ESMO ON AIR

# Rectal Cancer

## ESMO GUIDELINES : REAL WORLD CASES

**Ralf – Dieter Hofheinz,** *Chair*

Mannheim Cancer Center
University Hospital Mannheim
University of Heidelberg, Germany

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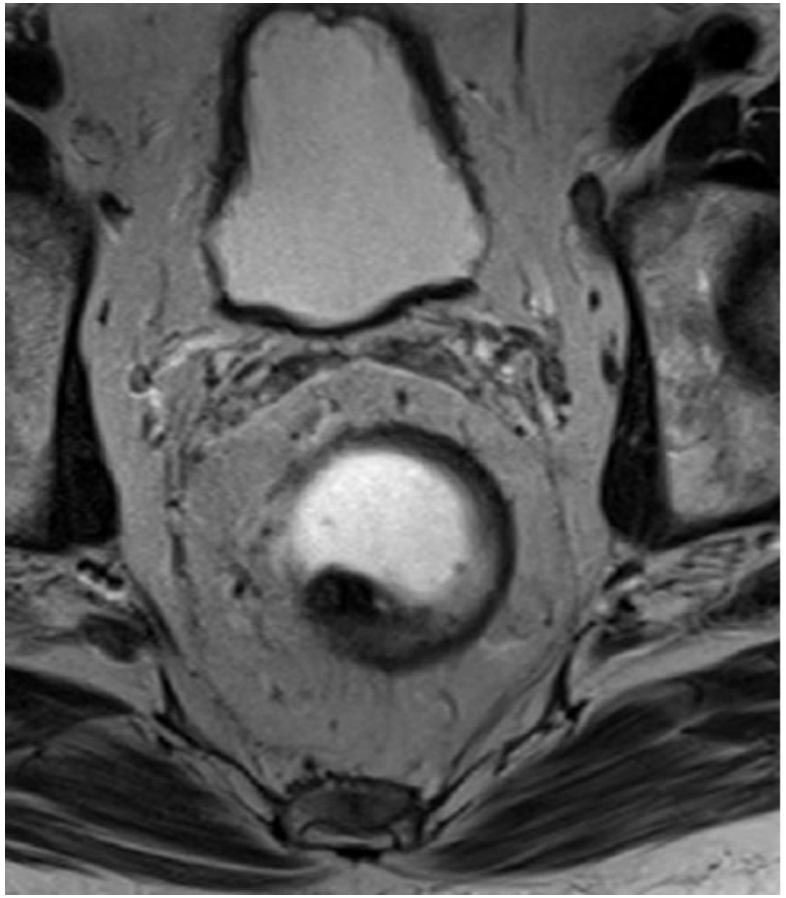
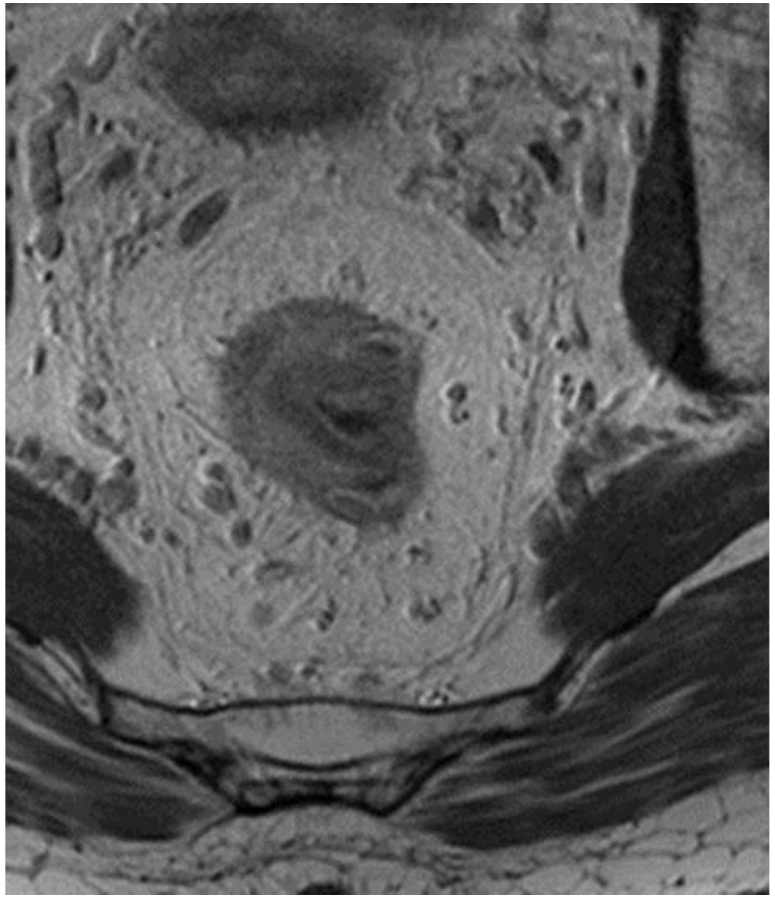
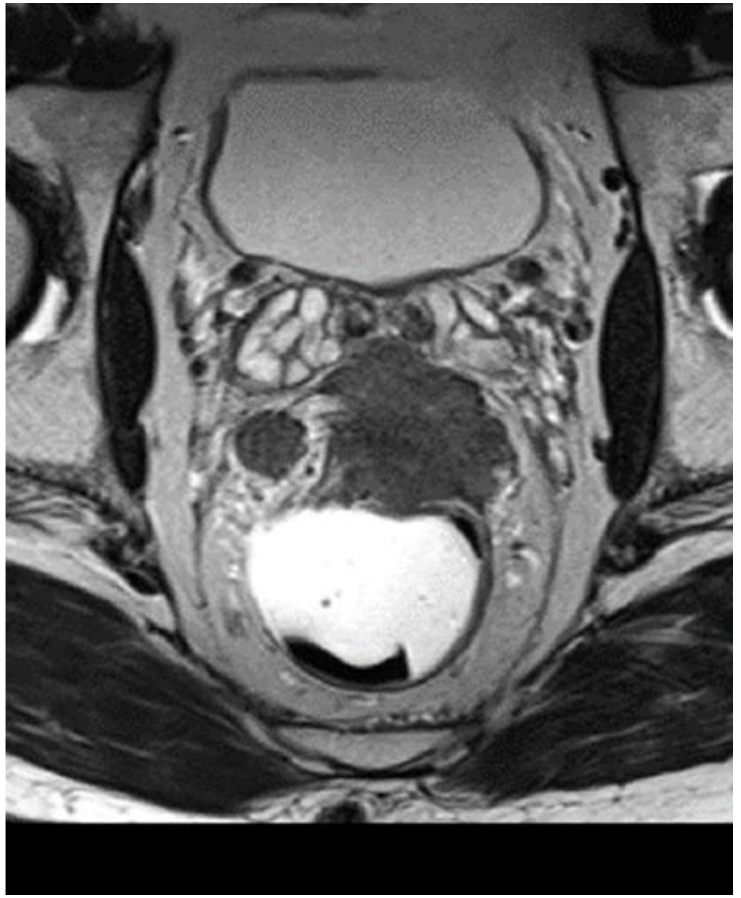
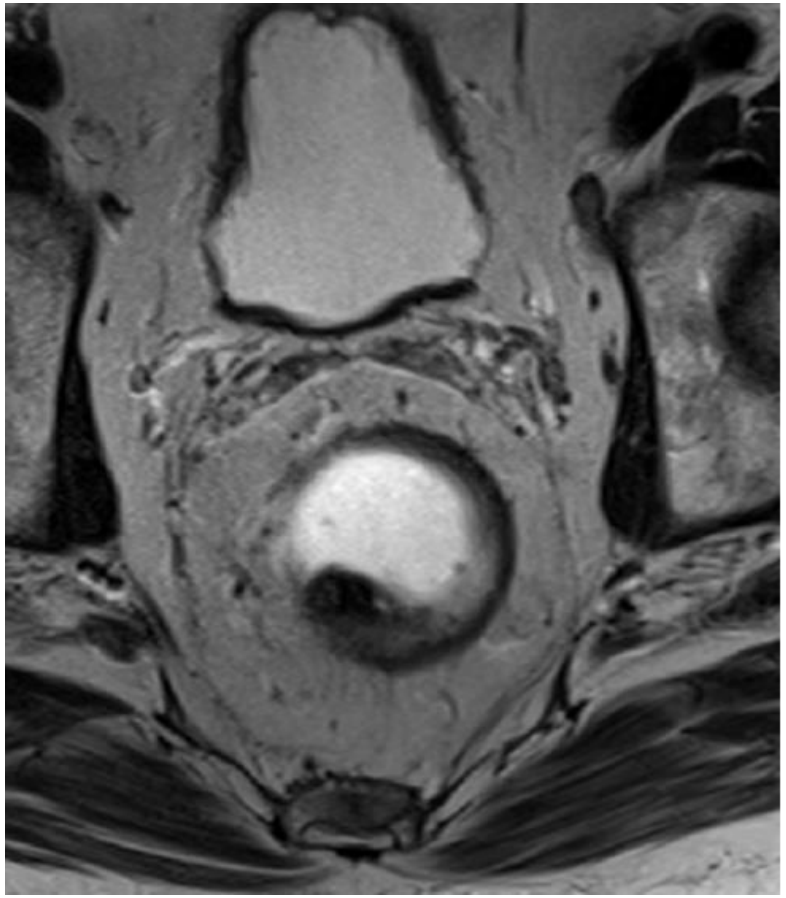
# Former approach in stage II / III rectal cancer: RT / CRT !!



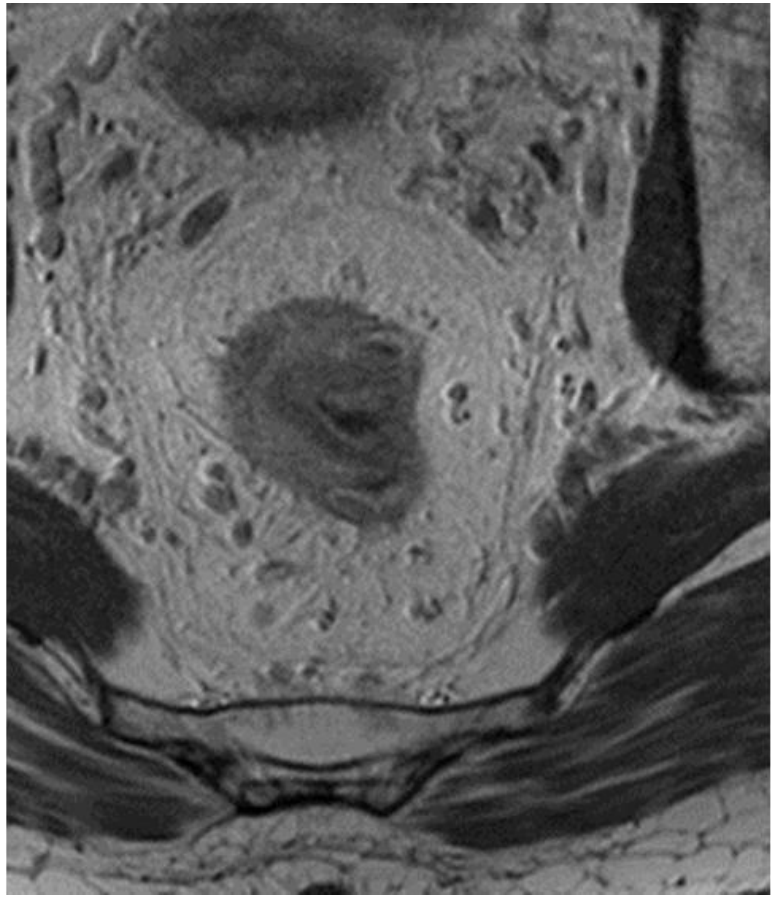




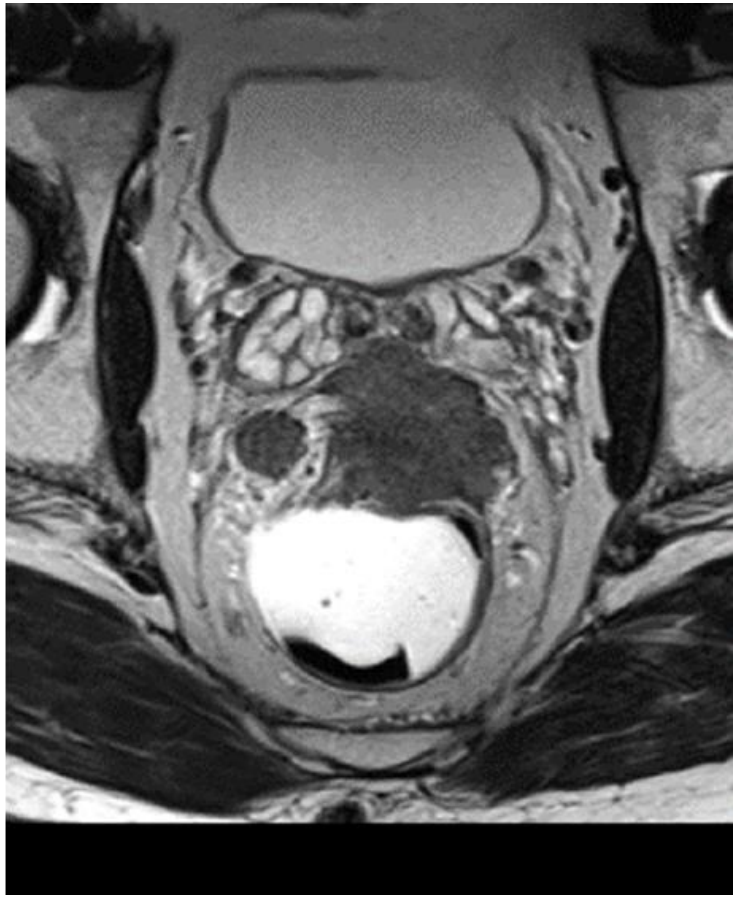
# Differential / alternative treatment options are available !!



Resection, neoad. chemo

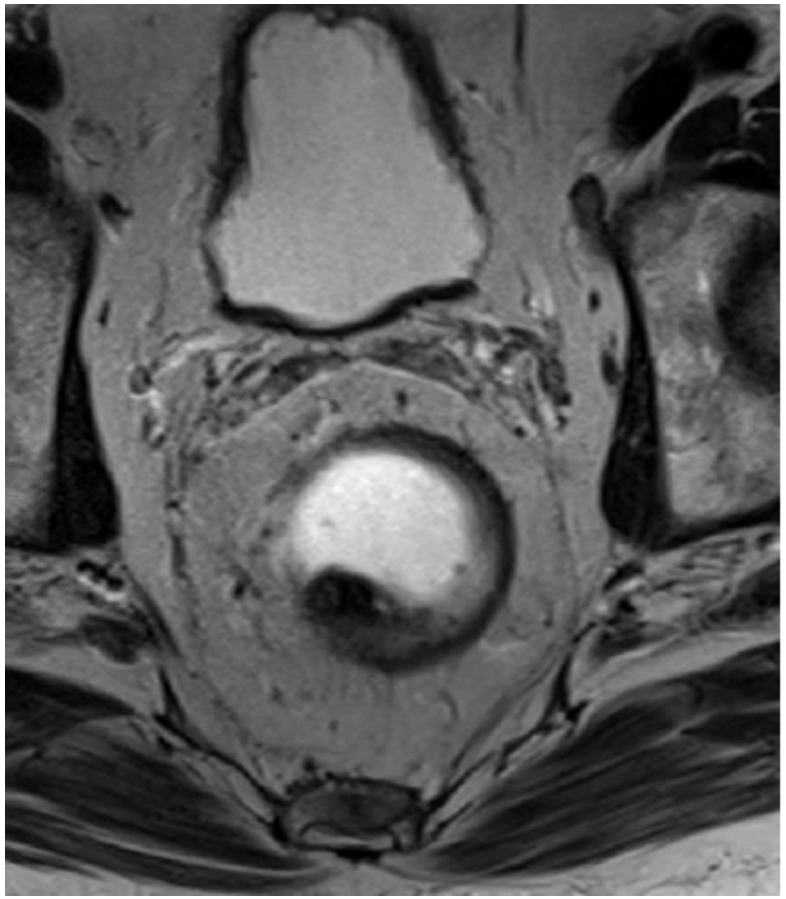


Neoad. chemo, resection

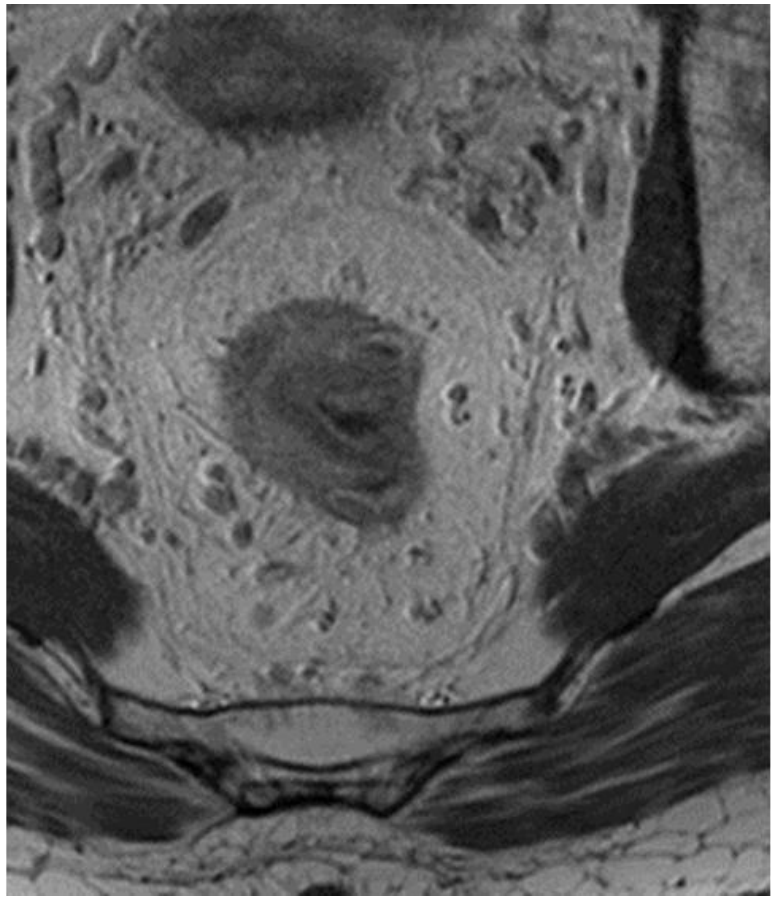


Total neoadjuvant therapy

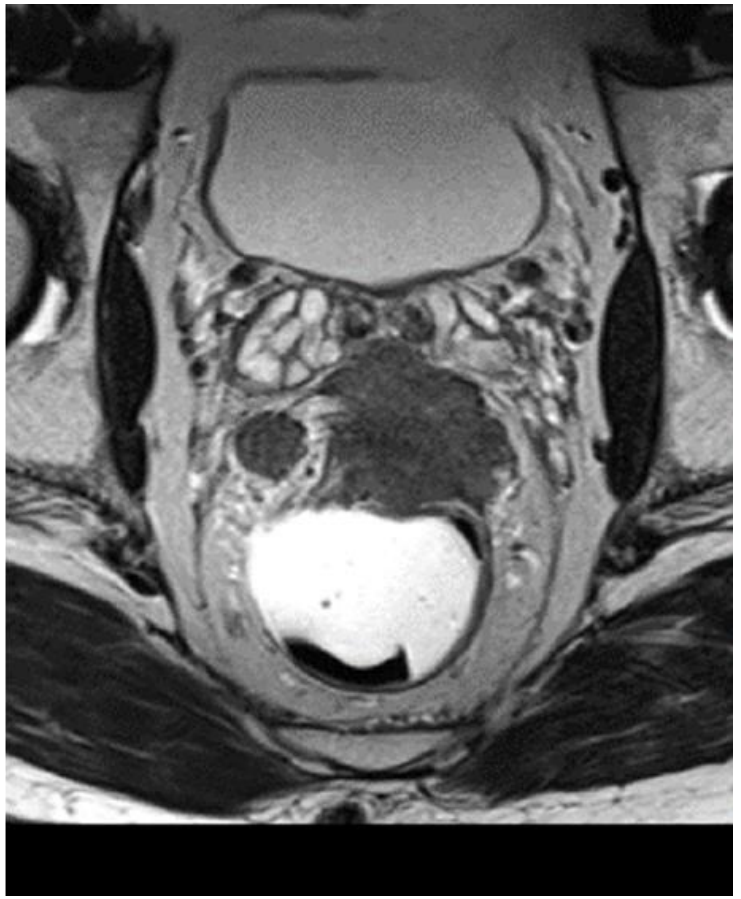
# Differential treatment option are available !!



Resection, neoad. chemo



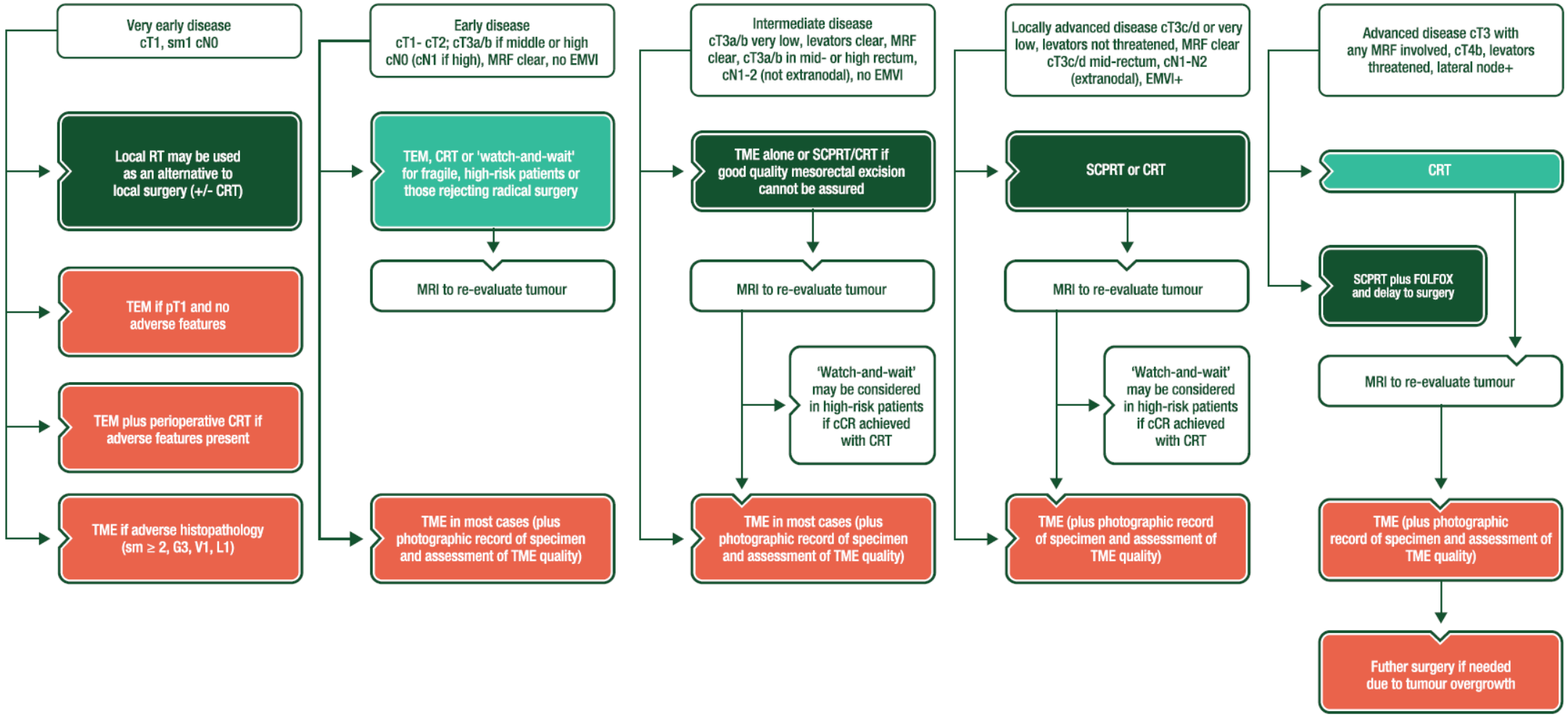
Neoad. chemo, resection



Total neoadjuvant therapy

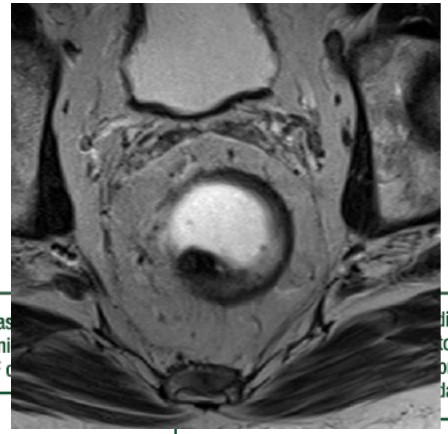
Organ preservation / IO in MSI

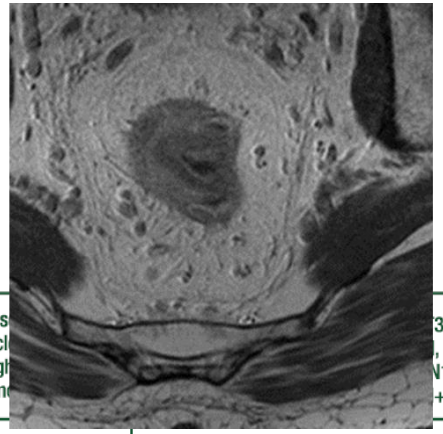
# Looking at ESMO CPG 2017 (Glynne-Jones et al.)

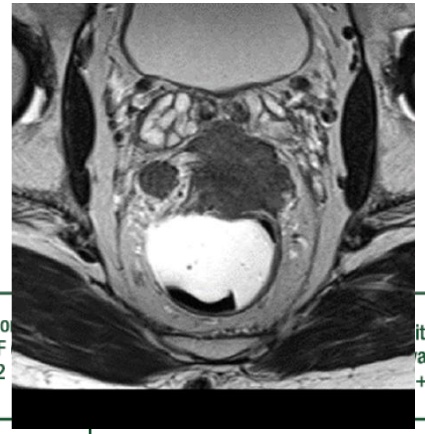





Glynne-Jones R Ann Oncol 2017 (suppl. IV)







Very early disease
cT1, sm1 cN0

Local RT may be used as an alternative to local surgery (+/- CRT)

TEM if pT1 and no adverse features

TEM plus perioperative CRT if adverse features present

TME if adverse histopathology (sm ≥ 2, G3, V1, L1)

Early diseas
cT1- cT2; cT3a/b if mi
cN0 (cN1 if high), MRF

TEM, CRT or 'watch-and-wait' for fragile, high-risk patients or those rejecting radical surgery

MRI to re-evaluate tumour

TME in most cases (plus photographic record of specimen and assessment of TME quality)

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TME alone or SCPRT/CRT if good quality mesorectal excision cannot be assured

MRI to re-evaluate tumour

'Watch-and-wait' may be considered in high-risk patients if cCR achieved with CRT

TME in most cases (plus photographic record of specimen and assessment of TME quality)

3c/d o
, MRF
N1-N2
+

SCPRT or CRT

MRI to re-evaluate tumour

'Watch-and-wait' may be considered in high-risk patients if cCR achieved with CRT

TME (plus photographic record of specimen and assessment of TME quality)

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ators
+

CRT

SCPRT plus FOLFOX and delay to surgery

MRI to re-evaluate tumour

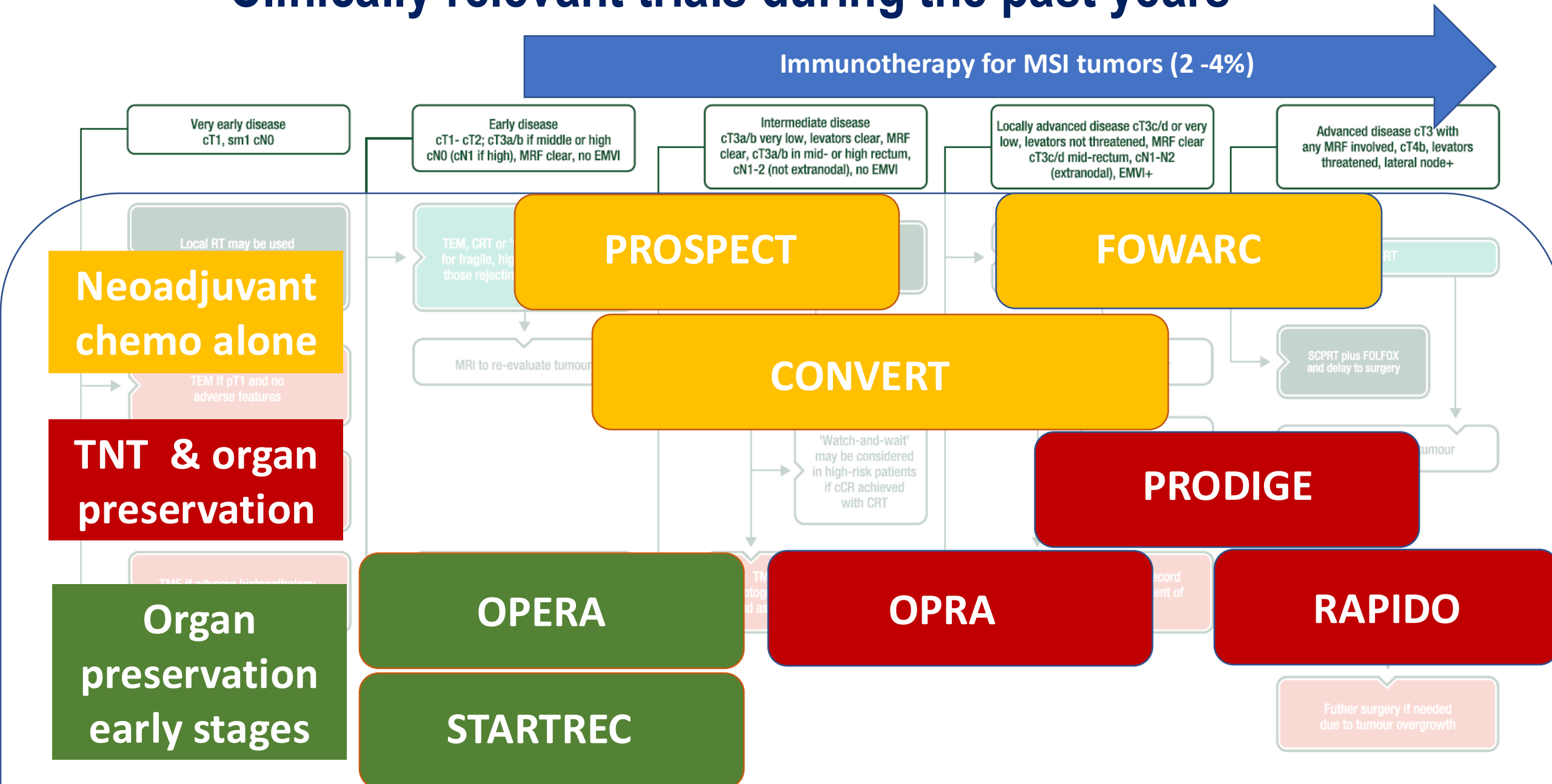
TME (plus photographic record of specimen and assessment of TME quality)

Futher surgery if needed due to tumour overgrowth

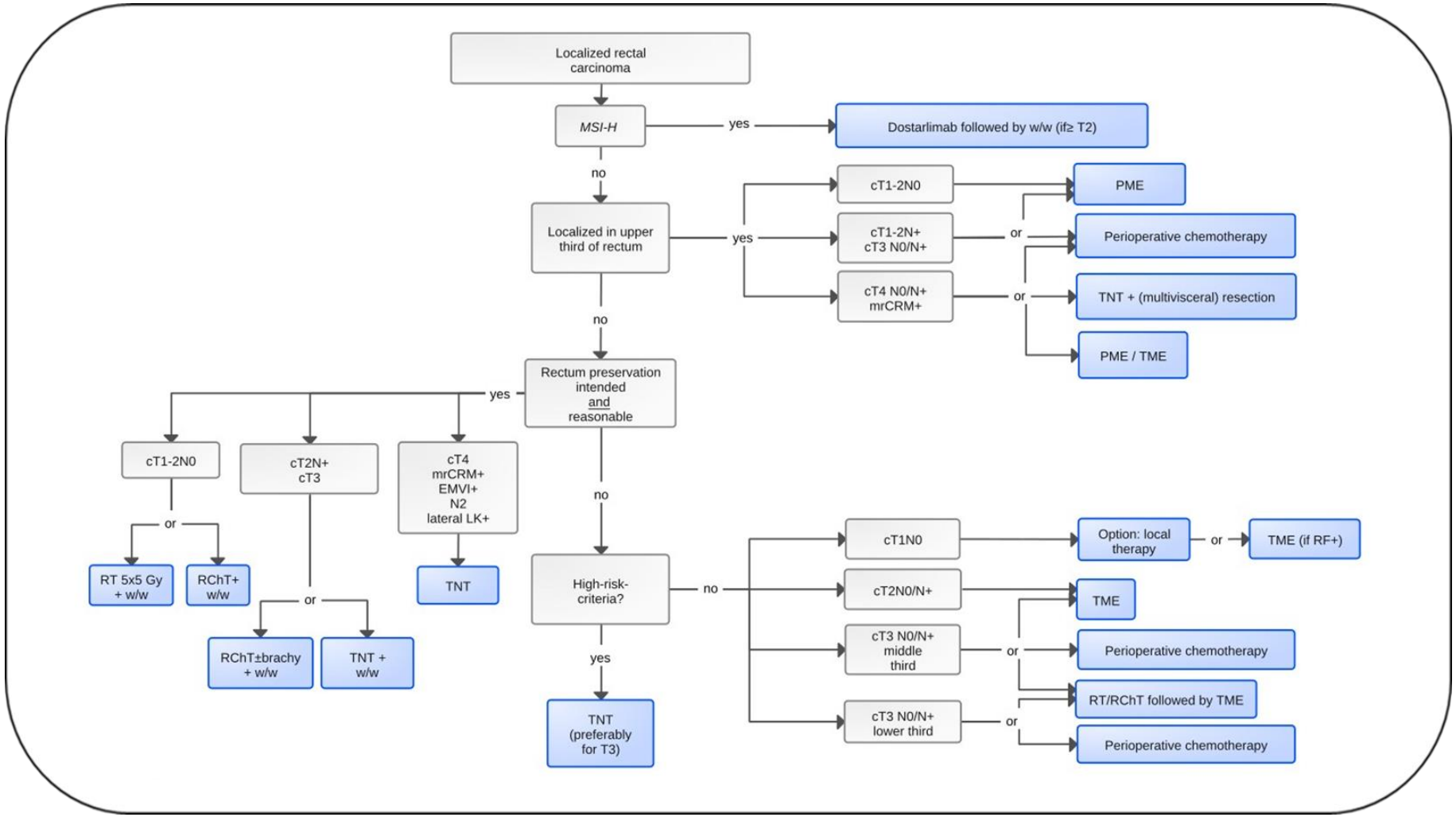


Glynne-Jones R Ann Oncol 2017 (suppl. IV)

# Clinically relevant trials during the past years



# One size fits all = history. Decision making starts with discussion on treatment goals, molecular aspects and risk factors




German, Swiss & Austrian *onkopedia* guideline 2025

## Programme

**30 April 2025**

| | |
|---|---|
| 10 min | **Welcome and introduction**<br>Ralf Hofheinz |
| 10 min | **Case Presentation**<br>Anderley Gordon |
| 20 min | **Presentation of the ESMO Clinical Practice Guideline for Critical Analysis of the Case**<br>Irit Ben Aharon |
| 10 min | **Considerations Related to Guideline Implementation in Everyday Clinical Practice and Discussion**<br>Gabor Liposits |
| 10 min | **Live Q&A and Discussion**<br>All speakers, Emmanouil Fokas |

**Ralf-Dieter Hofheinz**
**Chair**
Mannheim Cancer Center
University Hospital
Mannheim / University of
Heidelberg

**Anderley Gordon**
**Speaker**
The Royal Marsden Hospital

**Irit Ben-Aharon**
**Speaker**
Fishman Oncology Center,
Rambam Health Care
Campus

**Gabor Liposits**
**Speaker**
Western Hospital Trust

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# Learning objectives

- Promote evidence-based quality cancer care by disseminating the ESMO Clinical Practice Guidelines (CPG) in the oncology community.
- Present a clinical case for each of the selected topics for discussion in the context of the ESMO CPG recommendations.
- Present and critically review the ESMO CPG recommendations for each selected cancer type.
- Discuss the case, the ESMO CPG recommendations, their impact on care and implementability in the daily practice setting under the guidance of a moderator senior expert, with participation of the guideline authors, practicing oncologists and young oncologists.
- Audit the fulfillment of the learning objectives and acceptability of the ESMO CPG recommendations by means of an online questionnaire.

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# CASE PRESENTATION

## Rectal Cancer

**Dr Anderley Gordon**
Clinical Research Fellow
The Royal Marsden Hospital

30 April 2025

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# Declaration of interests

No disclosures

# Presentation

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**February 2024**

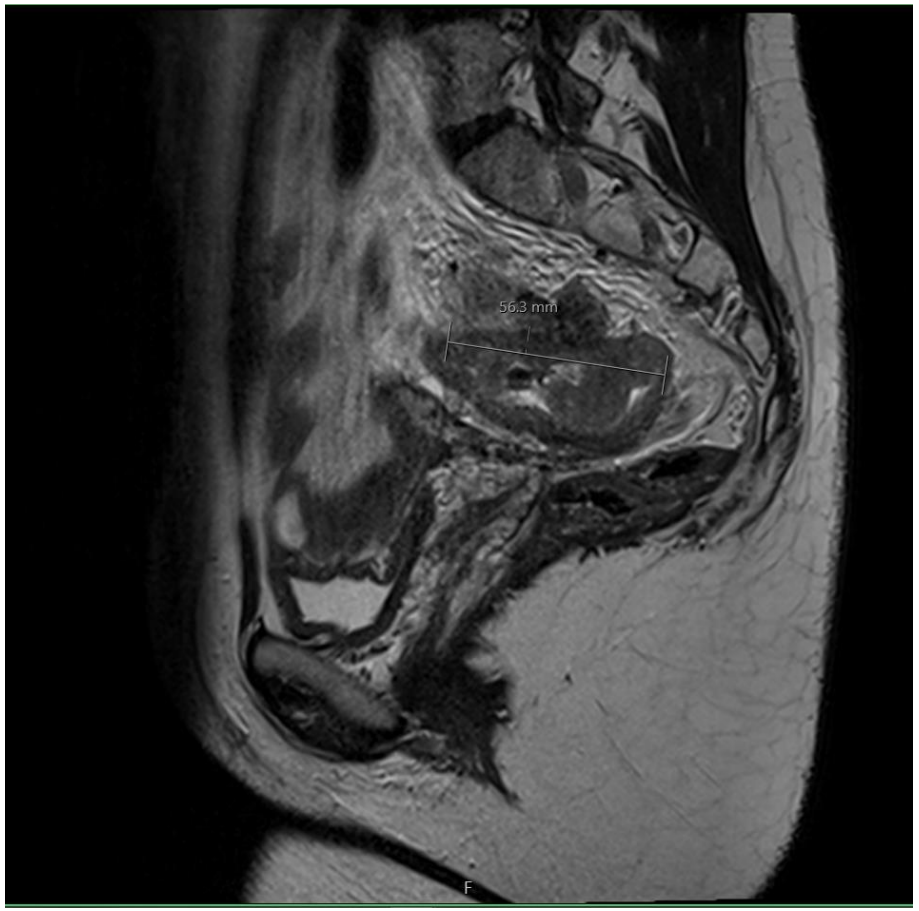
Presents with rectal bleeding, abdominal pain, fecal urgency and frequency (3-4 x day)

Stool FIT test positive >6000 ug/g

Colonoscopy – tumour in rectosigmoid colon, distal tumour margin 16cm

Moderately differentiated adenocarcinoma, MMR proficient

CEA <1

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Baseline CT TAP, MRI pelvis, FDG PET

- Mid-high rectal tumor arising 12cm from anal verge
- Numerous malignant nodes which threaten the margin at CRM (12 to 1 o'clock).
- No distant metastases
- Stage: **T3dN1 EMVI positive CRM at risk M0**.

MDT recommends upfront chemotherapy prior to consideration of CRT and surgery

Completes egg harvesting for fertility preservation

# Neoadjuvant treatment

**March – May 2024**

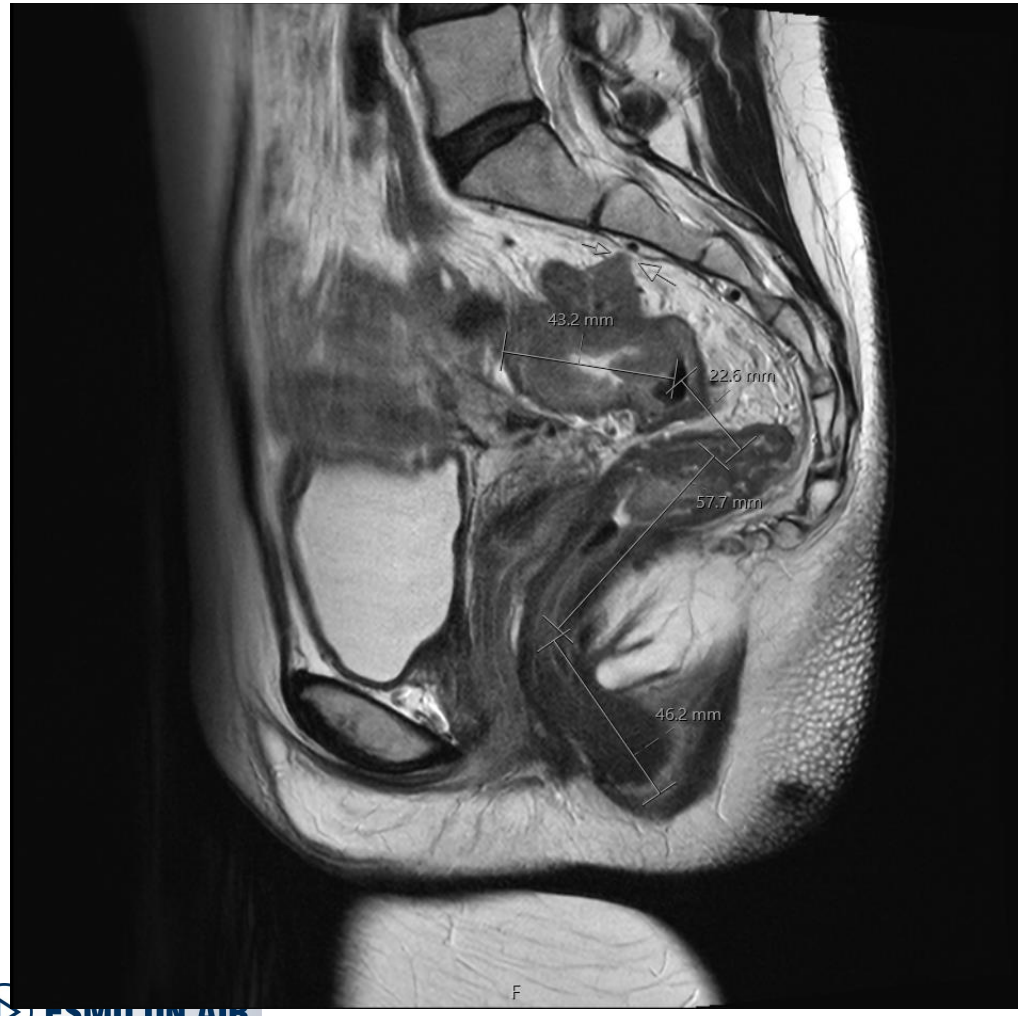
Receives 4 x neoadjuvant CAPOX

Starts with 50% dose reduction capecitabine due to DPYD variant of unknown significance

Toxicities

- During C1 admitted with G2 diarrhoea ?possible colitis. CT showed oedema in proximal and descending colon. Capecitabine paused and symptoms resolved.
- C2-C4 continues with 50% dose reduction without further occurrence.
- G1 peripheral sensory neuropathy, G1 fatigue, G2 nausea

# Post neoadjuvant CAPOX x4




**May 2024**

CT TAP

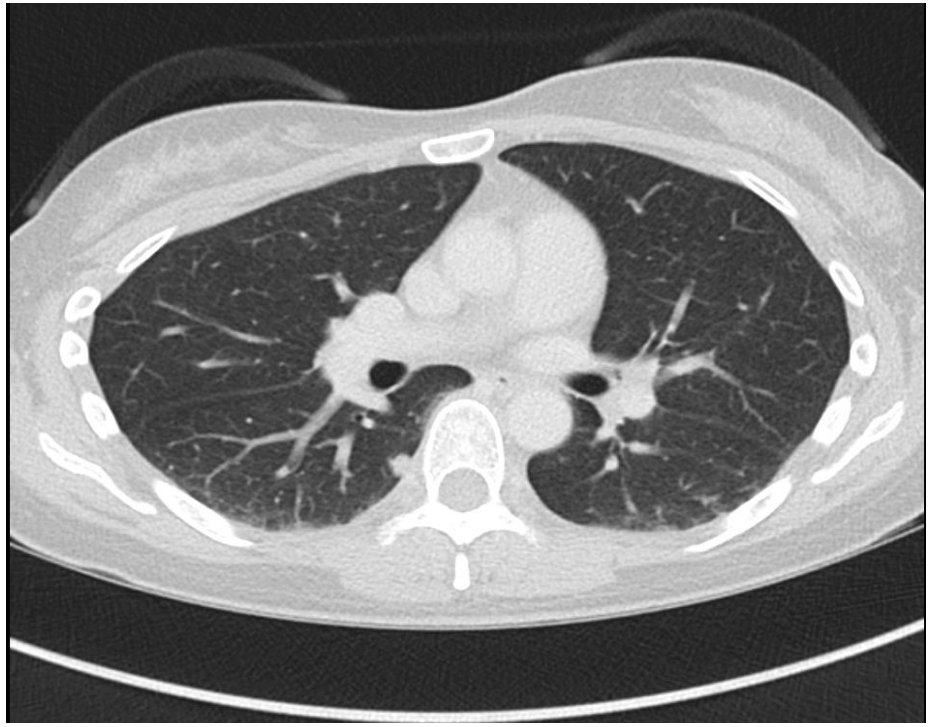
- Some response to primary and associated node on CT
- Indeterminate 1cm right subpleural lung nodule (increased from 0.4cm at baseline)

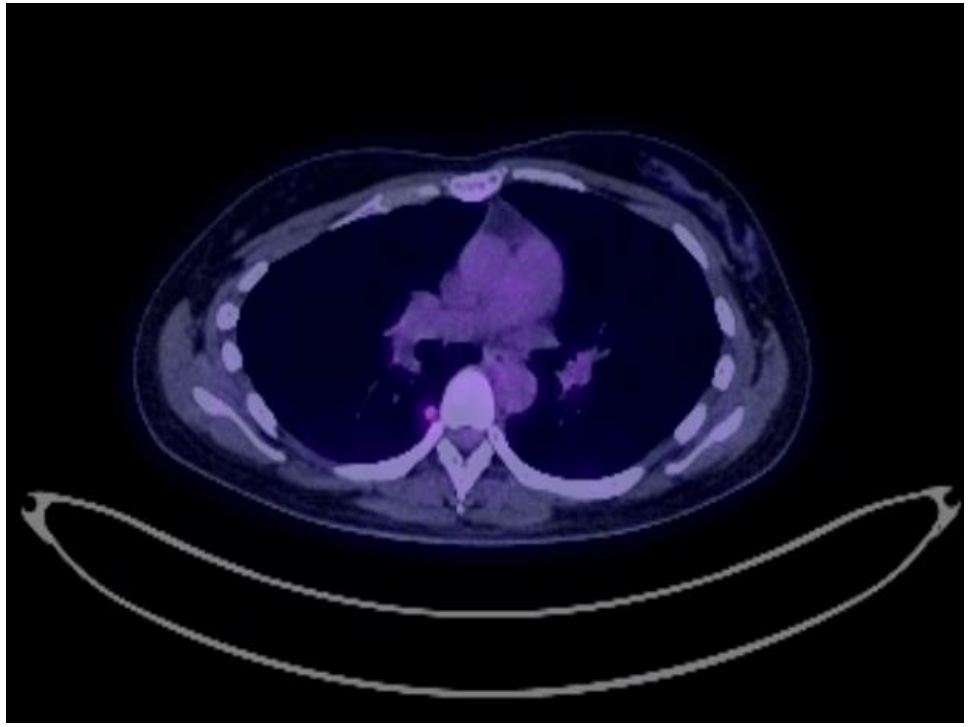
MRI pelvis

- Partial response tumour 56mm → 43mm
- ymr T3c N1c, CRM+, EMVI-
- TRG 4 suggesting residual active disease

CEA <1

# New solitary lung metastasis





**June 2024**

PET CT shows right subpleural lung nodule is hypermetabolic compared to baseline PET CT.

# Neoadjuvant treatment

**June 2024 MDT**

1. CRT to primary before surgery.
2. Ablation of solitary lung metastasis.
3. For 6 months total of CAPOX (4 x further CAPOX) post surgery

**July to August 2024**

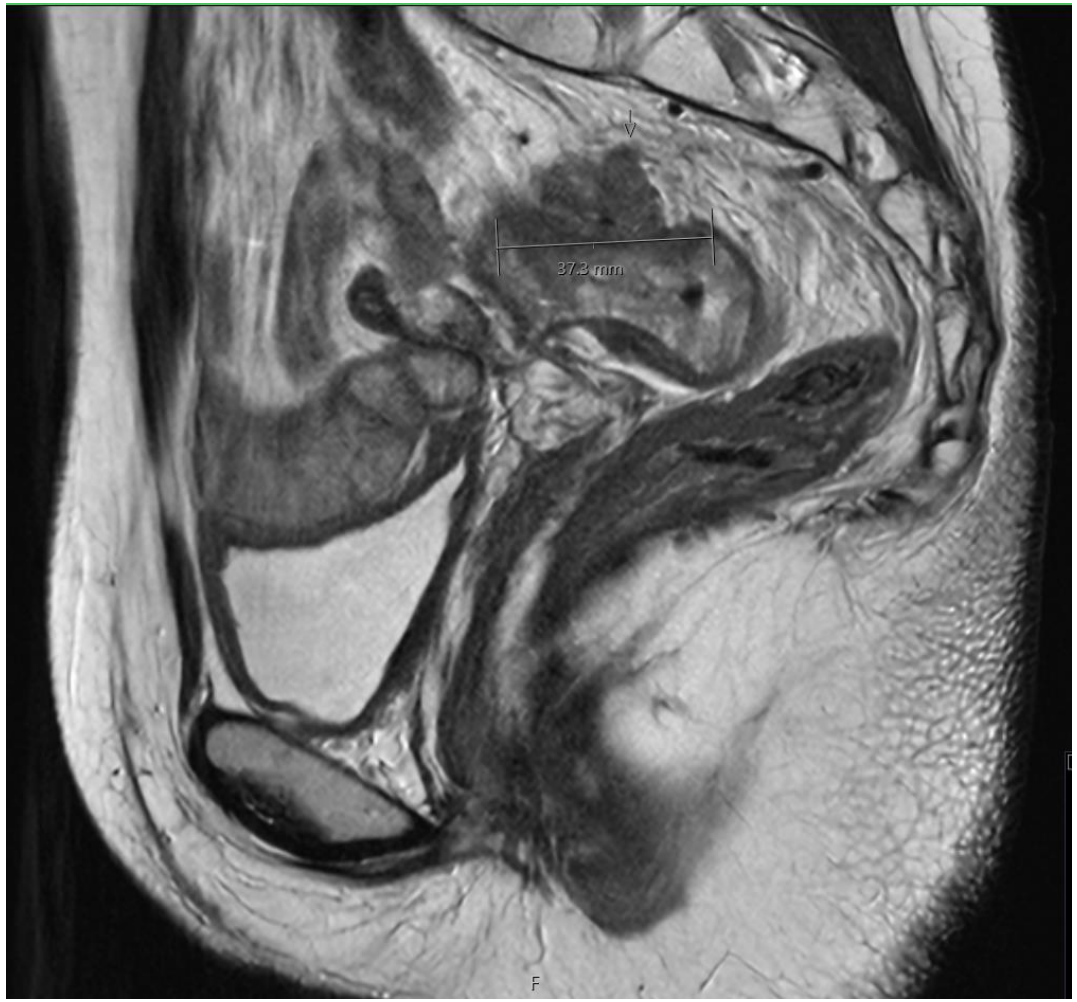
Receives radiation 52.5Gy/25 fractions to the rectum concurrent with capecitabine.

Cryoablation to right subpleural lung nodule 10/07/2024

G1 fatigue, G1 nausea, poor appetite

Struggling emotionally with treatment, referred to psychological support team

# Post neoadjuvant CRT




**September 2024**

CT TAP, MRI pelvis

- Further partial response but residual active tumour signal remains (mainly extraluminal)
- Posterior margin remains involved.
- Treated lung appearances, no new sites of disease

# Surgery & adjuvant chemotherapy

**October 2024**

Robotically assisted anterior resection with enbloc pre-sacral fascia excision and defunctioning ileostomy

Final histology: ypT3 N1a (1/47) L1 V1 Pn1 R0.

No post-operative complications

**Dec 2024 – Feb 2025**

Completes 4 x adjuvant CAPOX (8 cycles total)

CEA <1 prior to starting

Grade 2 nausea and vomiting, and oxaliplatin extravasation after C5. Improved with 25% dose reduction to oxaliplatin for C6-8.

Referred to genetics (delayed referral) and awaiting consultation

# Surveillance

**19 March:** CT scan no evidence of recurrence. CEA <1

**24 March 2025:**

Flexible sigmoidoscopy shows colorectal anastomosis intact and patent.

Undergoes Ileostomy reversal

- Bowels initially slow to open but now loose and frequent
- Requiring dietician support
- Minimal abdominal pain

**4 April 2025:** Follow up consultation. Continues surveillance with next review in 3 months which will be 1 year post lung ablation.

# Quality of Life

Residual chemotherapy

- G1 peripheral neuropathy persists of hands

Bowel / stoma reversal

- Feels very “relieved” to have stoma reversal but now struggling with loose and frequent stools
- On low residue diet with plans to slowly reintroduce fibre with dietician support
- Weight is stable 56kg at diagnosis, now 54kg.

Other impacts

- Significant health anxiety, particularly around CT scans
- Stopped working at time of diagnosis but plans to return to same job part time and eventually full time.
- Has not travelled since diagnosis and very motivated to take a summer holiday

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# CRITICAL ANALYSIS IN VIEW OF CLINICAL PRACTICE GUIDELINES

## Rectal Cancer

**Prof. Irit Ben-Aharon**

Rambam Health Care Campus

Haifa, Israel

30 April 2025

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

# Irit Ben-Aharon MD, PhD - Disclosure

Astra Zeneca – Invited speaker
MERCK– Invited speaker
MSD – Invited speaker
BMS – Invited speaker
Medison – Invited speaker
Astellas – Advisory Board
BeiGene - Advisory Board

**Editor role:** Editor in Chief – ESMO Gastrointestinal Oncology
EORTC GITCG – Chair, Young-adult Cancer Task Force

# Presentation

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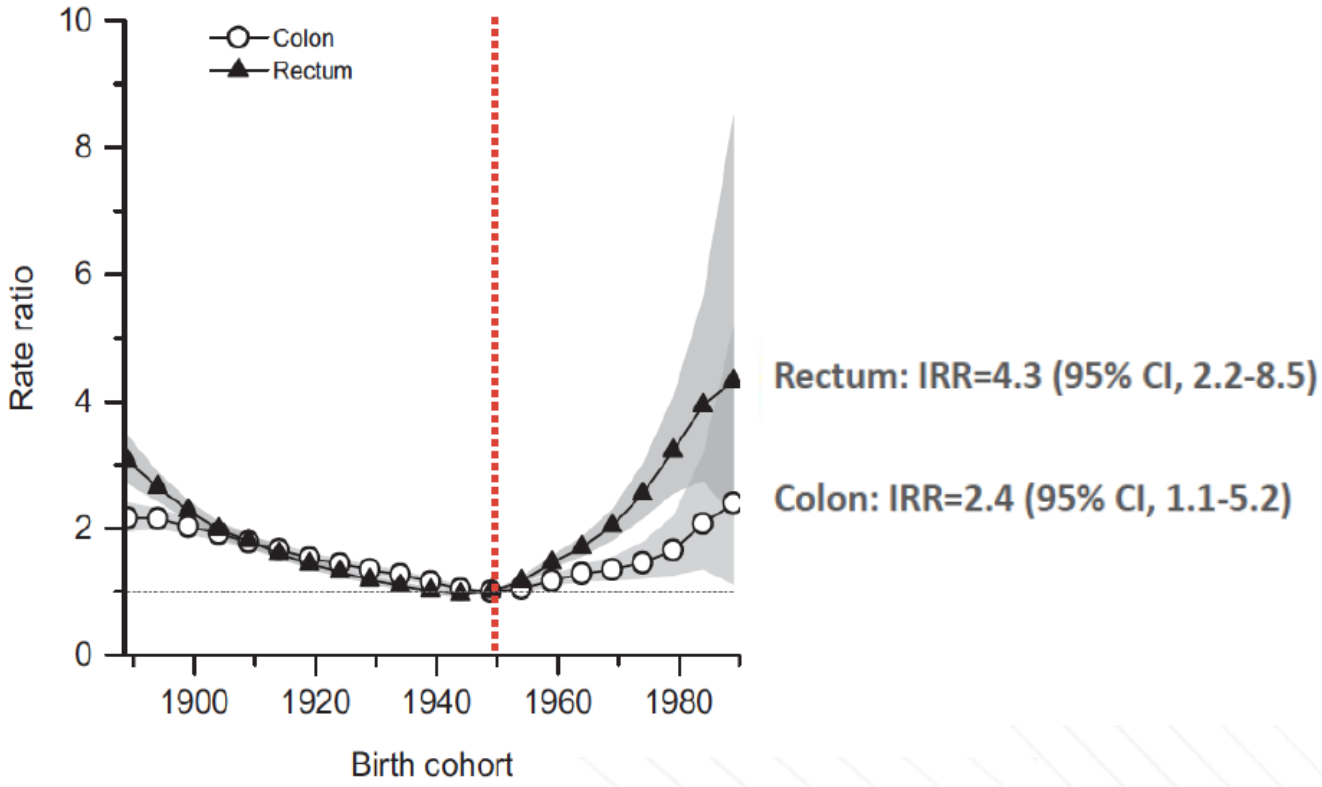
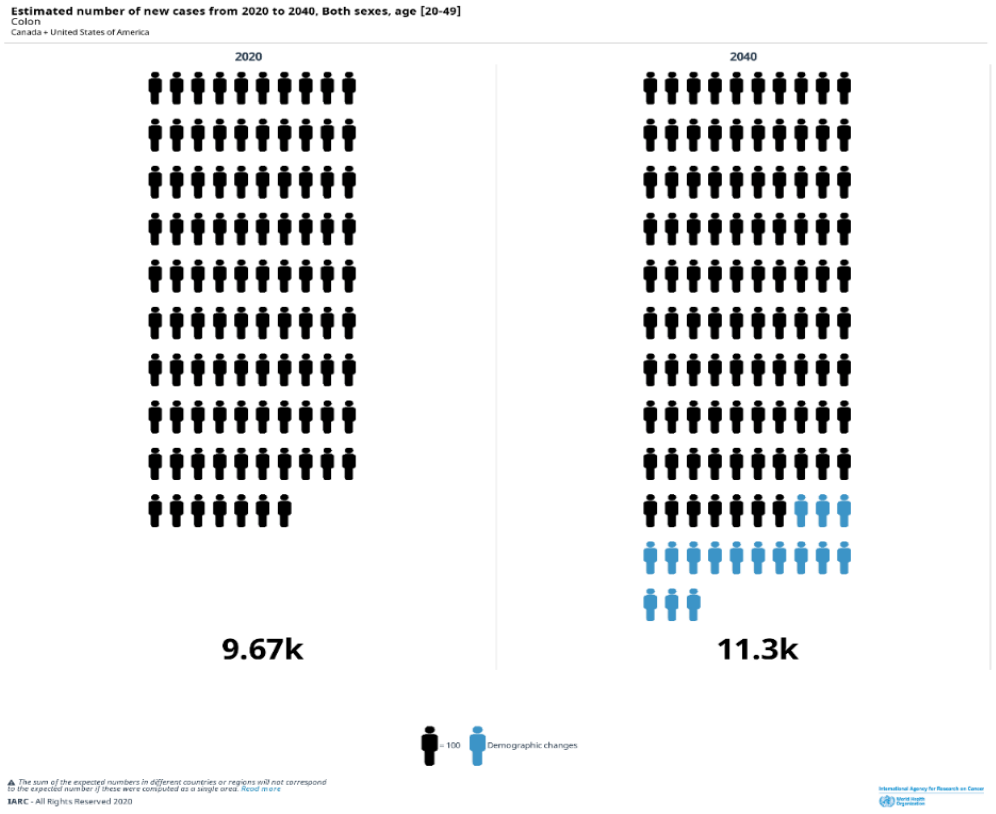
# Increase in EOCRC reflects a birth cohort effect



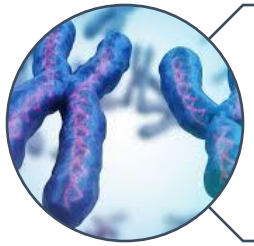

Rectum: IRR=4.3 (95% CI, 2.2-8.5)

Colon: IRR=2.4 (95% CI, 1.1-5.2)




Siegel RL, et al. *J Natl Cancer Inst* 2017; 109(8).

# Young-Onset Cancer – Unique Considerations

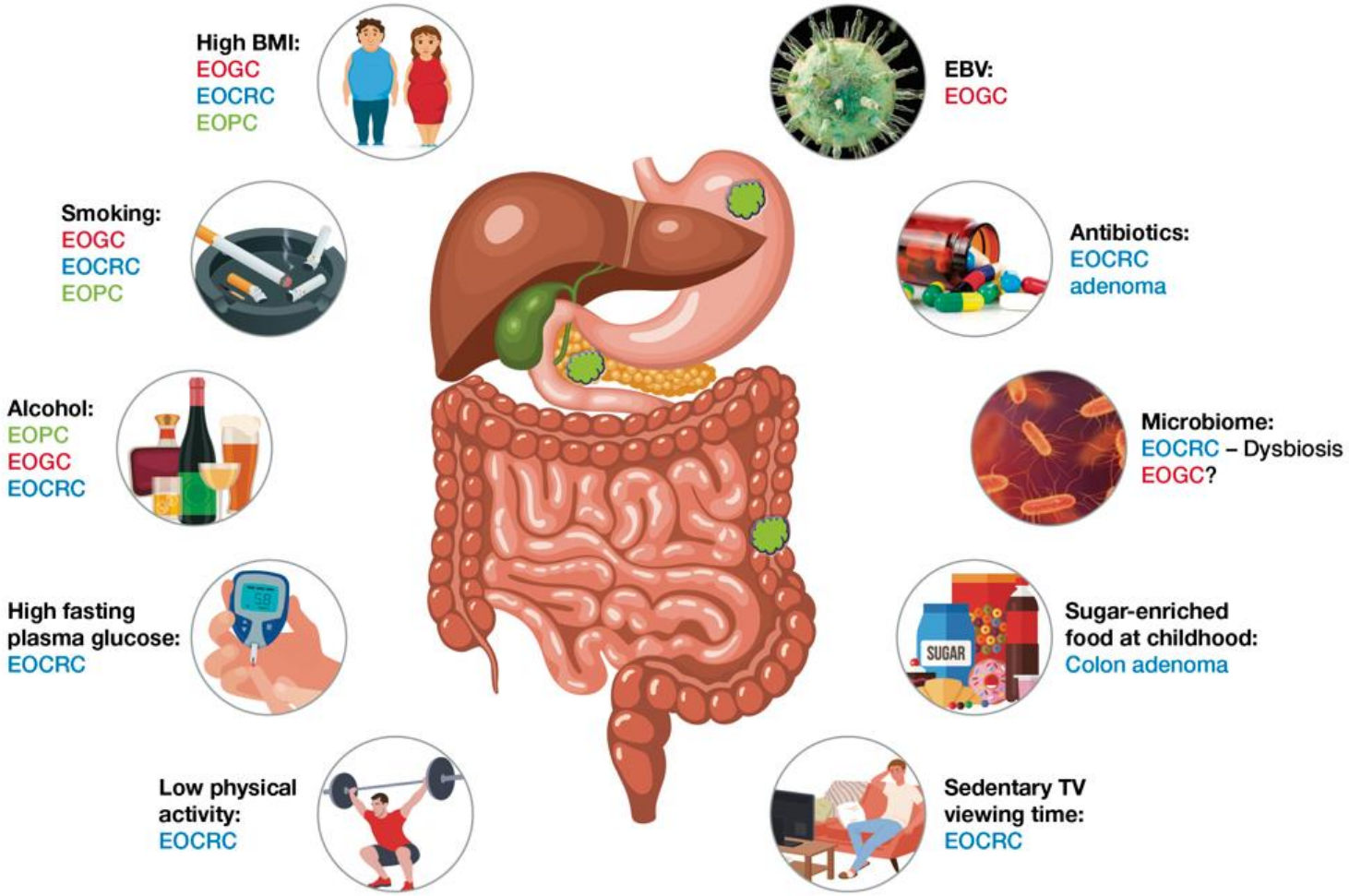


Biology and Etiology

Long-Term Toxicities

Unmet Needs

# Potential Etiological Factors in Sporadic EOCRC




Ben-Aharon et al., Cancer Disc 2023

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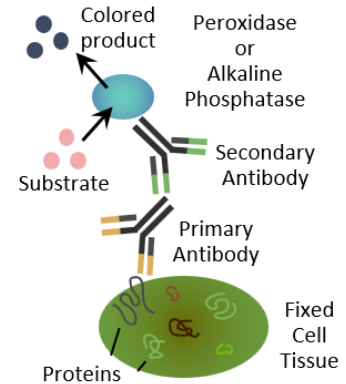
# MMR in the neoadjuvant setting -

Assessment of mismatch repair (MMR) proteins by is essential:

- IMMUNOHISTOCHEMISTRY (IHC)




Adapted from Rockland 2017[4]

Brown=target proteins
Blue=cell nuclei

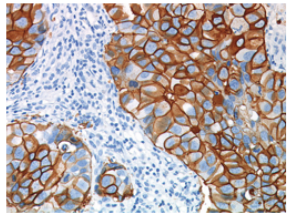
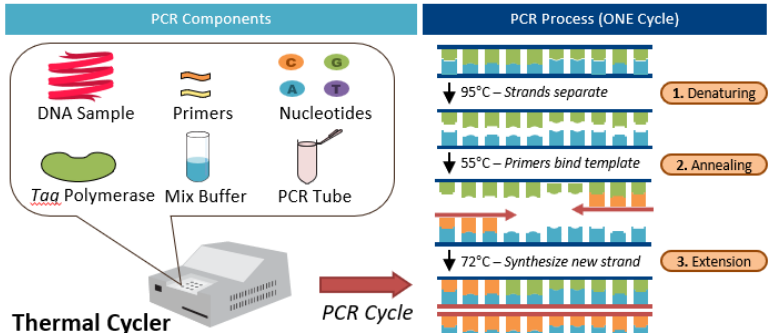


Image from Biocare 2017[5]

- POLYMERASE CHAIN REACTION (PCR)



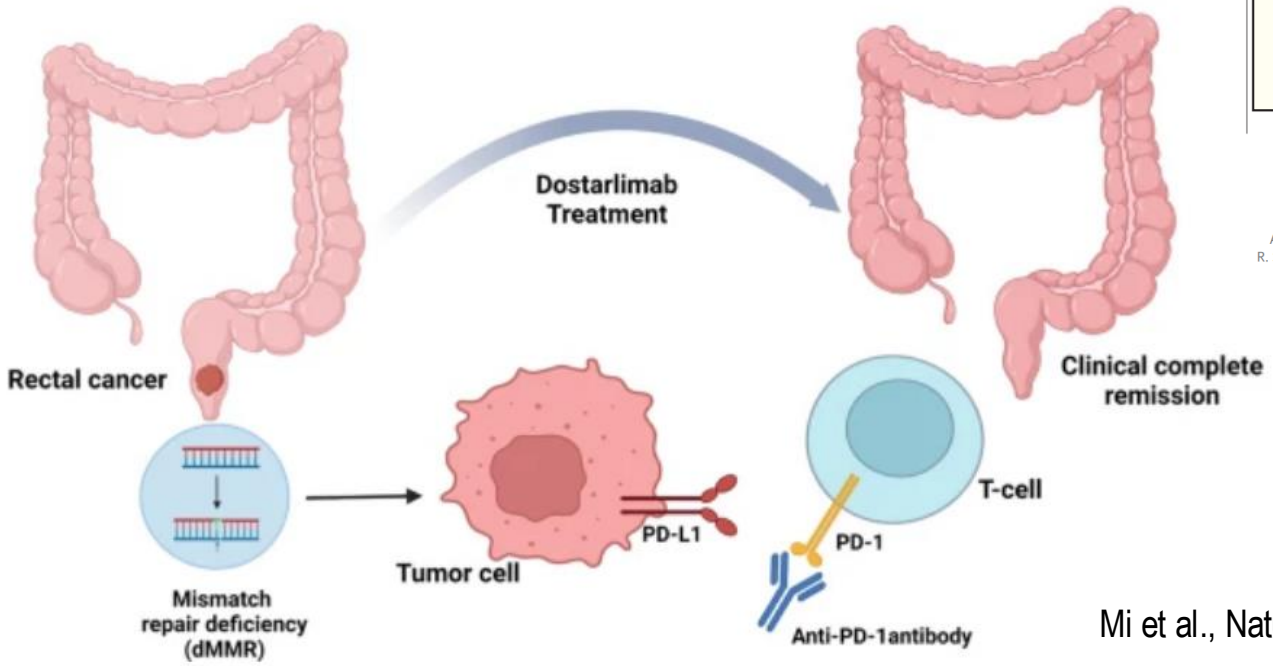

Adapted from Bioninja 2017[6]

- To identify patients with sporadic microsatellite instability-high (MSI-H) tumours or Lynch syndrome, who may benefit from treatment with immunotherapy
- In the case of Lynch syndrome, referral for genetic counselling.

# MMR in the neoadjuvant setting -

**Summary of published clinical trials of neoadjuvant immunotherapy in dMMR, locally advanced CRCs**

| Trials | Setting | Phase | Patients (lynch syndrome,%) | Therapy | Outcome |
|---|---|---|---|---|---|
| NICHE | Neoadjuvant | II | 32 (13, 41%) | Nivolumab+ipilimumab | pCR (69%) |
| PICC | Neoadjuvant | II | 17 vs 17 (4, 24% vs 1, 6%) | Toripalimab+celecoxib vs Toripalimab | pCR (88% vs 65%) |
| NCT04165772 | Neoadjuvant | II | 14 (8, 57%) | Dostarlimab | cCR (100%) |



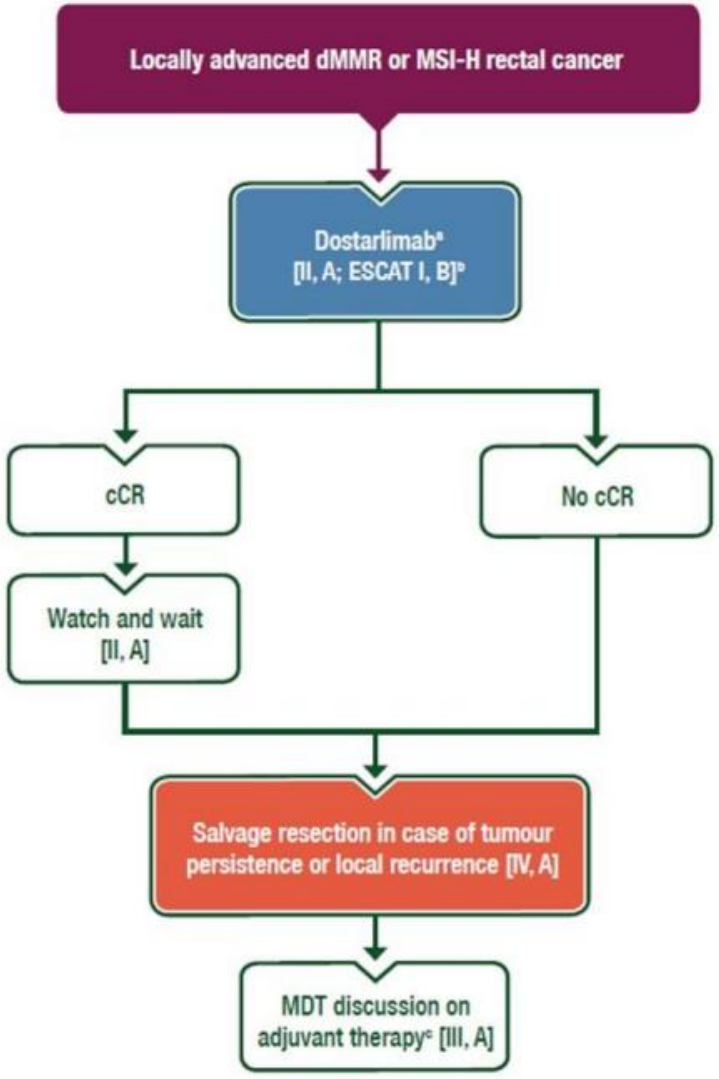

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 23, 2022 VOL. 386 NO. 25

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.

Mi et al., Nature 2022

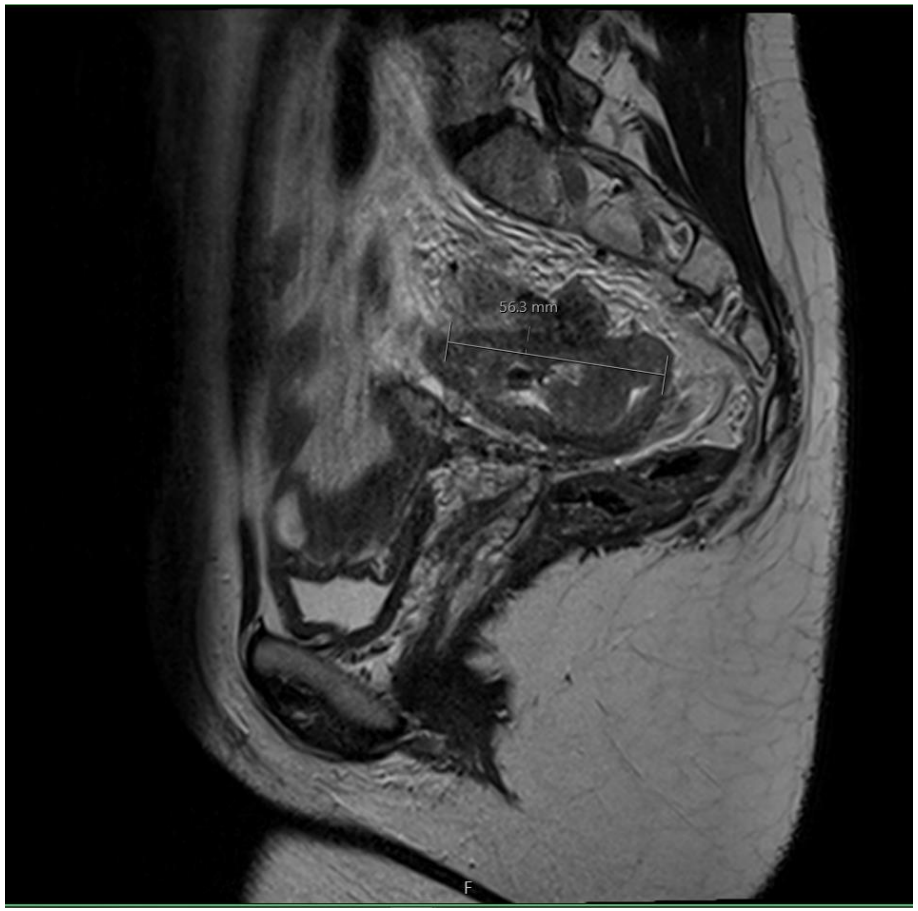
# MMR in the neoadjuvant setting -






Hofheinz et al., ESMO CPG 2025 in press

# STAGING -

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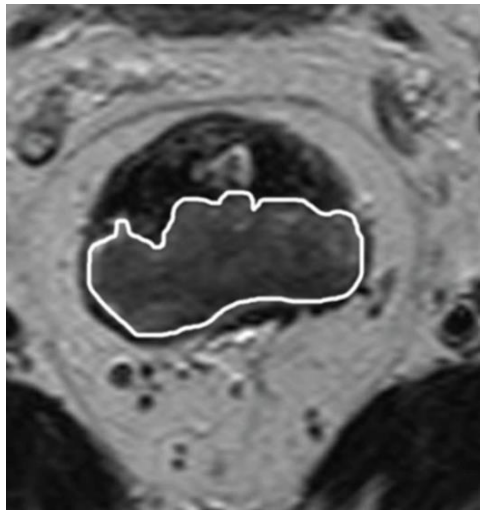
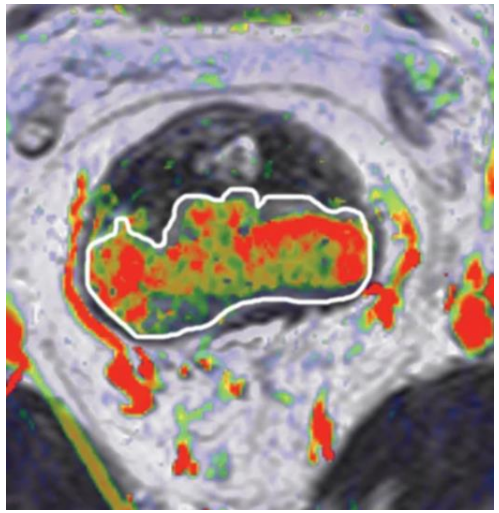
# STAGING

- MRI is the golden standard for local staging of rectal cancer.
- It is superior to Endorectal Ultrasound (ERUS) as ERUS accuracy for evaluating the mesorectal compartment is restricted.
- MRI is the best tool to identify the relationship between the tumor and the mesorectal fascia (MRF), and the involvement of the MRF.

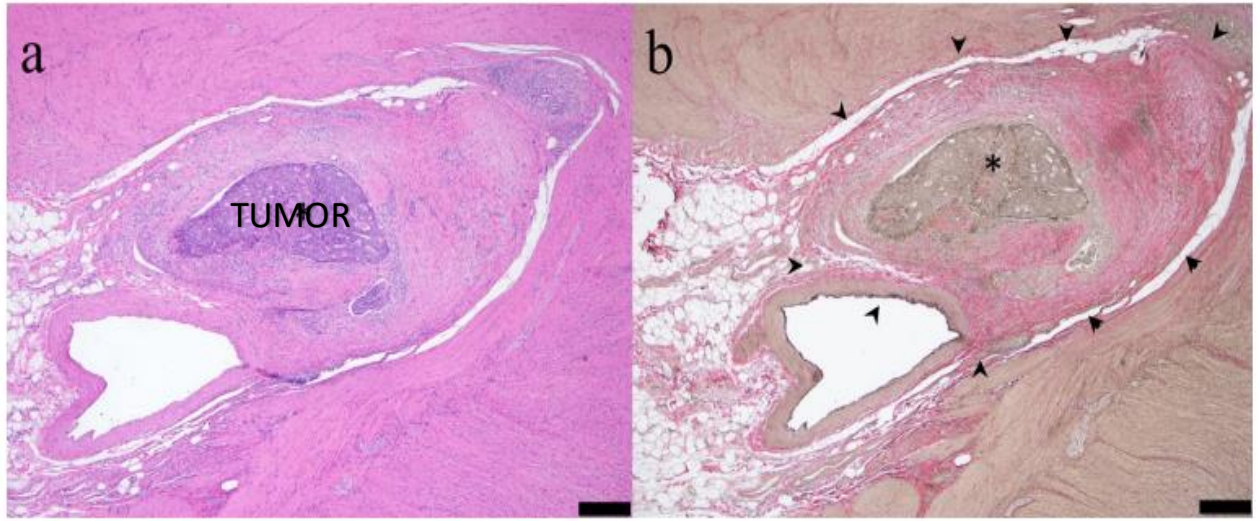
- T stage
- Nodal metastases
- A threatened or involved mesorectal fascia
- The presence of extramural venous invasion





# STAGING

- Direct tumor invasion into the extramural veins on histopathology, known as extramural venous invasion (EMVI), has been recognized as an indicator of poor prognosis
- EMVI is defined histopathologically as the presence of tumor cells within blood vessels located beyond the muscularis propria of the rectal wall
- Nevertheless, defining EMVI is challenging since the differential diagnosis includes desmoplastic reaction

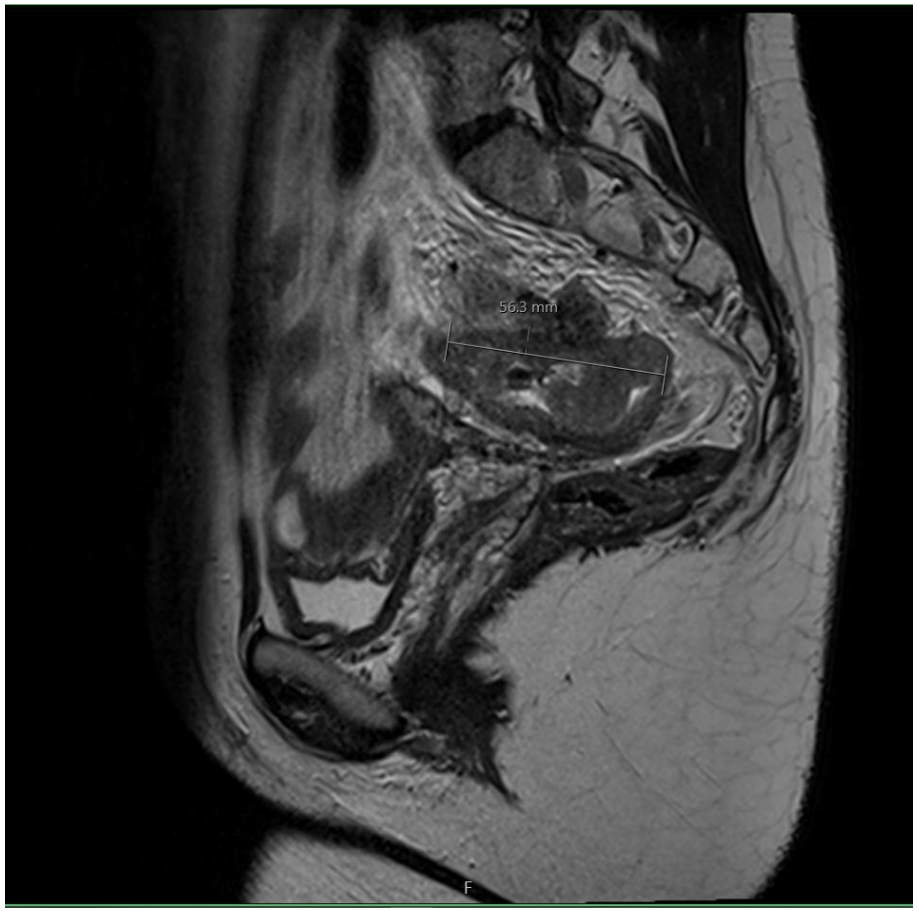



Elastin stain is helpful to depict EMVI by highlighting elastin fiber around tumor cells



Inoue et al. Insights Imaging 2021

# STAGING -



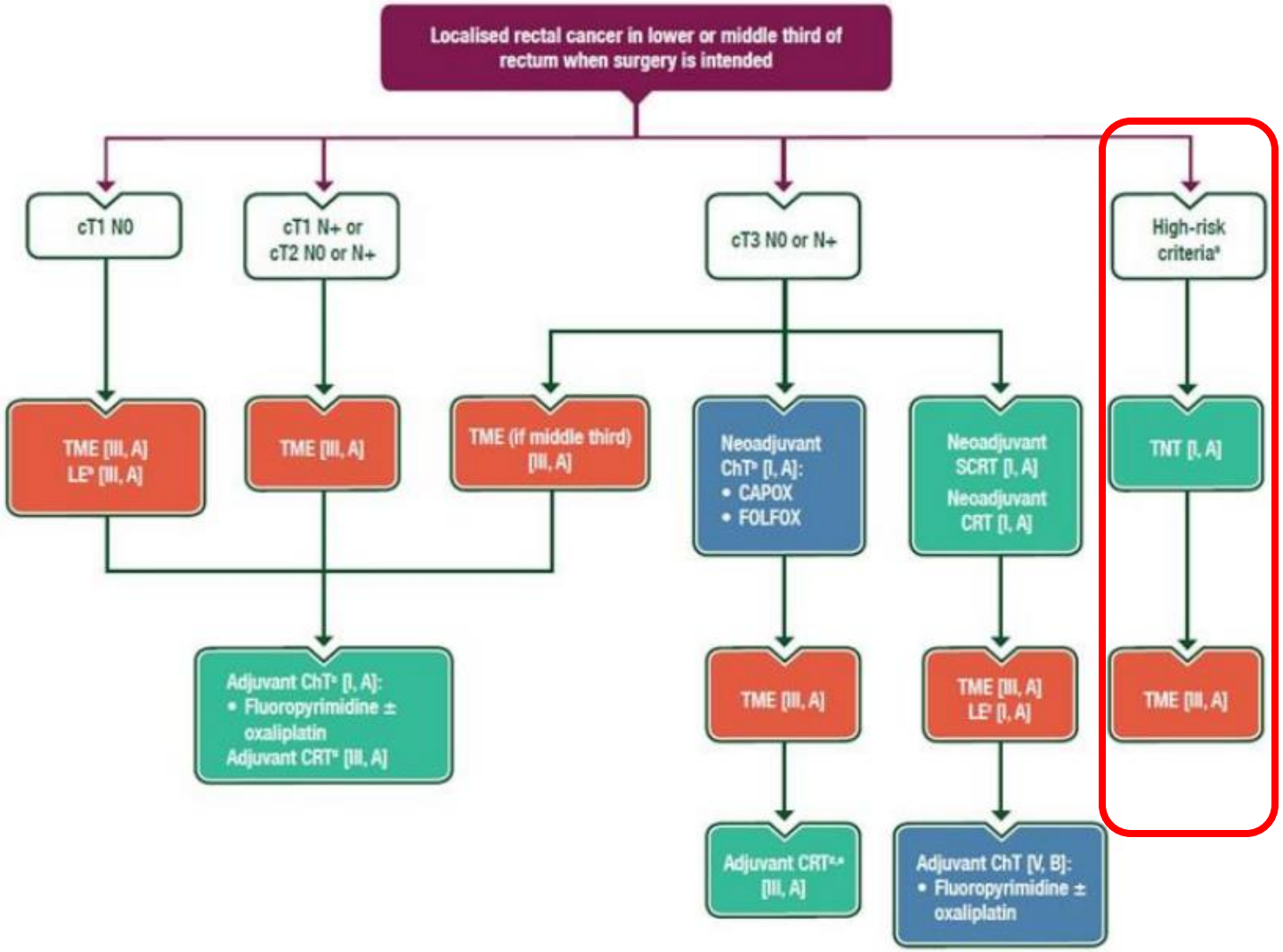

**February 2024**

Baseline CT TAP, MRI pelvis, FDG PET

- Mid-high rectal tumor arising 12cm from anal verge
- Numerous malignant nodes which threaten the margin at CRM (12 to 1 o'clock).
- No distant metastases
- Stage: **T3dN1 EMVI positive CRM at risk M0**.

**MDT** recommends upfront chemotherapy prior to consideration of CRT and surgery

Completes egg harvesting for fertility preservation




**High-risk criteria:**

- cT4
- cN2
- mrCRM+
- EMVI+
- lateral LN+



Hofheinz et al., ESMO CPG 2025 in press

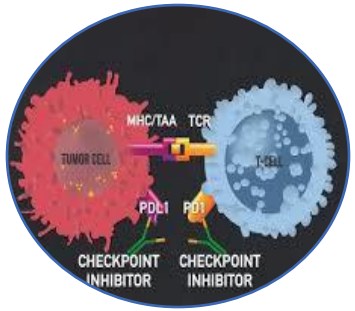
# Neoadjuvant options:

## Chemotherapy

- Doublet
- Triplet
- Sequence

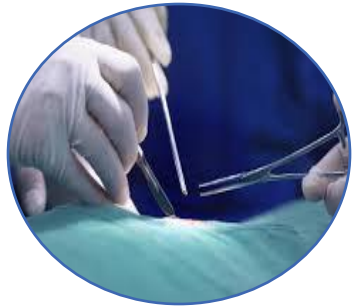
## Radiation

- SCRT
- CRT
- Sequence




## Immunotherapy

- MMR-D
- In combination with RT - experimental



## Surgery

- TME
- LE for near CR
- Watch and wait for cCR

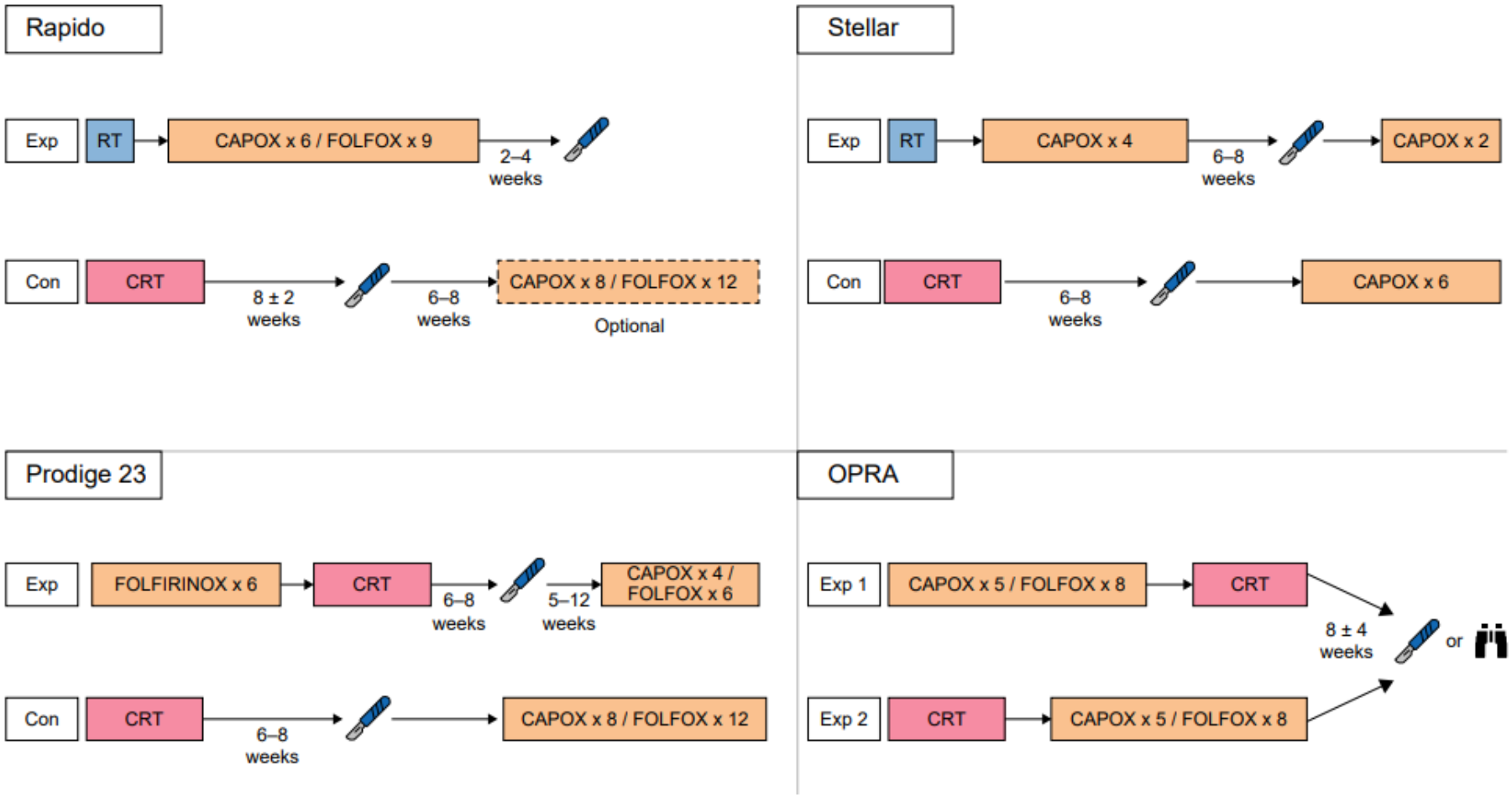
- Induction chemotherapy


- Consolidation chemotherapy:


- Neoadjuvant chemotherapy:


TNT –
Total Neoadjuvant Therapy

# TNT key Trials:






Smith et al., BJS Open, 2024

# TNT key Trials:

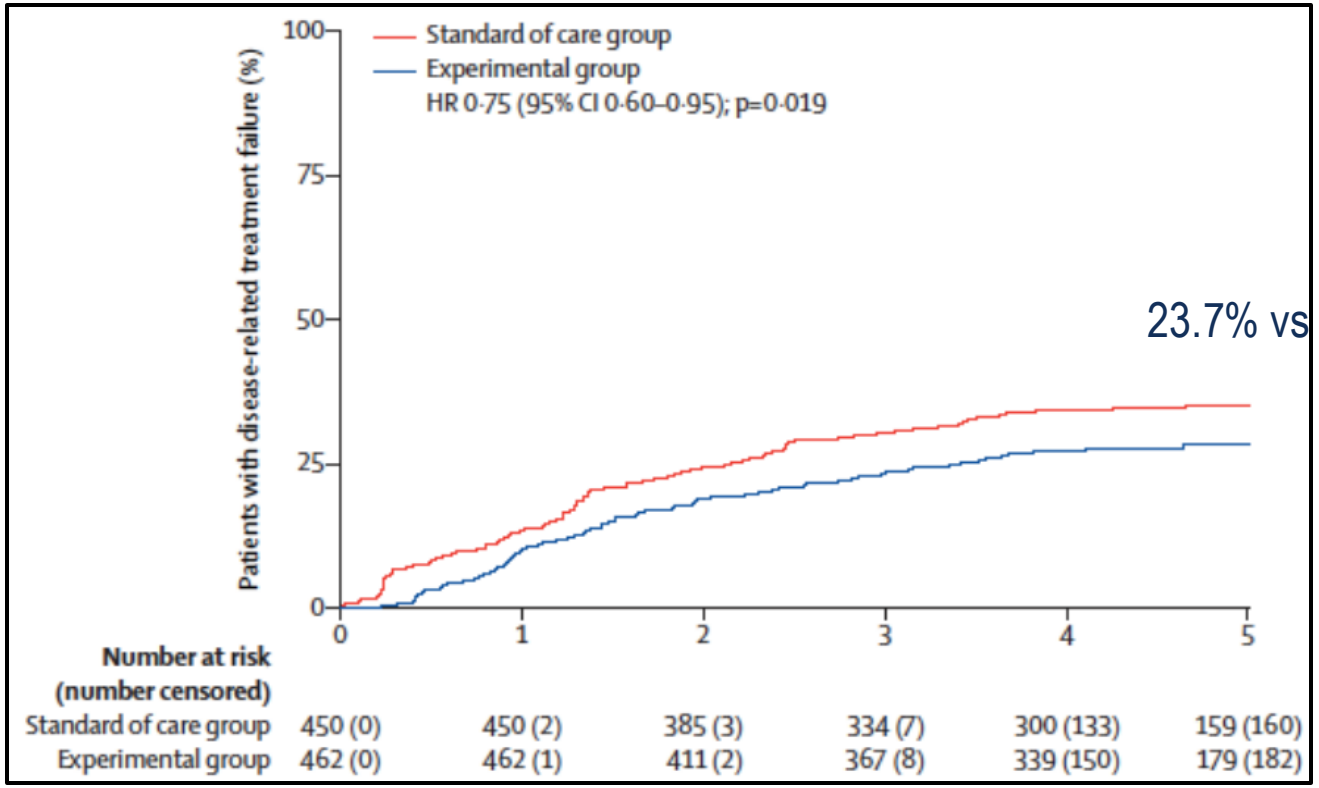
| Study (year) | Inclusion criteria | N | Primary endpoint | Treatment arms | pCR rate (%) | R0 rate (%) | DFS (%) | OS (%) | DM (%) | LRR (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| RAPIDO (2021) | At least one of: cT4a/b; EMVI; cN2; MRF+; LLN | 920 | 3-year DRTF | SCRT → CT→TME | 28 | 90 | 23.7 | 89.1 | 20.0 | 8.3 |
| | | | | CRT → TME | 14 | 90 | 30.4 | 88.8 | 26.8 | 6.0 |
| PRODIGE 23 (2021) | cT3/4 | 461 | 3-year DFS | CT → CRT→TME | 28 | 95 | 76 | 91 | 17 | 4 |
| | | | | CRT→TME | 12 | 94 | 69 | 88 | 25 | 6 |
| STELLAR (2022) | cT3/4 or cN+ | 599 | DFS | SCRT → CT→TME | 17.2 | 91.5 | 64.5 | 86.5 | 22.8 | 8.4 |
| | | | | CRT → TME | 13.9 | 87.8 | 62.3 | 75.1 | 24.7 | 11.0 |
| OPRA (2022) | cT3/4 or cN+ | 324 | DFS | CT → CRT→TME | NS | 91 | 76 | NS | 16 | 6 |
| | | | | CRT → CT→TME | NS | 88 | 76 | NS | 18 | 6 |



Smith et al., BJS Open, 2024

# TNT key Trials:

## Primary end-point RAPIDO Trial: Disease related treatment failure



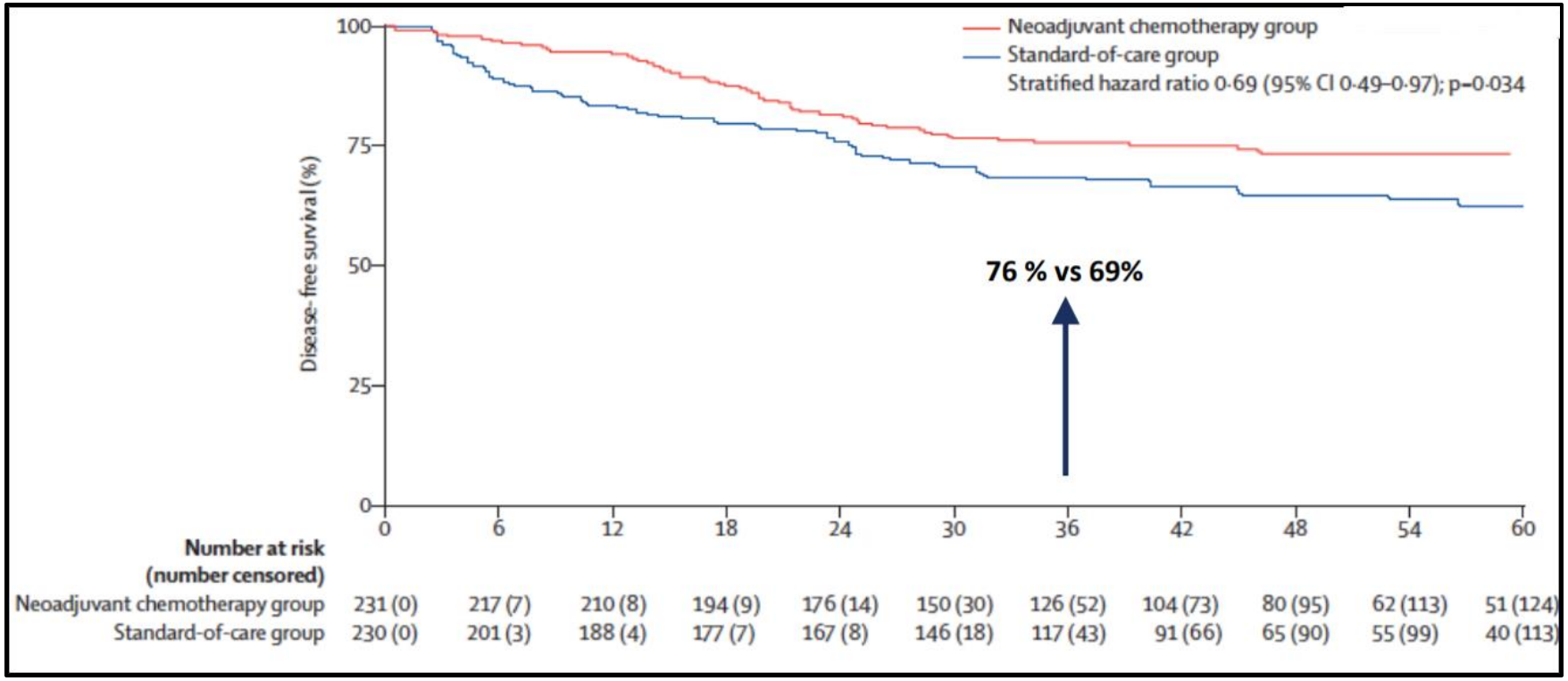

23.7% vs 30.4%



Bahadoer RR, et al. Lancet Oncol 2021; 22:29–42

# TNT key Trials:

## Primary end-point PRODIGE 23 Trial: DFS






Conroy T, et al. *Lancet Oncol* 715–22:702 ;2021

# TNT key Trials:

## Patient Demographics: RAPIDO and PRODIGE 23

| Patients Characteristics | RAPIDO | PRODIGE 23 |
|---|---|---|
| Median age | 61/61 y | 61/62 y |
| N | 462/450 | 231/ 230 |
| cT4 | 30.4% vs 31.8% | 17.8% vs 15.6% |
| cN2 | 68% vs 68% | NR |
| EMVI + | 32% vs 28% | NR |
| MRF+ | 62% vs 60% | 26.0% vs 27.7% |



Conroy T, et al. *Lancet Oncol* 715–22:702 ;2021
Bahadoer RR, et al. *Lancet Oncol*2021

# TNT key Trials:

## Clinical Outcomes: RAPIDO and PRODIGE 23

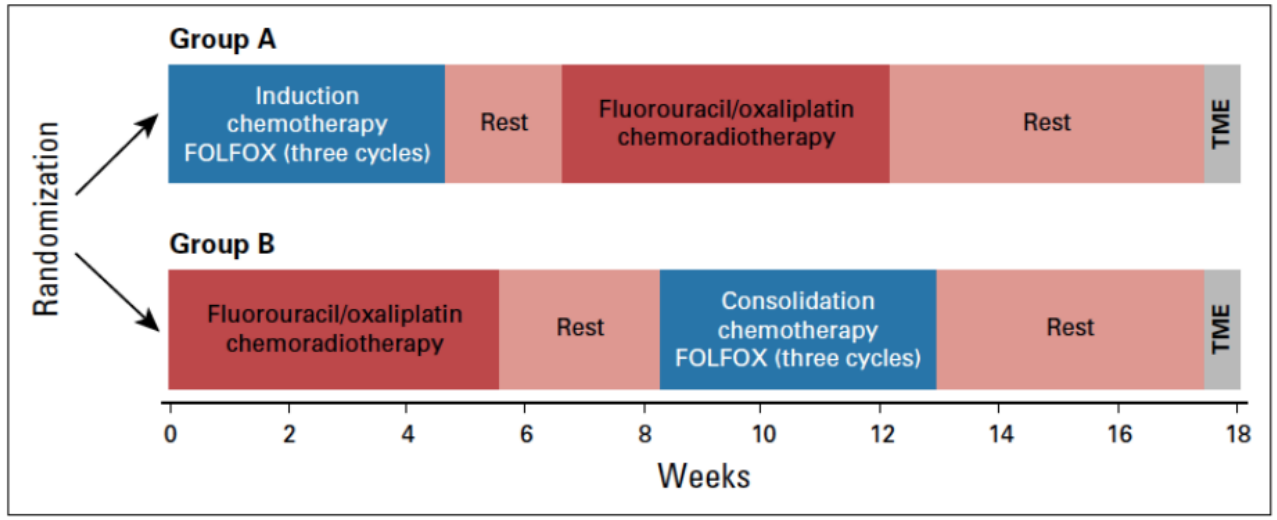
| OUTCOMES | RAPIDO | PRODIGE 23 |
|---|---|---|
| Median FOLLOW UP | 4.6 yrs | 4.6 yrs |
| Primary end point | 3-yrs DrTF | 3-yrs DFS |
| 3-yrs Primary event (Δ%) | 23.7% vs 30.4% (6.7%) | 76% vs 69% (7%) |
| 5-yrs | 27% vs 34% (7%) | – |
| HR (95% CI) p value | 0.75 [0.60–0.96] p=0.019 | 0.69 [0.49–0.97]; p=0.034 |
| 3-yrs Metastasis free | 80% vs 73.2% | 79% vs 72% |
| pCR rate | 28.4% vs 14.3% | 27.5% vs 11.7% |
| Local relapse rate | 10% vs 6% at 5 years | 4.8% vs 5.7% at 3 years |
| 3-yrs Overall Survival | 89.1% vs 88.8% | 91% vs 88% |



Conroy T, et al. Lancet Oncol 2021; 22:702–715
Bahadoer RR, et al. Lancet Oncol 2021; 22:29–42
Dijkstra E, et al. Ann Surg 2023: doi: 10.1097/SLA.0000000000005799

# TNT key Trials:

## Randomized Phase II Trial of Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: CAO/ARO/AIO-12




| N | pCR rate |
|---|---|
| 156 | 17% |
| 150 | 25% |

P<0.001

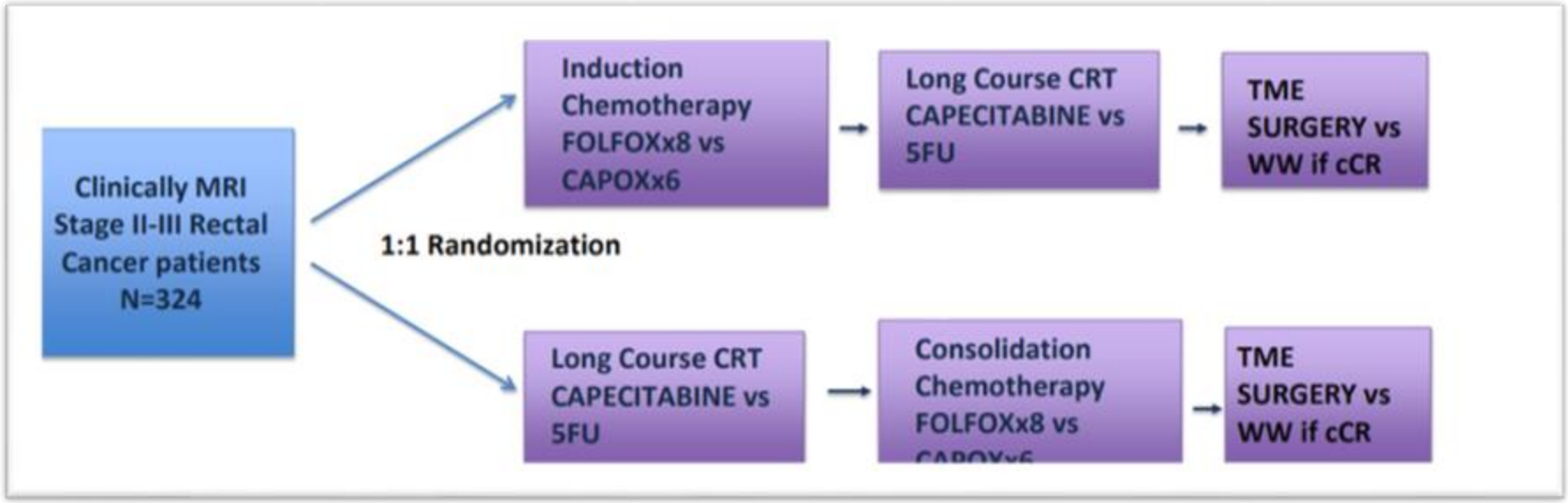
CRT first yields higher RR



Fokas E, et al. J Clin Oncol 2019; 37: 3212–3222

# TNT key Trials:

## Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy (Phase II randomised OPRA Trial)

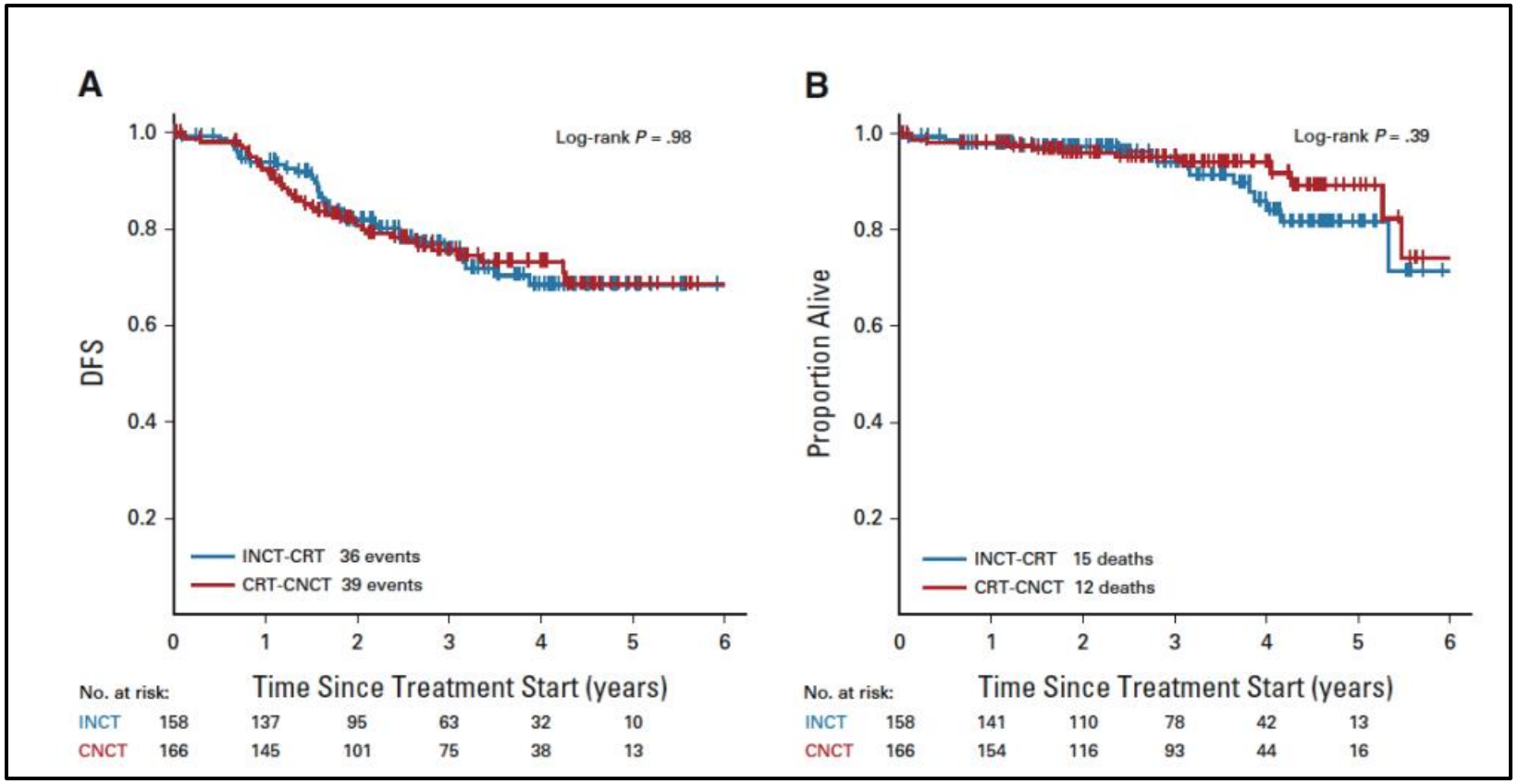





García-Aguilar et al. J Clin Oncol 2022; 40:2546–2556

# TNT key Trials:

## DFS and OS in Patients With Rectal Adenocarcinoma Treated With TNT (Phase II OPRA Trial)




ESMO ON AIR

García-Aguilar et al. J Clin Oncol 2022; 40:2546–2556

# TNT key Trials:

## Primary outcomes in RAPIDO, PRODIGE 23 and OPRA trials

| OUTCOMES | RAPIDO | PRODIGE 23 | OPRA |
|---|---|---|---|
| Median FU | 4.6 yrs | 4.6 yrs | 3 yrs |
| Primary end point | 3-yrs DrTF | 3-yrs DFS | 3-yrs DFS |
| 3-yrs Primary event (Δ%) | 23.7% vs 30.4% (6.7%) | 76% vs 69% (7%) | 76% vs 76% |
| 5-yrs | 27% vs 34% (7%) | – | – |

Conroy T, et al. Lancet Oncol 2021; 22:702–715
Bahadoer RR, et al. Lancet Oncol 2021; 22:29–42
Dijkstra E, et al. Ann Surg 2023: doi: 10.1097/SLA.0000000000005799
García-Aguilar et al. J Clin Oncol 2022; 40:2546–2556

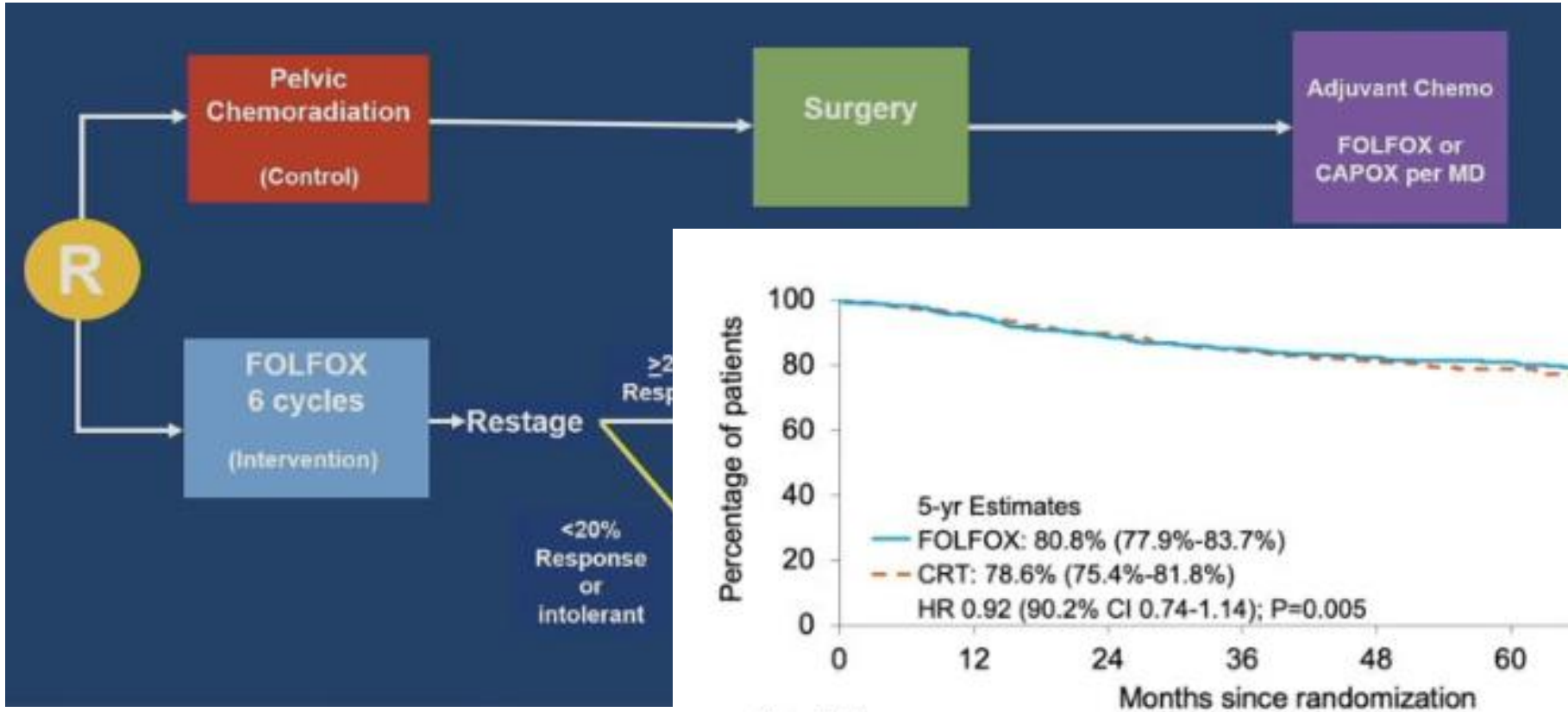
# Take home message:

TOTAL NEOADJUVANT TREATMENT SHOULD BE CONSIDERED:

- CRT followed by CT should be favored
- Higher pCR rates expected
- Better tolerance and compliance vs postoperative treatment
- Better Disease related treatment failure and better Disease free survival
- Better expectations for nonoperative approaches

In case of suspected systemic disease - start CHEMO first!

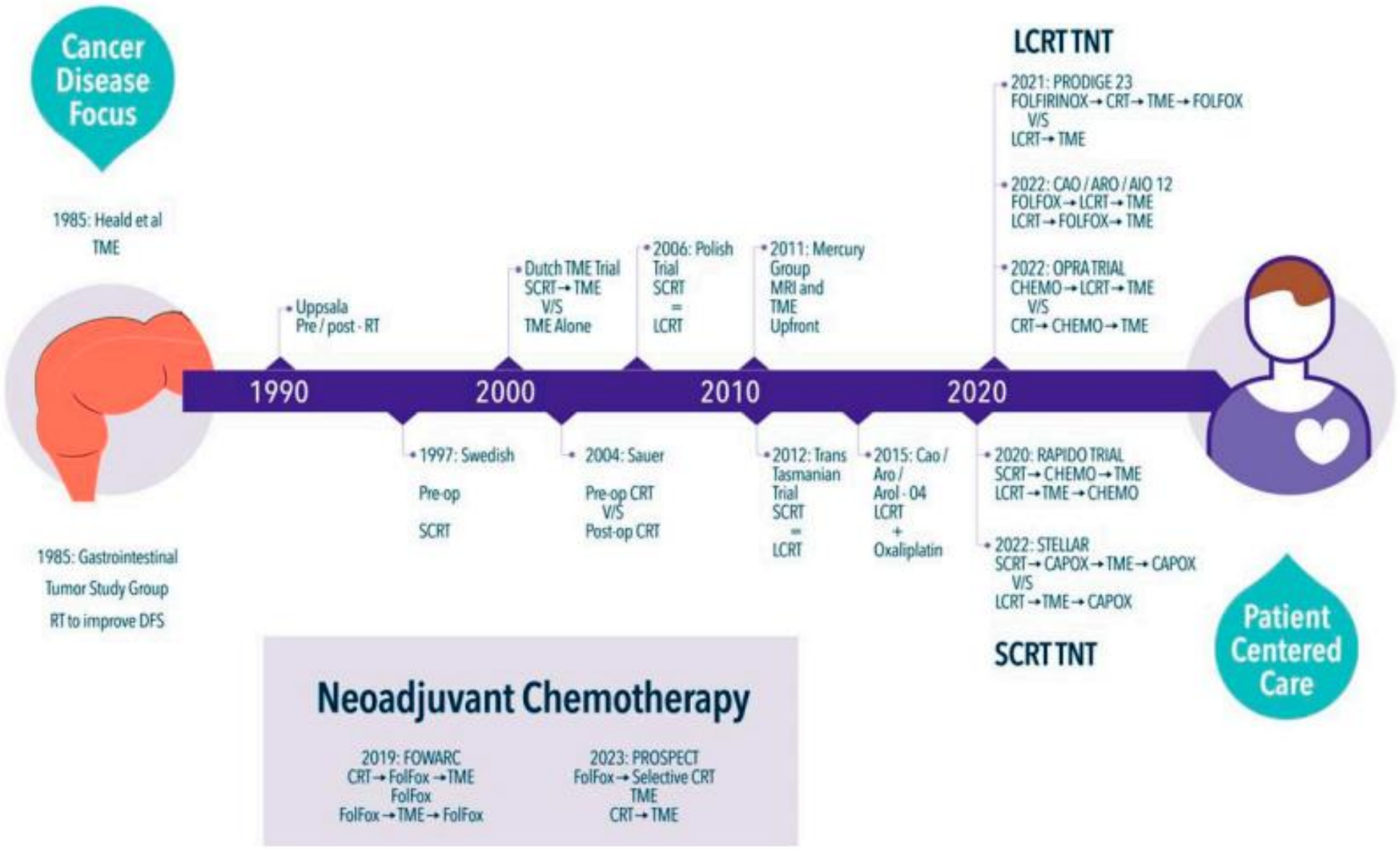
# Radiation - Free option:





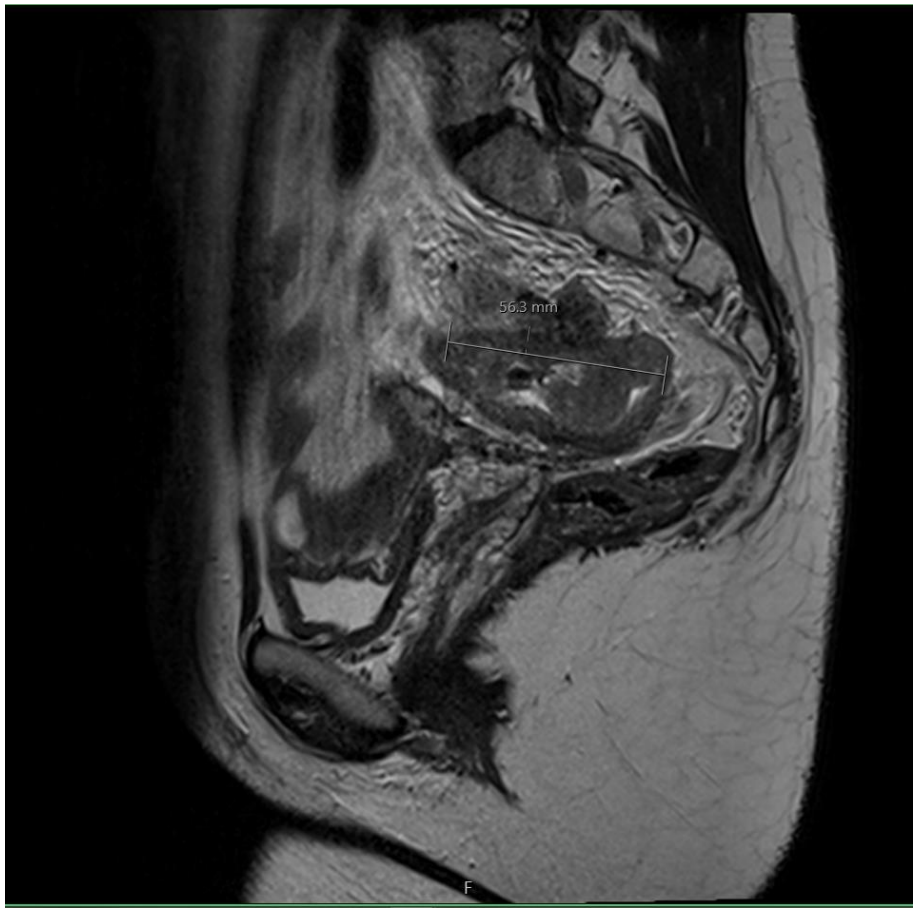


Schrag et al., NEJM 2023






Manriquez et al., Curr Onc 2024




**February 2024**

Baseline CT TAP, MRI pelvis, FDG PET

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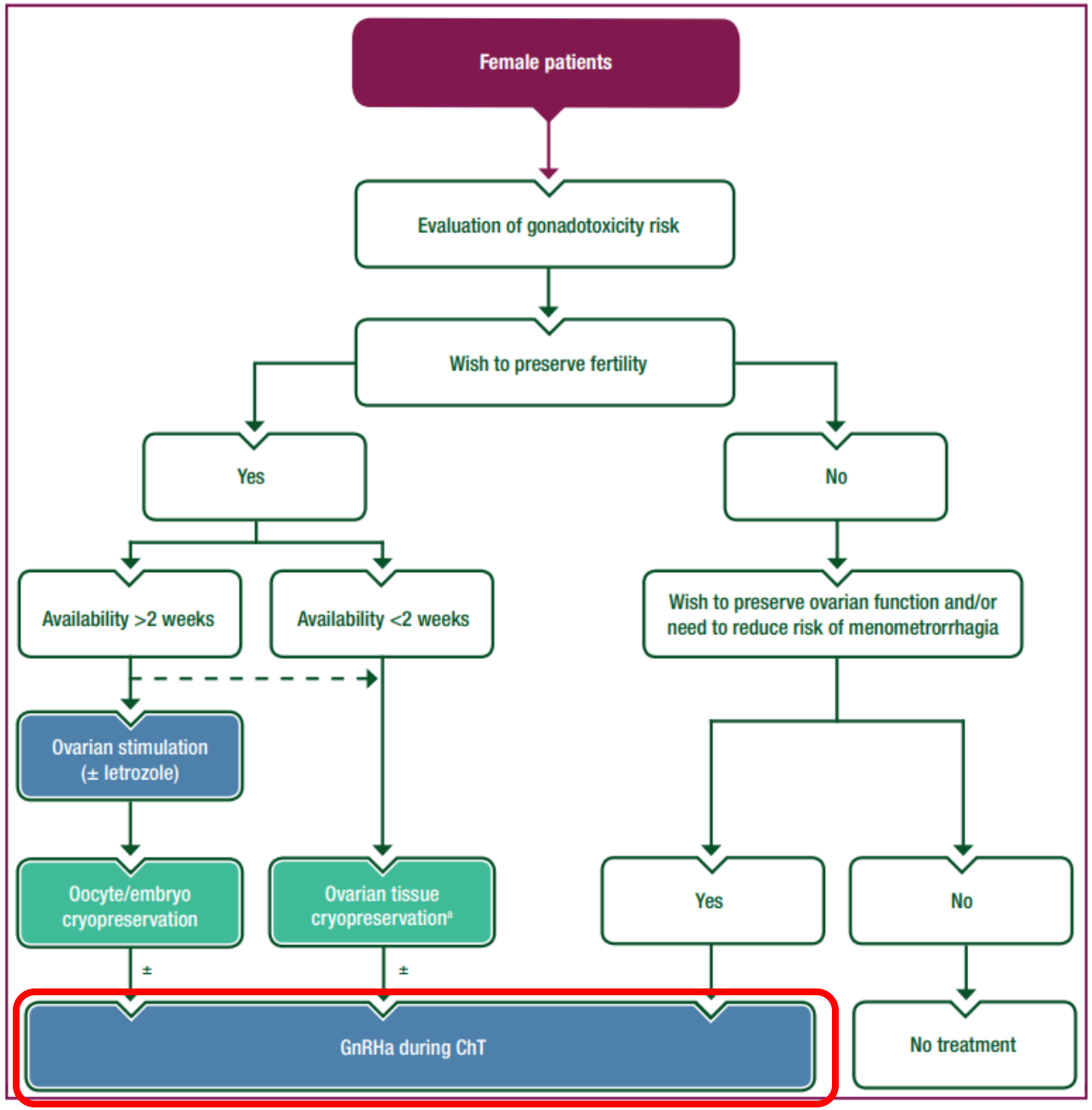
- Stage: **T3dN1 EMVI positive CRM at risk M0**.

MDT recommends upfront chemotherapy prior to consideration of CRT and surgery

**Completes egg harvesting for fertility preservation**




ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
Available online 22 September 2020
ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

## Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines†

M. Lambertini[1,2], F. A. Peccatori[3], I. Demeestere[4], F. Amant[5,6], C. Wyns[7], J.-B. Stukenborg[8], S. Paluch-Shimon[9], M. J. Halaska[10], C. Uzan[11], J. Meissner[12], M. von Wolff[13], R. A. Anderson[14] & K. Jordan[12], on behalf of the ESMO Guidelines Committee*

- Ovarian transposition should be considered in order to try to preserve ovarian function in women ≤40 years of age with an indication for pelvic RT [IV, A].
- Ovarian transposition should be carried out by experienced laparoscopists to minimise complications and maximise the chances of ovarian function preservation [IV, A].

# OVARIAN SUPPRESSION

**Available meta-analyses assessing the role of temporary ovarian suppression with GnRH-a during chemotherapy in cancer patients**

| Author(s), year (reference) | Disease type | No. of included studies (no. of RCTs) | No. of patients | Overall results |
|---|---|---|---|---|
| Clowse et al., 2009 | Autoimmune diseases, HL and NHL | 9 (2) | 366 | Protection for POI |
| Ben-Aharon et al., 2010 | Autoimmune diseases, breast cancer, HL and NHL | 16 (5) | 681 | Protection for POI (not in RCTs) |
| Kim et al., 2010 | Autoimmune diseases, breast cancer, HL and NHL | 11 (3) | 654 | Protection for POI |
| Bedaiwy et al., 2011 | Breast cancer, ovarian cancer, and HL | 6 (6) | 340 | Protection for POI (not for pregnancy) |
| Yang et al., 2013 | Breast cancer | 5 (5) | 528 | Protection for POI (not for pregnancy) |
| Wang et al., 2013 | Breast cancer | 7 (7) | 677 | Protection for POI |
| Zhang et al., 2013 | HL and NHL | 7 (3) | 434 | Protection for POI (not for pregnancy) |
| Sun et al., 2014 | Breast cancer, ovarian cancer, and HL | 8 (8) | 621 | Protection for POI (not for pregnancy) |
| Del Mastro et al., 2014 | Breast cancer, ovarian cancer, HL and NHL | 9 (9) | 765 | Protection for POI |
| Vitek et al., 2014 | Breast cancer (hormone receptor-negative only) | 4 (4) | 252 | No protection |
| Elgindy et al., 2015 | Breast cancer, ovarian cancer, HL and NHL | 10 (10) | 907 | No protection |
| Shen et al., 2015 | Breast cancer | 11 (11) | 1,062 | Protection for POI (not for pregnancy) |
| Lambertini et al., 2015 | Breast cancer | 12 (12) | 1,231 | Protection for POI (also for pregnancy) |
| Munhoz et al., 2016 | Breast cancer | 7 (7) | 856 | Protection for POI (also for pregnancy) |
| Silva et al., 2016 | Breast cancer | 7 (7)[a] | 1,002[a] | Protection for POI |
| Bai et al., 2017 | Breast cancer | 15 (15)[a] | 1,540[a] | Protection for POI (also for pregnancy) |
| Senra et al., 2018 | Breast cancer, HL, and NHL | 13 (13) | 1,208 | Protection for POI (also for pregnancy) |
| Hickman et al., 2018 | Breast cancer, ovarian cancer, HL, and NHL | 10 (10) | 1,051 | Protection for POI |
| Lambertini et al., 2018 | Breast cancer | 5 (5)[b] | 873 | Protection for POI (also for pregnancy) |
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*Note:* Updated and modified from Lambertini et al. (103).GnRH-a = gonadotropin-releasing hormone agonist; HL = Hodgkin lymphoma; NHL= non-Hodgkin lymphoma; POI = premature ovarian insufficiency; RCT = randomized controlled trial.

[a] Data from the two publications of the PROMISE-GIM6 trial, by Del Mastro et al. (40) and Lambertini et al. (81), were considered twice instead of as from the same study.

[b] Based on individual patient-level data.

*Dolmans. GnRH agonists and fertility preservation. Fertil Steril 2020.*

# OVARIAN SUPPRESSION

Lack of evidence for CRC!

**Available meta-analyses assessing the role of temporary ovarian suppression with GnRH-a during chemoti**

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|---|---|---|---|---|
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[b] Based on individual patient-level data.

*Dolmans. GnRH agonists and fertility preservation. Fertil Steril 2020.*

# Neoadjuvant treatment

**March – May 2024**

Receives 4 x neoadjuvant CAPOX

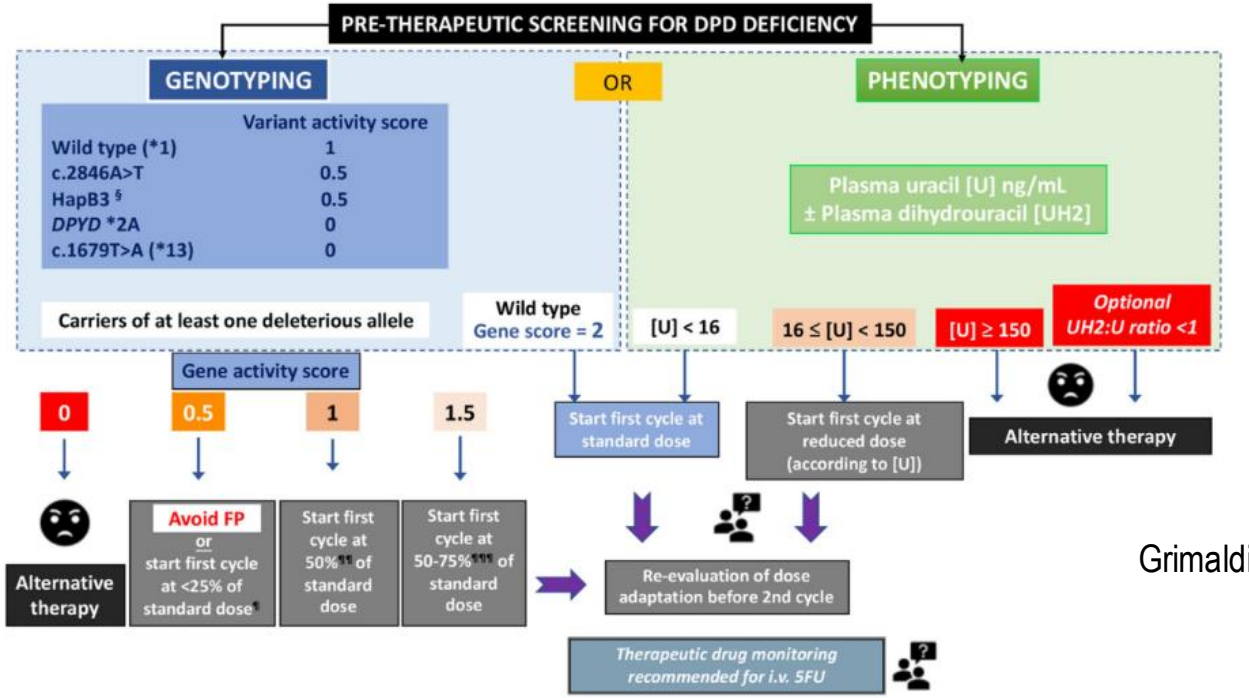
Starts with 50% dose reduction capecitabine due to DPYD variant of unknown significance

Toxicities

- During C1 admitted with G2 diarrhoea ?possible colitis. CT showed oedema in proximal and descending colon. Capecitabine paused and symptoms resolved.
- C2-C4 continues with 50% dose reduction without further occurrence.
- G1 peripheral sensory neuropathy, G1 fatigue, G2 nausea

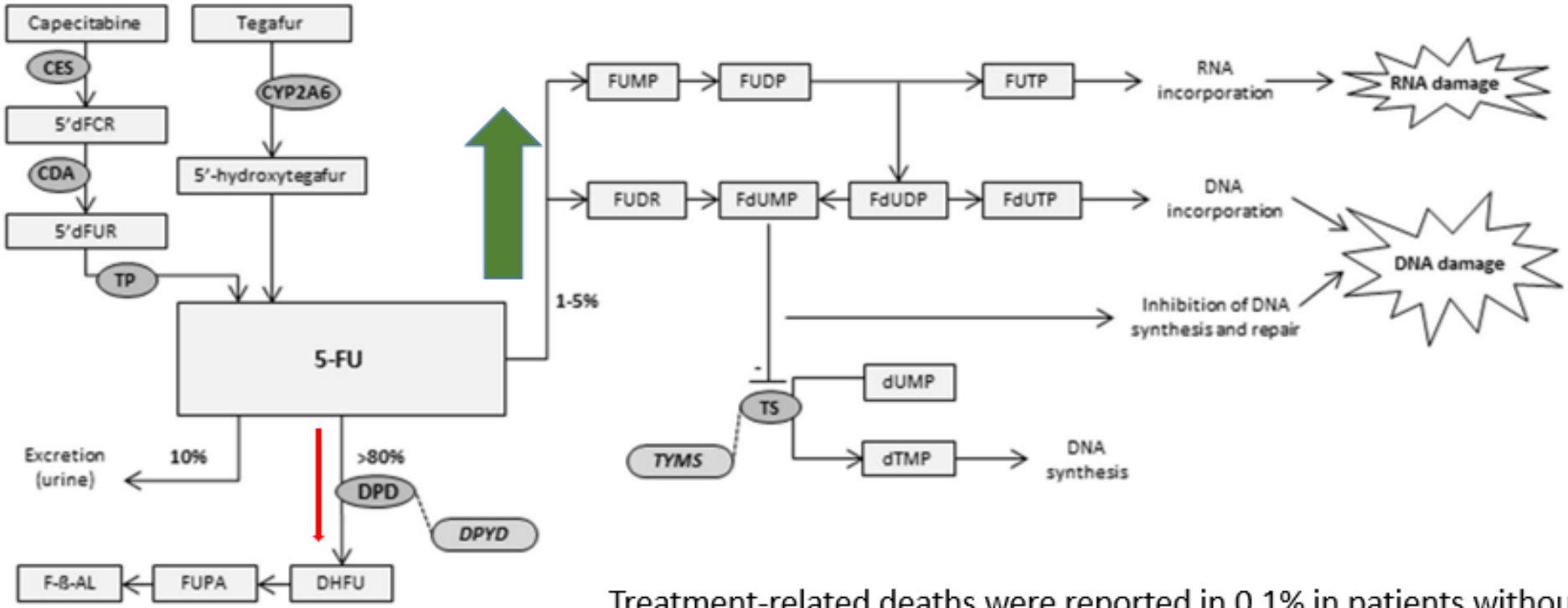
# Optimize 5FU therapy

- Personalized approach by improving dosing accuracy and reducing toxicity in 5-FU treatments.
- Pre therapeutic screening -DPYD genotyping/ (DPD phenotyping)
- Therapeutic drug monitoring- TDM




Grimaldi et al EJC 2021

# DPD DEFICIENCY




Treatment-related deaths were reported in 0.1% in patients without DPYD variants and in 2.3% of those with known DPYD variants (95% CI, 1.3%–3.9%)

Partial DPD Deficiency: Affects approximately 3–8% of individuals
0.1–0.2% has a complete DPD enzyme deficiency



Carin A *et al*, European Journal of Human Genetics,2020

# Nomenclature of DPYD

| Legacy name | rsID | Variant (NM_000110.4) | protein nomenclature | Allele frequency | Allele activity score |
|---|---|---|---|---|---|
| *2A | rs3918290 | c.1905+1G>A | Not changed | 0.3-0.5% | 0 |
| *13 | rs5588062 | c.1679T>G | p.I560S | 0.08% | 0 |
| N/A | rs67676798 | c.28464A>T | p.D949V | 0.37-1% | 0.5 |
| HapB3 | rs56038477<br>rs75017182 | c.1129-5923C > G<br>c.1236G >A | Not changed | 0.06-**2.4**% | 0.5 |

Over 1598 sequence variants in the DPYD gene have been identified

- An individual can have **more than two variants**.
- CPIC guideline uses a **DPD activity score**.

- **Normal function variants**: Assigned an activity value of **1**.
- **Nonfunctional variants**: Assigned an activity value of **0**.
- **Decreased activity variants**: Assigned an activity value of **0.5**.
- The **two lowest scoring variants** are used to calculate the **activity score**.

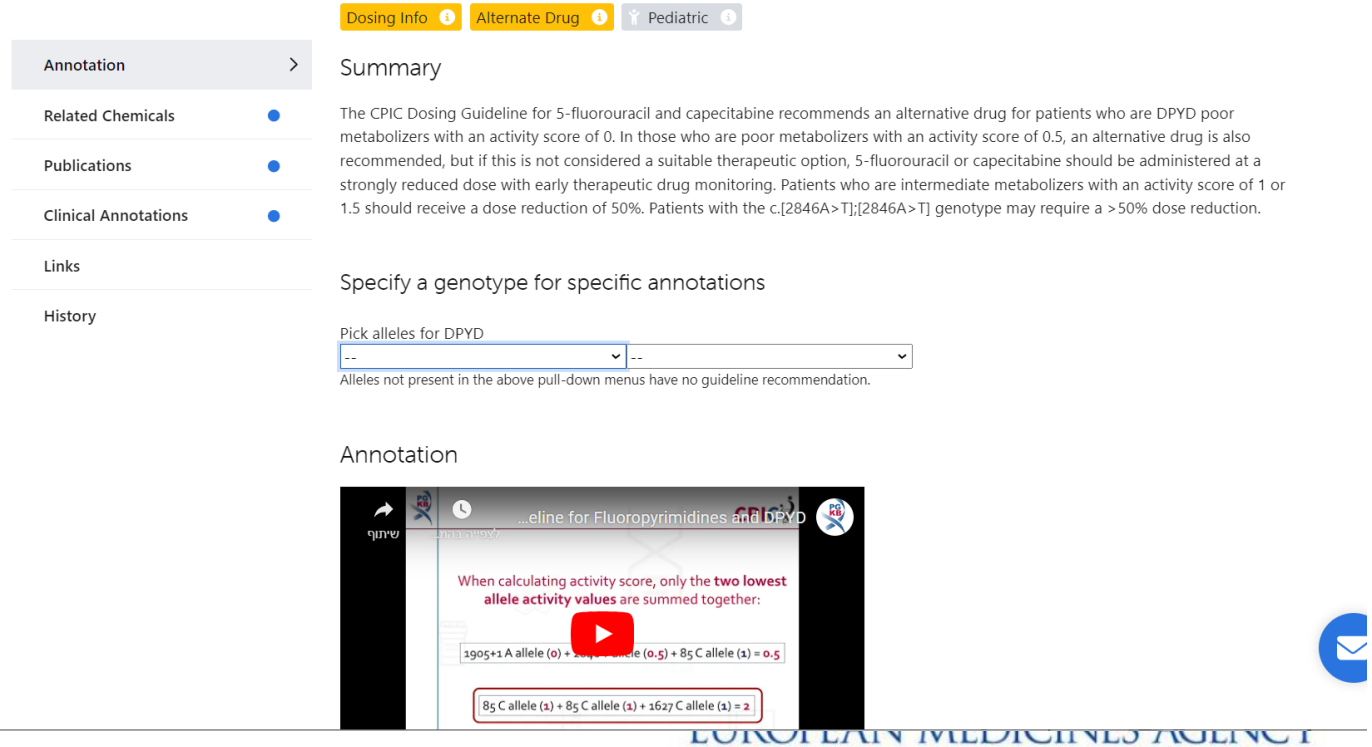
**Table 2 Recommended dosing of fluoropyrimidines[a] by DPD phenotype**

| Phenotype | Implications for phenotypic measures | Dosing recommendations | Classification of recommendations[b] |
|---|---|---|---|
| *DPYD* normal metabolizer | Normal DPD activity and "normal" risk for fluoropyrimidine toxicity. | Based on genotype, there is no indication to change dose or therapy. Use label-recommended dosage and administration. | Strong |
| *DPYD* intermediate metabolizer | Decreased DPD activity (leukocyte DPD activity at 30% to 70% that of the normal population) and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs. | Reduce starting dose based on activity score followed by titration of dose based on toxicity[c] or therapeutic drug monitoring (if available).<br>**Activity score 1:** Reduce dose by 50%<br>**Activity score 1.5:** Reduce dose by 25% to 50% | **Activity score 1:** Strong<br>**Activity score 1.5:** Moderate |
| *DPYD* poor metabolizer | Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs. | **Activity score 0.5:** Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. In the event, based on clinical advice, alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dose[d] with early therapeutic drug monitoring.[e]<br>**Activity score 0:** Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. | Strong |

# Testing for DPYD recommendation

**EMA- On 13 March 2020, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recommended Testing DPD before starting treatment fluoropyrimidines. Phenotyping dihydrouracil to uracil (UH2/U) ratio in plasma as surrogate marker for 5-FUH2/5-FU or genotyping for DPYD risk variant alleles**

https://www.pharmgkb.org/guidelineAnnotation/PA166109594

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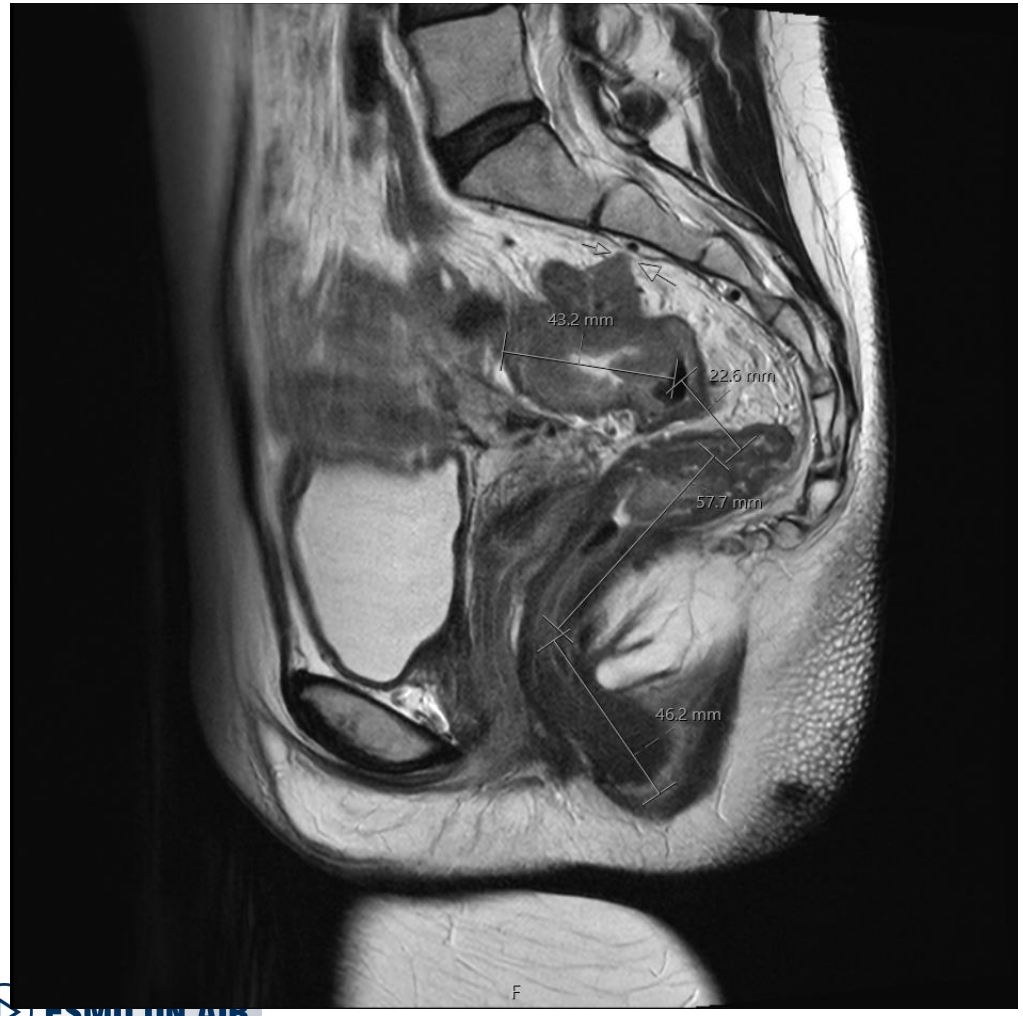
# Post neoadjuvant CAPOX x4




**May 2024**

CT TAP

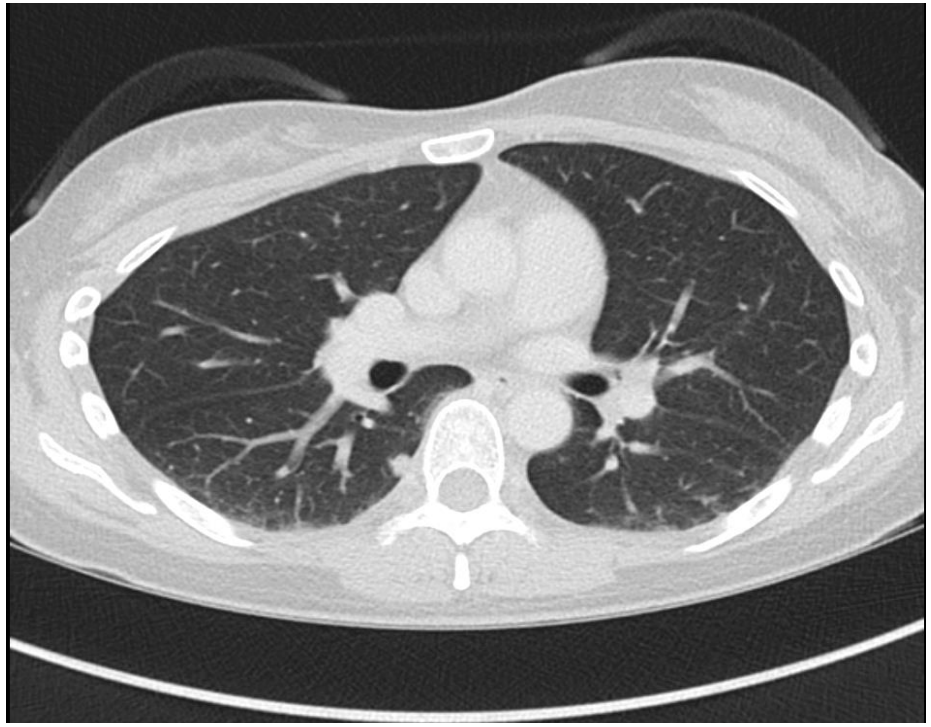
- Some response to primary and associated node on CT
- Indeterminate 1cm right subpleural lung nodule (increased from 0.4cm at baseline)

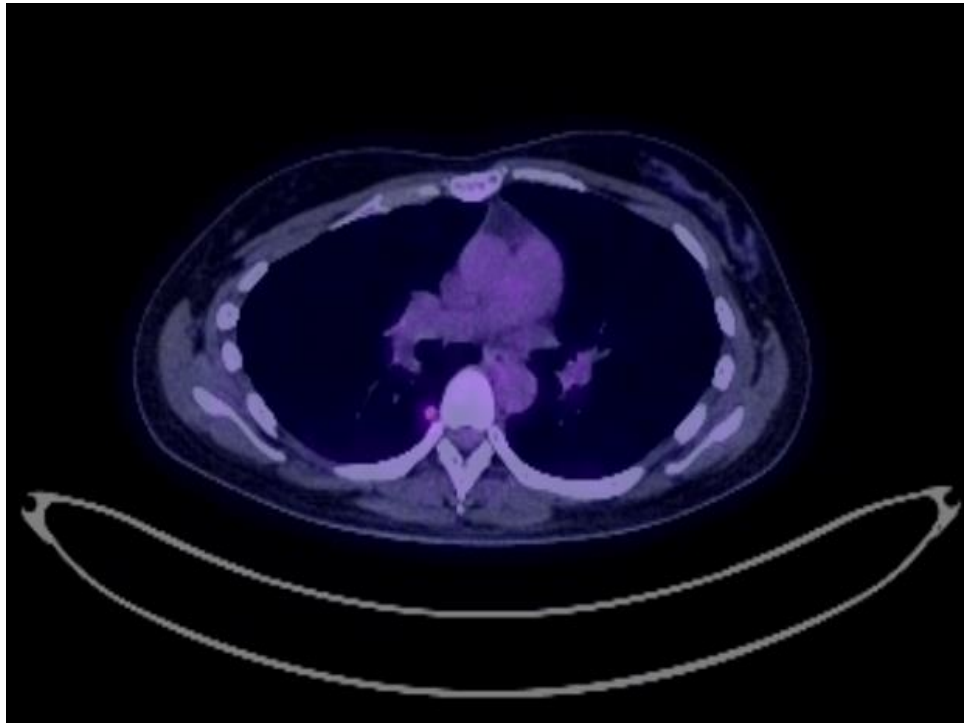
MRI pelvis

- Partial response tumour 56mm → 43mm
- ymr T3c N1c, CRM+, EMVI-
- TRG 4 suggesting residual active disease

CEA <1

# New solitary lung metastasis





**June 2024**

PET CT shows right subpleural lung nodule is hypermetabolic compared to baseline PET CT.

# Neoadjuvant treatment

**June 2024 MDT**

1. CRT to primary before surgery.
2. Ablation of solitary lung metastasis.
3. For 6 months total of CAPOX (4 x further CAPOX) post surgery

**July to August 2024**

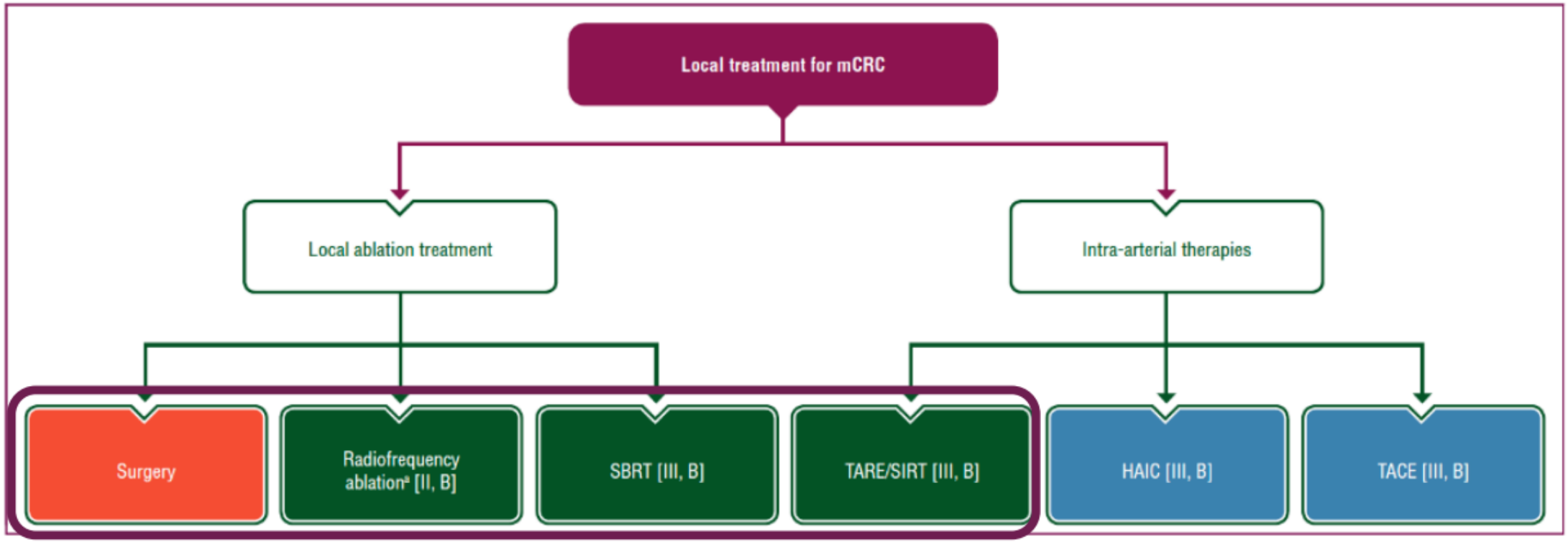
Receives radiation 32Gy/25 fractions to the rectum concurrent with capecitabine.

Cryoablation to right subpleural lung nodule 10/07/2024

G1 fatigue, G1 nausea, poor appetite

Struggling emotionally with treatment, referred to psychological support team

# Oligometastatic Colorectal Cancer:



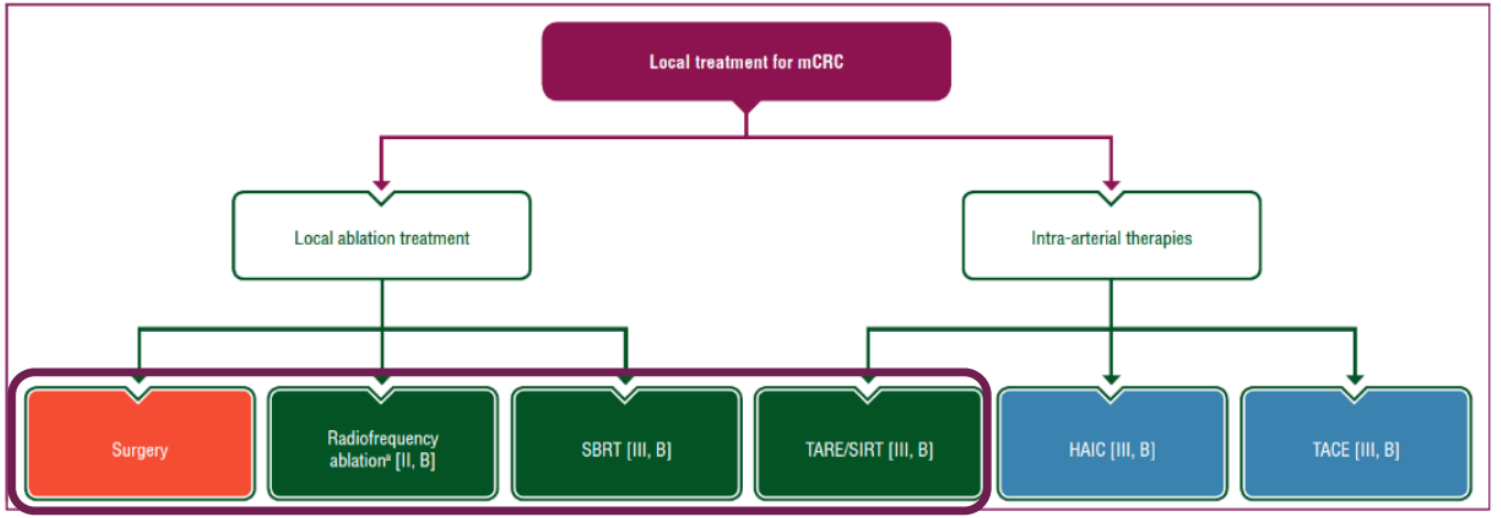

SBRT, stereotactic body radiotherapy, TARE, transarterial radioembolisation, SIRT, selective internal radiotherapy; TA, thermal ablation, HAIC, hepatic arterial infusion chemotherapy; TACE, transarterial chemoembolisation



Cervantes A. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023 Jan;34(1):10-32

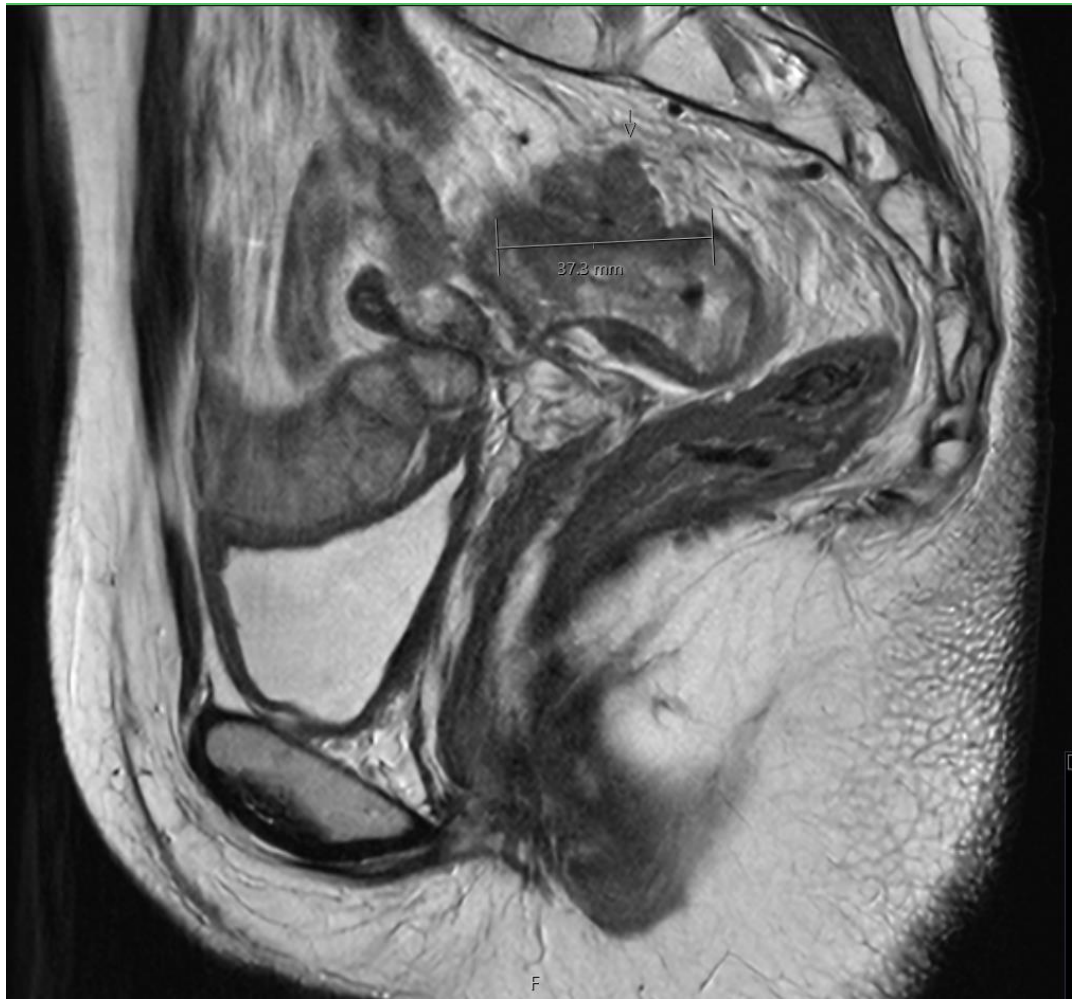
# Local Treatment for OMD according to CPG

- The majority of OMD studies were conducted in the setting of liver metastases.
- In patients with lung-only metastases or OMD including lung lesions, thermal ablation may be considered along with resection, according to tumour size, number, location, the extent of lung parenchyma loss, comorbidity or other factors [III, B].




SBRT, stereotactic body radiotherapy, TARE, transarterial radioembolisation, SIRT, selective internal radiotherapy; TA, thermal ablation, HAIC, hepatic arterial infusion chemotherapy; TACE, transarterial chemoembolisation

# Post neoadjuvant CRT




**September 2024**

CT TAP, MRI pelvis

- Further partial response but residual active tumour signal remains (mainly extraluminal)
- Posterior margin remains involved.
- Treated lung appearances, no new sites of disease

# Surgery & adjuvant chemotherapy

**October 2024**

Robotically assisted anterior resection with enbloc pre-sacral fascia excision and defunctioning ileostomy

Final histology: ypT3 N1a (1/47) L1 V1 Pn1 R0.

No post-operative complications

**Dec 2024 – Feb 2025**

Completes 4 x adjuvant CAPOX (8 cycles total)

CEA <1 prior to starting

Grade 2 nausea and vomiting, and oxaliplatin extravasation after C5. Improved with 25% dose reduction to oxaliplatin for C6-8.

Referred to genetics (delayed referral) and awaiting consultation

# Surveillance

**19 March:** CT scan no evidence of recurrence. CEA <1

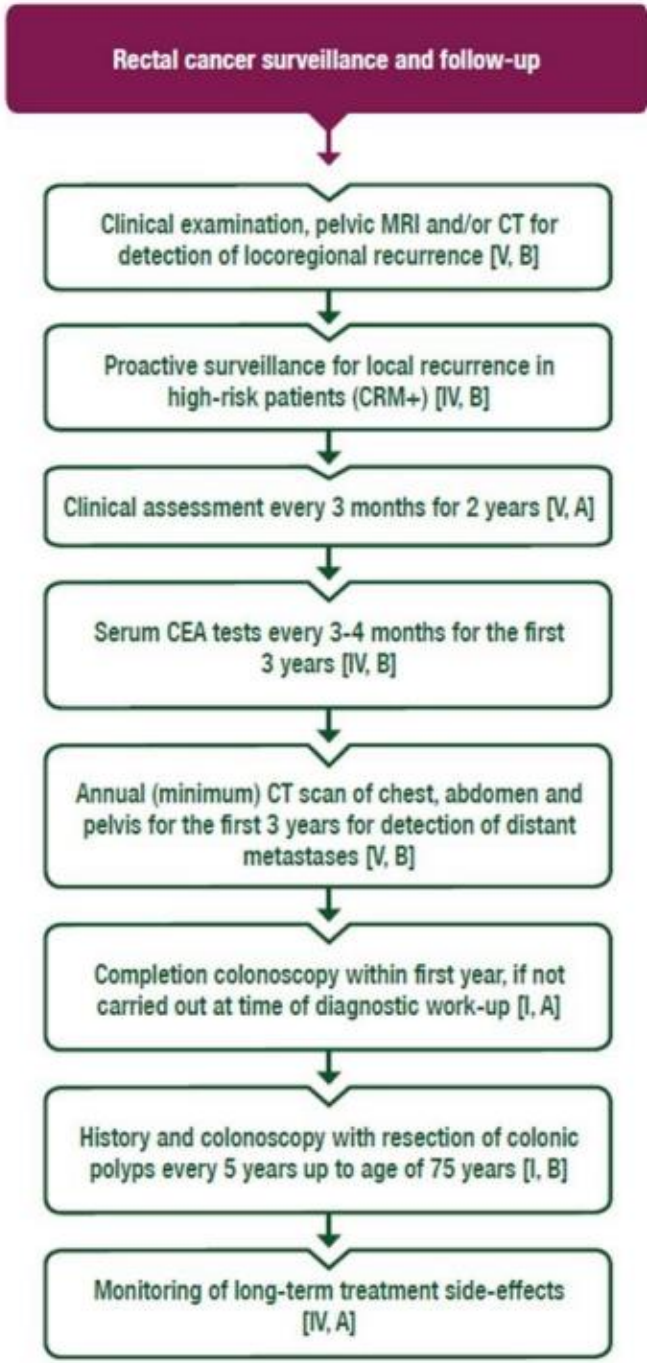
**24 March 2025:**

Flexible sigmoidoscopy shows colorectal anastomosis intact and patent.

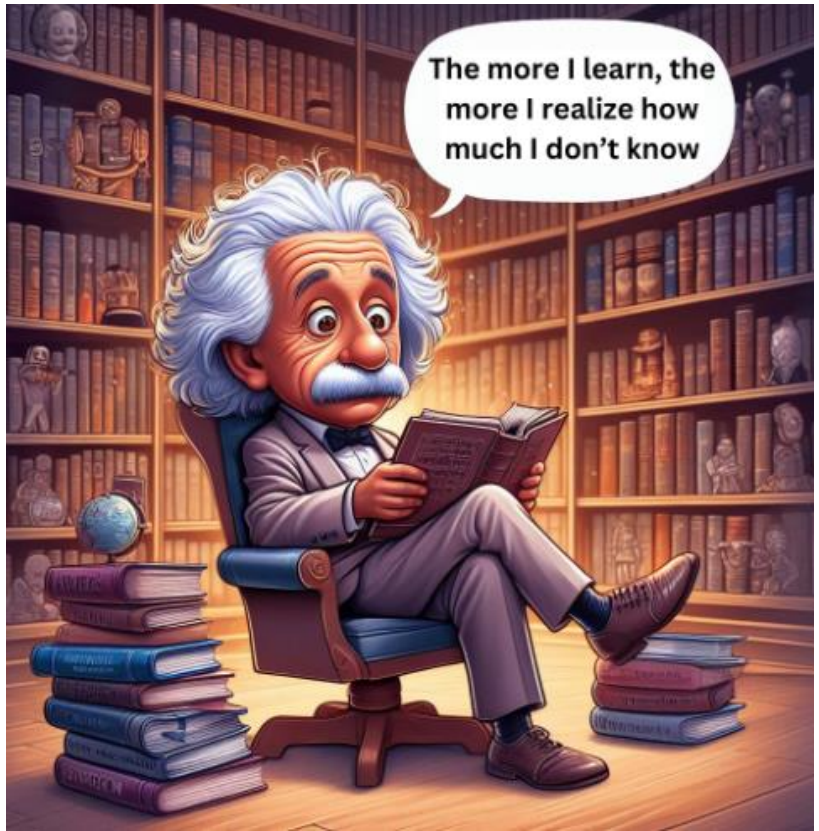
Undergoes Ileostomy reversal

- Bowels initially slow to open but now loose and frequent
- Requiring dietician support
- Minimal abdominal pain

**4 April 2025:** Follow up consultation. Continues surveillance with next review in 3 months which will be 1 year post lung ablation.


Rectal cancer surveillance and follow-up
Clinical examination, pelvic MRI and/or CT for detection of locoregional recurrence [V, B]
Proactive surveillance for local recurrence in high-risk patients (CRM+) [IV, B]
Clinical assessment every 3 months for 2 years [V, A]
Serum CEA tests every 3-4 months for the first 3 years [IV, B]
Annual (minimum) CT scan of chest, abdomen and pelvis for the first 3 years for detection of distant metastases [V, B]
Completion colonoscopy within first year, if not carried out at time of diagnostic work-up [I, A]
History and colonoscopy with resection of colonic polyps every 5 years up to age of 75 years [I, B]
Monitoring of long-term treatment side-effects [IV, A]

ESMO ON AIR




# *Thank you*

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EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

ESMO ON AIR

# ESMO Guidelines Webinar – Rectal cancer

**Gabor Liposits MD, PhD**
Innlandet Hospital Trust
Norway

30 April 2025

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

# Declaration of interest

**Gabor Liposits, MD, PhD**

**Financial interests**:

Honoraria: Danone, Servier, MSD
Congress support (travel and accommodation): Servier
Advisory board: MSD

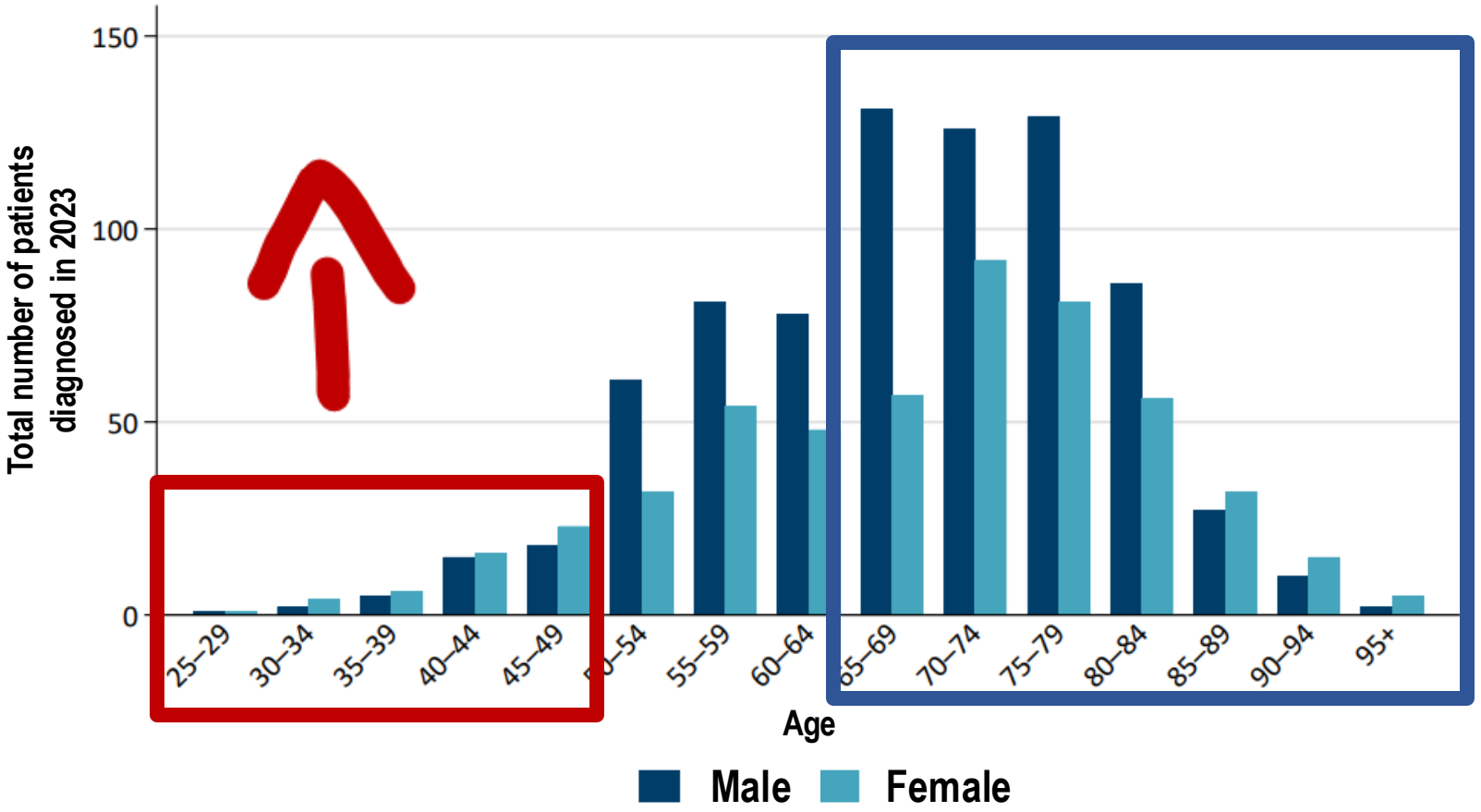
**Non-financial interests**:

ESMO COTF member
ESMO DCTF member
SIOG Board member

# Practice perspectives

## On behalf of the ESMO Community Oncologist Task Force

# Epidemiology – rectal cancer incidence in Norway




Median age >70 years

70% of patients ≥65 years

Early-onset colorectal cancer (age: 25-49)

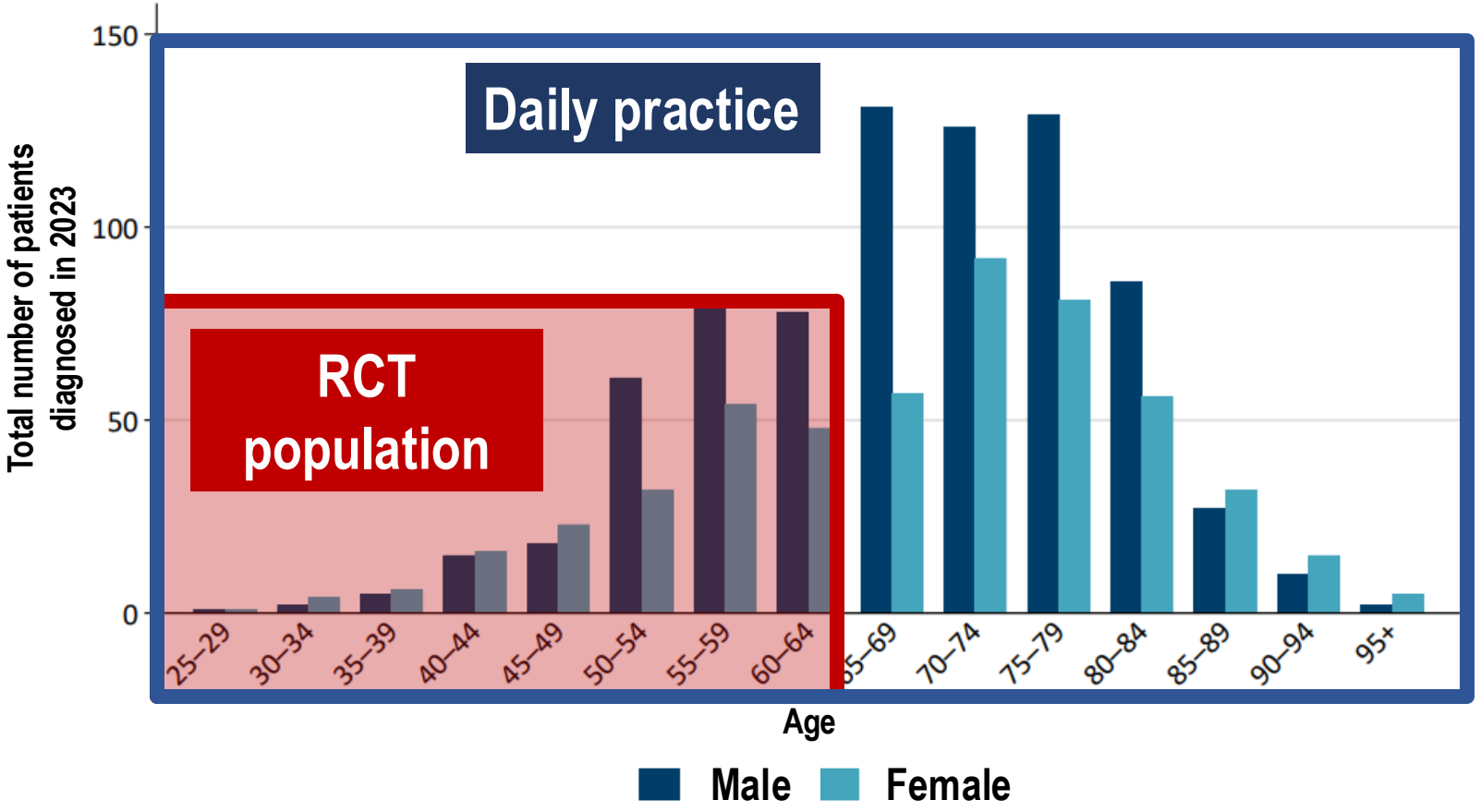
By 2030, 23% of rectal cancers will occur in adults <50 years



https://www.kreftregisteret.no/globalassets/publikasjoner-og-rapporter/arsrapporter/publisert-2024/arsrapport-2023-nasjonalt-kvalitetsregister-for-tykk--og-endetarmskreft.pdf
The rise in early-onset colorectal cancer: now a global issue, The Lancet Gastroenterology & Hepatology, 2025

# Evidence base vs clinical practice

## Significant gap in knowledge exists regarding the optimal management in unselected patients




Cancer is a disease of aging

Most patients in daily practice are not represented in RCTs

RCTs include young and fit adults

Unselected patients experience less benefit and more toxicities



https://www.kreftregisteret.no/globalassets/publikasjoner-og-rapporter/arsrapporter/publisert-2024/arsrapport-2023-nasjonalt-kvalitetsregister-for-tykk--og-endetarmskreft.pdf

# Median age and performance status in RCTs testing TNT

## Younger and fit population = clinical trial population

| RCT | N | Median age/ECOG | Neoadjuvant approach | Adjuvant chemotherapy |
|---|---|---|---|---|
| POLISH II | 261 | 60 / 0-1 | RT + FOLFOX x3 | |
| | 254 | 60 / 0-1 | CRT (FPOx) | |
| RAPIDO | 462 | 62 / 0-1 | RT + CapOx x 6 or FOLFOX x9 | |
| | 450 | 62 / 0-1 | CRT | CapOx x 8 or FOLFOX x 12 |
| STELLAR | 302 | 55 / 0-1 | RT + CapOx x 4 | CapOx x 2 |
| | 297 | 56 / 0-1 | CRT | CapOx x 6 |
| PRODIGE 23 | 231 | 61 / 0-1 | FOLFIRINOX x 6 ⇨ CRT | FOLFOX x 6 or Cap x 4 |
| | 230 | 62 / 0-1 | CRT | FOLFOX x 12 or Cap x 8 |

# Precision medicine – right treatment to the right patient

## IN-DEPTH CHARACTERIZATION OF THE TUMOR AND THE PATIENT


Diagnostic work-up

Early diagnosis – optimal age cut-off to start screening? Personalized strategies?

Delayed diagnosis in young patients – rectal cancer may occur in the 20s and 30s as well

Reflections:

Routine utilization of PET-CT is not recommended – limited added value (resource optimalization)

Normal CEA does not rule out locoregional advanced or metastatic disease – dynamics of CEA

DPD testing is essential to avoid serious/life threatening adverse events related to 5FU/capecitabine

# Precision medicine – right treatment to the right patient

## IN-DEPTH CHARACTERIZATION OF THE TUMOR AND THE PATIENT


Patient-related factors and preferences may substantially differ in young vs older adults

# Functional status - adults are heterogenous

Long life expectancy

High level of functioning

No significant comorbidities

Normal organ function

Available for intensive treatment

Short(er) life expectancy

Low level of functioning

Significant comorbidities

Impaired organ function

Geriatric syndromes

**Fit and young patients**
**Standard of care**
**Focus on survival**

**Vulnerable – personalized strategies**
**Balancing survival and QoL**

**Frail – best supportive care**
**Focus on quality of life**

# Issues and considerations in young and fit patients

Life-style factors – obesity, dietary habits, alcohol and smoking, sedentary lifestyle

(Colo)rectal cancer might be present in adults with healthy-lifestyle as well – the role of microbiome?

Genetic counseling is recommended < 50 years

Focus on fertility preservation and issues related to chemotherapy/pelvic radiotherapy

Timely access to fertility preservation counseling and oocyte/sperm cryopreservation might be limited

Patient preferences – survival, often willing to accept more toxicities

Shared decision-making

Long-term toxicities - CIPN, chronic pain, bowel disfunction, sexual functioning, fatigue, cognitive issues

Survivorship issues – QoL, psychological burden, increased risk for secondary cancer

# The right approach to vulnerable/older patients

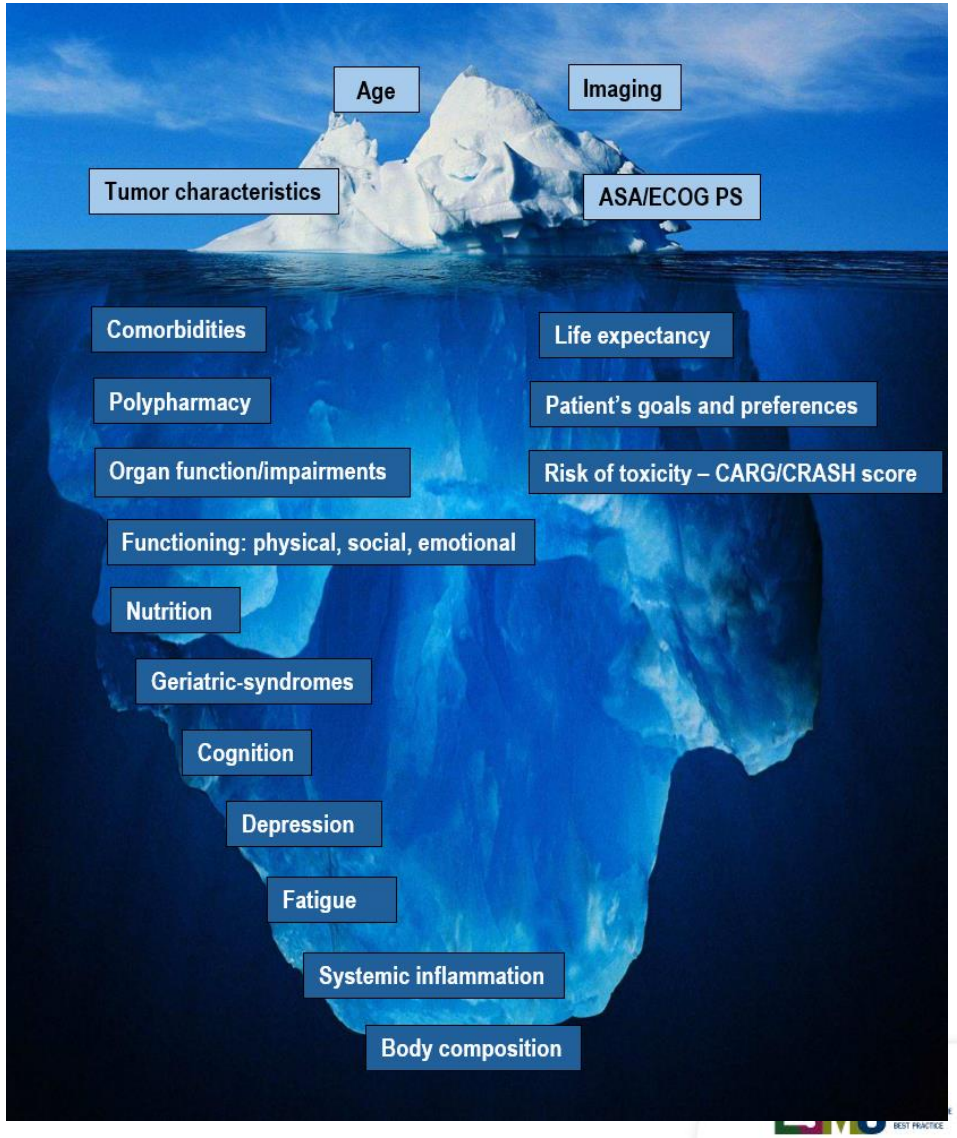
PATIENT

Geriatric screening/assessment

Aging is the strongest non-modifiable risk factor for cancer

Most patients are older

Patients-centered endpoints vs survival

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ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

REVIEW

Adequate assessment yields appropriate care—the role of geriatric assessment and management in older adults with cancer: a position paper from the ESMO/SIOG Cancer in the Elderly Working Group

Loh et al, ESMO Open, 2024

# Take aways

Rectal cancer may occur in young age as well

Focus should be on symptoms and low threshold for referral to coloscopy regardless of age

Coordinated resource intensive multidisciplinary effort foregoes optimally in high-volume centers

High quality radiology, pathology, surgery, radiotherapy, medical oncology, and geriatrics are crucial

In-depth characterization of the patient is also essential part of the strategy

Fit patients are available for intensive treatment, vulnerable adults often need personalized strategies

Patient preferences – shared decision-making

Management of chronic toxicities and survivorship issues need long-term follow-up and resources