Assessing response to RT/CT in colorectal cancer

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Tumour response - variable

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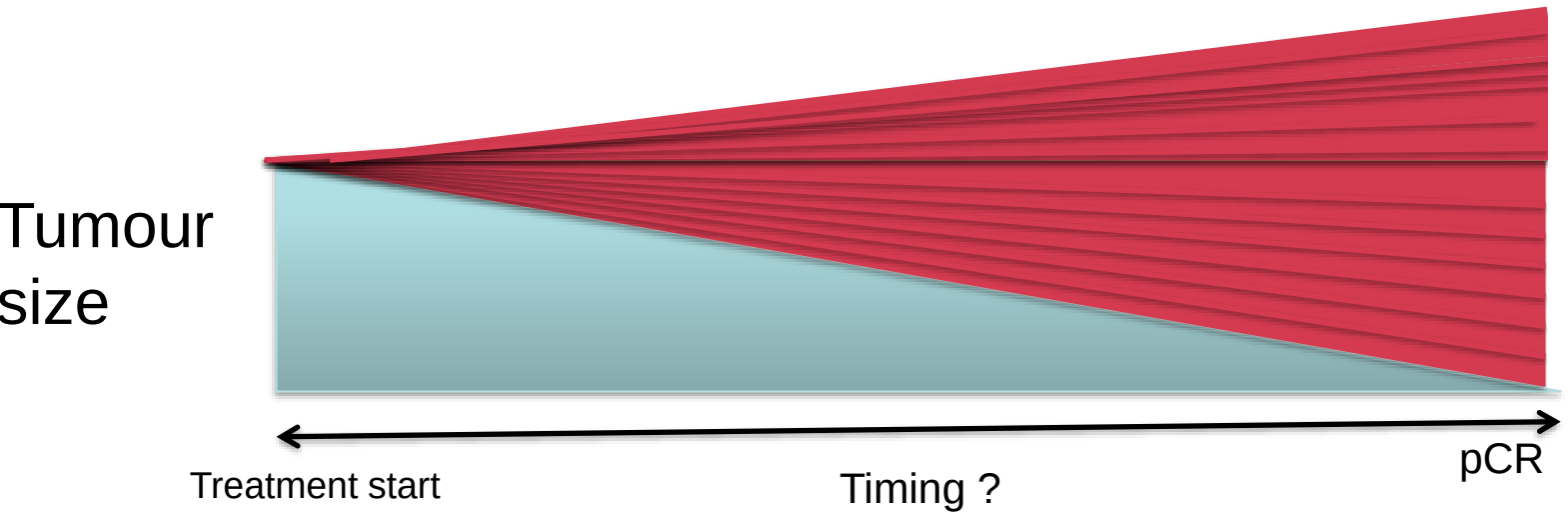
- Will the tumour respond?
- How much?
- How quickly and for how long?

Some response may still be beneficial e.g. CRM +ve to negative

40% no response – why?



Response and stage

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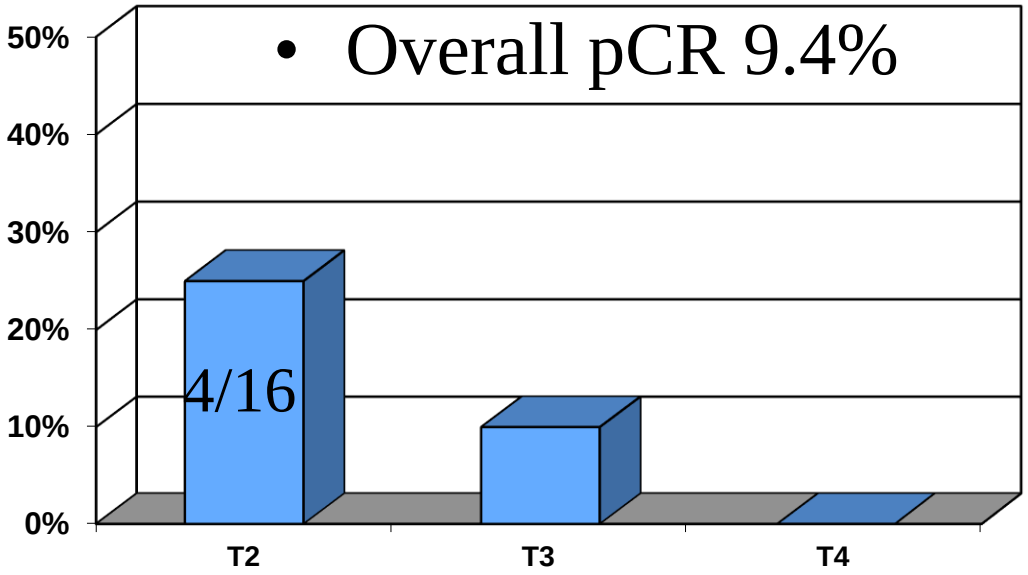
- Rodel et al 2005 better response in earlier stage
- Greccar 2 better response in early stage
- Perez cT2 vs cT3 pCR 67% vs 20%
- FDGF cT2 vs cT3 pCR 39% vs 9%



Rodel et al 2005

Factors that influence response

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- Degree of response may depend on:
  - Type of pre-operative therapy
  - Delay time between last dose and surgery
  - Quality of pathological assessment

Operation delay
1 week
6 weeks
8-12 weeks
Watch and wait

Therapy
Radiotherapy alone (short course / long course)
Chemoradiotherapy (1 or 2 drugs / biologicals)
Chemotherapy alone (multiple drugs)

Schedule and dose
Length of cycles
Number of cycles
Dose of RT
Dose/combination of drugs

d prefix

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- **We recommend that individual patients would have a 'd' prefix denoting the interval between the start of treatment and its assessment, local excision or definitive surgical procedure.**
- **This interval should be denoted in days, and might vary between 10 and 119 days e.g ypd10 T2 ypN0 or ypd119 T2 ypN0. Thus the overall trial could be analysed according to a median/mean 'd' score.**

Dis Colon Rectum. 2015 Jun;58(6):613-6. doi: 10.1097/DCR.0000000000000356.

The D prefix: toward a reproducible validated alternative end point in rectal cancer.

Glynne-Jones R[1], West NP, Quirke P.

Morphology

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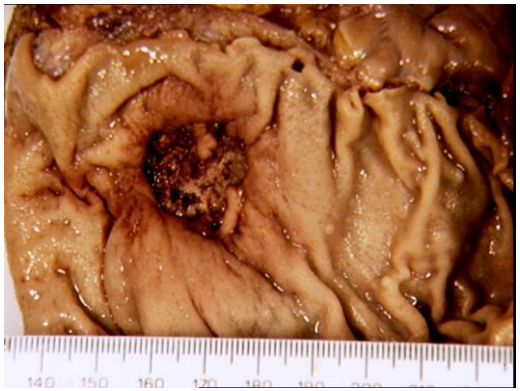
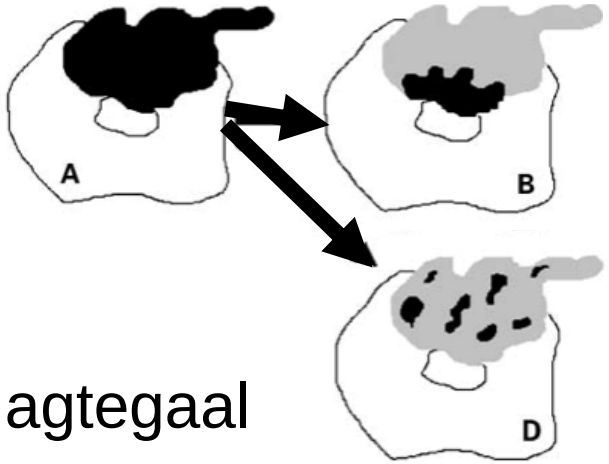
- Macroscopic lesion
  - Ulcer 13% ypCR
  - Scar 59% ypCR
  - No visible defect 66% ypCR

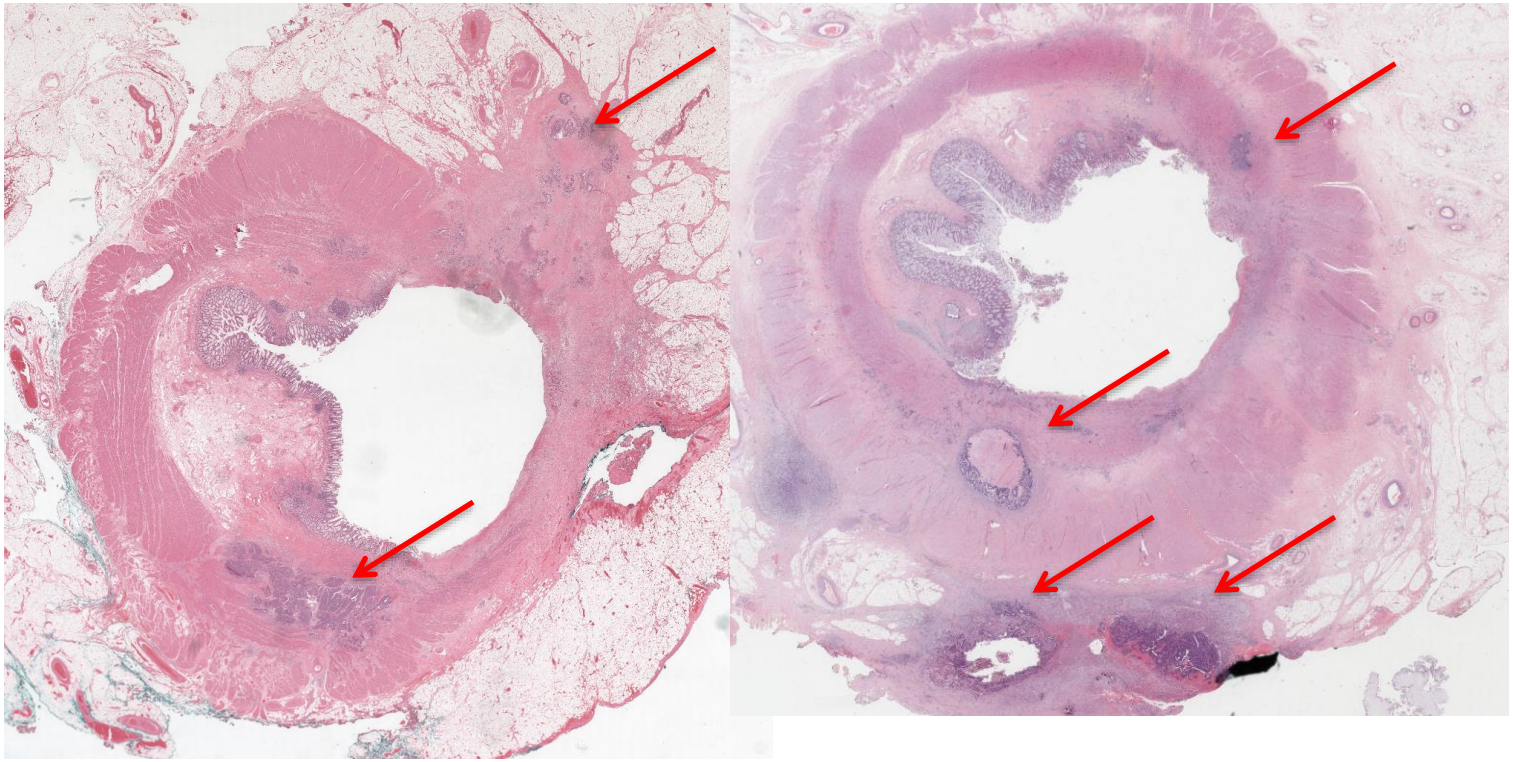


- Differential microscopic morphological response
  - Fragmentation
  - Shrinkage towards the lumen
  - Mucinous change



Nagtegaal

Fragmentation



Shrinkage to the lumen

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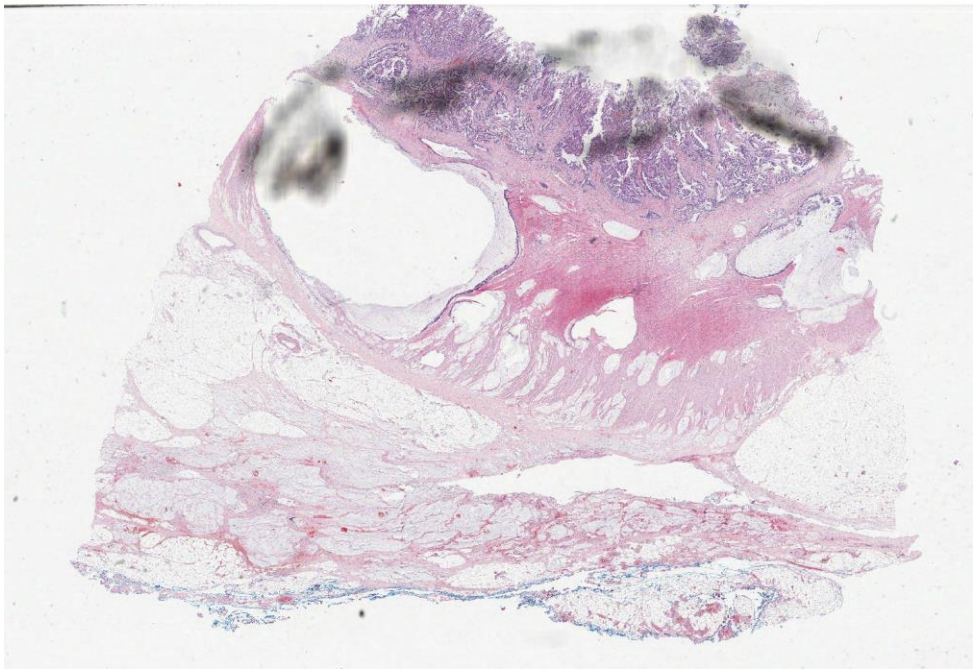

Mucoid pCR

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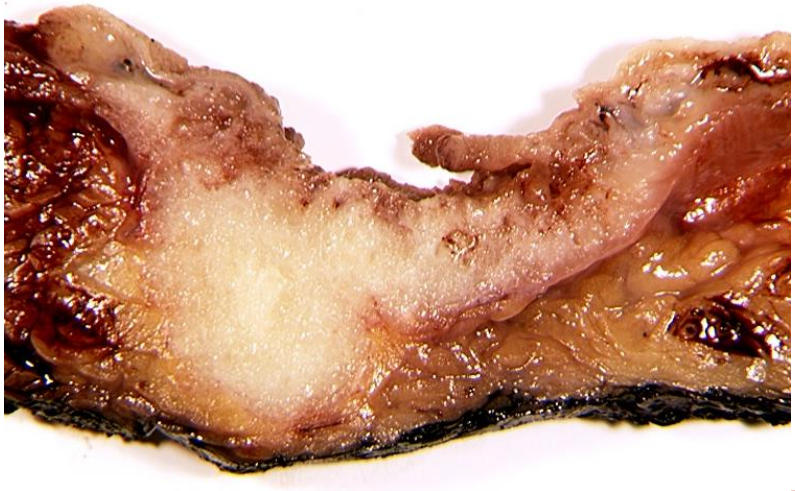

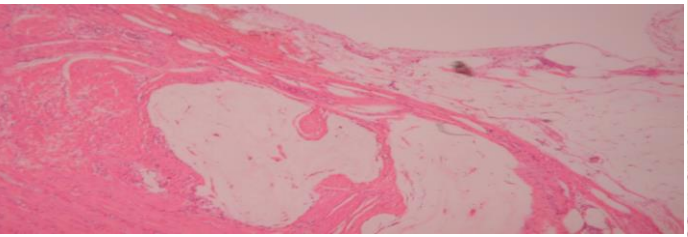

Response in colon cancer to chemotherapy

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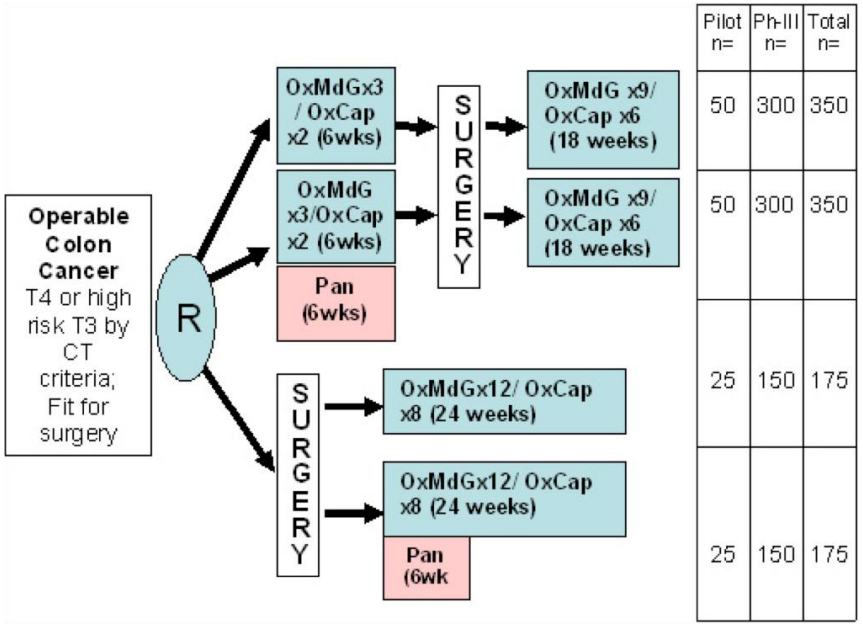
- Foxtrot trial advanced primary colon cancer
  - 6 weeks preoperative chemotherapy vs none



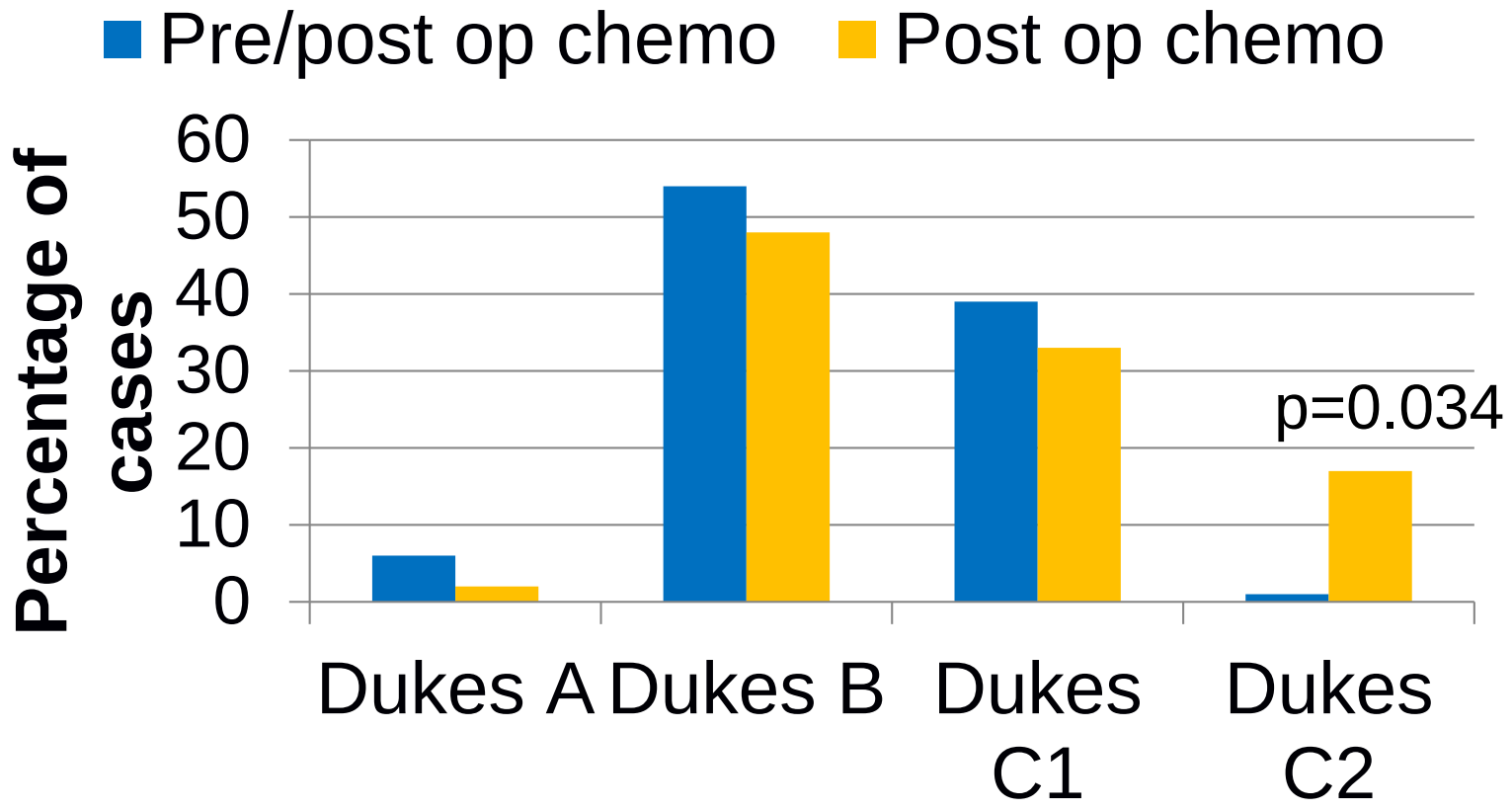
	Pilot n=	Ph-III n=	Total n=
	50	300	350
	50	300	350
	25	150	175
	25	150	175

Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial

*FOxTROT Collaborative Group**

Lancet Oncology 2012;13:1152-60

Colon cancer



Colon cancer - fragmentation

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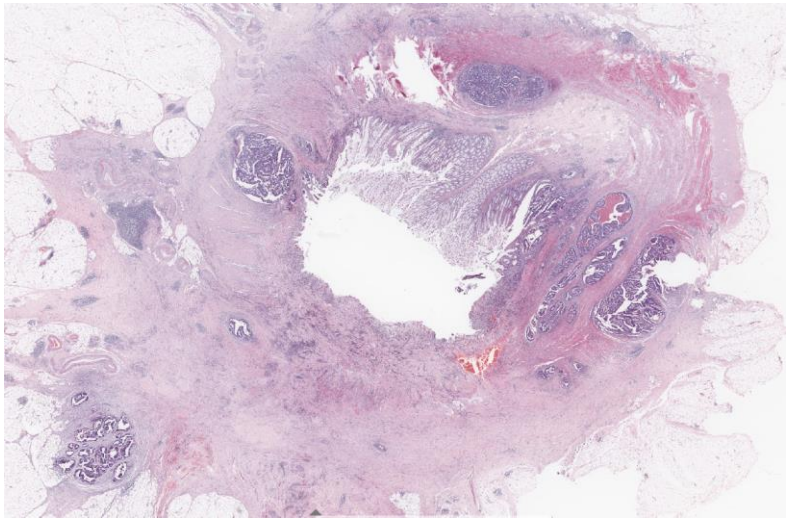

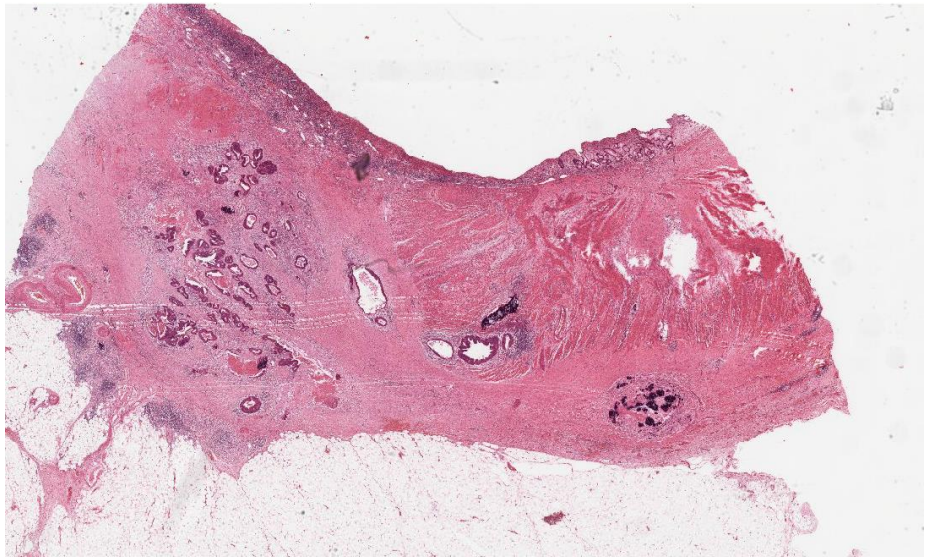

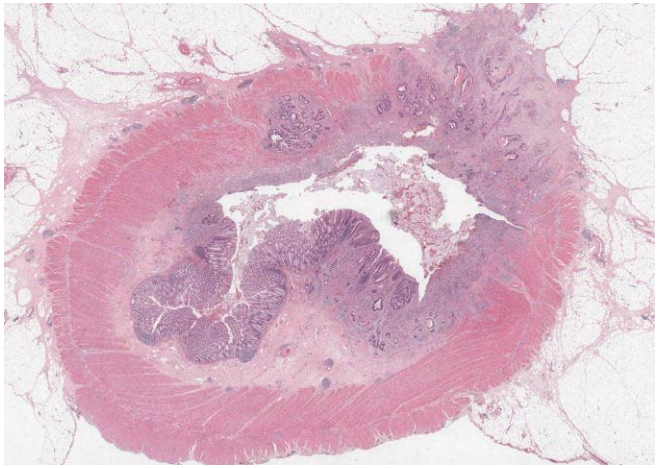

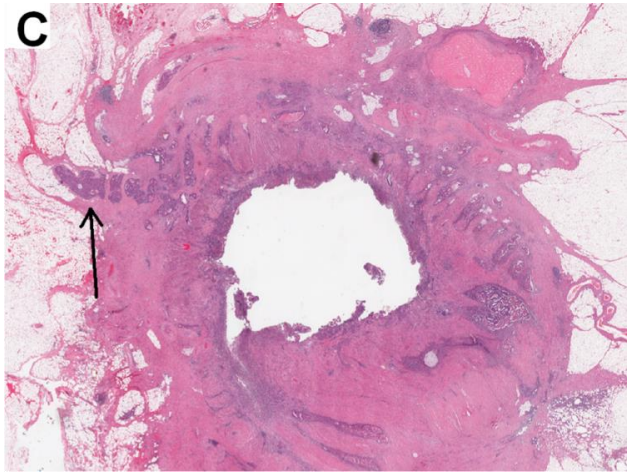

Regression to the lumen

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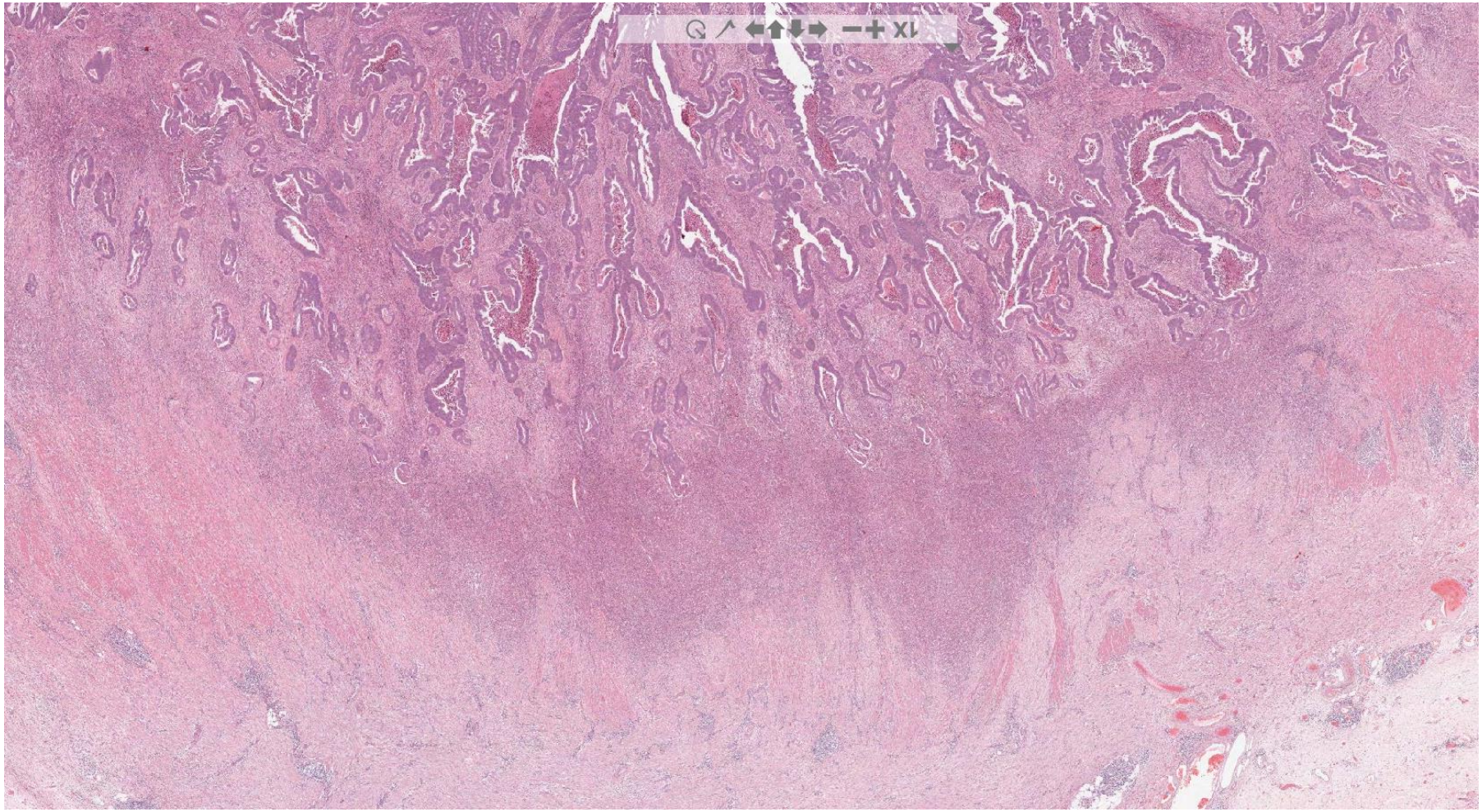
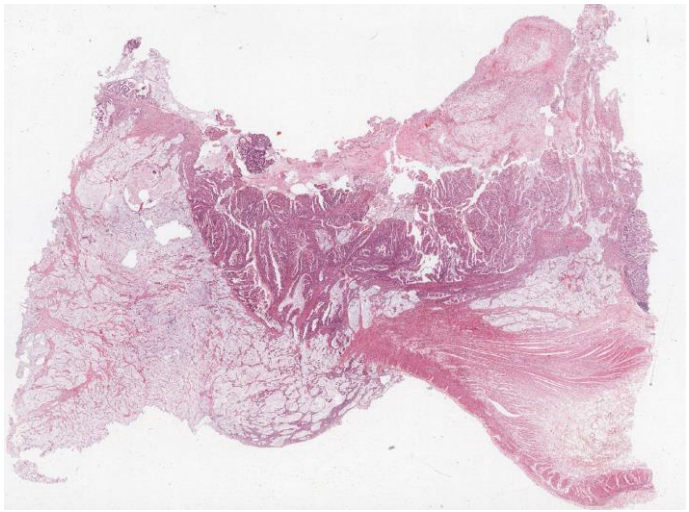
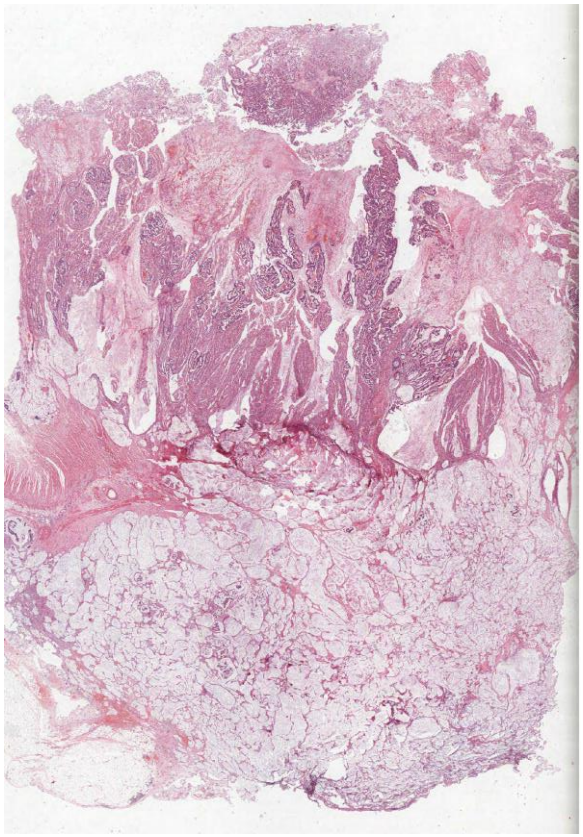
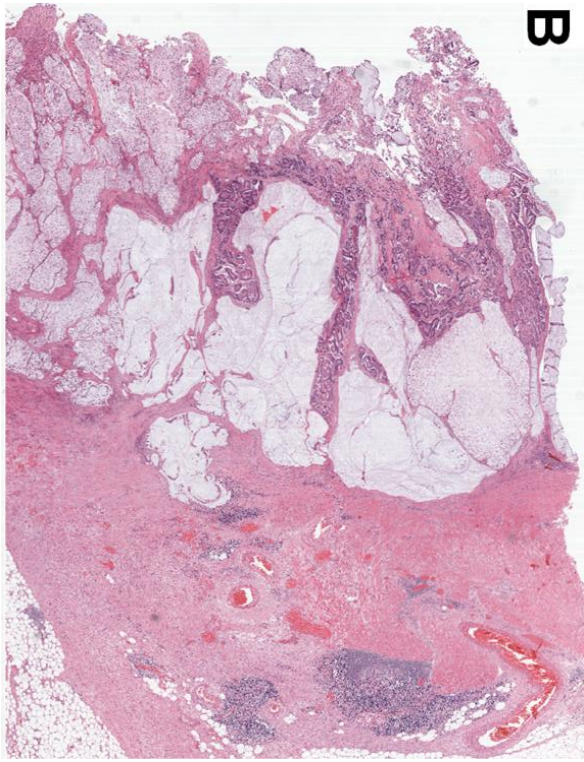


Mucoid change







Heterogeneity of response

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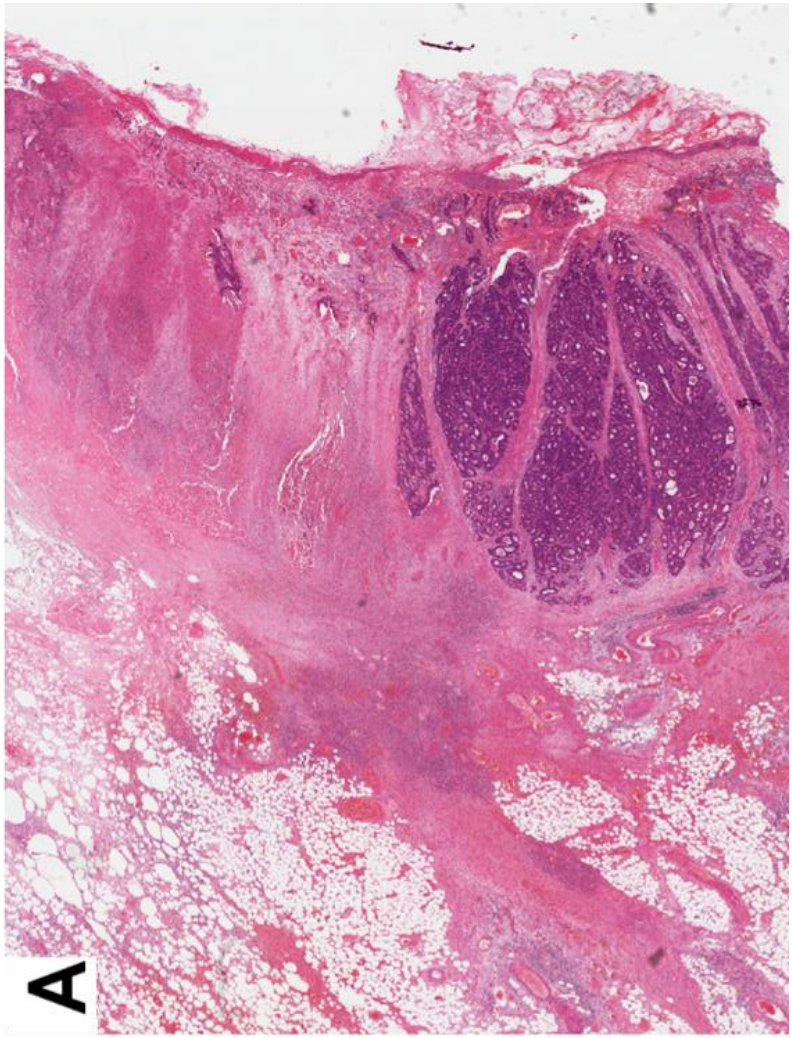

Complete response

Excellent response

Tumour response – TNM8

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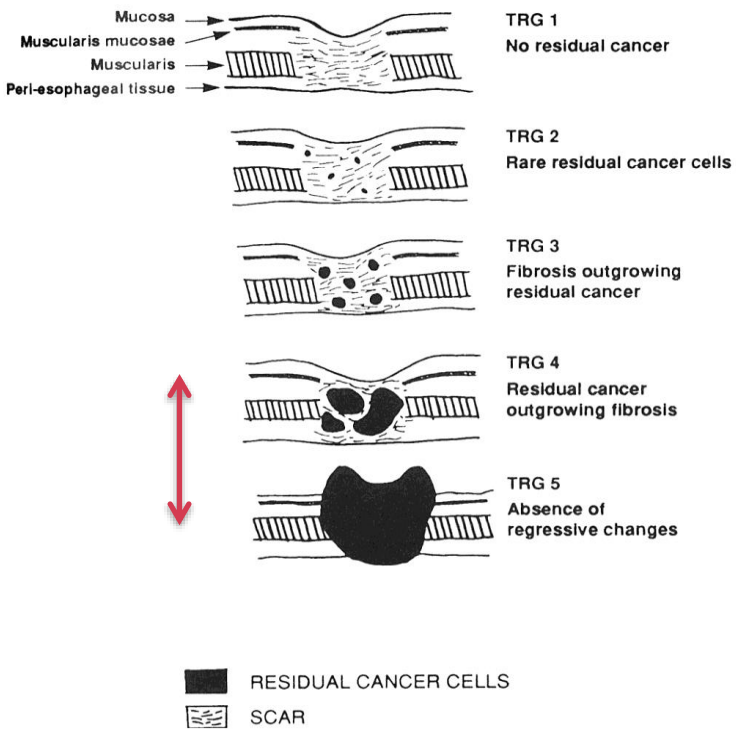
Mandard



TNM8 Ryan et al

Table 20.2 Modified Ryan scheme for tumor regression score

Description	Tumor regression score
No viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near-complete response)	1
Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumor regression (poor or no response)	3

(Adapted from Ryan et al[11,12,60] with permission).

Post therapy staging

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- Standardised dissection method
- Clear margin/CRM 1mm
- ypdTNM
- Degree and pattern of response
- ?% tumour cell density

Recommended method

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- Inking margins
- Cross sectional slicing
  - Good visualisation
  - Assessment of CRM
  - Assessment of quality of surgery
  - Allows comparison to MRI

Dissection method

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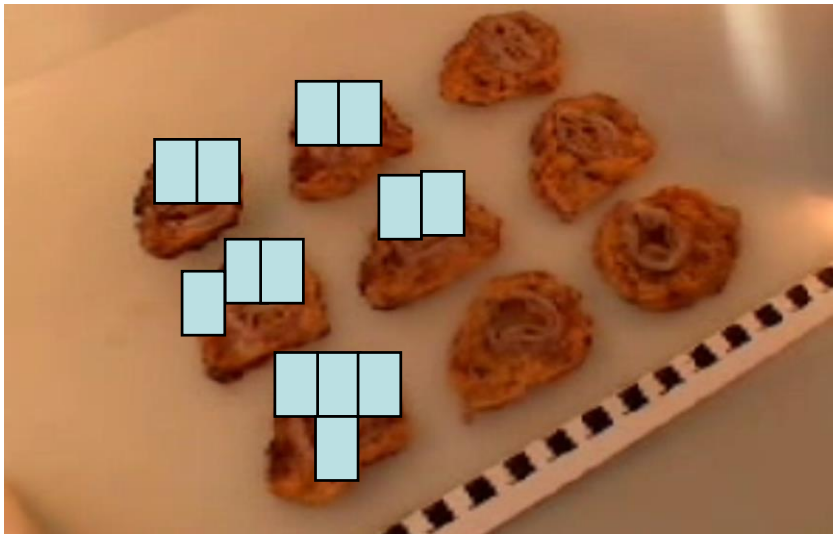
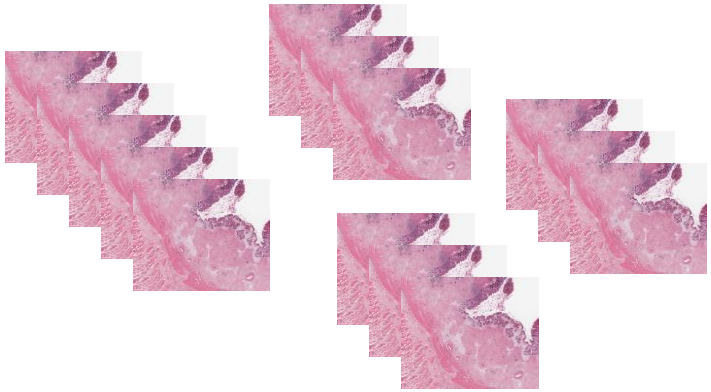
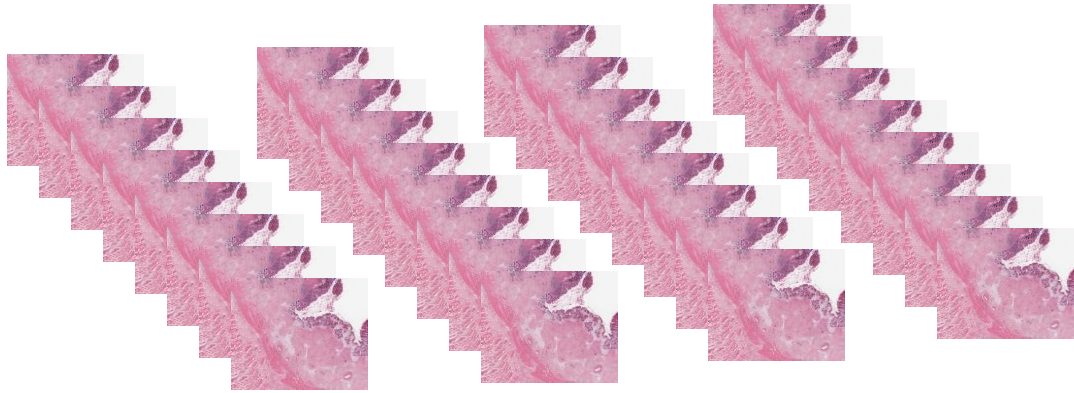
- Routine
  - 5 blocks 1 H&E
    - Levels x3 (20 slides)
  - No tumour – embed all of area where tumour was present +8 blocks
    - Levels x3 (32 slides)
  - Total = 52 slides







West et al
Tumour cell density – more sensitive predictor of response and helpful in improving MRI prediction of response?

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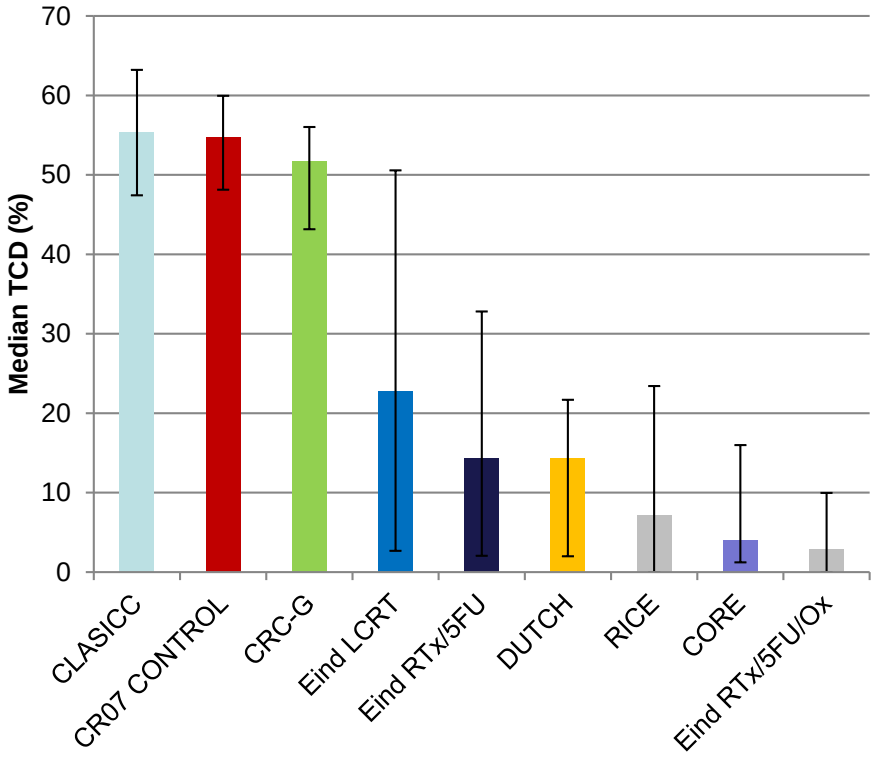
300 points



Short course 5x5 surgery at 1 week

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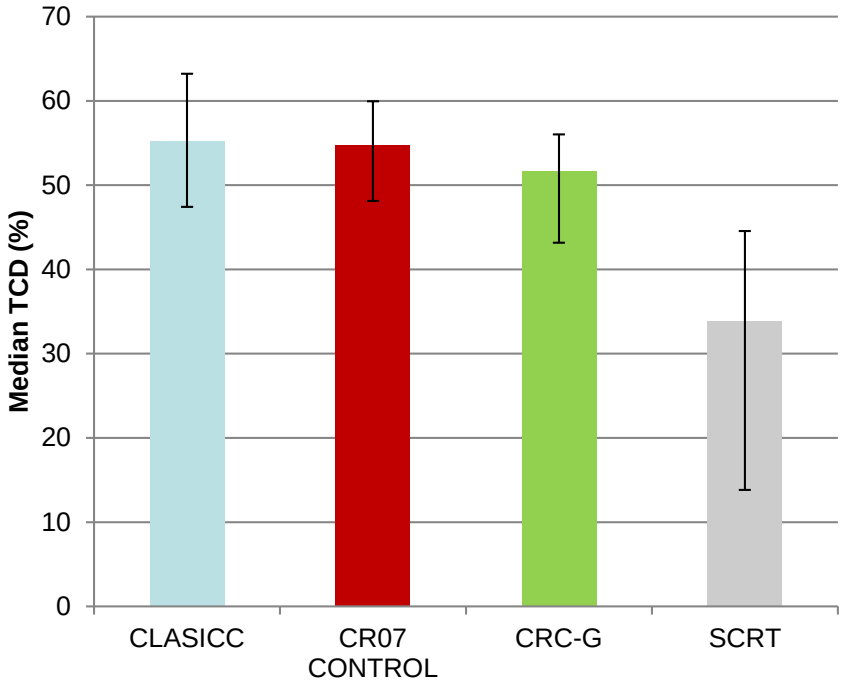
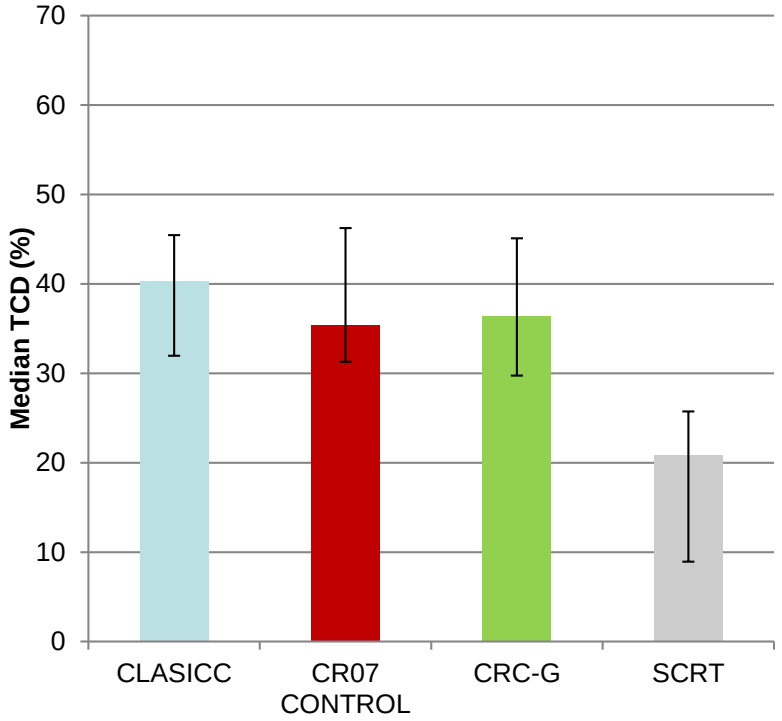
- Greatest tumour cell density



- Whole tumour



Summary

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- Response seen depends on stage, treatment and operation timing
- Use the d classification in studies
- Morphological changes seen in RT/CT and CT alone in rectum and colon appear similar
- TNM8 – fusion of no response/mild response
- Key is to use standard dissection method to assess response
- Is tumour cell density a better quantitative approach to assessing the effectiveness of new treatments in trials?

Thanks to:

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- Pathologists - Nick West, Emma Tinkler, Heike Grabsch, Iris Nagtegaal
- Radiotherapy colleagues – David Sebag-Montefiore, Rob Glynne-Jones, Corrie Marijnen
- Surgical collegues – Harm Rutten, Paul Finan
- CORE and CR07 trialists
- Funders Yorkshire Cancer Research, MRC