Maastricht UMC+

COLOSOS
COLOrectal and Surgical Oncology Symposium

Where does evidence stand?
Non-operative management strategies

Geerard Beets, surgeon
Maastricht University

Netherlands Cancer Institute
Amsterdam
The Netherlands

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

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No disclosures

Evidence - Guidelines

“Learn the rules like a pro, so you can break them like an artist”

Picasso


Oncological outcome
Functional outcome

What is important for patients?

Choice based conjoint experiment

- Patients highly value QoL and avoiding a stoma
- Apparently more than their doctors

	Patients (n=94)		Clinicians (n=128)	
	colostomy	24	worries about cancer recurrence	31
	faecal incontinence	20	fecal incontinence	21
	urinary dysfunction	20	sexual dysfunction	15
	worries about cancer recurrence	18	urinary dysfunction	12
	sexual dysfunction	11	colostomy	11
	to live longer	6	to live longer	10

Van der Valk, 2020 EJSO

Organ preservation – Watch & Wait

Where do we come from?

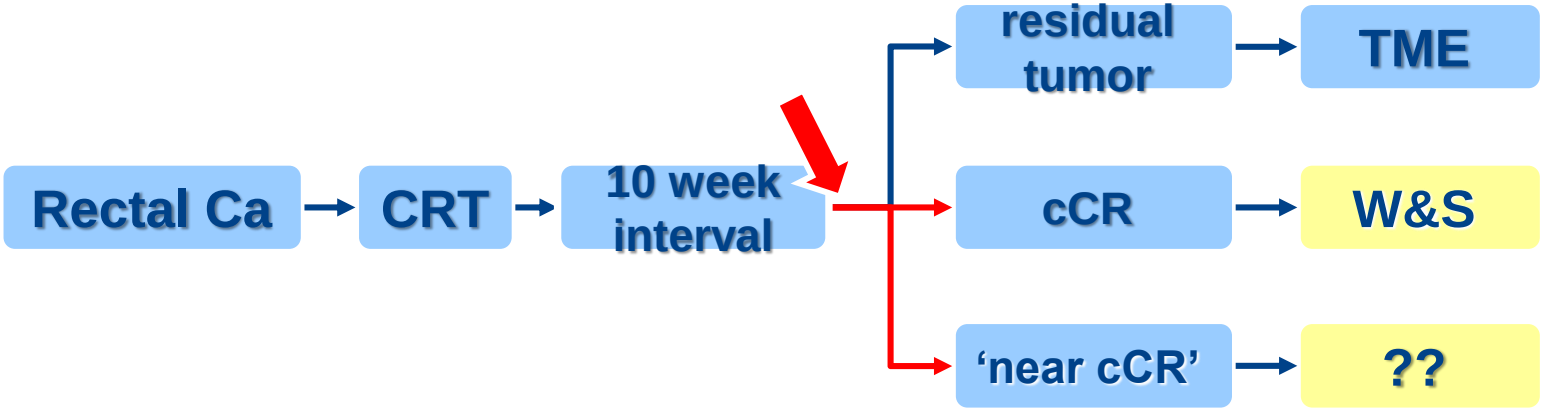
Large tumors

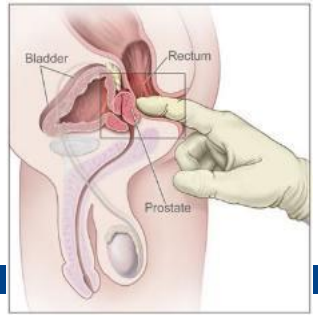
- ‘standard RTx’
- oncological indication
- **secondary** organ preservation
- Watch & Wait

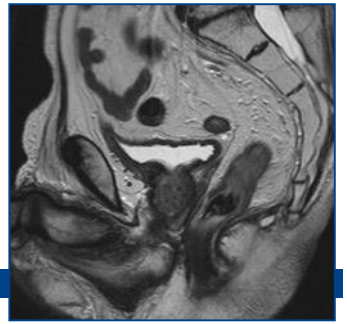
10-25%

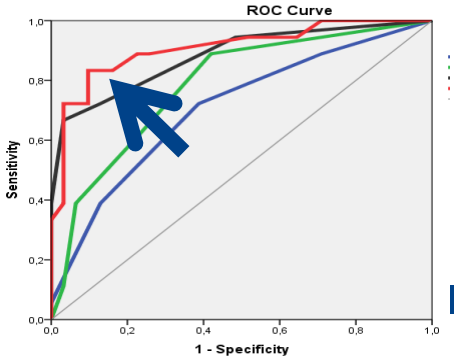
Organ Preservation

Secondary organ preservation



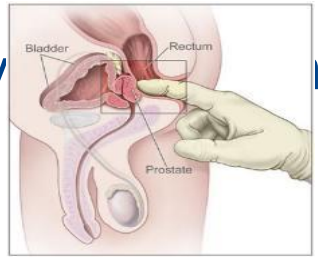


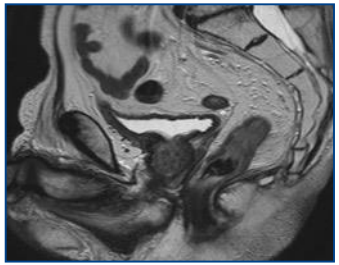




Response assessment and follow up

- Assessment of clinical complete respo
  - ≠100% accurate, ≈20% residual tumour
- Acceptable to wait when:
  - Persistence of tumour detected early
  - Delay

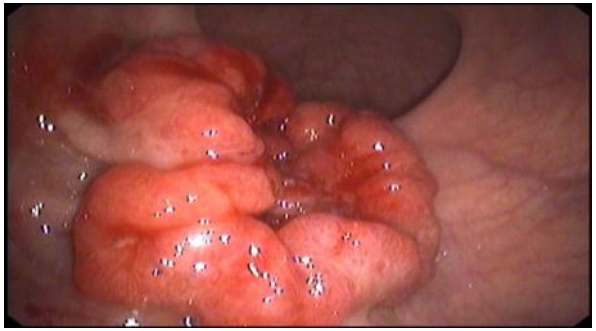




Year 1	Year 2	Year 3	Year 4	Year 5
4x MRI	2x MRI	1x MRI	1x MRI	1x MRI
4x Endoscopy	4x Endoscopy	2x Endoscopy	1x Endoscopy	1x Endoscopy

Endoscopic image complete response

Pre CRT

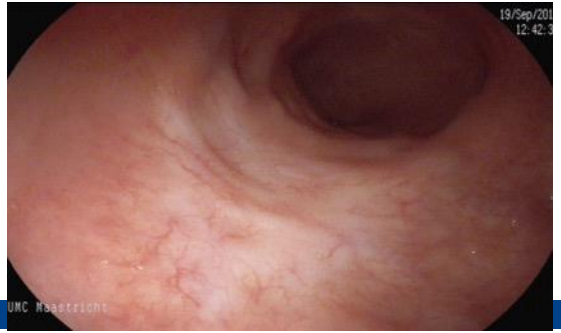


3 mths

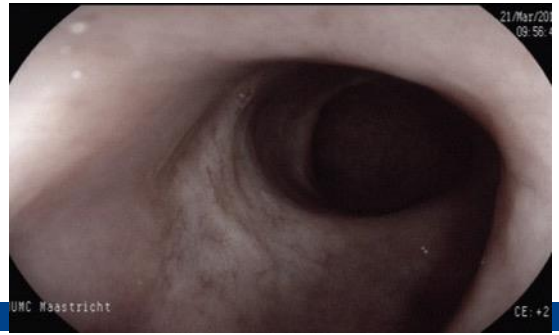
9 mths

14 mths

17 mths



23 mths



Watch & Wait

Operative Versus Nonoperative Treatment for Stage 0 Distal Rectal Cancer Following Chemoradiation Therapy

Long-term Results

VOLUME 29 · NUMBER 35 · DECEMBER 10 2011

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Wait-and-See Policy for Clinical Complete Chemoradiation for Rectal Cancer

ORIGINAL ARTICLE

Nonoperative Management of Rectal Cancer With Complete Response After Neoadjuvant Therapy

Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis

Andrew G Renehan, Lee Malcomson, Richard Emsley, Simon Gollins, Andrew M... Anthony Blower, Mark P Saunders, Malcolm S Wilson, Nigel Scott, Sarah T O'D...

High-dose chemoradiotherapy and watchful waiting for ...ancer: a prospective observational study

...arling, Frank S Jensen, Lars H Jensen, Jens C R Jørgensen, Jan Lindebjerg, Søren R Rafaelsen, Anders Jakobsen

Surveillance after neoadjuvant therapy in advanced rectal cancer ...complete clinical response can have comparable outcomes ...al excision

ARTICLE

Long-term Outcome of an Organ Preservation ... Treatment f...

Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study

Maxime J M van der Valk, Denise E Hilling, Esther Bastiaannet, Elma Meershoek-Klein Kranenbarg, Geerard L Beets, Nuno L Figueiredo, Angelita Habr-Gama, Rodrigo O Perez, Andrew G Renehan, Cornelis J H van de Velde, and the IWWD Consortium*

JAMA Oncology | Original Investigation

Assessment of a Watch-and-Wait Strategy for Rectal Cancer in Patients With a Complete Response After Neoadjuvant Therapy

J. Joshua Smith, MD, PhD; Paul Strombom, MD; Oliver S. Chow, MD; Campbell S. Roxburgh, MD, PhD; Patricio Lynn, MD; Anne Eaton, MS; Maria Widmar, MD; Karuna Ganesh, MD, PhD; Rona Yaeger, MD; Andrea Cercek, MD; Martin R. Weiser, MD; Garrett M. Nash, MD, MPH; Jose G. Guillem, MD, MPH; Larissa K. F. Temple, MD, MSc; Sree B. Chalasani, MD; James L. Fuqua, MD; Iva Petkovska, MD; Abraham J. Wu, MD; Marsha Reyngold, MD, PhD; Efsevia Vakiani, MD, PhD; Jinru Shia, MD; Neil H. Segal, MD, PhD; James D. Smith, MD, PhD; Christopher Crane, MD; Marc J. Gollub, MD; Mithat Gonen, PhD; Leonard B. Saltz, MD; Julio Garcia-Aguilar, MD, PhD; Philip B. Paty, MD

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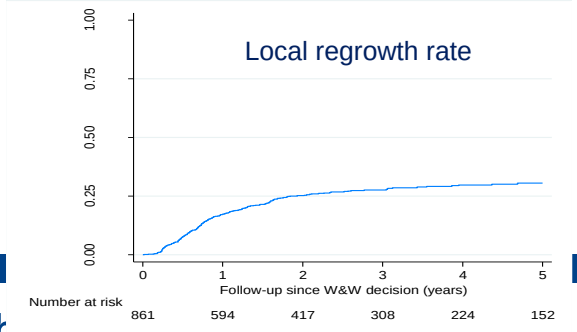
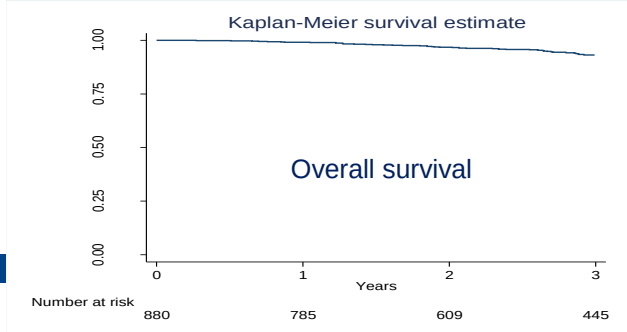
Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study

*Maxime J M van der Valk, Denise E Hilling, Esther Bastiaannet, Elma Meershoek-Klein Kranenbarg, Geerard L Beets, Nuno L Figueiredo, Angelita Habr-Gama, Rodrigo O Perez, Andrew G Renehan, Cornelis J H van de Velde, and the IWWD Consortium**

Vd Valk et al. Lancet 2018

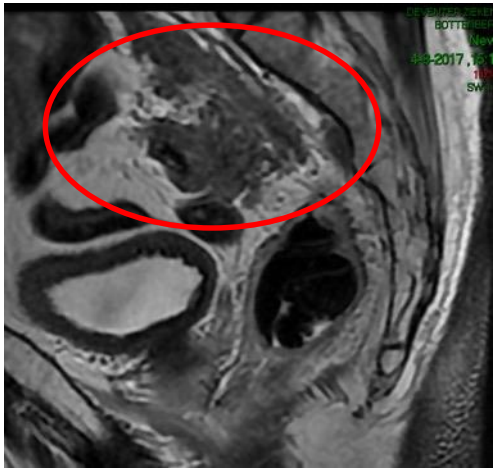
- 42 centers: 880 pts cCR, median FU 3.4 yrs
- 2yr local regrowth rate 25% (97% endoluminally)
- Overall Survival 3yr: 93.2%
- Cause of death: rectal cancer 4%

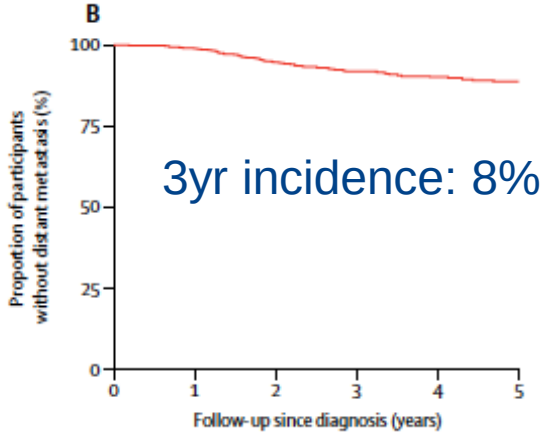




Potential risks organ preservation?

- Locally unsalvageable regrowth: 1%
- Distant metastases?
  - my own educated guess: 1-2%??





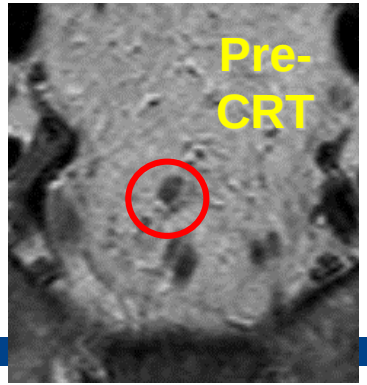
3yr incidence: 8%

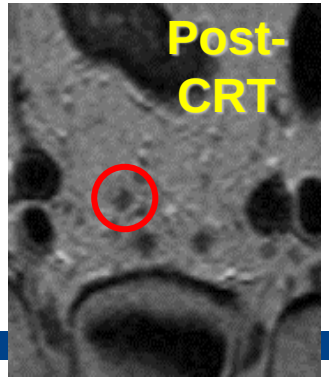
No regrowth	5%
Regrowth	18%

Vd Valk et al. Lancet 2018

Luminal - nodal regrowth

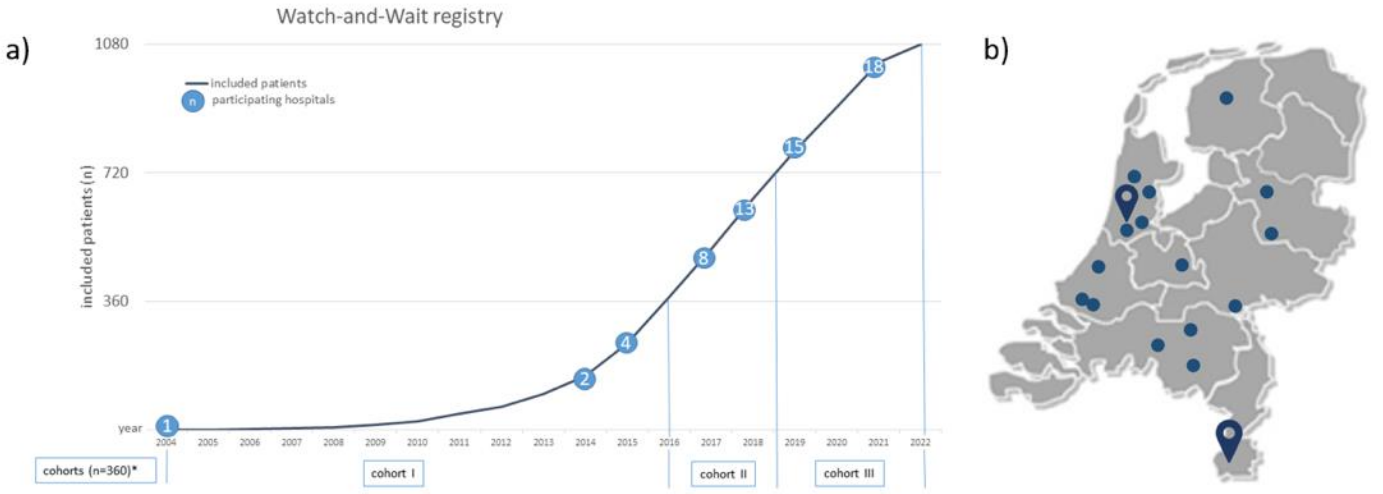
treatment: straightforward





Wider implementation safe?

- Prospective national implementation study
- Regional expert centers. training-supervision
- All data in prospective database. N>1000

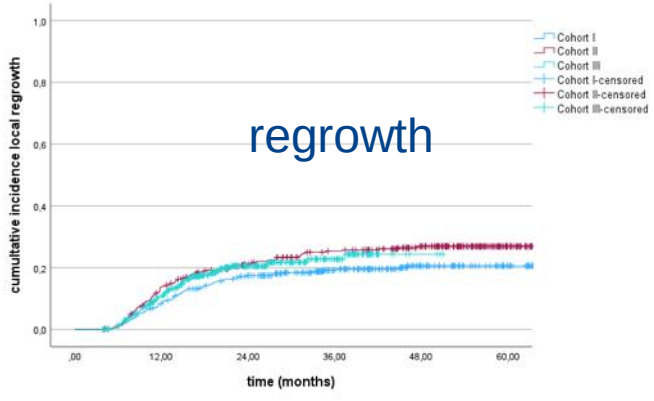


Geubels et al. 2024 BJS accepted

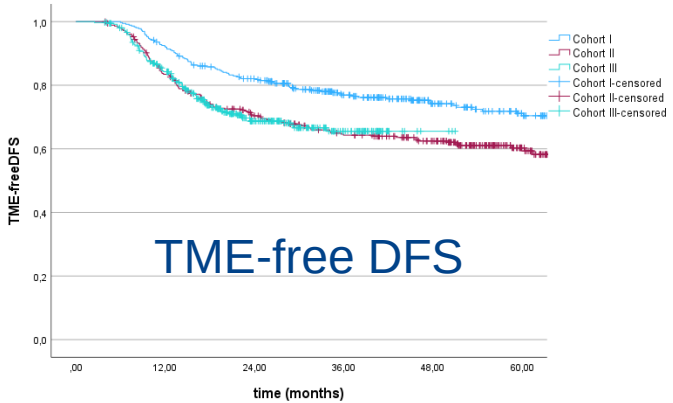
National Dutch registry
Watch & Wait
Rectal cancer

Dutch cohort > 1000 pts

- 3-yr local regrowth rate 22.5%
- 3-yr organ preservation rate 75.5%
- 3-yr distant metastases rate 10%
- 5-yr overall survival 92.7%



regrowth

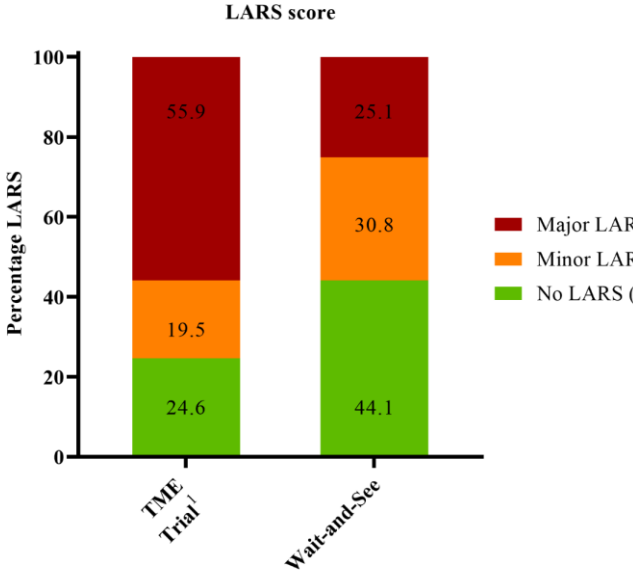


TME-free DFS

National Dutch registry
Watch & Wait
Rectal cancer

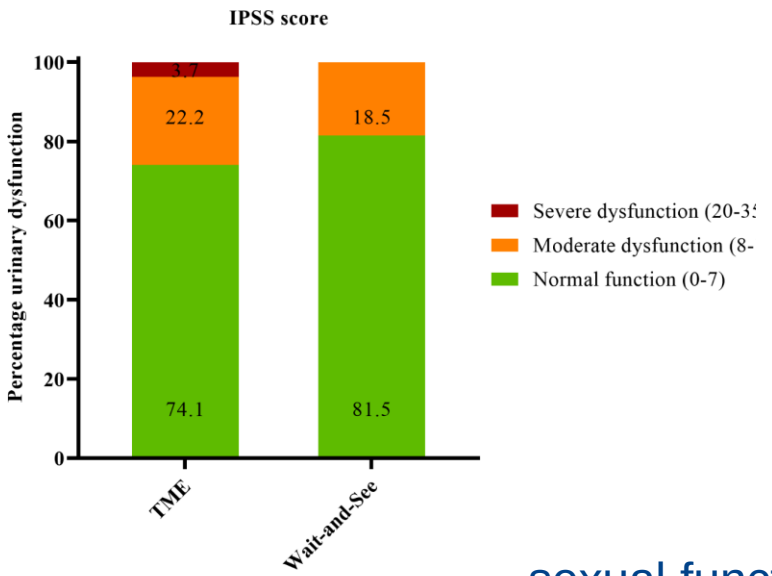
unctional outcome - QoL

LARS



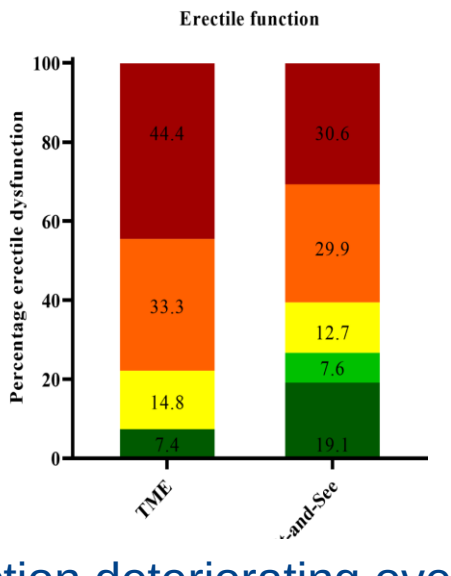
stable over time

urinary



men > women

erection



sexual function deteriorating over time, in both women and men

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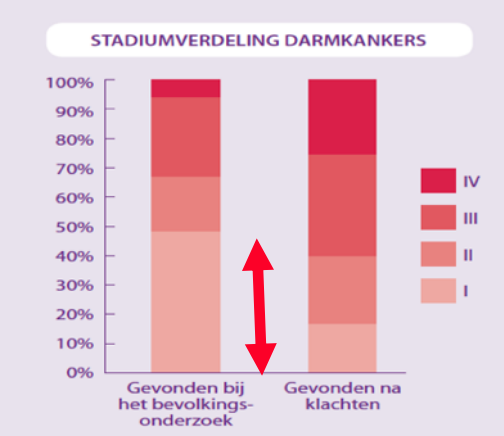
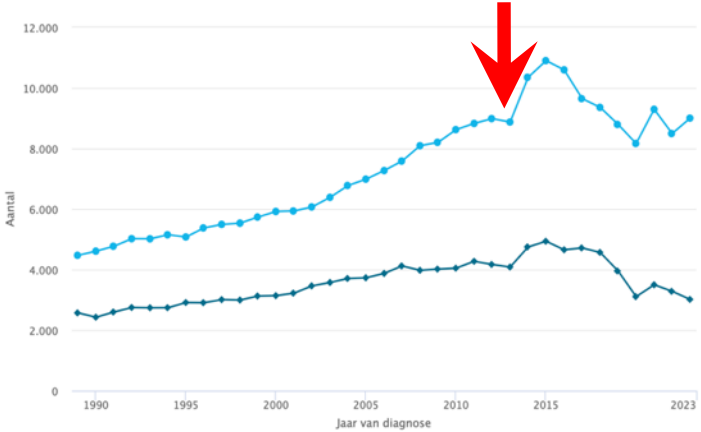
First Conclusion:
Secondary Organ Preservation

- Increases QoL – very high interest of patients
- Treatment of regrowths (20-30%) is straightforward
- Oncological risk is very low
- Proper selection and follow up – high quality program
- Shared decision making
- Successful in 15-30% of patients, depending on size tumor

Incidence CRC - Screening

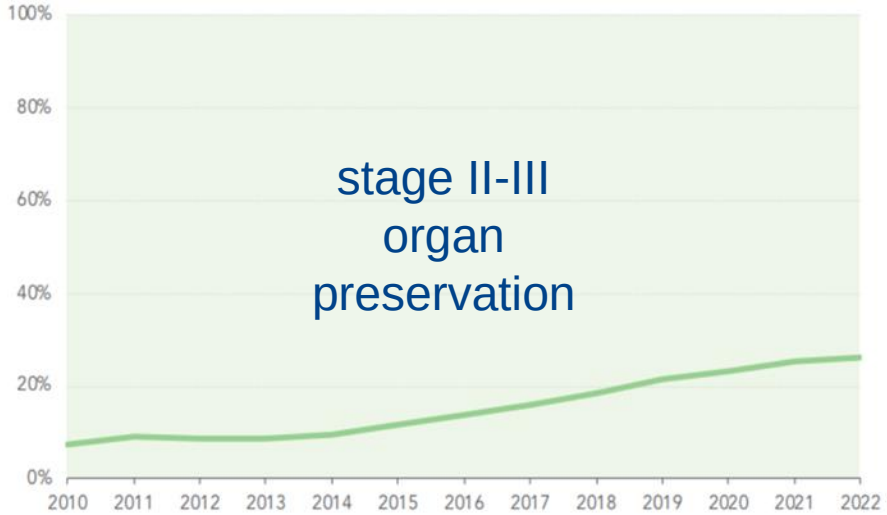
- Initial rise in incidence CRC, now ↓
- Asymptomatic small tumors
- Adenoma → surveillance → prevention CRC



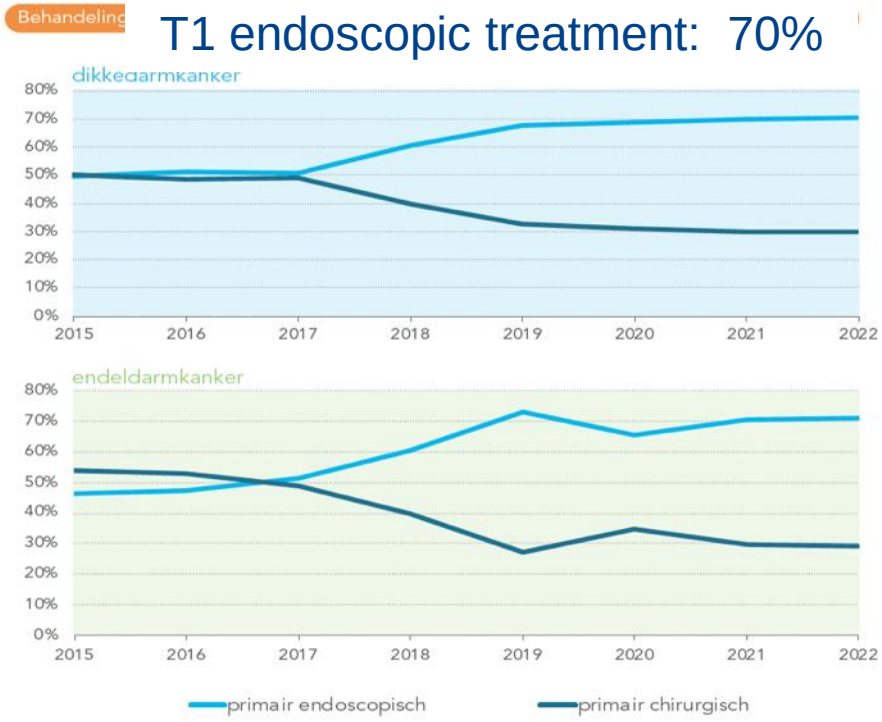


National trends rectal cancer

Netherlands Comprehensive Cancer Organisation



T1 endoscopic treatment: 70%



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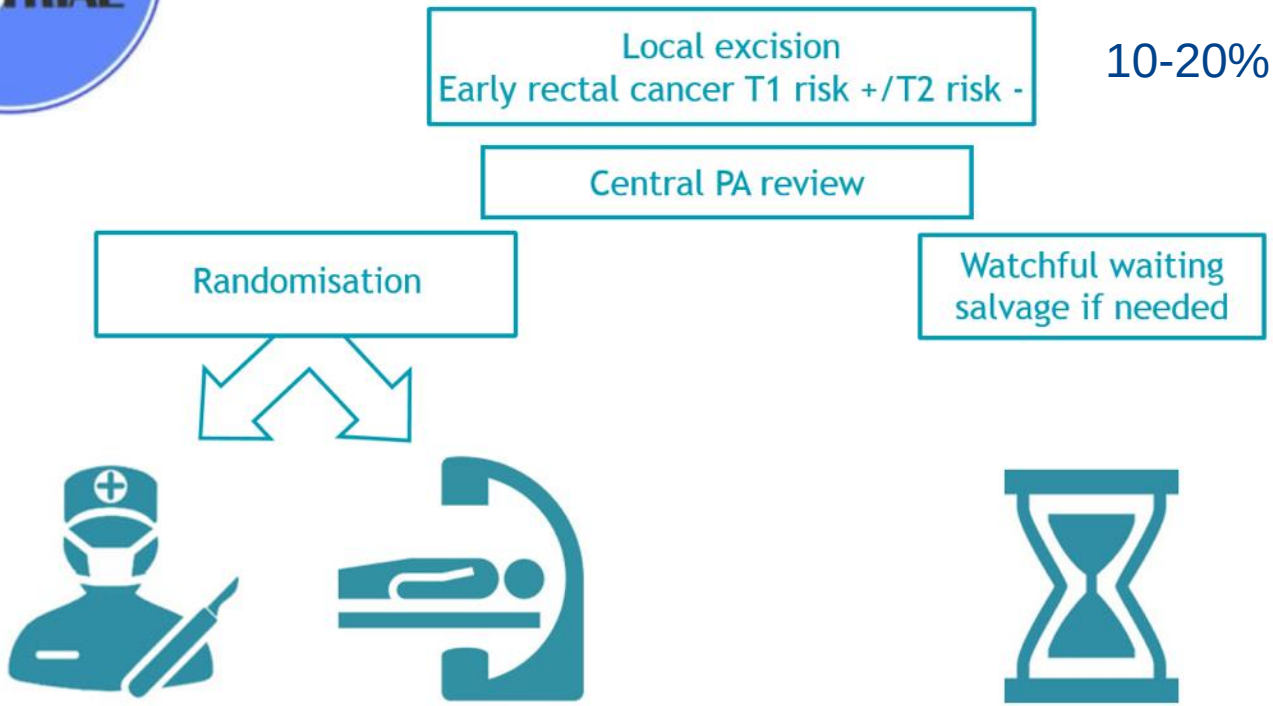
Very early rectal cancer

Primary local excision?

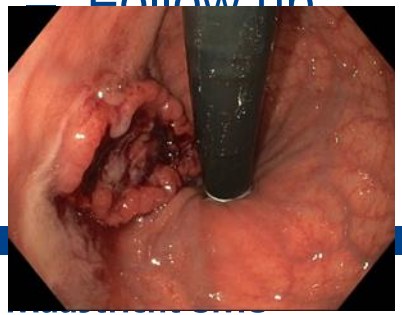


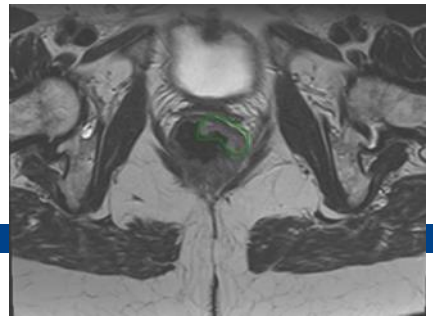
10-20% local failure

TME surgery Chemoradiation Observation

Case: 63 y woman asymptomatic

- T2N0 distal tumour: MDT recommends APR, no indication for RT
- Patient prefers organ preservation strategy
  - Benefit – harms – outcome
  - Treatment goals
  - What if not successful?
  - Follow up





Organ preservation – Watch & Wait
Where are we going?

Small tumors
- ‘additional RTx’
- functional indication
- **primary** organ preservation
- +/- local excision

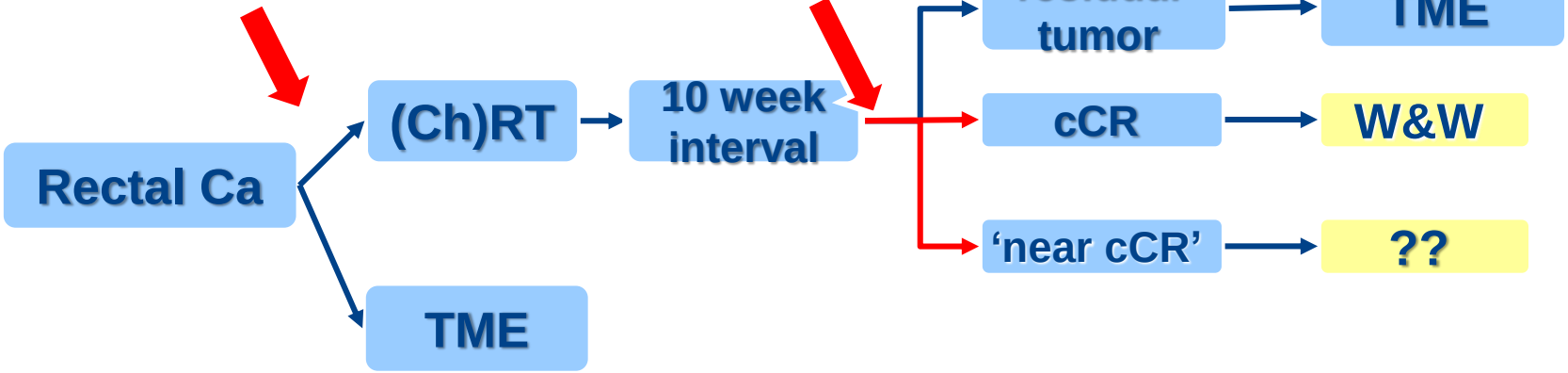
Large tumors
- ‘standard RTx’
- oncological indication
- **secondary** organ preservation
- Watch & Wait

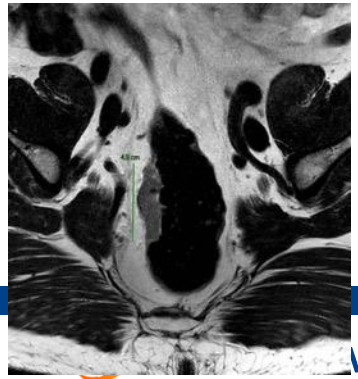
>50%

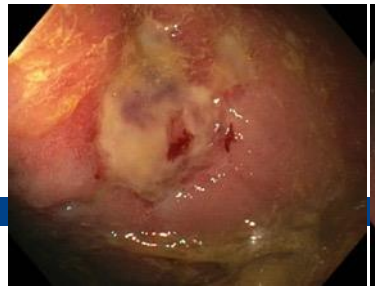
10-25%

Organ Preservation

Decision Making in Organ Preservation

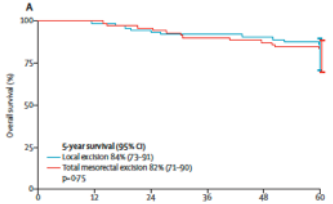






Primary organ preservation: randomized studies

- **GRECCAR 2** Low T2-3Nx, ≤4cm: CnRT good resp. → TME vs LE
  - 60% organ preservation
  - Oncological outcome similar
  - Overall no functional benefit!!??
    - Completion TME? LE or W&W?

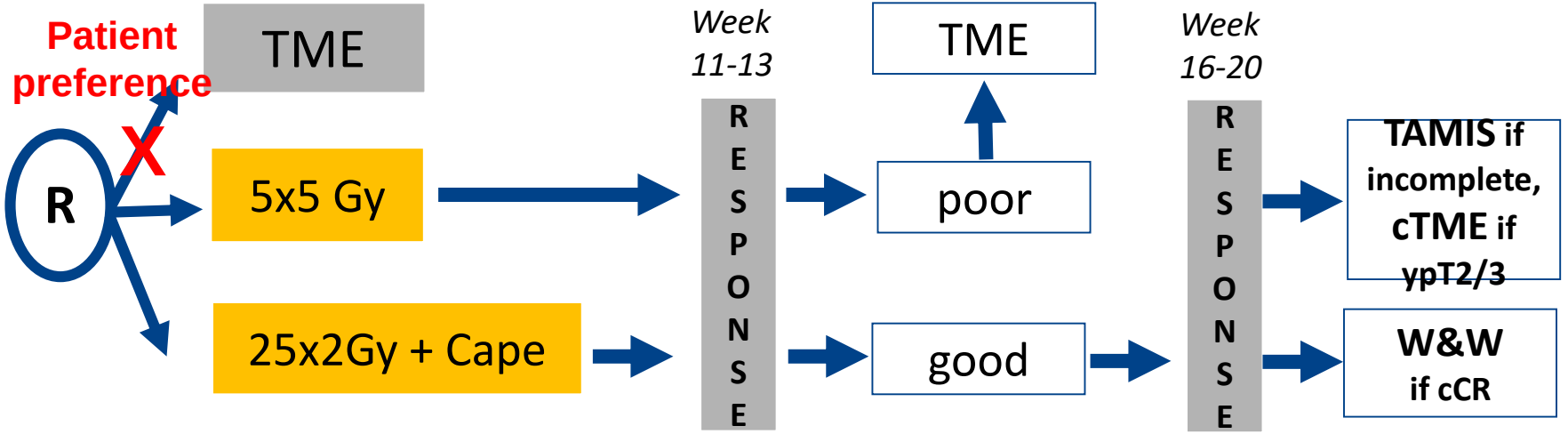


Rullier et al. 2017 Lancet, 2020 Lancet GH

- **TREC** T1-2N0 ≤3cm: TME vs 5x5Gy and LE
  - Small randomized cohort and observational cohort
  - 70% organ preservation
  - Oncological outcome similar
  - Overall substantial better QoL, less complications

Bach et al. 2021 Lancet GH

STARTREC: cT1-3b N0M0, < 4 cm



120 patients

60% organ preservation

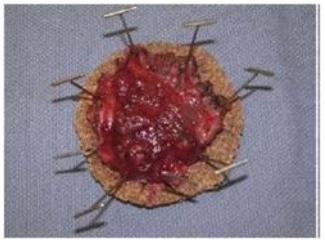
Second Conclusion: Primary Organ Preservation

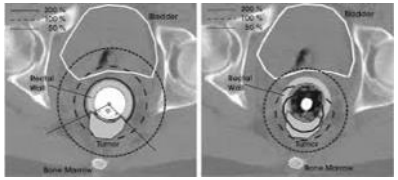
- Primary organ preservation successful in >50% of patients
- Smaller tumors: better response
- Local excision often performed (50% ypT0)

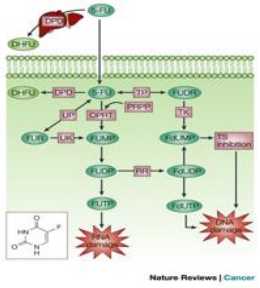
- What about those patients who still require TME?
  - They are worse off!

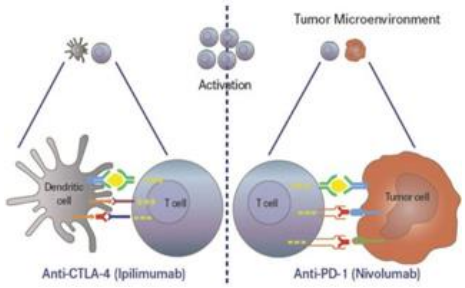
How to increase organ preservation?

- Waiting longer?
- Local excision?
- More radiotherapy?
- More chemotherapy?
- Immunotherapy?
- Combinations?

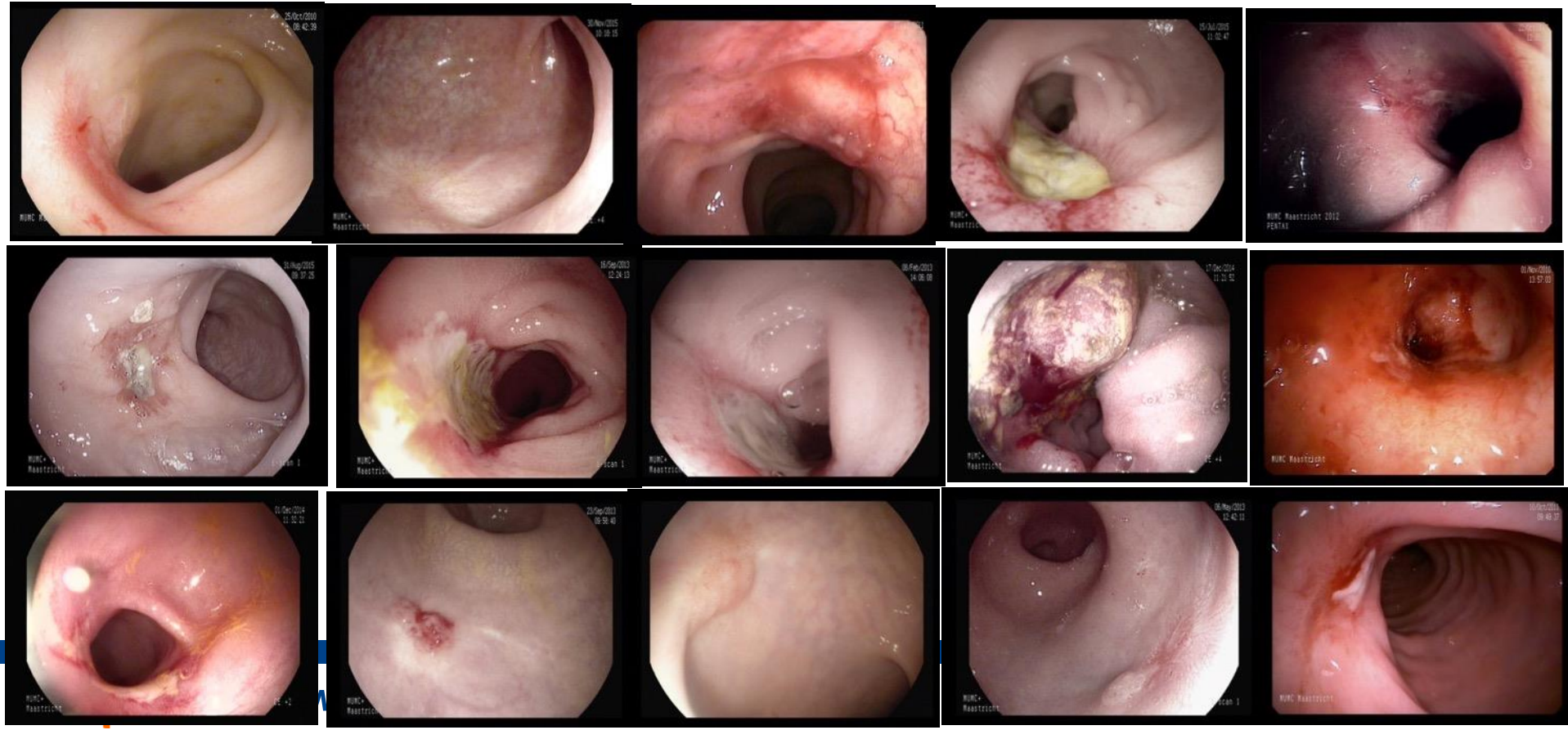


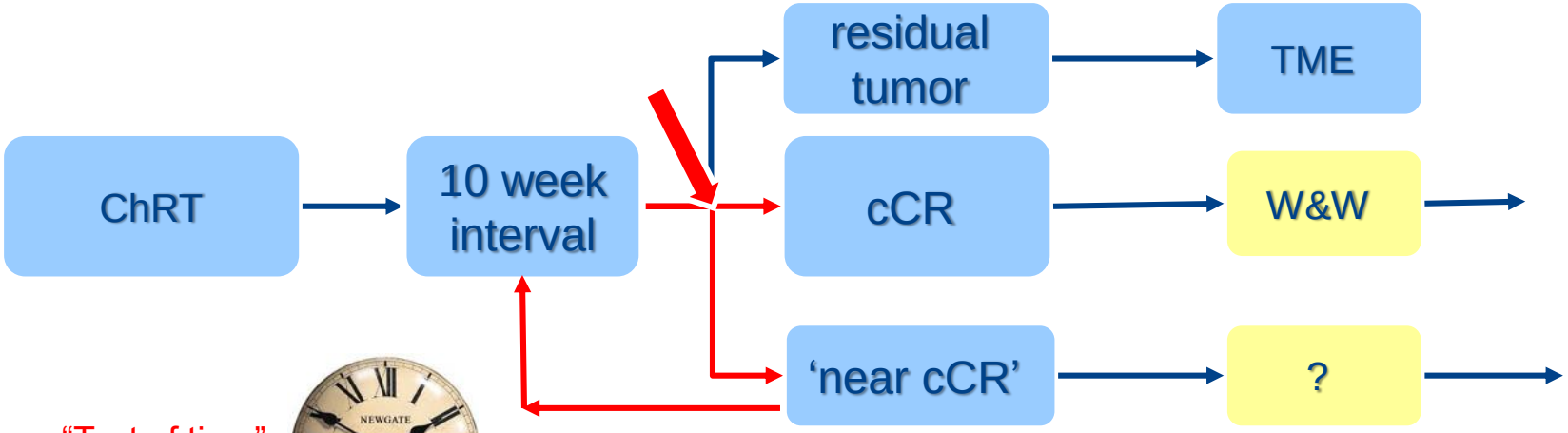




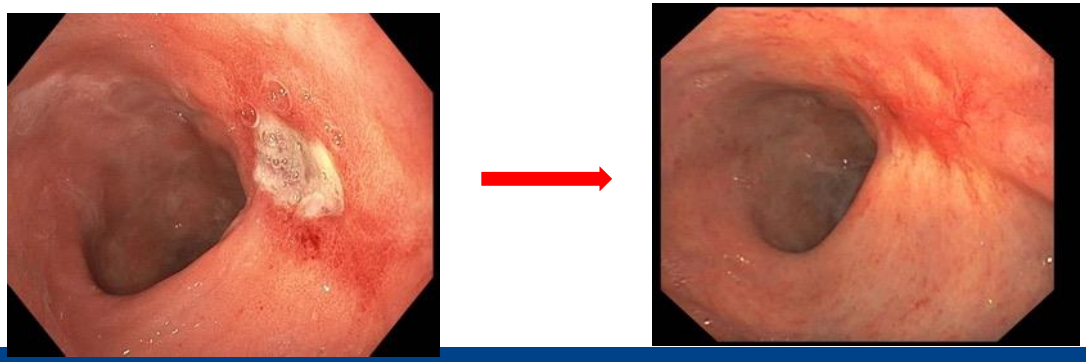


‘Near-complete responders’





Hupkens 2018 Ann Surg Oncol
Habr-Gama 2019 DCR

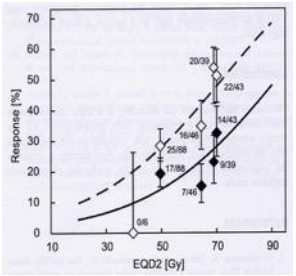


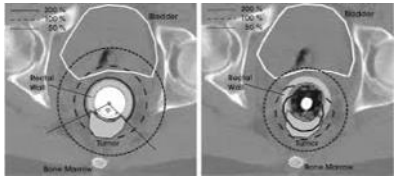
Improving response: more RT?

50 Gy: pCR 10-15%

65 Gy: pCR 20-25%

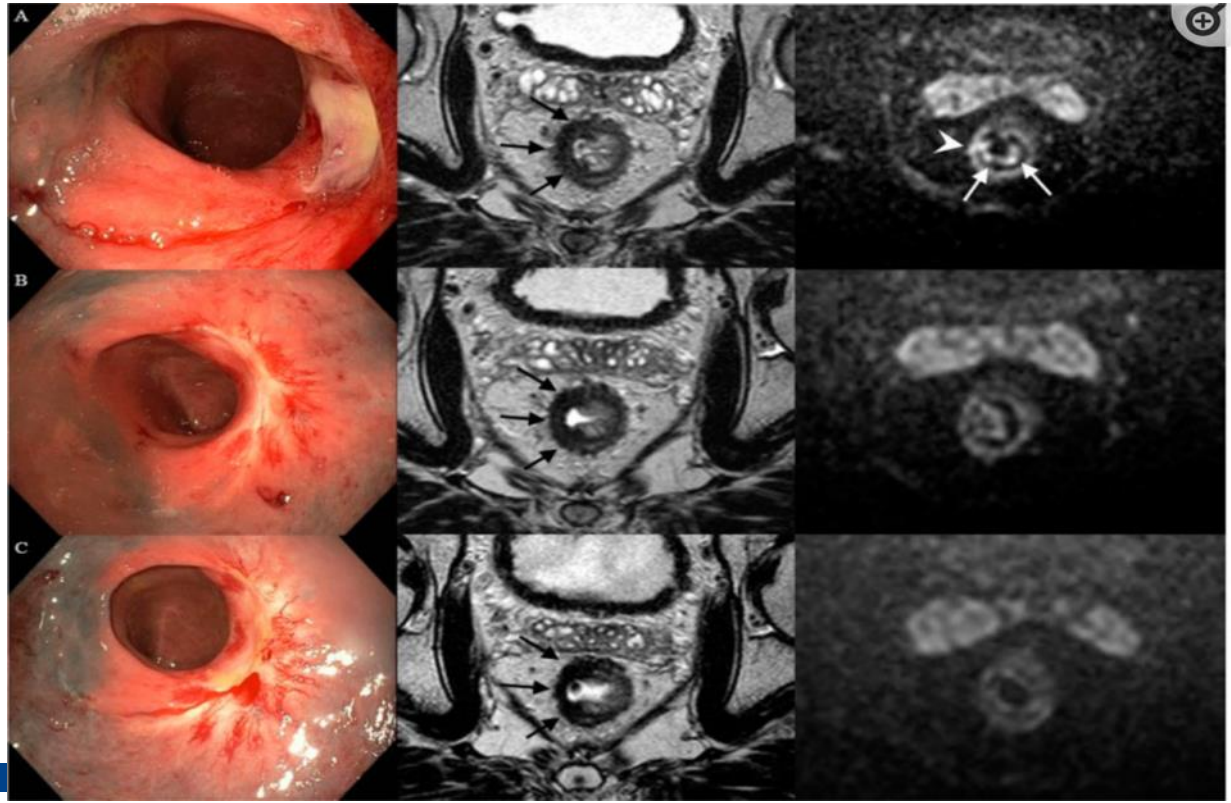
Appelt 2013 IJROBP





- Endorectal RT boost:
  - ~~brachyRT: Jakobsen =~~, Appelt +
  - contactRT: Opera ++
- External RT boost:
  - Habr Gama +, Utrecht boost =

Contact RT boost: 3x30 Gy



Sometimes ulcer with

- irregular fibrosis
- diffusion spots

Custers 2022 Cancers

Opera trial: external vs internal boost RT

ChRT 45 Gy + Capecitabine

R

EBRT Boost 9 Gy

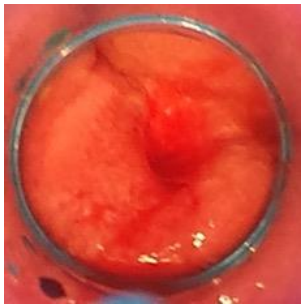
Contact 3x30 Gy
Before CRT < 3 cm

RESTAGING

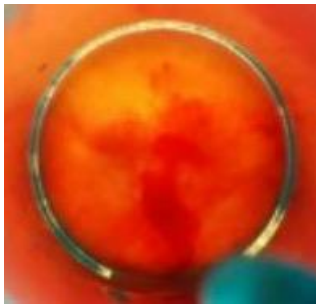
W&W

TME

baseline

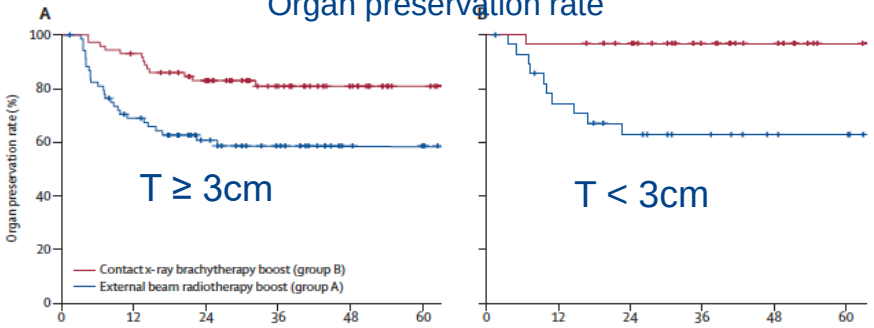


after contact RT



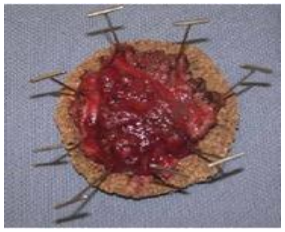
after 45Gy ChRT

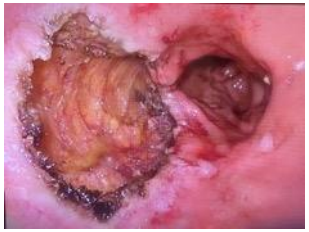
Organ preservation rate



JP Gerard Lancet Gastroenterol Hepatol 2023

Local excision





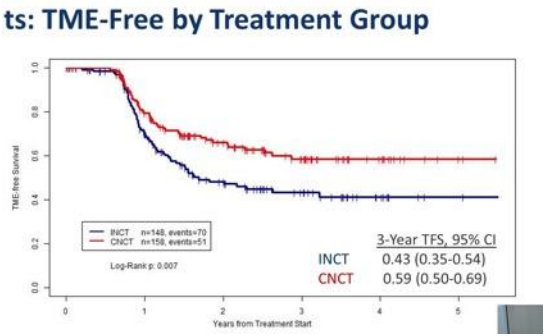
- Shown value in GRECCAR TREC CARTS ReSARCh …
- Therapeutic procedure
  - small tumour/adenomatous remnant
  - regrowth

- Opaxx trial: good but incomplete responders
  - Contact RT vs waiting longer/LE

OPAXX

Improving response: more systemic Tx?

- OPRA-TNT (US): intermediate tumours
  - ChRT + 5FU/oxali vs 5FU/oxali + ChRT
  - 3yr organ preservation: 58%vs 43%

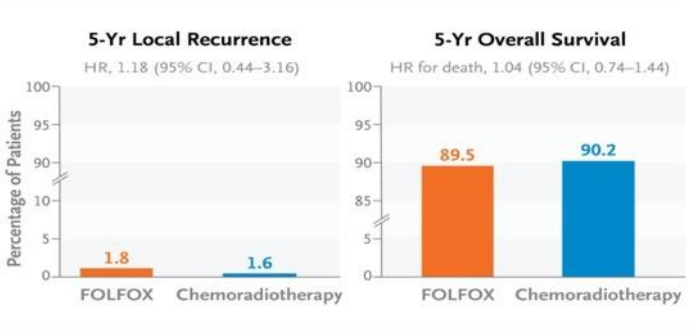


- GRECCAR 12 (Fr): intermediate tumours
  - ChRT vs folfirinox + ChRT

- TRESOR trial (Fr): Folfirinox + ChRT +/- 3x30 contact

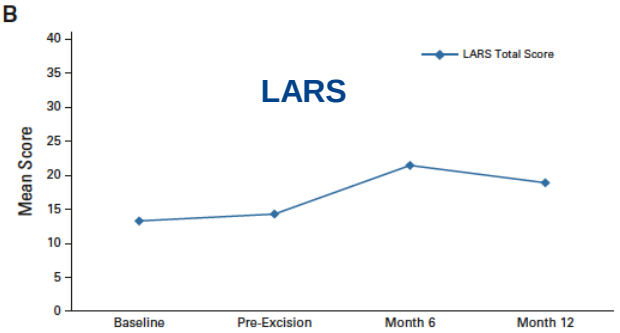
Systemic therapy only?

- Prospect trial: stage II/III
  - Preop ChRT vs 6x Folfox
  - pCR 24% 22%



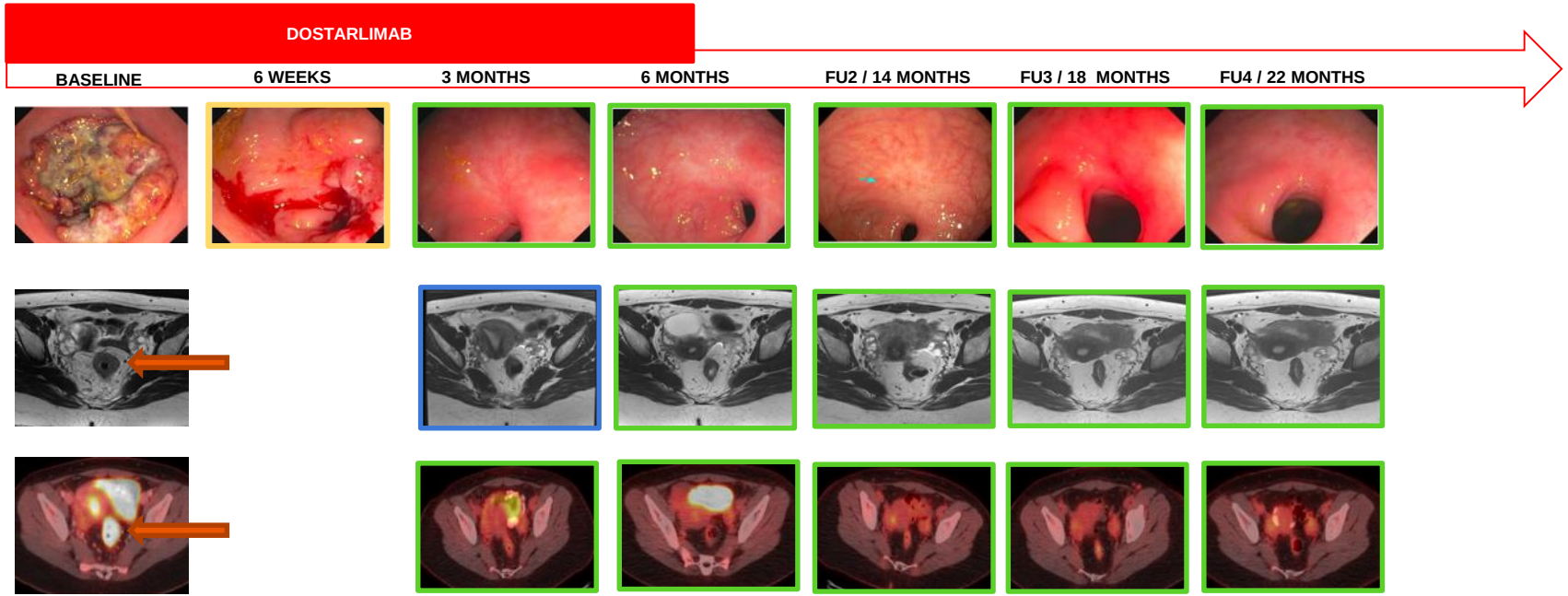
Schrag 2023 NEJM

- NEO trial: phase II T1-3abN0: 3mths induction capox → LE
  - 56/58 LE → 38% ypT0!
  - Organ preservation: 57% - 79%
  - Major LARS: 10% → 22% → 14%



Kennecky 2023 JCO

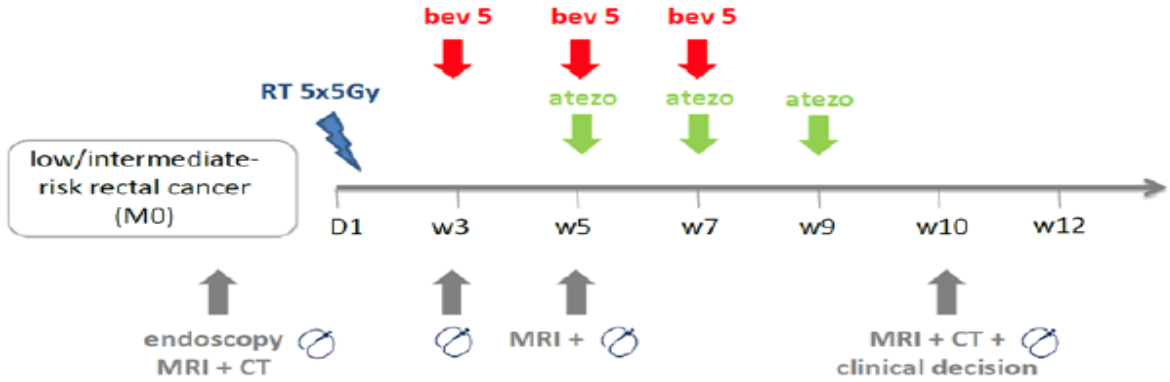
MSI rectal cancer: Immunotherapy



Cercek, et al NEJM 2022

Combined RT and

single-arm proof-of-concept phase Ib/II study



Conclusions

- Level 1 evidence?
- Organ preservation – Watch & Wait
  - Increases QoL – very high interest of patients
  - Oncological risk is very low
  - Selection and follow up – high quality program - shared decision making
- 50% of all rectal cancers organ preservation?
  - Early tumours!
  - Combining treatment modalities
- We will rediscover value of surgery

Thank you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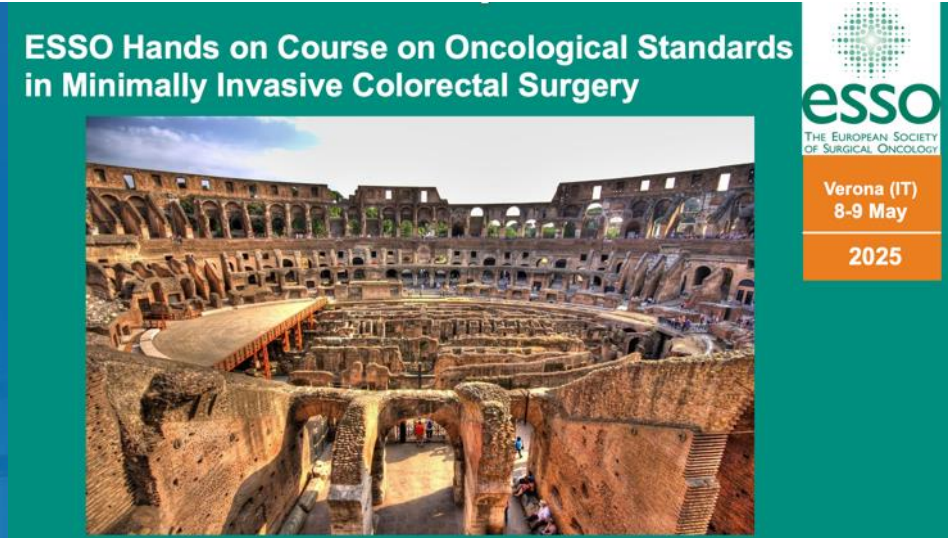
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