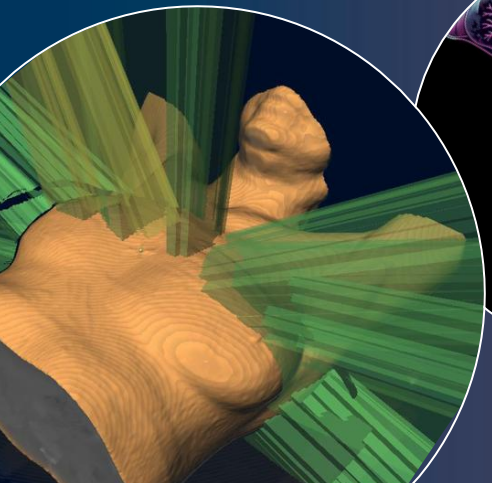
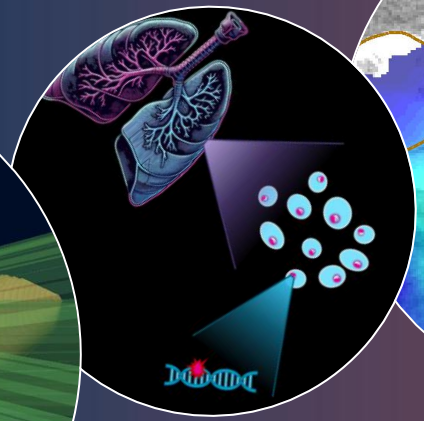
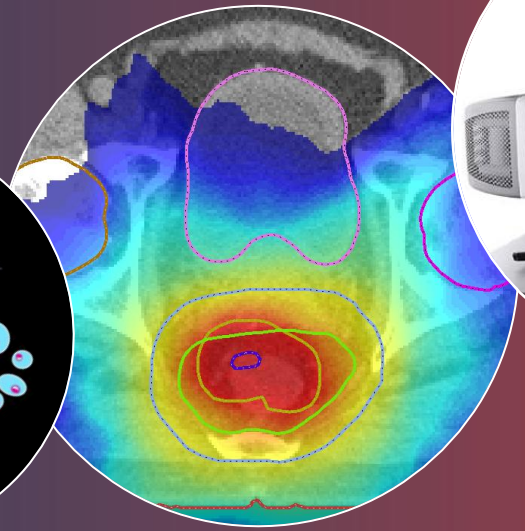
Optimising Radiotherapy for Organ Preservation in Early Rectal Cancer

JSRS 2026
Ane Appelt
Professor of Clinical Medical Physics
Rigshospitalet & DTU





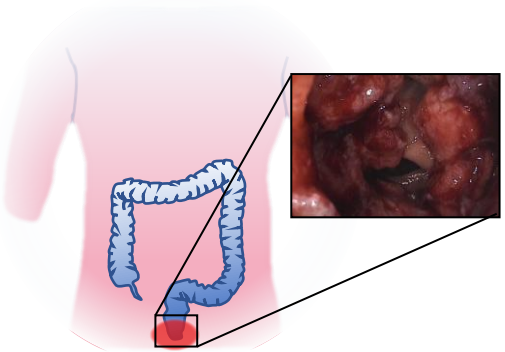


Technical University Hospital of Greater Copenhagen
Region Hovedstaden
DTU

IN MEMORIAM: ANGELITA HABR-GAMA 1933-2026

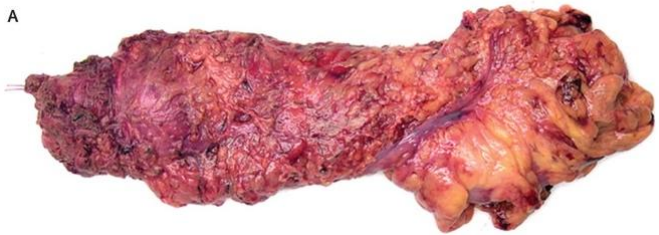
Painting by Prof Arthur Sun Myint

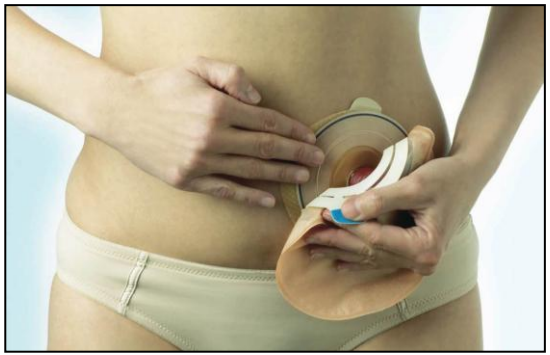
Rectal cancer & radiotherapy



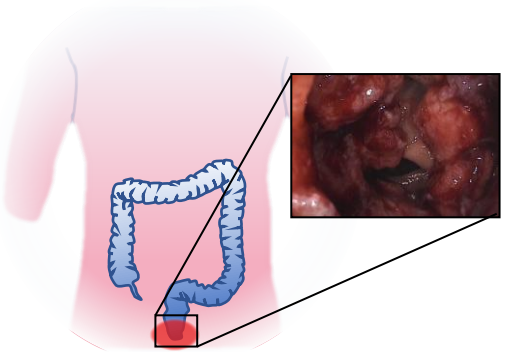
- Highly effective local treatment
- Significant degree of morbidity (bowel, bladder, sexual dysfunction)
- Mortality in elderly / frail patients

Current primary treatment modality: TME surgery

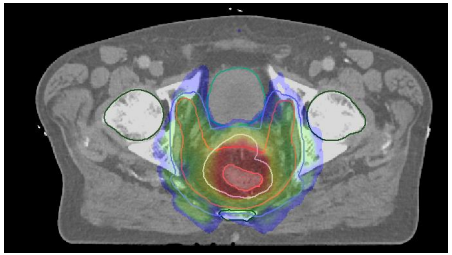




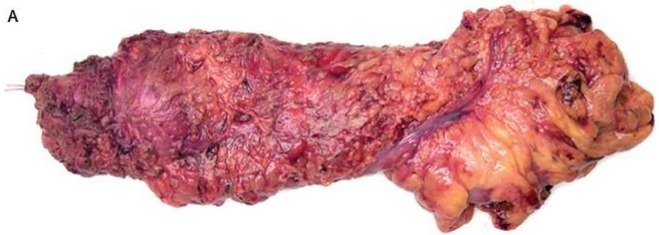
Rectal cancer & radiotherapy



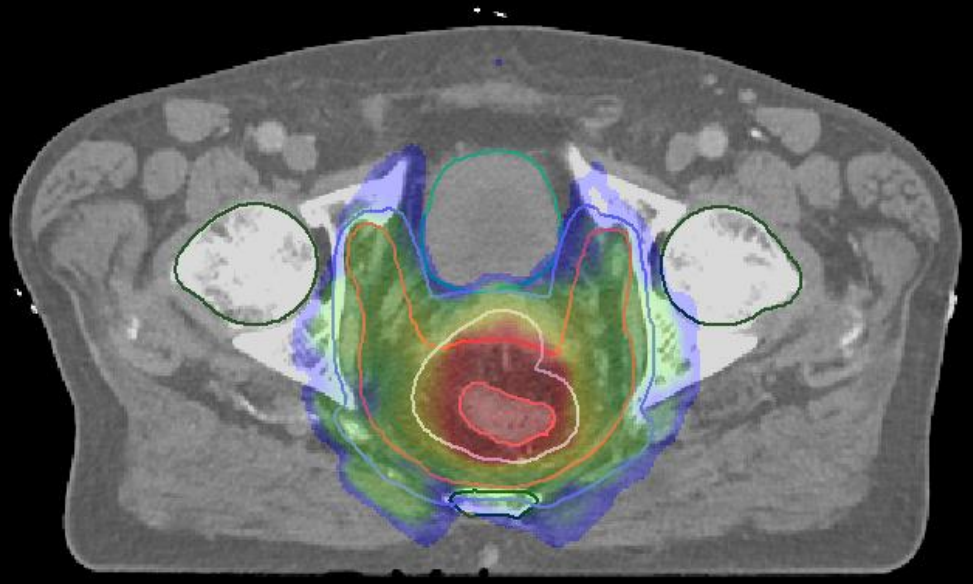
Preoperative radiotherapy in patients with advanced tumours



Surgery



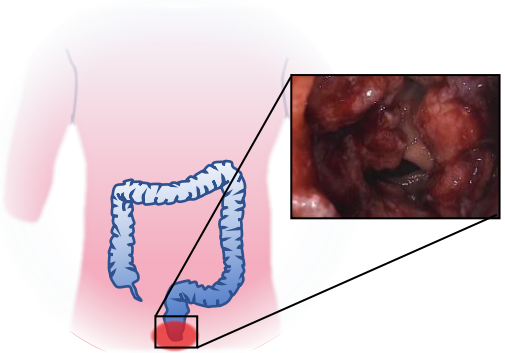
Rectal cancer & radiotherapy

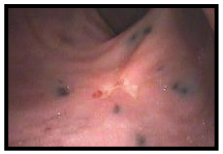


Radiotherapy for locally advanced rectal cancers

- Targeting volumes at risk of (locoregional) recurrence after surgery
  - Incomplete resection margins
  - Lymph node recurrences in unresected compartments
- Mesorectal, internal Iliac, obturator, pre-sacral, and obturator nodes
- Halves risk of locoregional recurrence
  - <5% for most patient groups

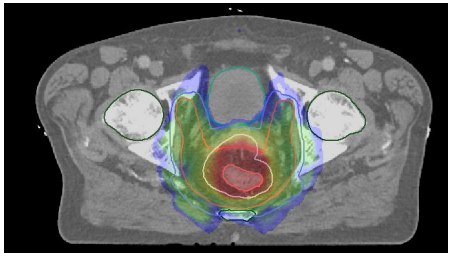
Rectal cancer & radiotherapy



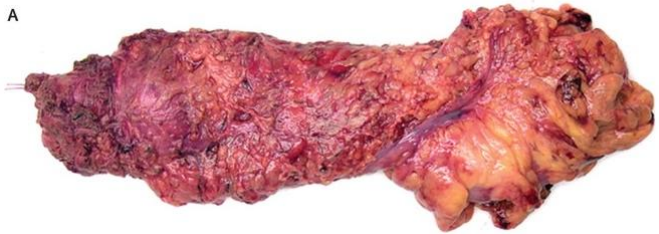


Clinical complete response (cCR) after radiotherapy

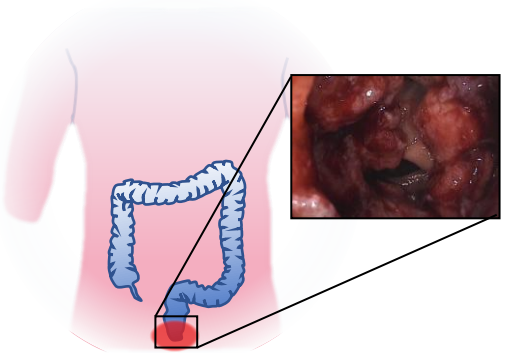
Preoperative radiotherapy in patients with advanced tumours

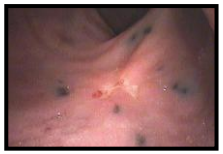


Surgery



Rectal cancer & radiotherapy





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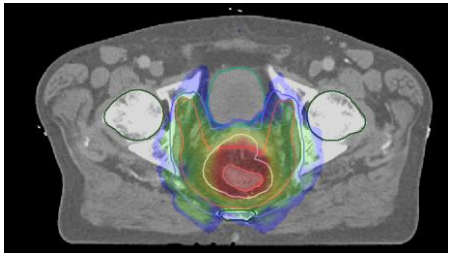


Can these patients avoid surgery?

Rectal cancer & radiotherapy

Can these patients avoid surgery?

Initial anecdotal and retrospective evidence

ORIGINAL ARTICLE

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

Long-term Results

Angelita Habr-Gama, MD, Rodrig*
Jorge Sabbaga, MD,† Ulysses Ribeiro
Fábio Guilherme Campos, MD, Desidério R*

VOLUME 29 · NUMBER 35 · DECEMBER 10 2011

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

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

Monique Maas, Regina G.H. Beets-Tan, Doenja M.J. Lambregts, Guido Lammering, Patty J. Nelemans, Sanne M.E. Engelen, Ronald M. van Dam, Rob L.H. Jansen, Meindert Sosef, Jeroen W.A. Leijtens, Karel W.E. Hulsewé, Jeroen Buijsen, and Geerard L. Beets

Rectal cancer & radiotherapy

Can these patients avoid surgery?

Randomised trial:
Surgery vs observation in complete responders

?

Terminated

During the execution time foreseen in the project, the expected number of patients was not reached.

Observation Versus Surgical Resection in Patients With Rectal Cancer Who Achieved Complete Clinical Response After Neoadjuvant Chemoradiotherapy

ClinicalTrials.gov ID NCT02052921

Sponsor Instituto do Cancer do Estado de São Paulo

Information provided by Instituto do Cancer do Estado de São Paulo (Responsible Party)

Last Update Posted 2020-05-11

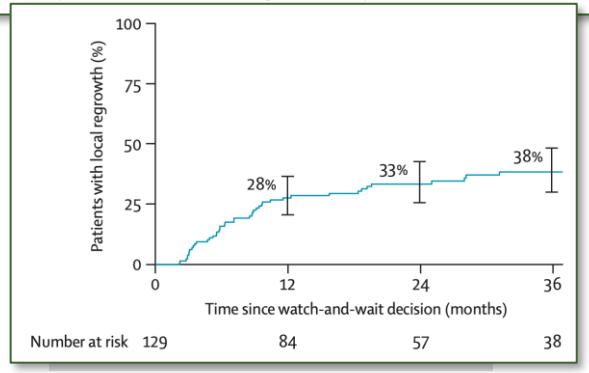
Original Enrollment (Estimated) *§ ICMJE	150	Enrollment (Actual) *§ ICMJE (Submitted: 2020-05-07)	13

Rectal cancer & radiotherapy

Can these patients avoid surgery?

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

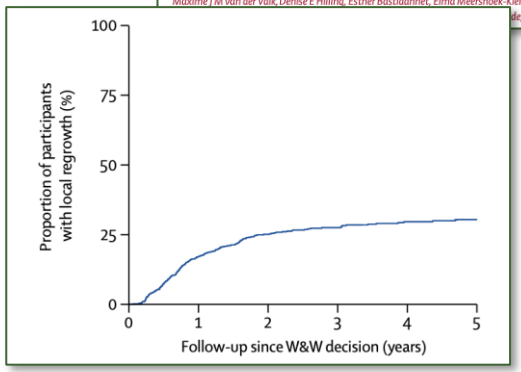
Andrew G Renehan, Lee Malcomson, Richard Emsley, Simon Gollins, Andrew Maw, Arthur Sun Myint, Paul S Rooney, Shabbir Susnerwala, Anthony Blower, Mark P Saunders, Malcolm S Wilson, Nigel Scott, Sarah T O'Dwyer

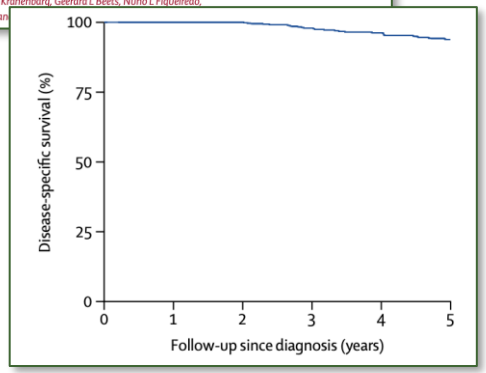


Prospective registries to systematically evaluate safety

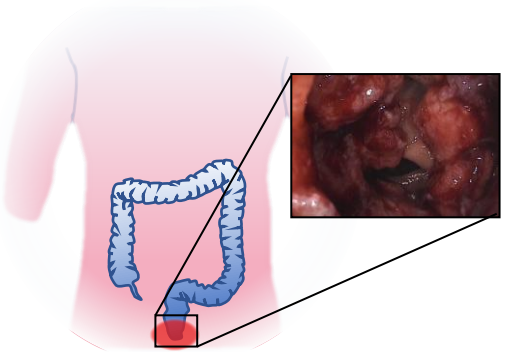
Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study

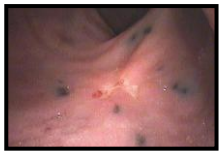
Maxime J M van der Valk, Denise E Hilling, Esther Bastiaannet, Elma Meershoek-Klein Kranenbarg, Geerard L Beets, Nuno L Figueiredo,





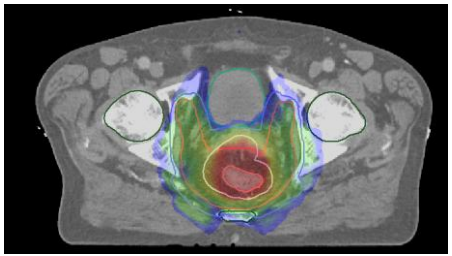
Rectal cancer & radiotherapy





Clinical complete response (cCR) after radiotherapy

Preoperative radiotherapy in patients with advanced tumours

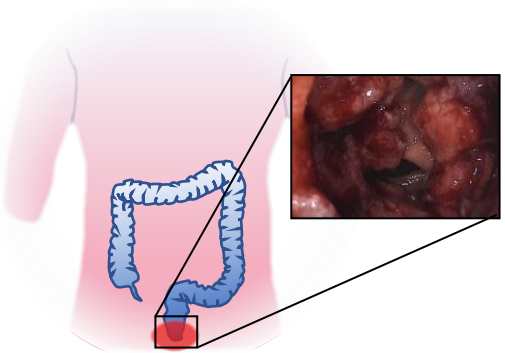


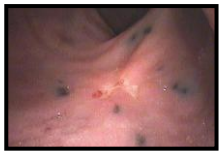
Can these patients avoid surgery?

Yes!

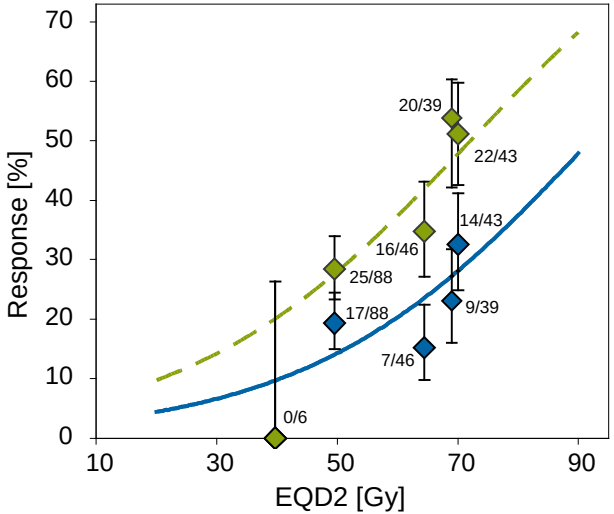
van der Valk et al. Lancet. 2018;391(10139):2537-2545.

Rectal cancer & radiotherapy





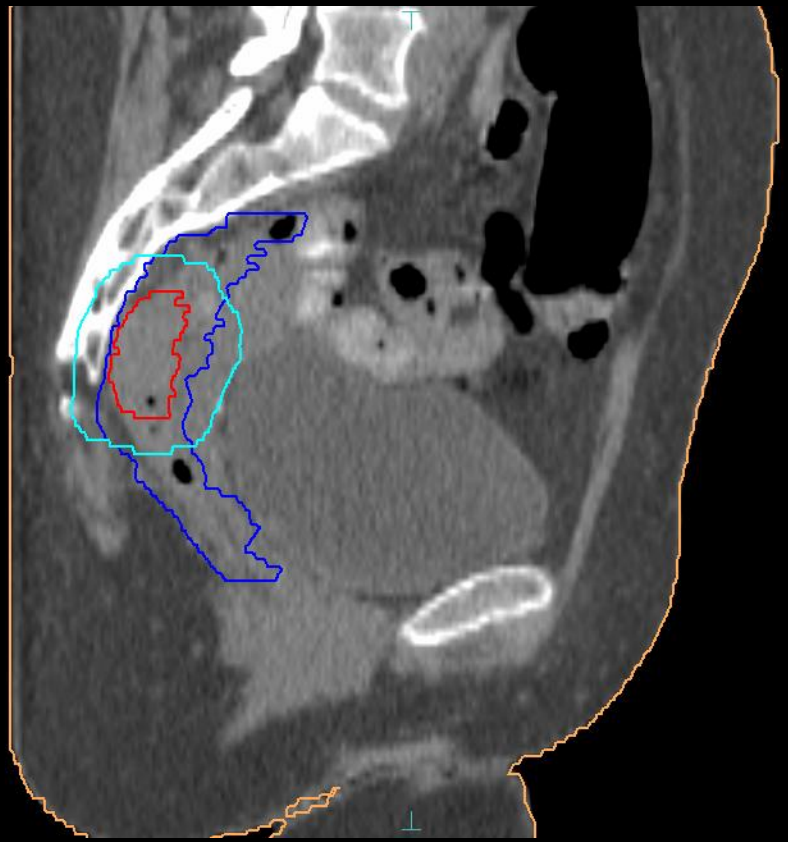
Probability of tumour disappearing (tumour regression) depends on the radiation dose

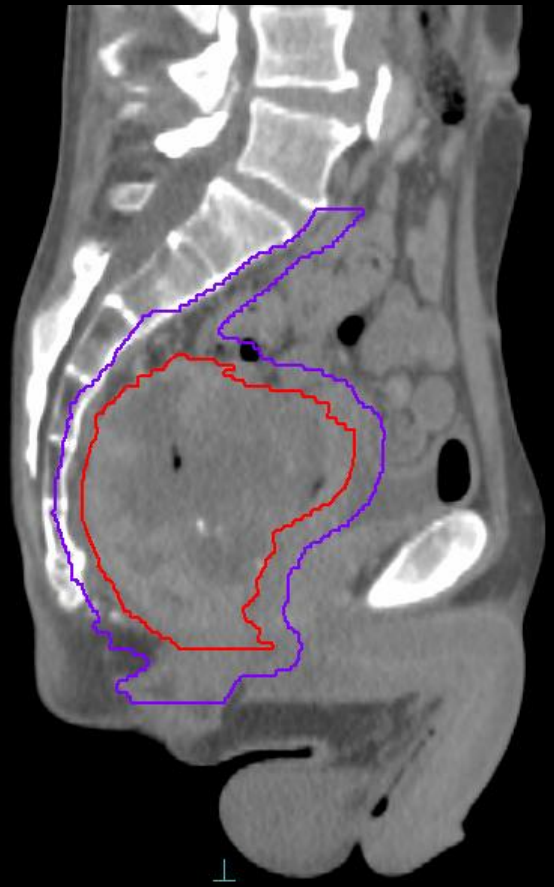


"Nearly gone" (TRG2)

"Completely gone" (TRG1)

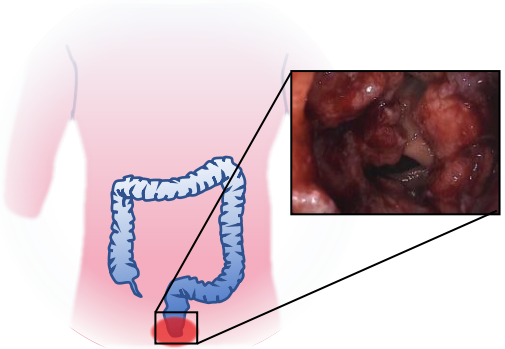
Appelt et al, IJROBP, 2013;85(1):74-80

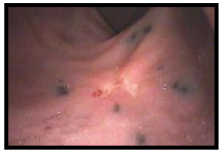




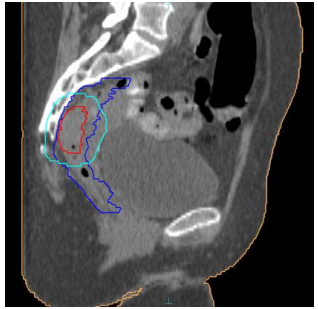
More patients (including elderly!) with small / early cancers

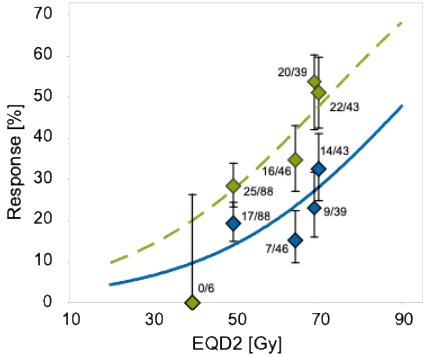
Rectal cancer & radiotherapy



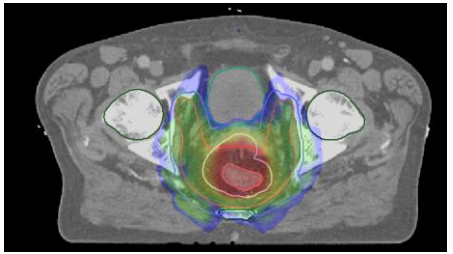


Complete response to radiotherapy





Definitive high-dose radiotherapy in patients with early / small tumours



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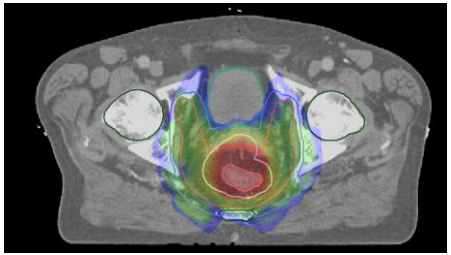


Anders Jakobsen

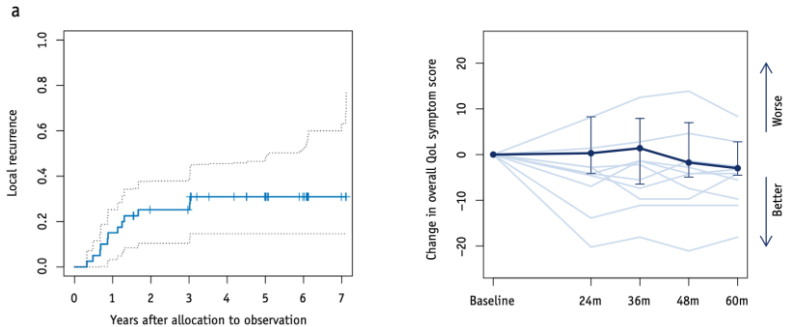
John Pløhn

Watchful Waiting I

Single centre, 51 patients, T1-3, N0-1

55% of treated patients avoided surgery
(at 5 years after treatment)

Quality of life maintained
(despite high dose radiotherapy)

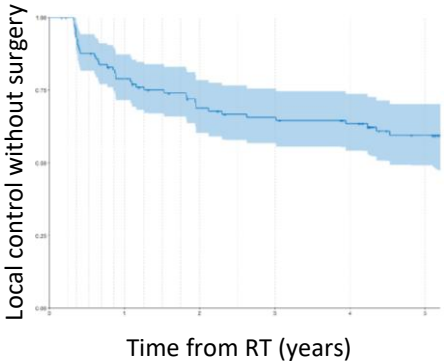


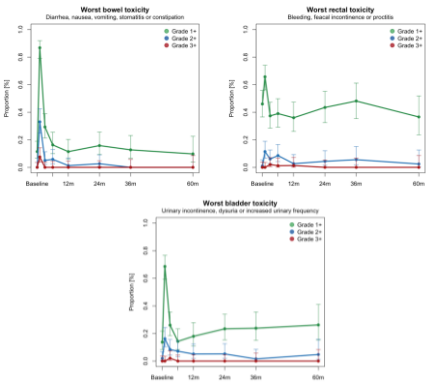
Appelt et al. Lancet Oncol 2015; Dizdarevic et al. IJROBP 2020

Watchful Waiting II

Multicentre, 108 patients, T1-3a, N0-1

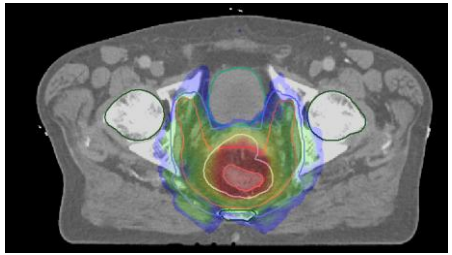
89% complete response
69% organ preservation with no surgery at 2 years
~80% with no TME



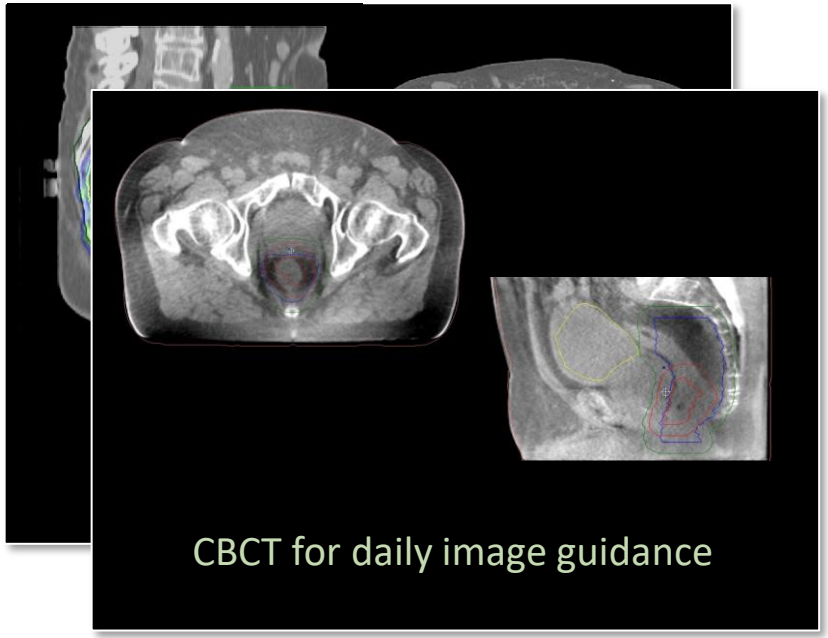


Poulsen et al (in preparation)

Definitive high-dose radiotherapy in patients with early / small tumours



- **What is the optimal radiotherapy technique?**



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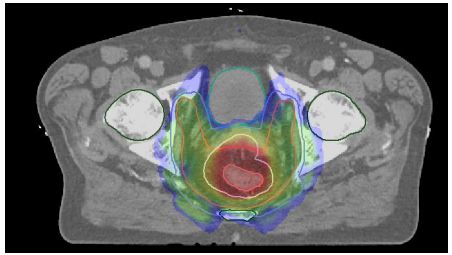
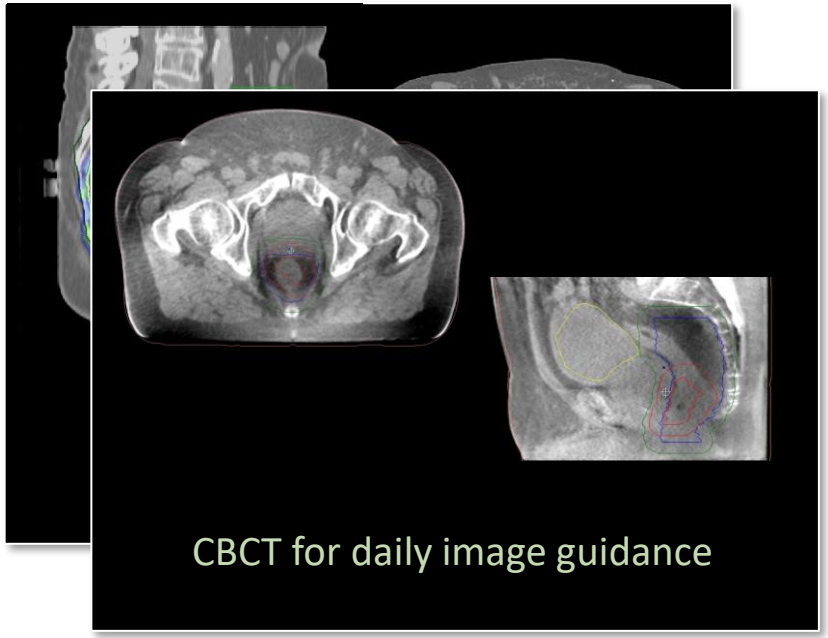
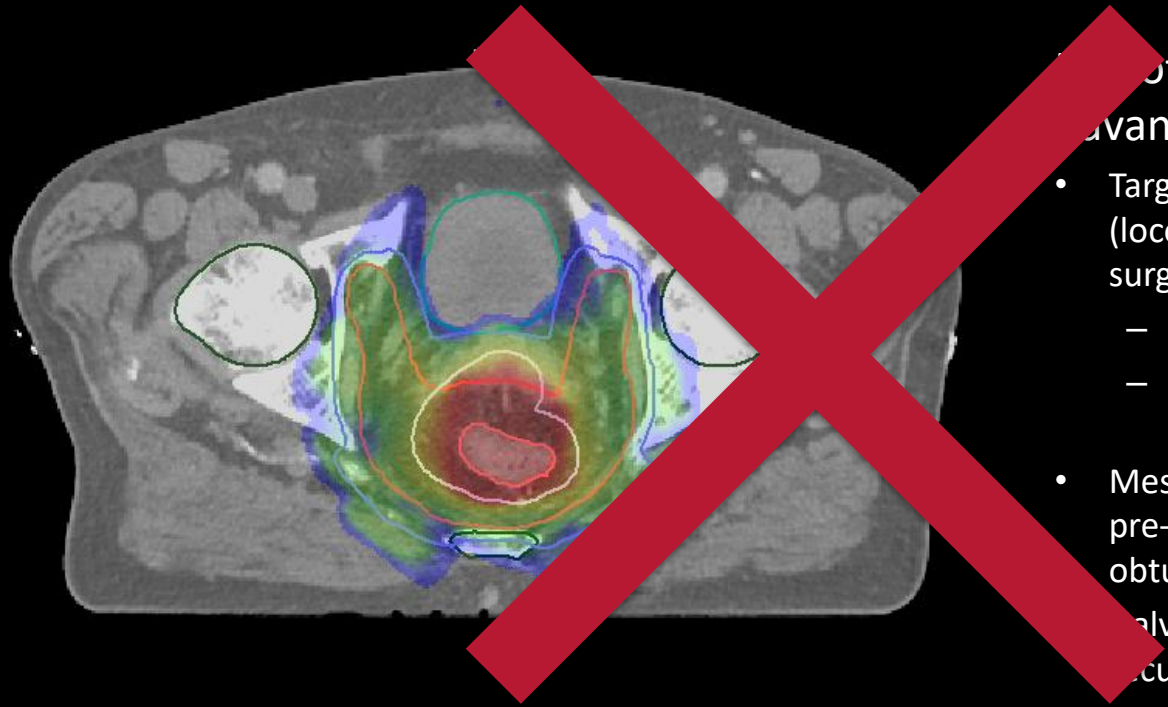


- What is the optimal radiotherapy technique?
- **What is the optimal radiotherapy target?**



Rectal cancer & radiotherapy



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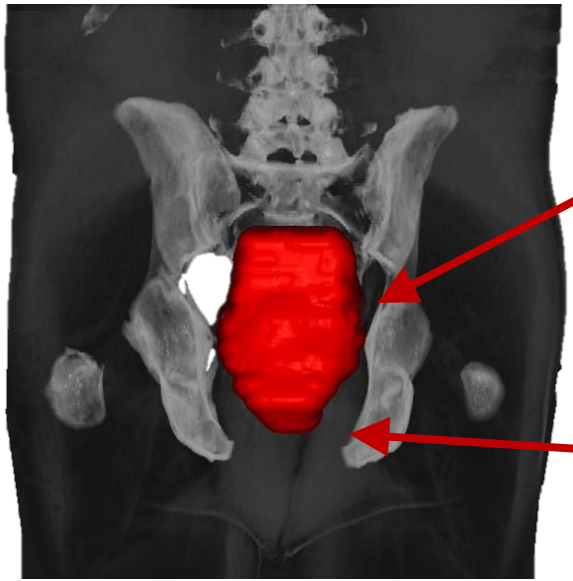
- Targeting volumes at risk of (locoregional) recurrence after surgery
  - Incomplete resection margins
  - Lymph node recurrences in unresected compartments
- Mesorectal, internal Iliac, obturator, pre-sacral, mesorectal and obturator nodes
- lves risk of locoregional currence
  - <5% for most patient groups

Overtreatment for early, low risk rectal cancers

Risk adapted radiotherapy volumes for early rectal cancers

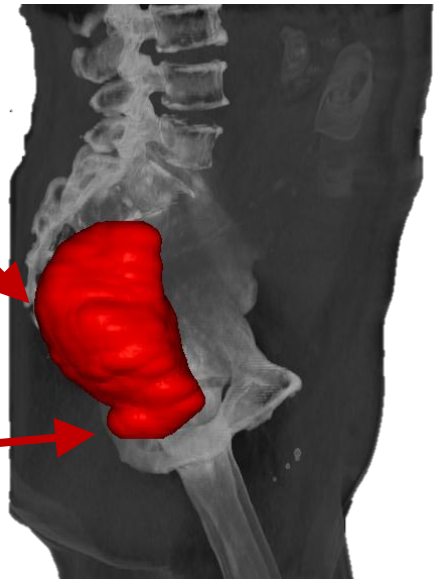


Mesorectum-only treatment

50% reduction in treatment volume (PTV)

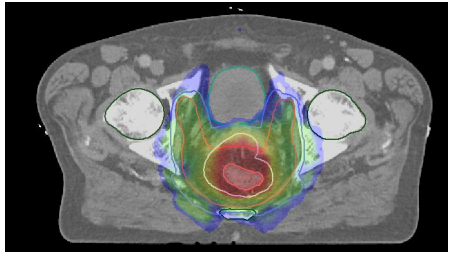
Limited irradiation of anal cancal

CTV 2cm below tumour, at most 1cm into anal canal



Peters et al. Clin Transl Radiat Oncol. 2020
Appelt et al. Tech Innov Patient Support Radiat Oncol. 2019

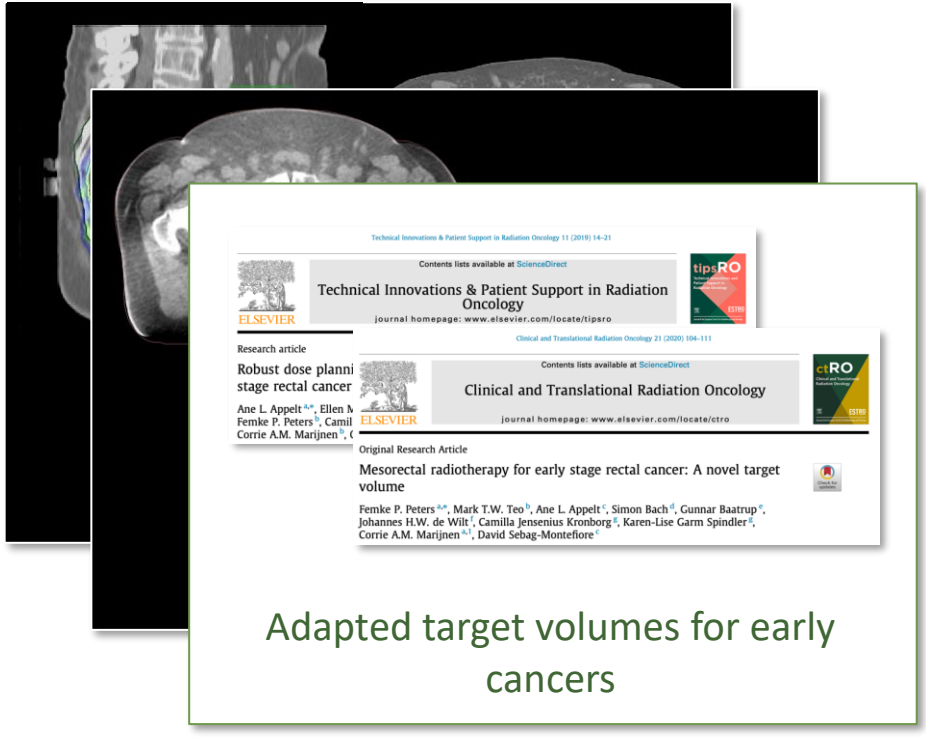
Definitive high-dose radiotherapy in patients with early / small tumours



- What is the optimal radiotherapy technique?
- **What is the optimal radiotherapy target?**

David Sebag Montefiore

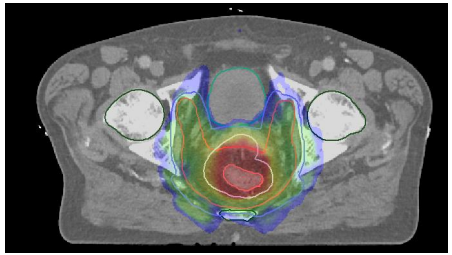
Corrie Marijnen



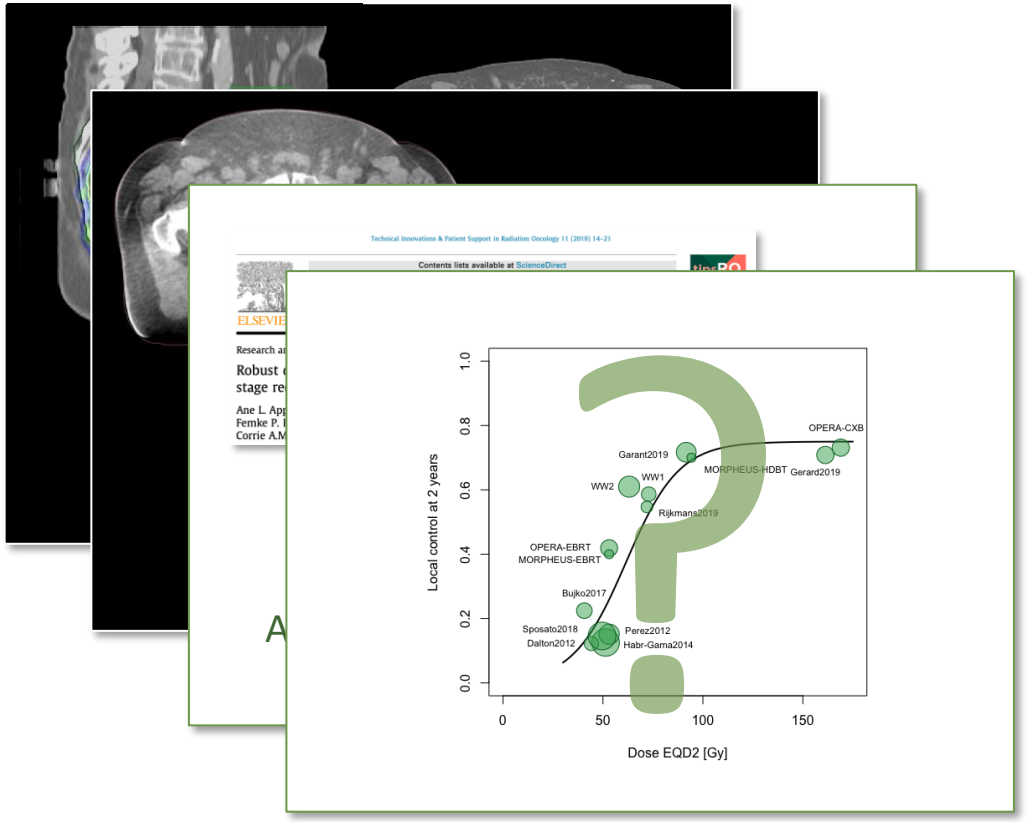
Adapted target volumes for early cancers

Developed for the STAR-TREC trial

Definitive high-dose radiotherapy in patients with early / small tumours



- What is the optimal radiotherapy technique?
- What is the optimal radiotherapy target?
- **What is the optimal combination of radiotherapy dose and volume?**



APHRODITE

A Phase II trial of Higher RadiOtherapy Dose In The Eradication of early rectal cancer

Early (T1-3b, N0-N1b), small (≤5 cm) tumours

T1-3b, N0-1b
rectal cancer

A Phase II trial of Higher RadiOtherapy Dose In The Eradication of early rectal cancer

T1-3b, N0-1b rectal cancer

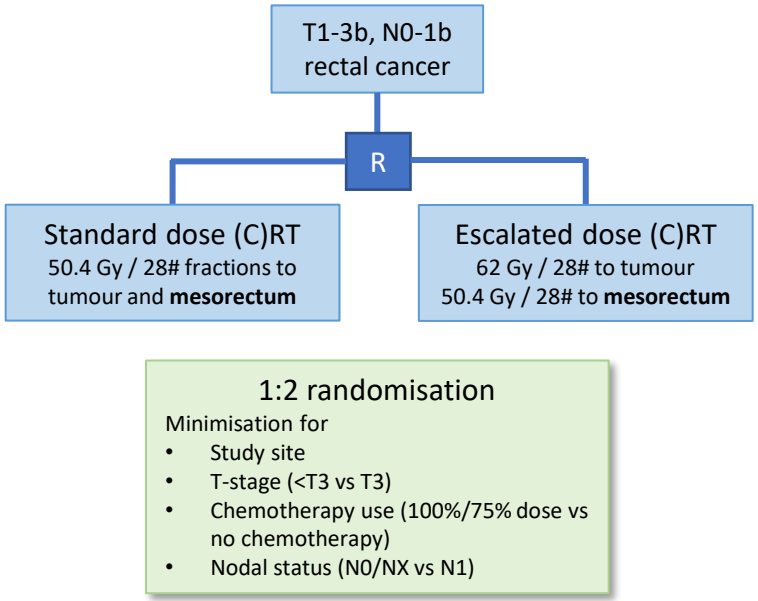
Early (T1-3b, N0-N1b), small (≤5 cm) tumours

Patients not candidates for primary surgery

- Frailty, comorbidities or other surgical risks
- Unable to manage stoma
- Strong patient preference for organ preservation

APHRODITE

A Phase II trial of Higher RadiOtherapy Dose In The Eradication of early rectal cancer



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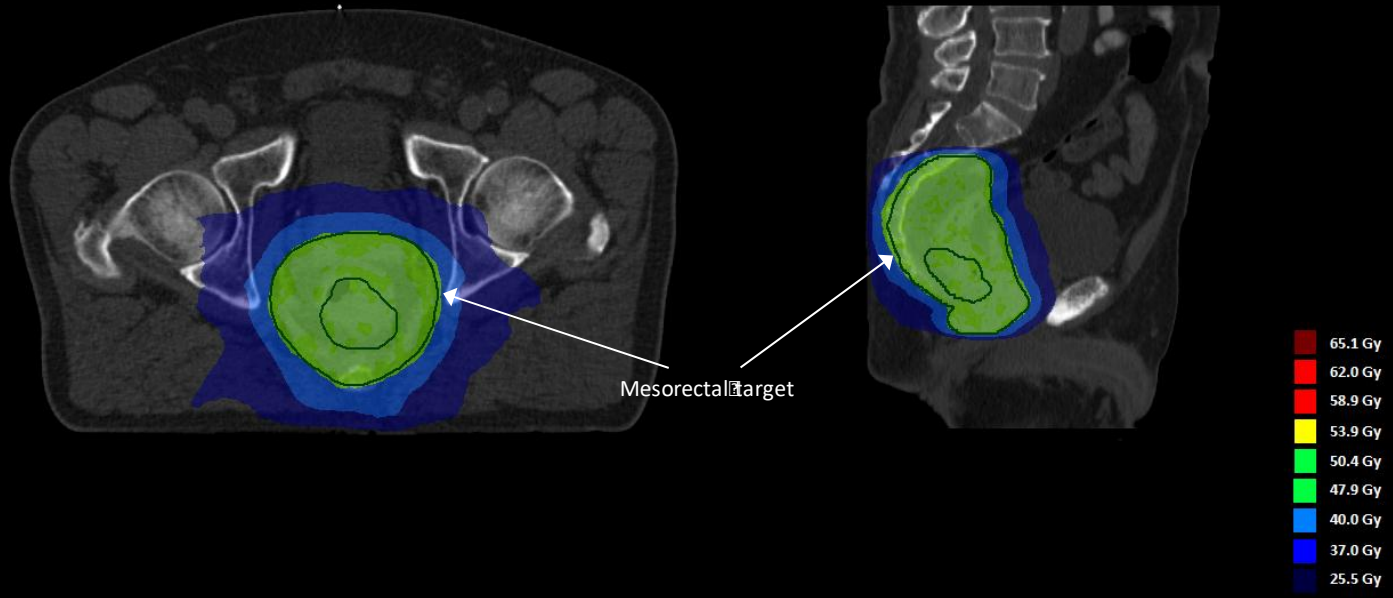
Risk-adapted (chemo)radiotherapy

- Mesorectal only radiotherapy

Hudson et al. BMJ Open 2022;12:e049119 (ISRCTN16158514)

Mesorectal radiotherapy – 50.4 Gy to mesorectum and primary tumour



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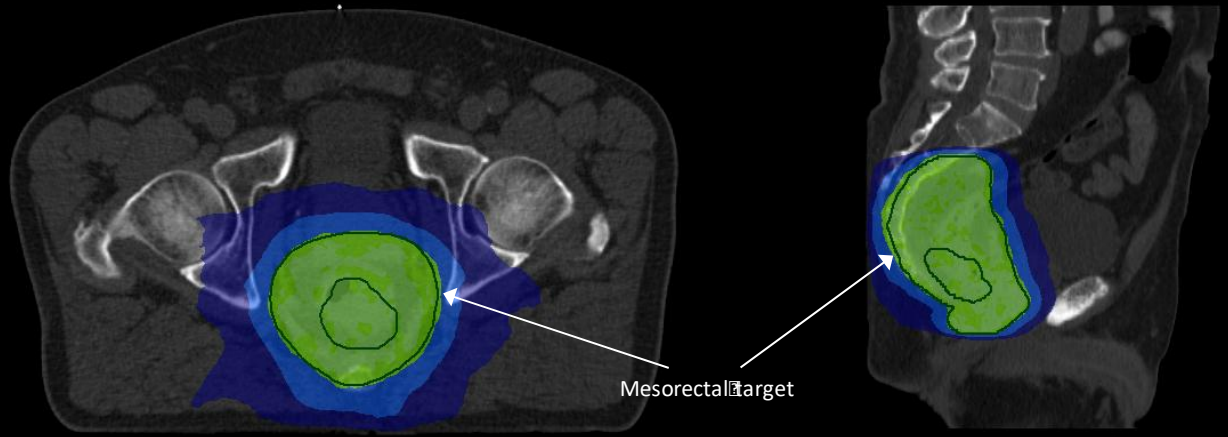
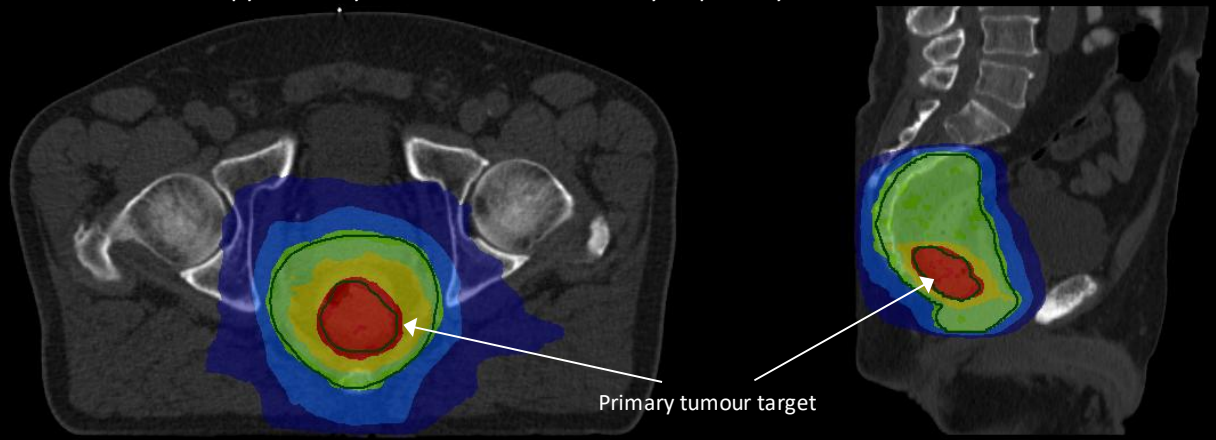
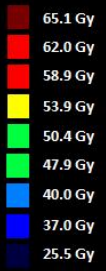


Mesorectal radiotherapy - 50.4 Gy to mesorectum and 62 Gy to primary tumour





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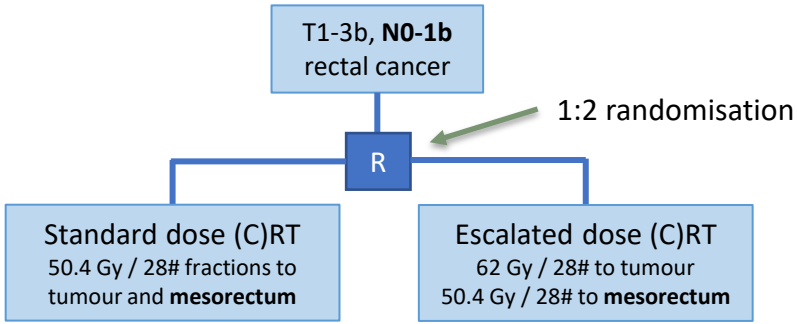

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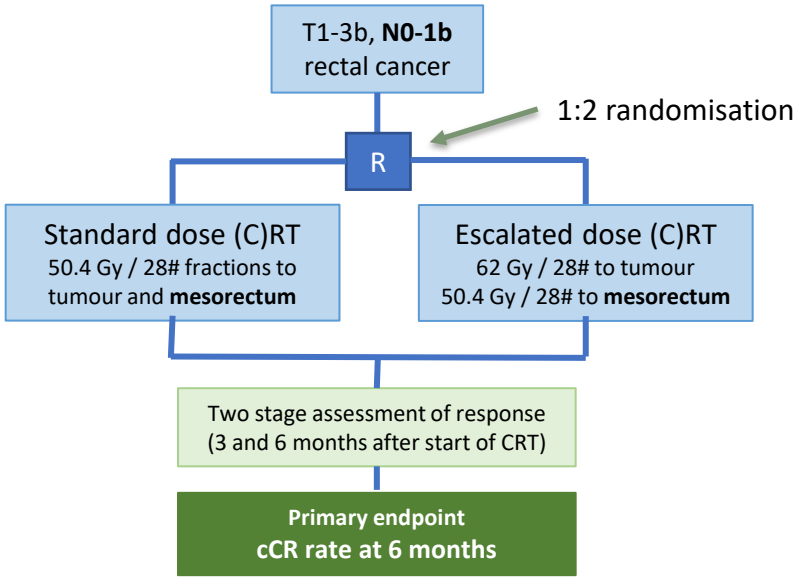

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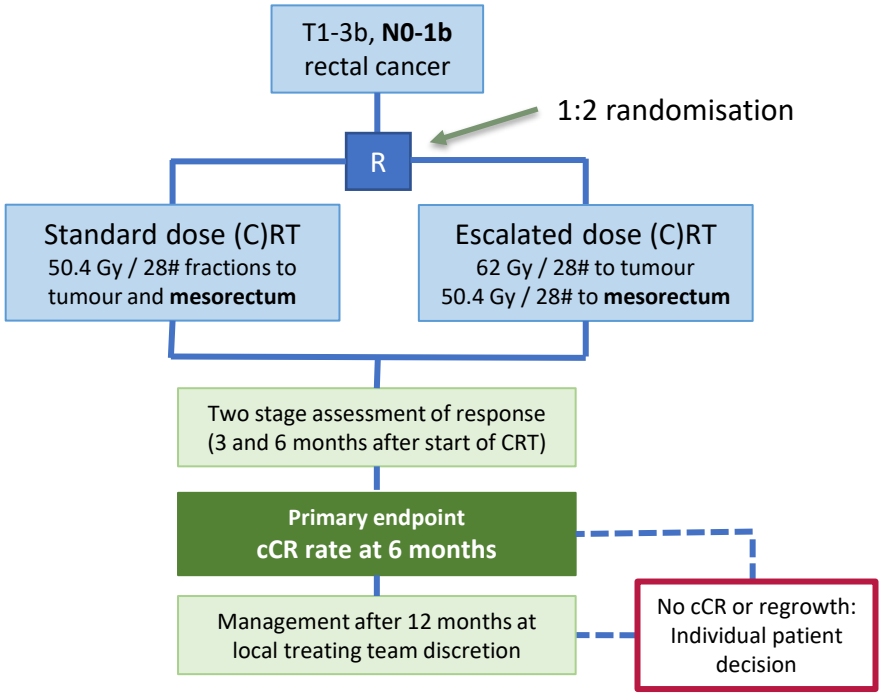

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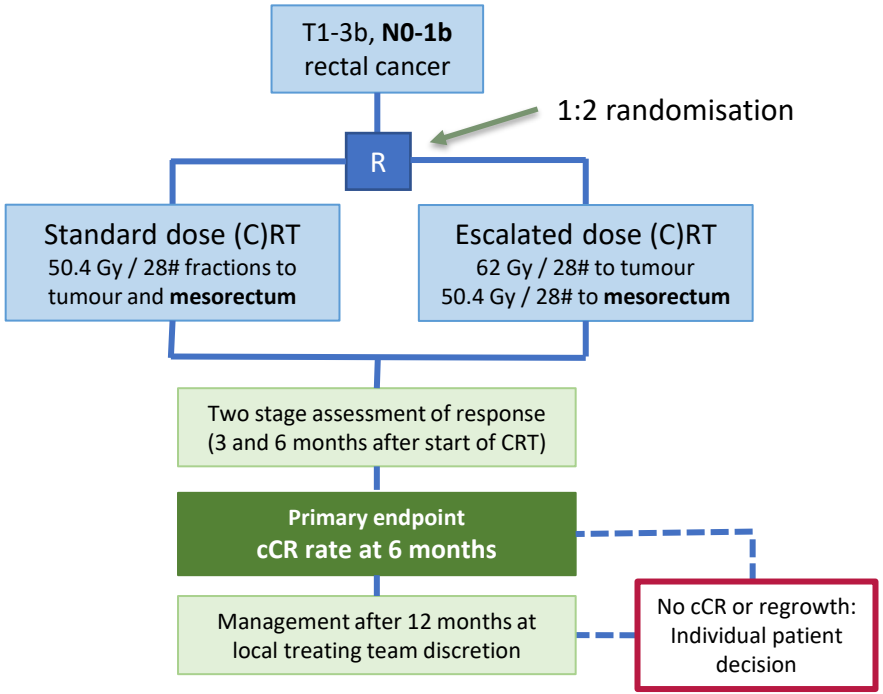

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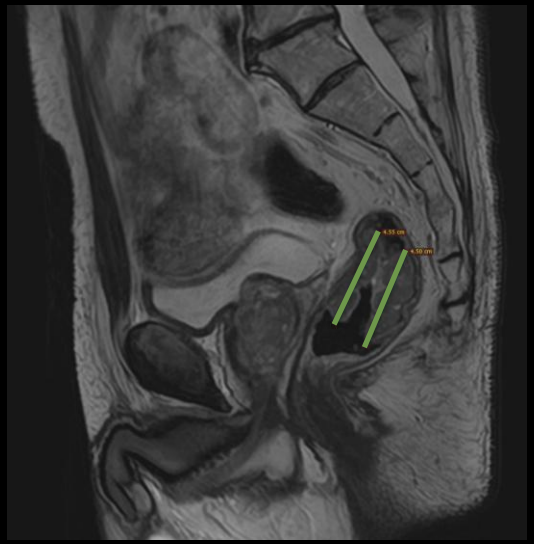
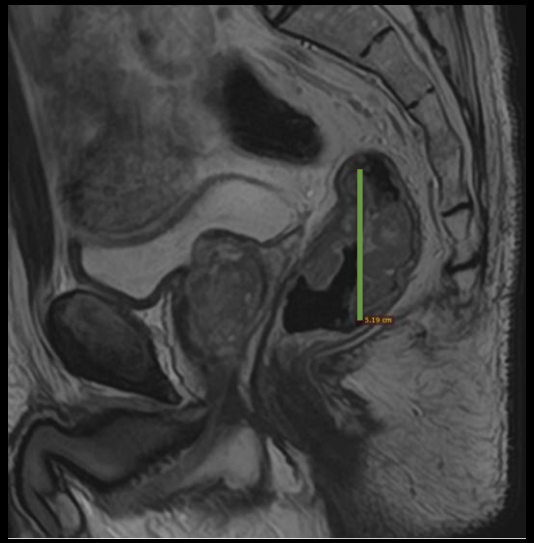
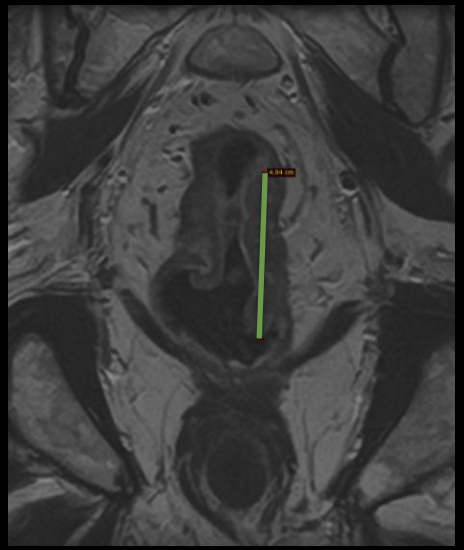
How do you define tumour size??

5cm? In which direction? In which plane?







“The tumour needs to be 5cm or less in the craniocaudal diameter to be eligible, irrespective of the longest diameter in any other plane.”

Actual longest length of tumour in a coronal oblique plane

APHRODITE

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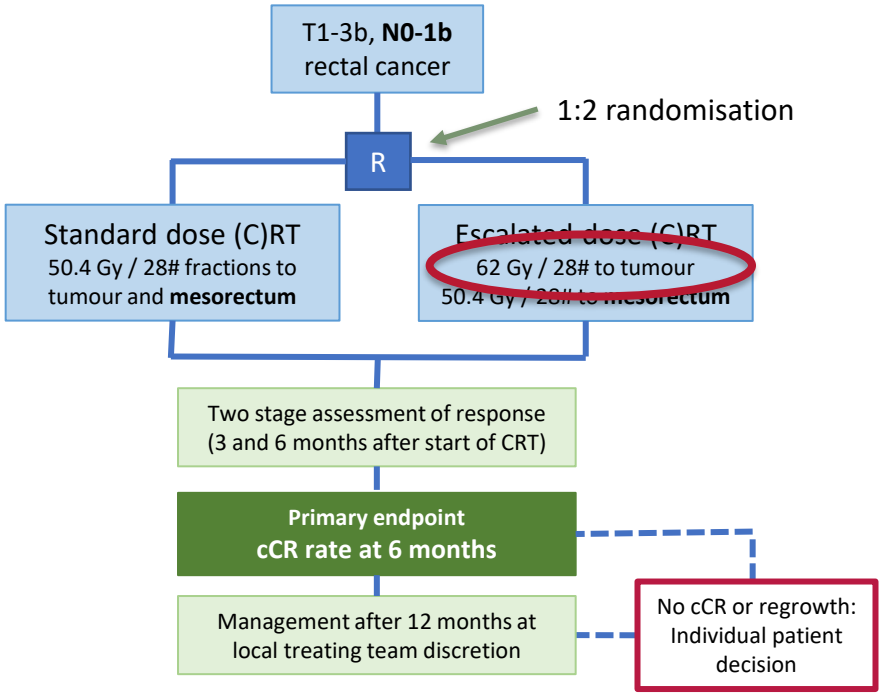

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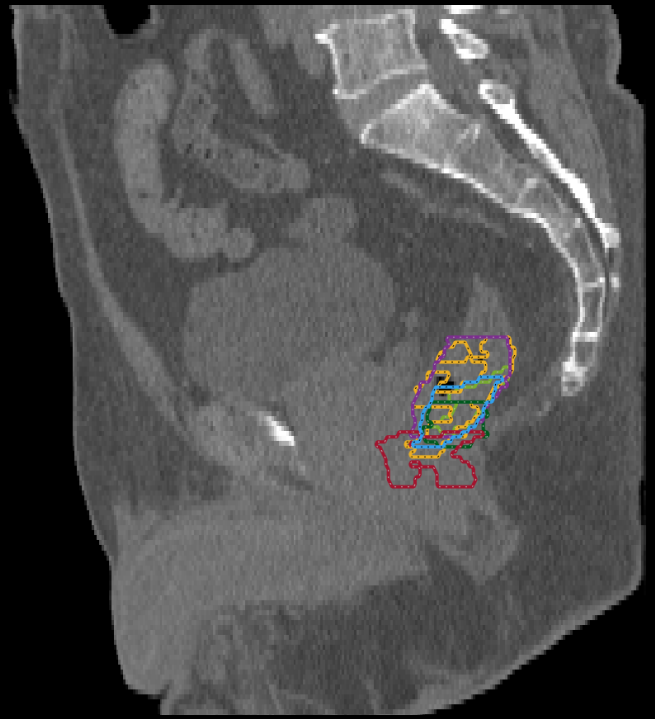
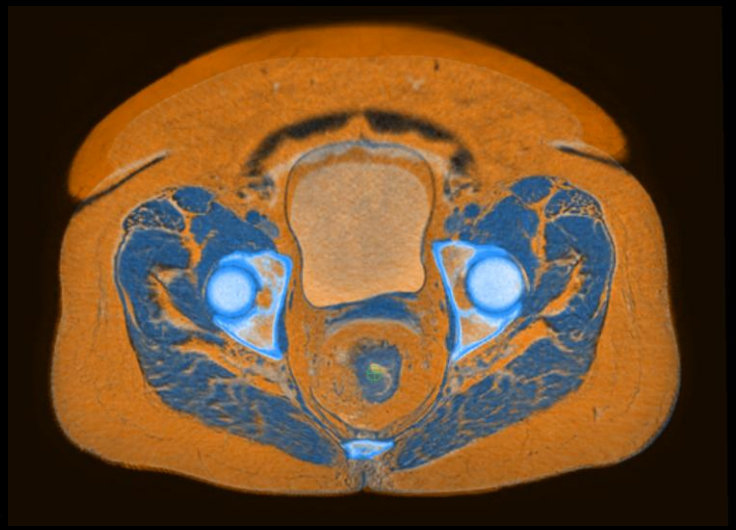
Variation in tumour outlining may impact boost planning





APHRODITE radiotherapy workshop, unpublished data

Radiotherapy treatment planning MRI from LTHT, UK

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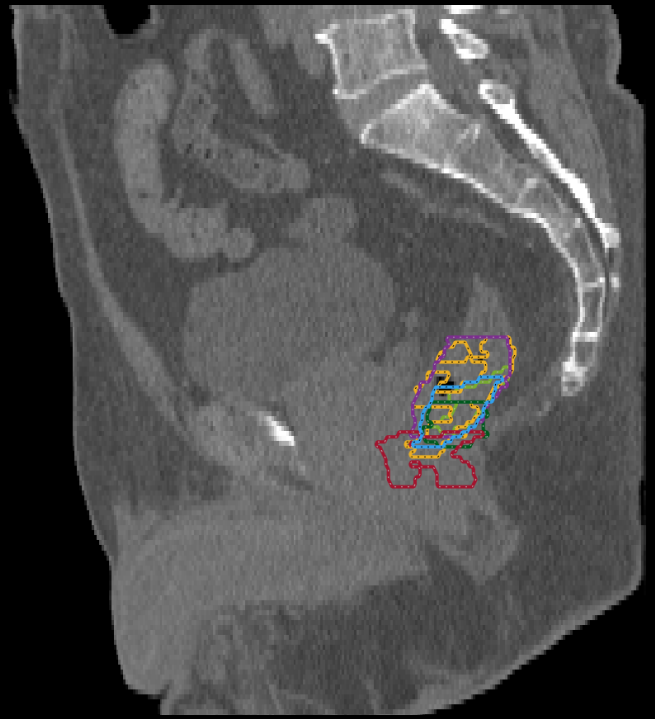

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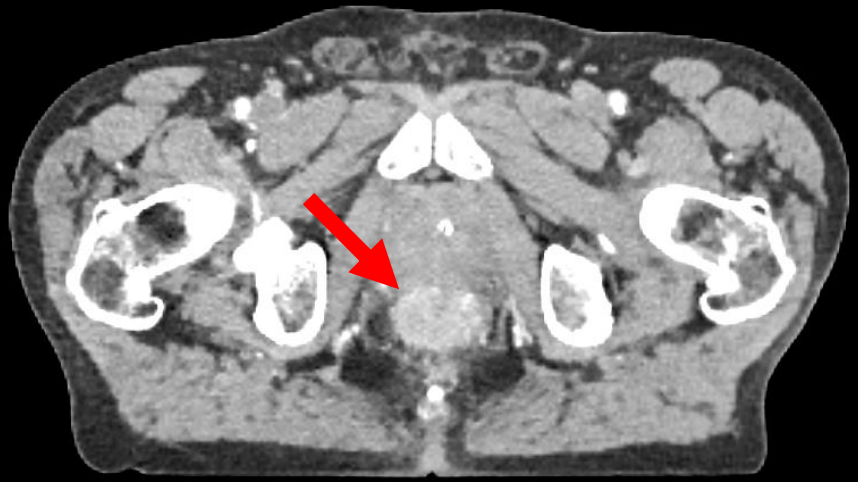
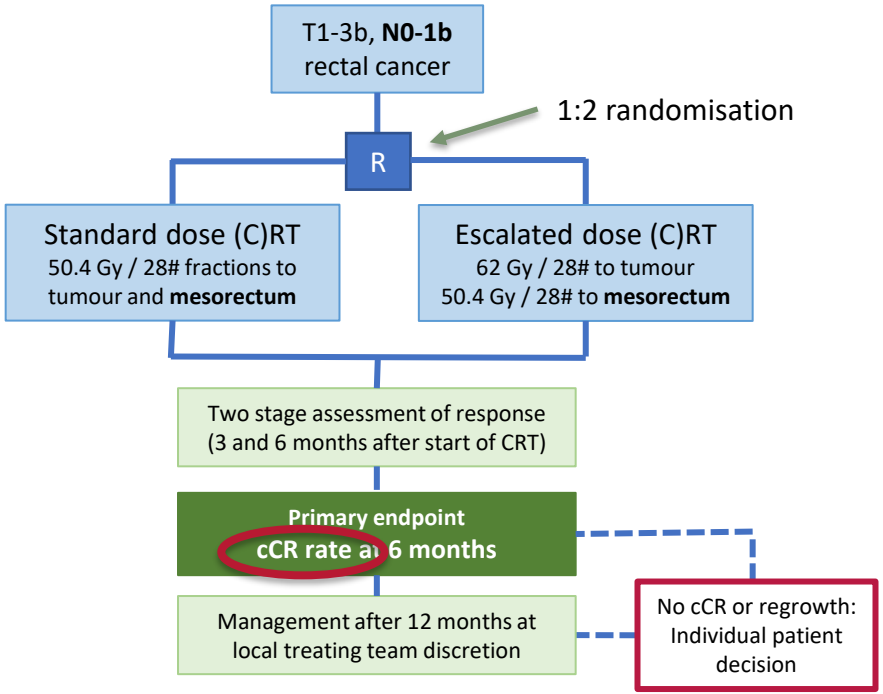


Radiotherapy planning CT for locally advanced cancer, Rigshospitalet, DK

APHRODITE

A Phase II trial of Higher RadiOtherapy Dose In The Eradication of early rectal cancer



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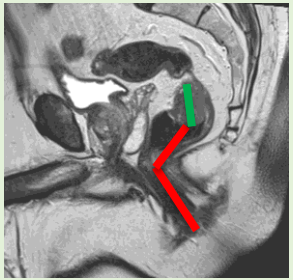
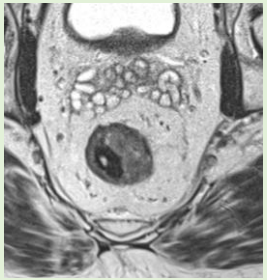
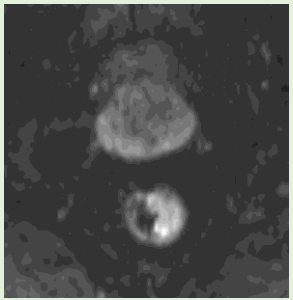
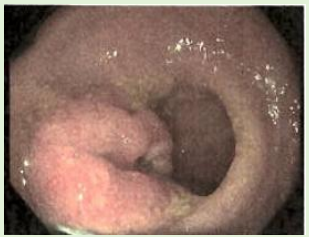
APHRODITE primary endpoint

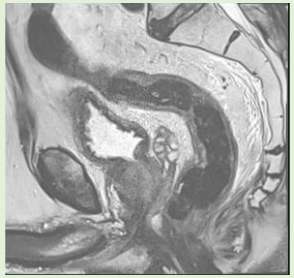
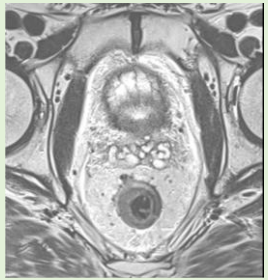
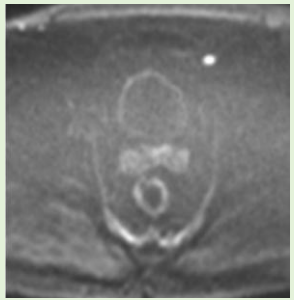
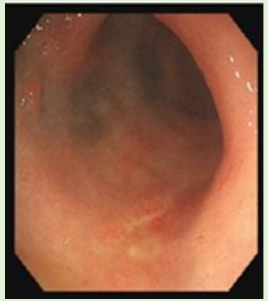
Clinical complete response

Baseline imaging

T2, N0, 4.2cm
CRM-, EMVI-

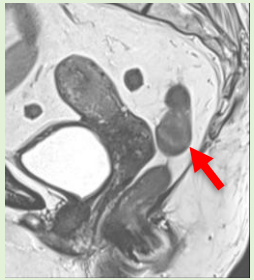
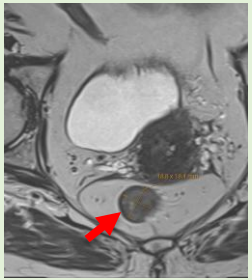
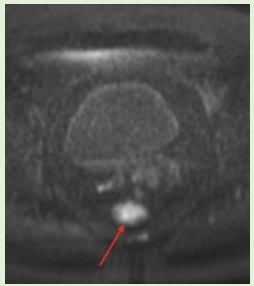
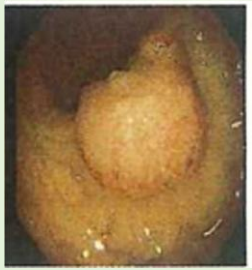
6 months assessment

APHRODITE primary endpoint

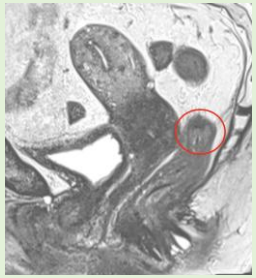
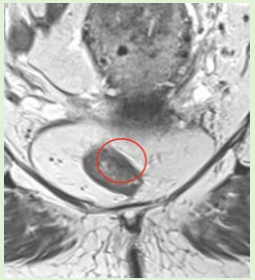
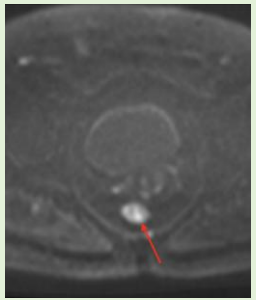
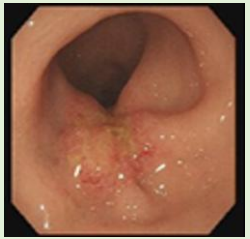
Clinical incomplete response

Baseline imaging

T2, N0, 3.2cm
CRM-, EMVI-

6 months assessment

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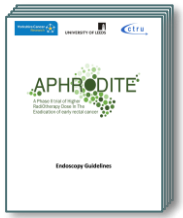
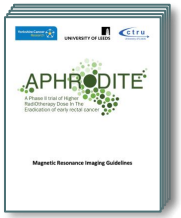


Endoscopy guidelines



MRI assessment guidelines

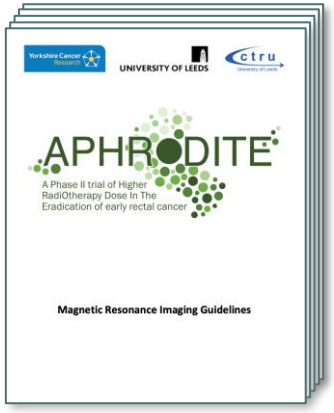
Radiology / MRI workshop

On-trial QA

Central review of first two patients from each site
- Endoscopy images (baseline, 3m, 6m)
- MRIs (baseline, 3m, 6m)

Fokas et al. International consensus recommendations on key outcome measures for organ preservation after (chemo)radiotherapy in patients with rectal cancer. Nat Rev Clin Oncol. 2021 Dec;18(12):805-816

APHRODITE primary endpoint



MRI assessment guidelines

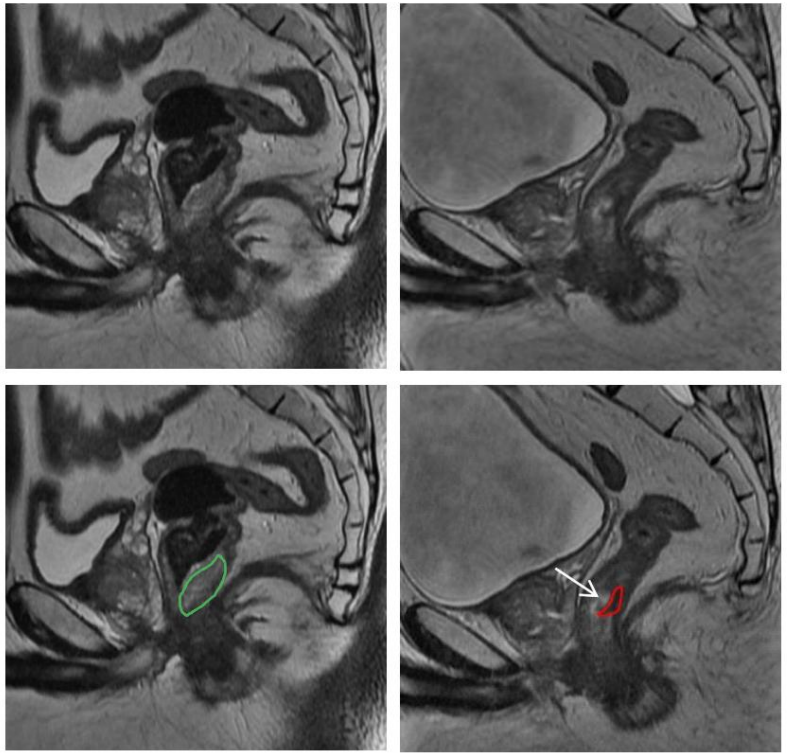
Rohit Kochhar

Ravi Adapala

mrTRG Grade 1

Pre-treatment T2-weighted sagittal MRI :Green outline indicates substantial low rectal tumour of intermediate signal intensity T2N0

MRI at 3 months post-CRT: Complete resolution of tumour with a small fibrotic low signal scar (red outline) and high signal intensity submucosal oedema (white arrow)



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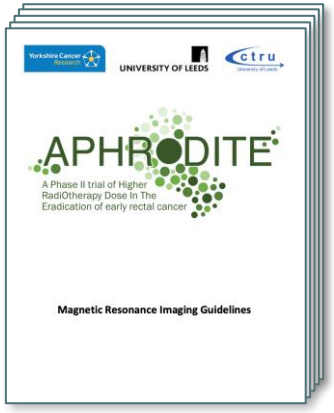

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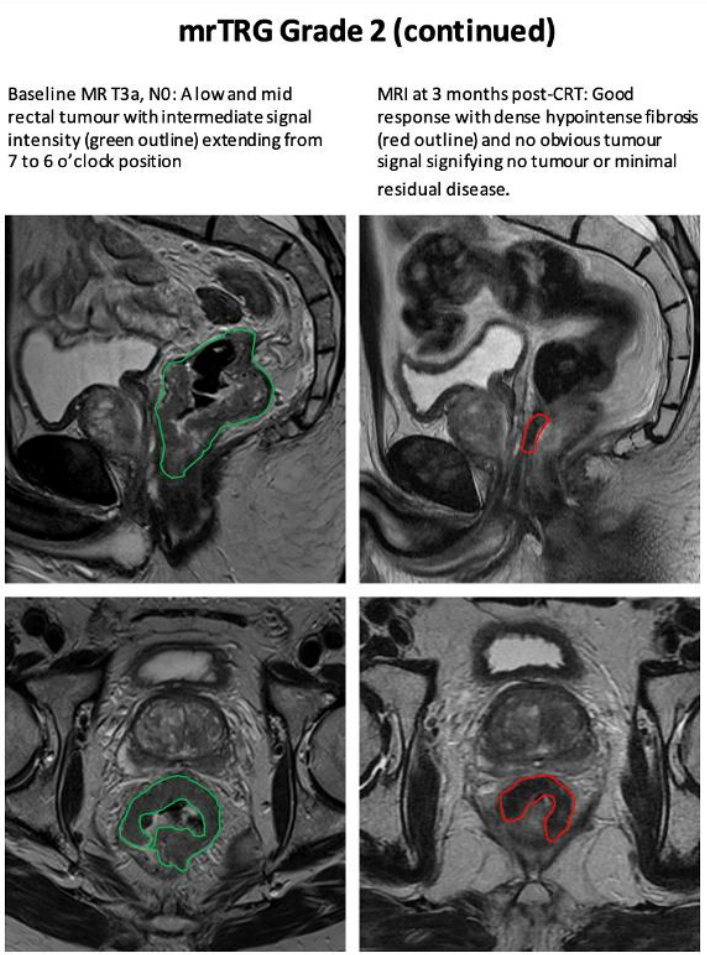

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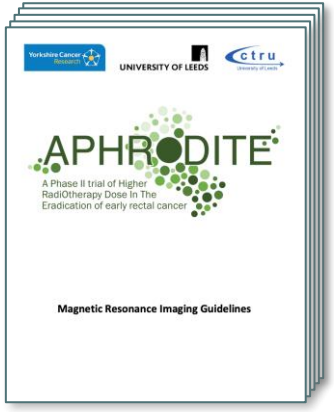


MRI assessment guidelines

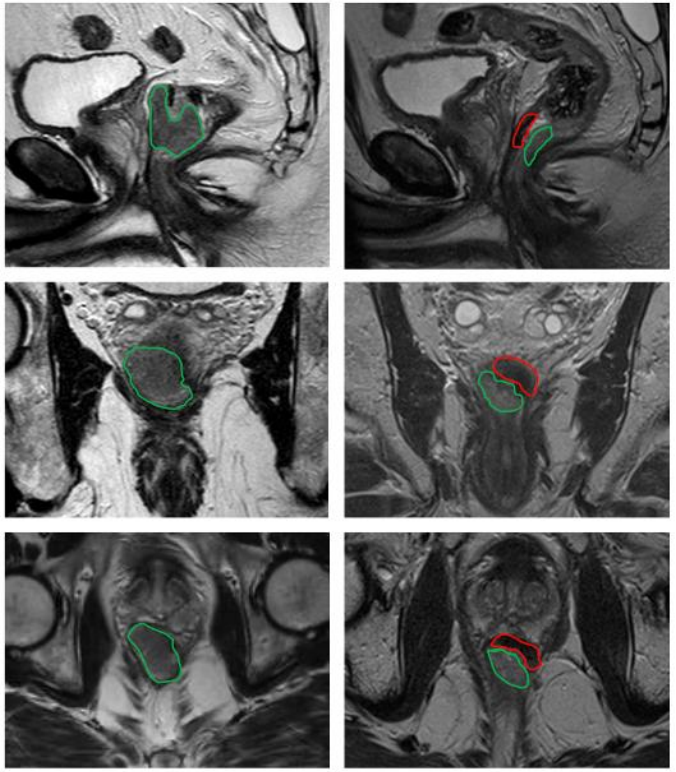
Rohit Kochhar

Ravi Adapala

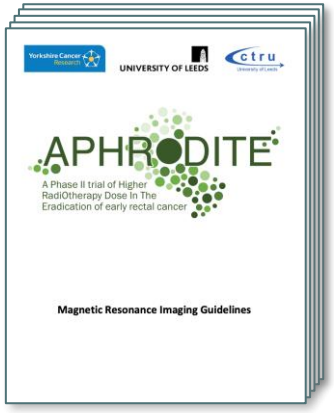
mrTRG Grade 3 (continued)

Pre-treatment MRI showing a polypoidal low rectal tumour with intermediate signal intensity T2NX (green outline)

MRI 3 months post-CRT showing moderate response with both intermediate signal intensity (green outline) signifying residual tumour and fibrosis (red outline)



APHRODITE primary endpoint



MRI assessment guidelines

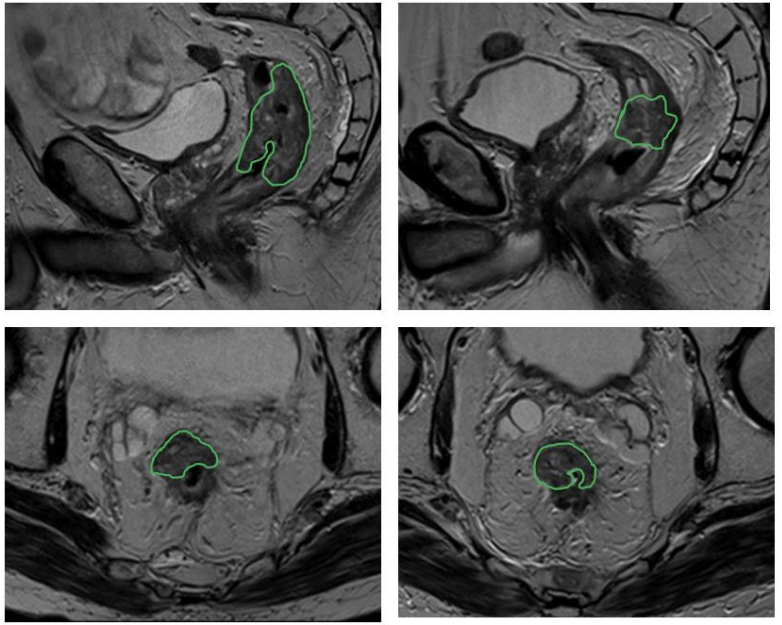
Rohit Kochhar

Ravi Adapala

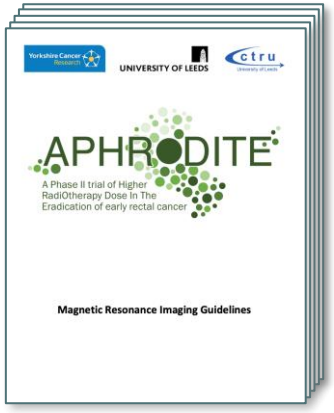
mrTRG Grade 4 (continued)

Pre-treatment MRI showing a circumferential mid rectal tumour with intermediate signal intensity T3N0 (green outline)

MRI 3 months post-CRT showing minimal response with mostly tumour signal (green outline) and minimal fibrosis



APHRODITE primary endpoint



MRI assessment guidelines

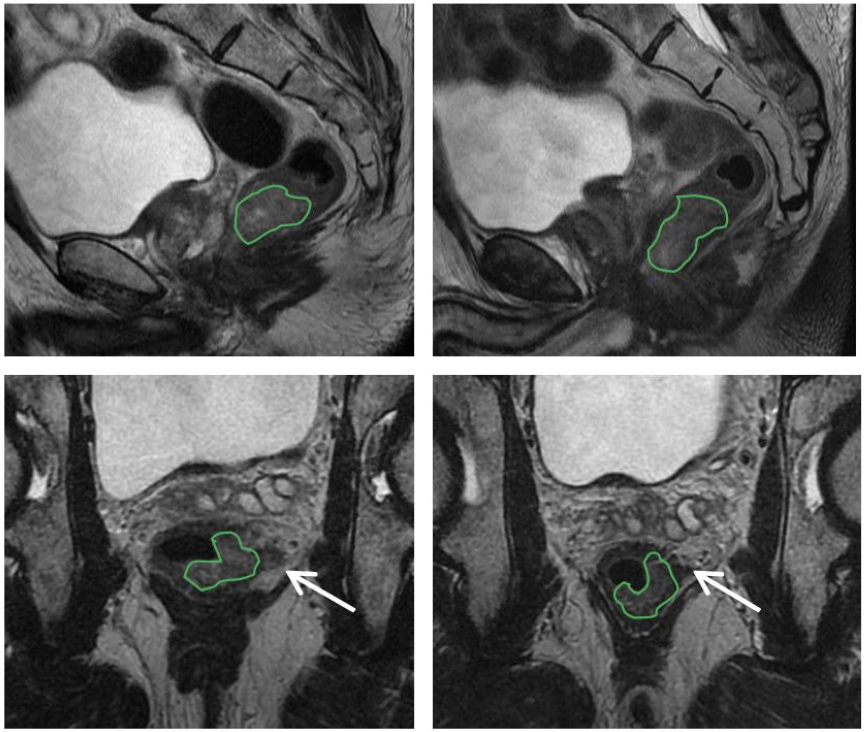
Rohit Kochhar

Ravi Adapala

mrTRG Grade 5 (continued)

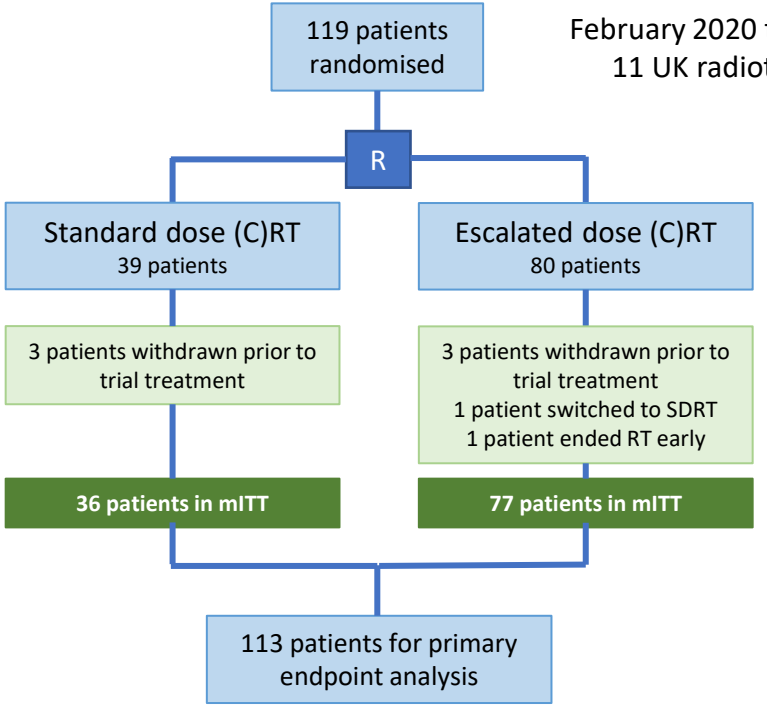
Pre-treatment MRI showing a low rectal tumour extending from 1 to 7 o'clock position (green outline) with contiguous EMVI (white arrow)

MRI 3 months post CRT shows essentially no change in the primary tumour (green outline) and some response in the EMVI (white arrow)



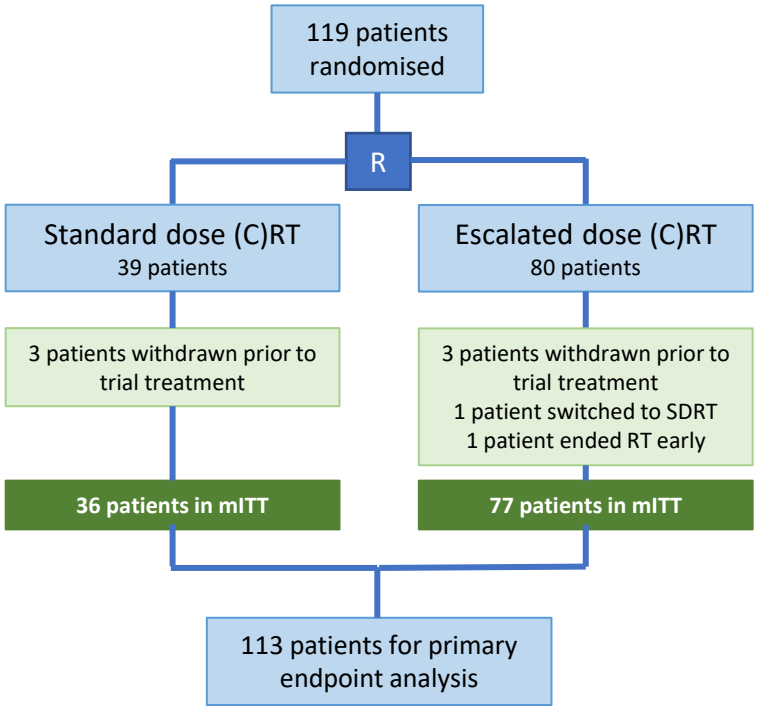
APHRODITE

A Phase II trial of Higher RadiOtherapy Dose In The Eradication of early rectal cancer



February 2020 to November 2024
11 UK radiotherapy centres

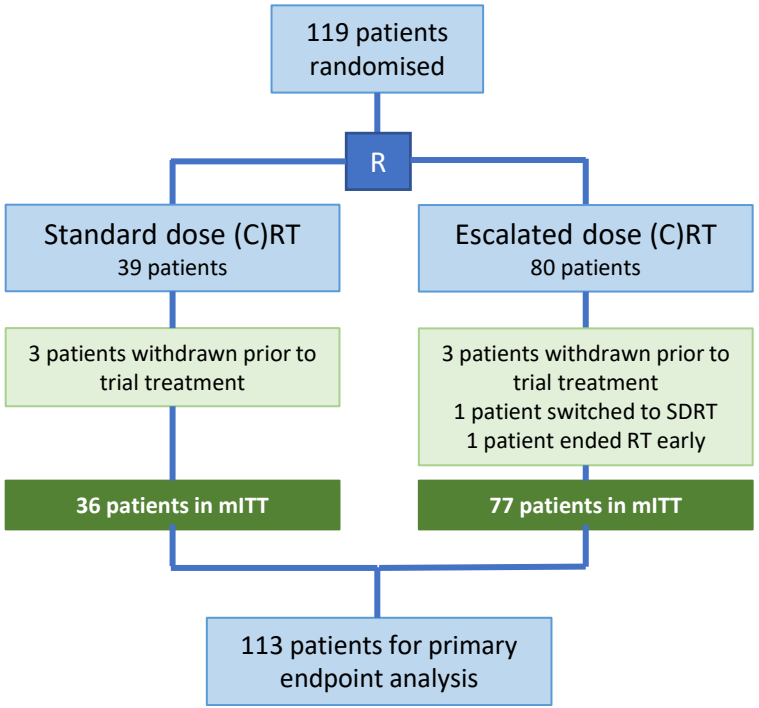
A Phase II trial of Higher RadiOtherapy Dose In The Eradication of early rectal cancer



	Standard dose CRT	Escalated dose CRT
Sex		
Male	20 (55.6%)	51 (66.2%)
Female	16 (44.4%)	26 (33.8%)
Age (years)		
Median (IQR)	70.5 (60.8, 80.9)	70.2 (60.5, 76.6)
Baseline PS		
0	21 (58.3%)	55 (71.4%)
1	11 (30.6%)	15 (19.5%)
2	4 (11.1%)	7 (9.1%)
Baseline T stage		
T1	2 (5.6%)	4 (5.2%)
T2	25 (69.4%)	51 (66.2%)
T3a	6 (16.7%)	15 (19.5%)
T3b	3 (8.3%)	7 (9.1%)
Tumour size – diameter (mm)		
Median (IQR)	31.5 (25.0, 38.0)	33.0 (25.0, 39.0)
Baseline N stage		
NX	5 (13.9%)	8 (10.4%)
N0	29 (80.6%)	60 (77.9%)
N1a-b	2 (5.6%)	9 (11.7%)
Reasons for non-surgical management		
Unsuitable - co-morbidities	14 (38.9%)	24 (31.2%)
Anticipated issues managing stoma	11 (30.6%)	14 (18.2%)
Marked anxiety at idea of stoma?	4 (11.1%)	9 (11.7%)
Prefers attempt at organ preservation?	20 (55.6%)	44 (57.1%)

APHRODITE

A Phase II trial of Higher RadiOtherapy Dose
In The Eradication of early rectal cancer



Primary endpoint

	Standard dose (C)RT	Escalated dose (C)RT
Is there a cCR at 6 months?		
Yes	12 (33.3%)	38 (49.4%)
No	18 (50.0%)	26 (33.8%)
Excluded (outside +/-5 week window)	4 (11.1%)	10 (13.0%)
Missing	2 (5.6%)	3 (3.9%)

OR=2.27 (80% one-sided CI: 1.54, Inf), p=0.038 (one-sided)

Multivariable logistic regression model output (missing & excluded cCR values imputed)

Patients with predefined intercurrent events (e.g. pelvic surgery before 6 months) were evaluated as 'no cCR' (3 patients in SDRT arm, 4 patients in EDRT arm)

APHRODITE primary endpoint – inclusion of ‘uncertain’ cCR

Clinical complete response (cCR) at 6 months

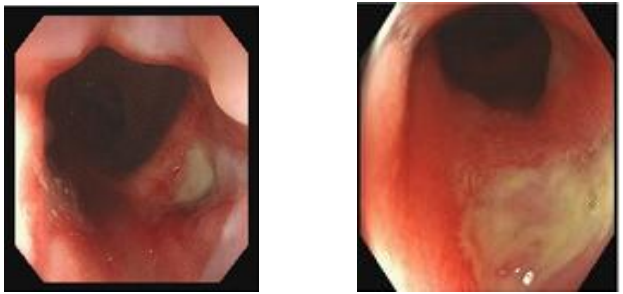
Digital rectal examination
- No palpable tumour

Sigmoidoscopy
- No evidence of either mucosal tumour or submucosal swelling
- Only a flat white scar
- With or without telangiectasia

MRI
- Complete response in primary tumour (mrTRG 1 or 2)
- Complete response in any involved nodes

Is this definition valid after high-dose radiotherapy?

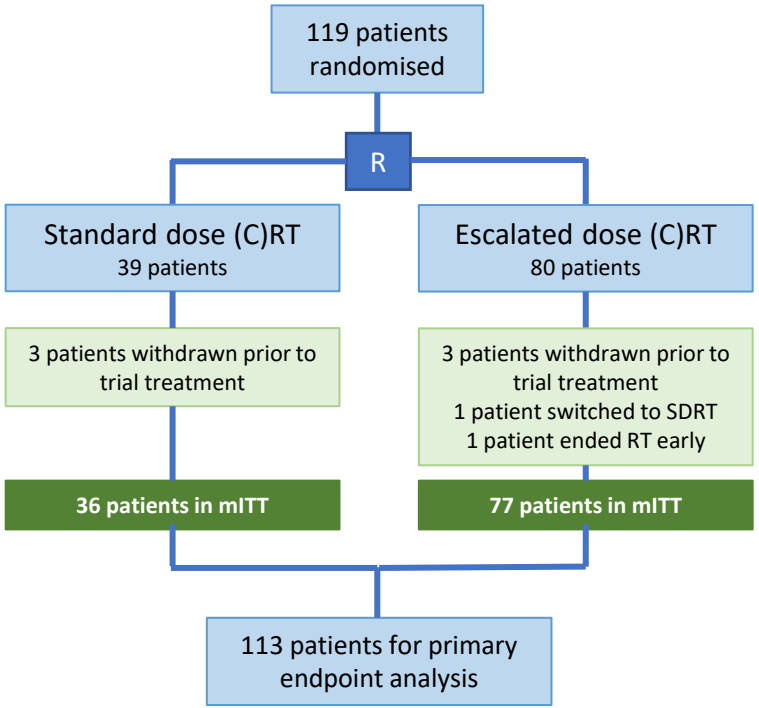
‘Uncertain’ cCR
- Allow for superficial mucosal ulceration on endoscopy



Ulceration on endoscopy at 6 months
(patients receiving escalated dose)

APHRODITE

A Phase II trial of Higher RadiOtherapy Dose
In The Eradication of early rectal cancer



Sensitivity analysis

Including 'uncertain' cCR

	Standard dose (C)RT	Escalated dose (C)RT
Is there a cCR? (Extended cCR definition)		
Yes	13 (36.1%)	44 (57.1%)
No	17 (47.2%)	20 (26.0%)
Excluded (outside +/-5 week window)	4 (11.1%)	10 (13.0%)
Missing	2 (5.6%)	3 (3.9%)

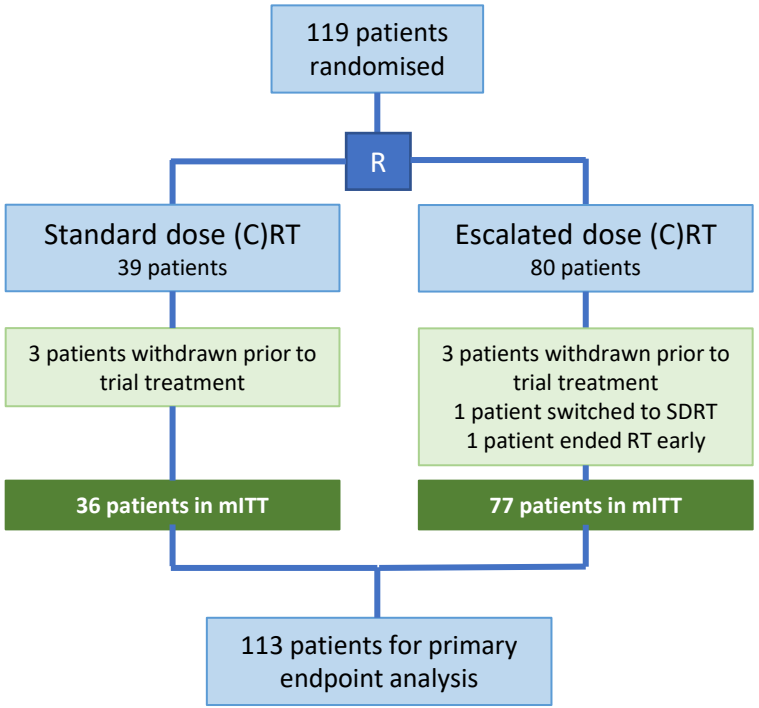
OR=2.79 (80% one-sided CI: 1.89, Inf), p=0.014 (one-sided)

Multivariable logistic regression model output (complete case analysis, n=94)

Intercurrent events same as for primary analysis

APHRODITE

A Phase II trial of Higher RadiOtherapy Dose
In The Eradication of early rectal cancer



Sensitivity analysis

Including 'uncertain' cCR + assessments outside window

	Standard dose (C)RT	Escalated dose (C)RT
Is there a cCR? (Extended cCR definition)		
Yes	16 (44.4%)	52 (**67.5%**)
No	18 (50.0%)	22 (28.6%)
Missing	2 (5.6%)	3 (3.9%)

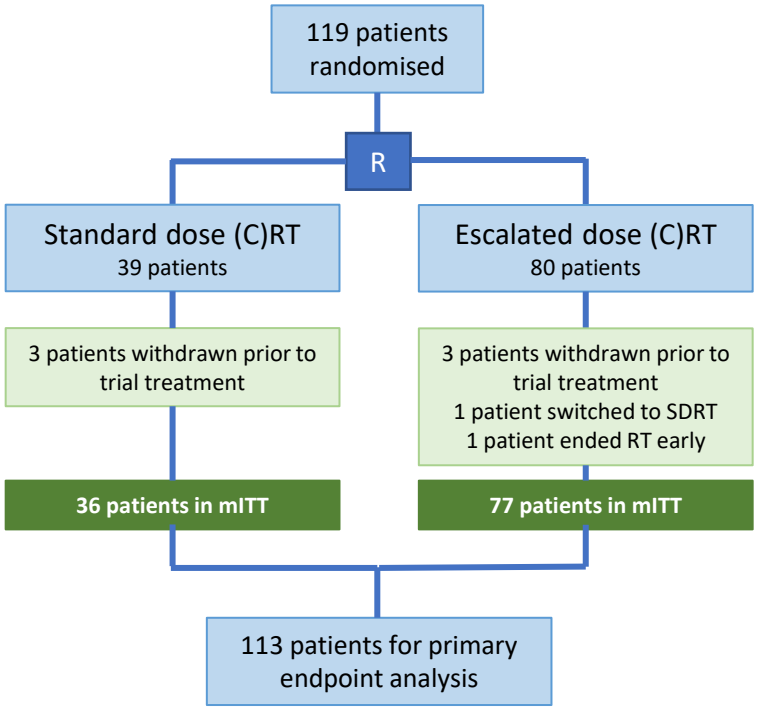
OR=2.70 (80% one-sided CI: 1.86, Inf), p=0.012 (one-sided)

Multivariable logistic regression model output (complete case analysis, n=108)

Intercurrent events same as for primary analysis

APHRODITE

A Phase II trial of Higher RadiOtherapy Dose
In The Eradication of early rectal cancer



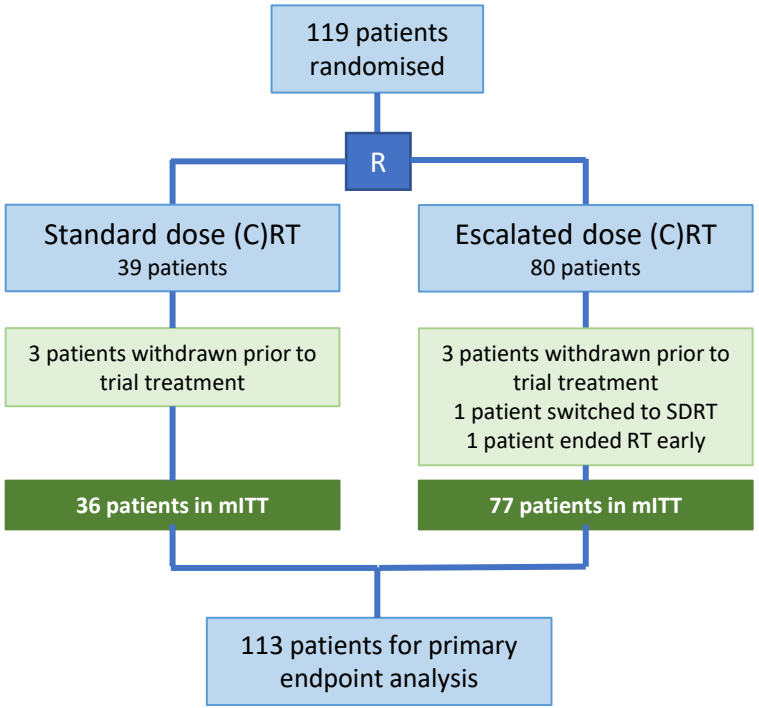
Side effects

(CTCAE up to 6 months)

	Standard dose CRT	Escalated dose CRT
Any grade 3 or above side effect?		
Yes	4 (11.1%)	10 (13.0%)

APHRODITE

A Phase II trial of Higher RadiOtherapy Dose
In The Eradication of early rectal cancer

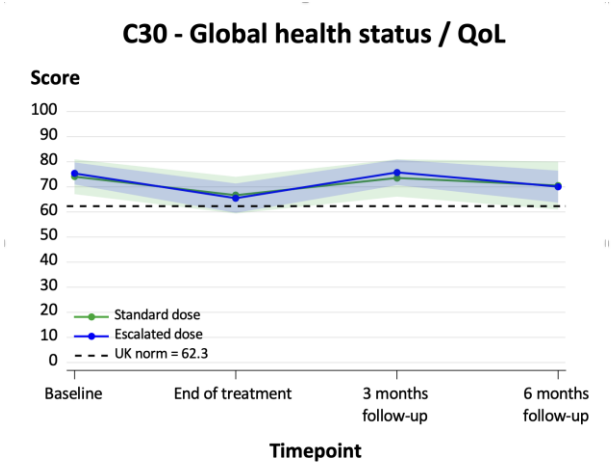


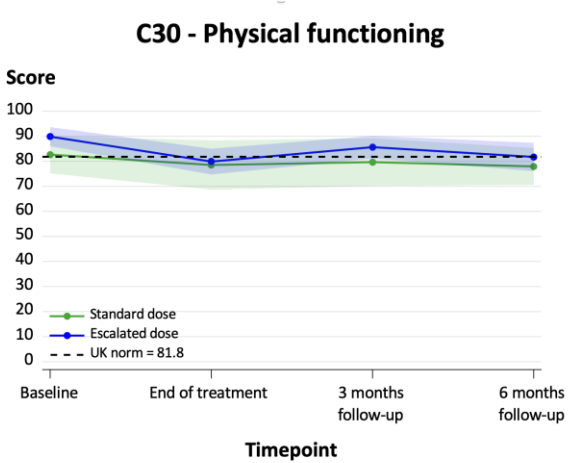
Side effects

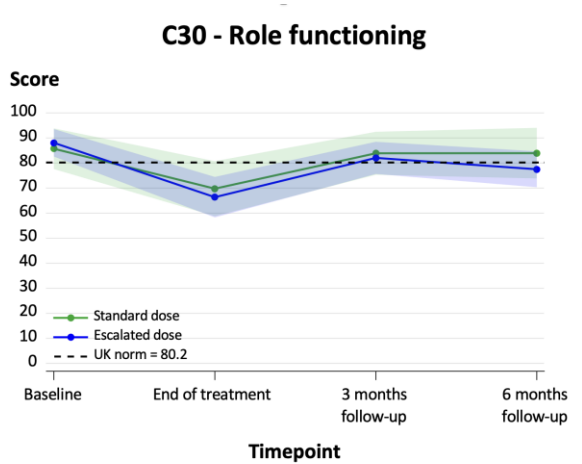
(CTCAE up to 6 months)

	Standard dose CRT	Escalated dose CRT
Any grade 3 or above side effect?		
Yes	4 (11.1%)	10 (13.0%)
Grade 2+ side effects		
Anorectal	6 (16.7%)	21 (27.3%)
Bowel	7 (19.4%)	23 (29.9%)
Urinary	3 (8.3%)	8 (10.4%)
Haematological	10 (27.8%)	16 (20.8%)

Patient-reported Quality-of-Life outcomes

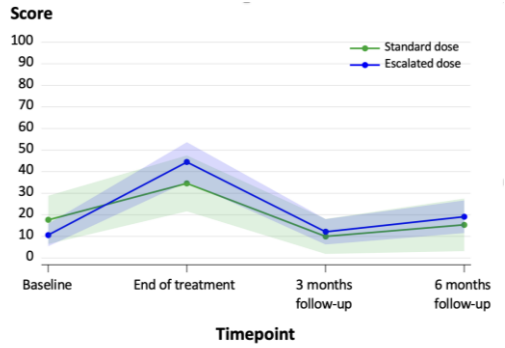




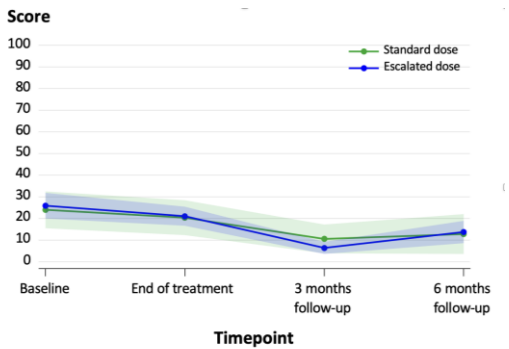


Patient-reported Quality-of-Life outcomes

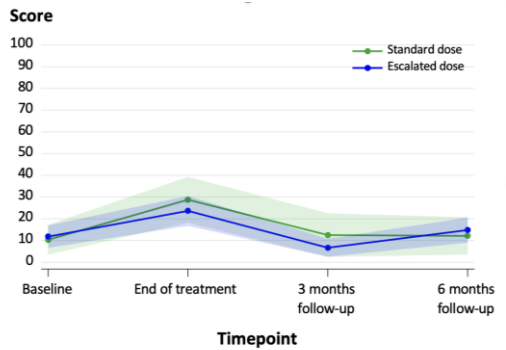
Buttock pain (CR29)



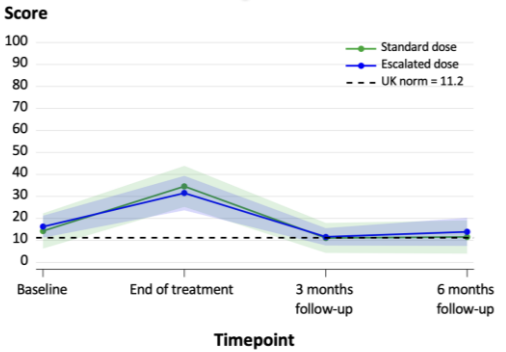
Blood and mucus in stool (CR29)



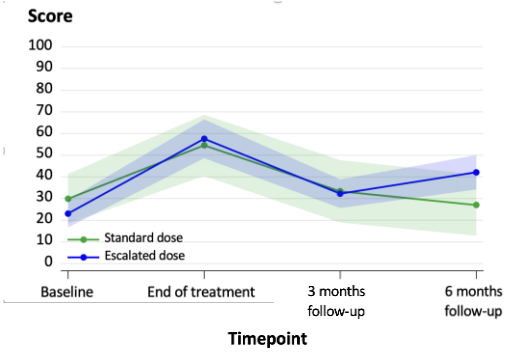
Faecal incontinence (CR29)



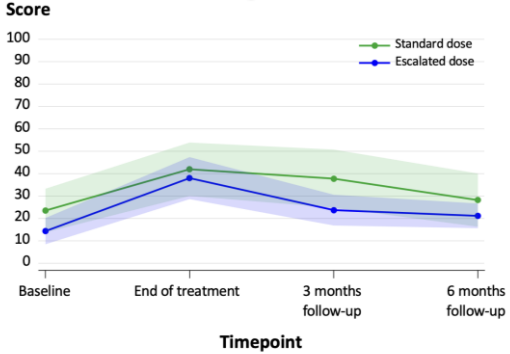
Diarrhoea (C30)



Bowel urgency (additional item)



Urinary urgency (additional item)



MRI-guided boost

Radiotherapy and Oncology 164 (2021) 37–42

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

A novel approach for radiotherapy dose escalation in rectal cancer using online MR-guidance and rectal ultrasound gel filling – Rationale and first in human

Cihan Gani [a,b,*,1], Monica Lo Russo [a], Simon Boeke [a], Daniel Wegener [a], Sergios Gatidis [c], Sarah Butzer [a], Jessica Boldt [a], David Mönnich [d], Daniela Thorwarth [d], Konstantin Nikolaou [c], Daniel Zips [a,b], Marcel Nachbar [d]

Clinical and Translational Radiation Oncology 37 (2022) 153–156

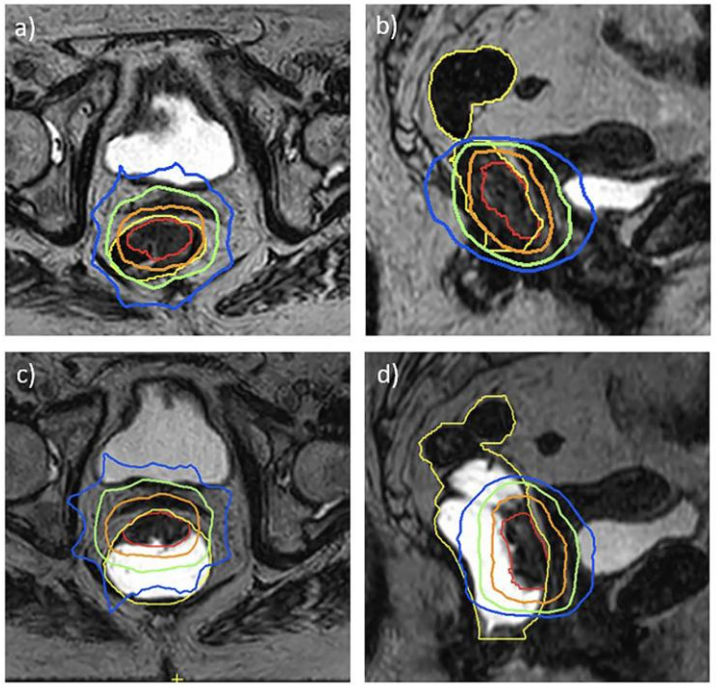
Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Online MR guided dose escalated radiotherapy for organ preservation in distal rectal cancer

Simon Boeke [a], Laura Uder [a], Jakob Ehlers [a], Sarah Butzer [a], Sabrina Baumeister [a], Jessica Boldt [a], Marcel Nachbar [b], Monica Lo Russo [a], David Mönnich [b], Konstantin Nikolaou [c], Daniel Zips [a,d,e], Daniela Thorwarth [b,e], Cihan Gani [a,e,*]



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Alwyn Burrage

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Rebecca Muirhead

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Rebecca Day

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- Signe Skriver (Rigshospitalet, Copenhagen)
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- Anna-Lene Fromm (Herlev, Copenhagen)
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- John Pløen (Vejle)
- Birgitte Mayland Havelund (Vejle)
- Lars Fokdal (Vejle)

Key physicists

- Henrik Nissen (Vejle)
- Dennis Tideman Arp (Aalborg)

Thank you to our patients!

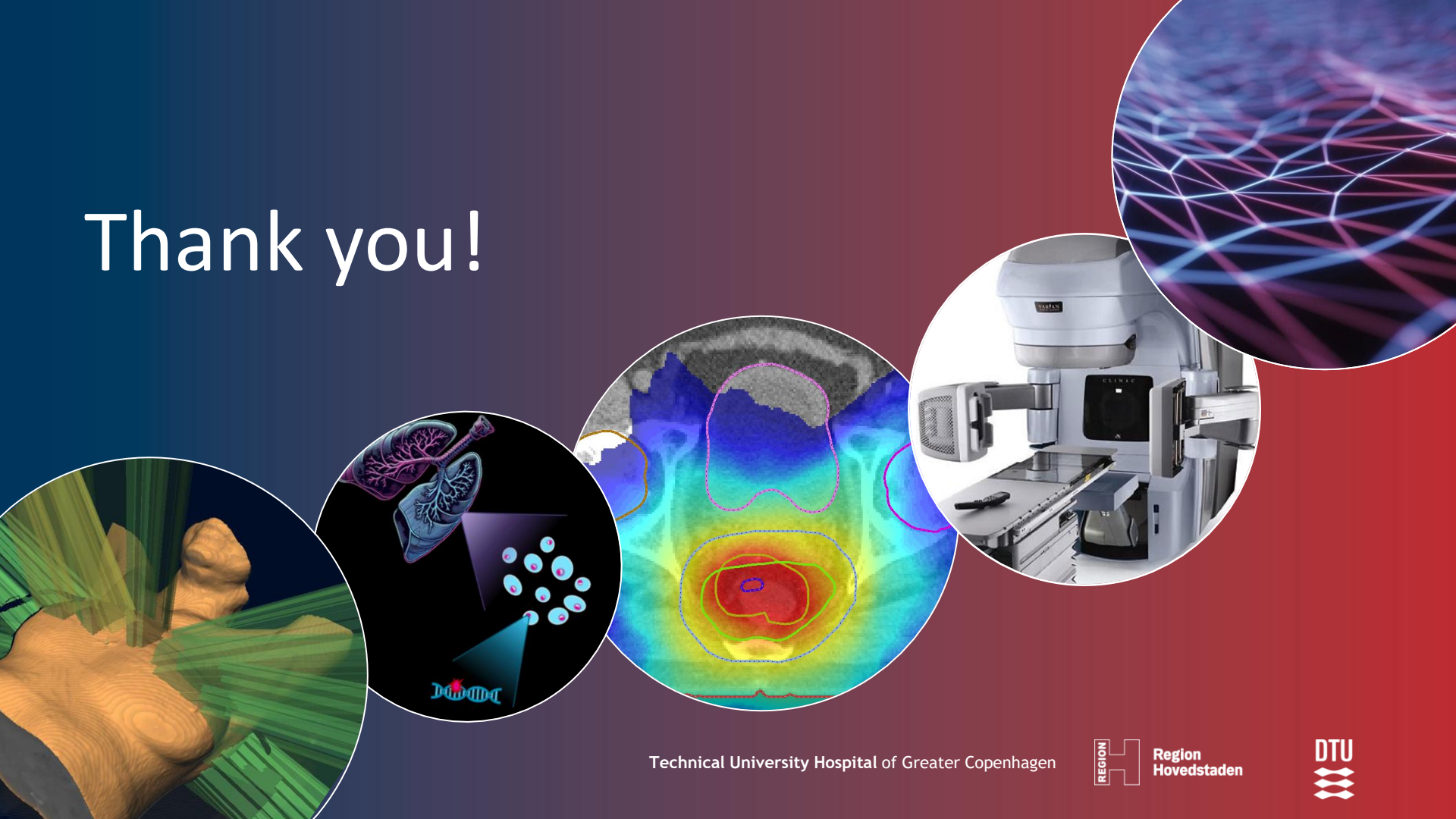
"I feel APHRODITE is such a positive step forward in the way bowel cancer is treated. (…) At the end of the day, it could not only benefit me, but other people as well."

Brian, trial participant, Leeds, UK

"I thought the trial could help me but it will also help somebody else. (…) As it happens, the treatment has worked amazingly. There are no signs of cancer – it's gone completely."

Tom, trial participant, Manchester, UK

Thank you!



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