# MRI Tumor Regression Grading in Rectal Cancer - How to report tumor response

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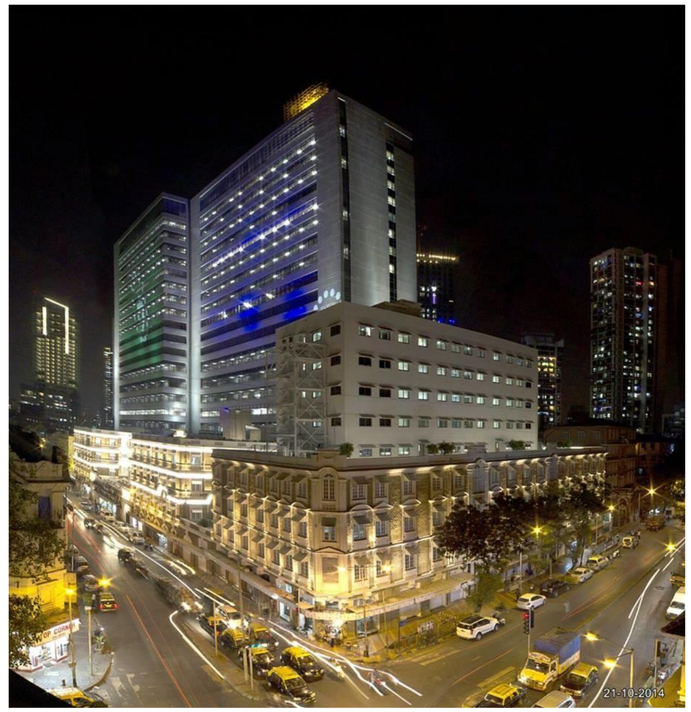


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# Learning Objectives

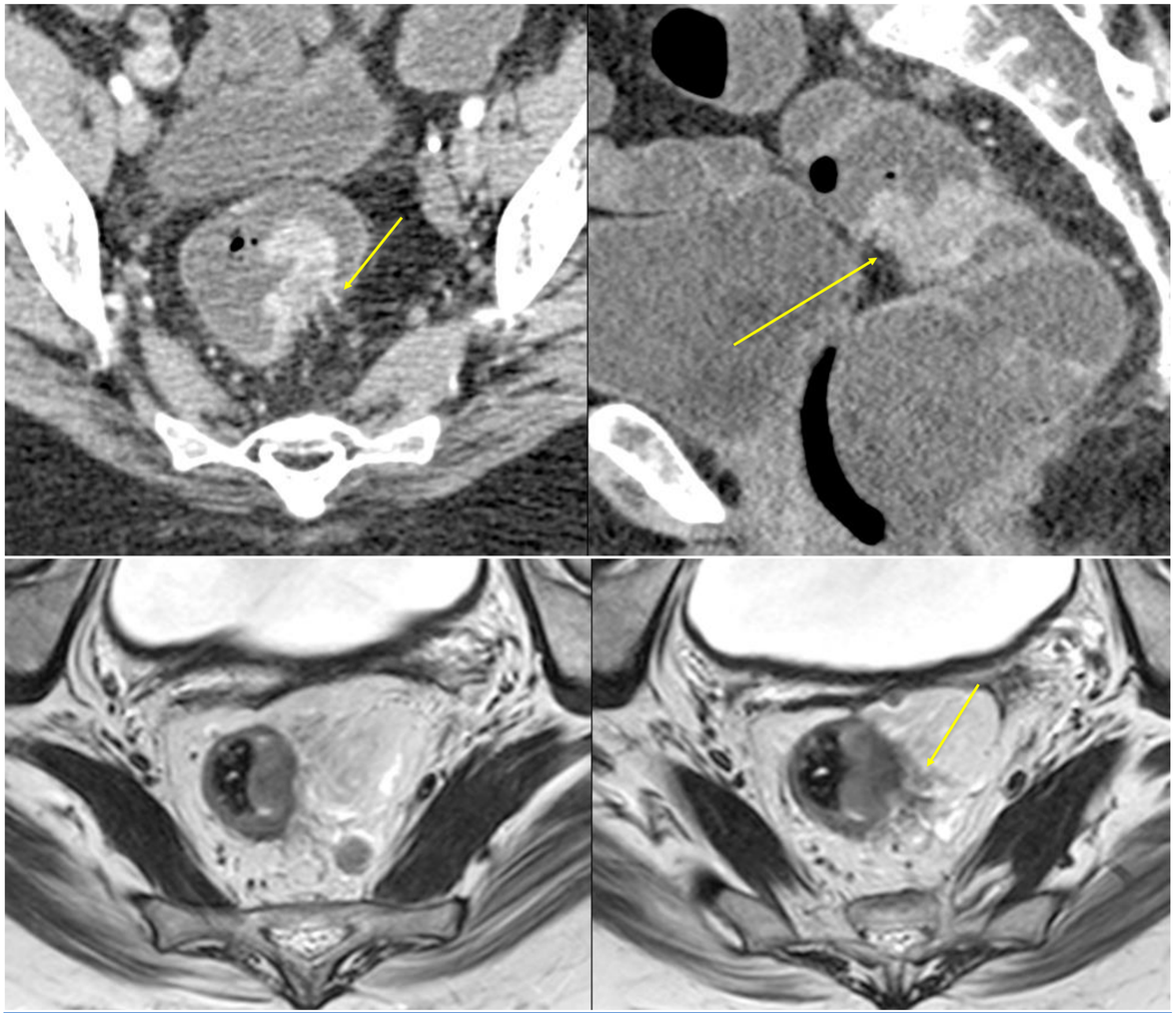
After reviewing this exhibit the participants will know the following:

- What is Locally Advanced Rectal Cancer [LARC] ?
- What are the management options for LARC ?
- What are the morphological and functional MR criteria for tumor re-staging ?
- Standardized reporting template for MR Tumor Regression Grading [TRG]
- What are the limitations of MR TRG ?

# What is Locally Advanced Rectal Cancer (LARC)?

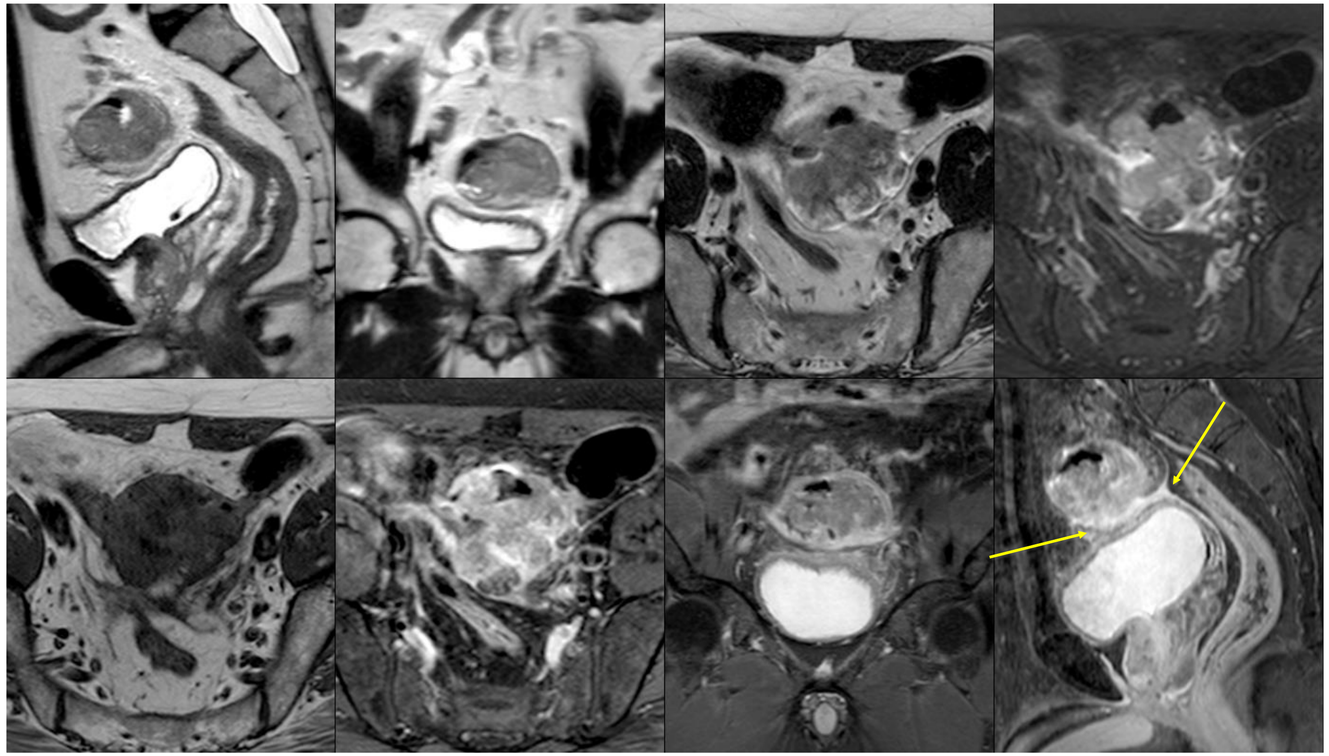
- The terminology "Locally Advanced Colorectal Cancer" has not been standardized in literature.
- There is no official definition of locally advanced rectal cancer (LARC) by any recognized organization in this arena, nor within the AJCC TNM staging classification, NCI nor by NCCN.
- *By Convention, LARC constitutes*:
  - T3/4, N0
  - Any T-Stage, Node positive disease

# T3 Lesion



56-year old woman presented with bleeding PR. CECT reveals an intensely enhancing eccentric infiltrative lesion with an intraluminal polypoidal component. Note the puckering and increased linear streakiness of the adjacent mesorectal fat (red arrow), with few discrete enhancing mesorectal nodes. T2-w Images reveal full thickness mural invasion with infiltration of the mesorectum [T3 disease], with an enlarged metastatic left mesorectal node

# T4 Lesion



58-year old man with a large transmural infiltrative mass involving the rectosigmoid invading the mesosigmoid and anterior peritoneal reflections along the posterosuperior surface of the urinary bladder (red arrow). There is no bladder mucosal invasion.

# MR Imaging - "Reference Standard" for Non-Invasive Assessment of Rectal Cancer

| Parameter | Sensitivity | Specificity |
|---|---|---|
| T Stage[1] | 87%(81-92) | 75% (68-80) |
| N Stage[1] | 77% (69-84) | 71%(59-81) |
| CRM[1] | 77% (57-90) | 94%(88-97) |
| Muscularis Propria & Adjacent Organ invasion[2] | 97% | 97% |

1.Avanish Saklani et al, Magnetic resonance imaging in rectal cancer: A surgeon's perspective, World of Gastroenterol. 2014 Feb 28, 20(8): 2030–2041.
2.Ge Zhang et al, Diagnostic Accuracy of MRI for Assessment of T Category and Circumferential Resection Margin Involvement in Patients With Rectal Cancer: A Meta-Analysis , Diseases of the Colon & Rectum. 59(8):789–799, AUG 2016

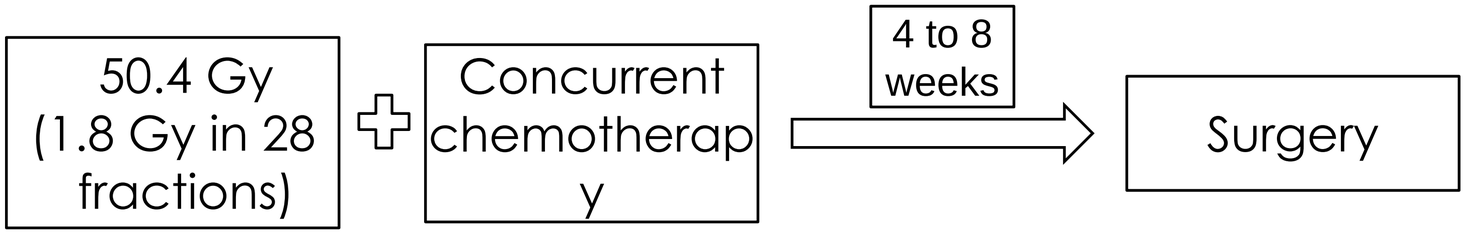
# Treatment Options for LARC

Pre-operative options for chemotherapy and radiotherapy in LARC

- Pre-operative short course radiotherapy (SCRT)
- Pre-operative long course chemoradiotherapy (LCCRT)
- Consolidation - Waiting for 6 to12 weeks post LCCRT or SCRT prior to surgery

# Long Course Chemoradiotherapy [LCCRT]

- Pre-operative 3- or 4-field radiation with concurrent fluoropyrimidine-based chemotherapy (5-FU or capecitabine) and subsequent total mesorectal excision (TME) is "*current standard care of treatment for locally advanced rectal cancer*".




- Mechanism of Action: Carcinomatous cells are replaced by fibrous or fibroinflammatory tissue.

- Pros
  - Chemotherapy potentiates local RT sensitisation
  - Induce tumor downsizing +/- downstaging
  - Better sphincter preservation
  - Lower rate of recurrence
- Cons
  - Long waiting period for surgery
  - Higher Cost
  - Lower patient compliance

# Rectal Cancer - Pathological Tumor Regression Grade [TRG] Systems

| | Dworak [5-point] | Mandard [5-point] | Ryan [3-point] | AJCC [4-point] | Modified Dworak [pT + pN] |
|---|---|---|---|---|---|
| Complete Regression | No tumor cells [TRG4] | No residual cancer cells [TRG1] | No viable cancer cells, or single cells, or small groups of cancer cells [TRG 1] | No viable cancer cells [TRG 0] | No tumor cells [TRG 4] |
| Near Complete Regression | Very Few Tumor cells [TRG 3] | Rare residual cancer cells [TRG 2] | | Single or small groups of tumor cells [TRG 1 - moderate response] | Very few tumor cells [one or two microscopic foci of <0.5cm in diameter] [TRG 3] |
| Moderate Regression | Dominantly fibrotic changes with few tumor cells or groups [TRG 2] | Predominant fibrosis with increased number of residual cancer cells [TRG 3] | Residual cancer outgrown by fibrosis [TRG 2] | Residual cancer outgrown by fibrosis [TRG 2: minimal Response] | Dominantly fibrotic changes with few tumor cells or groups [TRG 2] |
| Minimal Regression | Dominant Tumor mass with obvious fibrosis [TRG 1] | Residual cancer outgrowing fibrosis [TRG 4] | Significant fibrosis outgrown by cancer, or no fibrosis with extensive residual cancer [TRG 3] | Minimal or no tumor cells killed [TRG 3 - poor response] | Dominant Tumor cell mass [>50%] with obvious fibrosis or no regression [TRG 1] |
| No Regression | No Regression [TRG 0] | No regressive change [TRG 5] | - | - | - |

# Limitations of Pathologic Tumour Regression Grading (pTRG)

- "Limited reliability of biopsy" to judge whether a patient has achieved a cCR [clinical complete response].
- "Inability to assess infiltration of mesorectal fascia" from biopsy tissue.
- Most of the pathologic systems [except for the Modified Dworak staging] "do not consider the nodal disease".
- If a pre-operative imaging is performed, it can evaluate disease status post CRT and further management depending upon of the existing disease burden can be formulated. "Hence there is a need for a tumour regression grading system using non-invasive techniques like MRI [mrTRG]".

# MRI Tumour Regression Grading [mrTRG]

- By applying the principles of histopathological TRG and by exploiting the characteristic MRI low-signal–intensity appearances of fibrosis, it has been possible to develop a MRI-based TRG system.
- The "extent of the tumour and qualitative assessment of change in signal intensity" [tumour regression grade (TRG)] are the main criteria for response evaluation.
- "mrTRG may supercede pTRG", as it has the advantage of assessing tumour response before surgery. As such, it has the potential for enabling response-orientated tailored treatment, including alteration of the surgical planes, additional use of chemotherapy, or deferral of surgery.
- The MRI-assessed TRG (mrTRG) was found to be an independent prognostic factor for overall survival (OS) and disease free survival (DFS)

# mrTRG as a "Prognostic and Predictive Biomarker"

mrTRG shows good interobserver radiology agreement & reproducibility based on the following trials

- MERCURY trial (JCO 2011- multiple radiologists)
- The EXPERT C trial identified 40% of patients with mrTRG 1/ 2 - 89.8% overall survival. Compared with only 15% pathologic CR rate (90% survival)
- GEMCAD study (17 radiologists)
- CORE study (interobserver agreement)
- MERCURY 2 Trial (risk factor for CRM involvement)

"Therefore mrTRG could be justified as a more clinically relevant endpoint"

# Morphologic responses to chemoradiotherapy

- Morphologic changes in surgical specimens after CRT include collagen, fibrosis, desmoplasia, mucin, inflammatory change resulting in submucosal edema, and necrosis.
- Fibrotic Changes to tumor and Rectal Wall: Fibrosis appears as low T2 signal intensity with respect to the gluteal muscle (cf. tumour which shows intermediate T2SI)
- Desmoplastic Reaction: Low-intensity spicules or strands in the perirectal fat radiating from the residual tumor. More nodular tissue is likely to be tumor rather than desmoplasia.
- Pseudotumor response: The circumferential tumor often has central indentation with rolled everted edges and invasion or ulceration at its posterior border. The remaining rectal luminal mucosa and submucosa often appear heaped up into the lumen due to edema - a pseudotumor appearance. This effect can get exaggerated after treatment and may result in near-normal thickness of treated rectal wall but the unaffected submucosa can become edematous, thickened, and of intermediate intensity adjoining  the fibrotic wall, leading to potentially false interpretation.

# Morphologic Responses to Chemoradiotherapy - Mucinous Change in Tumours

| | | | |
|---|---|---|---|
| Baseline MRI | Intermediate SI Tumour | Intermediate SI Tumour with hyperintense cellular mucin | Intermediate SI Tumour with hyperintense cellular mucin |
| Post Treatment MRI | Hyperintense pools of mucin within isointense tumour | Pools of featureless acellular T2 high-signal Intensity (fluid like) that contain no / minimal intermediate signal intensity | No change in morphology |
| Interpretation of MR Signal alterations | Represents Treatment Response | Represents Treatment Response | No response to Treatment |

# MR Tumor Regression Grading (TRG) System

## "Based on T2-w Images"

| | |
|---|---|
| TRG 1 | Complete Response: No evidence of residual disease |
| TRG 2 | Good Response: > 75% fibrosis; no obvious/ minimal residual tumour |
| TRG 3 | Moderate Response: 50% fibrosis or mucin and 50% visible intermediate signal |
| TRG 4 | Slight Response: <25% fibrosis or mucin but mostly tumour |
| TRG 5 | No Response: No fibrosis, Only intermediate signal intensity with same appearances as original tumour |

# MR Tumor Regression Grading (TRG) System

## "DW and Perfusion Imaging are Ancilliary Tools"

## Diffusion Weighted MR

- After CRT, reduction in cellularity and development of fibrosis or necrosis in responders results in an increase in diffusivity and increase in ADCs.
- Changes in ADC after 2 weeks of CRT serve as an early and reproducible indicator of tumor response, which may allow development of individualized regimens.
- DW-MRI increased accuracy in detecting viable tumor cells from 64–76% to 86–90% *(Song I et al)*.
- Addition of DWI to T2-weighted imaging improve detection of complete response after therapy, with a sensitivity of 52–64% (compared with 0–40% for T2-weighted imaging alone) and specificity of 89–98% *(Lambregts DM et al)*

## MRI Perfusion

Recently, few studies have suggested that the quantification of vascular permeability of the tumoral tissue represented as the $K^{trans}$ (volume transfer constant) may aid in the prediction of pathologic response. These results showed that a large decrease in the mean $K^{trans}$ after CRT is associated with a good response for locally advanced rectal tumors.

## Extramural Vascular Invasion (EMVI)

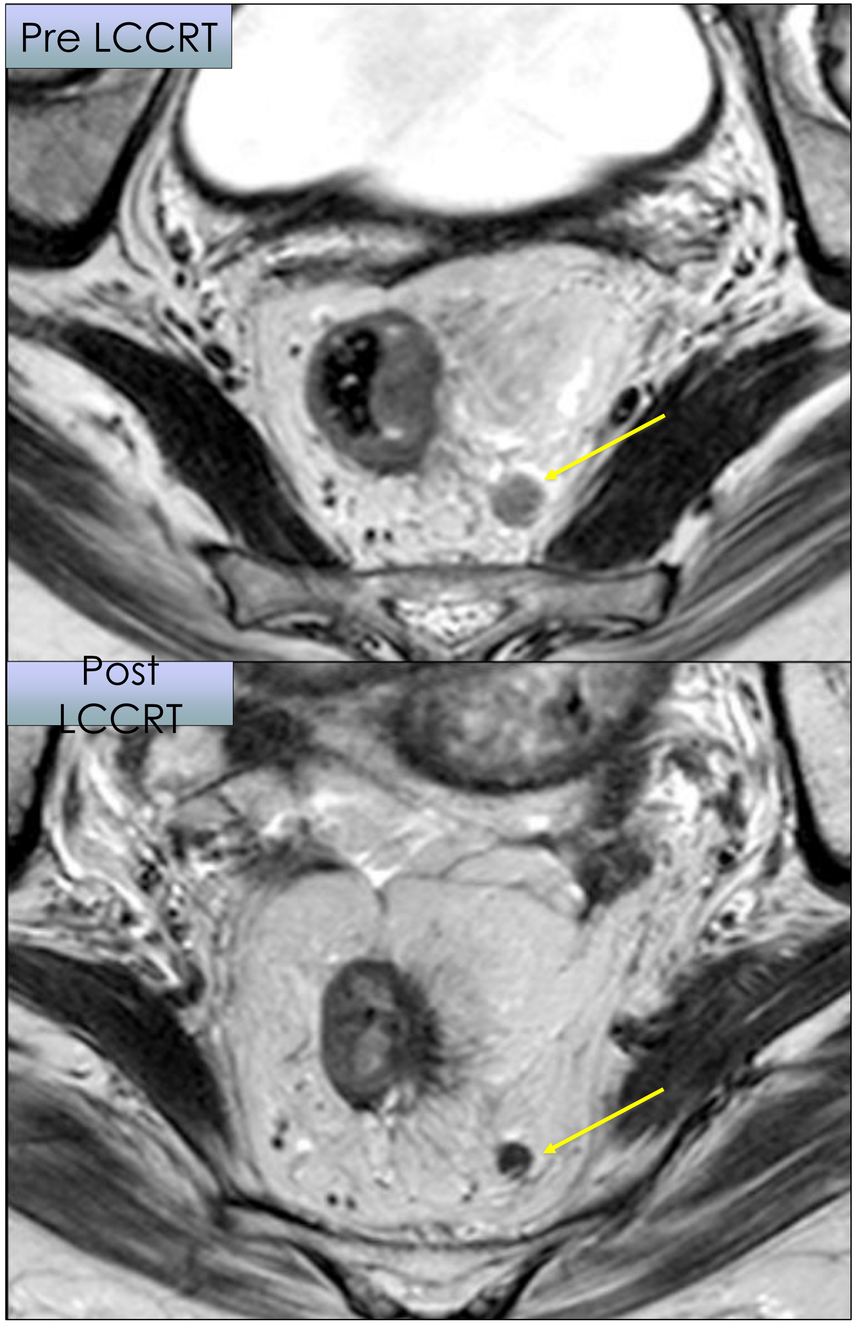
- T2-w - Discrete serpiginous or tubular projections of intermediate signal into perirectal fat following the course of a visible vessel to in more advanced cases, the vessel being expanded by intermediate signal tumor and having an irregular contour.
- EMVI may completely resolve with CRT. Intensely low T2 signal fibrotic strands suggest complete response.

## Nodal Characterization

- Malignant node shows irregular outlines or internal signal heterogeneity.
- Intermediate SI node on baseline MRI followed by hyperintense signal on post Treatment scans suggests Treatment related intranodal mucinous change.
- Following LCCRT, nodes usually shrink in size and appear dark on the T2-w images

## Mesorectal Fascia Assessment

- MRI has shown approximately 76% sensitivity and 86% specificity for assessment of MRF in the irradiated pelvis.




- Post LCCRT shows reduction in size of the left mesorectal node as well as its T2 signal, which now appears hypointense on the T2-w due to desmoplasia

# MR Imaging Protocol

High resolution T2-w images are the cornerstone of Post Rx assessment & TRG

Injection Buscopan – 0.5mg (Hyoscine butylbromide)
Mechanism: antispasmodic
- 5 min before procedure

MR Advantages
- Tissue resolution
- Rectal wall anatomy
- Contrast dynamics
- DW contrast

We do not use rectal distension

Pre-contrast → MR Perfusion → Delayed PC

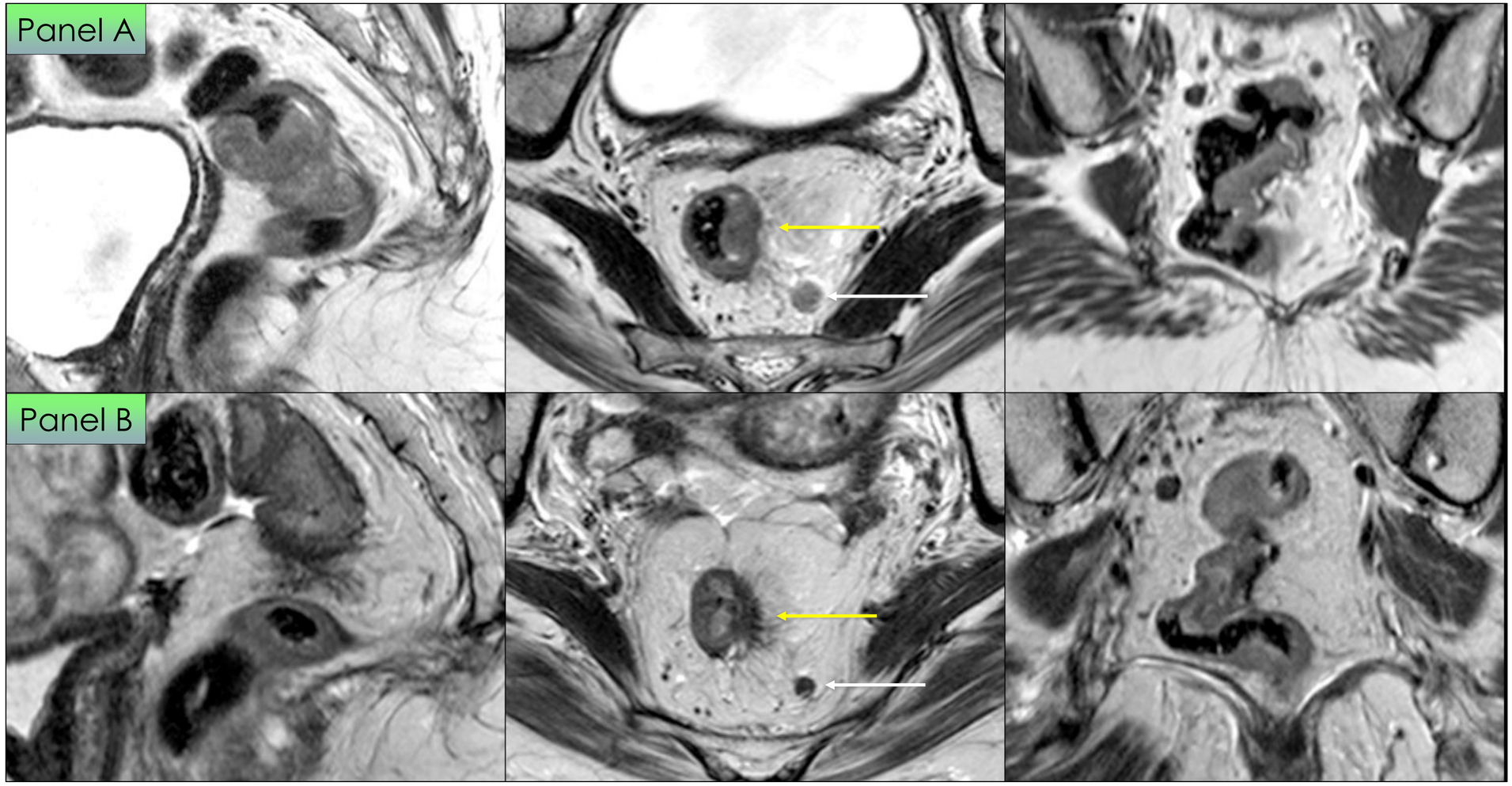
- T2TSE sagittal
- T2TSE coronal
- T2TSE axial (ortho)
- T1TSE axial
- DWI (b = 0, 500)
- T1-w 5mm slices to cover the entire pelvis

- 3D T1-w GRE
  - Dynamic
  - Sagittal plane
  - ST=1.5mm
  - 40 slices
  - Temp Res =7sec
  - NEX = 30
- DWI (b = 0, 500)

- T1TSE FS axial, coronal and sagittal
- DWI (b = 0, 500)

- Abdominal Screening
  - T2TSE ax + cor
  - 3DT1 GRE
  - DW (b=0, 500)

## Case 1: TRG 1 - Complete Response: No evidence of residual disease

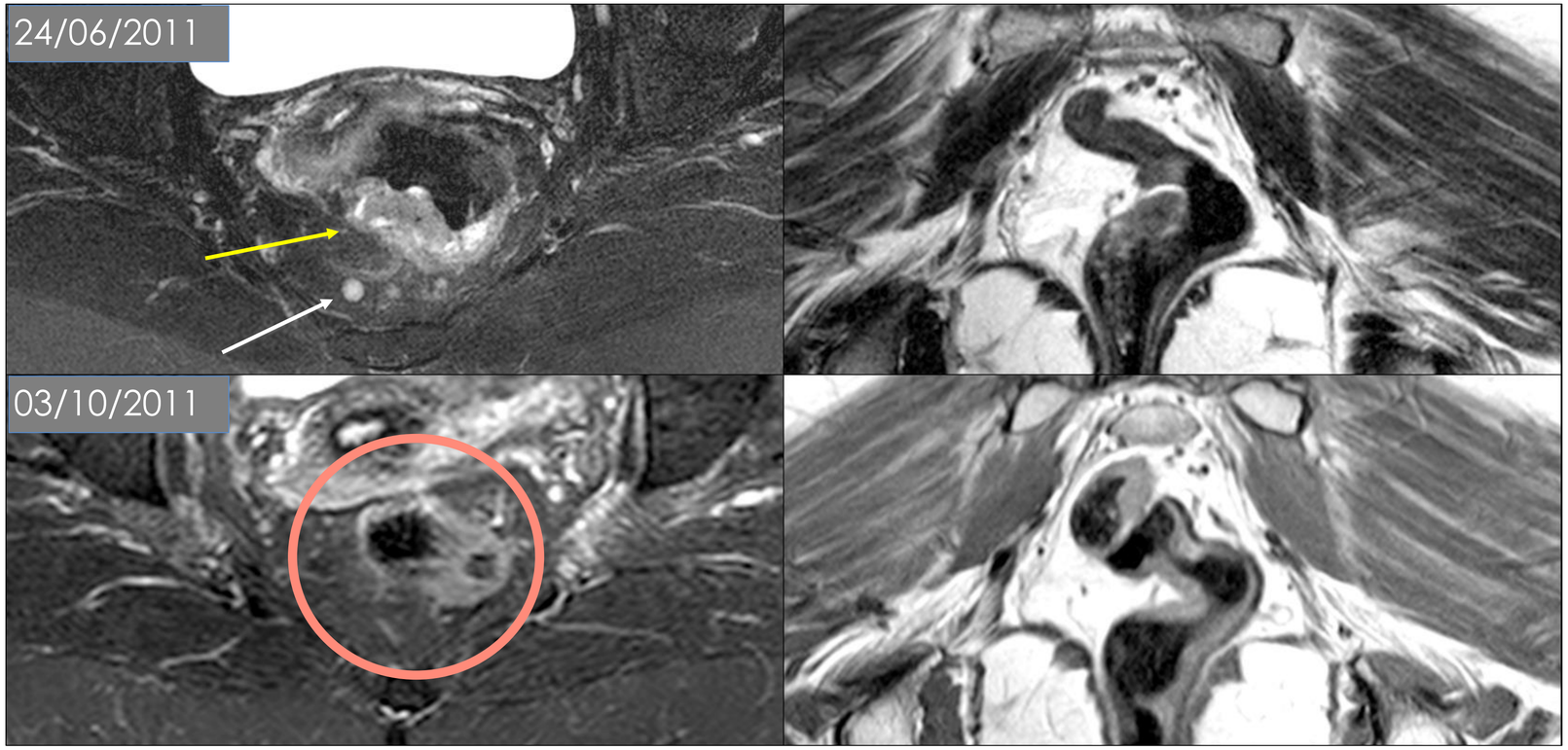



Pre (Panel A) and Post LCCRT follow-up (Panel B) MRI: Compared to Panel A, the T2-w sagittal, axial and coronal images in Panel B reveal reduction in bulk of the primary rectal mass, with residual wall thickening seen which reveals low T2 signal, associated with increased low T2 linear areas radiating into the mesorectal fat (desmoplastic reaction). Note that the mesorectal node has also regressed in size with a residual low T2 signal node seen [also representing treatment response]. Resection was done. H.P showed no residual disease in the resection specimen [pTRG - Complete Regression as per Modified Dworak Staging]

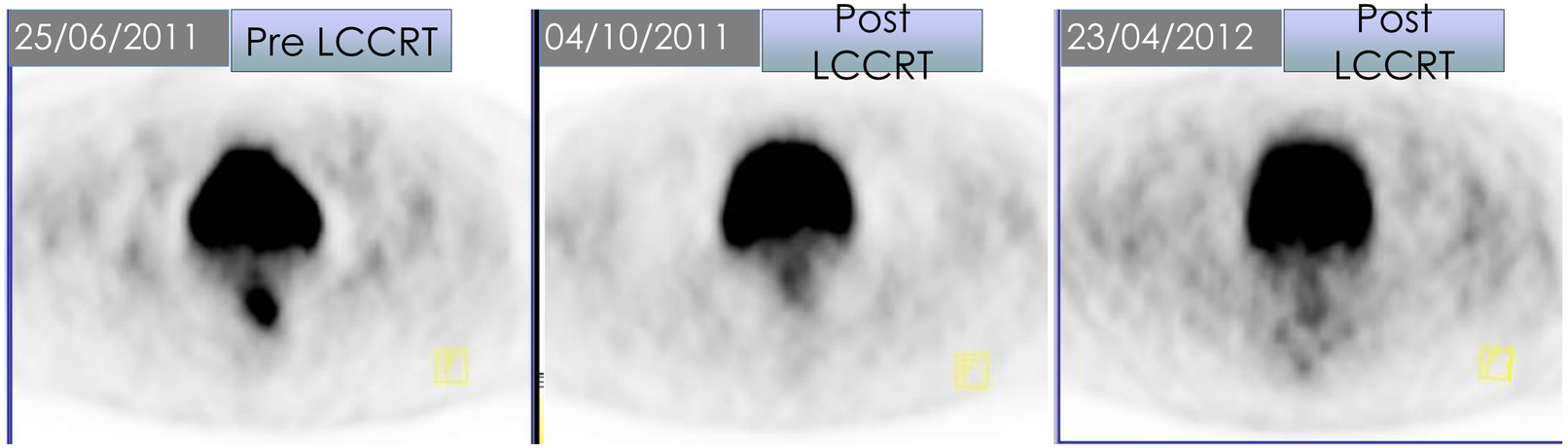
# Case 2: TRG 1 - Complete Response: No evidence of residual disease. Serial PET/CTs corroborate with post LCCRT MR TRG

Pre LCCRT

Post LCCRT

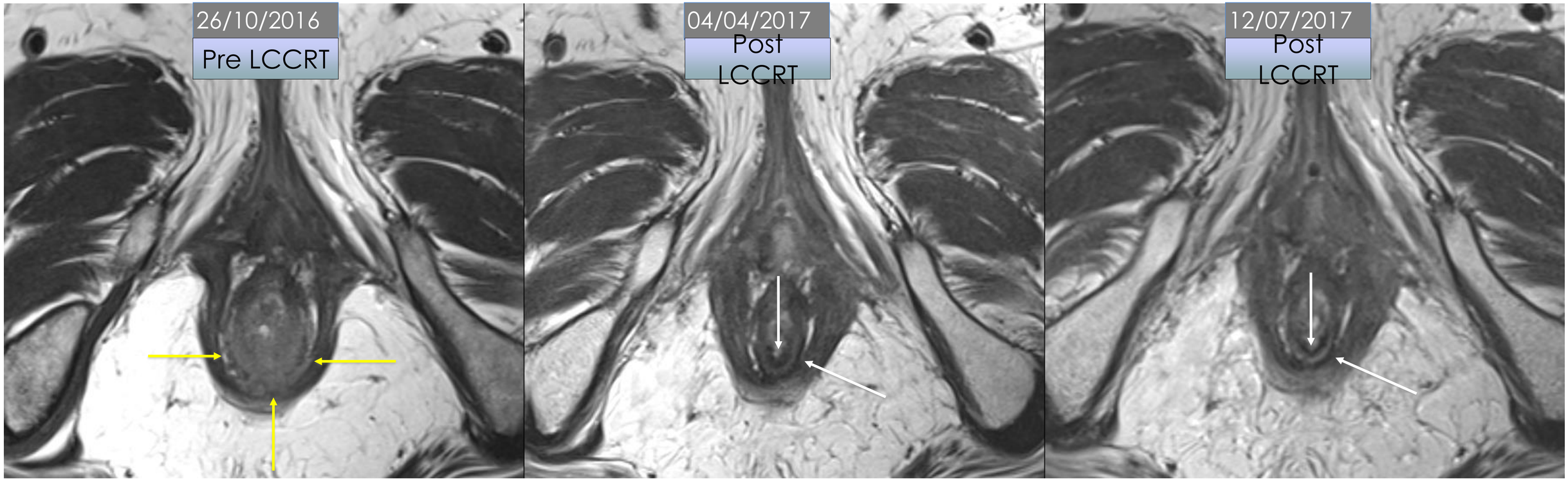



PET/CT



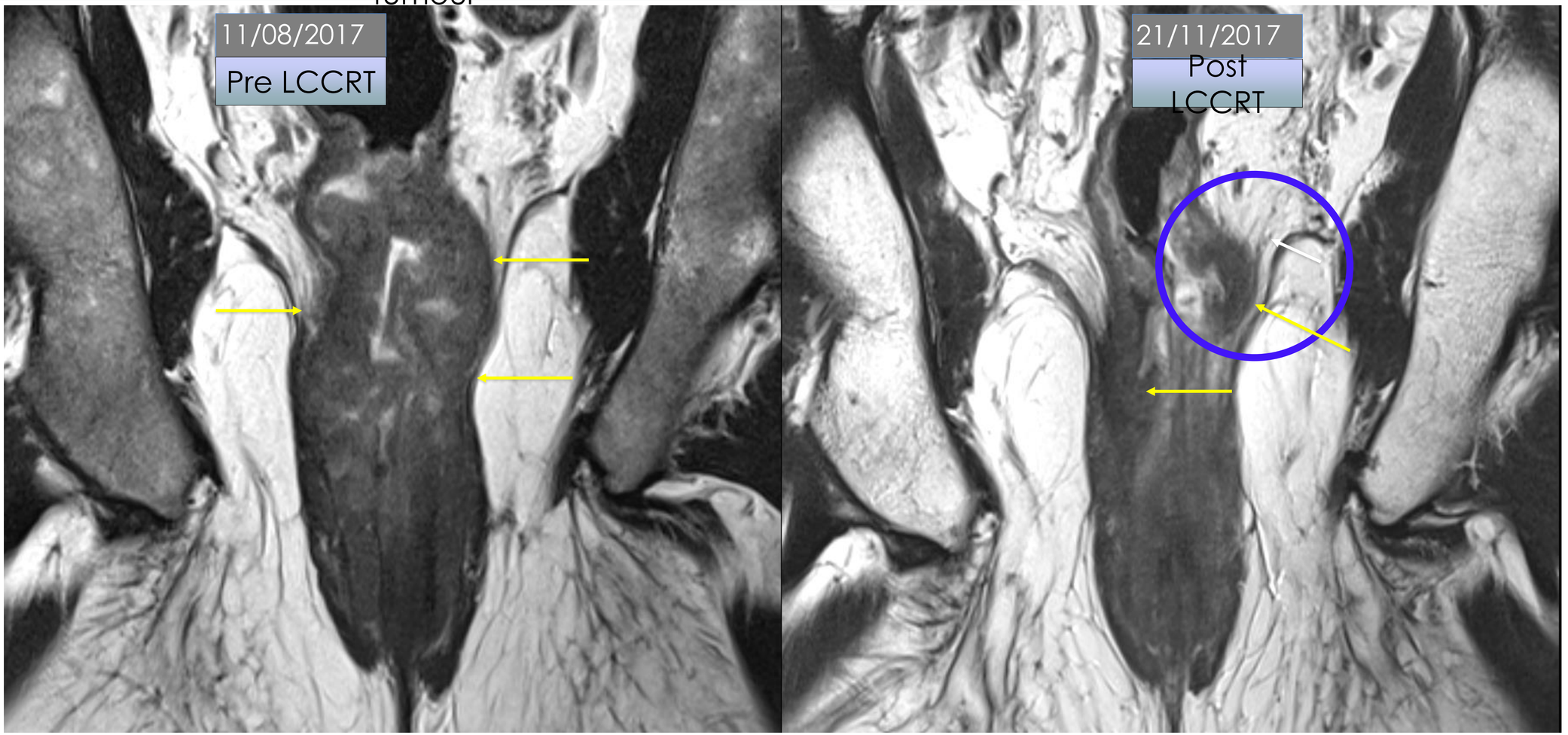

55-year old woman with a T3 rectal adenocarcinoma with mesorectal invasion and nodes. Patient underwent LCCRT and serial follow-up showed no residual lesion on on the post LCCRT MRI and PET-CTs. Robotic resection of the treated lesion was done. H.P showed no residual disease in the resection specimen [pTRG - Complete Regression as per Modified Dworak Staging]

## Case 3 - TRG 1 - Complete Response: No evidence of residual disease.




66-year old woman with a moderately differentiated SCCa [Stage T3] of the anal canal. Patient underwent LCCRT and serial follow-up showed no residual lesion on on the post LCCRT MRI. Post LCCRT MRI performed on 4th April 2017 showed complete response with reduction in bulk of the primary rectal mass, and, residual wall thickening which has a layered morphology consisting of an inner and outer low T2 signal fibrotic stripe surrounding a mildly hyperintense submucosa [white arrows]. Patient adopted a Wait-And-Watch Policy and a third follow-up MRI confirmed the stable appearances of the anal canal, with no recurrent lesion.

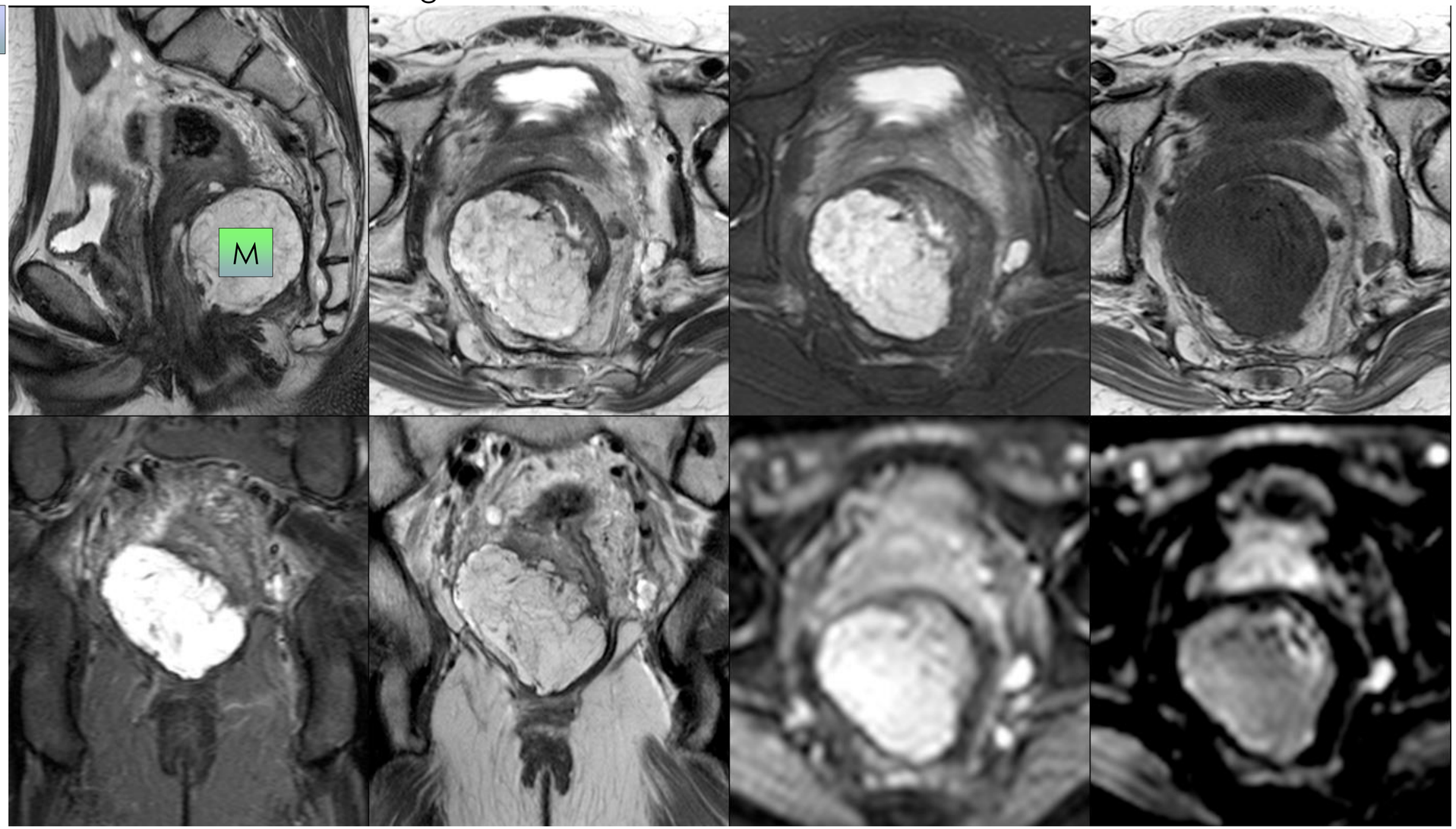
## Case 4 - TRG 2 - Good Response: > 75% fibrosis; no obvious/ minimal residual tumour




39-year old man with a moderately differentiated adenocarcinoma [Stage T3] of the mid and lower rectum. Patient underwent LCCRT and serial follow-up showed no residual lesion on on the post LCCRT MRI. Post LCCRT MRI performed on 21st November 2017 showed good response with complete reduction in bulk of the primary rectal mass, no obvious residual tumour with, and, [> 75% fibrosis] residual wall thickening which is identified as low T2 signal fibrotic stripe [yellow arrows]. Note the linear low T2 signal speculations in the mesorectum representing demsoplastic response [white arrow].

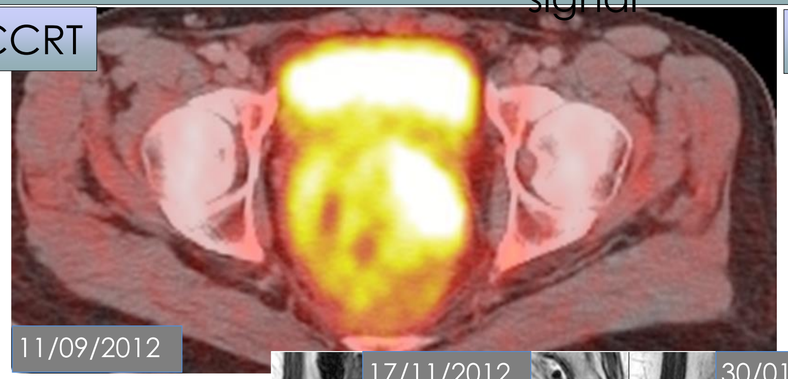
# Case 5 - TRG 3 - Moderate Response: 50% fibrosis or mucin and 50% visible intermediate signal

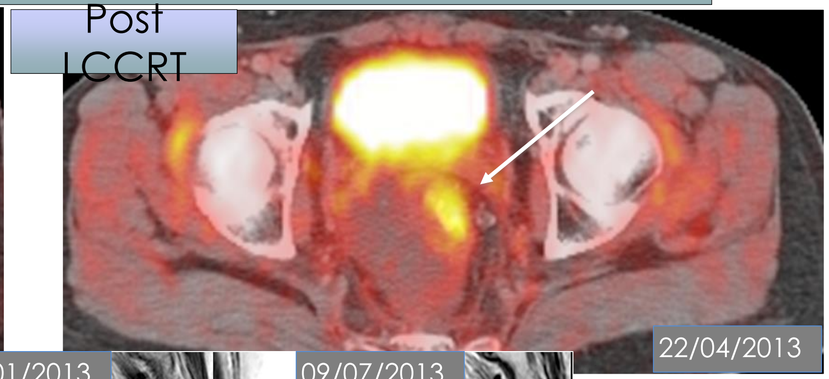
Pre LCCRT



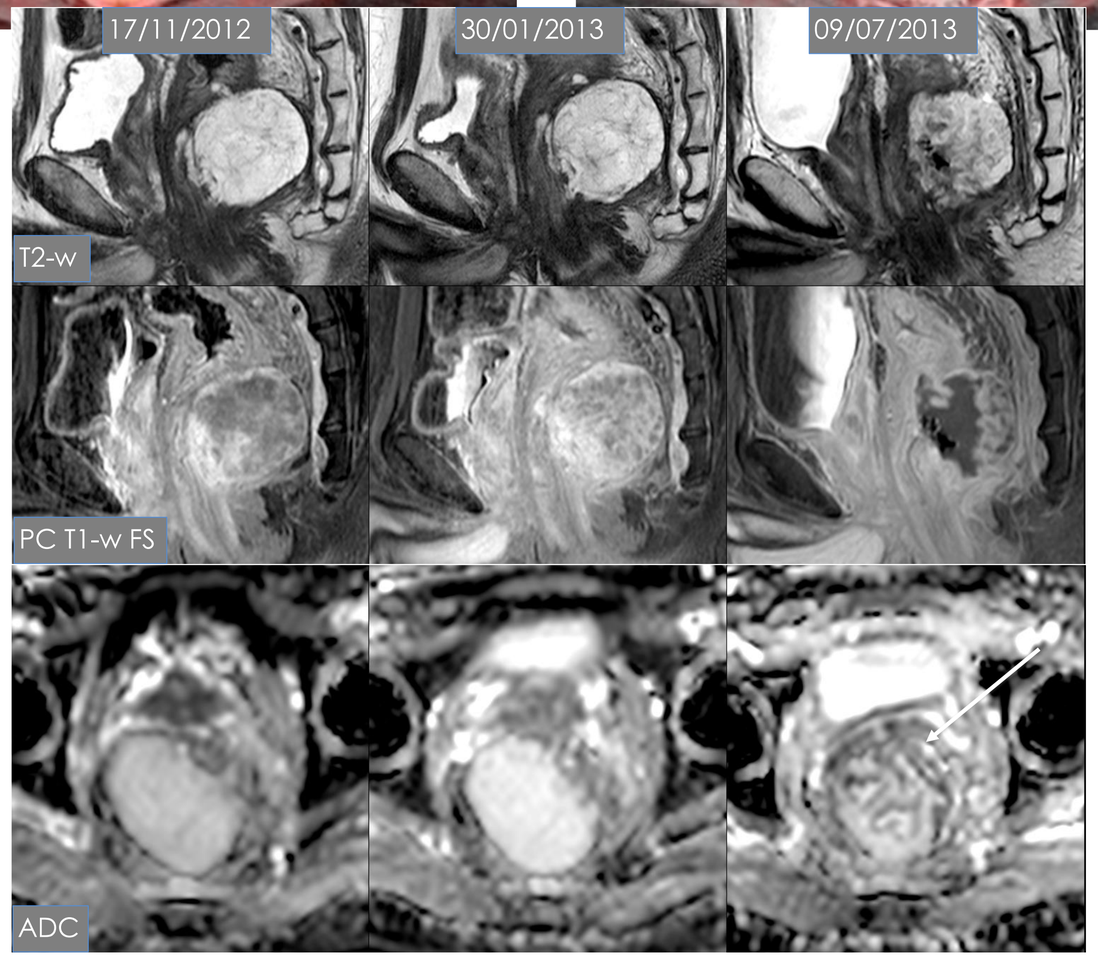

58-year old male with stage T4 disease with a large proliferative rectal mass [Mucin containing - Note Marked T2 hyperintense signal] invading the mesorectal fat, mesorectal and denonvillier's fascial reflection and appearing adherent with the right seminal vesicle. Note similar morphology mesorectal and extramesorectal pelvic sidewall nodes.

# Case 5 - TRG 3 - Moderate Response: 50% fibrosis or mucin and 50% visible intermediate signal



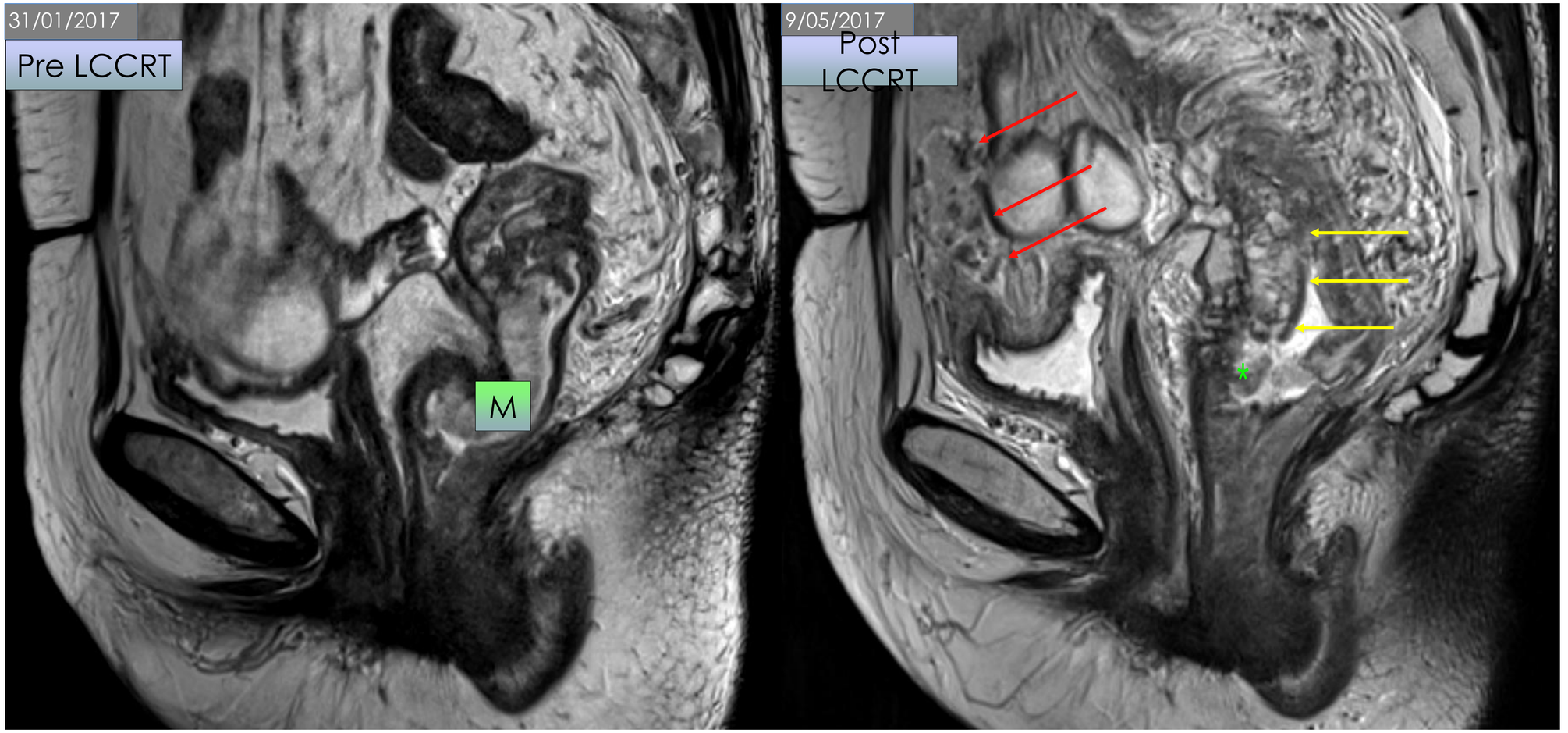




Follow-up PET-CT showed
- Reduction in size of lesion
- Reduction in intensity and extent of FDG uptake
- Small residual FDG avid lesion in ventro-lateral aspect on the left



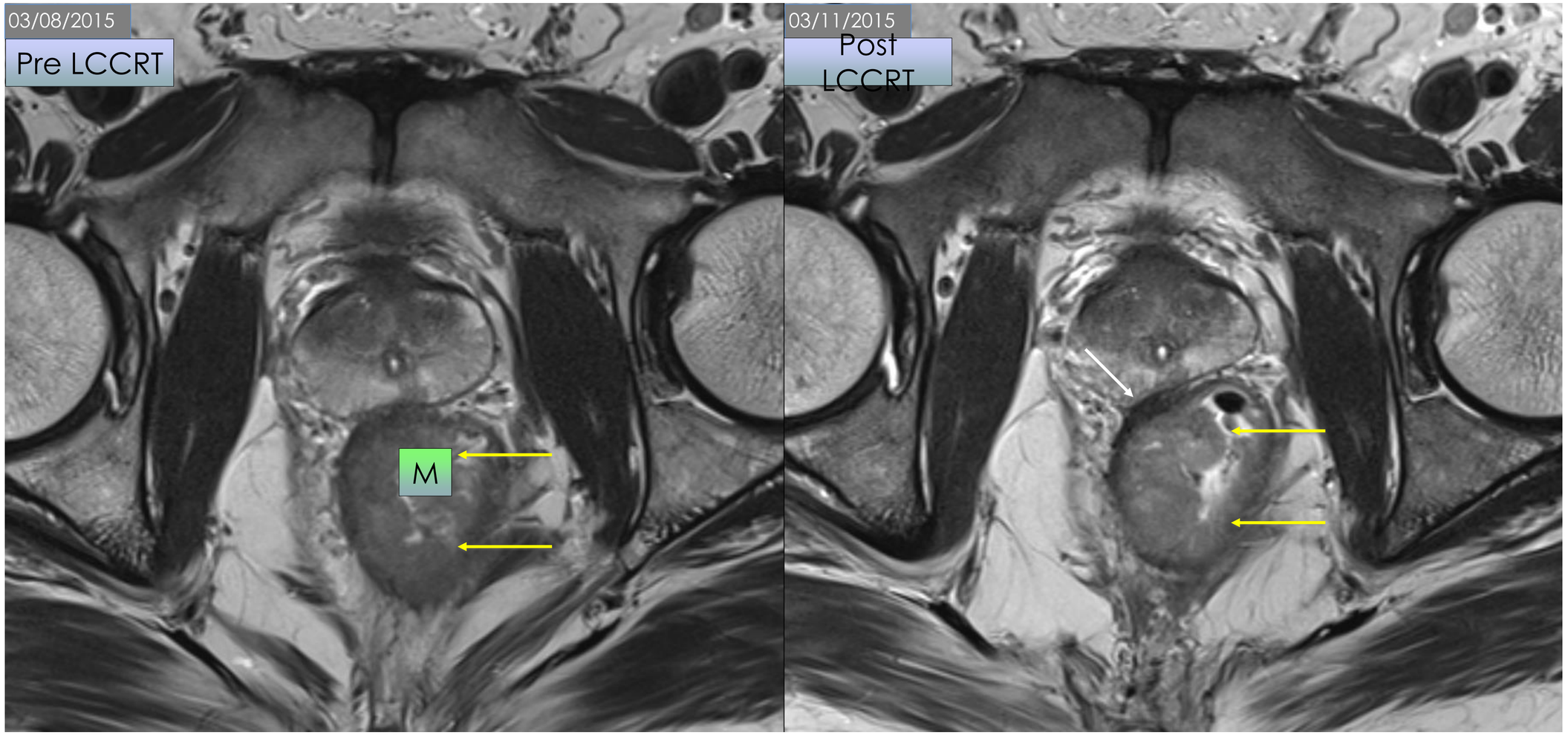

Serial FU MRI showed….
- Reduction in size of lesion
- Change in internal morphology
  - Reduction in T2 signal
  - Air within lesion – due to necrosis
  - Change in enhancement with large non-enhancing necrotic core
- Progressive prolongation of ADCs [increased intralesional diffusivity]
- Residual low ADC viable lesion seen along the ventro-lateral aspect of the treated lesion on left corresponds to the metabolically active lesion on PET-CT

## Case 6 - TRG 4 - Slight Response: <25% fibrosis or mucin but mostly tumour




70-year old woman with stage T3 disease with a large proliferative rectal mass [Mucin containing - Note Marked T2 hyperintense signal] along the anterior wall of the mid and lower rectum, straddling the peritoneal reflection, invading the mesorectal fat, with CRM compromise [mesorectal fascial reflection involvement], with nodes above the lesion level. Post LCCRT, note reduction in tumor bulk primarily along the inferior third [*], with residual T2 hyperintense lesion [yellow arrows] still seen more rostrally, with <25% desmoplastic response in the anterior wall [TRG 4]. However, NOTE the nodularity and excessive streakiness of the fat within the inframesocolic momentum and supravesical pouch which are signs of subperitoneal dissemination and OVERALL disease progression.

## Case 7 - TRG 4 - Slight Response: <25% fibrosis or mucin but mostly tumour




44-year old man with stage T3 disease with a large proliferative rectal mass along the right lateral wall of the mid and lower rectum, straddling the peritoneal reflection, invading the mesorectal fat, with CRM compromise [mesorectal fascial reflection involvement]. Post LCCRT, note no significant reduction in tumor bulk with <25% desmoplastic response along the lateral wall [white arrow] and mesorectum [TRG 4].

# "Newer Concepts in Treatment of LARC"

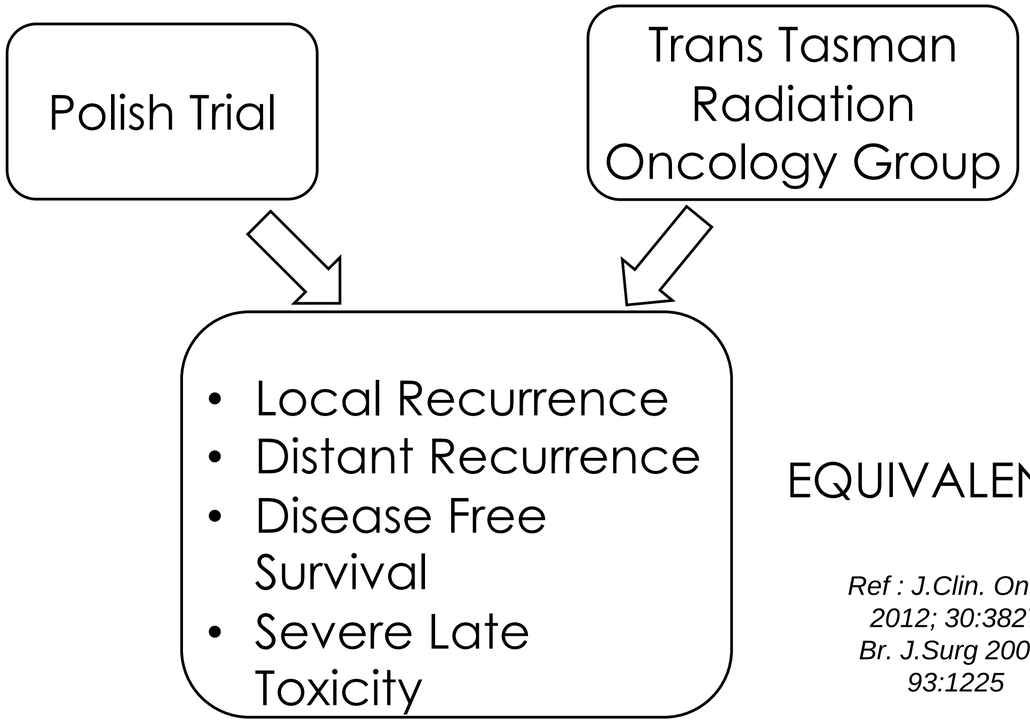
## A. Short course Radiotherapy

25 GY (5 x 5 Gy) ⟹ Surgery

Mechanism

- The Dutch trial showed a small reduction in size of rectal tumors, possibly due to apoptotic death of intratumoral lymphatic cells and also a reduction of detected lymph nodes but no impact on tumor stage and number of metastatic lymph nodes is obtained.
- Does not have an impact on rectal cancer regression and no downstaging occurs if immediate surgery is performed.

## Short course Radiotherapy vs LCCRT




No current prospective randomised imaging studies available in literature assessing the impact of Short course Radiotherapy in LARC

# "B. Short course radiotherapy with Delayed Surgery"

Effect of interval between SCPRT and Surgery

SCPRT with 1 week interval from surgery

1 week

Small Reduction in:
- Tumour Size
- Size of detected Lymph Nodes

No Impact on:
- Tumour Regression
- Number of metastatic Nodes

Increased interval between SCPRT & Surgery

Ideally 8 to 10 weeks

Positive Effect on
- Tumor Regression
- Better Complete Response

- SCPRT can downstage tumour if surgery is delayed. A higher rate of TRG1-2 is achieved if interval between RT and surgery is 8 weeks or more. (D Rega et al, 2016)
- Stockholm III trial reported similar results of complete response, rate of complications and toxicity after preoperative long-course or short-course radiotherapy with delayed surgery.(Petersson et al (Stockholm III trial) , 2010)

No current imaging studies available in literature assessing the impact of Short course radiotherapy with delayed surgery in LARC

# C. Wait-and-Watch Approach

Bujko et al, 2016

- Watch-and-wait policy can be used, not only after chemoradiation, but also after 5 × 5 Gy
- Short-course radiotherapy with delay might be especially useful in elderly fragile patients either with small tumours before local excision or in those with locally advanced tumours that needs shrinkage before abdominal surgery.

Habr-Gama et al

Among 90 patients who had complete clinical remission and who were offered the wait-and-watch policy, local recurrence developed in 31%. Salvage therapy was possible in > 90% of recurrences, leading to 94% local disease control, with 78% organ preservation.

- A watch-and-wait approach for patients with clinical complete response to neoadjuvant chemoradiation could avoid morbidity of conventional surgery for rectal cancer.
- "Despite the impressive results of intensive wait and watch in patients who achieve clinical CR, surgery is still the standard of care".

MRI-detected CR may be used as a marker to select patients who may be candidates for a watchful policy, especially those who may lose sphincter control with surgery.

# Reporting Template for Post treatment Rectal Cancer Assessment

- Compared with previous pre-treatment MRI scan dated……
- Morphological assessment in terms of dominant signal for residual tumor / fibrosis. Development of mucin if applicable
- Craniocaudal extent of lesion is …mm as compared to …mm previously. Leading edge of tumor extends from … o'clock to …o'clock position
- Distal edge of tumor lies about …mm from anal verge / Distal edge of tumor lies …mm [at, above , below] level of puborectalis sling compared to … mm
- Proximal edge of tumor lies …mm [at, above , below] level of peritoneal reflection
- Tumor signal / fibrotic signal [confined to /extends beyond muscularis propria]
- Extramural spread: [ mm] for tumor/ [ mm] for fibrotic signal
- yMR T stage: T1 T2 T3a T3b T3c T3d T4 visceral T4 peritoneal
- Extramural venous invasion: Present /absent
- CRM
  - Minimal distance between residual tumor and CRM
  - CRM clear / involved
  - Closest CRM is at …o'clock position from direct spread of tumor / EMVI / tumor deposit / node
- Anal sphincter [for low rectal lesions- at/below puborectalis sling]
  - Involvement of Internal sphincter, intersphincteric space, external sphincter
  - Extension beyond sphincter into adjacent structures like prostate/vagina
- Lymph Nodes
  - None/only benign present [N0]
  - Morphology: Homogenous/ Heterogeneous internal signal , regular/irregular margins
  - Number of positive nodes [ N1/N2]
  - Location: Mesorectal, extramesorectal, pelvic side walls (Right/Left)),Retroperitoneal
- Peritoneal deposits: Present/absent

## Summary

yMRI overall stage:

- ymrT stage
- ymrN stage
- ymrM stage

CRM: Present /absent

EMVI:Present /absent

Overall TRG:

# Limitations of MRI TRG

- Requires considerable experience and prolonged learning curve.
- Underestimates the presence of residual submucosal / microscopic disease
- Accuracy of MR for re-staging is generally lower than accuracy of MR for initial staging
  - Inability to failure to differentiate tumoral infiltration from desmoplastic reaction
  - Overstaging of nodal disease
  - Misinterpretation of radiation proctitis as local invasion.
- Evaluation of mucinous adenocarcinomas on post-treatment MR is considerably challenge.
- TRG for non-adenocarcinoma rectal cancer subtypes (neuroendocrine tumors and sarcomas) - not well described.