



Watch-and-Wait

Patient Selection, Surveillance, and Failures

By

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2026

Five Questions This Talk Will Answer

1

Why organ preservation?

Rationale, history, and the shift from radical TME to non-operative management

2

Who qualifies?

Defining complete / near-complete response, and selecting the right patient

3

How do we watch?

Structured surveillance protocols and the DRE-endoscopy-MRI assessment triad

4

What does the evidence show?

The IWWD registry, the OnCoRe cohort, and the randomized OPRA trial

5

How do we fail safely?

Local regrowth, distant metastasis, salvage surgery, and oncologic safety

THE RATIONALE

Radical Surgery Cures — But at a Price

Neoadjuvant chemoradiotherapy plus total mesorectal excision (TME) has been the standard of care since the CAO/ARO/AIO-94 trial established preoperative CRT as superior to postoperative treatment. Yet TME carries durable functional cost — the very cost that a clinical complete response may let a patient avoid.

●
~15–25%

of patients achieve a
pathological complete
response (ypT0N0) after long-
course CRT

●
≥40%

experience major low-anterior-
resection
syndrome (LARS) after
sphincter-preserving TME

●
5–10%

permanent stoma rate even
after
sphincter-sparing surgery

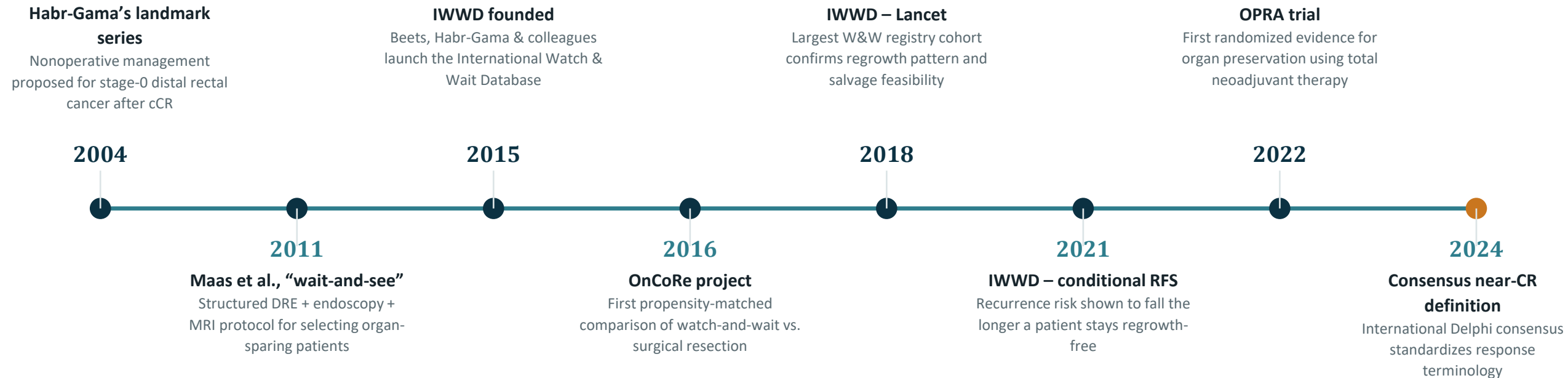
●
30–60%

report new sexual or urinary
dysfunction
after pelvic dissection

The organ-preservation question: if the tumor has clinically disappeared, does the rectum still need to be removed to cure the patient — or can the same oncologic outcome be achieved by watching, and operating only if disease returns?

TWO DECADES IN THE MAKING

The Evolution of Watch-and-Wait, 2004–2024

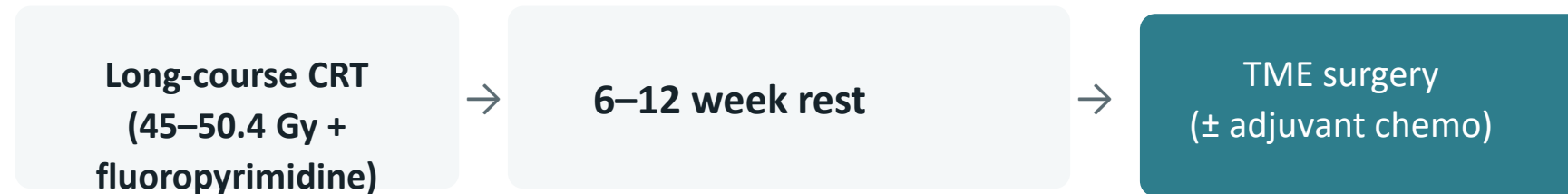


THE NEOADJUVANT BACKBONE

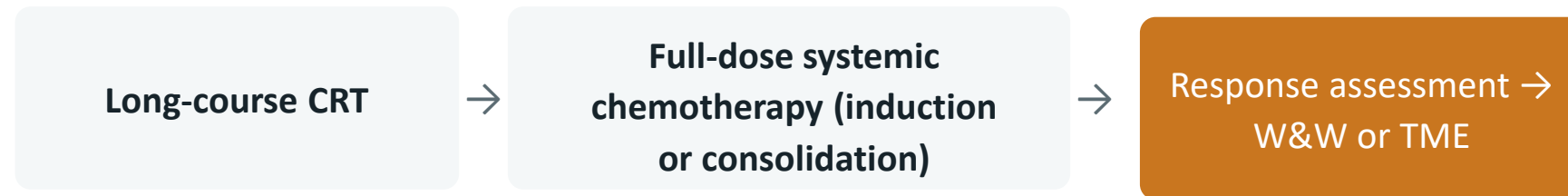
From Long-Course CRT to Total Neoadjuvant Therapy

Delivering chemotherapy and radiotherapy in full — all before surgery — improves systemic control and dramatically increases the chance of a clinical complete response, expanding the pool of watch-and-wait candidates.

Conventional sequencing



Total Neoadjuvant Therapy (TNT)



Key effect: TNT raises clinical/near-complete response rates to roughly **40–60%** in modern series, versus **~15–20%** with CRT alone — directly enlarging the watch-and-wait eligible population.

TRIAL DESIGN IN FOCUS — OPRA

Two Ways to Sequence Total Neoadjuvant Therapy

INCT-CRT

Induction chemo → chemoradiation

- 1 Induction FOLFOX/CAPOX × 4–8 cycles
- 2 Chemoradiation (long-course)
- 3 Restage → W&W or TME

CRT-CNCT

Chemoradiation → consolidation chemo

- 1 Chemoradiation (long-course)
- 2 Consolidation FOLFOX/CAPOX × 4–8 cycles
- 3 Restage → W&W or TME

OPRA (n=324, stage II/III): restaging occurred 8–12 weeks after TNT; patients with complete or near-complete response were offered **watch-and-wait**, others proceeded to **TME**. Long-term follow-up shows organ preservation sustained in 50% of all patients at 5 years, with 94% of regrowths occurring within 2 years and 99% by 3 years.

DEFINITIONS MATTER — PART 1

Clinical Complete Response (cCR): The Habr-Gama Criteria

A cCR is a clinical, not pathological, diagnosis — built from the concordant absence of residual tumor across three independent modalities.

Modality	Feature consistent with cCR
Digital rectal examination	Smooth, supple wall; no palpable mass, nodule, or induration
Endoscopy	Flat whitish scar ± telangiectasia; no ulcer, no nodularity, no residual mucosal irregularity
MRI (T2 + DWI)	Dark T2 signal, wall no thicker than normal rectum, no restricted diffusion / no visible signal on high b-value or ADC map, no suspicious mesorectal nodes

Diagnostic accuracy: each modality alone is imperfect — combined **DRE + endoscopy + MRI concordance reaches ~98% accuracy for excluding residual disease**, which is why no single test is used in isolation to commit a patient to non-operative management.

DEFINITIONS MATTER — PART 2

Near-Complete Response: The Grey Zone Formalized

The 2024 international Delphi consensus formally defines a near-complete response (near-CR) — a category historically managed inconsistently across centers.

Complete response (cCR)

- No visible/palpable tumor on any modality
- Flat white scar, no nodularity
- **Standard pathway:** enter watch-and-wait

Near-complete response (near-CR)

- Small residual irregularity, erythema, or minor nodularity
- Superficial ulcer <1 cm without deep features
- **Pathway:** short-interval re-assessment (6–12 wks) before committing

Incomplete response

- Residual mass, deep ulcer, or fixed induration
- Suspicious residual signal / restricted diffusion on MRI
- **Standard pathway:** proceed to TME

RESPONSE ASSESSMENT

The Assessment Triad — No Single Test Is Enough

● Digital Rectal Examination

Bedside, immediate, operator-dependent; misses submucosal & nodal disease

AUC ~0.75–0.85

● Endoscopy

Best mucosal detail; blind to deeper wall layers and mesorectum

Sens. ~80%

● MRI (T2 + DWI/ADC)

Assesses wall, mesorectum, and nodes; limited for scattered microscopic residual tumor

AUC ~0.79

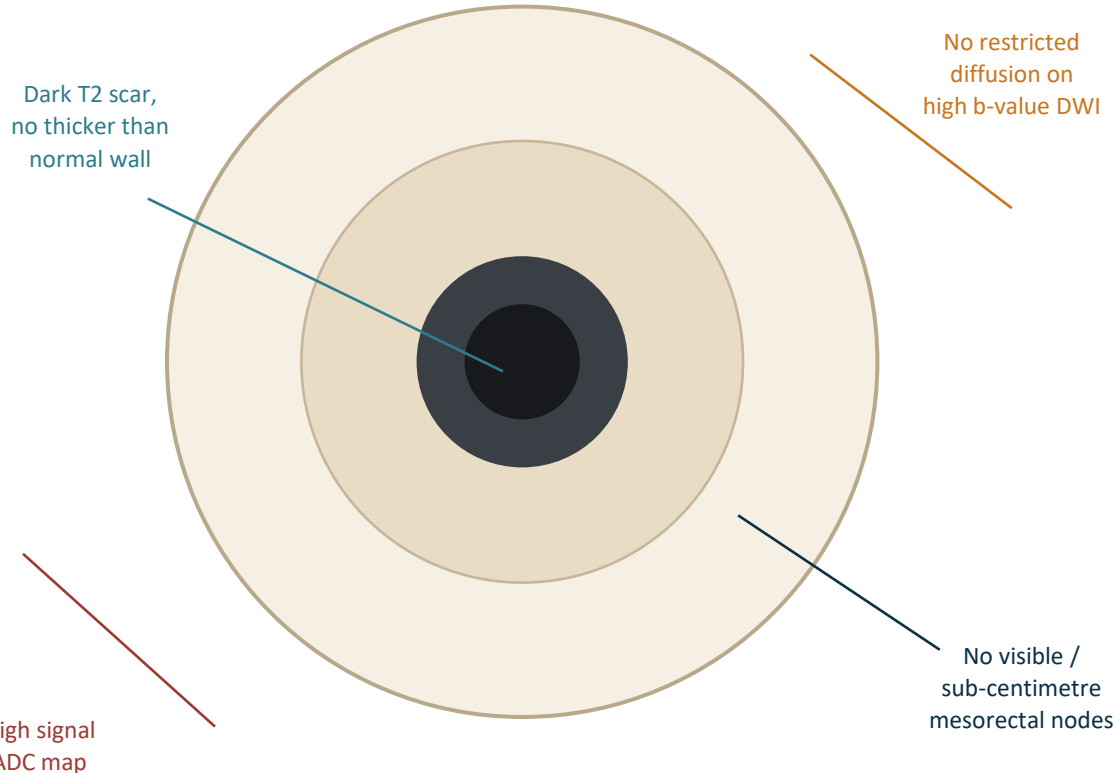
Combined performance

When DRE, endoscopy, and MRI *all* indicate no residual tumor, concordant accuracy for a true complete response rises to approximately **98%**. Discordance between modalities — or **any single “suspicious” finding** — should trigger **biopsy, short-interval re-assessment**, or reconsideration of surgery rather than immediate commitment to watch-and-wait.

IMAGING DEEP-DIVE

MRI Hallmarks of a True Complete Response

Schematic T2-weighted axial section



Reassurance checklist — cCR on MRI

- ✓ Fibrotic dark-signal scar replacing the original tumor mass
- ✓ Wall thickness $\leq$ normal rectal wall (no residual bulk)
- ✓ No restricted diffusion / no high signal on ADC map
- ✓ No mesorectal or lateral nodes meeting size/morphology criteria
- ✓ No extramural vascular invasion signal
- ✓ Findings concordant across two consecutive MRI studies where near-CR is suspected

A PRACTICAL PEARL

“It May Take Longer Than You Think”

Habr-Gama’s group showed that a substantial proportion of eventual complete responders are not yet complete at the first restaging — tumor regression continues for weeks after chemoradiation ends, especially with consolidation chemotherapy.

Week 6–8

First restaging

DRE + endoscopy + MRI. Complete → W&W. Near-CR → re-assess.
Incomplete → TME



Week 10–12

Second restaging (if near-CR)

Many near-CR tumors convert to true cCR with additional time / consolidation chemo



Week 16–18+

Late reassessment

Reserved for persistent near-CR; still-converting patients may be offered further short-interval surveillance rather than reflex surgery

Clinical implication: a near-CR at first restaging is not a failure — it is a prompt for patience and a repeat, structured assessment before committing to surgery.

PATIENT SELECTION — PART 1

Tumor-Related Selection Criteria

Factor	Favorable for Watch-and-Wait	Caution / Relative Exclusion
Response category	True cCR on triad assessment	Incomplete response; unresolved near-CR after re-assessment
Baseline stage	cT1–T3, any cN if downstaged	cT4 with persistent extramural extension
Histology	Adenocarcinoma, moderately/well differentiated	Mucinous or signet-ring histology (poorer response, higher regrowth risk)
Distance from anal verge	Any level — most impactful for low/mid rectal tumors where TME risks stoma	—
Baseline size / circumference	Smaller, non-circumferential tumors	Bulky, circumferential baseline tumors (higher regrowth risk even after cCR)
Nodal status after treatment	No residual suspicious nodes on MRI	Persistent suspicious mesorectal or lateral nodes

PATIENT SELECTION — PART 2

The Patient Must Be as Ready as the Tumor

Supports Watch-and-Wait

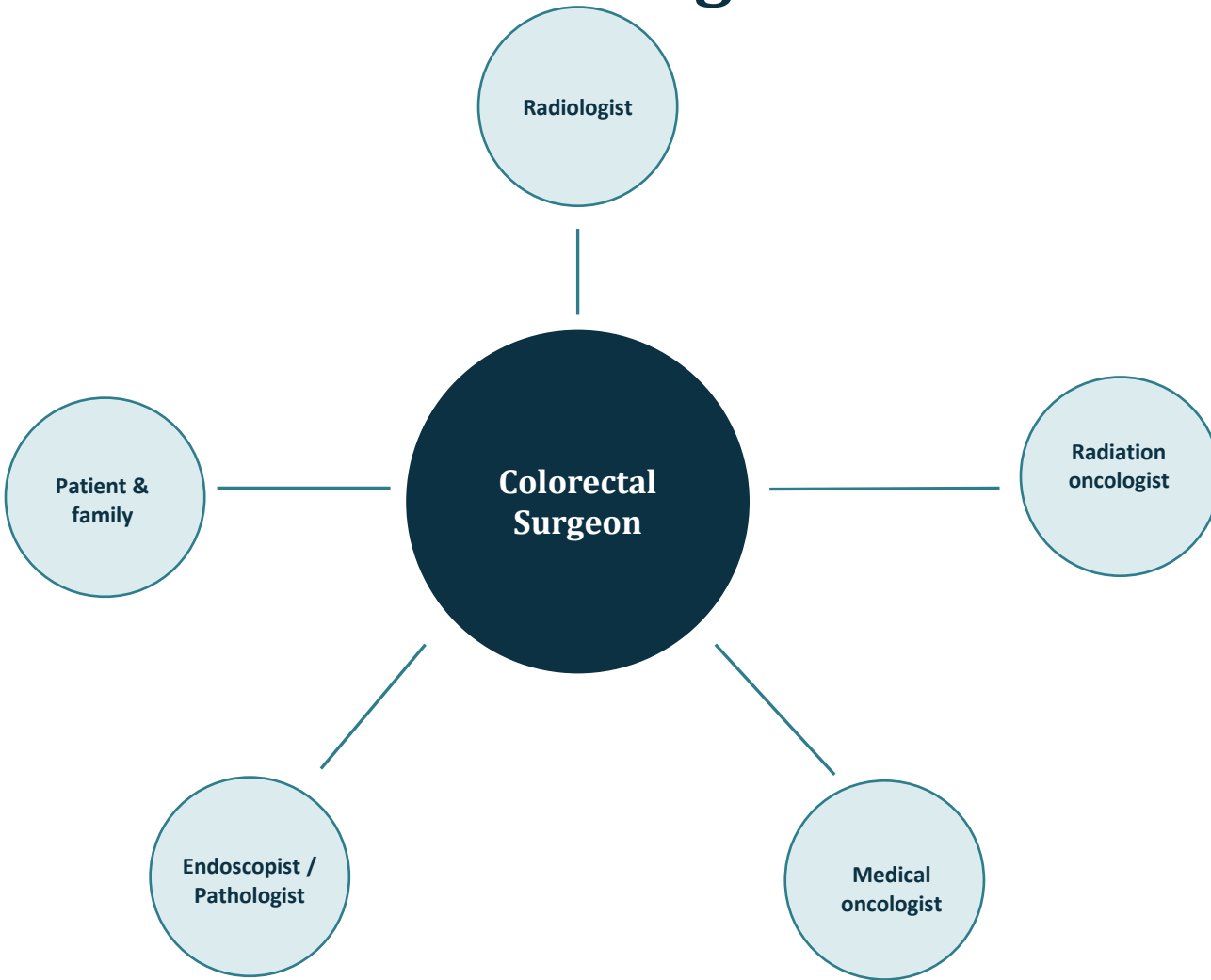
- Fully understands and accepts the ~25–30% regrowth risk requiring salvage surgery
- Able and willing to comply with intensive surveillance (visits every 1–3 months, years 1–2)
- Reasonable access to endoscopy, MRI, and a colorectal surgical team
- Realistic surgical candidacy preserved in reserve (fit for salvage TME if needed)
- Shared decision made without excessive fear of stoma

Relative Contraindications

- Inability to attend structured, lifelong surveillance
- Limited geographic / logistic access to timely imaging and endoscopy
- Poor surgical fitness that would preclude safe salvage TME later
- Cognitive or psychiatric barriers to informed, sustained consent
- Genetic predisposition syndromes with field risk (e.g., unresected synchronous pathology)

GOVERNANCE OF THE DECISION

The Colorectal Surgeon Anchors the MDT



Why the surgeon leads

- Owns the salvage pathway — must judge resectability and timing if regrowth occurs
- Performs / supervises the serial DRE and endoscopic surveillance
- Best positioned to counsel on functional hazards of TME vs. surveillance burden
- Documents a clear informed-consent discussion at each decision point

HOW WE WATCH

A Structured Surveillance Protocol

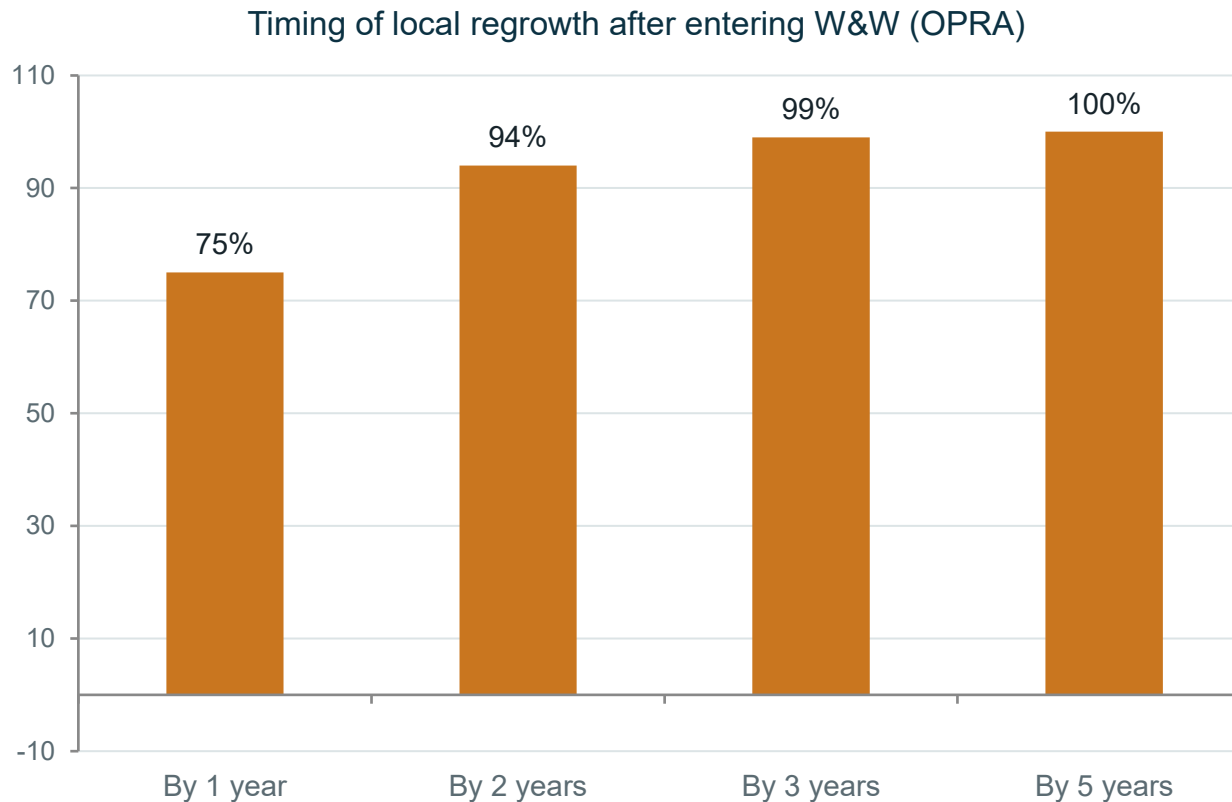
Interval	DRE + Endoscopy	Pelvic MRI	CEA	CT Chest/Abd/Pelvis
Months 1–6 (Year 1)	Every 1–2 months	Every 3–4 months	Every 3 months	Every 6 months
Months 7–12 (Year 1)	Every 2–3 months	Every 4 months	Every 3 months	Every 6 months
Year 2	Every 3–4 months	Every 6 months	Every 6 months	Annually
Years 3–5	Every 6 months	Annually	Every 6–12 months	Annually

After Year 5

Principle: surveillance intensity mirrors risk — heaviest in years 1–2 when nearly all regrowth occurs, tapering thereafter as conditional recurrence-free survival improves.

JUSTIFYING THE SCHEDULE

Nearly All Regrowth Happens Early



What this means for practice

- Of 81 OPRA regrowths, 94% occurred within 2 years and 99% within 3 years
- IWWD confirms local regrowth clusters in the first 2 years and predominantly within the bowel wall (endoluminal)
- This is exactly why endoscopic surveillance — not imaging alone — is emphasized early
- Beyond year 3, surveillance can safely de-escalate without meaningfully raising missed-regrowth risk

THE EVIDENCE — REGISTRY DATA

The International Watch & Wait Database (IWWD)

793 clinical complete responders across multiple continents; median follow-up 55 months — the largest dataset informing modern watch-and-wait practice.

~25%

cumulative local regrowth
(mostly within 2 years)

~10%

develop distant metastases
during follow-up

≥90%

of local regrowths are
surgically salvaged

Rare

unsalvageable local disease
after watch-and-wait

Key registry milestones

2018 — Lancet: First large IWWD report; confirmed regrowth mostly endoluminal, emphasizing endoscopic surveillance

2021 — Lancet Oncol: Conditional recurrence-free survival modelling — the longer a patient stays free of regrowth, the lower their subsequent risk

THE EVIDENCE — RANDOMIZED DATA

OPRA: The First Randomized Organ-Preservation Trial

Design

- Phase II, multicenter, randomized (n = 324)
- Stage II/III rectal adenocarcinoma
- Randomized: induction chemo → CRT vs. CRT → consolidation chemo
- Restaging 8–12 weeks after TNT completion
- Complete / near-complete response → offered watch-and-wait
- Incomplete response → total mesorectal excision
- Primary endpoint: disease-free survival (DFS)

Headline results

~76%

3-year disease-free survival, overall cohort

~1 in 2

patients achieved sustained organ preservation

**TME-free
survival higher**

with consolidation chemotherapy sequencing (CRT–CNCT) than induction sequencing in the initial report

THE EVIDENCE — DURABILITY

OPRA at 5 Years: Organ Preservation Holds Up

The 2024 long-term update addressed the central worry about watch-and-wait — does the risk of regrowth simply reappear later, eroding the benefit?

Regrowth timing

94% of regrowths
by 2 years · 99% by 3 years

5-year organ preservation

Sustained in roughly
half of all TNT patients

DFS: planned TME after restaging

64%
(95% CI 53–78)

DFS: salvage TME after W&W regrowth

64%
(95% CI 53–78) · $p = 0.94$

Bottom line: disease-free survival was statistically identical whether TME was performed **early** (for incomplete responders) or later as **salvage** surgery after regrowth in watch-and-wait — supporting that **deferring surgery does not compromise oncologic outcome** in appropriately selected, closely surveilled patients.

SECTION 5 — HOW WATCH-AND-WAIT CAN FAIL

Three Distinct Patterns of “Failure”

Local regrowth

Tumor reappears within the rectal wall/mesorectum, typically within 2 years

Managed with salvage TME — usually curable

Distant metastasis

Systemic recurrence, occurring in ~10% — can arise even without local regrowth

Reflects tumor biology, not a failure of local surveillance

Unsalvageable local disease

Regrowth detected too late for curative salvage — rare with structured surveillance

The scenario intensive follow-up is designed to prevent

LOCAL REGROWTH IN DETAIL

Where and When Regrowth Happens

Location

The large majority of regrowths are endoluminal — arising within the bowel wall / mucosa rather than in the mesorectal nodes alone — which is precisely why endoscopy remains central to surveillance, not MRI alone.

Timing

- ~75% of regrowths detected within the first year of surveillance
- ~94–99% detected by year 2–3 (IWWD, OPRA concordant)
- Late regrowth beyond year 3–5 is uncommon but reported — supports lifelong, lower-intensity monitoring

Practical surveillance program

Endoscopic surveillance should not be relaxed in favor of imaging-only follow-up, even when MRI is reassuring — mucosal recurrence can precede clear radiologic change.

MANAGING REGROWTH

Salvage Surgery: Effective, but Technically Demanding

≥90%

of local regrowths are
salvaged with surgery

88%

of non-metastatic regrowths
salvaged in OnCoRe (n=41)

64%

DFS after salvage TME —
equal to planned early TME

Technical considerations for the operating surgeon:

- **Radiation fibrosis** make TME dissection technically harder than in the neoadjuvant-naïve pelvis
- **Abdominoperineal resection rates** are higher after salvage than after upfront surgery for equivalent baseline stage
- **Anastomotic leak and morbidity risk** are high — careful patient counseling before entering W&W should include this issue
- **Rapid referral** at first sign of regrowth is essential — delay narrows the surgical options and worsens outcomes

THE FAILURE MODE WHICH SURGERY CANNOT FIX

Distant Metastasis: A Biology Problem, Not a Surveillance Problem

Roughly **10%** of watch-and-wait patients develop distant metastases — a rate **similar to** that seen after upfront TME for comparable stage, underscoring that this risk reflects tumor biology rather than the decision to defer surgery.

Occurs independent of local regrowth

Distant metastasis can arise in patients who never experience local regrowth — confirming it is a separate biological event, driven by micrometastatic disease present at diagnosis, not by local tumor left in situ.

Effects on practice

- Systemic staging (CT chest/abdomen/pelvis) must continue on schedule even in a reassuring local exam
- Reinforces the rationale for total neoadjuvant (systemic) therapy up front, not local treatment alone
- An emerging role for ctDNA surveillance to detect molecular relapse before radiologic change

RISK STRATIFICATION

Predictors of Local Regrowth (InterCoRe Consortium)

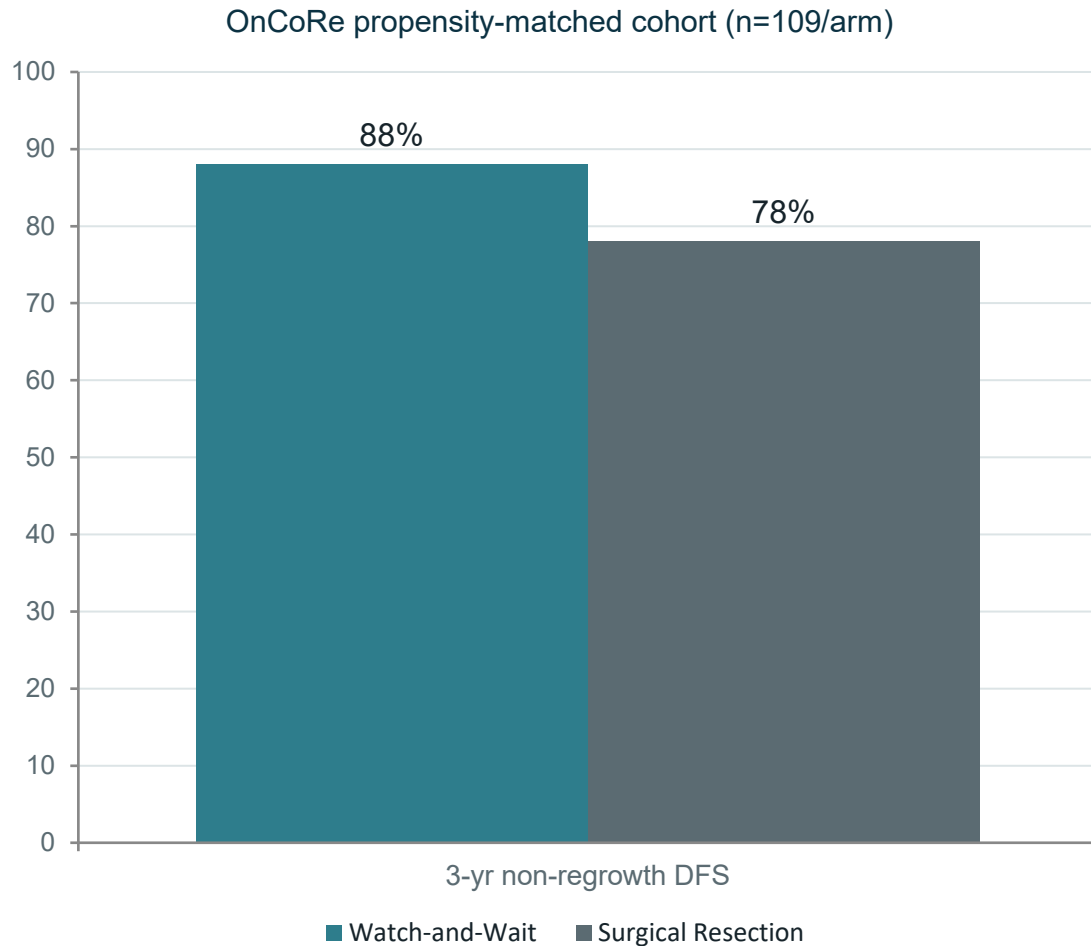
An individual-participant-data meta-analysis pooling multiple watch-and-wait cohorts identified consistent, reproducible risk factors for later local regrowth.

Risk Factor	Association with Regrowth
Higher baseline cT stage (cT3–T4)	Increased risk vs. cT1–T2
Baseline cN-positive disease	Increased risk vs. cN0
Larger / circumferential baseline tumor	Increased risk vs. smaller, non-circumferential tumors
Near-complete (vs. true complete) response at final assessment	Higher regrowth rate than a clean cCR
Shorter interval to first assessment of cCR	Some evidence of higher subsequent regrowth if assessed very early

Clinical use: these factors do not exclude a patient from watch-and-wait, but they should intensify counseling and surveillance frequency for higher-risk responders.

IS IT ONCOLOGICALLY SAFE?

Watch-and-Wait vs. Upfront TME: Comparable Survival



Convergent evidence across study designs

- **OnCoRe**: no significant difference in 3-year non-regrowth DFS or overall survival between matched W&W and surgery cohorts
- **Systematic reviews** and meta-analyses of pooled cohorts show comparable overall and disease-free survival
- **OPRA** (randomized): DFS equivalent whether TME is performed early or as salvage after regrowth
- **Caveat**: no trial has been powered to formally prove statistical non-inferiority against upfront TME

BEYOND SURVIVAL

Organ Preservation Is a Quality-of-Life Intervention

● Bowel function

- Avoids LARS in patients who never undergo TME
- Preserves native rectal reservoir and continence

● Stoma avoidance

- Eliminates permanent-stoma risk for the ~half who avoid surgery entirely
- Removes a major driver of patient anxiety and treatment refusal

● Sexual & urinary function

- Spares pelvic autonomic nerve territory from dissection
- Lower rates of new sexual/urinary dysfunction versus TME cohorts

WHERE EXPERTS STILL DISAGREE

Open Controversies in Watch-and-Wait

- ? **How long is “long enough” to wait for a near-CR to convert before committing to surgery?** No consensus interval; practice ranges 6–18+ weeks depending on trajectory
- ? **Should induction or consolidation chemotherapy be preferred within TNT?** OPRA suggested a possible organ-preservation advantage for consolidation sequencing, but debate continues over regrowth-rate interpretation
- ? **Is local excision (TEM/TAMIS) a useful adjunct for equivocal near-CR?** Attractive concept for pathologic confirmation, but adds morbidity and is not yet standardized
- ? **How should older or frailer patients unfit for salvage surgery be counseled?** The safety net of W&W assumes a fit salvage candidate — this assumption weakens in frail patients
- ? **Can watch-and-wait be safely extended to bulky or node-positive tumors achieving cCR?** Registry data are reassuring but the randomized evidence base (OPRA) enrolled a broad stage II/III population, not a uniformly low-risk one

WHAT COMES NEXT

Future Directions: Sharpening Patient Selection

● Circulating tumor DNA (ctDNA)

Molecular surveillance to detect microscopic recurrence before it is clinically or radiologically visible

● AI-assisted endoscopic & MRI interpretation

Deep-learning image analysis to standardize response assessment and reduce inter-observer variability

● Biomarker-driven risk stratification

Combining tumor genomics, regression grade, and imaging radiomics to individualize surveillance intensity

● Ongoing & planned randomized trials

Further prospective trials refining TNT sequencing, near-CR management windows, and long-term functional outcomes

TAKE-HOME MESSAGES

From Radical Resection to organ preservation

- 1 TNT has expanded the pool of true complete and near-complete responders eligible for organ preservation
- 2 Surveillance rests on a rigorous, concordant DRE + endoscopy + MRI triad — never a single test
- 3 Surveillance must be front-loaded : because ~95% of regrowth occurs within 2–3 years, and is predominantly endoluminal
- 4 Failure is not uniform — local regrowth is usually salvageable; distant metastasis reflects biology, not surveillance gaps
- 5 Randomized (OPRA) and registry (IWWD, OnCoRe) data converge: oncologic outcomes are comparable to upfront TME in well-selected patients

