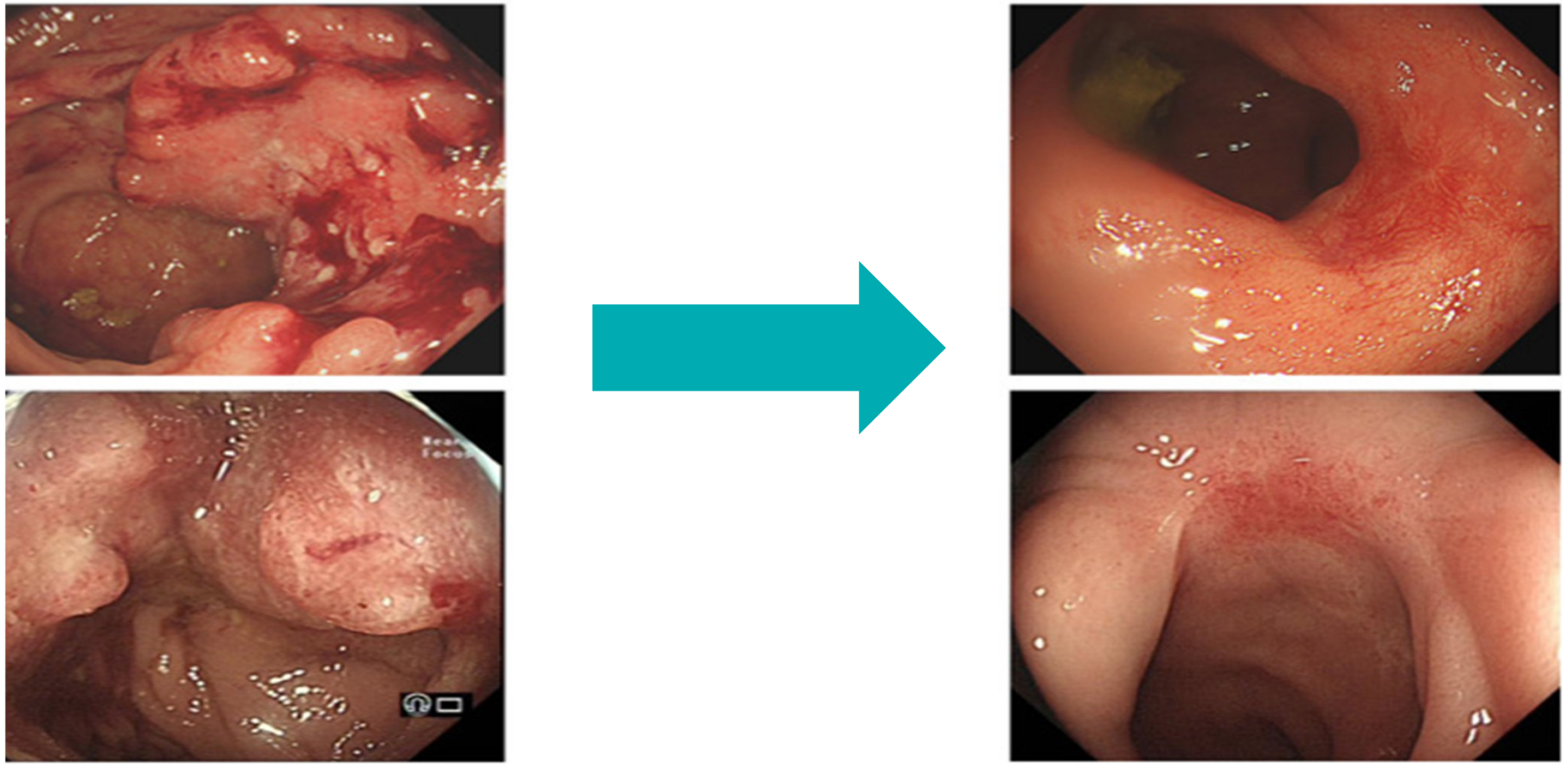
# TNT for organ preservation

Dr Alexandra Gilbert

Associate Professor and Honorary Consultant in Clinical Oncology

University of Leeds, UK

# Aim of organ preservation



https://www.sciencedirect.com/science/article/pii/S0936655522004885#fig1

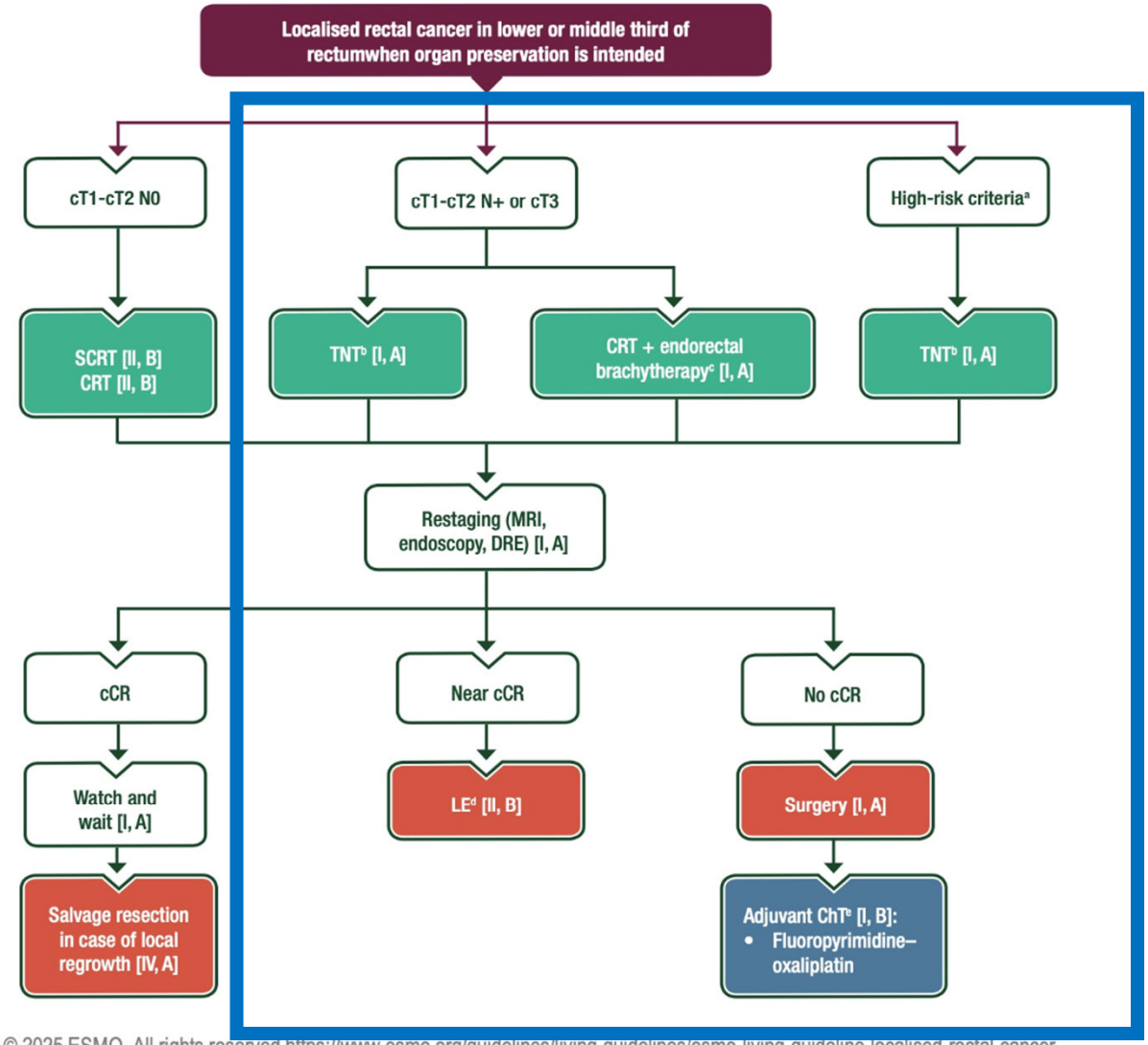
# CLINICAL PRACTICE GUIDELINES

ESMO Localised Rectal Cancer Living Guideline v1.0
July 2025

# Management of Localised Rectal Cancer

## Lower or Middle Third of the Rectum when Organ Preservation is Intended

[a]cT4, cN2, mrMRF+, EMVI+, lateral LN+
[b]Upfront CRT followed by consolidation ChT can be recommended to increase the likelihood of cCR [I, B]
[c]cT2-cT3b N0-1 tumours <5 cm
[d]Patients with baseline cT2 or cT3a N0 with a near cCR
[e]On a case-by-case basis after fluoropyrimidine-based CRT in patients with initial cN+ disease




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# How to increase chances of OP

- Patient selection
- Interval to surgery
- TNT
- Brachytherapy
- EBRT dose escalation
- MR-guided and adapted therapy

# TNT: The balance of costs

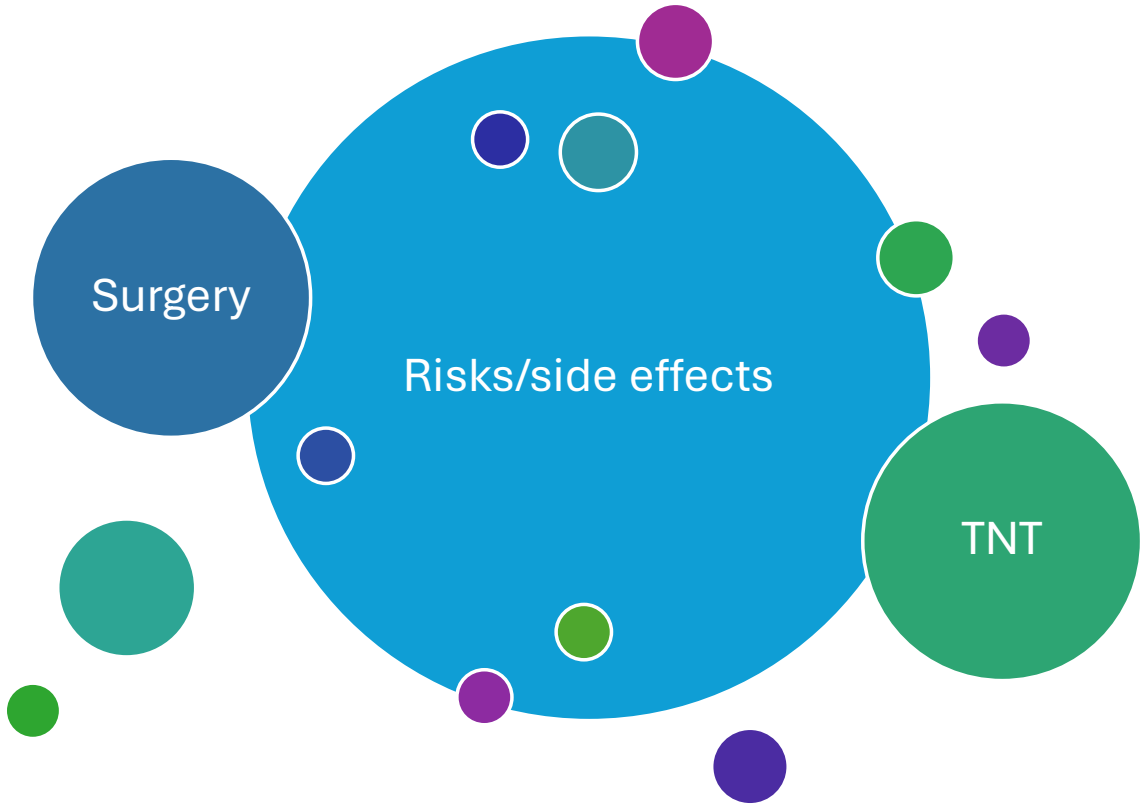
## Surgical Toxicity

- Stoma: permanent or temporary
- Avoidance of surgery at any cost
- Avoidance of in patient stay
- Acute complications
- Life threatening
- Late effects e.g. LARS

## TNT toxicity: Radiotherapy/SACT

- Not guaranteed
- Outpatient: multiple visits
- RT toxicity: bowel, urinary, fatigue, skin
- SACT toxicity: BMS, bowel, peripheral neuropathy, cardiac
- Life threatening
- Late effects

# Not mutually exclusive



# Consider who to offer this approach to?

- Early rectal cancer?
- ‘Intermediate’ rectal cancer?
- High-risk?
- Only consider opportunistically?

# Historic pCR rates with CRT: 15-25%

| | Study design | pCR | Factors associated with pCR |
|---|---|---|---|
| **Sanghera et al. Clin Oncol 2008** | Meta-analysis: n=4732 | **14.8%** | Use of 2 drugs, infusional 5-FU, RT dose |
| **Maas et al. Lancet Oncol 2010** | Meta-analysis: 14 studies, n=3105 | **16%** | More T1-T2 |
| **Martin et al. BJS 2012** | Meta-analysis: 16 studies, n=3363 | **24.4%** | |
| **Macchia et al. Clin Transl Radiat Oncol 2017** | Population study: n=2094 | **22.3%** | Longer interval to surgery |

Slide courtesy of K Haustermans

# TNT RCTs

| TRIAL | N | Primary outcome | Control | Experimental |
|---|---|---|---|---|
| RAPIDO (PhIII, 7 countries) | 920 | DrTF | CAP CRT (50-50.4Gy) – TME - +/- 12xFOLFOX4/8xCAPOX | RT (25Gy) – 6xCAPOX/9xFOLFOX4 – TME |
| STELLAR (PhIII, China) | 599 | DFS | CAP CRT (50Gy) – TME – 6xCAPOX | RT (25Gy) – 4xCAPOX – TME – 2xCAPOX |
| Prodige-23 (PhIII, France) | 461 | DFS | CAP CRT (50Gy) – TME – 12xFOLFOX6/ 8xCAP | 6xFOLFIRINOX – CRT CAP (50Gy) – TME – 6xFOLFOX6/ 4xCAP |
| CAO/AIO/ARO-12 (PhII, Germany) | 306 | pCR | 3xFOLFOX6 – 5FU/OX CRT (50.4Gy) - TME | 5FU/OX CRT (50.4Gy) – 3xFOLFOX6 - TME |
| OPRA (PhII, US) | 324 | DFS | 8xFOLFOX6/5xCAPOX – CRT CAP/5FU(50-56Gy) – W+W/TME | CRT CAP/5FU (50-56Gy) - 8xFOLFOX6/5xCAPOX – W+W/TME |

DrTF*: disease-related treatment failure; DFS: disease free survival

# Inclusion criteria recent TNT RCTs

| | MRI predicted staging (% overall) | | | | | | | Distance from anal verge (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **TRIAL** | **T2** | **T3** | **T4** | **N0** | **MRF+** | **EMVI** | **LLN** | <=5cm | 5.1-10cm | 10.1-15cm |
| **RAPIDO (van der Valk 2020)** | 3 | 66 | 33 | 9 | 61 | 30 | 15 | 24 | 37 | 33 |
| **STELLAR (Jin 2022)** | 3 | 83 | 14 | 15 | 56 | 48 | ns | 49 | 50 | 1 |
| **Prodige-23 (Conroy 2021)** | 1 | 83 | 17 | 10 | 22 | ns | 10 | 37 | 50 | 13 |
| **CAO/AIO/ARO-12 (Fokas 2022)** | 5 | 81 | 15 | 10 | 27 | ns | ns | 41 | 46 | 9 |
| **OPRA (Garcia-Aguilar 2022)** | 10 | 77 | 13 | 29 | ns | ns | ns | Median distance anal verge 4.4cm (3-6.5 IQR) | | |

ns: not specified

# pCR rates in the era of TNT

| | N | Treatment | TNT | CRT | |
|---|---|---|---|---|---|
| **RAPIDO** | 920 | SCRT – doublet chemo – TME vs LCCRT – TME - +/- d. chemo | **28%** | 14% | p<0.0001 |
| **STELLAR** | 599 | SCRT – doublet chemo – TME vs LCCRT – TME - d. chemo | **21.8%** | 12.3% | p=0.002 |
| **PRODIGE 23** | 461 | Triplet chemo – LCCRT – TME – d. chemo vs LCCRT – TME – d. chemo | **28%** | 12% | p<0.0001 |

**Higher pCR rate with TNT**

Adapted slide courtesy of K Haustermans

# TNT sequencing

| | N | Consolidation SACT | Induction SACT |
|---|---|---|---|
| **OPRA**<br>pCR and sustained cCR | **324** | **78%** | **75%** |
| **CAO/ARO/AIO-12**<br>pCR | **306** | **25%** | **17%** |

**More cCR/pCR with RT first**

Adapted slide courtesy of K Haustermans

| TRIAL | N | Primary outcome | Control | Experimental | pCR (or cCR) | 3-year DFS |
|---|---|---|---|---|---|---|
| **RAPIDO (PhIII, 7 countries)** | 920 | DrTF | CAP CRT (50-50.4Gy) – TME - +/- 12xFOLFOX4/8xCAPOX | RT (25Gy) – 6xCAPOX/9xFOLFOX4 – TME | 14% vs 28% | 30% vs 24%* |
| **STELLAR (PhIII, China)** | 599 | 3y DFS | CAP CRT (50Gy) – TME – 6xCAPOX | RT (25Gy) – 4xCAPOX – TME – 2xCAPOX | 12% vs 22% | 62% vs 68% |
| **Prodige-23 (PhIII, France)** | 461 | 3y DFS | CAP CRT (50Gy) – TME – 12xFOLFOX6/ 8xCAP | 6xFOLFIRINOX – CRT CAP (50Gy) – TME – 6xFOLFOX6/ 4xCAP | 12% vs 28% | 69% vs 78% |
| **CAO/AIO/ARO-12 (PhII, Germany)** | 306 | pCR | 3xFOLFOX6 – 5FU/OX CRT (50.4Gy) | 5FU/OX CRT (50.4Gy) – 3xFOLFOX6 | 21% vs 28% | 73% vs 73% |
| **OPRA (PhII, US)** | 324 | 3y DFS | 8xFOLFOX6/5xCAPOX – CRT CAP/5FU(50-56Gy) – W+W/TME | CRT CAP/5FU (50-56Gy) - 8xFOLFOX6/5xCAPOX – W+W/TME | 43% vs 59% | 76% vs 76% |

DrTF*: disease-related treatment failure; DFS: disease free survival

# Organ preservation – tumour related outcomes

## International consensus recommendations on key outcome measures for organ preservation after (chemo)radiotherapy in patients with rectal cancer

*Emmanouil Fokas[1,2,3,4,30]✉, Ane Appelt[5,30], Robert Glynne-Jones[6], Geerard Beets[7,8], Rodrigo Perez[9], Julio Garcia-Aguilar[10], Eric Rullier[11], J. Joshua Smith[10], Corrie Marijnen[12], Femke P. Peters[12], Maxine van der Valk[8], Regina Beets-Tan[7,13], Arthur S. Myint[14], Jean-Pierre Gerard[15], Simon P. Bach[16], Michael Ghadimi[17], Ralf D. Hofheinz[18], Krzysztof Bujko[19], Cihan Gani[20,21], Karin Haustermans[22], Bruce D. Minsky[23], Ethan Ludmir[23], Nicholas P. West[24], Maria A. Gambacorta[25], Vincenzo Valentini[25], Marc Buyse[26,27], Andrew G. Renehan[28,29], Alexandra Gilbert[5,30], David Sebag-Montefiore[5,30] and Claus Rödel[1,2,3,4,30]*

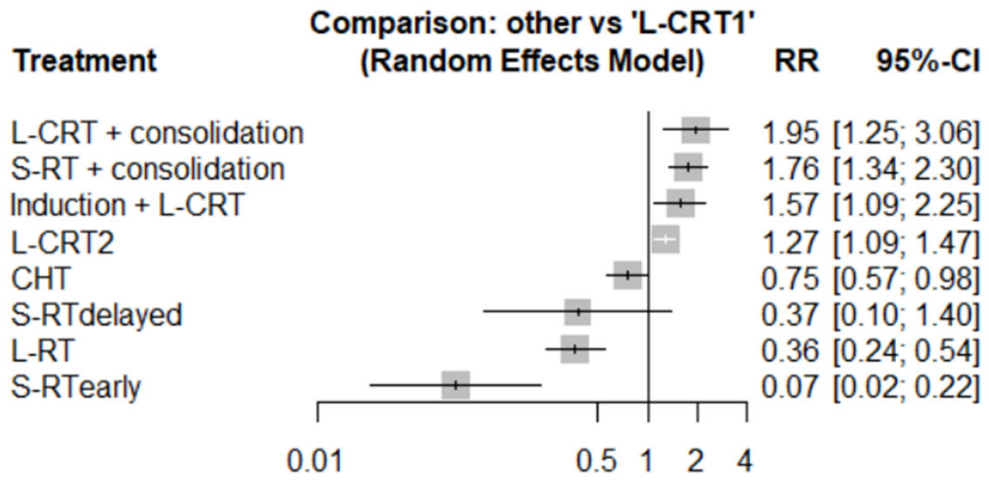
# Consensus recommendations on the optimal response assessment time points for cCR determination

| Total neoadjuvant treatment with CRT and either induction or consolidation chemotherapy (duration of 16–20 weeks) | Total neoadjuvant treatment with standard short-course radiotherapy or CRT followed by prolonged consolidation chemotherapy (duration of 26–34 weeks). |
|---|---|
| • cCR should be determined at 24 weeks after start of treatment, as performed in the GRECCAR12 and ACO/ARO/AIO-18.1 trials | • cCR should be determined at 34–38 weeks after start of treatment, as performed in the OPRA and TRIGGER trials |

# Comparison of outcomes: Metaanalysis TNT era

Tutti et al JAMA Network Open (2024)

27 RCTs published up to March 2024

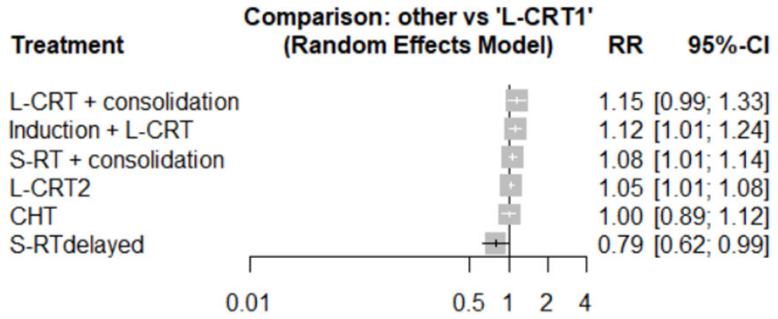


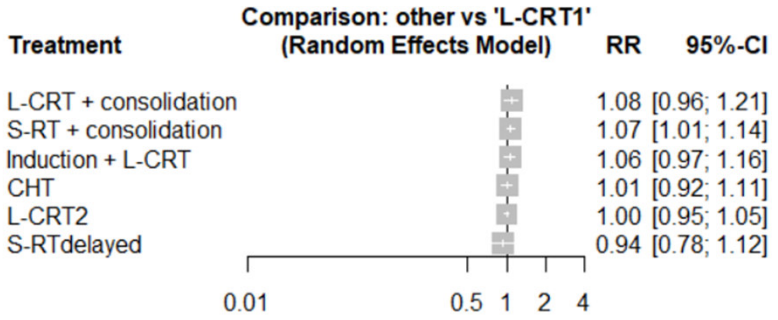

Primary outcome of metaanalysis: pCR

Favouring neoadjuvant chemo regimens

Long course CRT + chemo optimal approach for pCR

DFS at 3 years: similar, favouring neoadjuvant chemo regimes




OS at 3 years: similar, favouring addition of neoadjuvant chemo regimens

# What are (some of) the unanswered questions: early stage setting

SCRT vs LCCRT

STAR TREC

Radiotherapy volumes

STAR TREC

Biomarker driven approaches

dMMR/MSI etc

Role of brachytherapy: OPERA – widespread availability?

Role of chemotherapy

PROSPECT

Role of TNT ?ctDNA guidance

# What are (some of) the unanswered questions: locally advanced

Triplet vs doublet chemotherapy

JANUS Ph II/III

SCRT vs LCCRT + Doublet

ACO/ARO/AIO-18.1 Ph III

Role of brachytherapy

TRESOR and OPAXX

Novel agent drug combinations

ARTEMIS

Biomarker driven combinations

FOXTROT (colon)

Position of rectal cancer

Heterogeneity

# How to increase chances of OP

Patient selection: early cancers

Interval to surgery: optimal follow up assessment key

TNT: how to identify earlier stage cancers who may benefit vs increased toxicity

Brachytherapy: OPERA: role in more locally advanced setting needed

EBRT dose escalation: application of APHRODITE findings

MR-guided and adapted therapy: early data promising (widespread application)

# Summary

- TNT in locally advanced disease is optimal to improve OP rates and outcomes
- What schedule is optimal is challenging to establish as all TNT trials have evaluated something slightly different
- Consolidation chemotherapy provides increased chance for OP
- Optimal assessment: Triple assessment (DRE, flexi sig, MRI), timing key
- Current and future trials will hopefully help us to address some of these unanswered questions