially circumferential middle rectal mass with slight extension into mesorectal fat (white arrow) is visualized on baseline axial oblique T2WI. Fibrosis at the site of tumor is present on restaging MRI, with areas of T2 intermediate signal suspicious for residual tumor (blue arrow).	Baseline  Restaging  T2WI showing a partially circumferential low rectal mass (white arrow on baseline T2WI). On restaging MRI, residual tumor with T2 intermediate signal and no fibrosis is visualized (blue arrow).

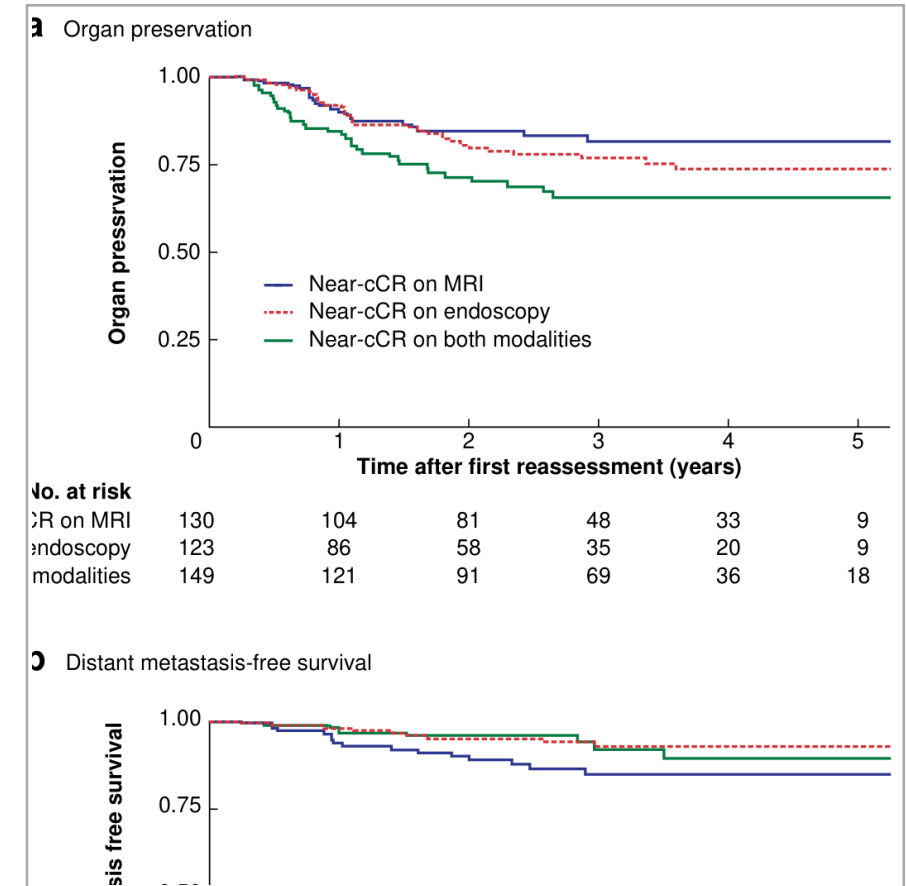
MRI-DW Criteria	Absent signal on high b-value*	Significant regression of signal on high b-value* from baseline	Insignificant regression of signal on high b-value* from baseline
	Baseline  Restaging  Restricted diffusion is present on baseline DWI and is absent on restaging images (yellow arrows).	Baseline  Restaging  Restricted diffusion is present on baseline DWI and is equivocal at restaging (yellow arrows).	Baseline  Restaging  Restricted diffusion is present on baseline and restaging DWI (yellow arrows).
Lymph Node Criteria	No visible or few nodes <5mm in short axis diameter	Partial regression of lymph nodes from baseline, but still ≥5mm in short axis diameter	Persistently enlarged lymph nodes ≥5mm in short axis diameter

*high b-value 800 or higher

Williams H, et al. Radiology. 2024;312(3):e232748. Figure 2.

Endoscopy vs MRI

- **Endoscopy:** Shows the mucosal surface: the ulcer, the scar, the nodule.
- **MRI (mrTRG):** Shows the wall. mrTRG 1 is a complete radiological response; nCR is mrTRG 2 or higher.
- **Key Finding (Temmink, 2023):** When the near-cCR was defined on MRI alone and the endoscopy was favourable, organ preservation was higher than when the abnormality was on endoscopy (**P = 0.020**).
- **Takeaway:** Do not discard the MRI when the endoscopy looks favourable. Read DRE, endoscopy and MRI together.



Organ preservation by modality of near-cCR. Temmink et al., Br J Surg 2023 (IWWO).

MRI-only near-cCR does better than an endoscopic abnormality (P = 0.020).

**DECIDING
FROM
MRI ALONE**



**MRI +
ENDOSCOPY +
DRE**



You need all three.

The central question

**Does early-onset rectal cancer
respond differently to neoadjuvant therapy?**

Conflicting Signals from Retrospective Data

Sileo et al. (Ann Surg Oncol, 2025)

Young respond better

pCR **29%** vs 18.8%

- Early vs late onset ($p = 0.035$).
- Young age an independent predictor of pCR (OR 2.68).
- 381 patients, single centre, retrospective.
- This study excluded MSI tumors.

Foppa et al. (Cancers, 2023)

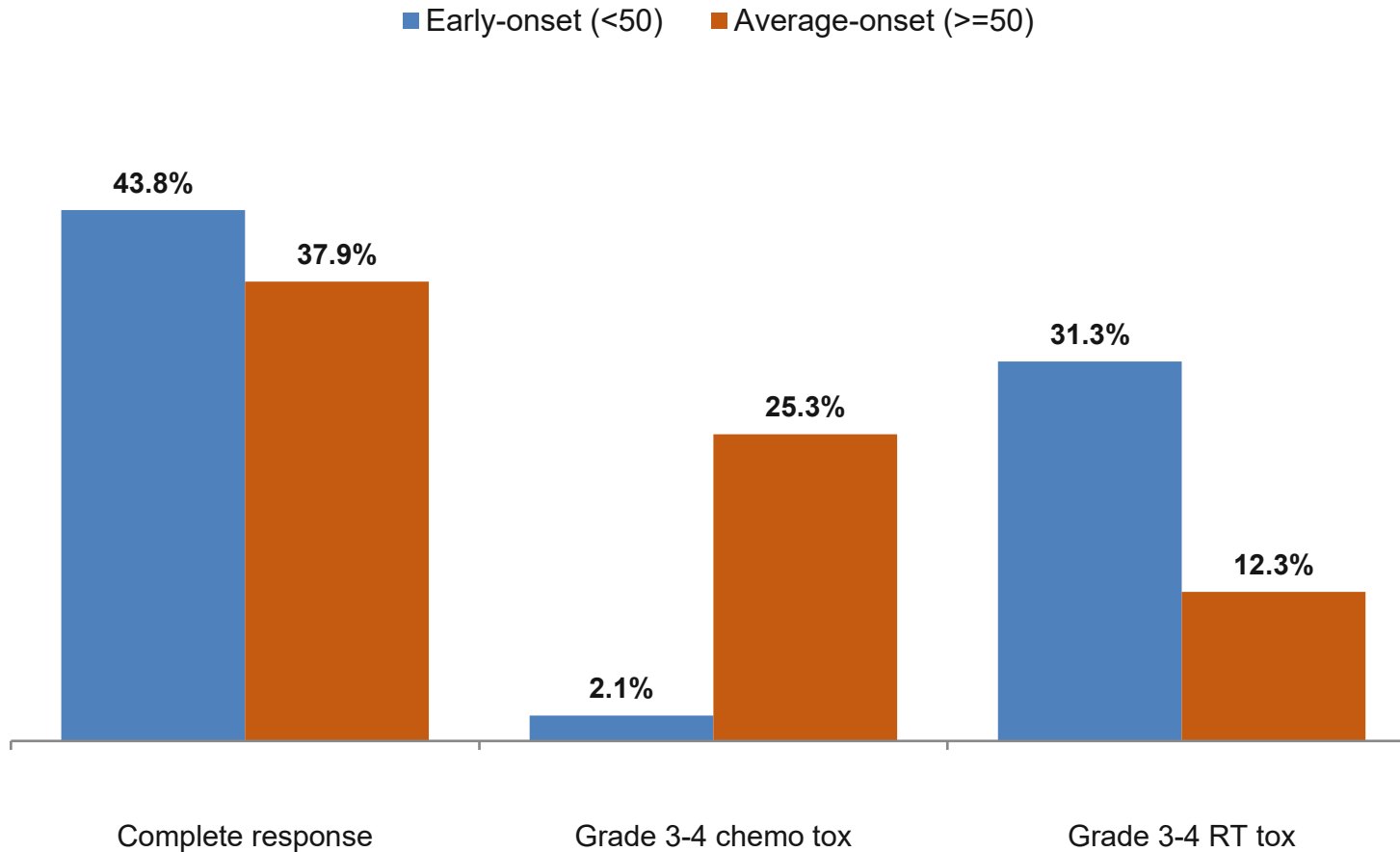
Young respond worse

Incomplete **49%** vs 35%

- Dworak 0-2, early vs late onset ($p = 0.028$).
- Early onset an independent risk factor for worse response.
- 405 patients, single centre, retrospective.
- This study included MSI tumors.

The likely explanation (from Sileo's discussion): MSI tumors respond poorly to chemotherapy. Excluding them raises the pCR rate; including them lowers it.

The Strongest Study: Similar Response, Different Tolerance



- **Design:** Multicentre, prospective, 202 patients.
- **Response:** No difference by age (43.8% vs 37.9%, $p = 0.470$).
- **Toxicity:** Much less severe chemotherapy toxicity in the young, but more radiotherapy toxicity.
- **Takeaway:** Response rates are similar. What differs is how the treatment is tolerated.



A Different Failure Pattern in the Young

Early-Onset Rectal Cancer: Different Baseline Risk

Higher local recurrence as the distinct failure pattern in early-onset rectal cancer: a tailored MRI score to guide therapy

Study: Multicenter retrospective cohort of 1,289 LARC patients treated with neoadjuvant chemoradiotherapy + surgery across 5 Chinese institutions.

- * 387 early-onset (<50 yr); median age 43
- * 902 late-onset (≥50 yr); median age 61
- * Median follow-up: 3.6 years

Early-onset patients had more adverse MRI features

- * Advanced mrT stage: 46.8% vs 34.6%
- * MRI tumor deposits (mrTD): 23.3% vs 17.4%
- * Lateral lymph-node involvement (mrLLN): 14.7% vs 10.3%

But response to neoadjuvant treatment was similar:

pCR:
25.5% early-onset vs 21.2% late-onset
P = 0.22

→ Young patients presented with higher-risk MRI features, but did not respond worse to neoadjuvant treatment.

Early-Onset Rectal Cancer: Local Recurrence & MRI Risk Stratification

The Key Difference: Local Recurrence

Local recurrence was higher in early-onset patients

After propensity-score matching:

- Early-onset: 4.9%
- Late-onset: 1.7%
- P = 0.03

→ Around 3× higher local recurrence in younger patients.

mrTML MRI Risk Score

Based on 3 pretreatment MRI features:

- mrTD — tumor deposits
- mrMRF — mesorectal fascia involvement
- mrLLN — lateral lymph-node involvement

Score 0-3: higher score = higher recurrence risk.

mrTML 3 vs 0 → adjusted HR for local recurrence ≈ 33.99

Take-home:

Adverse pretreatment MRI features strongly predicted local recurrence.

Early-Onset Rectal Cancer: Local Recurrence & MRI Risk Stratification

Why Does This Matter for Organ Preservation?

Baseline MRI risk may persist despite pCR

Even among patients who achieved pathological complete response, high-risk pretreatment MRI features remained associated with increased recurrence:

HR 12.02 | P = 0.003

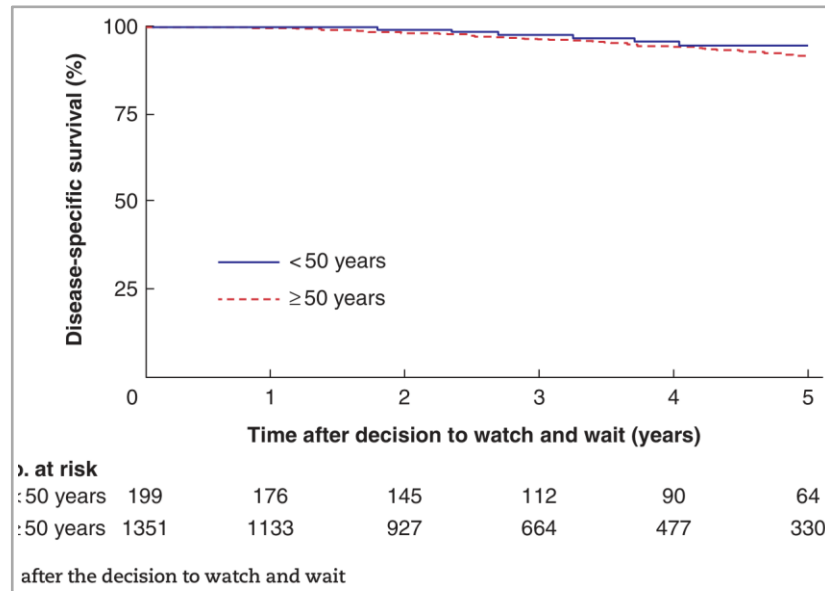
Key Take-Home

- Early-onset rectal cancer may have a higher local recurrence risk despite good treatment response.
- Pretreatment mrTD, MRF involvement, and lateral nodes may remain clinically relevant after response.
- These features could help refine selection and surveillance for organ preservation / Watch & Wait.

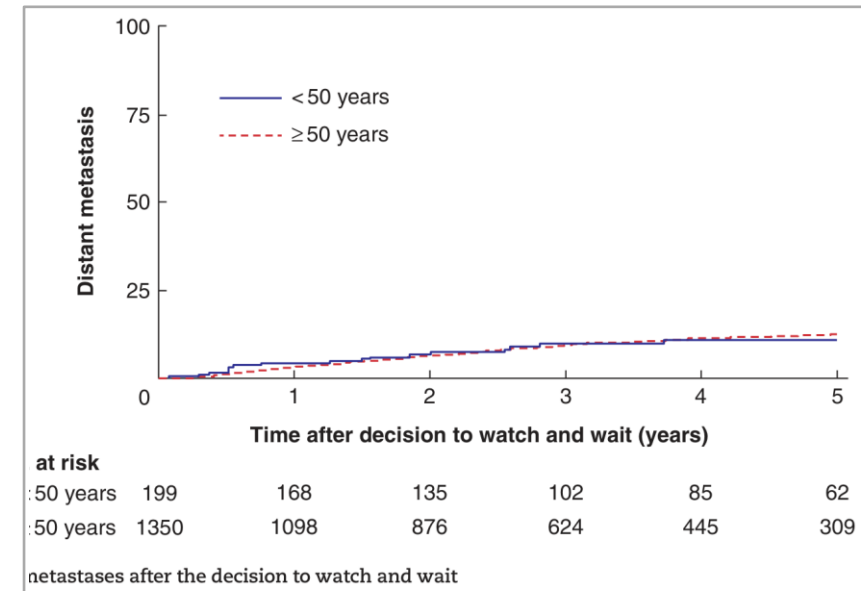
Important: This study did not directly evaluate Watch & Wait, so it does not prove that W&W is unsafe in younger patients.

Watch and Wait in the Under-50: the IWWD Data

- **Cohort:** 199 of 1552 Watch and Wait patients were under 50 (Bahadoer et al., 2022). The young had a higher T category at diagnosis.
- **Outcomes:** Disease-specific survival **98% vs 97%** at 3 years. Distant metastasis 10% in both groups. Local regrowth was the same (24% vs 26%).
- **Conclusion:** Organ preservation carries no extra oncologic risk in the young. It should be discussed, not withheld.



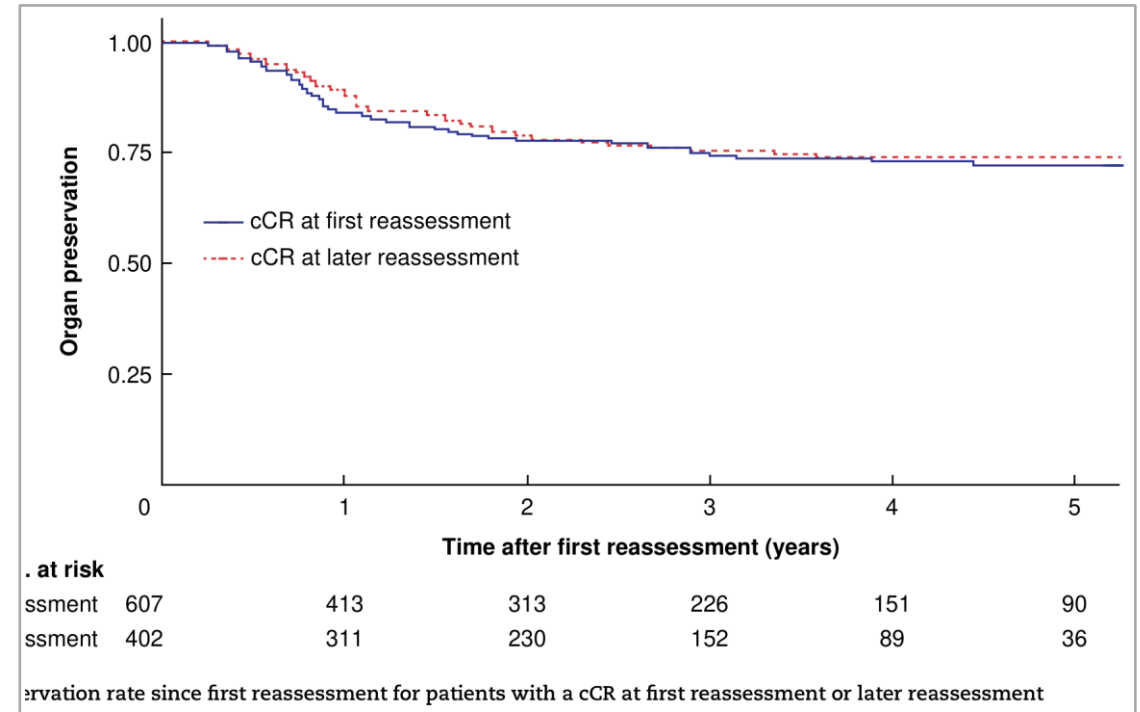
Disease-specific survival, under 50 vs 50 and over ($P = 0.199$).



Distant metastasis, under 50 vs 50 and over ($P = 0.998$).

Strategy A: Nonoperative Management and Waiting a Bit Longer

- **Hypothesis:** An nCR can keep regressing to a cCR over time.
- **Evidence (Zivanov et al., 2025):** 61 nCR patients. **63.9% went from nCR to cCR**. 59% kept organ preservation at 26 months. No difference in overall survival by regrowth status. 95.5% of regrowths had an R0 salvage.
- **Evidence (Temminck, 2023):** An nCR that later becomes a cCR does as well as an early cCR. Organ preservation 79.3% vs 77.8% ($P = 0.499$).

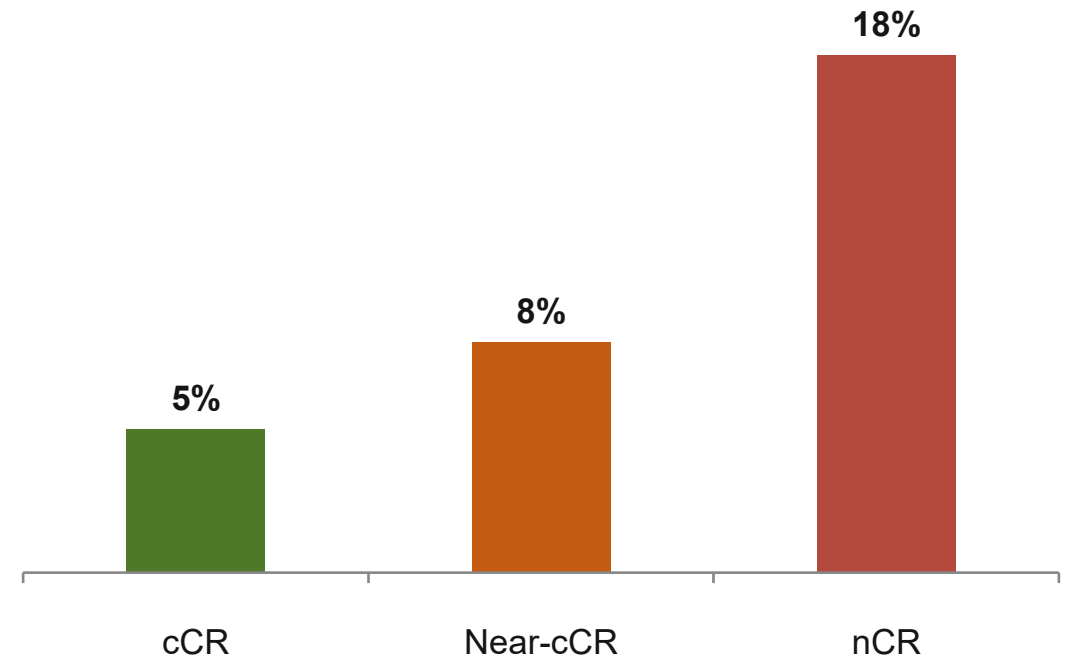


Organ preservation: cCR at first vs later reassessment. Temminck et al., Br J Surg 2023.

A later cCR is not worse than an early one ($P = 0.499$).

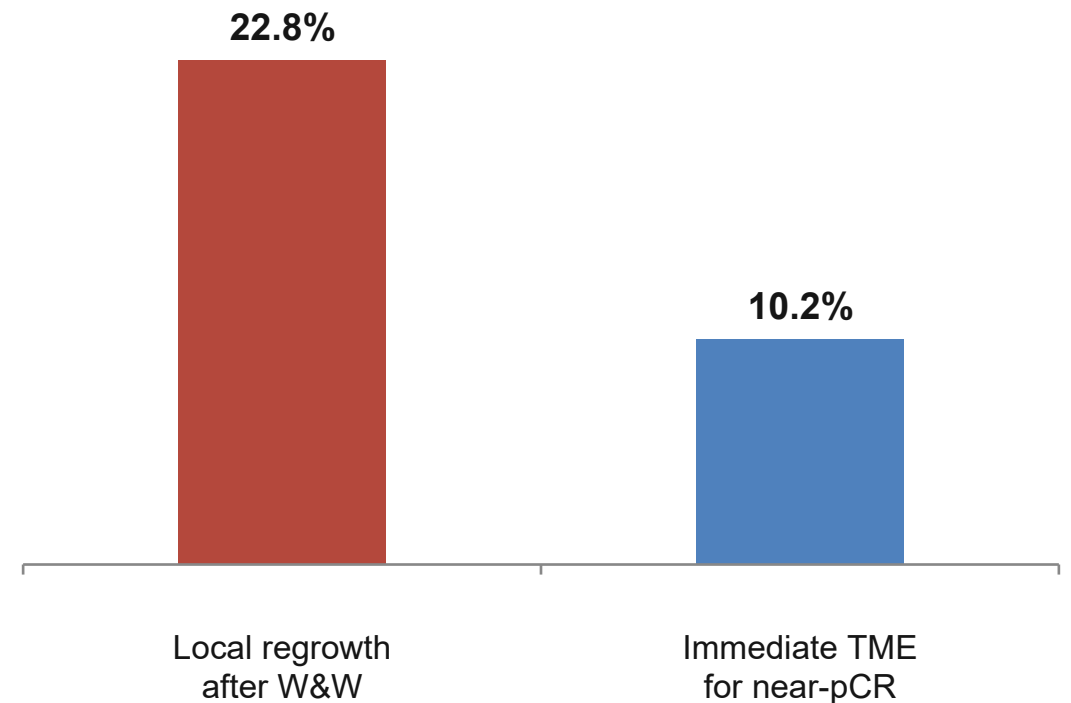
What is the Oncologic Risk of Waiting a Bit Longer?

- **Evidence (Beets, 2023 / IWWD):** The extra oncologic risk of waiting a bit longer is small, **about 0 to 2%**.
- **The Payoff:** A short interval separates a true residual tumor from a genuine complete response.
- **The Signal:** Distant metastasis rose with residual disease: 5% in cCR, 8% in near-cCR, and 18% in nCR.
- **The Nuance:** That is an average. The young, with a different failure pattern, may sit at the top of the range.



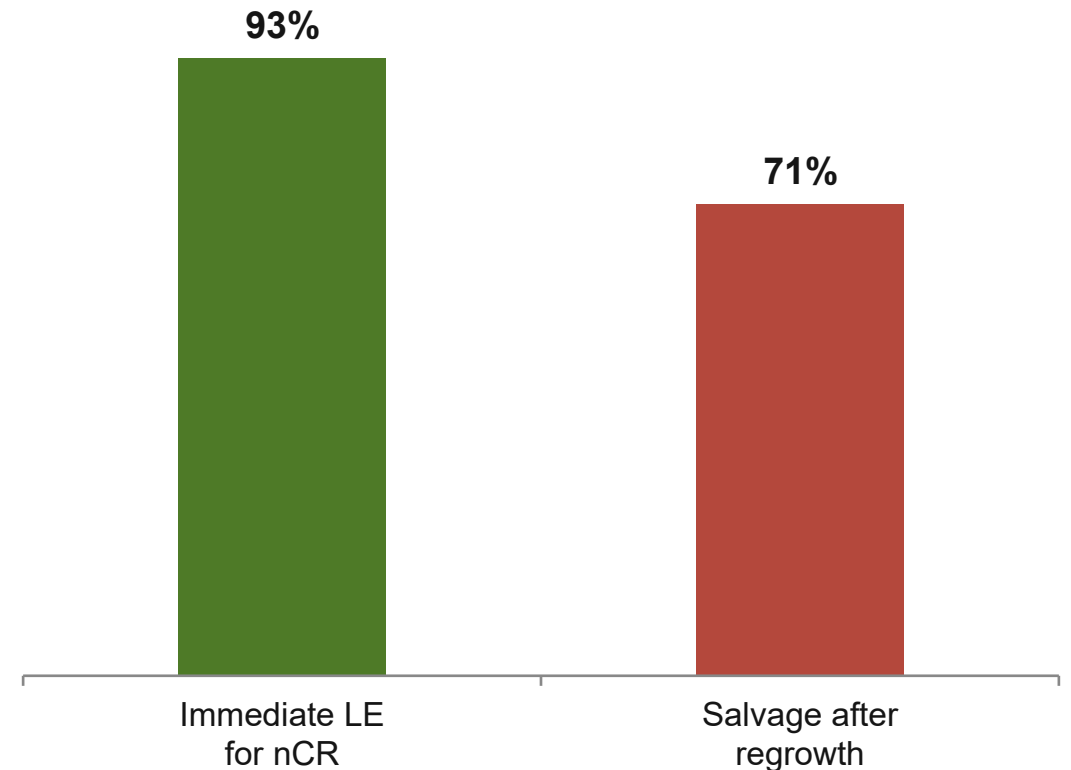
The Red Flag: The Risk of Distant Metastasis

- **The Concern:** Does leaving the primary in place, even microscopically, seed distant metastasis?
- **Evidence (Fernandez et al., IWWD and VIKINGO, 2024):** Distant metastasis was higher after local regrowth (22.8%) than after immediate TME (10.2%).
- **Key Finding:** Local regrowth is an independent risk factor for distant metastasis (HR 3.89, Jehaes et al.).
- **Implication:** Waiting until regrowth appears can cost the patient, and more so in the young.



Strategy B: Local Excision as a Compromise

- **Rationale:** Local excision gives pathological staging (ypT) and keeps the rectum. It sits between Watch and Wait and radical surgery.
- **Outcomes (McLoughlin et al., 2025):** Local recurrence a little higher with LE (8.3%) than TME (5.5%) in the pooled data, but not in the RCT subgroups. No difference in distant metastasis, DFS or OS. Much lower morbidity (OR 0.30).
- **Immediate LE vs salvage (Jehaes / GRECCAR, 2025):** 5-year distant-metastasis-free survival **93% with immediate LE vs 71%** with salvage after regrowth.
- **Conclusion:** For ypT0-1 with tight surveillance, LE is oncologically safe, and it heads off the spread that follows a regrowth.



Mismatch Repair Changes the Plan

- **The Biology:** dMMR / MSI-high disease is over-represented in young-onset and Lynch cancers, about **6 to 10%** of rectal cancers.
- **A Different Disease:** More often mucinous, poorly differentiated and higher T category, and resistant to fluoropyrimidine chemotherapy. This is part of the worse-response signal in some series.
- **The Point:** Test MMR / MSI before planning neoadjuvant therapy in a young patient. It changes the whole plan.

Immunotherapy in dMMR Disease

100%

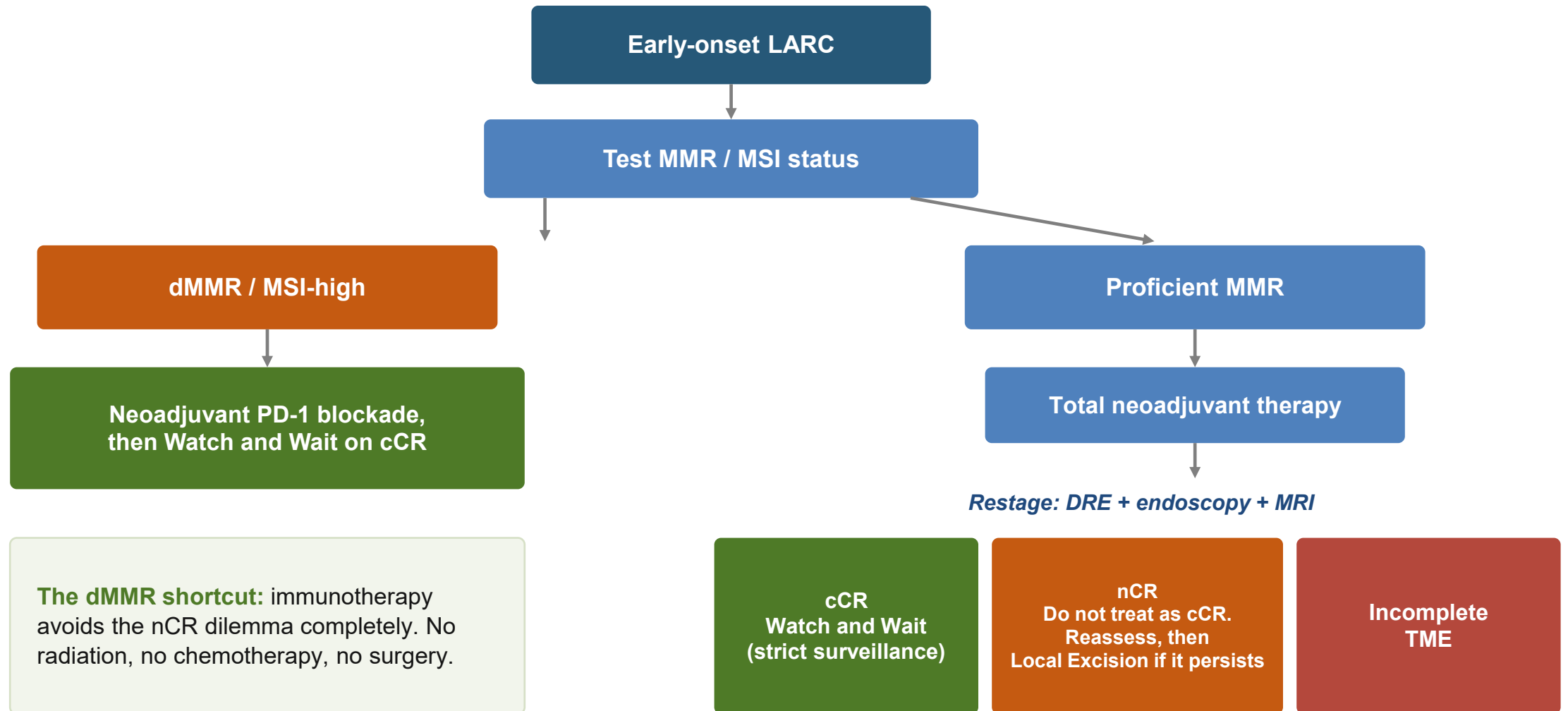
clinical complete response in the dMMR rectal cohort. Every patient avoided chemoradiation and surgery.

- **Evidence (Cercek et al., NEJM 2022 and 2025):** Six months of single-agent dostarlimab (PD-1 blockade).
- **Result:** 100% clinical complete response in the dMMR rectal cohort, first in 12 patients and then across all 49.
- **Durability:** 96% recurrence-free at 2 years.
- **Standard of care (Marmorino, 2025):** Dostarlimab and Watch and Wait for dMMR / MSI-high locally advanced rectal cancer.
- **Meaning:** For the dMMR young patient there is no nCR dilemma. They avoid it.

Turning evidence into a plan

**So, how long should we wait,
and when should we act?**

Proposed Decision-Making Algorithm



Putting it Together: a Practical Framework

- **1. Genotype first.** MMR / MSI status is the first decision, not age. dMMR goes to immunotherapy.
- **2. Respect the spectrum.** cCR to Watch and Wait, incomplete to TME. Do not default the nCR to either.
- **3. Give a converting nCR time.** Reassess at 8 to 12 weeks. Over 60% convert, and a converting nCR does as well as an early cCR.
- **4. But do not wait for regrowth.** Regrowth doubles the risk of distant metastasis. For a persisting nCR, local excision heads it off and gives ypT staging.
- **5. Individualise for the young.** Higher local recurrence and decades of life ahead lower the threshold to act and tighten follow-up.

Synthesizing the Data: the Trade-Off

The case for surveillance

(Zivanov / Beets)

- Over 60% convert to cCR.
- Salvage TME is R0 in about 95% of cases.
- Avoids surgery in true responders, with an extra risk of only 0 to 2%.

The case for intervention

(Fernandez / Jehaes)

- Regrowth is not benign. It doubles distant metastasis (22.8% vs 10.2%).
- Immediate local excision gives better distant-metastasis-free survival (93% vs 71%).

In the young: a higher local recurrence rate and decades at stake lower the threshold to intervene with local excision.

Take-Home Messages

- **Early onset RC should not simply be regarded as the same disease occurring at young age .**
- **Is nCR safe to surveil in the young?** Yes, with tighter caveats than in older patients.
- **Organ preservation:** Feasible in over half of nCR patients, with conversion to cCR in over 60%.
- **A complete pathological response in young does not necessarily mean that the biological/radiological risk present at diagnosis has disappeared .**
- **Oncologic compromise:** Regrowth carries a real risk of distant metastasis, and early-onset disease recurs locally more often.

Final Recommendations

- Test MMR / MSI first. dMMR goes on an immunotherapy pathway.
- Do not treat an nCR as a cCR.
- For a young pMMR patient, favour local excision (TEM / TAMIS) as the bridge between Watch and Wait and radical surgery.
- Manage the nCR as a shared decision within the patient and the multidisciplinary team. Consider expertise , skills availability.

Thank you

 ijuma@rcsi.com
 Prof. Isam Juma
 [prof.isam_juma](https://www.instagram.com/prof.isam_juma)