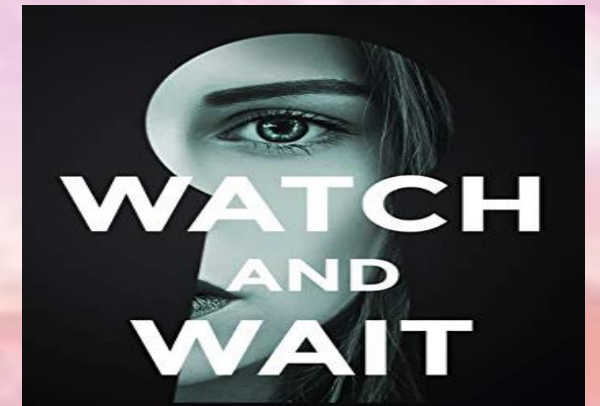
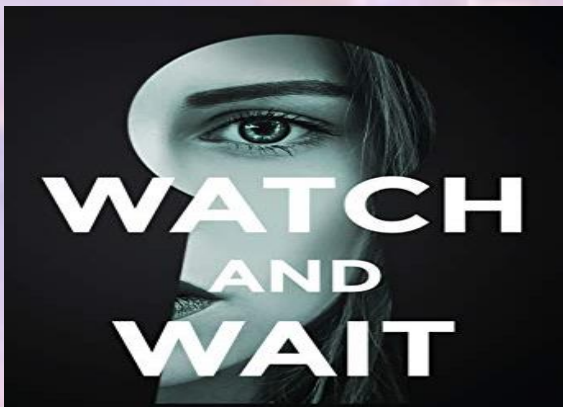




Wait & Watch

What if regrowth happened

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RECTAL CANCER

- Management of rectal cancer has considerably changed over the last few decades.
- While radical surgical resection with total mesorectal excision (TME) remains as one of the pillars of treatment
- Introduction of multimodality therapy with radiation and chemotherapy was fundamental for the development and proposal of organ-preservation strategies
- Initially used to improve local disease control, radiation alone or chemoradiation used in the preoperative (neoadjuvant) period was shown to be more effective than postoperative (adjuvant) treatment

WAIT AND WATCH PHILOSOPHY

- Observation of complete disappearance of the primary tumor (clinical complete response—cCR) led surgeons to consider avoiding immediate resection in select patients
- Since the initial reported outcomes of this non-operative treatment for patients who achieved a cCR, many changes have developed in terms of
 - Baseline assessment
 - Neoadjuvant treatment regimens
 - Assessment studies and timing of assessment.

WAIT AND WATCH PHILOSOPHY

- With time data become available, there is more information available regarding
 - the risk of **local regrowth** of tumors which achieved a cCR
 - also regarding the **risk of subsequent distant metastases** development .
- Finally, molecular markers have been able to distinguish a **specific subtype** of rectal cancer where a distinct treatment alternative may lead to an opportunity for organ-preservation in a significant proportion of cases

WAIT AND WATCH PHILOSOPHY



MAINTAIN SPHINCTER & FUNCTION

Local Control

Equivalent Survival



RATIONALE

- The reason why non-operative treatment of rectal cancer is attractive is related to the fact that TME surgery is associated with significant morbidity, mortality and functional consequences.
- Significant disturbances associated with urinary and sexual function have been reported.
- Depending on the level of the tumor in the rectum, level of the anastomosis and the requirement for partial or total intersphincteric resection, patients may experience variable levels of symptoms associated with **Low Anterior Resection syndrome** .

Low Anterior Resection Syndrome

Symptoms



Variable, unpredictable bowel function



Emptying difficulties



Altered stool consistency



Urgency



Increased stool frequency



Incontinence



Repeated painful stools



Soiling

Consequences

Impact on:



Toilet dependence



Mental and emotional wellbeing



Preoccupation with bowel function



Social and daily activities



Dissatisfaction with bowels



Relationships and intimacy



Strategies and compromises



Roles, commitments and responsibilities

At least one of these symptoms resulting in at least one of these consequences

RATIONALE

- Finally, the requirement of a temporary or definitive stoma may be very critical to many of these patients and avoiding it remains an important, if not **the most important, patients' expectation from rectal cancer treatment.**
- Here, it should be considered that many patients who undergo primary anastomosis for rectal cancer with a temporary stoma may ultimately **develop a failed anastomosis.** Reasons for a failed anastomosis may include leaks, stenosis, recurrence and poor function.
- Therefore, a number of patients thought to have received a temporary stoma are **ultimately faced with a definitive stoma.** Over time, the rate of definitive stomas may be nearly triple initial estimates

CAUTION SHOULD BE TAKEN IN PATIENTS ENTERING A WATCH AND WAIT (W&W)

- Proportion of patients entering a watch and wait (W&W) protocol will go on to develop a **local regrowth of the primary tumor** and therefore will require surgical resection. This means not all patients with a cCR will avoid surgery
- **Function outcome after W&W** may ultimately not be as perfect as one would expect or hope .
- Interesting data suggest that functional outcomes of patients undergoing W&W are not necessarily perfect, possibly due to the effects of radiation therapy to the rectum and anal sphincters

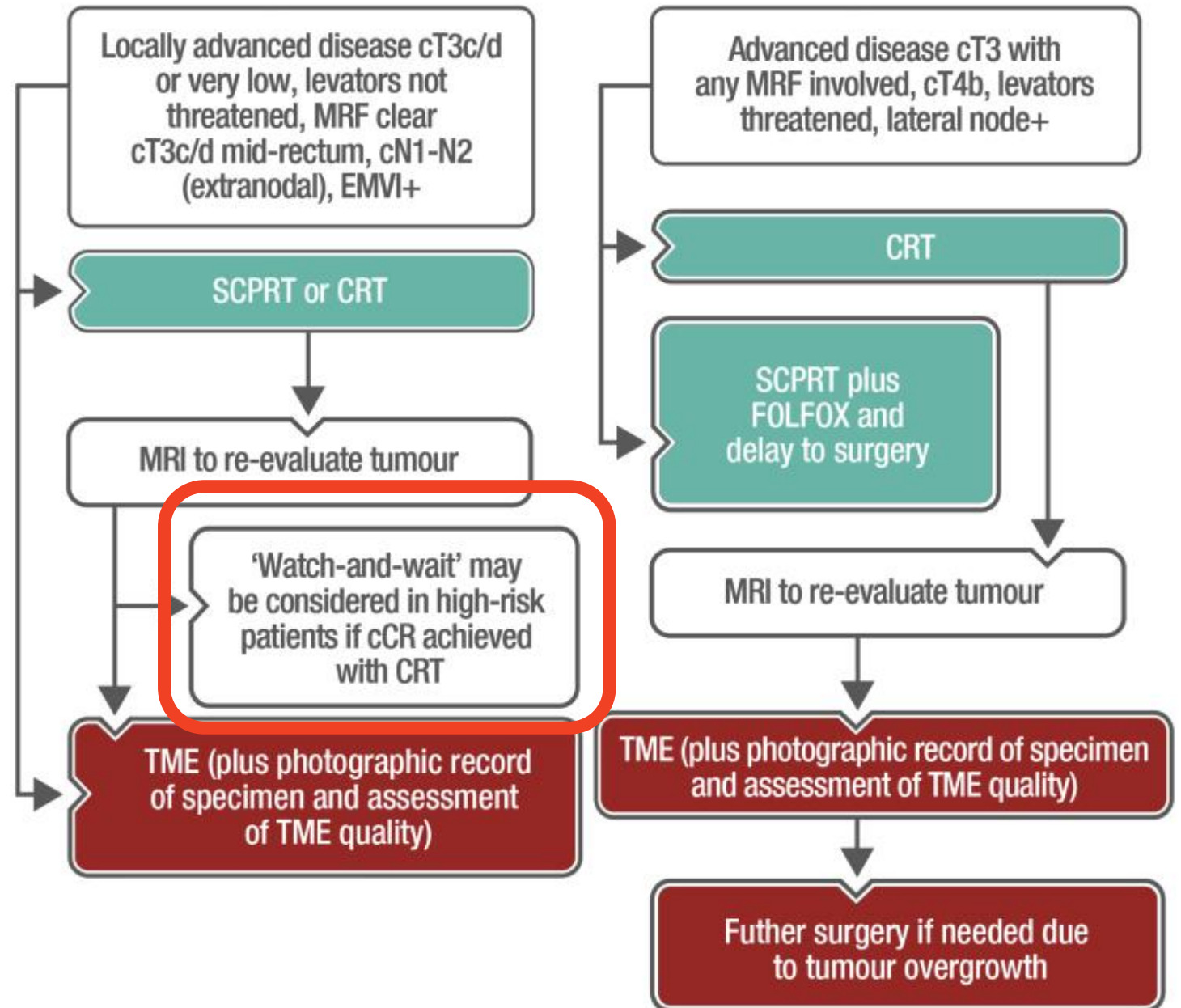
BASELINE FEATURES & SELECTION CRITERIA

- Patients were undergoing neoadjuvant chemoradiation for oncological purposes—to improve local disease control—and, by **accident or chance**, achieved a cCR
- **MRI interpretation** became standardized, allowing for the stratification of patients and tumors based on risk factors for local and distant failure.
- This led to a clearer distinction between patients with
 - **high-risk features**— requiring nCRT for oncological purposes
 - **low-risk features**— where perhaps the only benefit of nCRT would be the achievement of a cCR in an attempt to avoid TME surgery.
- Even though these two scenarios have been referred to as an “accidental” versus an “intentional” organ-preservation approach, one could argue that W&W is **never truly “intentional” as guaranteed achievement of cCR is not yet possible.**

CLINICAL PRACTICE GUIDELINES

Treatment recommendations

Locally advanced and advanced disease



ASCRS GUIDELINES

- Patients with an apparent complete clinical response to neoadjuvant therapy should typically be offered radical resection. A “watch and wait” management approach can be considered for **highly selected patients in the context of a protocolized setting.**

Grade of recommendation: Strong recommendation based upon moderate quality evidence, 1B.

ASSESSMENT OF TUMOR RESPONSE (THREE-PILLAR ASSESSMENT CRITERIA)

- **Clinical assessment using DRE** remains of critical relevance here. Clearly, it should be stressed that tumors beyond the reach of the finger during DRE should perhaps be considered suboptimal candidates for W&W.
- **Endoscopic assessment** is the second pillar in reassessment of response to nCRT/TNT. Usually, flexible endoscopy is currently preferred
- **MRI rectal assessment** with proposed classification system has been commonly used to grade response (similarly to the pathological grading system; MRI Tumor regression grade - TRG) according to the presence of low-signal intensity areas.

ASSESSMENT OF TUMOR RESPONSE (THREE-PILLAR ASSESSMENT CRITERIA)

CLINICAL ASSESSMENT USING DRE

- Findings consistent with a cCR include a smooth surface of the rectal wall at the area harboring the initial tumor and minimal induration of the rectal wall. There should be **no ulceration, palpable mass or stenosis of the rectum**
- Clearly, it should be stressed that **tumors beyond the reach of the finger during DRE should perhaps be considered suboptimal candidates for W&W.**

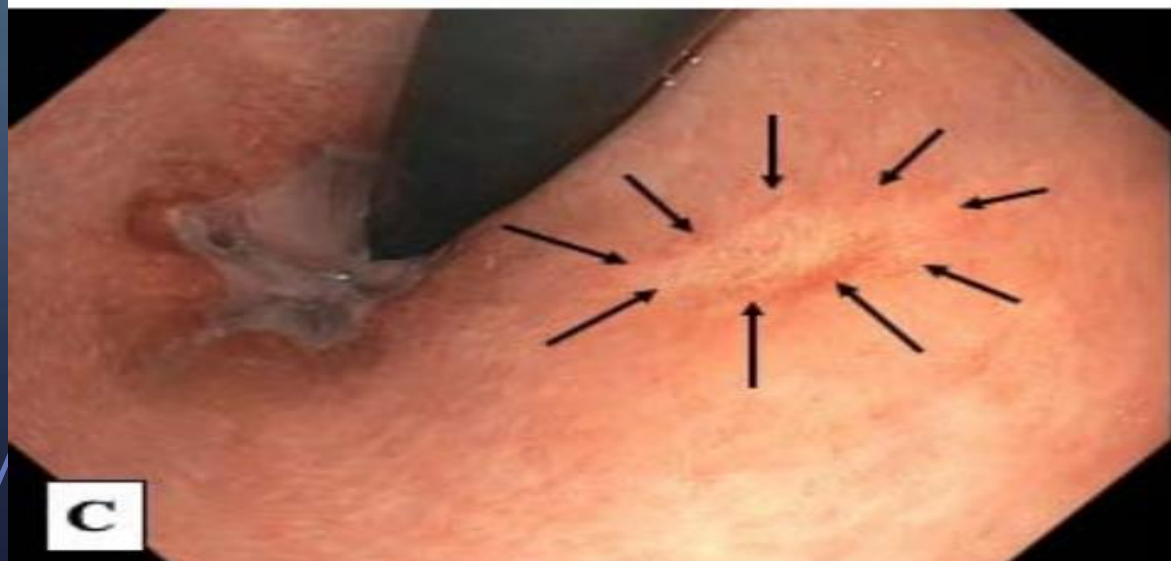
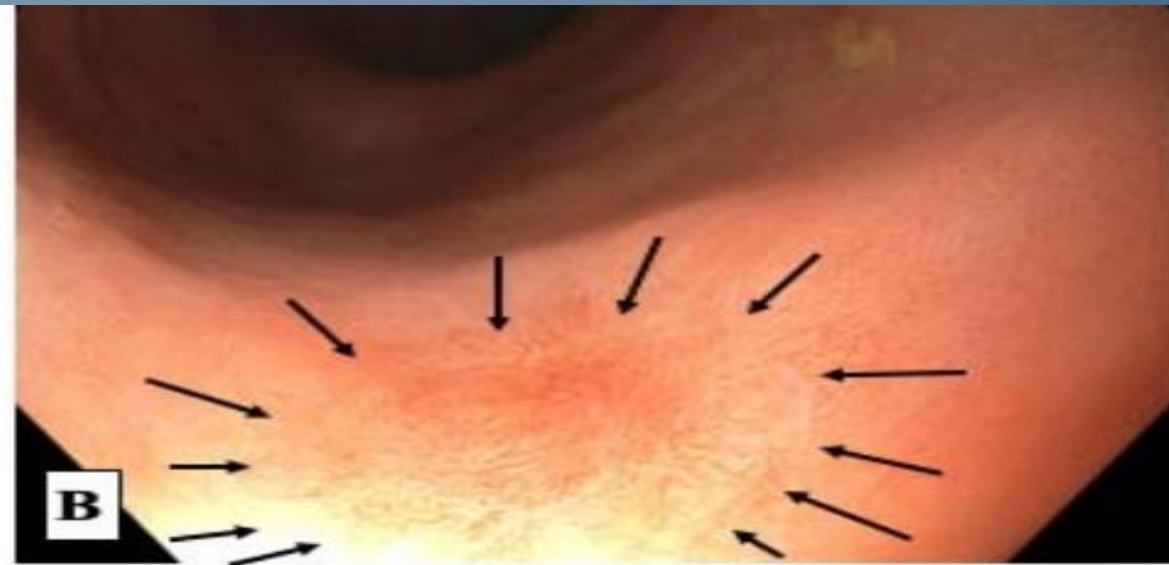
TUMORS BEYOND THE REACH OF THE FINGER DURING DRE SHOULD BE CONSIDERED SUBOPTIMAL CANDIDATES FOR W&W. WHY?

- Tumors above/beyond the reach of the finger are probably best treated by TME surgery
 - far fewer functional consequences,
 - less morbidity
 - lower risk of definitive stomas.

ASSESSMENT OF TUMOR RESPONSE (THREE-PILLAR ASSESSMENT CRITERIA)

ENDOSCOPIC ASSESSMENT

- Endoscopic assessment is the second pillar in reassessment of response to nCRT/TNT. Usually, flexible endoscopy is currently preferred in order to
 - (1) **provide documentation** of the endoscopic appearance of the residual scar/tumor;
 - (2) to allow advanced imaging techniques such as **narrow band imaging**
 - (3) to allow **retroflexive view of the anal canal and fully appreciate tumors** close to anal canal and dentate line.
- Endoscopic findings consistent with a cCR include a **white scar, no ulceration of the rectal wall or no irregularities**



ASSESSMENT OF TUMOR RESPONSE (THREE-PILLAR ASSESSMENT CRITERIA)

ENDOSCOPIC ASSESSMENT

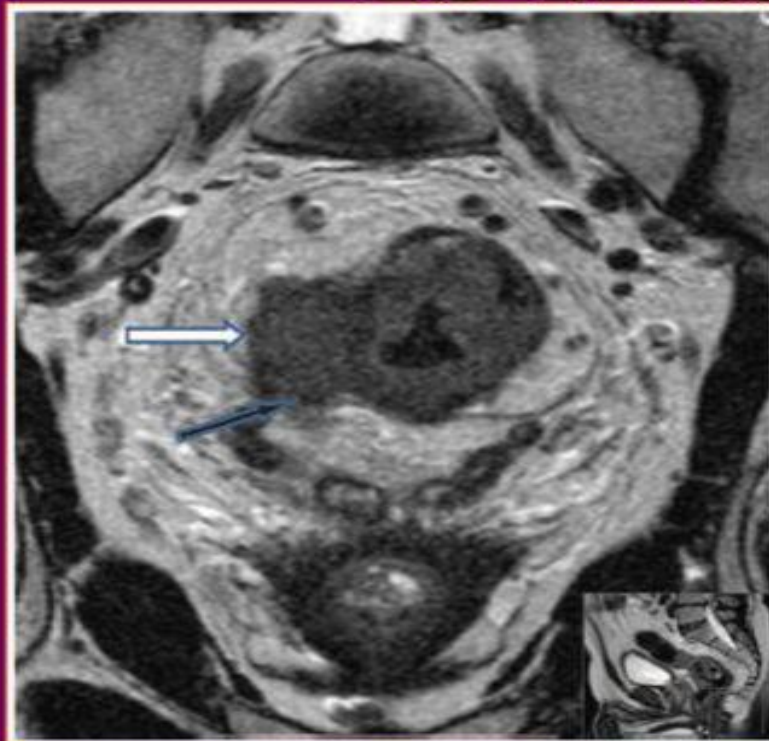
- Endoscopic biopsies are not included as one of the pillars for the diagnosis of a cCR. .
- This is due to the low negative predictive value of this diagnostic tool in this setting (nearly only 20%).
- However, a positive endoscopic biopsy may be informative and useful in such patients with very significant yet incomplete responses (“near-complete” responses).

ASSESSMENT OF TUMOR RESPONSE (THREE-PILLAR ASSESSMENT CRITERIA)

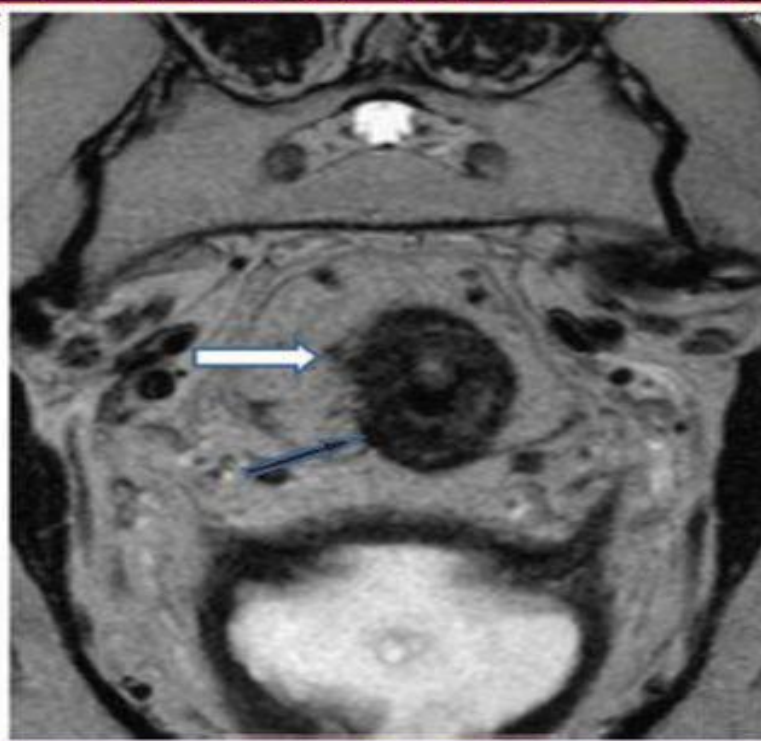
MRI RECTAL ASSESSMENT

- MRI rectal assessment with proposed classification system has been commonly used to grade response (similarly to the pathological grading system; MRI Tumor regression grade - TRG) according to the presence of low-signal intensity areas.
- mrTRG1-2 are usually associated with complete or near-complete tumor response (suggesting a significant replacement by fibrotic tissue) in contrast with mrTRG3-5

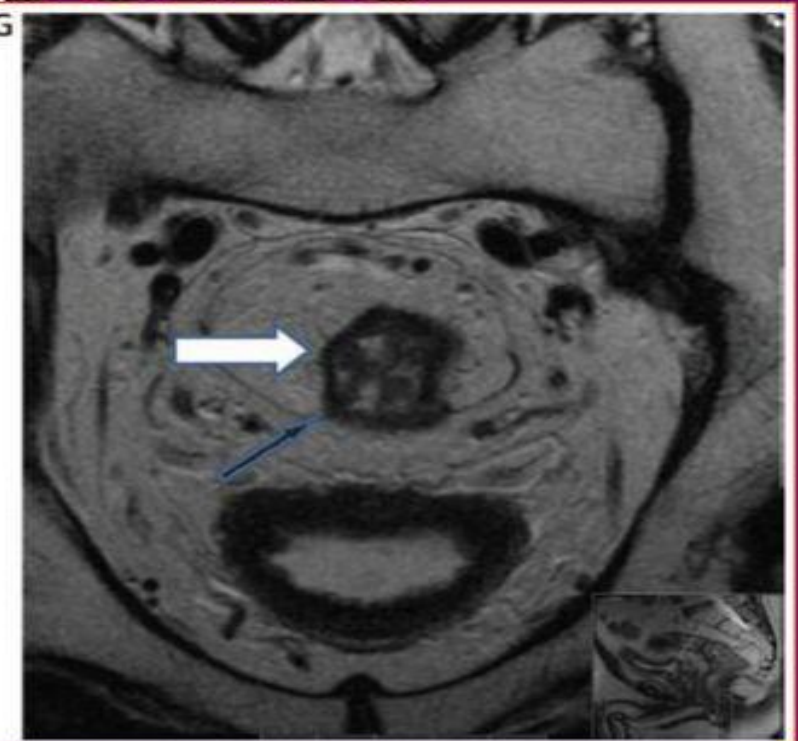
Timing after CRT? When is maximum response



Baseline
mrT4



6 weeks
mrT3b



12 weeks
mrT2

Final Pathology: ypT2N0

ASSESSMENT OF TUMOR RESPONSE (THREE-PILLAR ASSESSMENT CRITERIA)

- **PET-CT** used for the purpose of tumor response assessment in several studies and may be useful for the identification of appropriate candidates for W&W in this setting.
- However, reassessment by PET-CT preferably
 - requires a baseline assessment using PET-CT,
 - considerable costs
 - the requirement of radiation associated with PET-CT (contrasting with MRI)

TIMING

- First assessment of response between **6–8 weeks** to attest significant response taking place early on as a sign of promising outcomes in achieving a cCR and successful W&W
- **Second every 8 to 12 weeks for 3 years**
- Second, surveillance is recommended for life even though the risk of regrowth becomes very low after 3 years being disease-free. **Every 6 months for 5 years**
- **After the 5th year, patients can follow-up yearly**
- Metastatic disease surveillance should follow the usual guidelines and should only be intensified in the case of (1) a local regrowth and/or (2) clinical suspicion.

PARAMETERS OF GOOD RESPONSE

- First, tumors should have **exhibited significant response** in their very first assessment round.
 - Comparison with baseline assessment information may be helpful in identifying patients who truly exhibit very significant responses
 - (**nearly 75–80% of the tumor volume** is gone by endoscopic assessment and only a minor irregularity is detected)
- Second, there should be **ongoing response in between rounds**, meaning that there is no stable incomplete clinical response. Instead, clear subsequent regression needs to be clearly documented with any of the assessment studies .

PARAMETERS OF GOOD RESPONSE

- Third, endoluminal response seems to be the driver of response. This means that **endoscopy and DRE showing complete disappearance of the tumor** should be considered more significant than radiological disappearance of the disease.
- Finally, most cCR are usually achieved within 6 months from RT completion. **If incomplete response is still obvious after 24–26 weeks** from RT completion, surgical resection of the primary is perhaps preferred

LOCAL REGROWTH

- Local regrowth is, by definition, the **reappearance of the primary tumors within the rectal wall, the mesorectum or within the lateral pelvic compartment after the achievement of a cCR.**
- It seems that nearly **25–30%** of patients who achieve a cCR and are managed non-operatively will eventually develop a local regrowth.
- This risk is **highest within the 3 years** immediately after the achievement of a cCR

LOCAL REGROWTH

- The term regrowth instead of recurrence was originally proposed to distinguish this clinical entity from **local recurrences after TME surgery**.
- The idea was to attempt to avoid the stigma associated with local recurrences following TME frequently associated with poor outcomes, often unresectable and frequently associated with debilitating condition

SALVAGE RESECTION, POSSIBLE ?

- In local regrowth the majority of the cases amenable to salvage resection, possible through an **R0 resection in nearly 90% of the cases.**
- In fact, surgical salvage of local regrowth provides excellent local disease control with subsequent **re-recurrence in $\leq 5\%$ of the cases.**

WHAT TYPE OF SALVAGE RESECTION, POSSIBLE ?

- Depending on the site and local stage of the tumor
- **APR is more common than sphincter saving surgeries** WHY?
- **Second chance for organ preservation** with trans-anal local excision is possible surprisingly with better outcome than TME WHY?

APR IS MORE COMMON THAN SPHINCTER SAVING SURGERIES WHY?

- A significant proportion of patients requiring salvage TME at the time of local regrowth ultimately require an abdominal perineal resection (APR)
- In fact, the rates of **APR among regrowth seem to be higher than in patients proceeding straight to TME** after treatment completion and incomplete clinical response.
 - These differences may be due to distinct features between patients being offered W&W versus those undergoing TME **related to tumor location**. Since ideal candidates for W&W are those with tumors located at the reach of the finger during DRE and located at the level of or below the insertion of the levator ani muscles, it is not surprising that local regrowth at this level would frequently require APR
 - also may be **delay in follow up** depending on success of W&W

SECOND OPPORTUNITY FOR ORGAN-PRESERVATION ? BETTER OUTCOME WHY?

- Trans-anal local excision of the regrowth.
- This has been recently reported in two independent series. Curiously, disease-free survival among local regrowth salvaged by local excision was better than patients undergoing TME for salvage.
- However, locally-excised regrowth was more likely to have early-stage disease at baseline.
- Therefore, such differences in survival may possibly be **reflecting intrinsic differences in baseline stages rather than the actual type of** salvage employed at the time of regrowth

RISK FACTORS FOR REGROWTH

- Risk factors for development of local regrowth after the achievement of a cCR appear to be related exclusively to baseline T stage. Apparently, there seems to be a 10% increase in the risk of local regrowth for every increase in T stage category:
 - 20% for cT2,
 - 30% for cT3
 - 40% for cT4
- Curiously, baseline N stage has not been associated with the risk of a local regrowth in these patients.
- Interestingly, when patients sustain a cCR longer than 3 years, the risk of local recurrence becomes minimal.

DISTANT METASTASES RISK

- The risk of distant metastases among patients who achieve a cCR after treatment is considerably low
- the only identifiable risk factor for development of distant metastases was **development of local regrowth**
- Patients who have **excellent (but incomplete) response managed by TME straight after treatment respond better than those undergoing salvage TME** at the time of local regrowth so patient go to W&W should know this risk.

MSI RECTAL CANCER AND WATCH AND WAIT

- Patients with high-level microsatellite instability (**MSI-high**) adenocarcinomas were found to have worse rates of complete response to standard nCRT
- The development of **PD1 checkpoint inhibitors** led to the observation of significant tumor response in multiple tumors with MSI status
- PD-1 is a checkpoint protein on immune cells called T cells. It normally acts as a type of “off switch” that helps keep the T cells from attacking other cells in the body. It does this when it attaches to PD-L1, a protein on some normal (and cancer) cells.

MSI RECTAL CANCER AND WATCH AND WAIT

- One recent single-arm clinical trial including **primary MSI-high rectal adenocarcinoma** offered PD-1 checkpoint inhibitors leading to a surprisingly 100% cCR rate among 14 patients, without the use of radiation or standard chemotherapy

Cercek, A.; Lumish, M.; Sinopoli, J.; Weiss, J.; Shia, J.; Lamendola-Essel, M.; El Dika, I.; Segal, N.; Shcherba, M.; Sugarman, R.; et al. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. *N. Engl. J. Med.* 2022, 386, 2363–2376.

MSI RECTAL CANCER AND WATCH AND WAIT

- The possibility of treatment with immunotherapy potentially leading to avoidance of TME in the vast majority (if not all!) patients





Thank you