2016
ESTRO SCHOOL
LIVE COURSE

NEW

LOWER GI: TECHNICAL AND CLINICAL CHALLENGES FOR RADIATION ONCOLOGISTS

25 - 27 May 2016 | Brussels, Belgium

MULTIMODAL CANCER TREATMENT

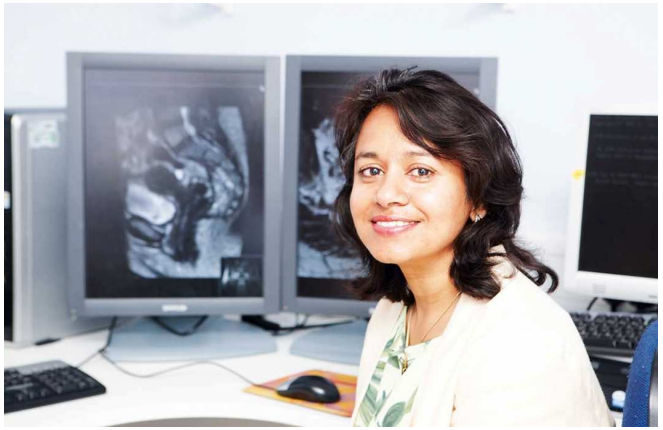
WHO?

Welcome in Brussels

Your Team of Teachers

Maria A. Gambacorta
Rom, Italy

Karin Haustermans
Leuven, Belgium



Gina Brown
London, United Kingdom

Claudio Fiorini
Milan, Italy

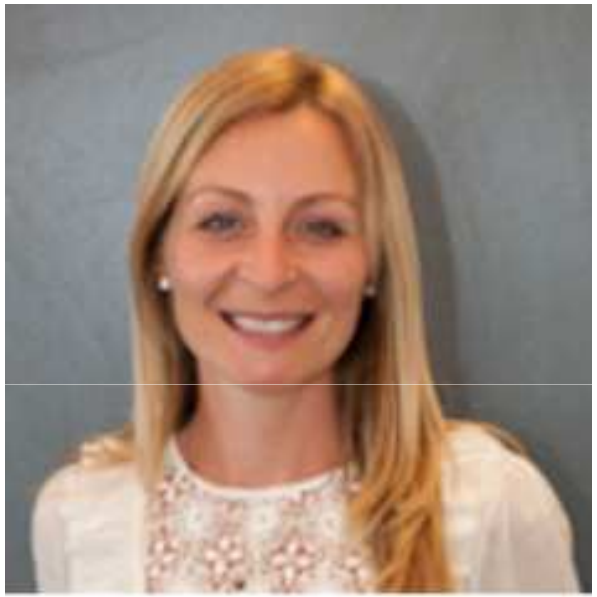
Chris Cunningham
Oxford, UK

Rob Glynne-Jones
London, UK

Claus Rödel
Frankfurt, GE

Nigel Scott,
Leeds, UK

Your ESTRO Project Manager



Laura La Porta, Brussels

Thursday May 26

19:00 Guided Tour
Departing from Grand Place and
ending at Brasserie Bozar

20:30 Dinner at Brasserie Bozar

A minute's silence in memory of

Prof. Lars Påhlman
Uppsala, Sweden
Died on November 2015

Honoured member of ESTRO 2003

Outstanding teacher of
ESTRO Rectal cancer Course

A minute's silence in memory of

the victims of the Brussels terrorist attack

Lower GI course

Brussels 25-27 May 2016

Case presentation 1

Maria Antonietta Gambacorta

Radiotherapy Department
Università Cattolica del Sacro Cuore
Rome-Italy

Gemelli ART
Advanced Radiation Therapy

Overview

- Anamnesis
- Diagnosis
- Staging
- Treatment
- Re-staging

- Voting

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Anamnesis

- Male
- 68 years old
- WHO PS O
- No co-morbidity
- No family history of cancer
- Symptoms:
  - Rectal bleeding
  - Altered bowel habits
  - Bowel cramps
  - Bloating

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Diagnosis

- **DRE:**
  - At 5 cm from the internal anal sphincter:
    - Circumferential tumor
    - Fixed
    - Blood on the exploring finger

- **Colonoscopy:**
  - Bleeding tumor at 7 cm from the anal verge, extending for 5 cm.

- **Biopsy:**
  - Moderately differentiated adenocarcinoma

- **Blood Tests:** Elevated CEA (>30 ng/ml), other blood tests normal

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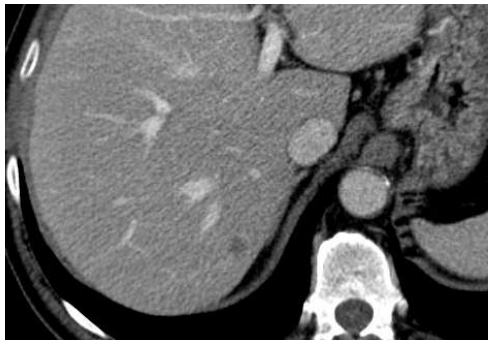
Staging



- **CT Scan Thorax + Abdomen:**
  - Circumferential lesion in the high/mid rectum reaching the mesorectal fascia
  - Hepatic VII segment, superficial hypodense lesion of 1 cm, to be confirmed with MRI
  - No other suspect lesions in the lungs or in the lymph nodes

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Staging

- **Pelvic MRI:**
  - Circumferential tumor at 5.5 cm from the anorectal junction, longitudinal extension of 4 cm
  - Branches in the mesorectum reaching the mesorectal fascia
  - “Multiple lymph nodes” in the mesorectum, globular and infiltrating the mesorectal fascia on the postero-lateral left side

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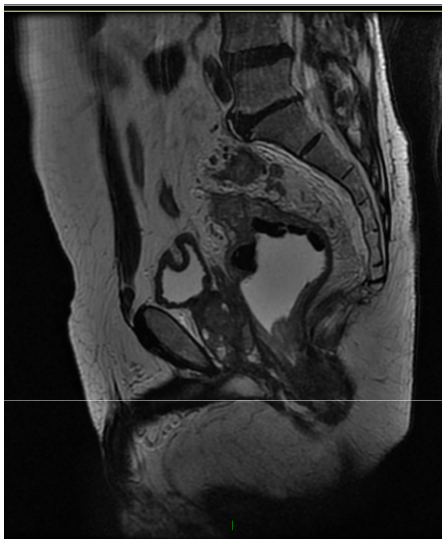
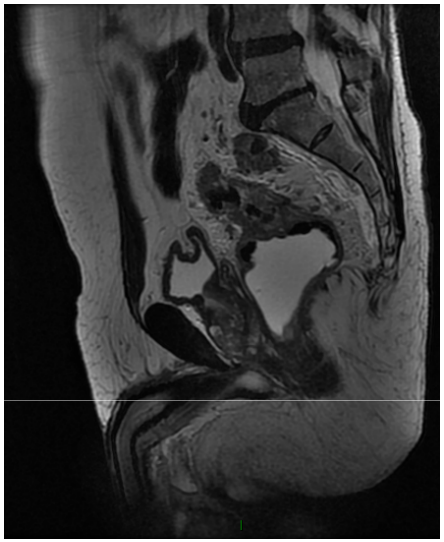
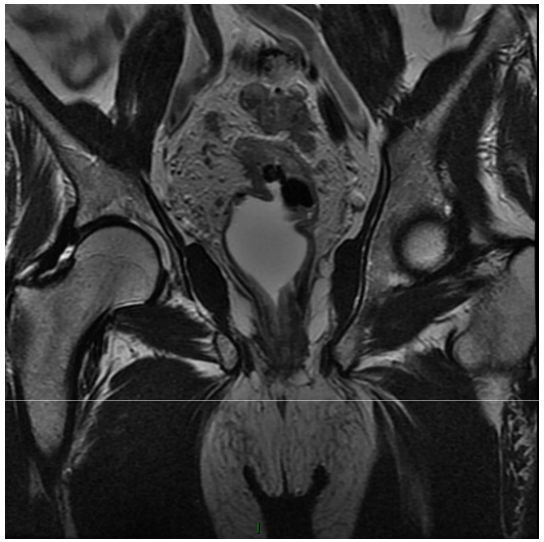
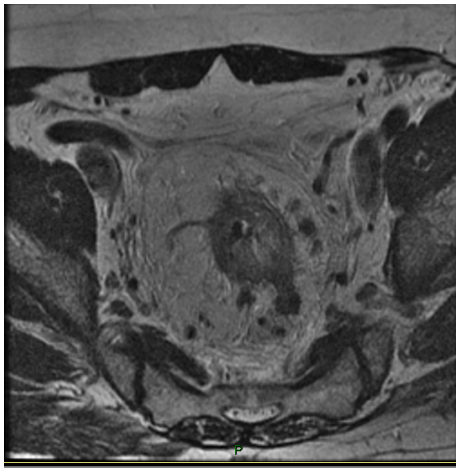
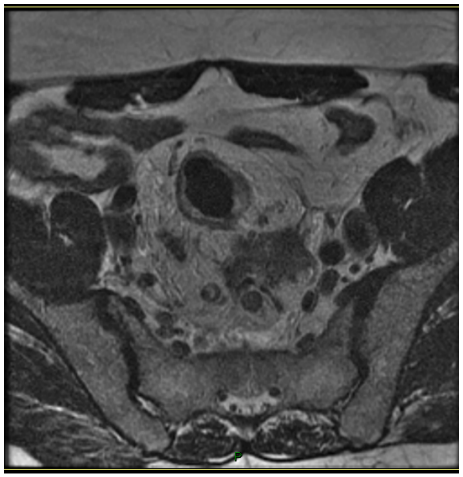
Pelvic MRI











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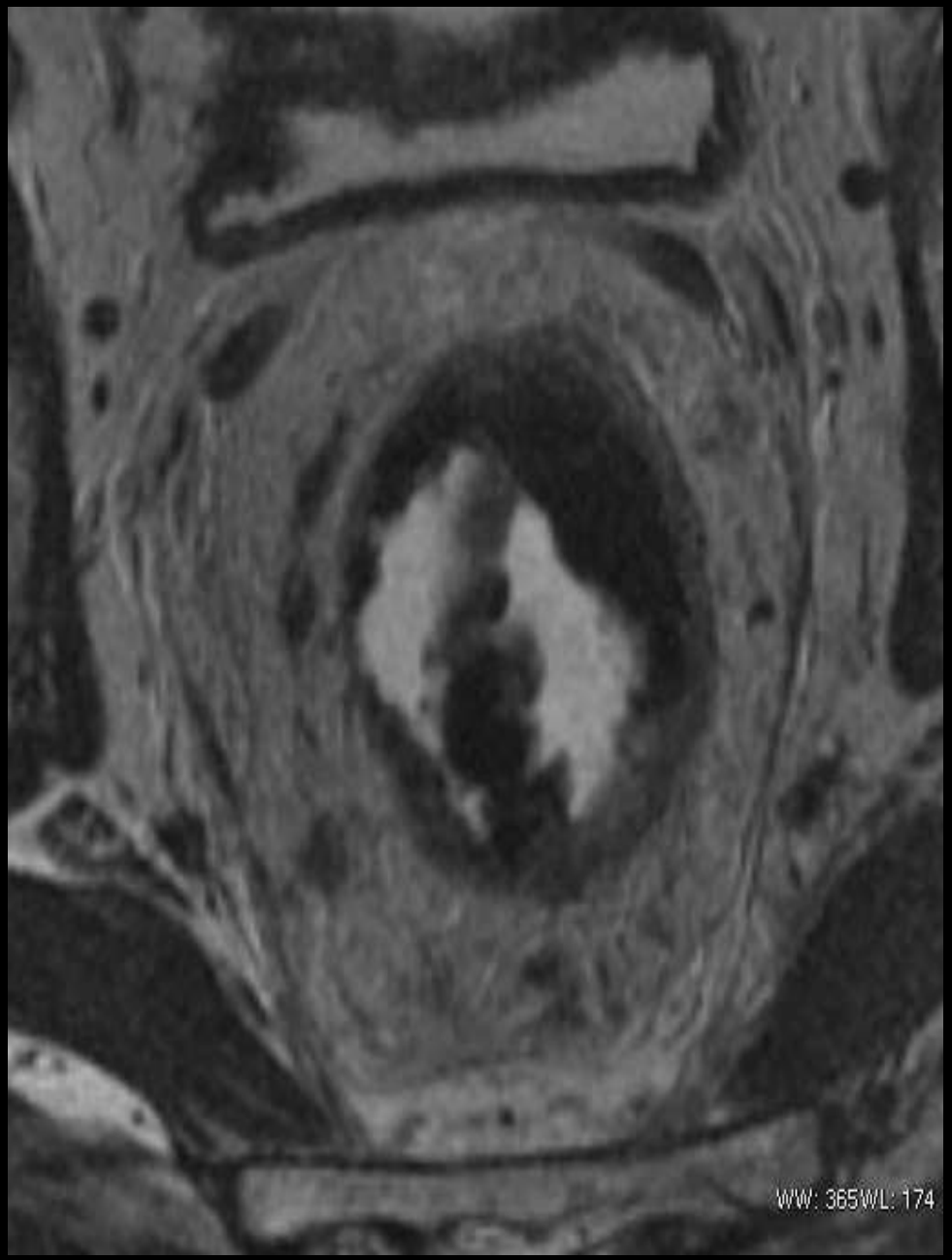
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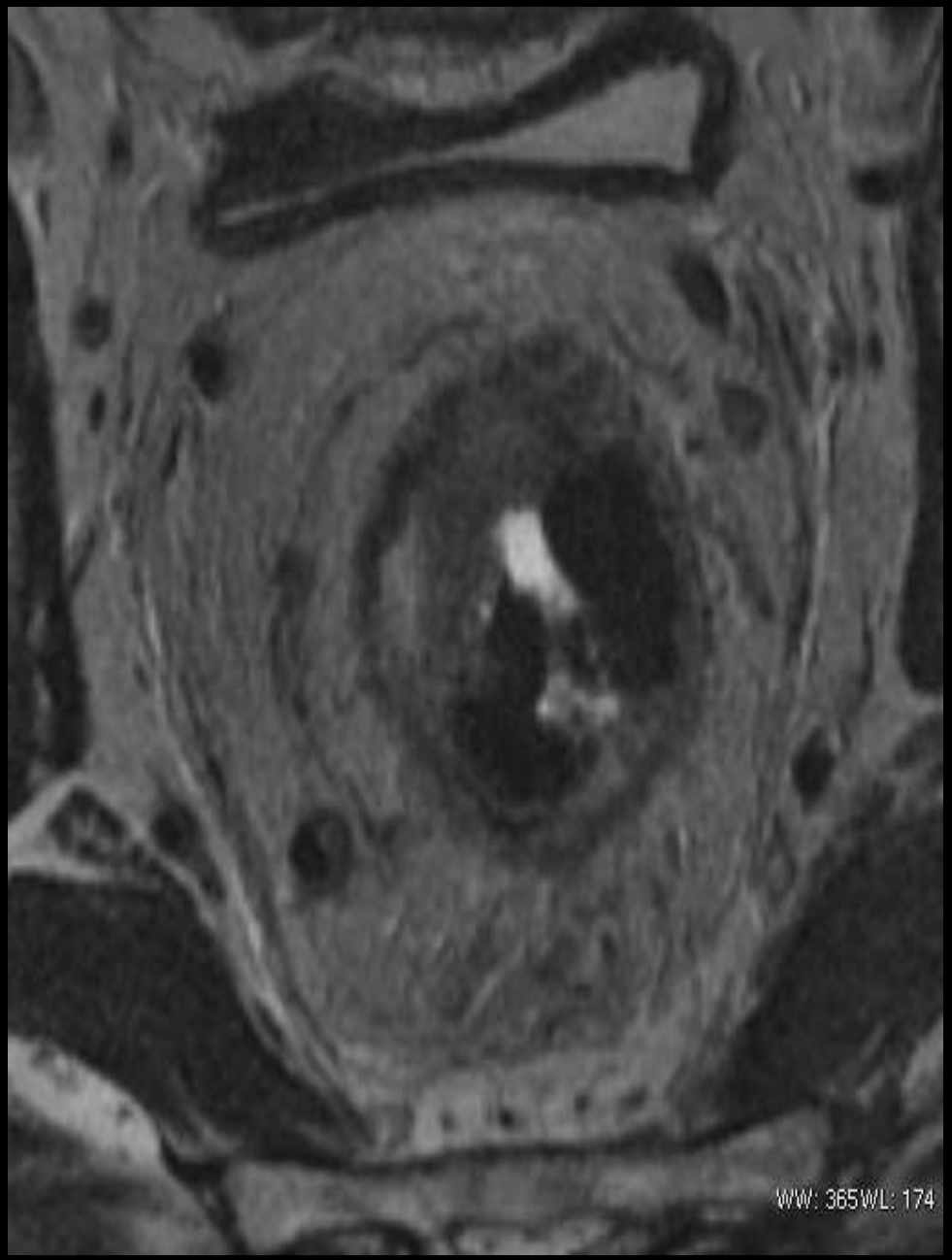
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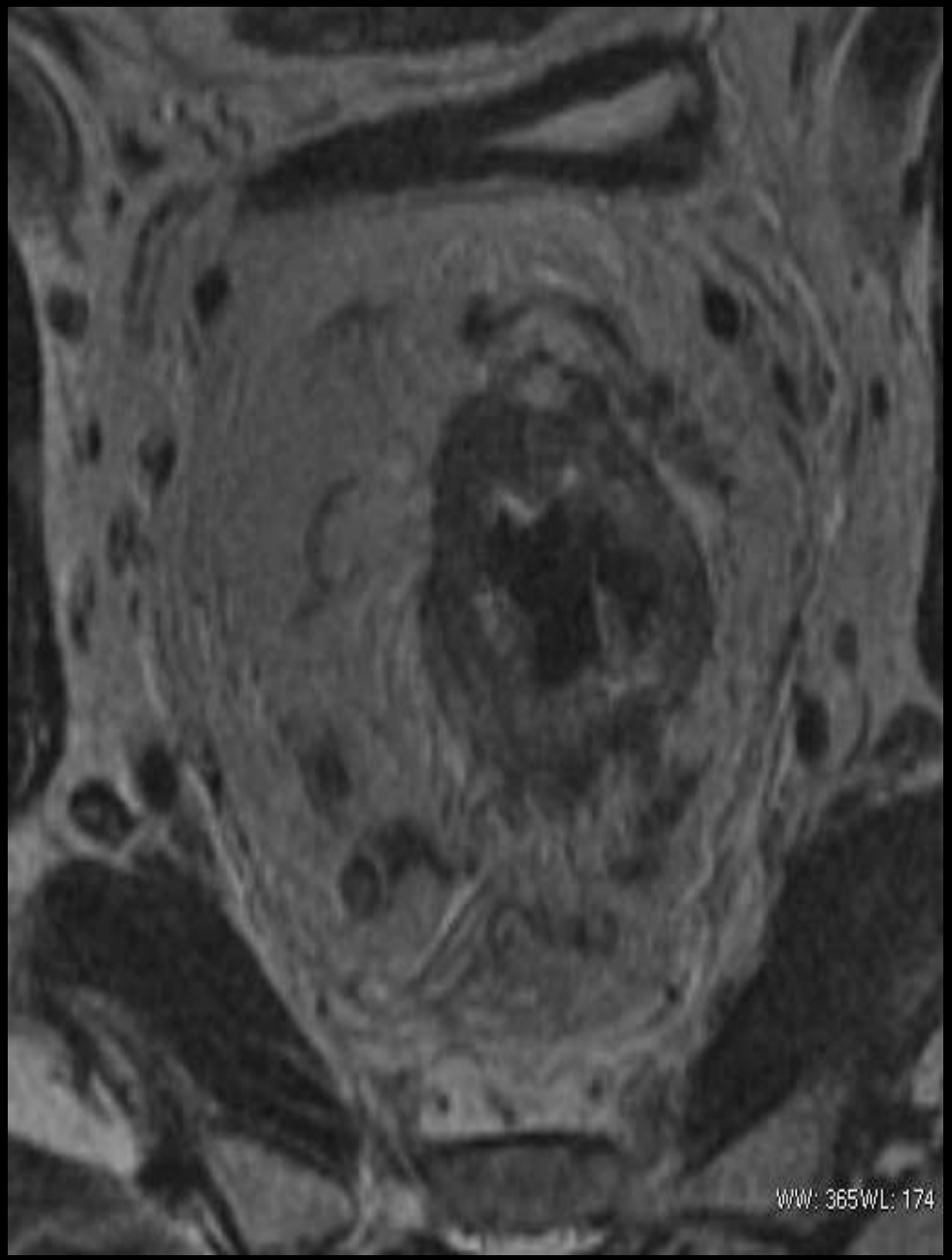
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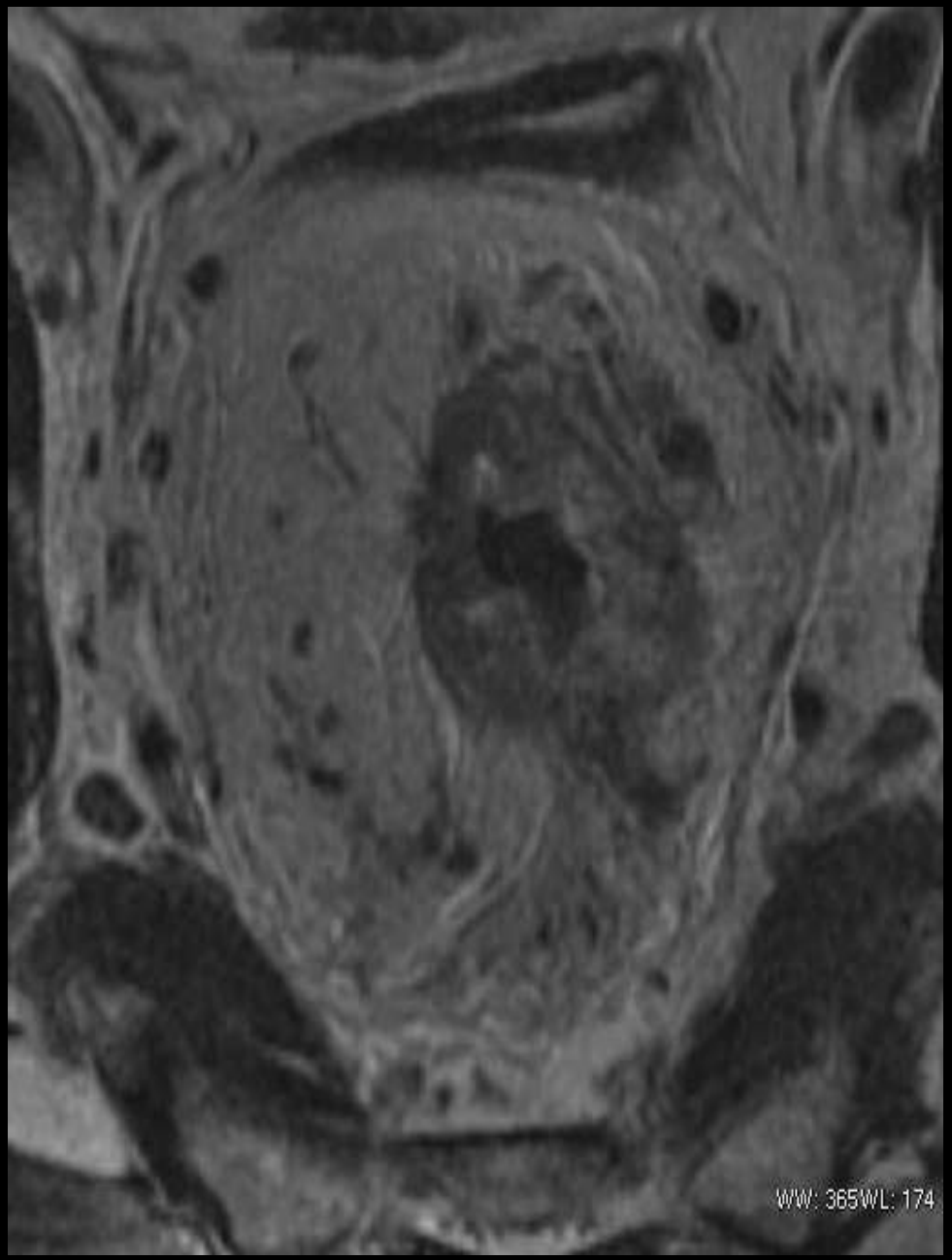
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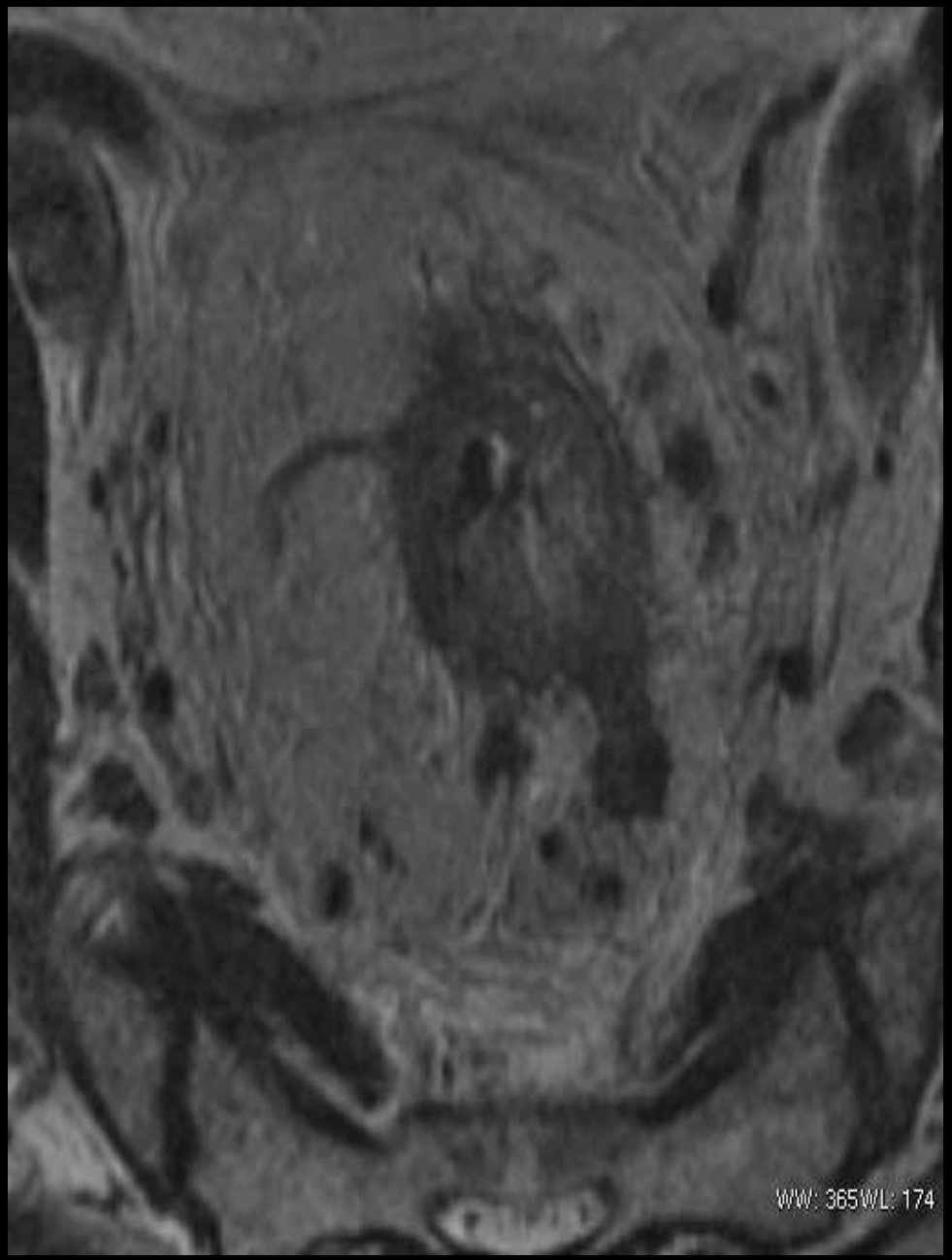
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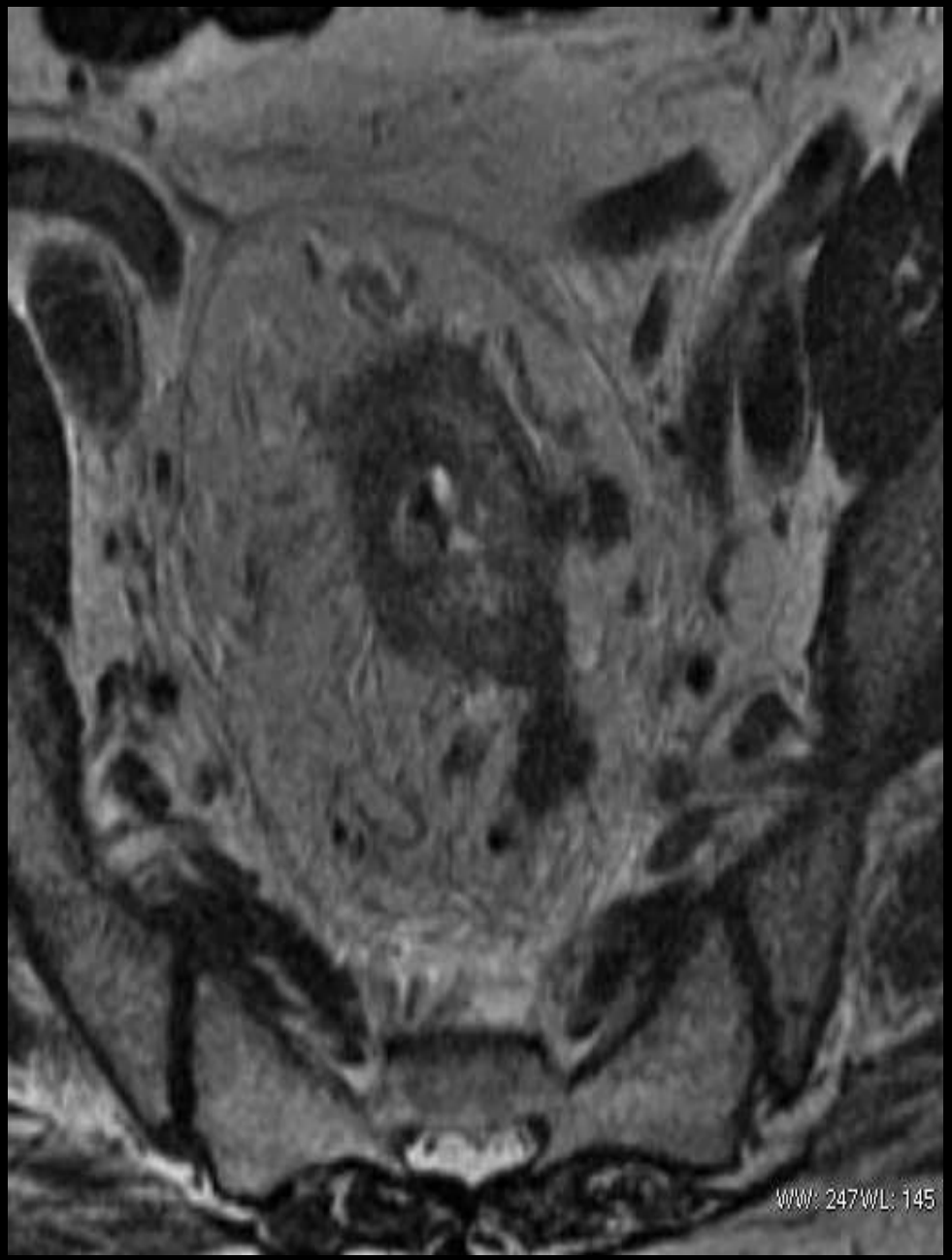
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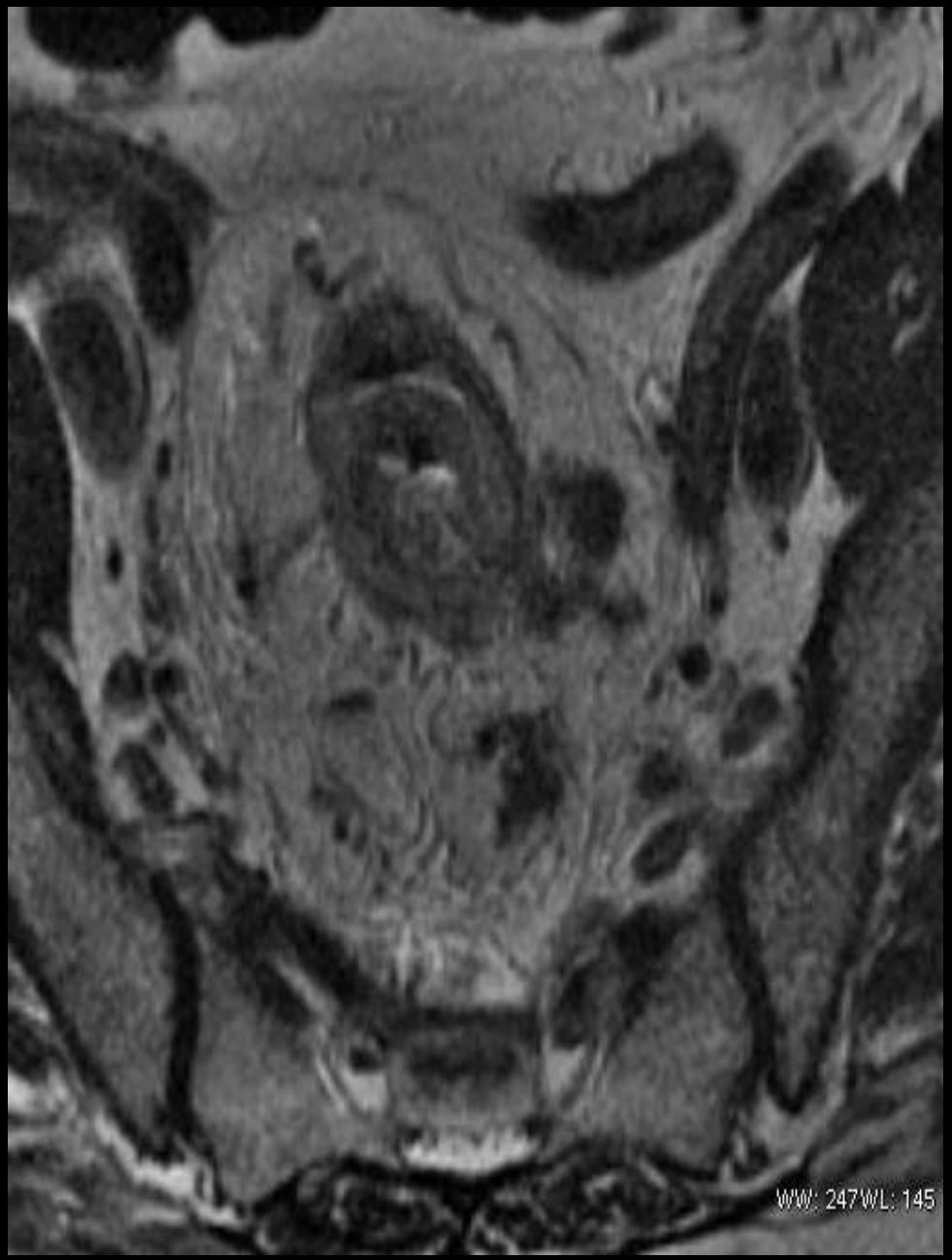
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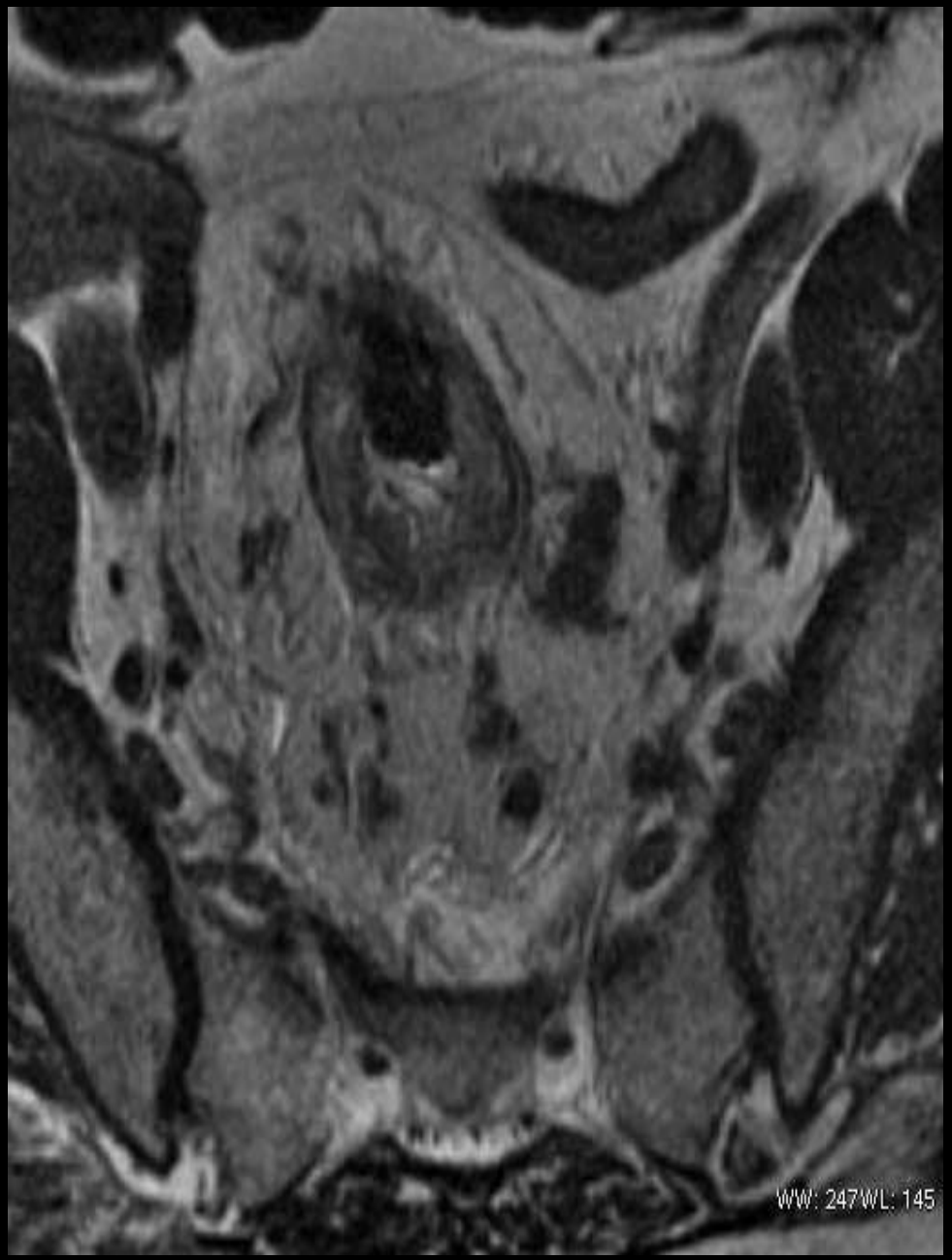
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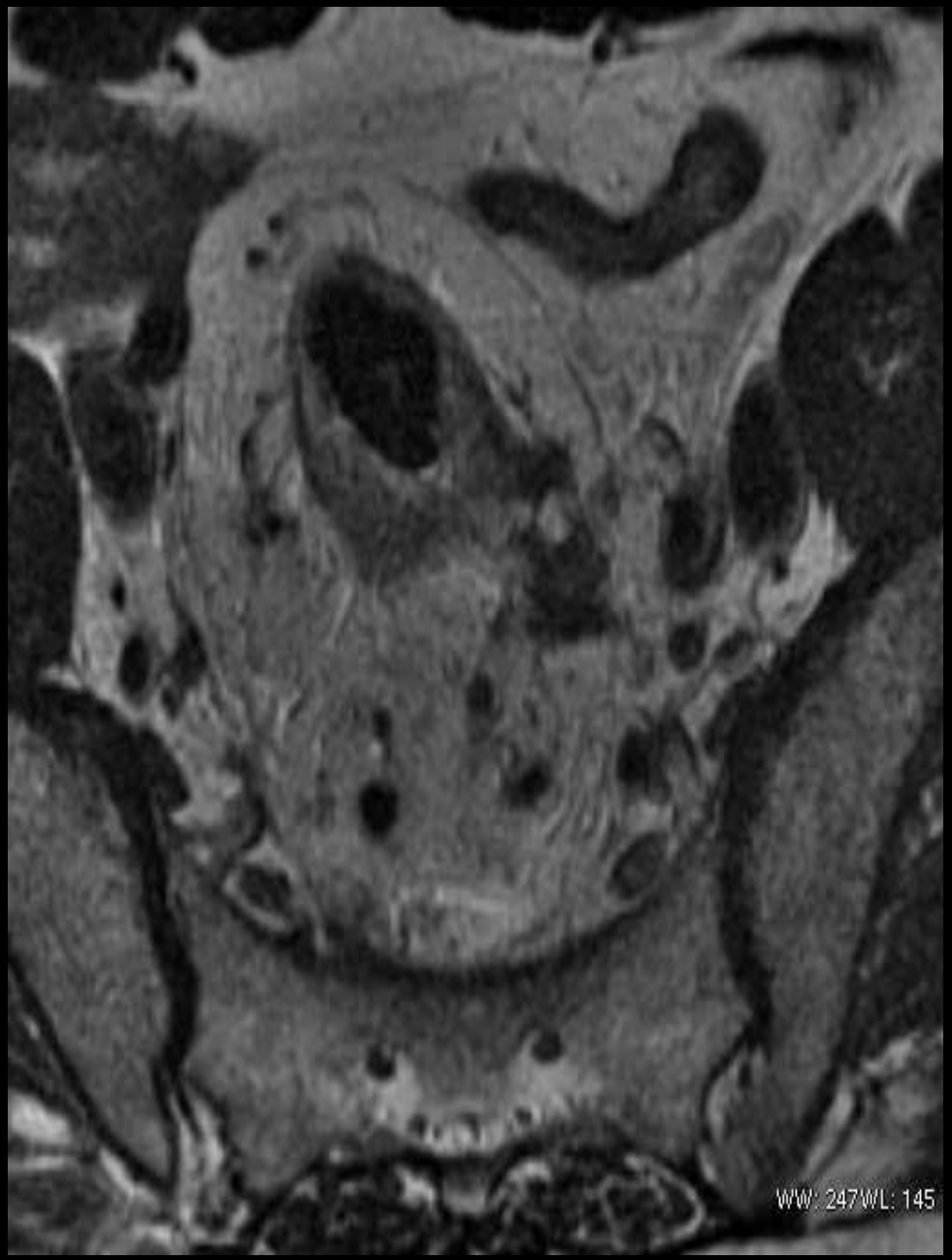
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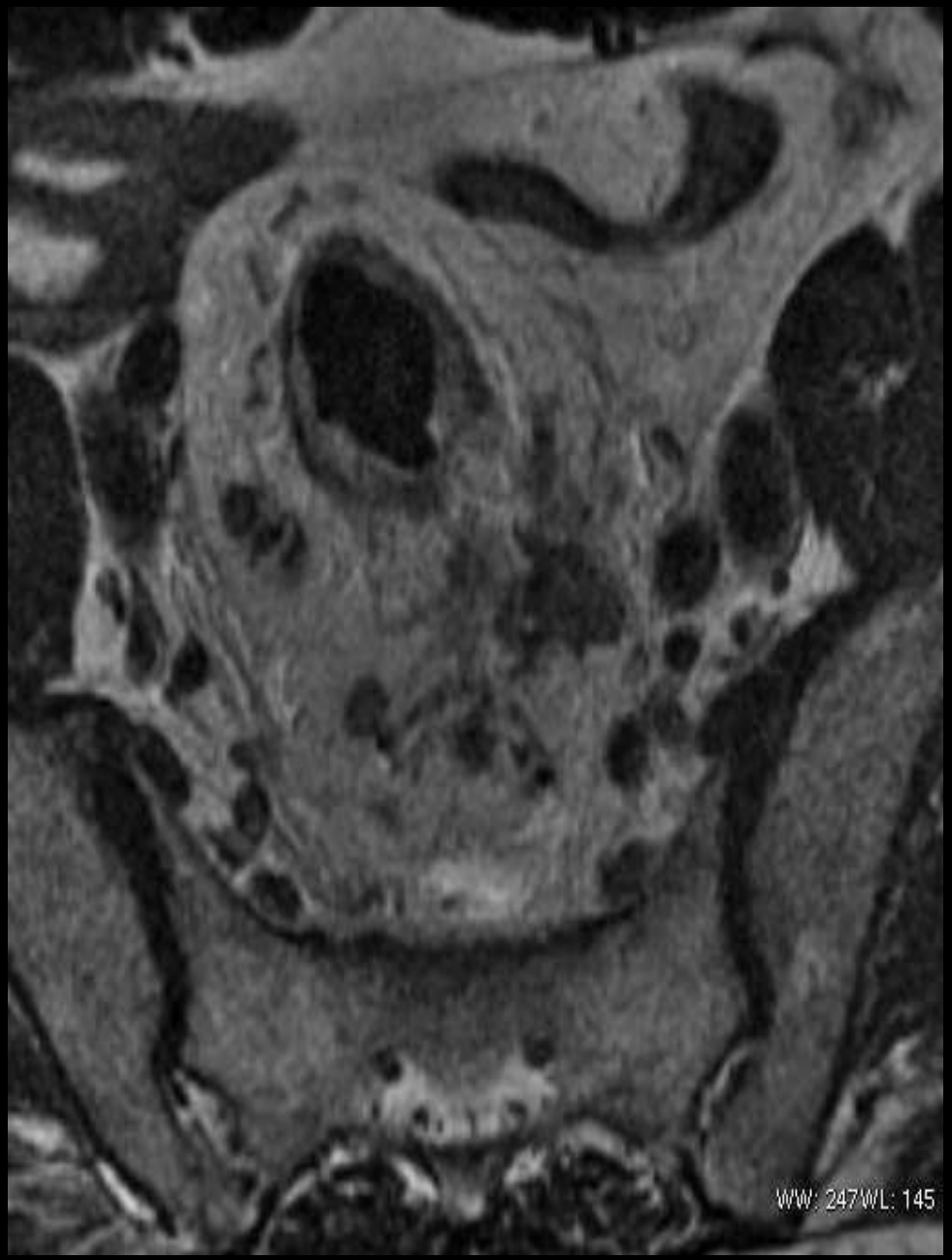
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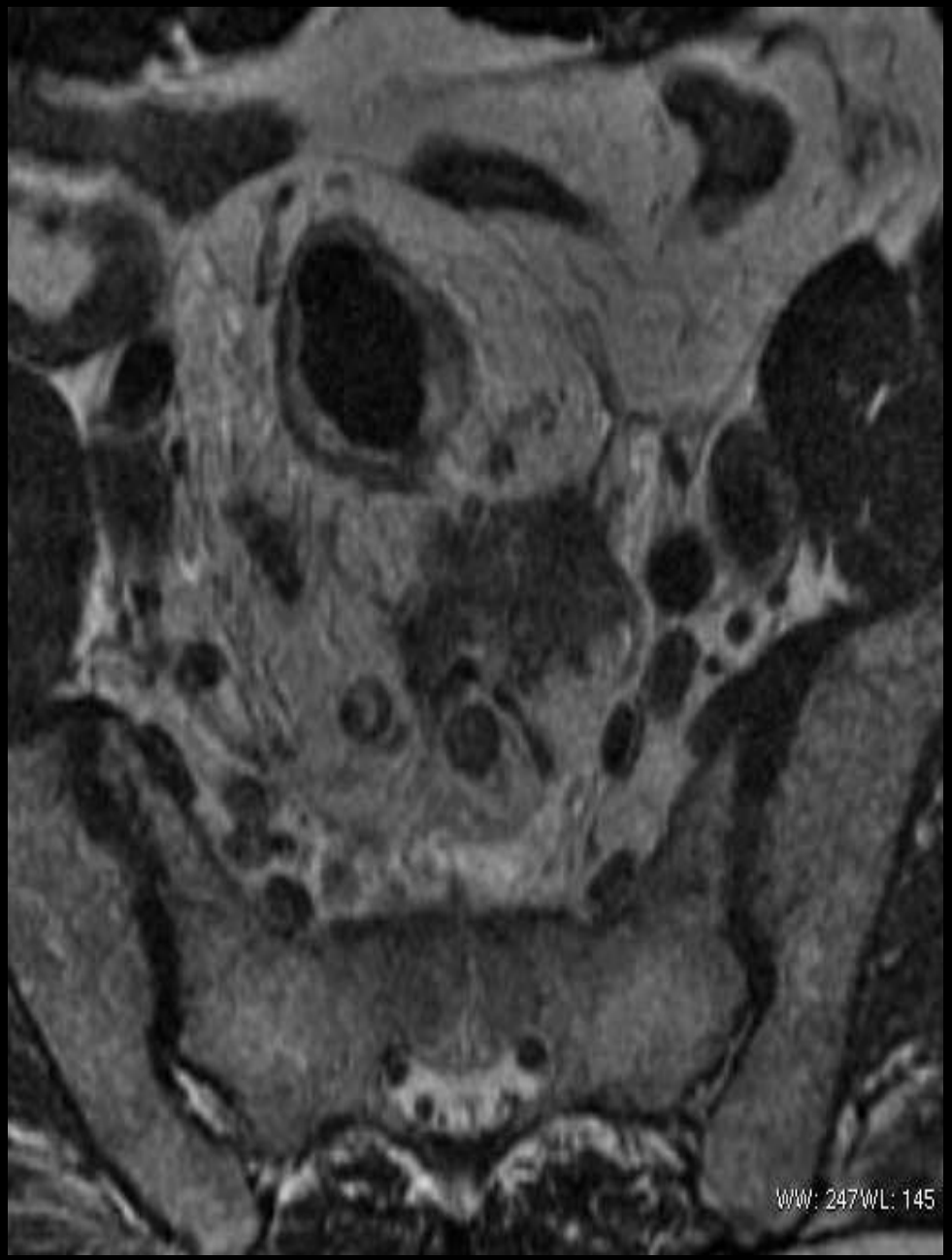
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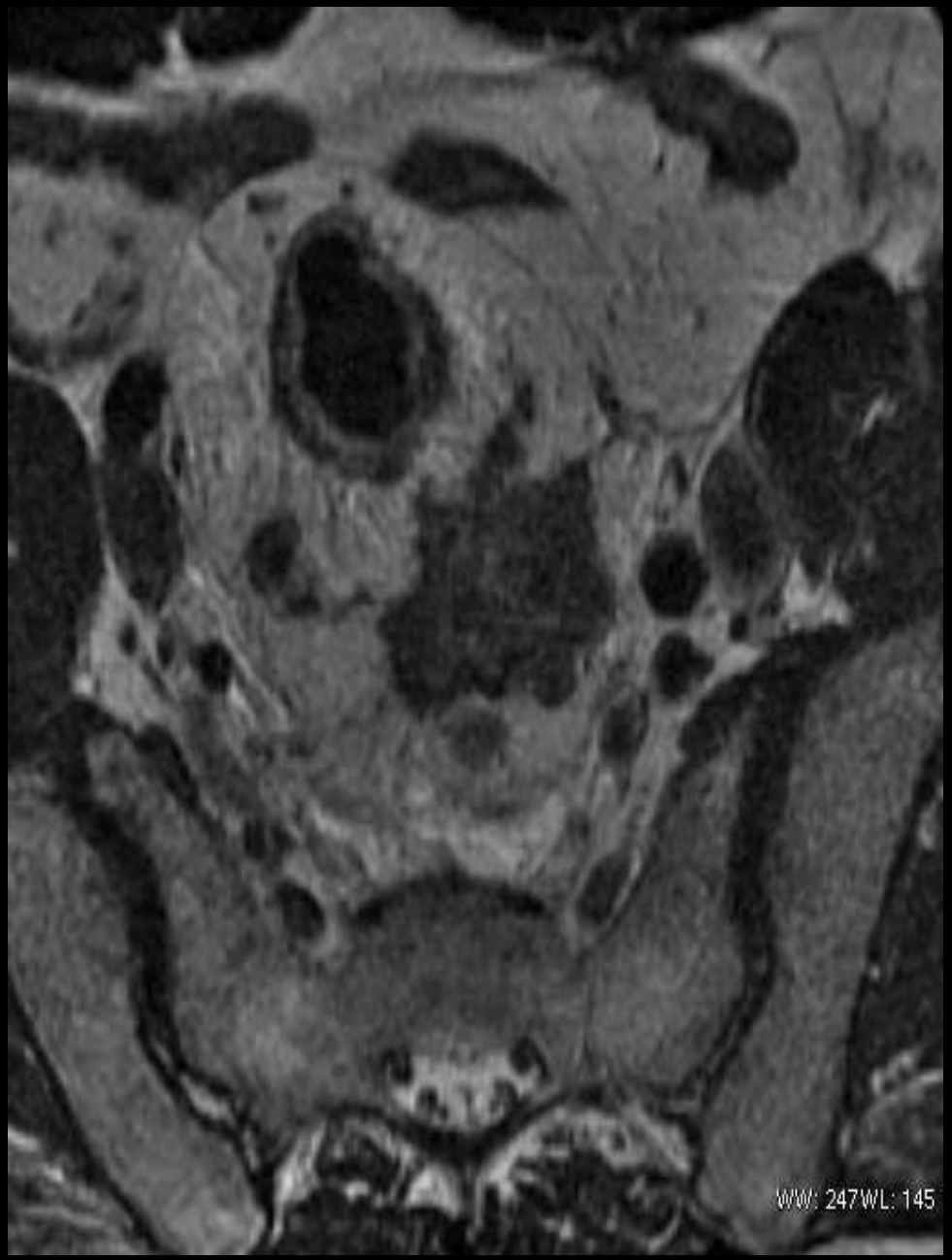
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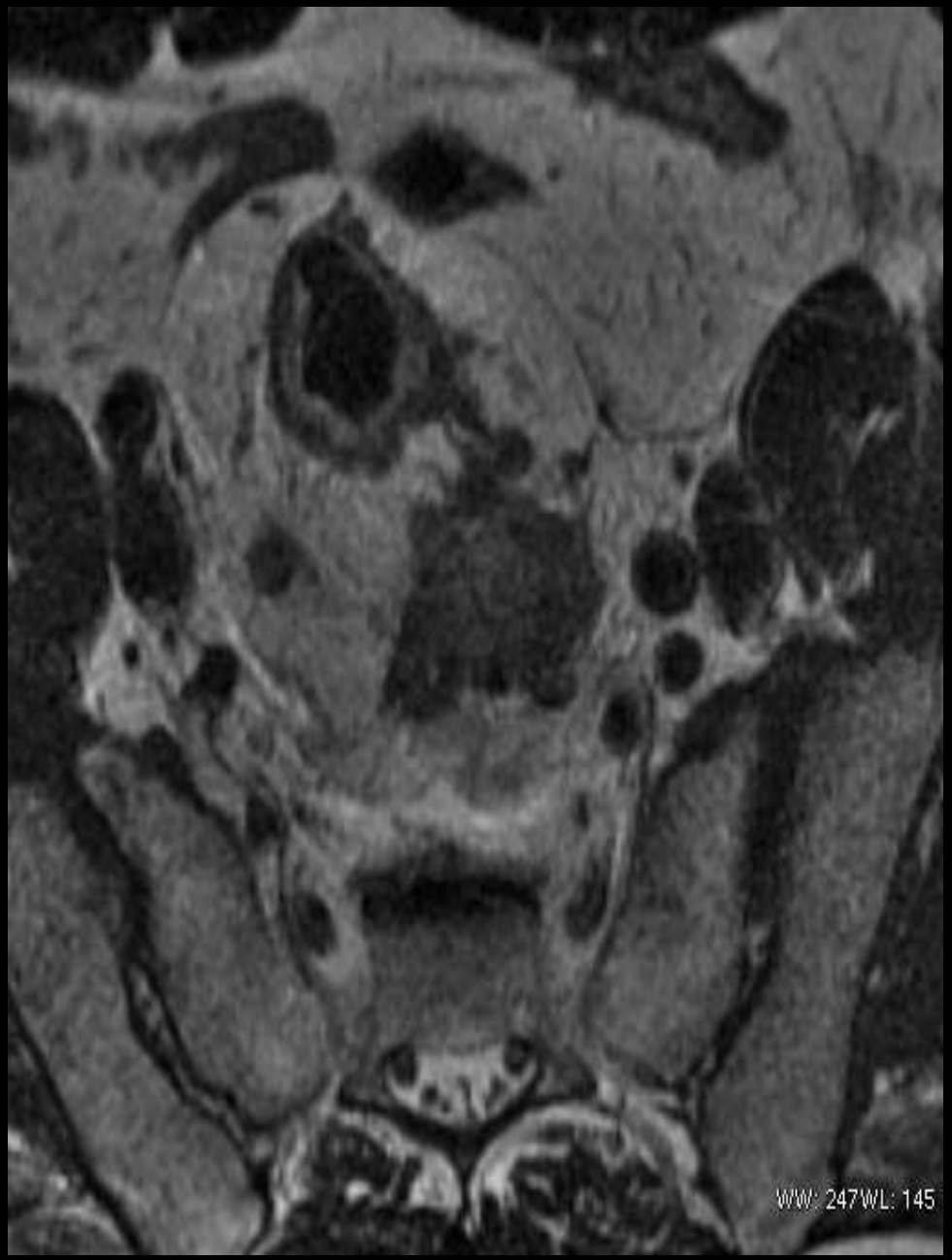
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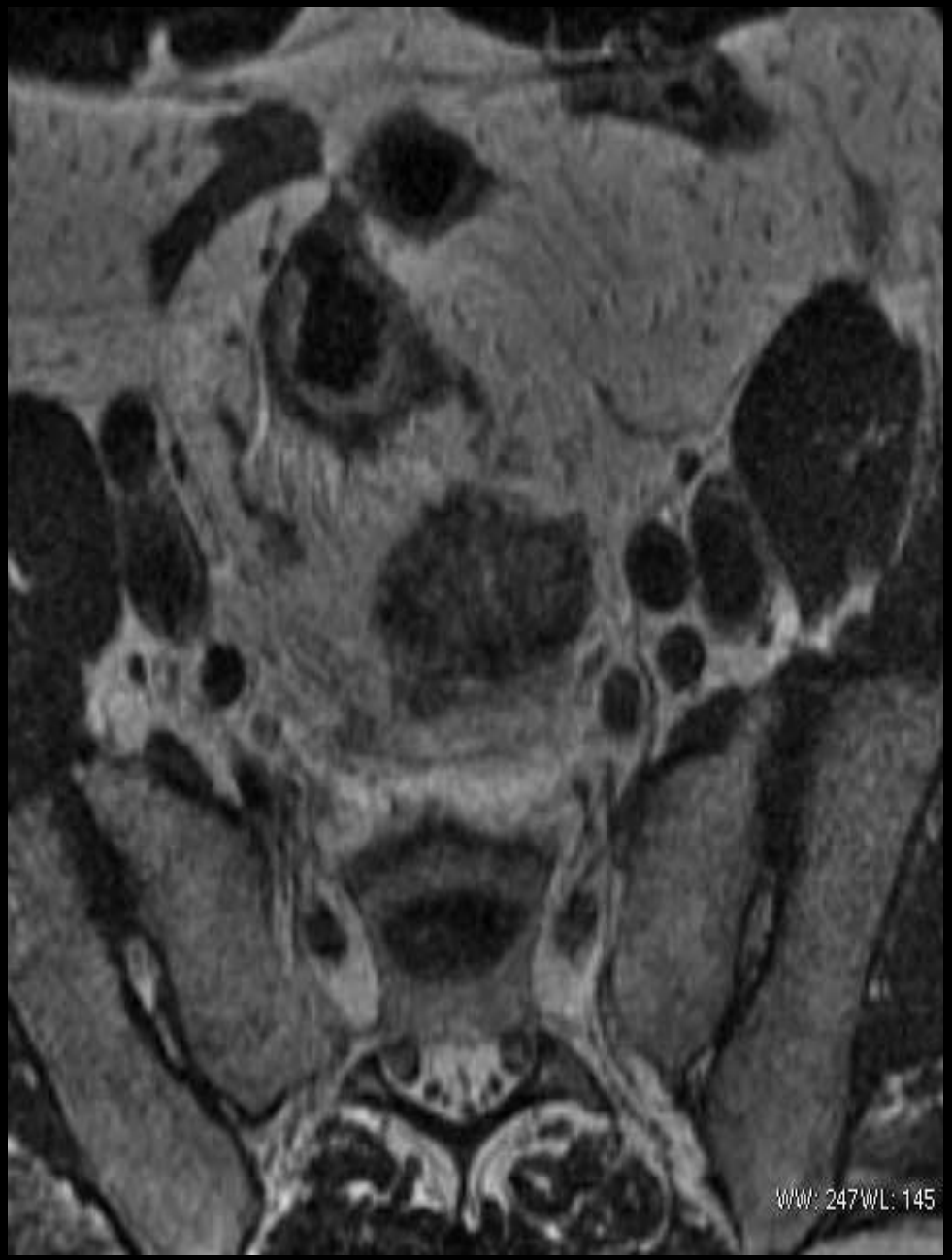
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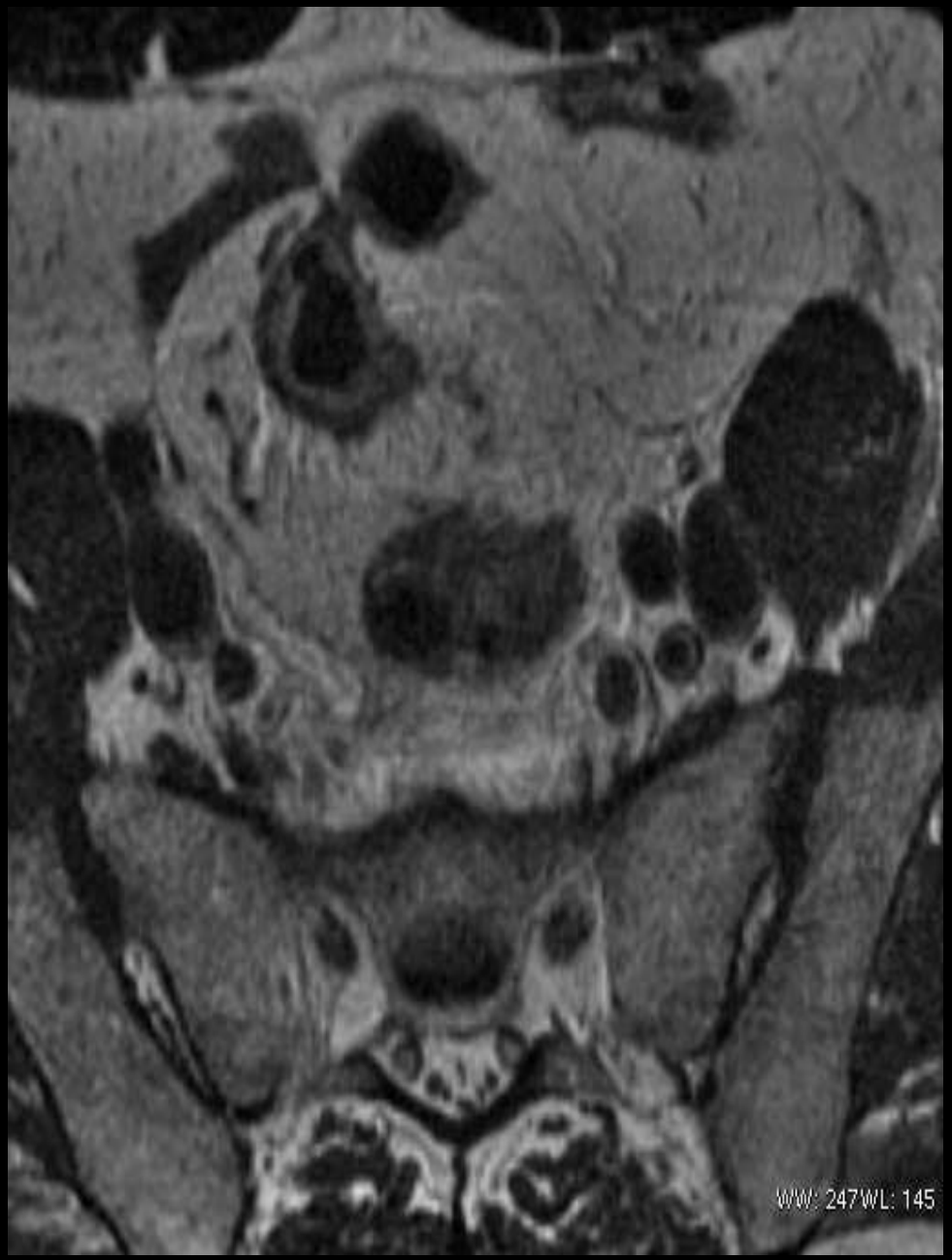
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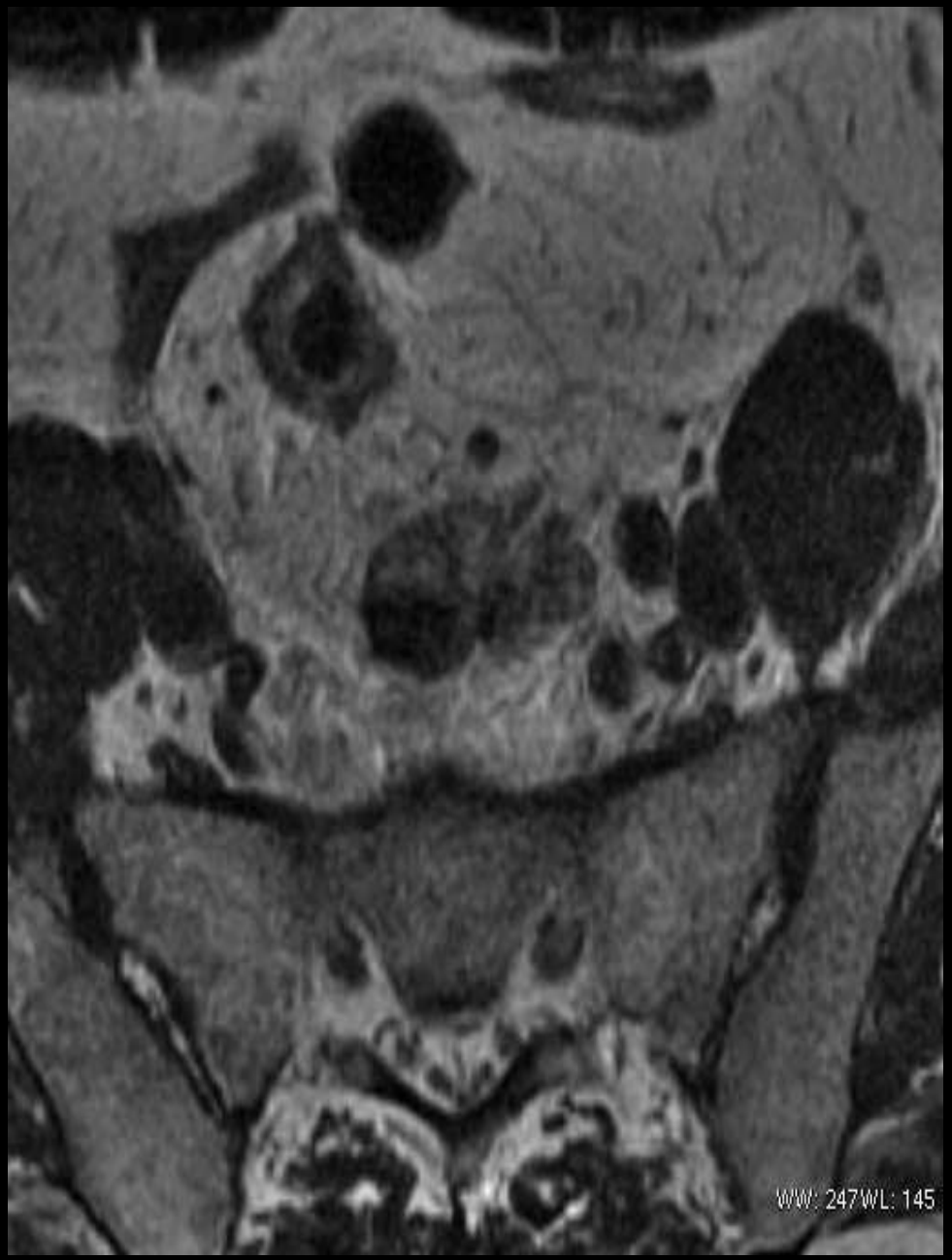
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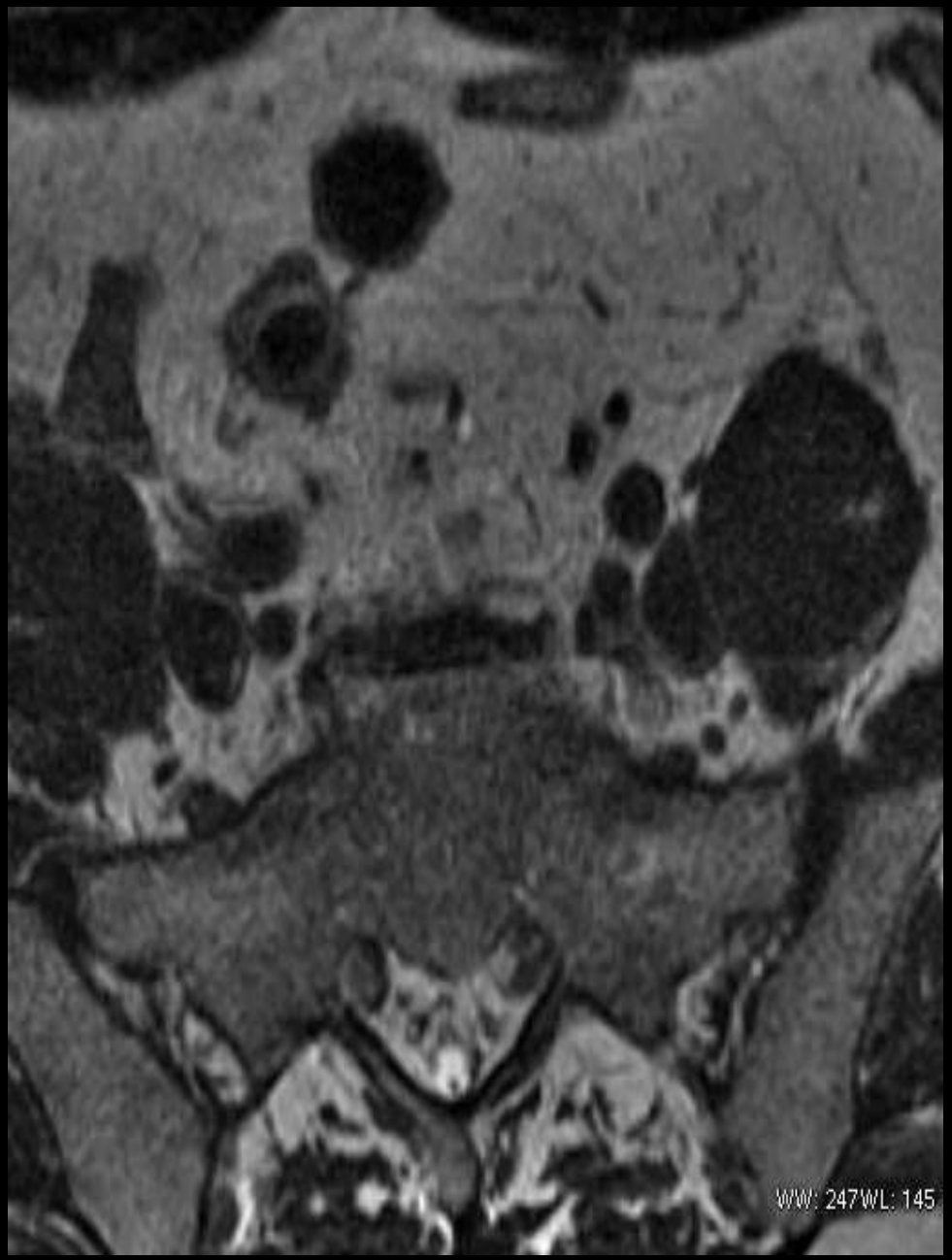
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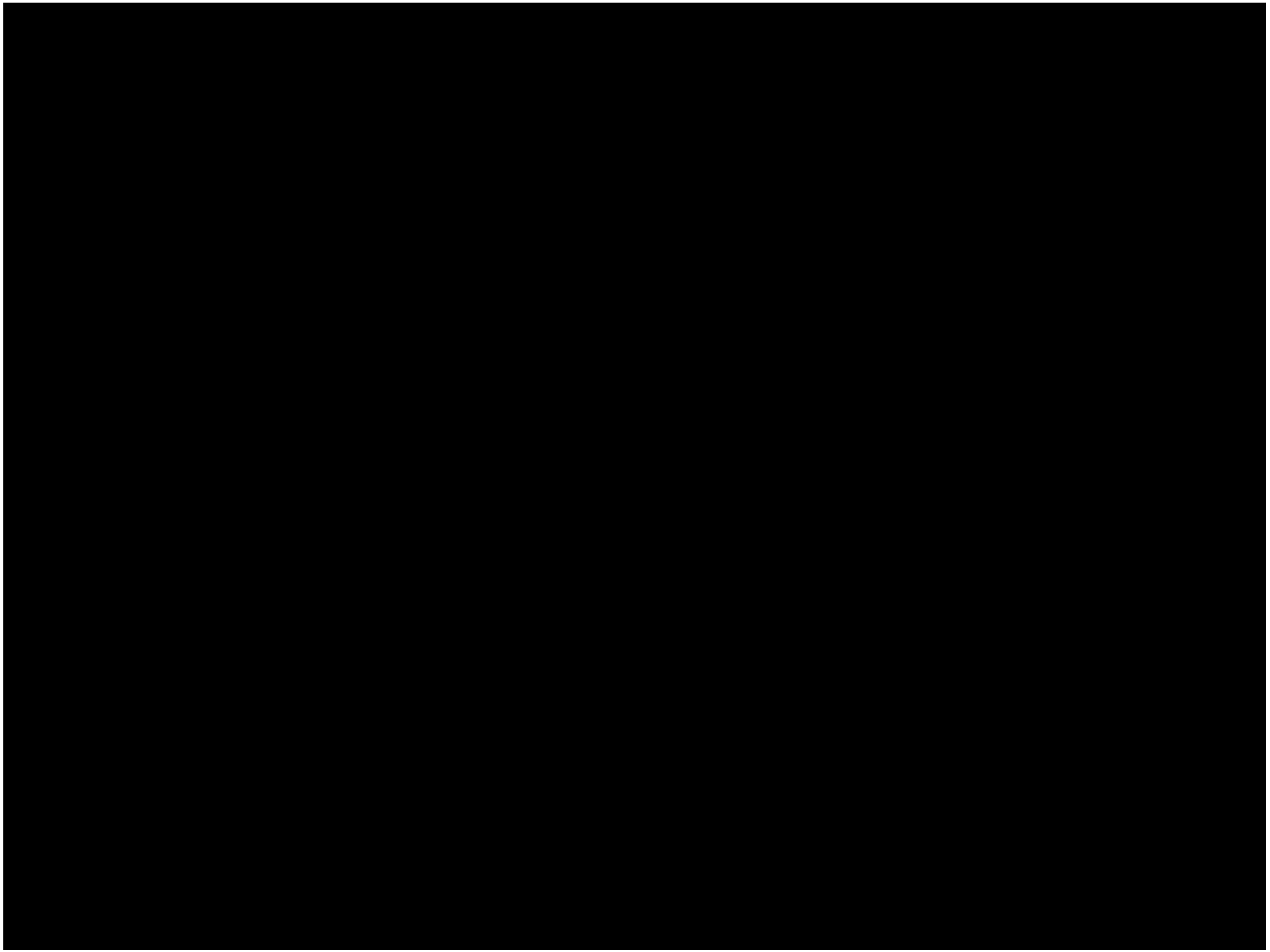

Staging

- **MRI abdomen:**
  - At the level of the hepatic VII segment, 1.4 cm superficial lesion hypointense on T1 and hyperintense on T2, no other hepatic lesions

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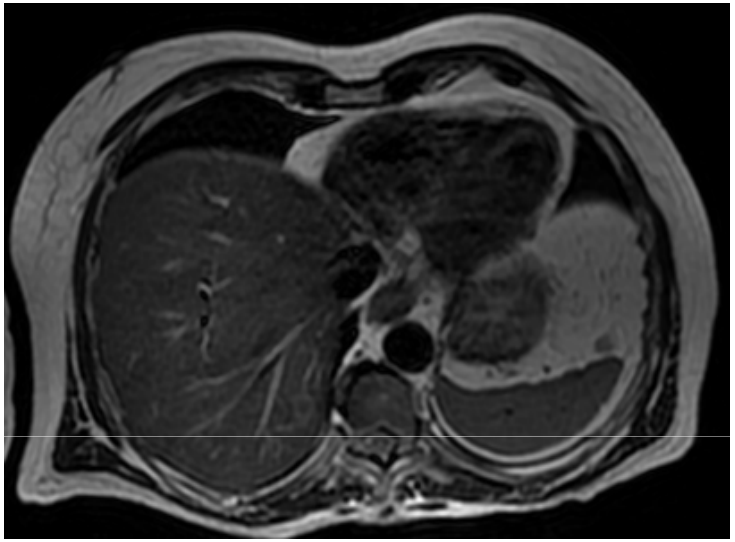
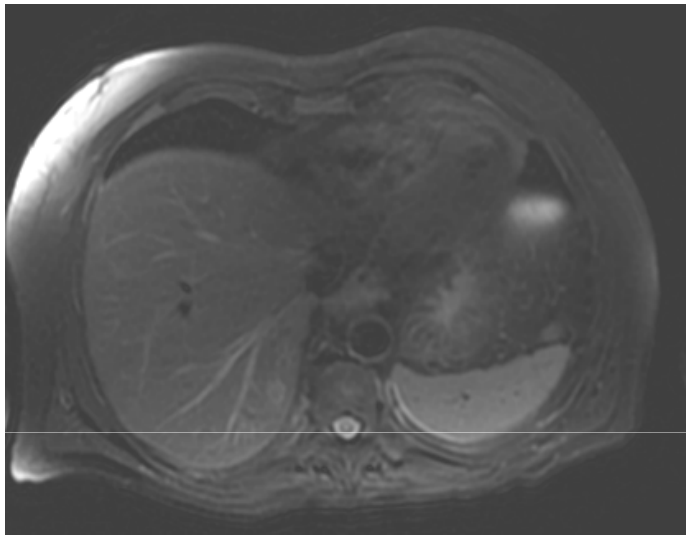
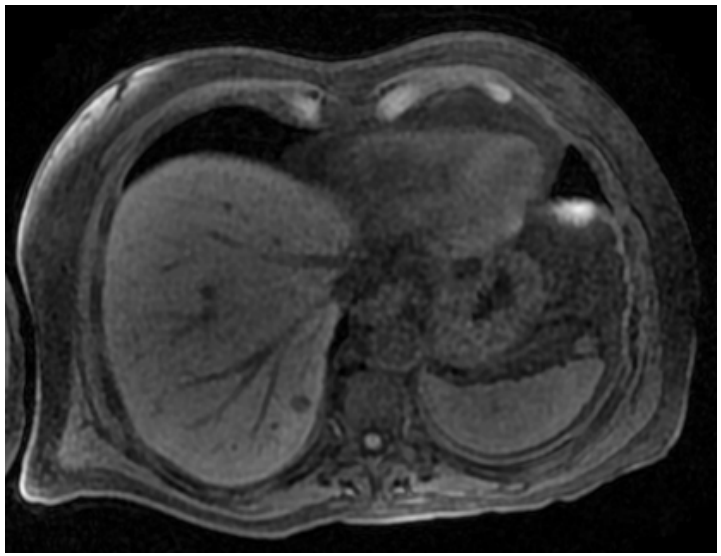
Upper Abdomen MRI







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Question 1

Do you need additional imaging?

A. No

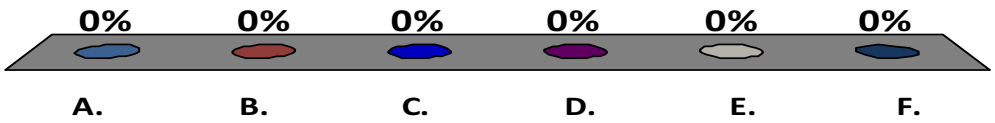
B. FDG PET-CT Scan

C. Pelvic MRI with Diffusion weighted imaging (DWI) sequences

D. Abdominal MRI hepatospecific contrast-enhanced

E. Ultrasound of the liver

F. Other



Staging

- **PET-CT:**
  - **Increased metabolic activity** at the level of the known **rectal lesion** with a longitudinal extension of about 4 cm and **SUV max of 11.9**; **perirectal nodes** and **presacral** globular nodes with an axial diameter of 34 mm and **SUV max of 6.2**.
  - Focal area of **increased metabolism** in the **VII hepatic segment**, superficial.
  - No other pathologic accumulation of FDG.

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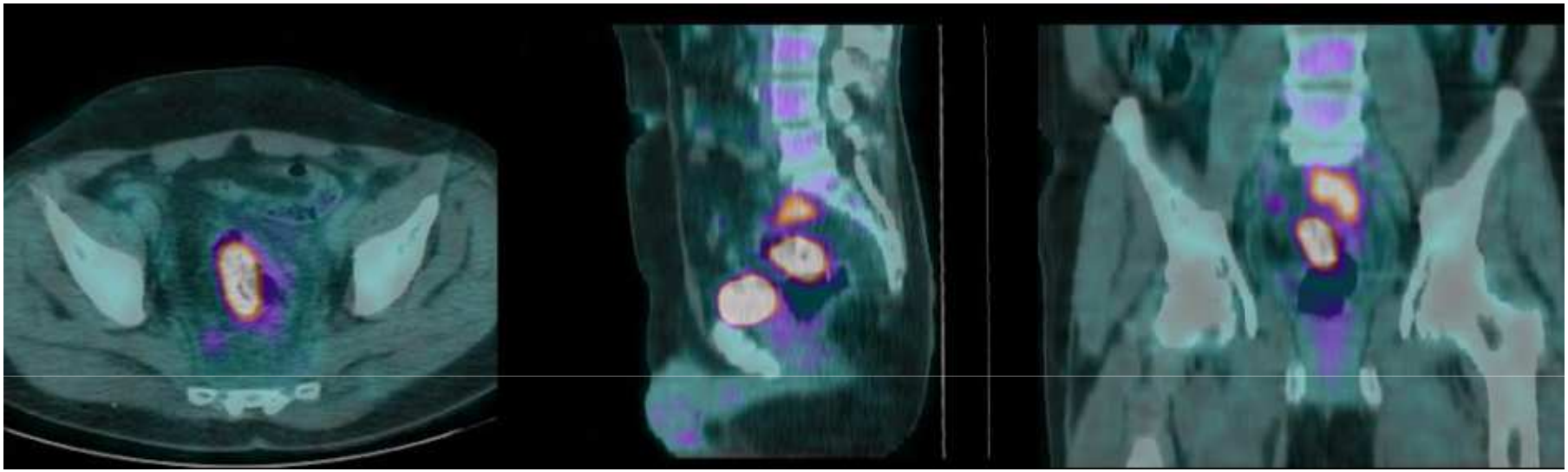
fdg PET-CT



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Question 2

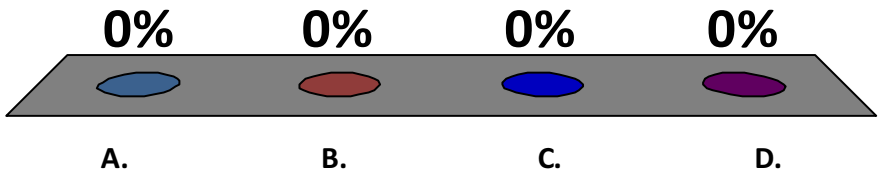
What is the Clinical Stage in this patient?

A. T3 N1 M1

B. T3 N2 M1 (MRF+)

C. T4 N1 M1

D. T4 N2 M1



Staging

Stage: IV

cT3; N2; M1 (liver)

MRF +

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Question 3

What treatment would you propose ?

A. Upfront Surgery (liver and rectum)

B. Short-Course RT → Surgery (rectum) → CT → Surgery (liver)

C. Short-Course RT → Surgery (rectum) → CT → Surgery (liver)

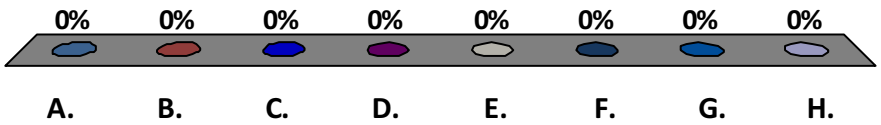
D. Short-Course RT → Chemotherapy → Surgery (liver and rectum) Long-Course RT-CT → Chemotherapy → Surgery (liver and rectum)

E. Long-Course RT-CT → Chemotherapy → Surgery (liver and rectum)

F. Chemotherapy →Short-Course RT→ Surgery (liver and rectum)

G. Chemotherapy →Long-Course RT-CT → Surgery (liver and rectum)

H. Other



Treatment (1/3) Clinical Trial

- **Radiotherapy**
- 45 Gy/25 fx/1.8 Gy on the CTV2:
  - Pelvic subsites (M, PS,IIN,ON)
- 10 Gy 1 Gy delivered concomitantly , 2 days a week on the CTV1: GTV + corresponding mesorectum
  - Total dose 55 Gy on the CTV1 in 5 weeks

- **Concomitant chemotherapy**
  - Capecitabine 1650 mg/m^2 a day

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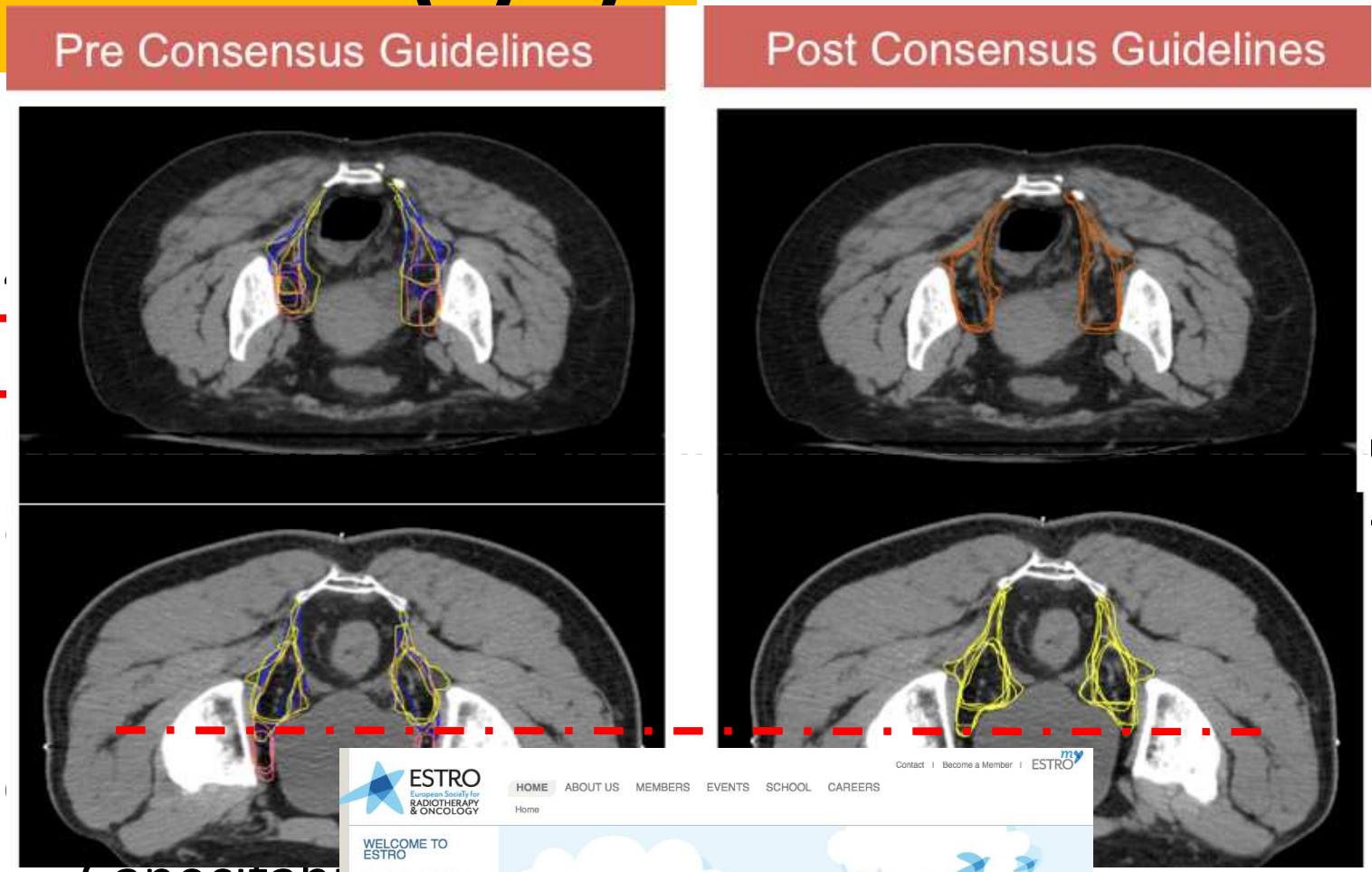
Treatment (1/3)

Clinical Trial



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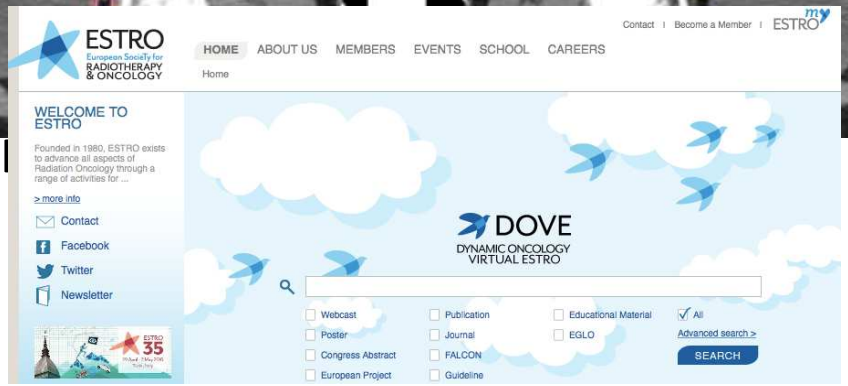

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Treatment (2/3)

- **Preoperative chemotherapy**
  - FOLFOX-4: 3 cycles in the rest period between the end of radiochemotherapy and preoperative re-evaluation

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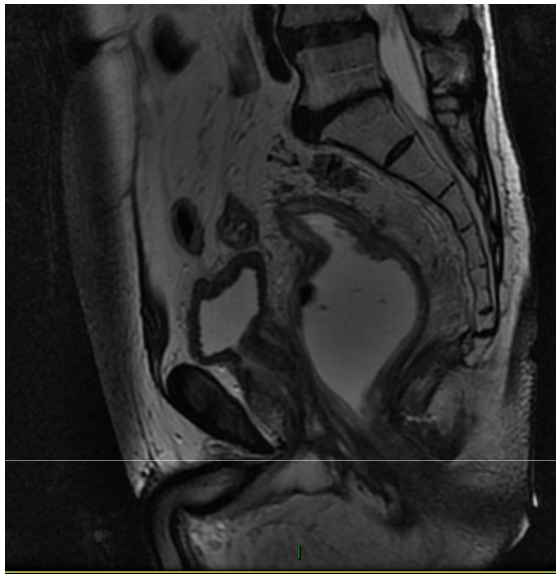
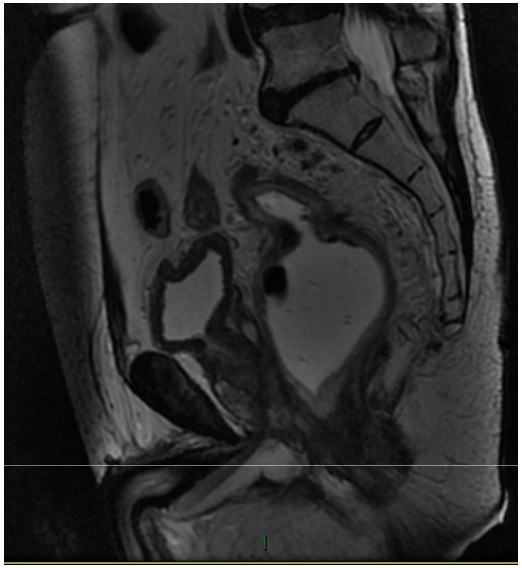
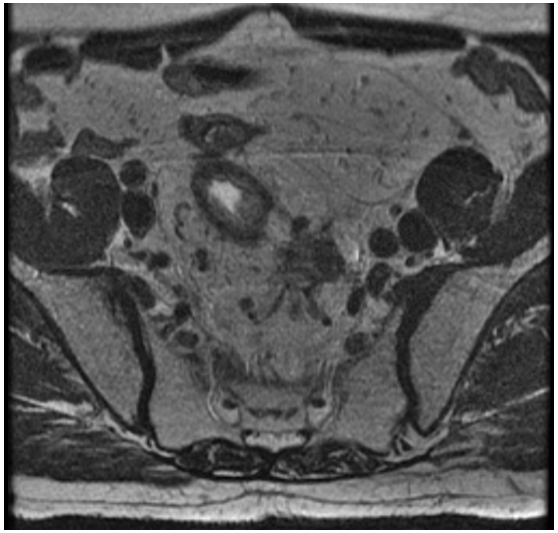
Re-Staging

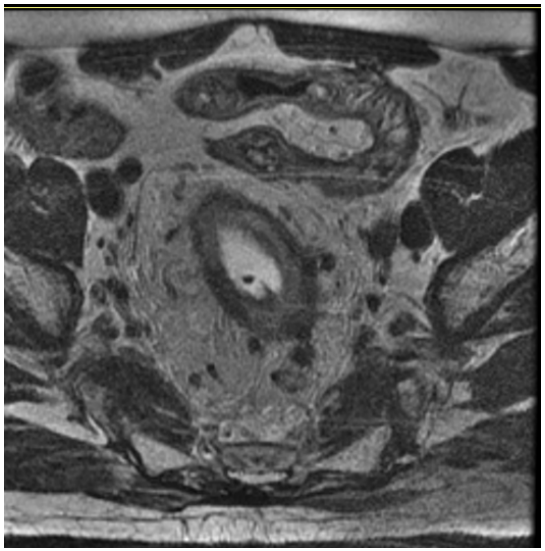
- **Pelvic MRI:**
  - Reduction of the circumferential tumor mass of the high-mid rectum
  - Reduction of the branches in the mesorectum
  - Reduction of number and dimension of the lymph nodes. Some of them globular (size 26 **x** 20 **x** 17 vs 34 **x** 29 **x** 25 mm) and retraction of postero-lateral mesorectal fascia
  - Reduction of dimension of the *metastatic lesion* at the VII hepatic segment (7 mm vs 14 mm). The lesion is hypointens in the central part and with a peripheral hyperintens contrast enhancement

Pelvic MRI









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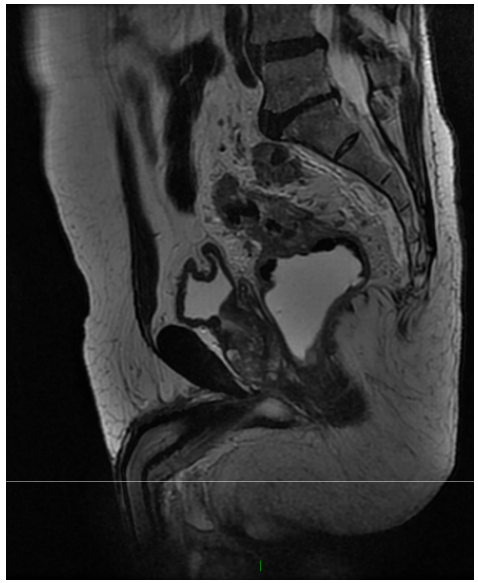
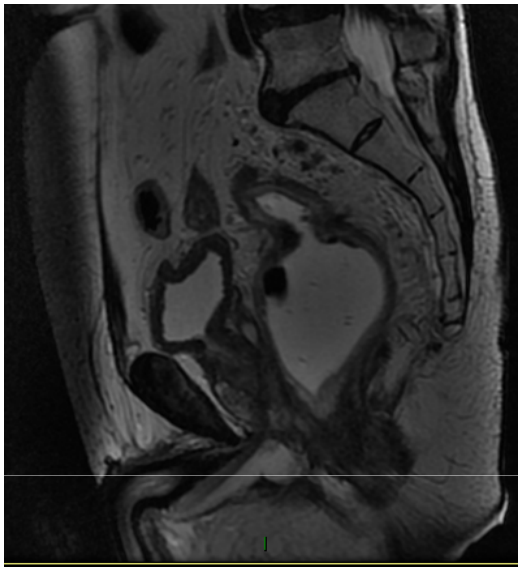
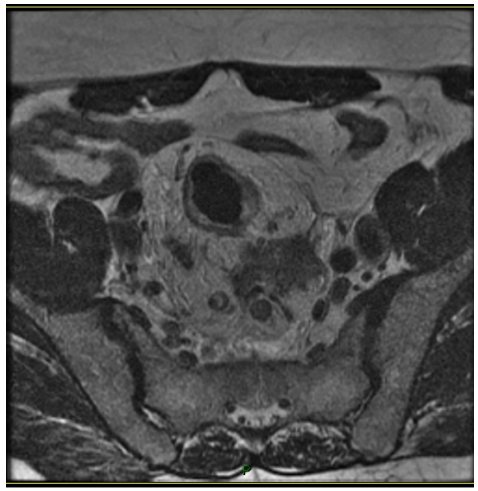
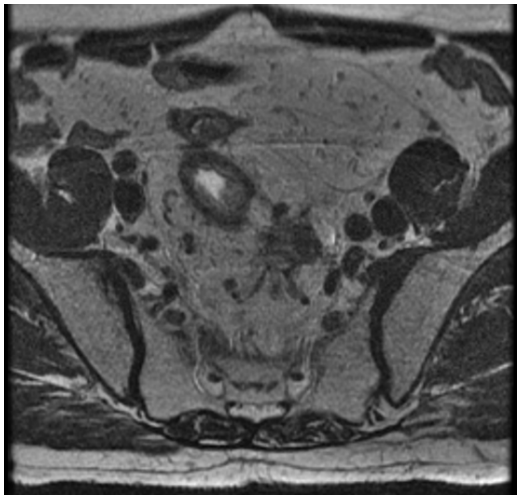
Pelvic MRI









Pre RT-CT

Post RT-CT

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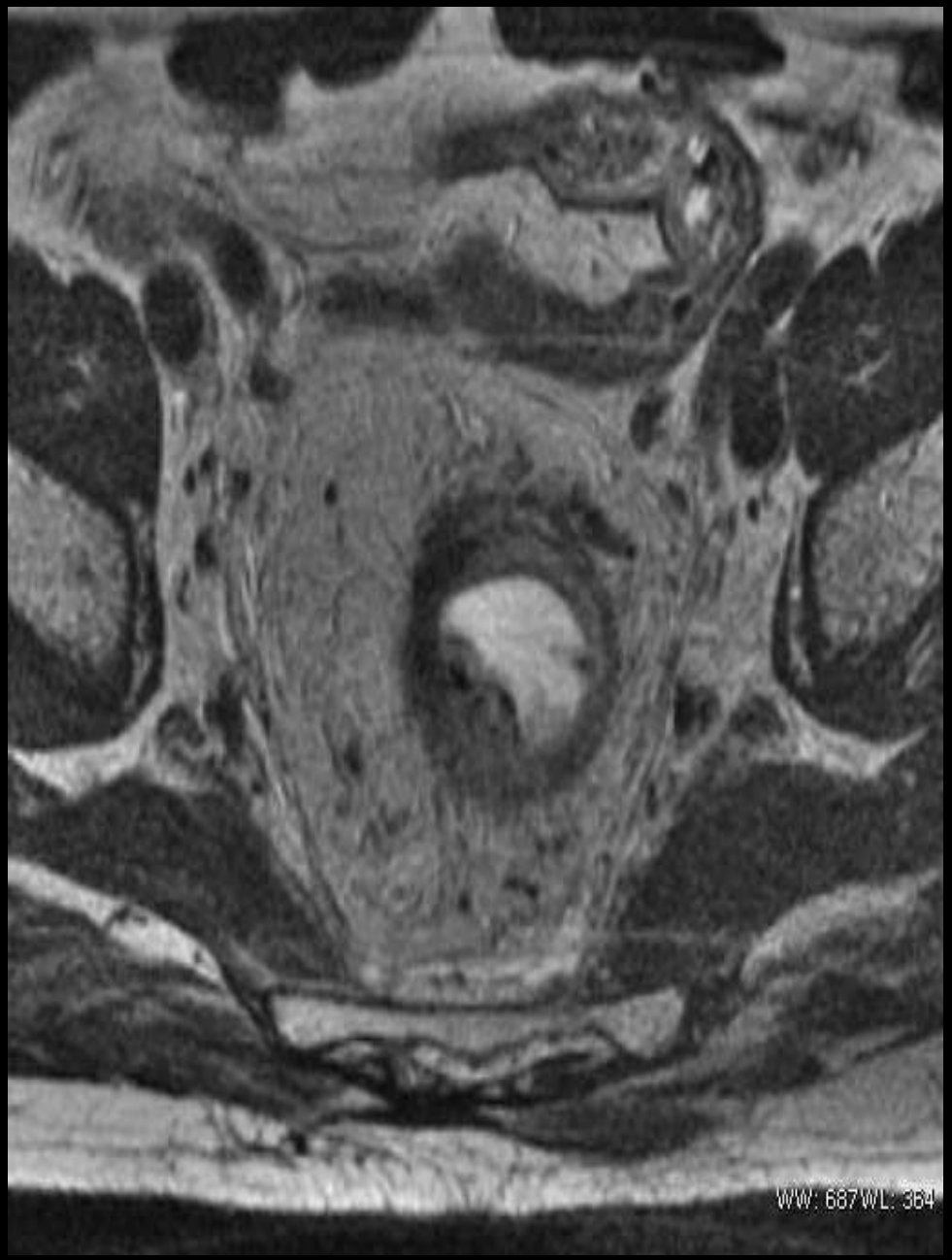
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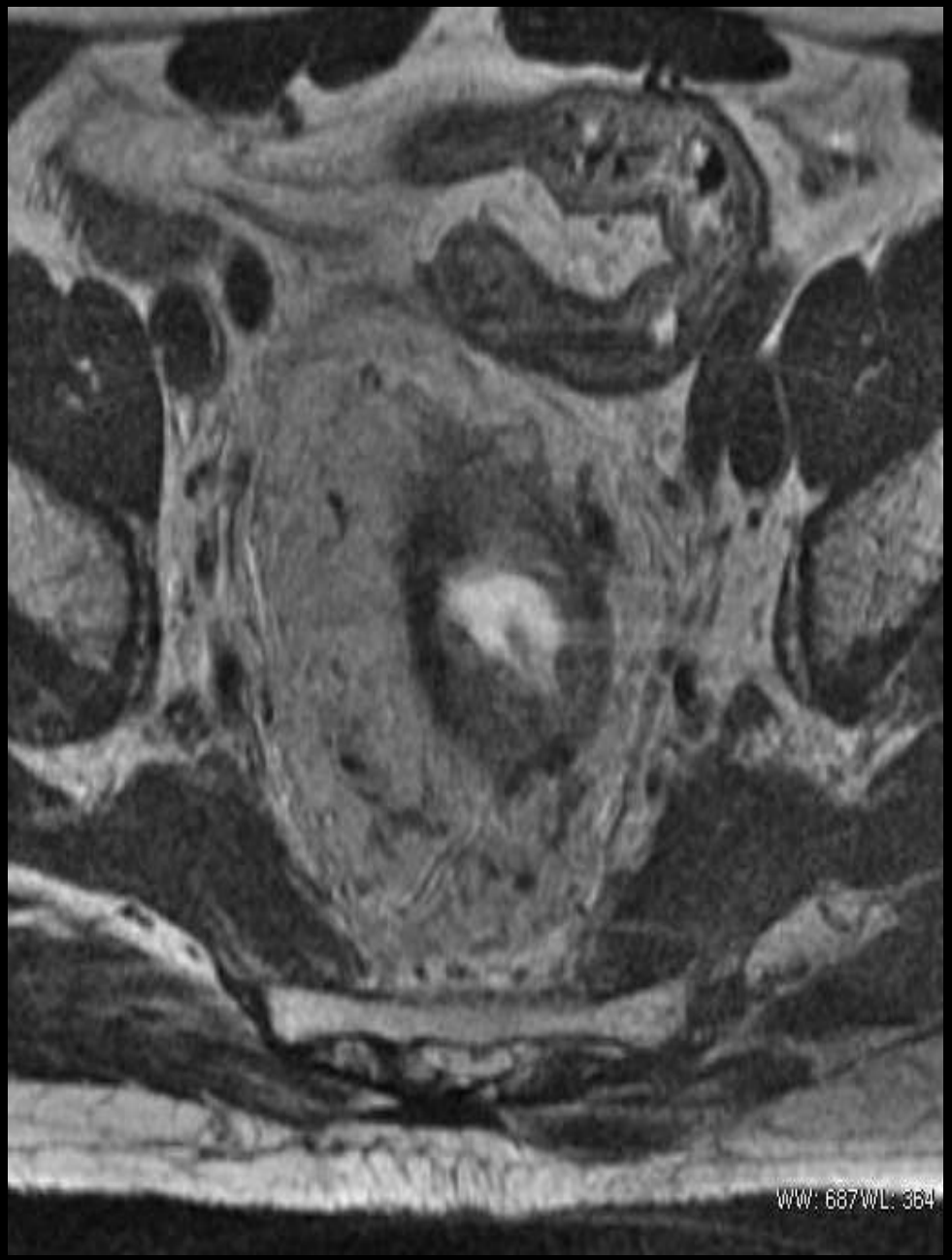
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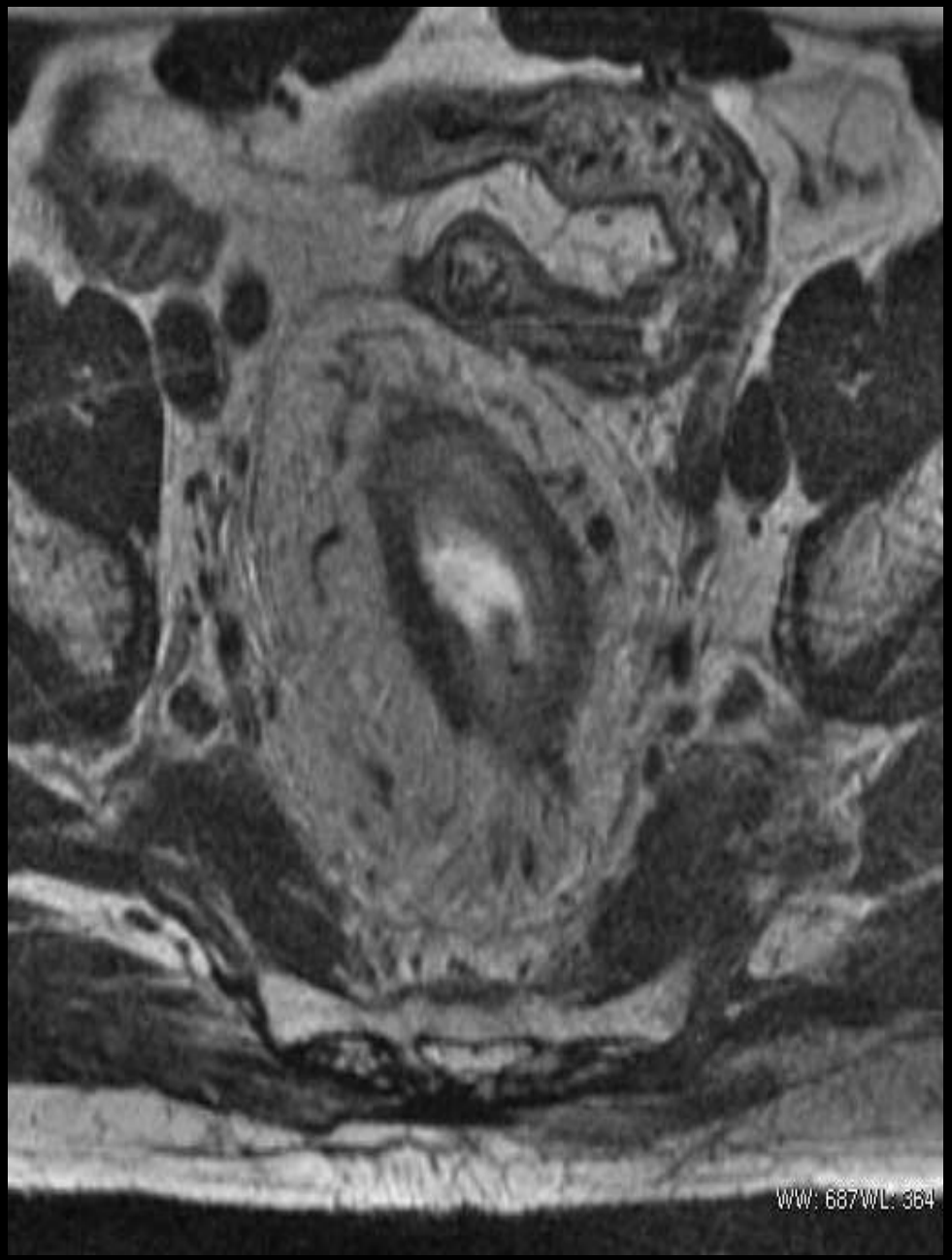
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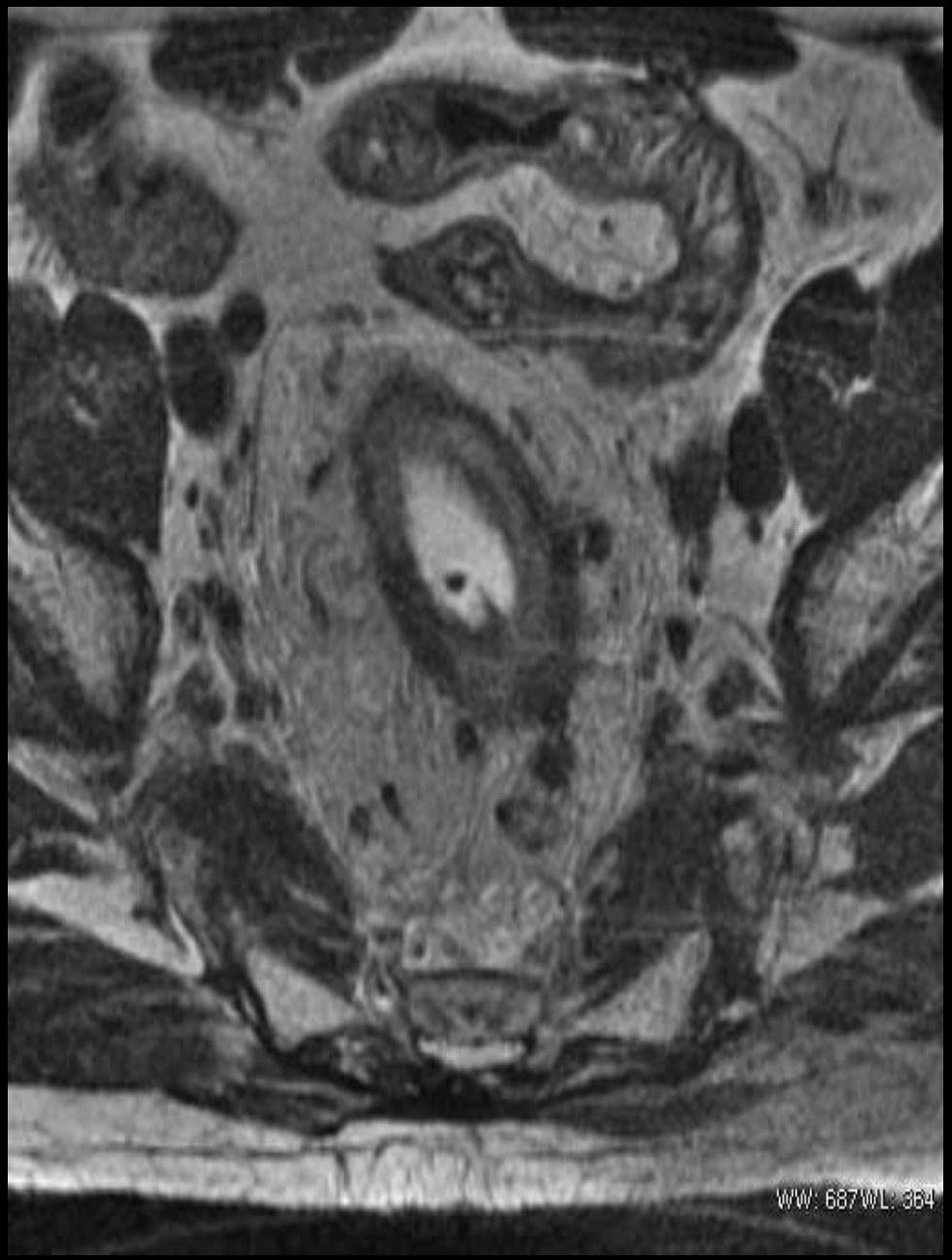
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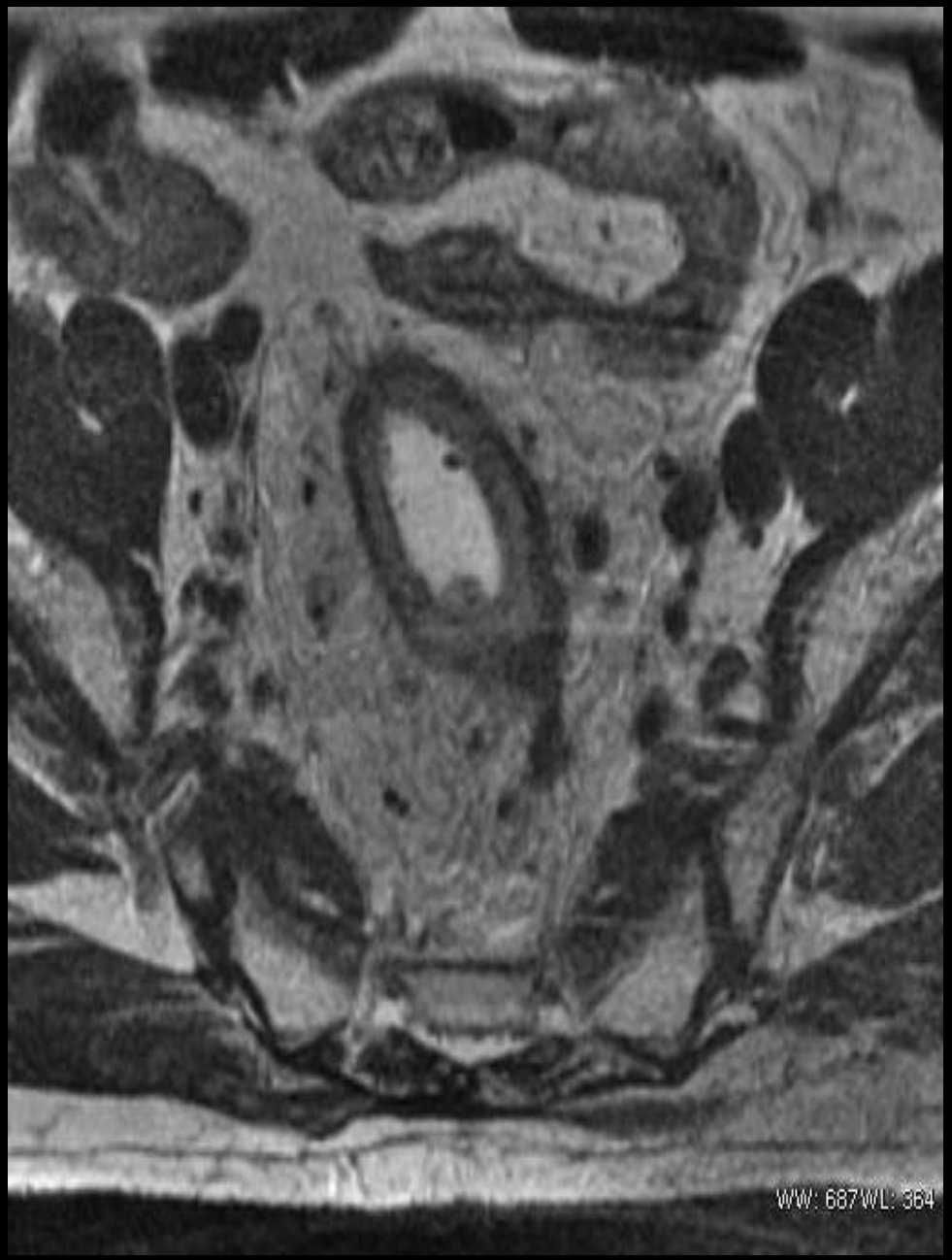
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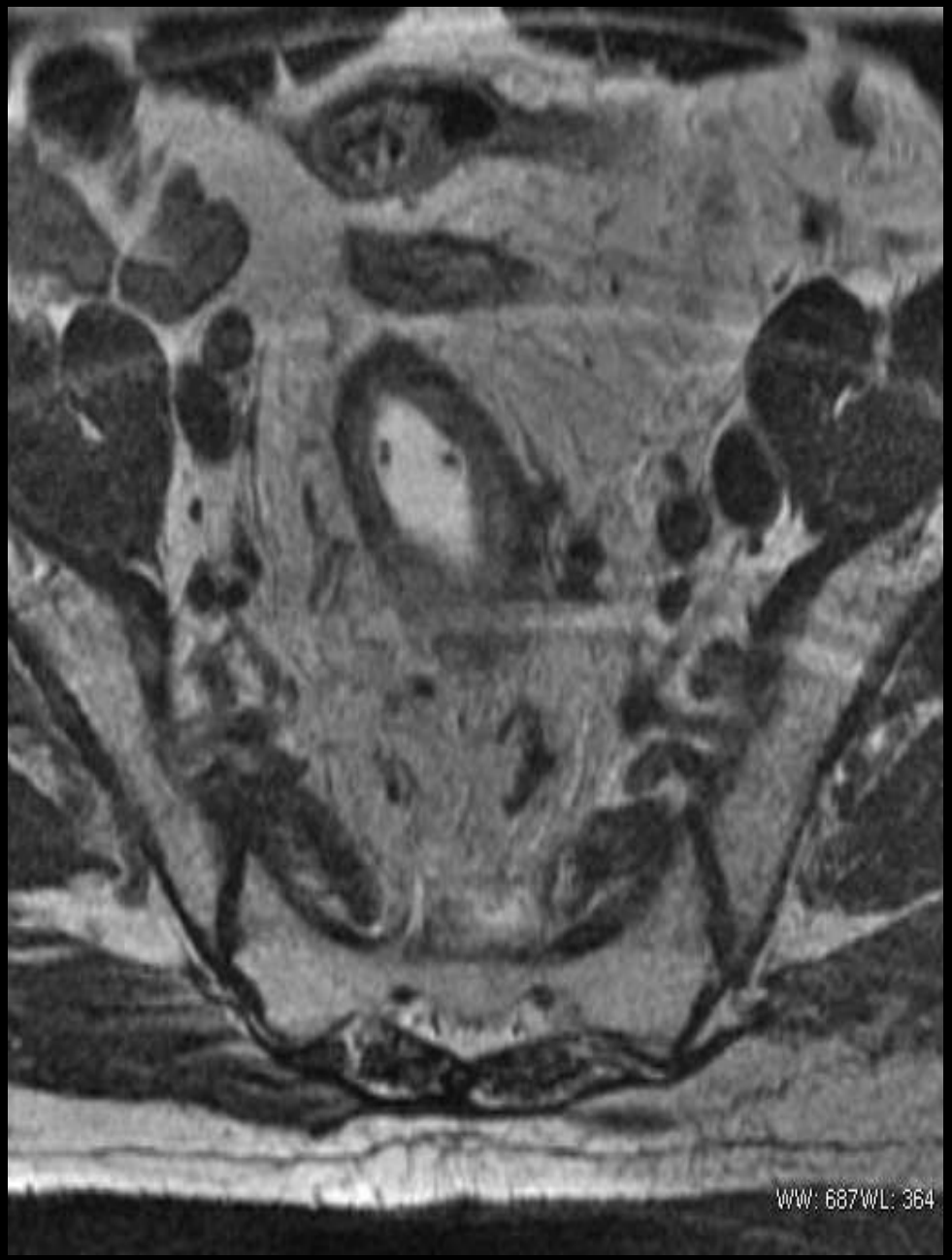
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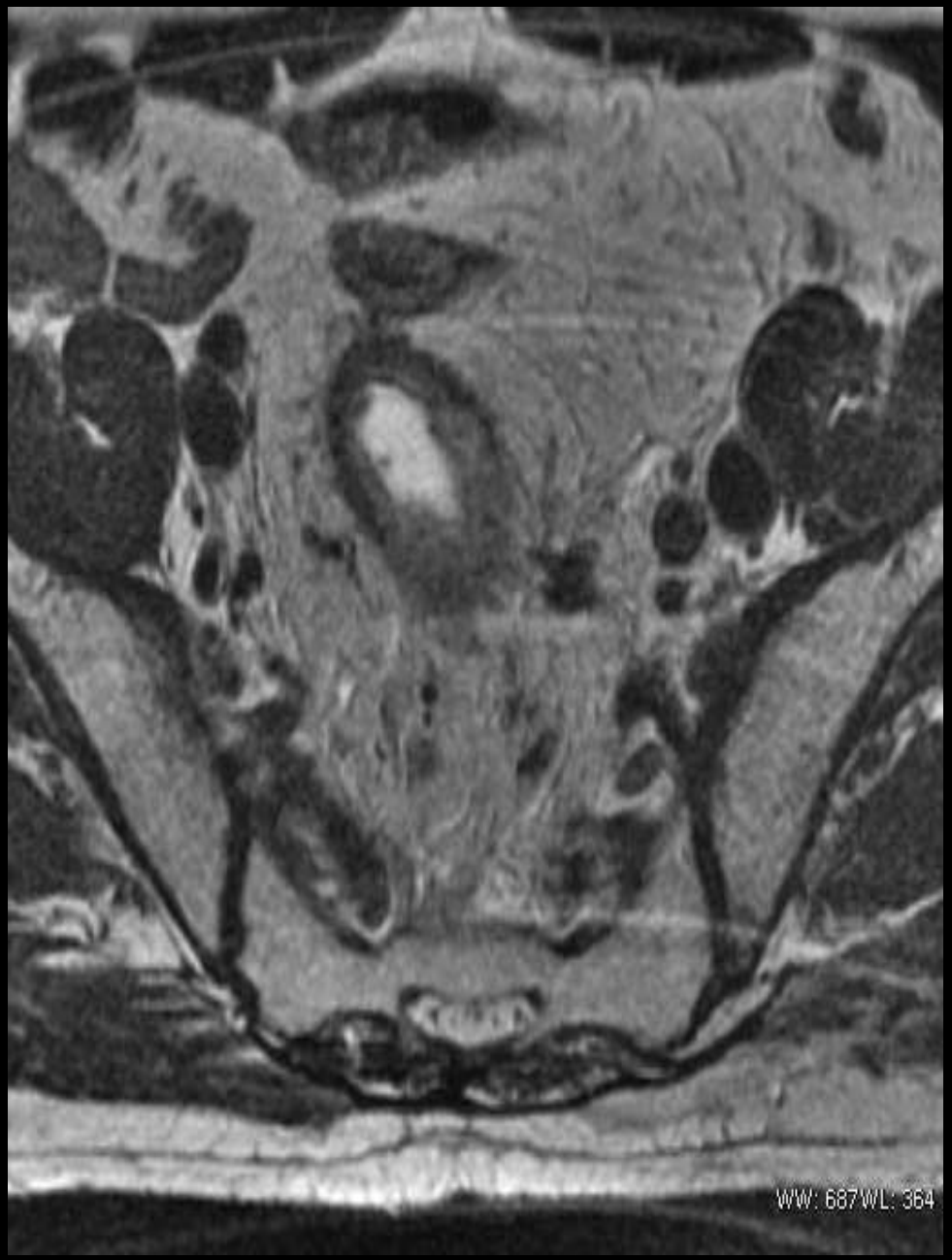
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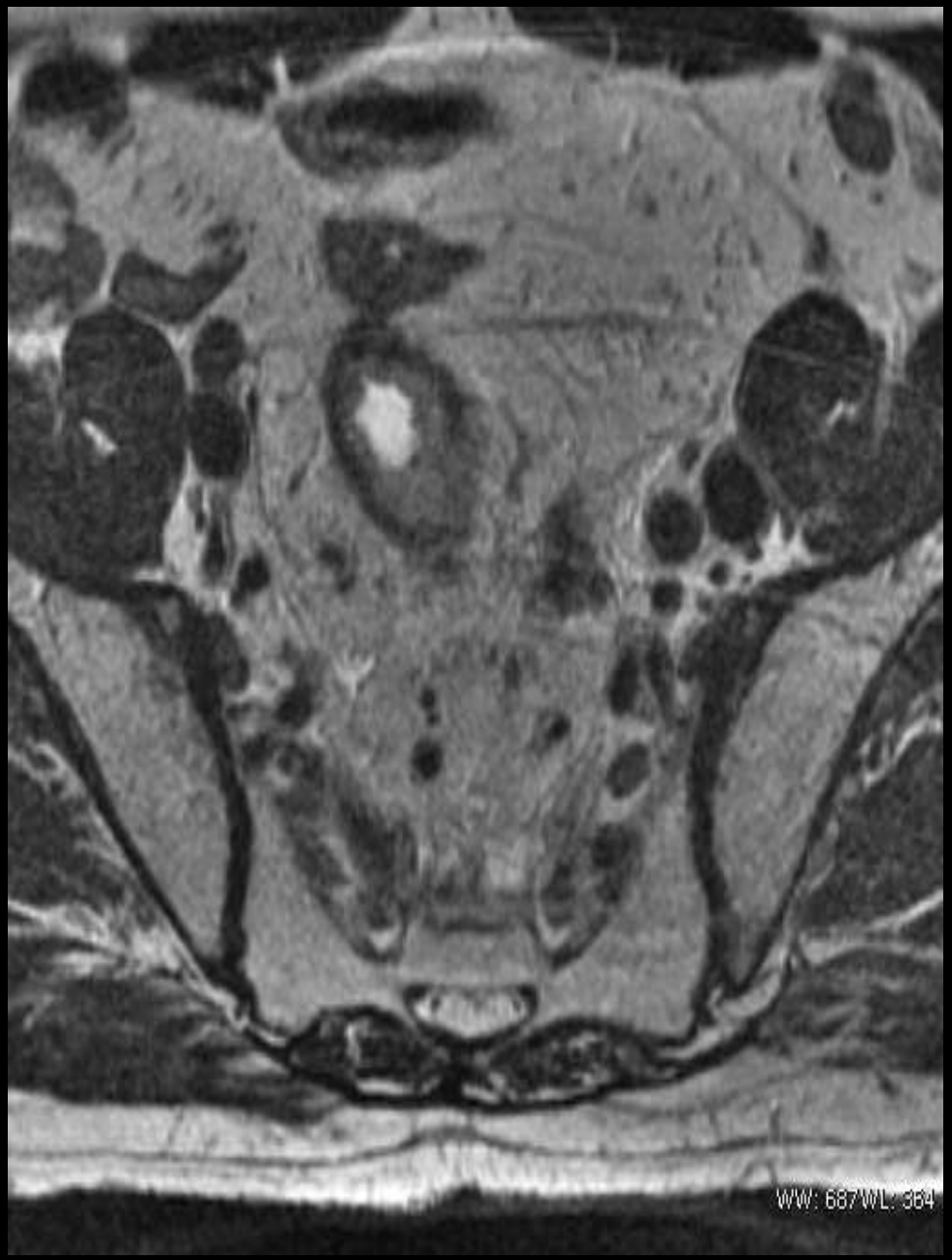
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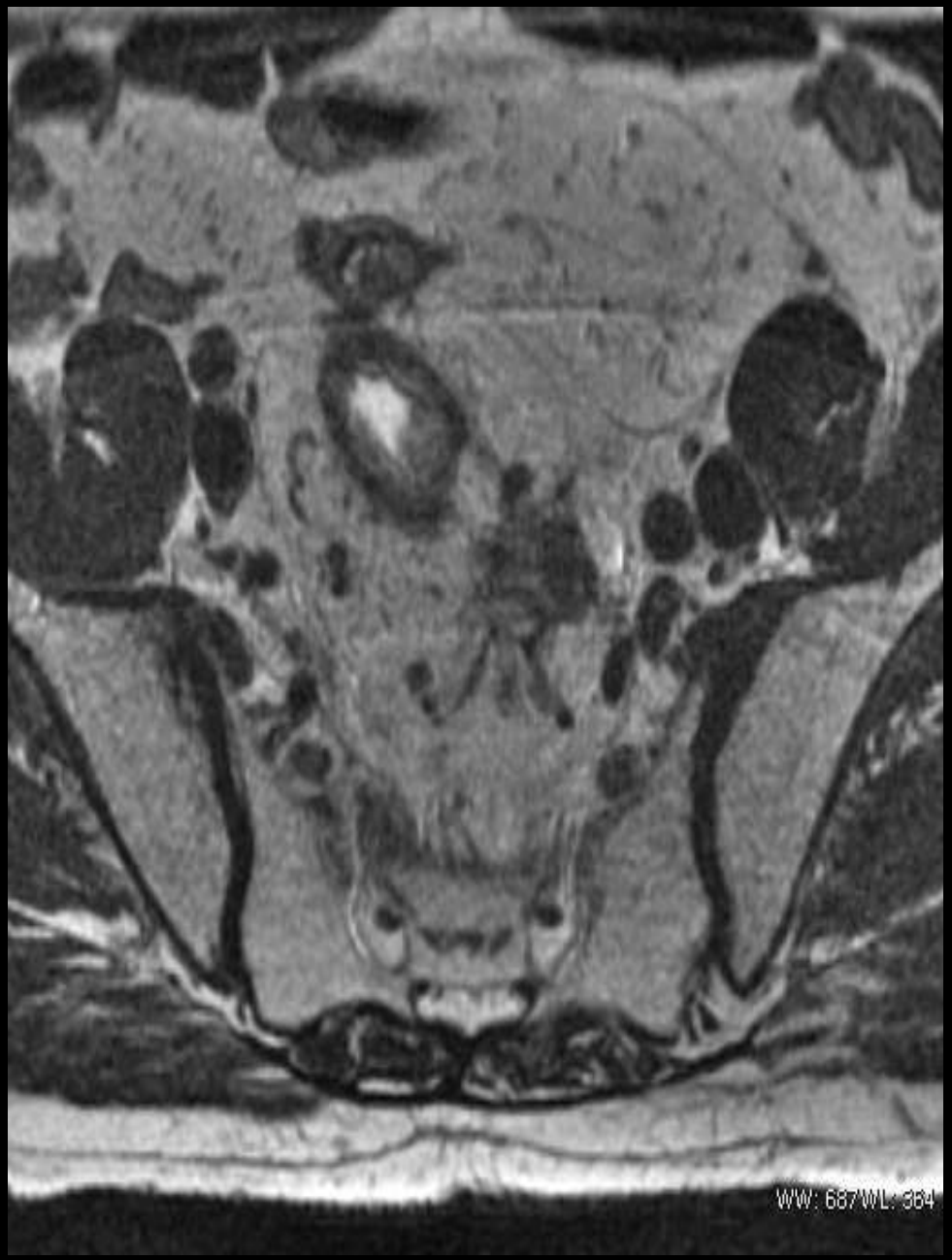
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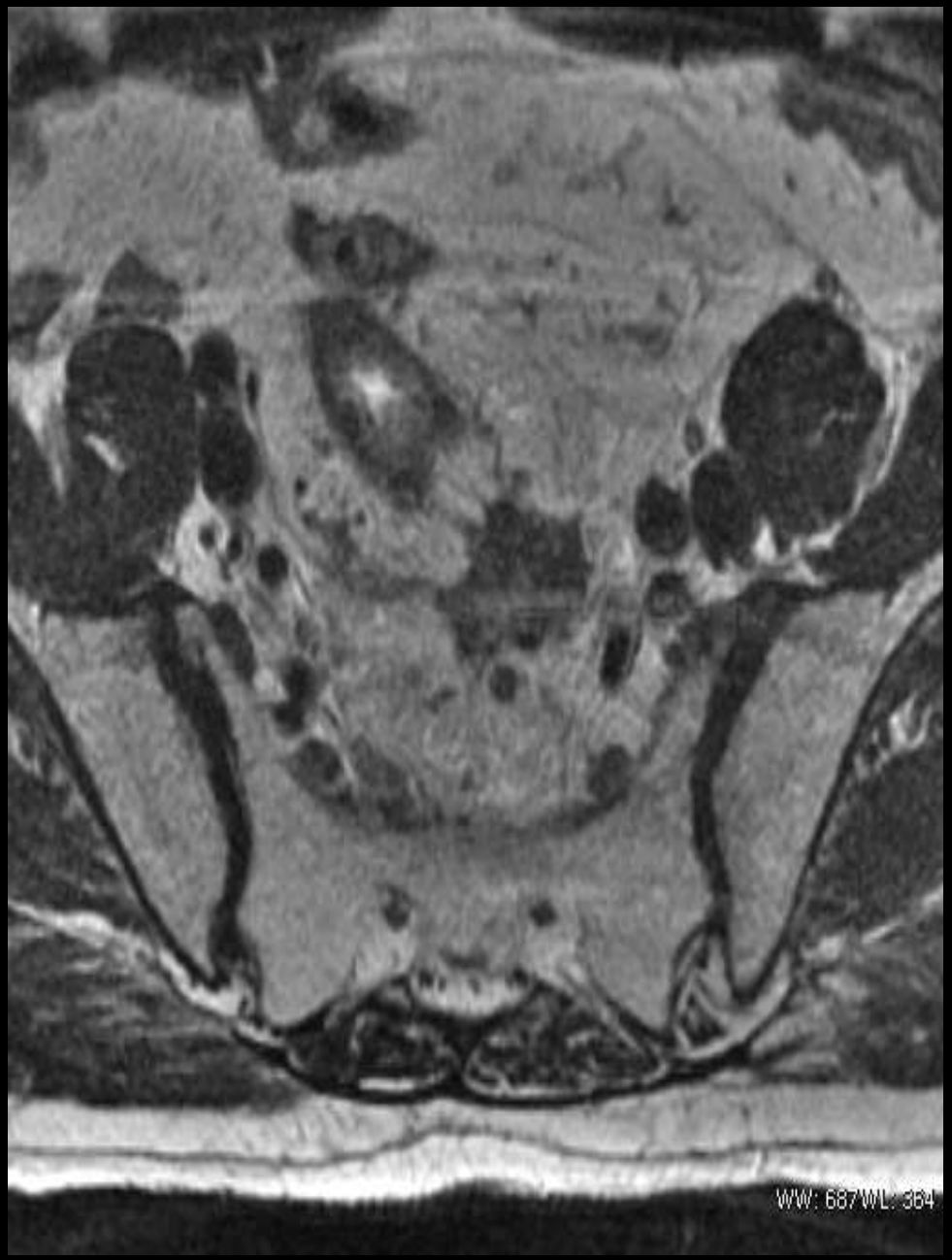
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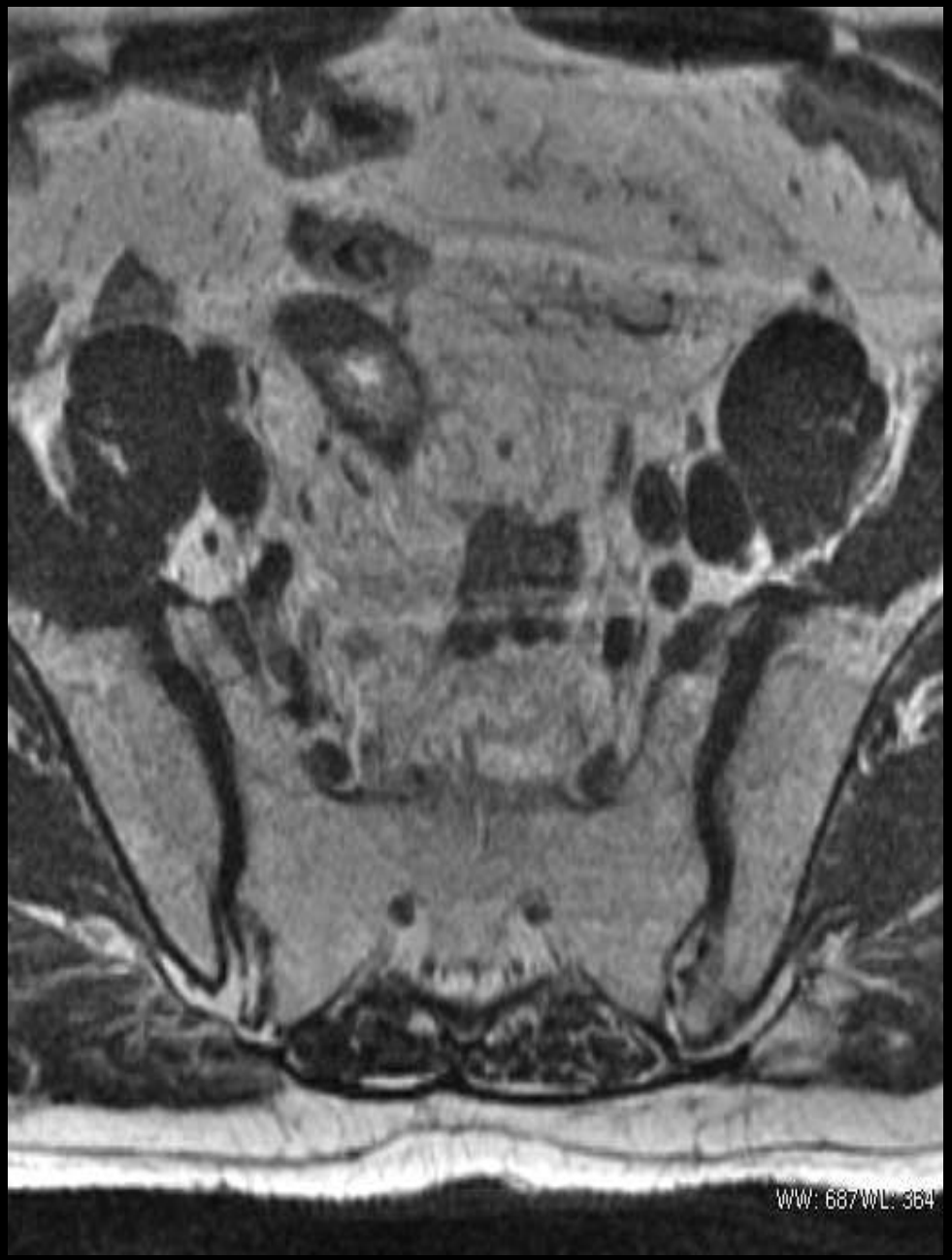
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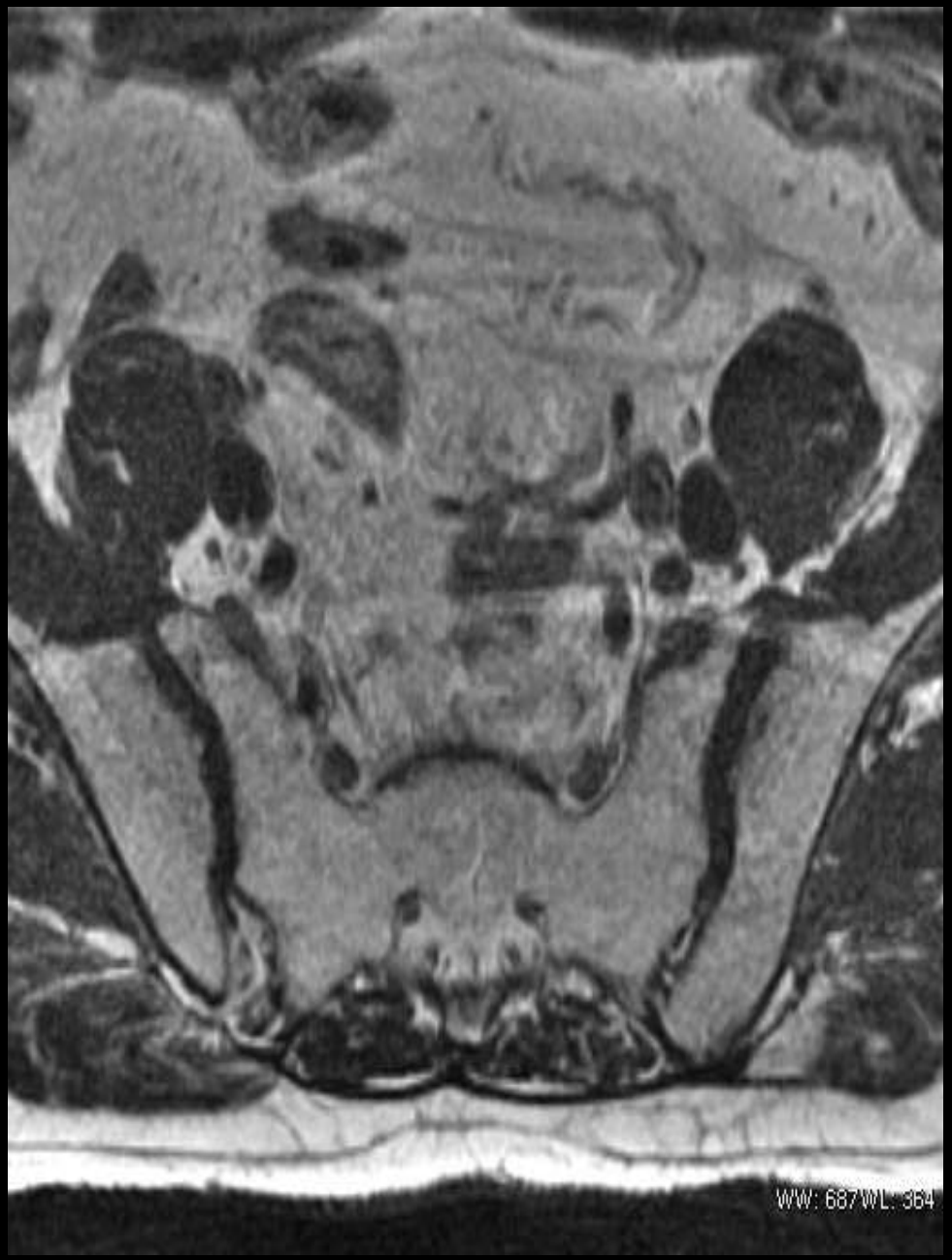
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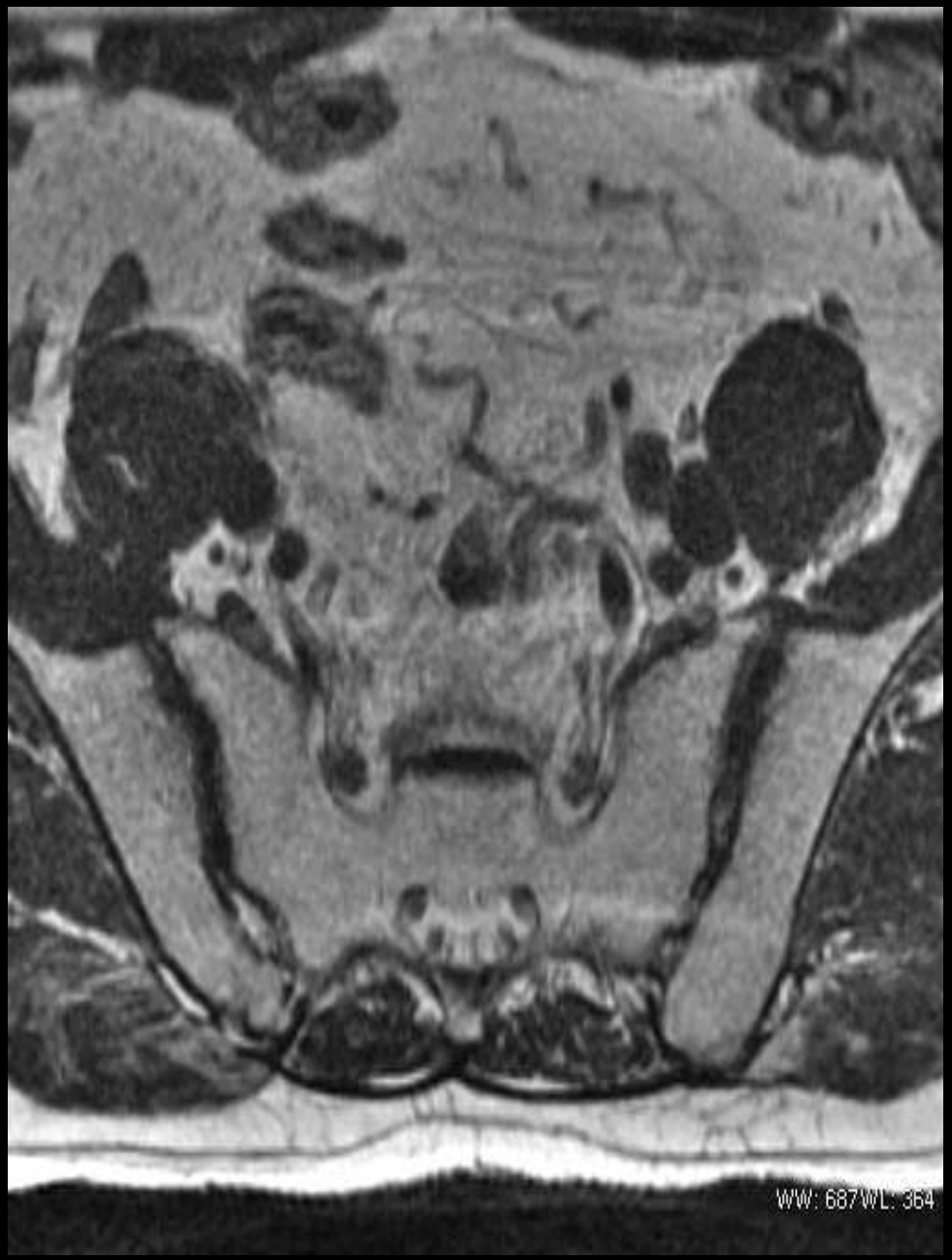
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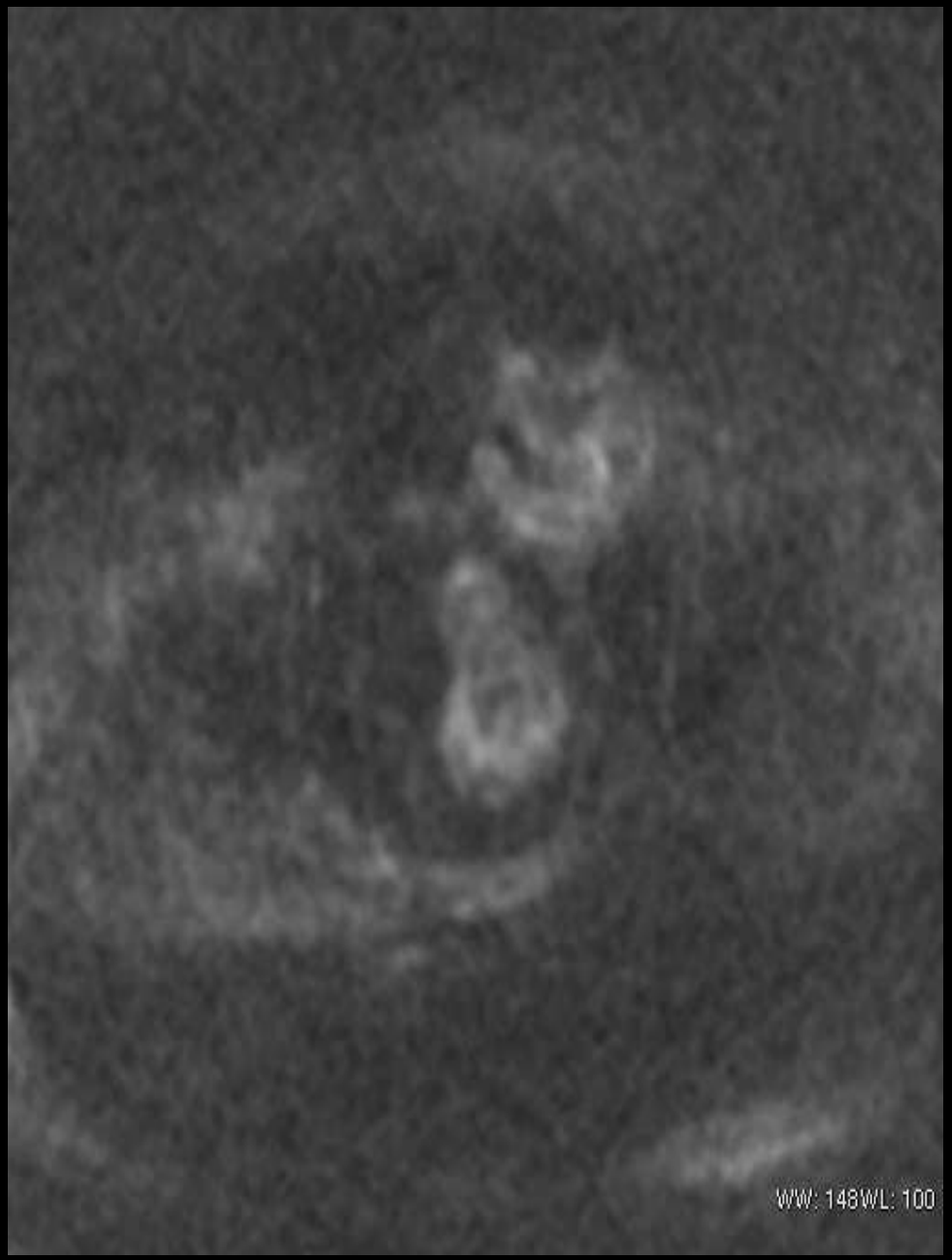
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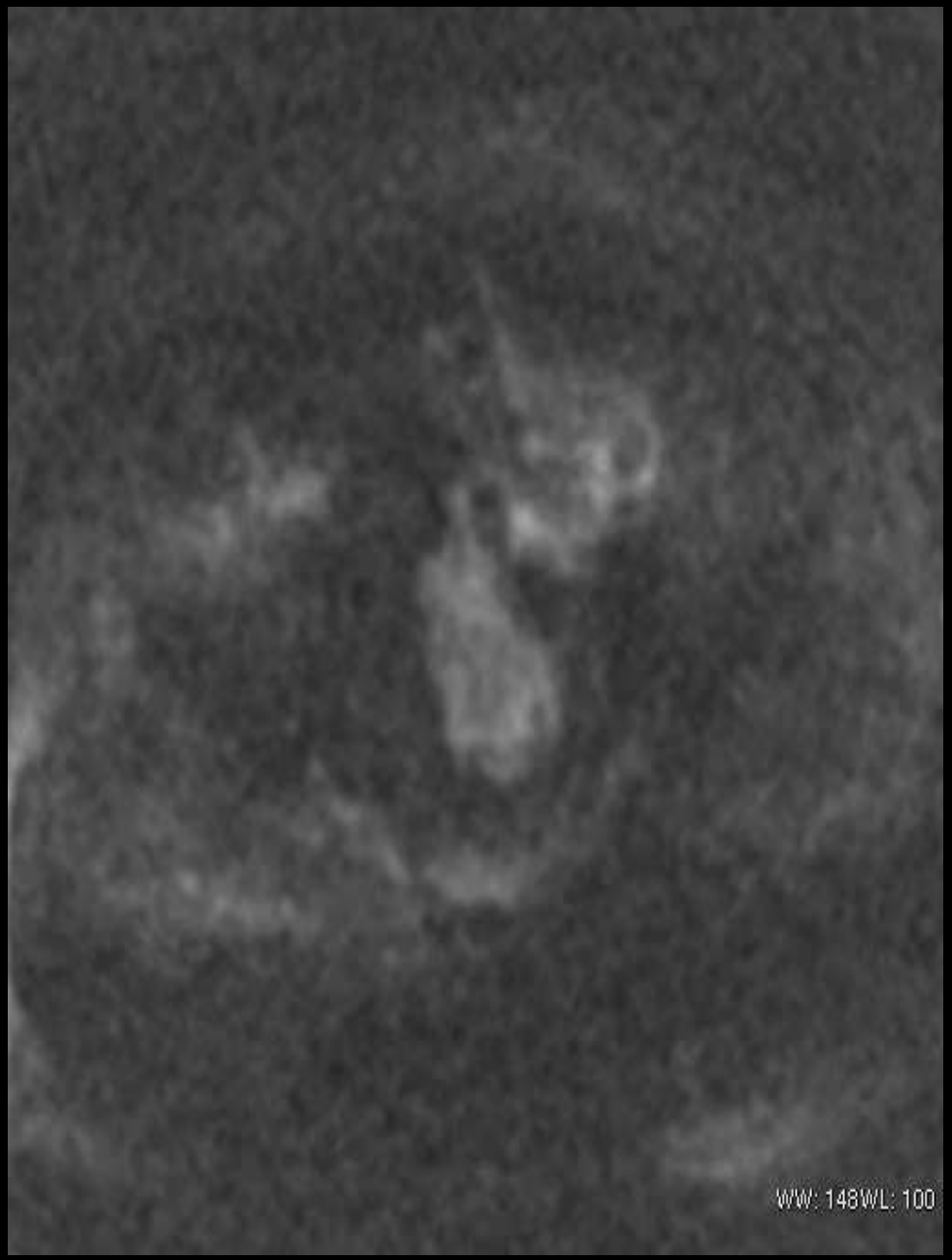
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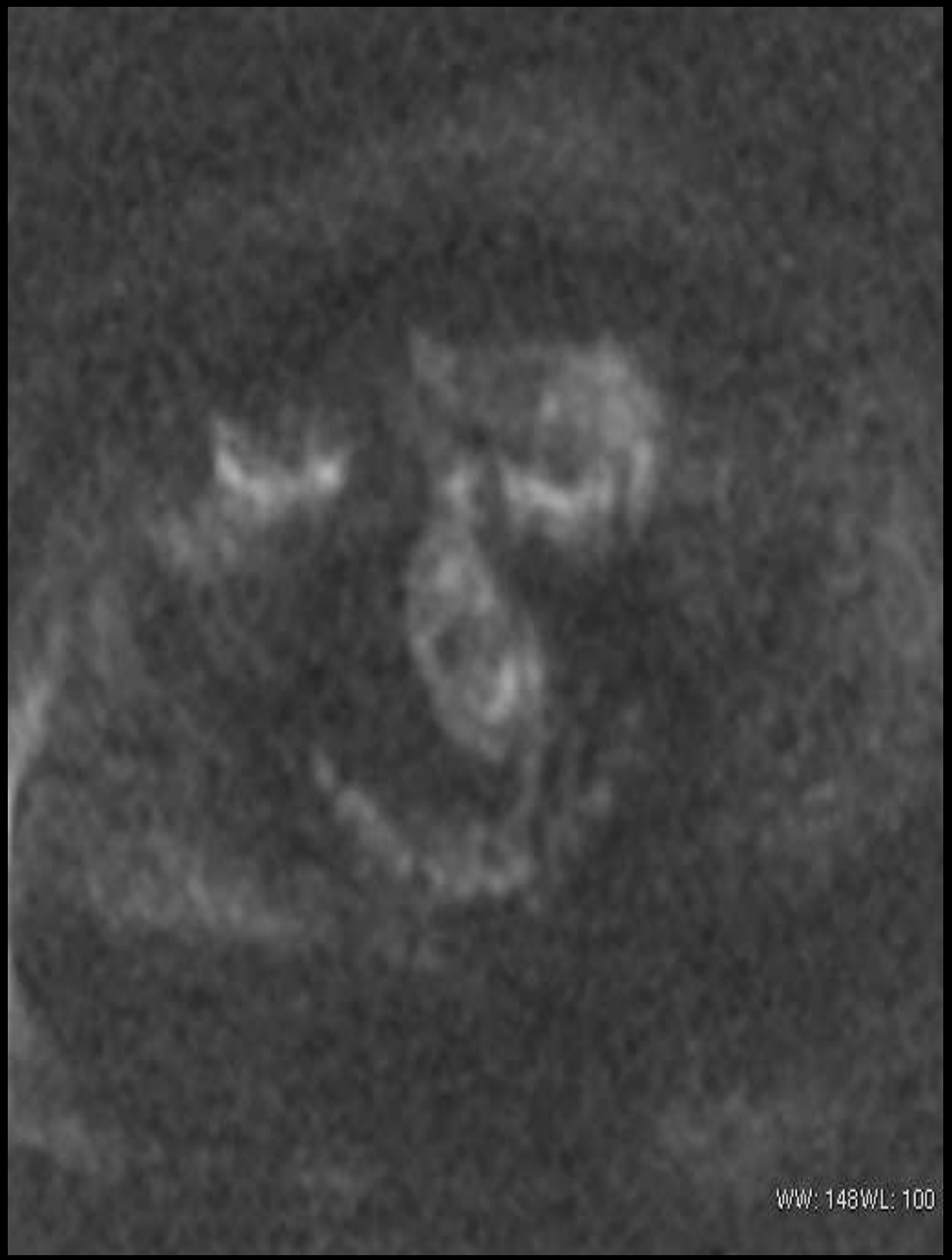
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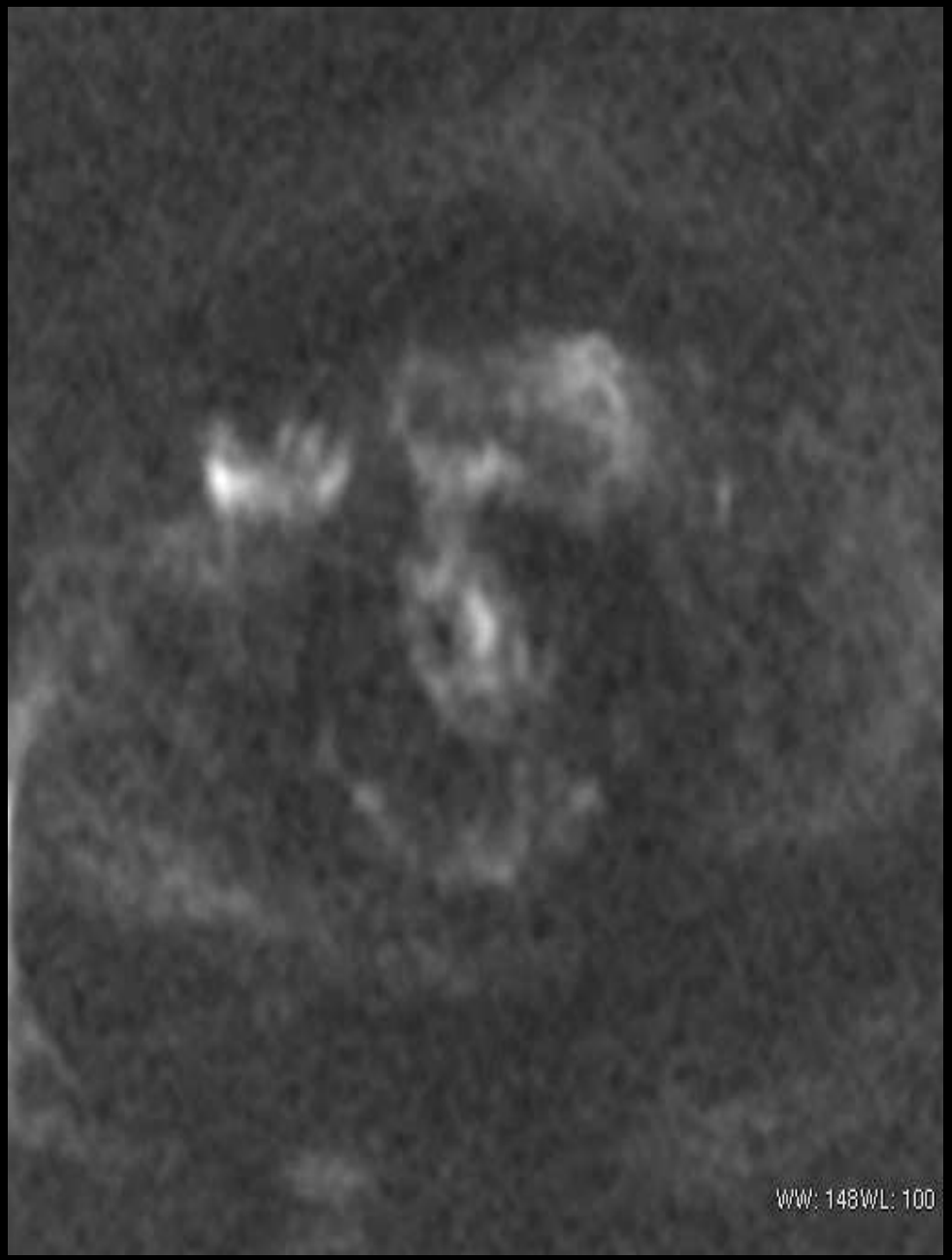
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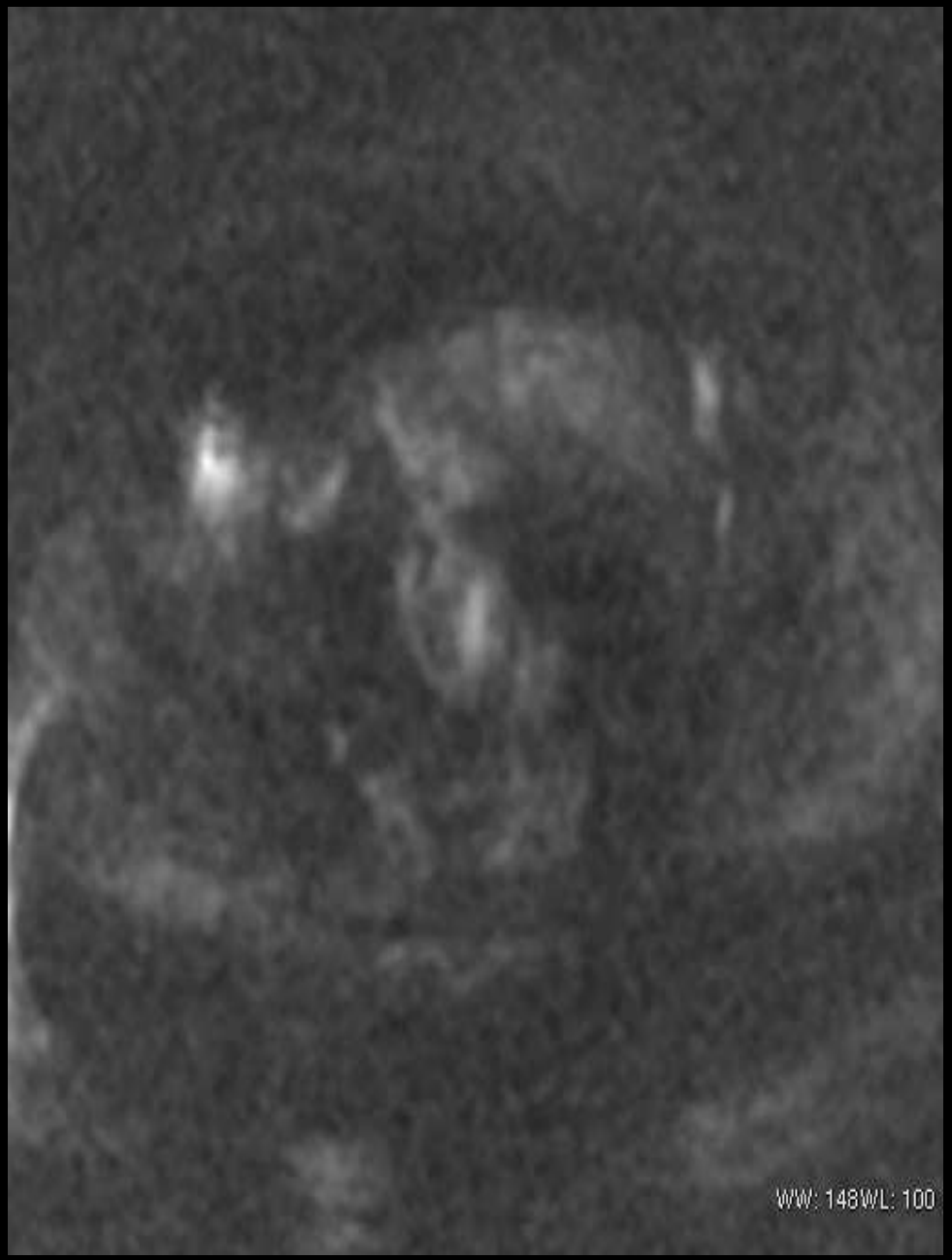
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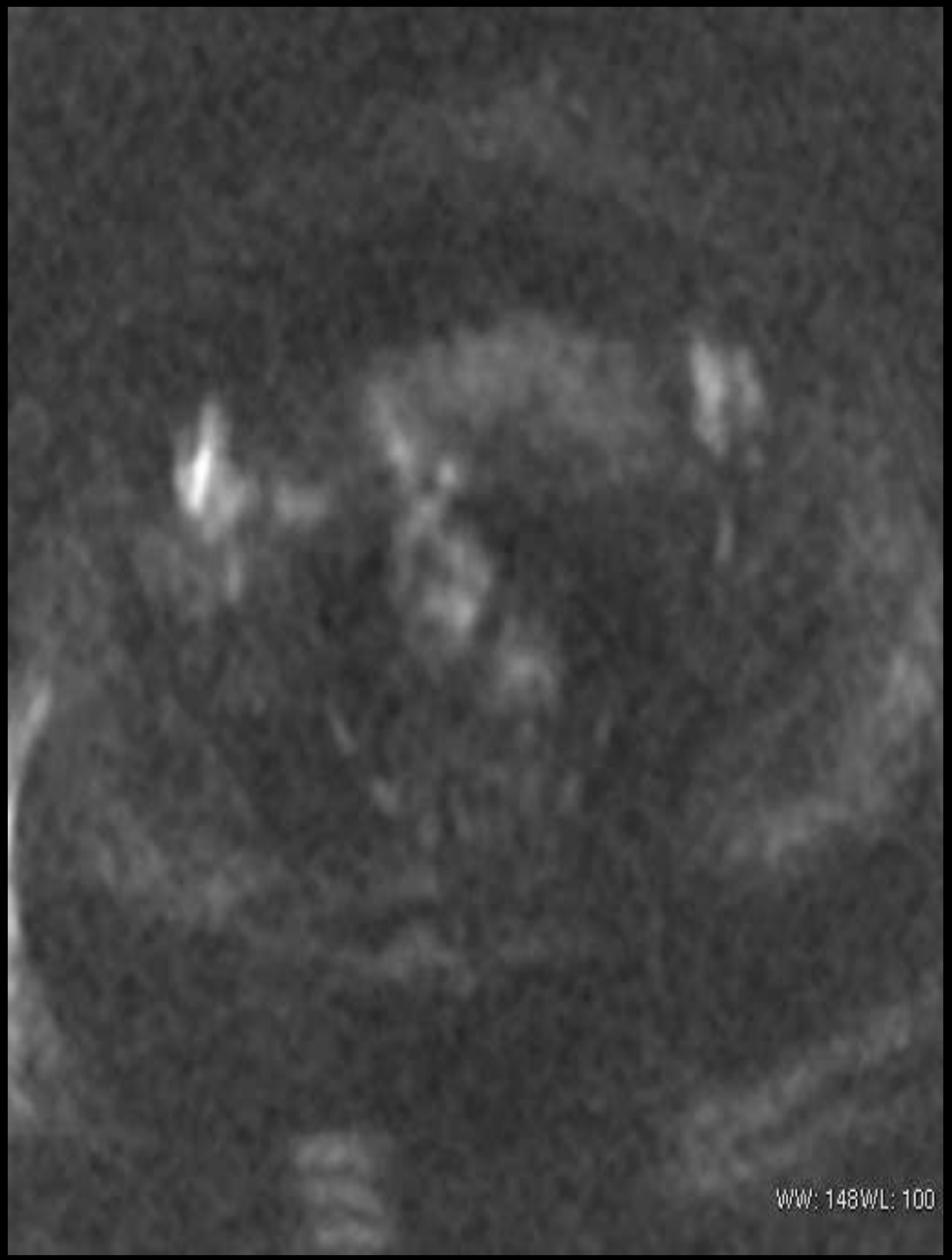
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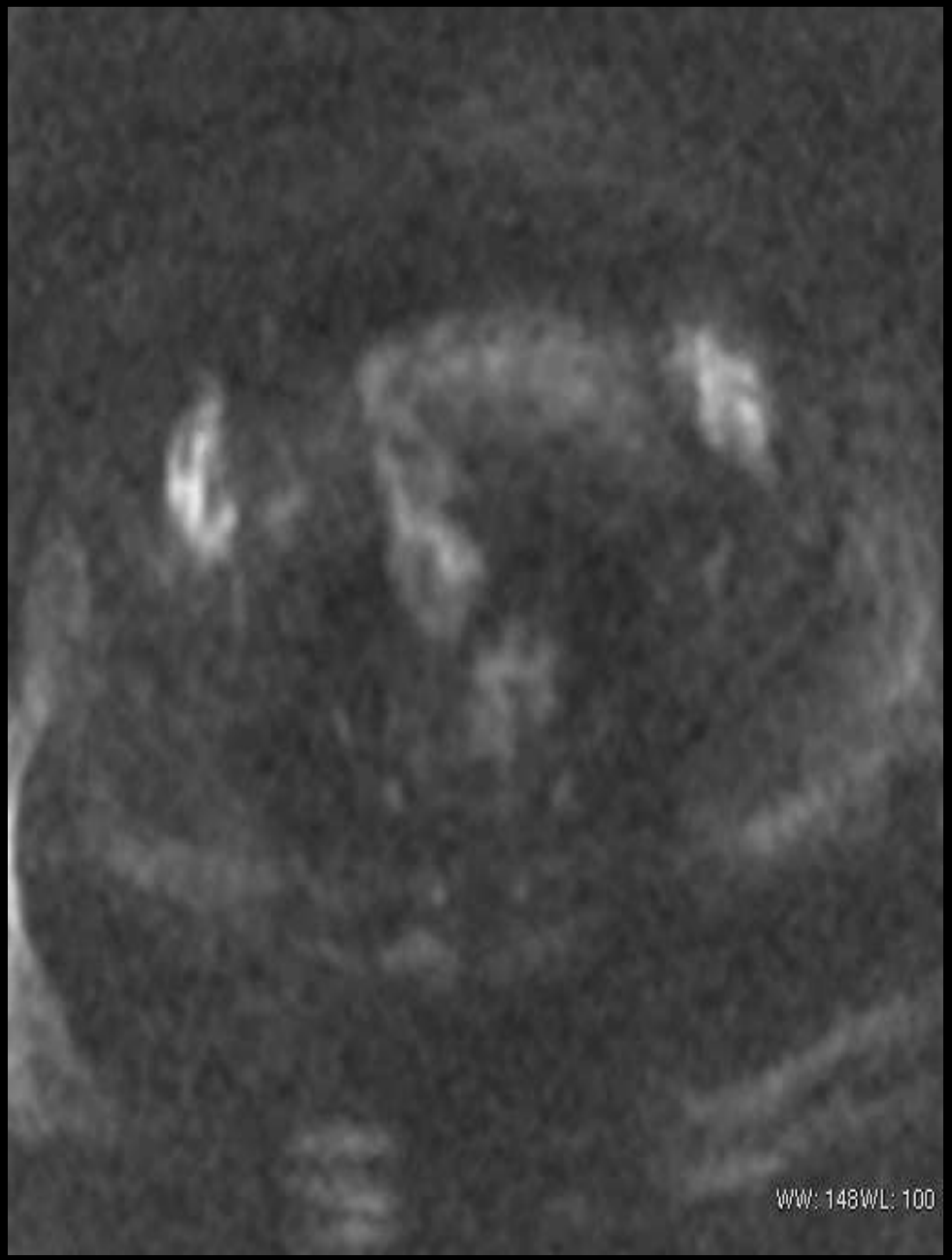
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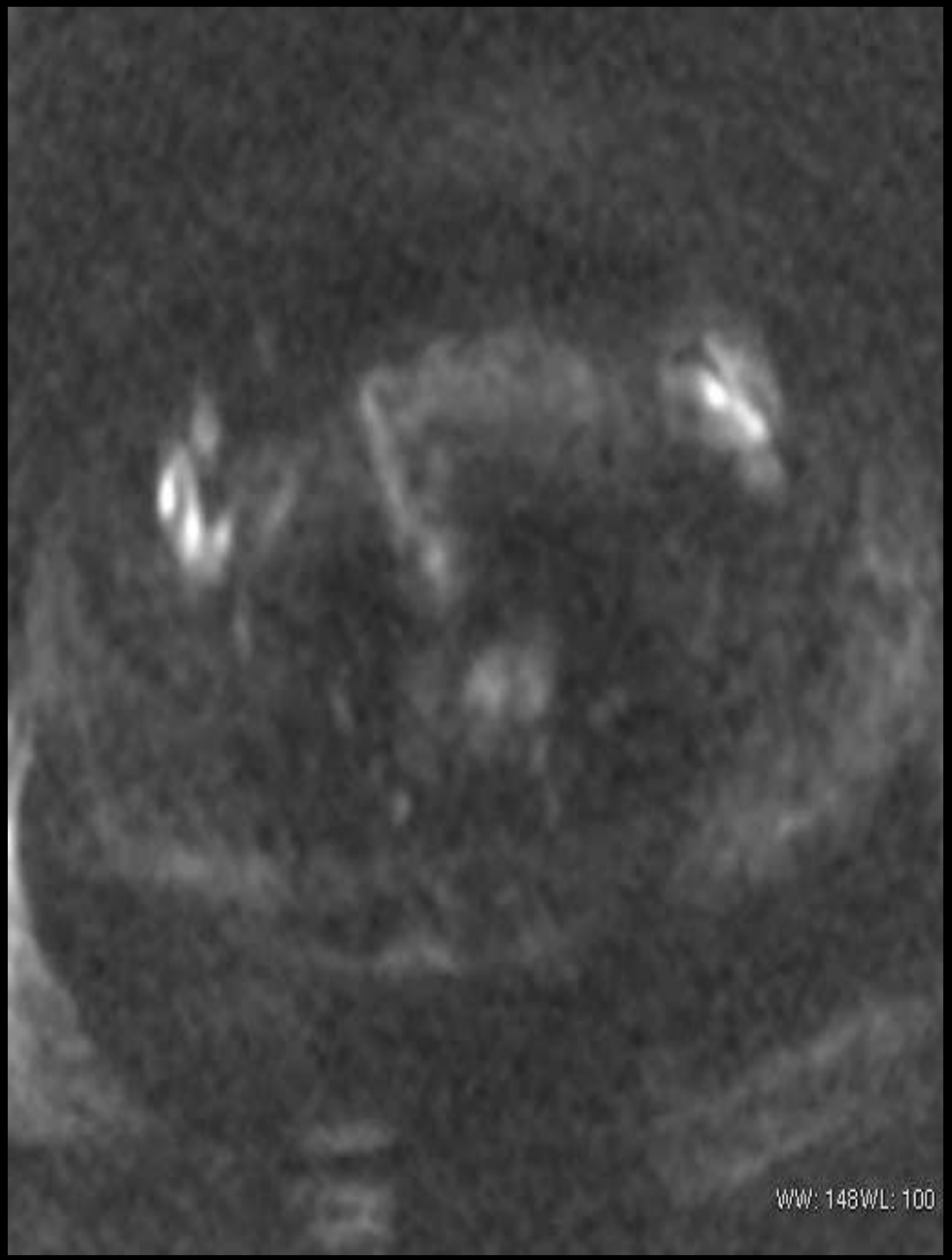
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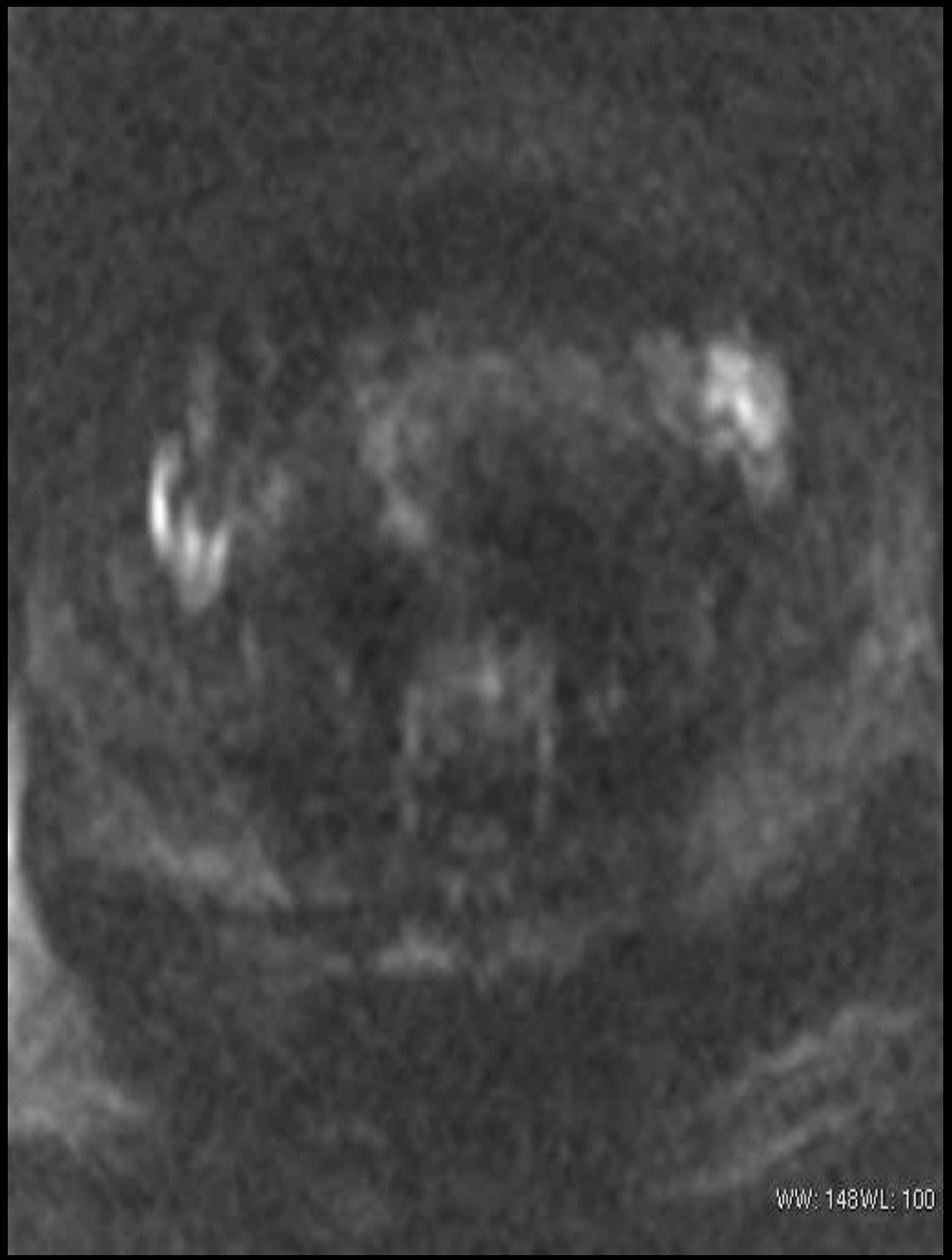
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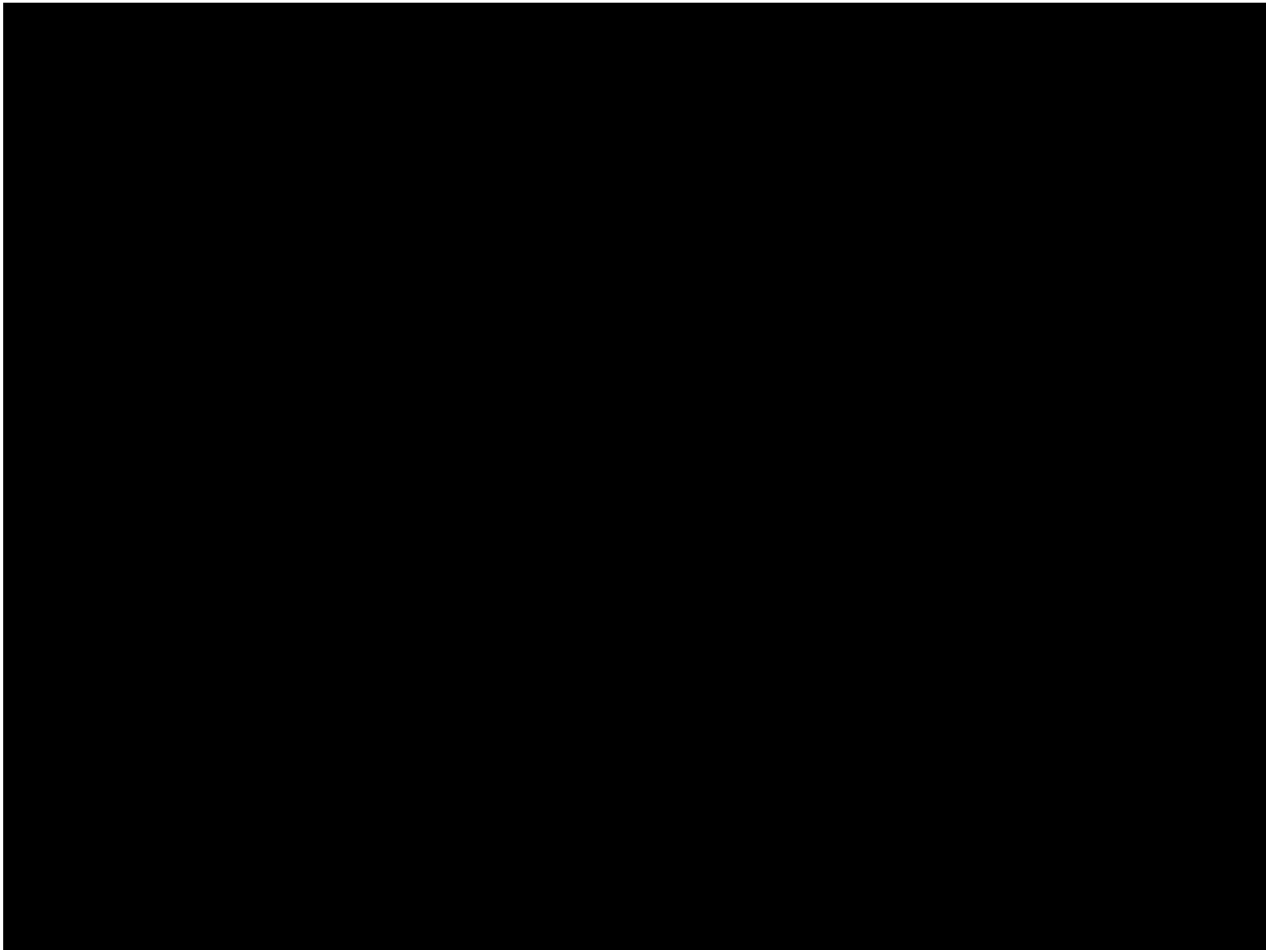
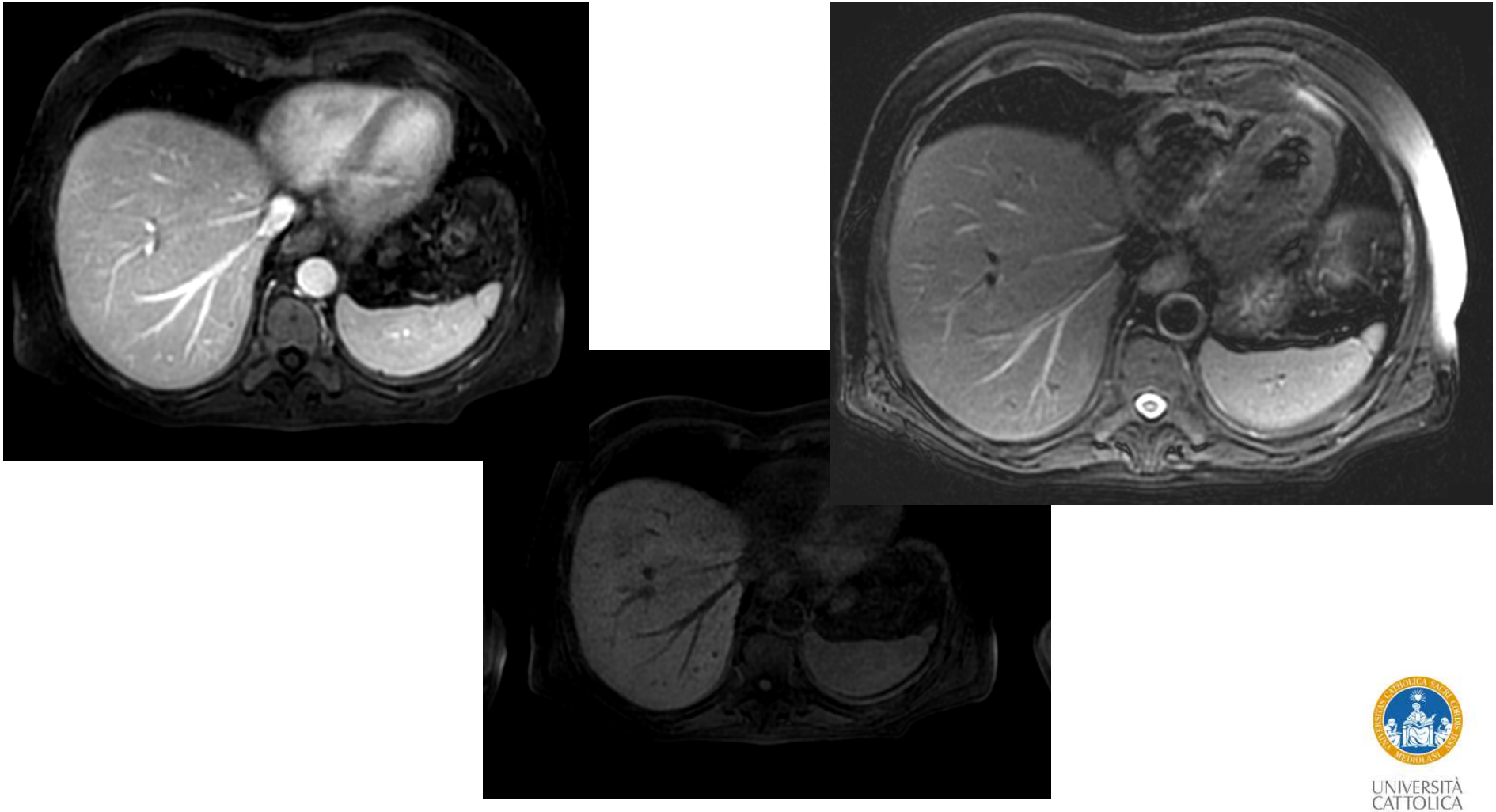


Upper Abdomen MRI



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Re-Staging

- **PET-CT:**
  - Reduction of the thickening and activity of the rectal lesion, SUV max 4 vs 11.9
  - Reduction in size and activity of the perirectal and presacral nodes, diam max 2.4 vs 3.4 and SUV max of 2.7 vs 6.2
  - Reduction in size of the metastatic nodule in the VII hepatic segment

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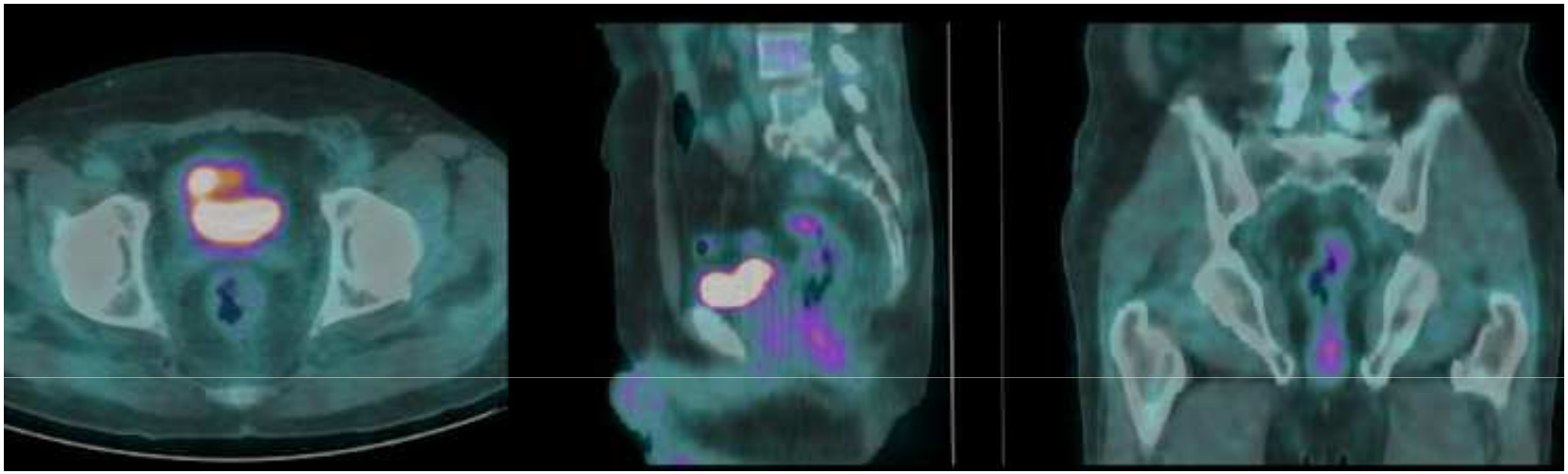
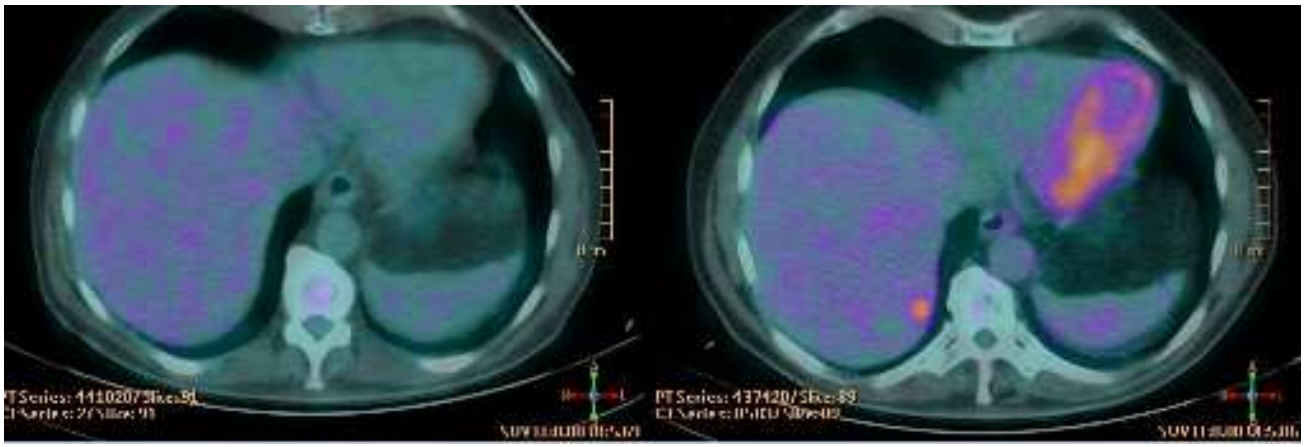
fdg PET-CT





Post RT-CT **Pre RT-CT**

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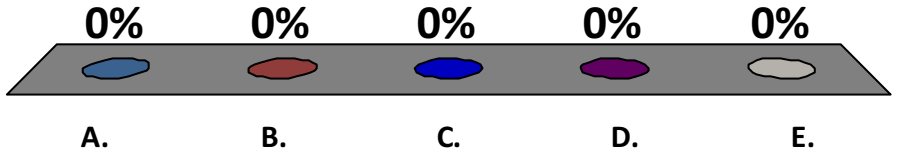
Question 4

What further treatment would you propose?

A. Surgery on the primary tumor only
B. Surgery on the liver metastasis only
C. Surgery on both sites
D. Further Chemotherapy
E. Other



Treatment (3/3)

- **Surgery:**
  - Anterior Resection with TME + sampling of suspicious extra mesorectal tissue on the posterior- left lateral pelvic wall
  - Partial hepatectomy

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Pathological Report

- Residual adenocarcinoma post-neoadjuvant therapy infiltrating the perirectal tissue; extramural invasion.
- Metastases in 9/16 lymph nodes.
- Negative circumferential, proximal and distal margins

- Nodule of 7 mm, metastasis of adenocarcinoma; Ras and B-raf WT

ypT3, ypN2b, ypM1
TRG 3/5 (Mandard's score)

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Question 5

What next option would you propose at this point?

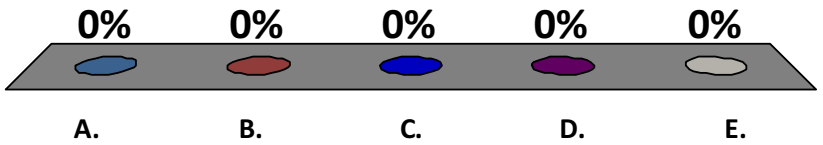
A. Follow–up

B. Adjuvant Chemotherapy with same regimenAdjuvant

C. Chemotherapy adding monoclonal antibodies

D. Adjuvant Chemotherapy with different/multiple drugs

E. Other



Treatment (4/4)

- **Adjuvant chemotherapy:**
  - FOLFOX-4, 5 cycles, up to a total of 6 months CT

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Lower GI course

Brussels 25-27 May 2016

Case presentation 2

Maria Antonietta Gambacorta

Radiotherapy Department
Università Cattolica del Sacro Cuore
Rome-Italy

Gemelli ART
Advanced Radiation Therapy

Initial work-up

- **Pt's characteristics:** Female, 71 years old. No familiarity for cancer**.**
- **Comorbidities**: Diabetes Type 2 treated with insuline; allergy to FANS

- **Symptoms:** she started 4 month erlier with rectal bleeding, alternating stipsis/diarrhea, mucous discharge, anal-rectal pain during defecation

Initial work-up

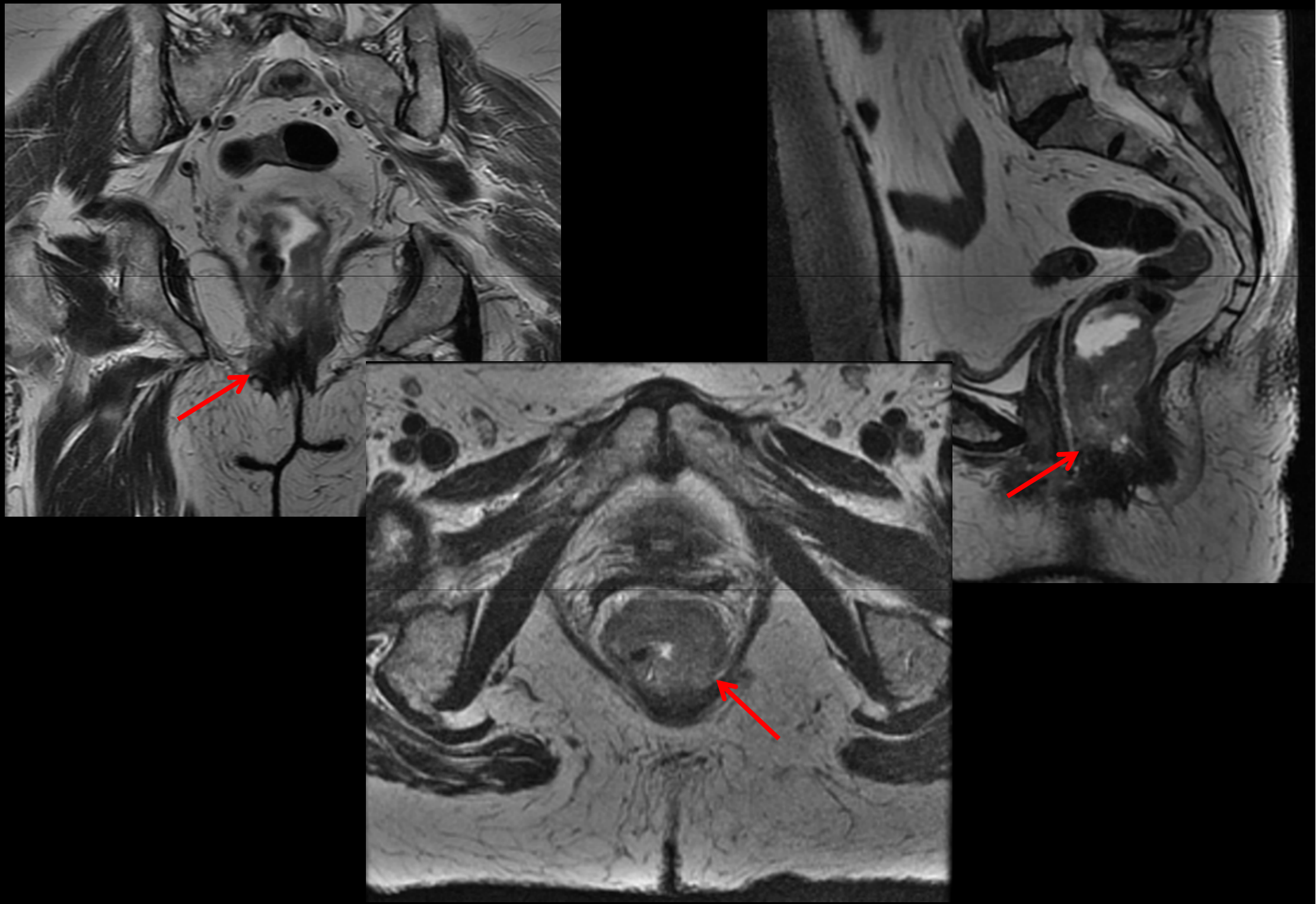
- **DRE:** Lesion starting from the **anal canal**, located to the anterior left lateral and posterior wall of the rectum, extending cranially for 5 cm, fix. Blood on the finger
- **Pt's Colonoscopy:** Lesion starting from the **anal canal** extending on the left lateral wall of the pelvis, extending for **6 cm**, **ulcerated** and **bleeding**. Biopsies.

- **Biopsy:** Poor differentiated adenocarcinoma

Staging Imaging

- **Thorax-abdomen CT:** Negative for M
- **MRI:** Lesion located in the antero left lateral rectal wall extending on the ¾ of the rectal circunference, beyond the anal-rectal junction. The lesion infiltrates the external anal sphincer on the left side. At the level of the rectum the tumor infiltrates the perirectal fat. More than 3 enlarged lymph nodes in the mesorectum, the biggest has a diameter of 7 mm. Bilateral aspecific inguinal lymph nodes. Rectovaginal septum not infiltrated by the disease.

Previous hysterectomy.



PELVIC MR IMAGES

Question 1

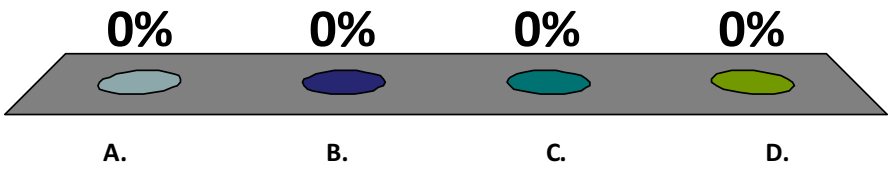
What is the Clinical Stage in this patient?

A. T3 N1 M0

B. T3 N2 M0 MRF+

C. T4 N1 M0

D. T4 N2 M0



Staging

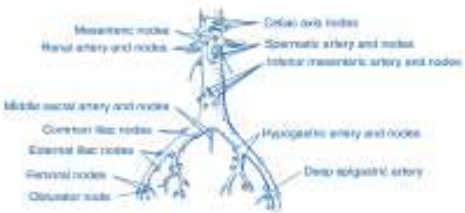
Stage: IIIC
cT4b*; N2; M0

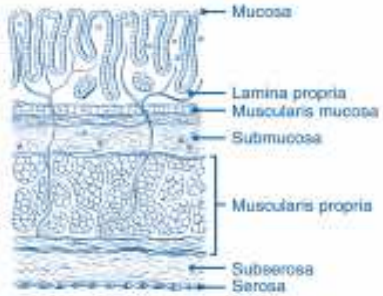
* Sphincter complex

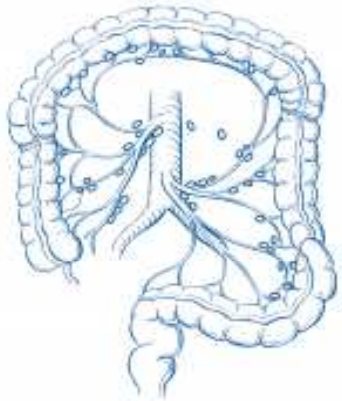
American Joint Committee on Cancer

Colon and Rectum Cancer Staging

7th EDITION







Definitions

Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ: intraepithelial or invasion of lamina propria[1]
- T1 Tumor invades submucosa
- T2 Tumor invades muscularis propria
- T3 Tumor invades through the muscularis propria into pericolorectal tissues
- T4a Tumor penetrates to the surface of the visceral peritoneum[2]
- T4b Tumor directly invades or is adherent to other organs or structures[2,3]

Regional Lymph Nodes (N)[4]

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in 1–3 regional lymph nodes
- N1a Metastasis in one regional lymph node
- N1b Metastasis in 2–3 regional lymph nodes
- N1c Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- N2 Metastasis in 4 or more regional lymph nodes
- N2a Metastasis in 4–6 regional lymph nodes
- N2b Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)

- M0 No distant metastasis
- M1 Distant metastasis
- M1a Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
- M1b Metastases in more than one organ/site or the peritoneum

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage	T	N	M	Dukes*	MAC*
0	Tis	N0	M0	–	–
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1–T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3–T4a	N1/N1c	M0	C	C2
	T2–T3	N2a	M0	C	C1/C2
	T1–T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3–T4a	N2b	M0	C	C2
	T4b	N1–N2	M0	C	C3
IVA	Any T	Any N	M1a	–	–
IVB	Any T	Any N	M1b	–	–

NOTE: cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (for example, ypTNM). Patients who have a complete pathologic response are ypT0N0cM0 that may be similar to Stage Group Over I. The r prefix is to be used for those cancers that have recurred after a disease-free interval (rTNM).
* Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (any T N1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

ajcc

American Cancer Society

Financial support for AJCC 7th Edition Staging Posters provided by the American Cancer Society

Notes

1 Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

2 Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (that is, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).

3 Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1–4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion, whereas the Pn site-specific factor should be used for perineural invasion.

4 A satellite peritumoral nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule may represent discontinuous spread, venous invasion with extravascular spread (TV2), or a totally replaced lymph node (N1/2). Replaced nodes should be counted separately as positive nodes in the N category, whereas discontinuous spread or venous invasion should be classified and counted in the Site-Specific Factor category Tumor Deposits (TD).

Question 2

What treatment would you propose ?

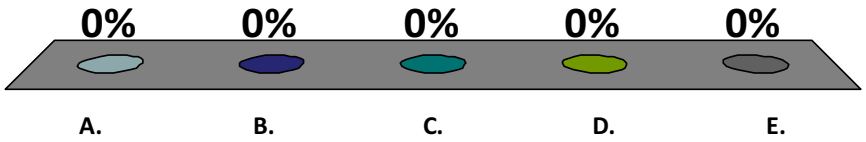
A. Surgery→ long course RT-CT

B. Short-Course RT → Surgery

C. Long-Course RT-CT → Surgery

D. Short-Course RT → Chemotherapy → Surgery

E. Other



Tretatment

Radiotherapy: IMRT-SIB

CTV2= T + Mesorectum + Anal Canal + sphincter complex + lateral lymph nodes (anterior IIN and posterior ON) + External Iliac lymph nodes + Inguinal Lymph nodes

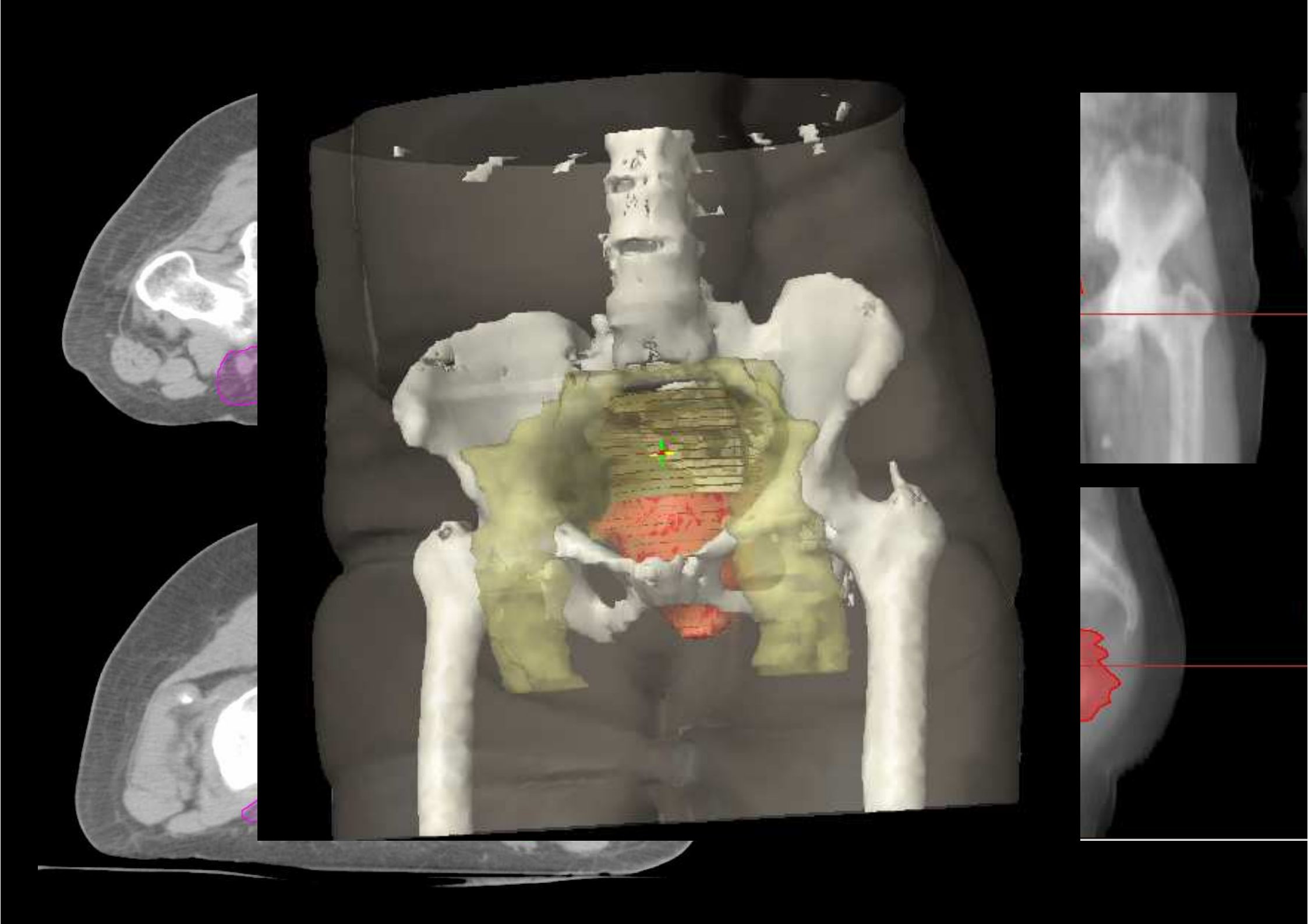
- **Total Dose 4500 cGy/180 cGy in 25 fractions**

CTV1 = T + anal canal + sphincter complex + correspondent mesorectum

- **Total Dose 5500 cGy/220 cGy in 25 fractions**

Concomitant Chemotherapy:

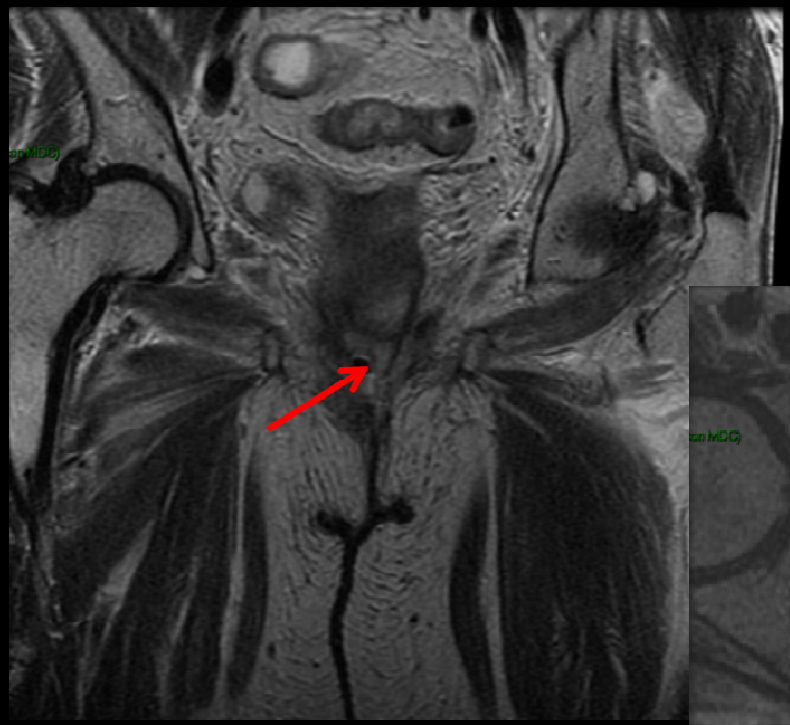
- Capecitabine

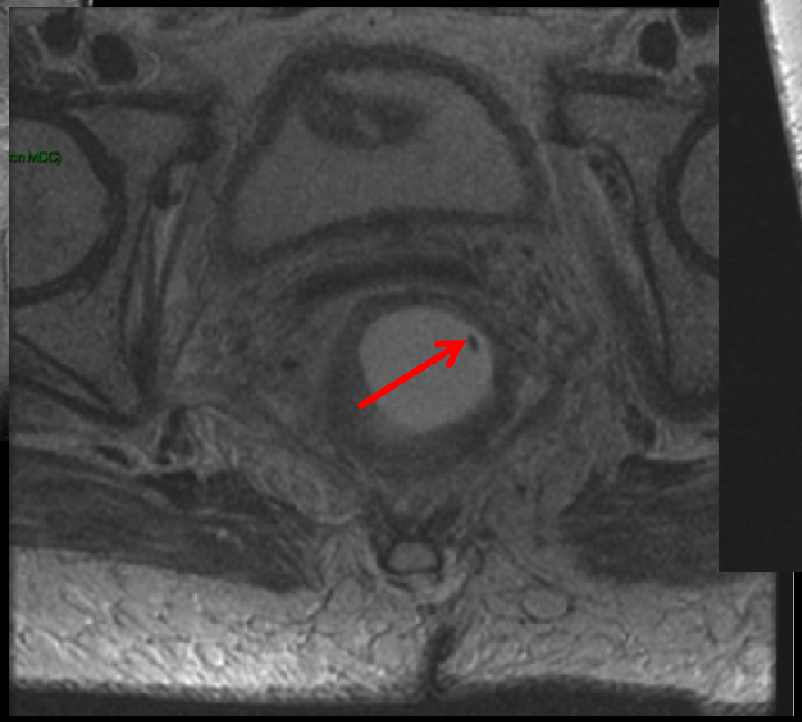


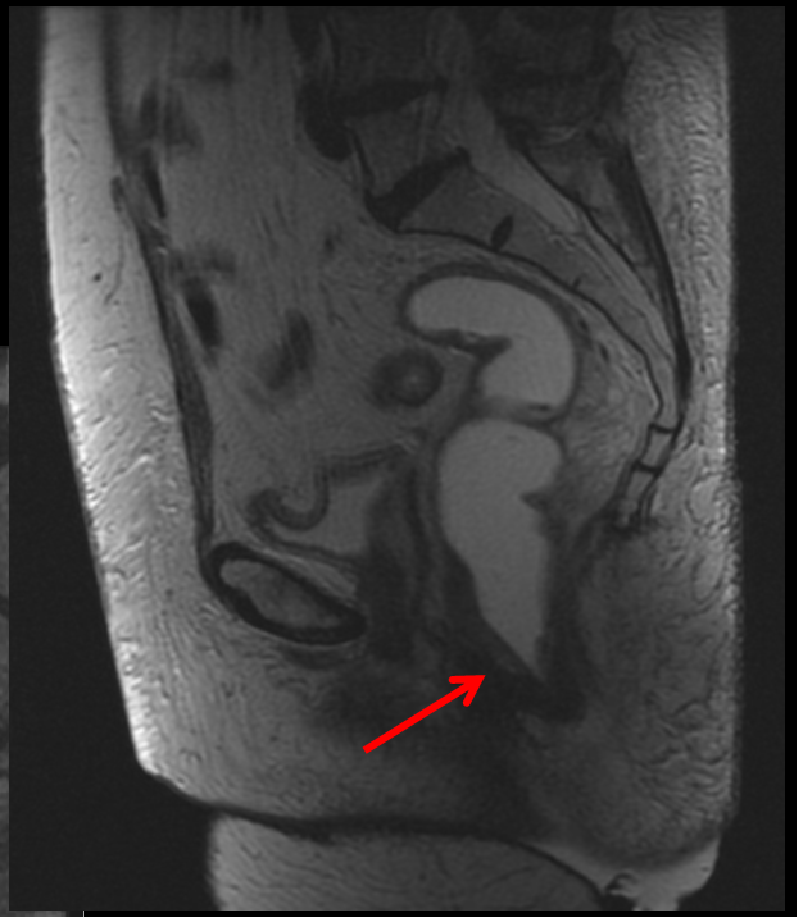
Re-staging Imaging

MRI: persistence of residual disease with the prevalence of **fibrosis**, which is in continuity with the **internal anal sphincter and left levator ani**. Small residual with **restricted diffusion** in correspondence of the front wall of the low rectum **(yc T1-T2).**

Restaging imaging

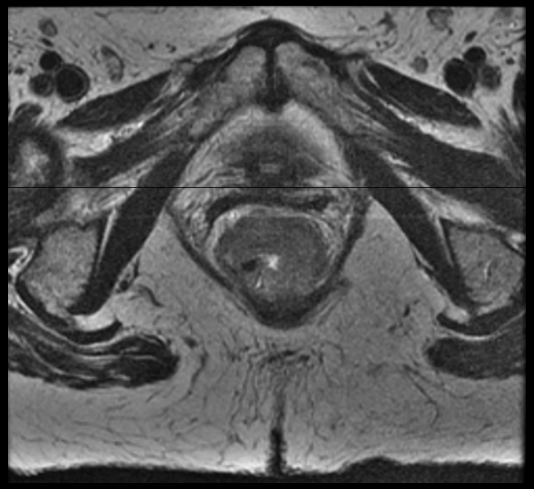


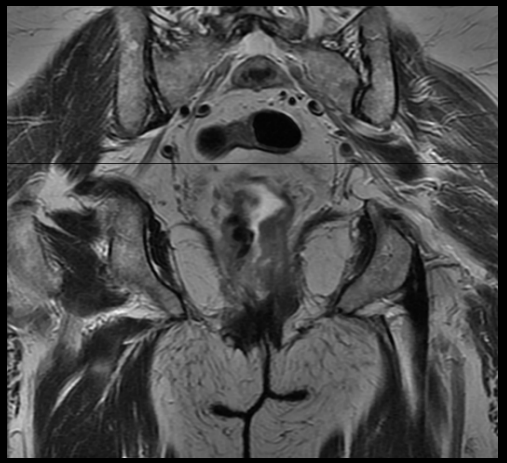


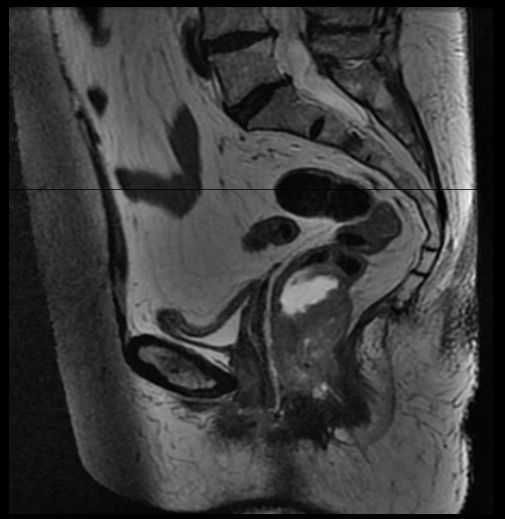


Imaging pre-post comparison

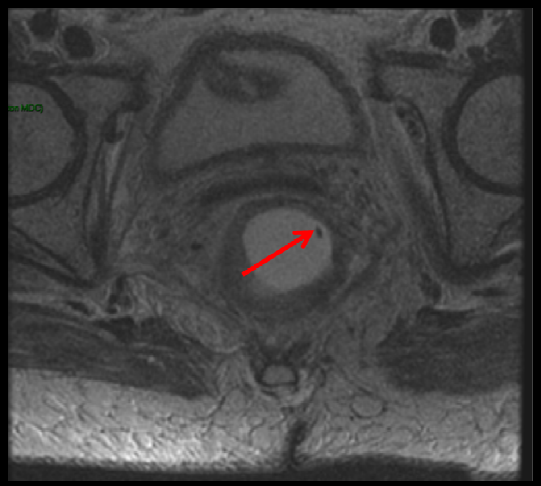
PRE

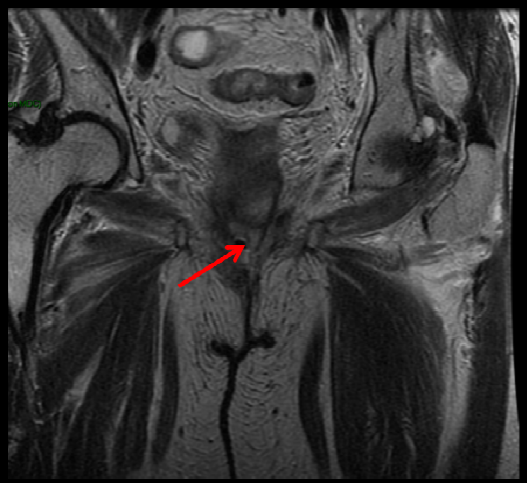


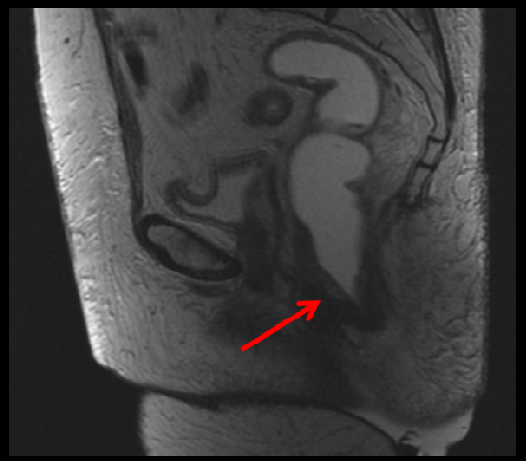




POST



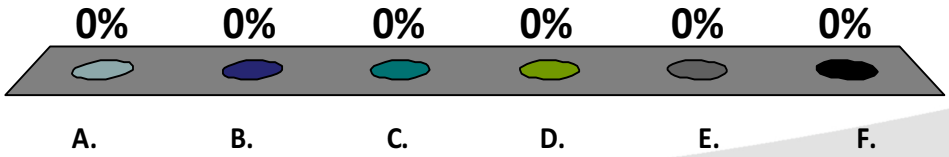




Question 3

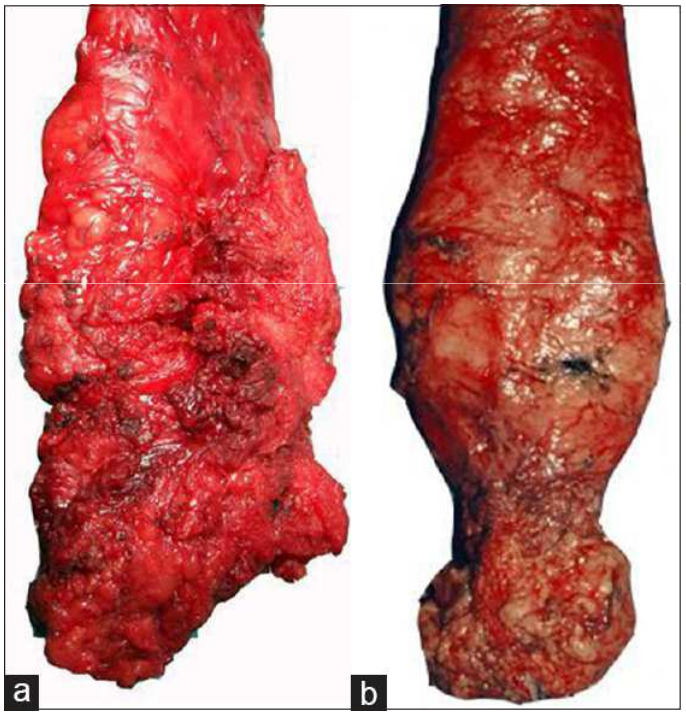
What treatment would you propose after RT-CT?

A. Abdominal-perineal resection
B. Cilindric APR
C. Low Anterior Resection
D. Brachytherapy boost
E. Watchful waiting
F. Other



Surgery

Abdominal Perineal Resection



Pathological findings

:

Macroscopic description:

22 cm of large bowel. At 4 cm from the distal margin is visible a **depressed lesion 1.3 cm**, site of treated neoplasia. The lesion is all included and examined also with seriated samples starting from the lesion margins, as for protocol

Diagnosis:

chronic flogistic process with erosive and fibro-productive aspects, compatible with the result of the NAD treatment. Absence of of residual tumor foci. Reactive lymphoadenite in 4/4 examined lymph-nodes

ypT0 ypN0

TRG 1/5 according to Mandard's score

Question 4

What would you propose ?

A. Adjuvant chemotherapy

B. FUP

Subsequent procedure

usually we propose adjuvant chemotherapy in cT4 tumors at diagnosis

However no Adjuvant CT was delivered due to delay in the healing of the surgical wound

The Royal Marsden

Imperial College London

Staging Standards ESTRO course

Professor Gina Brown

gina.brown@rmh.nhs.uk

www.slideshare.net/gina brown3

NHS

Recommended Standards

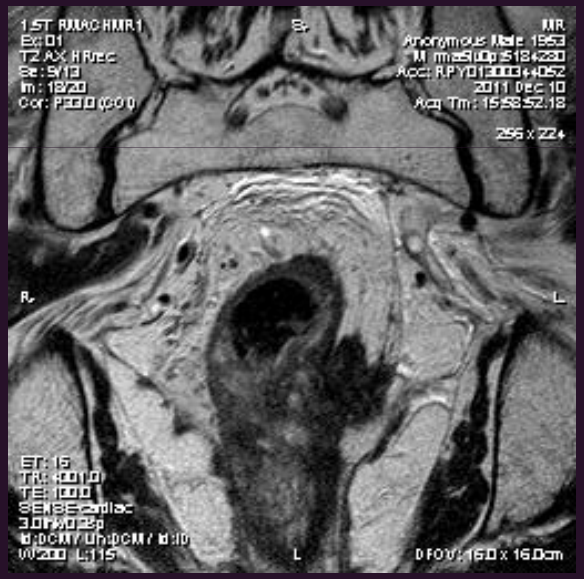
- MRI staging assessment of all primary rectal cancer
- CT Thorax Abdomen and Pelvis for routine staging for metastatic disease
- ERUS : optional in addition to MRI
- PET-CT: in selected cases

The problems with TNM

- T3 category is enormous and survivals range from 90% (same as Dukes A) to 25% (T3 depth is far more important)
- Stage III classification is too heterogenous
- TNM does not take into account CRM status
- TNM does not take into account extramural vascular invasion
- TNM does not take into account low rectal cancer stage system
- Using T and N staging does not perform adequately in the assessment following neoadjuvant therapy

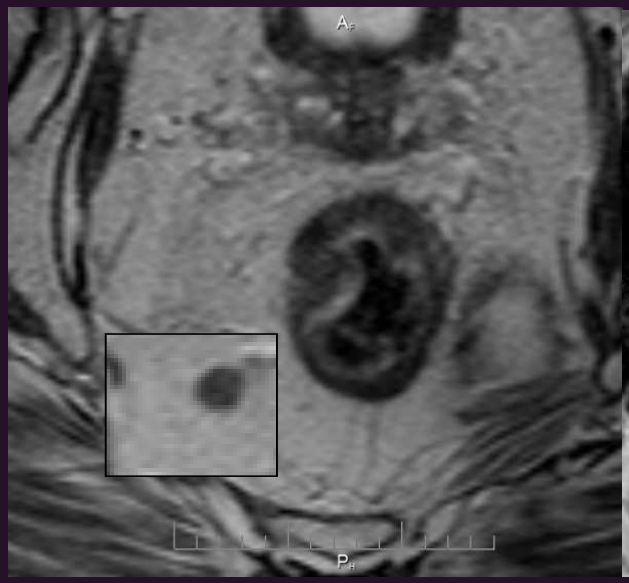
These tumours have entirely different prognostic outcomes

Stage II (T3N0)



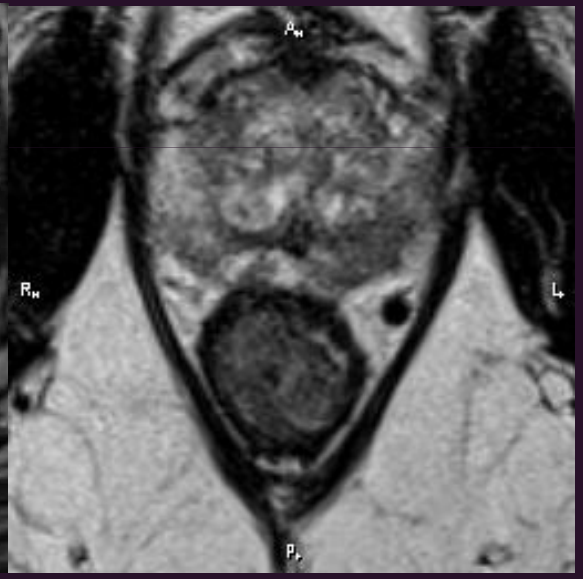
mrT3dN0EMVI pos CRM+ CRT+chemo + beyond TME surgery

Stage III (T3N1)

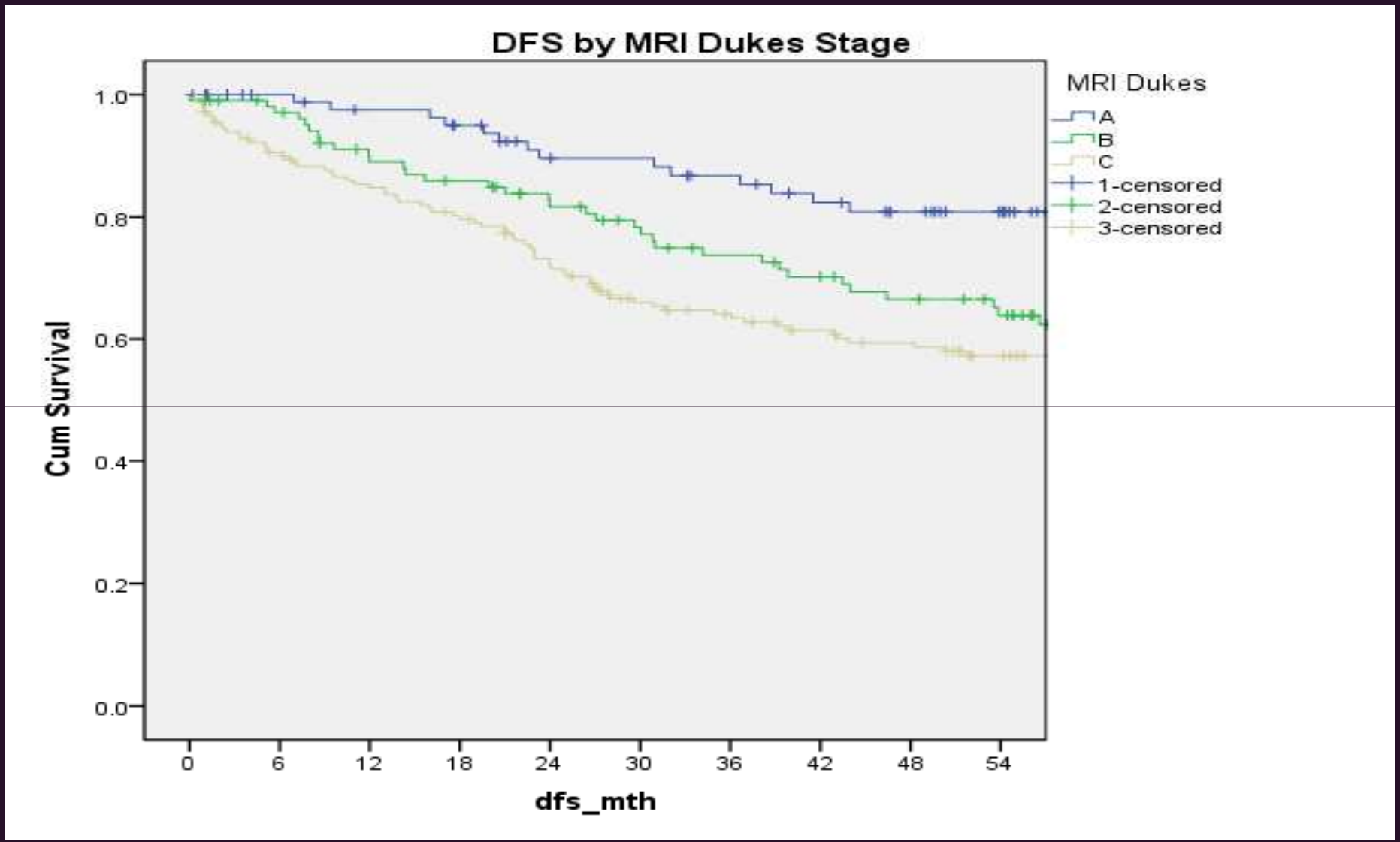


mrT3aN1CRM-ve
Primary TME surgery

Stage I (T1N0)



mrT1 EMVI deposit, CRM+ve, Preoperative CRT and ELAPE


DFS by MRI Dukes Stage
MRI Dukes
A
B
C
1-censored
2-censored
3-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
6
12
18
24
30
36
42
48
54
dfs_mth

PET-CT Recommendations

- The routine use of PET is not recommended for the diagnosis or staging of clinical stage I-III CRC.
- PET is recommended for determining management and prognosis if conventional imaging is equivocal for the presence of metastatic disease.
- The routine use of PET is not recommended for the measurement of treatment response in locally advanced rectal cancer before and after preoperative chemotherapy.
- PET is also not recommended for routine surveillance in patients with CRC treated with curative surgery at high risk for recurrence.
- PET is recommended to determine site of recurrence in the setting of rising CEA when conventional work-up fails to unequivocally identify metastatic disease.
- PET is recommended in the preoperative assessment of CRC liver metastasis before surgical resection.

Commonly encountered equivocations:

- Indeterminate pulmonary nodule
- Lesion – “too small to characterise”
- Multiple lesions in liver…
- Prominent retroperitoneal lymph nodes
- Stranding/nodularity

When is it important to know?

- Patients undergoing major radical surgery with curative intent: e.g. ELAPE/ extenteration
- Oligometastatic disease – potentially resectable vs widespread metastatic disease
- Synchronous metastatic disease control – liver first/ primary first?
- Type and duration of adjuvant chemotherapy
- Biomarker for resistance to 1st line chemotherapy
- Unexplained rise in CEA level

The indeterminate pulmonary nodule

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DOI 10.1245/s10434-013-3062-y

Annals of SURGICAL ONCOLOGY
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REVIEW ARTICLE – THORACIC ONCOLOGY

Indeterminate Pulmonary Nodules at Colorectal Cancer Staging: A Systematic Review of Predictive Parameters for Malignancy

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ABSTRACT

Background. This study aimed to estimate the prevalence of indeterminate pulmonary nodules and specific radiological and clinical characteristics that predict malignancy of these at initial staging chest computed tomography (CT) in patients with colorectal cancer. A considerable number of indeterminate pulmonary nodules, which cannot readily be classified as either benign or malignant, are detected at initial staging chest CT in colorectal cancer patients.

Methods. A systematic review based on a search in EMBASE, Medline, the Cochrane library and science citation index, PubMed databases, Google scholar, and relevant conference proceedings was performed in cooperation with the Cochrane Colorectal Cancer Group.

Results. A total of 2,799 studies were identified, of which 12 studies met the inclusion criteria. The studies primarily consisted of case series and included a total of 5,873 patients. Of these patients, 9 % (95 % confidence interval [95 % CI] 8.9–9.2 %) had indeterminate pulmonary nodules at chest CT, of which 10.8 % (95 % CI 10.3–11.2 %) turned out to be colorectal cancer metastases at follow-up. Generally, regional lymph node metastasis, and multiple numbers of indeterminate pulmonary nodules were reported to predict malignancy, whereas calcification of the nodules indicated benign lesions.

Conclusion. It was found that 1 in 100 colorectal cancer patients subjected to preoperative staging chest CT will have an indeterminate pulmonary nodule that proves to be metastatic disease. Such a low risk suggests that indeterminate pulmonary nodules should not cause further preoperative diagnostic workup or follow-up besides routine regimens.

Colorectal cancer (CRC) is common; there were more than 1.2 million new cases and more than 600,000 deaths worldwide in 2008.[1]. An initial staging procedure is necessary in all patients for allocation to the optimal treatment, and survival is highly related to the extent of disease at the time of diagnosis. The lungs are the second most common location of metastasis in CRC, surpassed only by the liver. The reported prevalence of synchronous lung metastases in CRC patients at the time of diagnosis varies between 2 and 18 %.[2–6]

According to the National Comprehensive Cancer Network, the Association of Coloproctology of Great Britain and Ireland, and the Danish Colorectal Cancer Group, the initial staging procedure should include a preoperative chest computerized tomography (CT).[7–10] The use of CT is justified by a higher sensitivity than chest X-ray and a higher sensitivity than positron emission tomography (PET) for pulmonary metastases of less than 1 cm in diameter.[4,11–14]

The high sensitivity of CT scans is not accompanied by an equally distinguished specificity. Thus, this staging procedure reveals lung lesions of uncertain nature, supposed indeterminate pulmonary nodules (IPN), in up to one-third of patients, some of which prove to be metastatic disease.[4,15–19]

The clinical significance of IPN and the further diagnostic approach are debated.[20] In an era with increasing focus on overtreating, overdiagnosing, and overpromising in cancer treatment, this debate is relevant.[21] As most of the nodules ultimately prove to be benign and therefore of no clinical relevance, there is a need to identify possible

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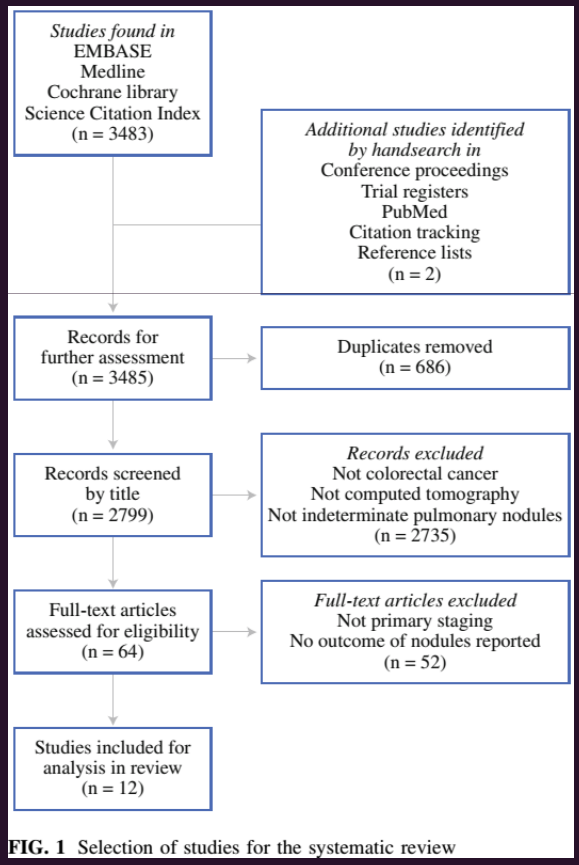
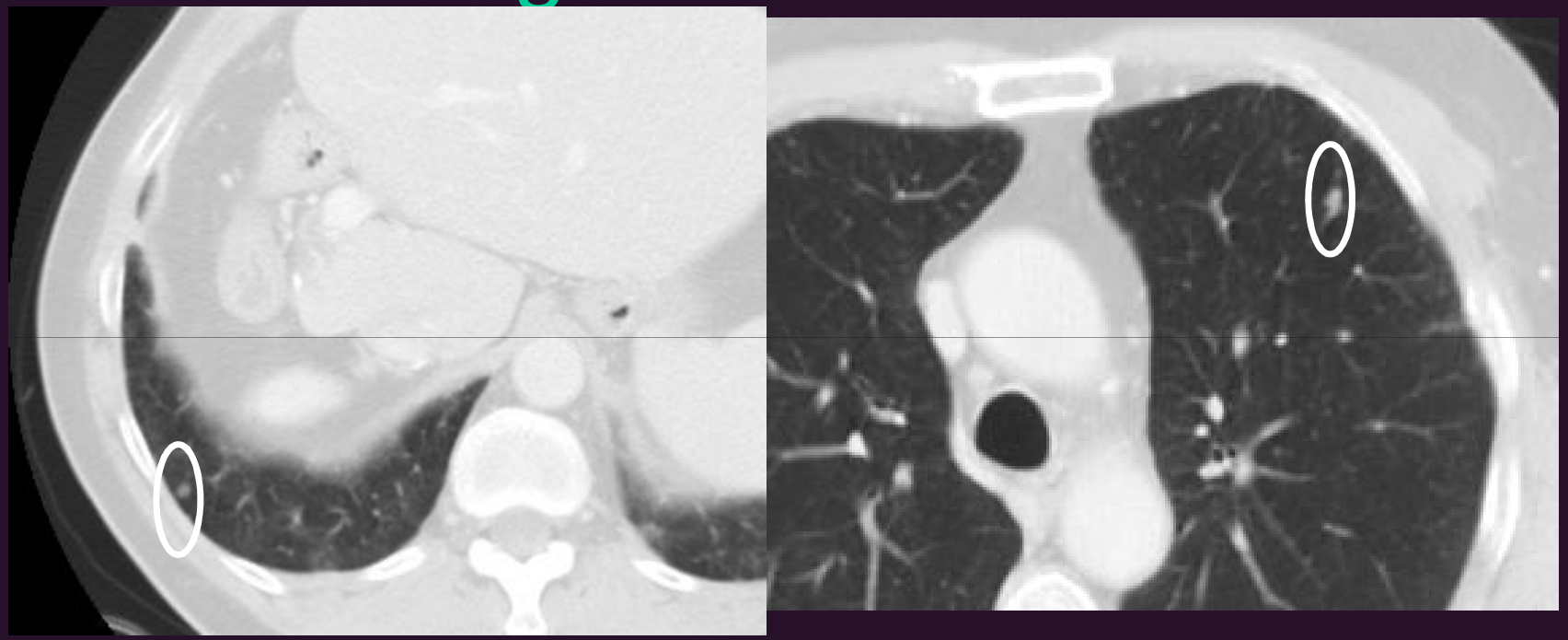


FIG. 1 Selection of studies for the systematic review

Definition of an Indeterminate pulmonary nodule

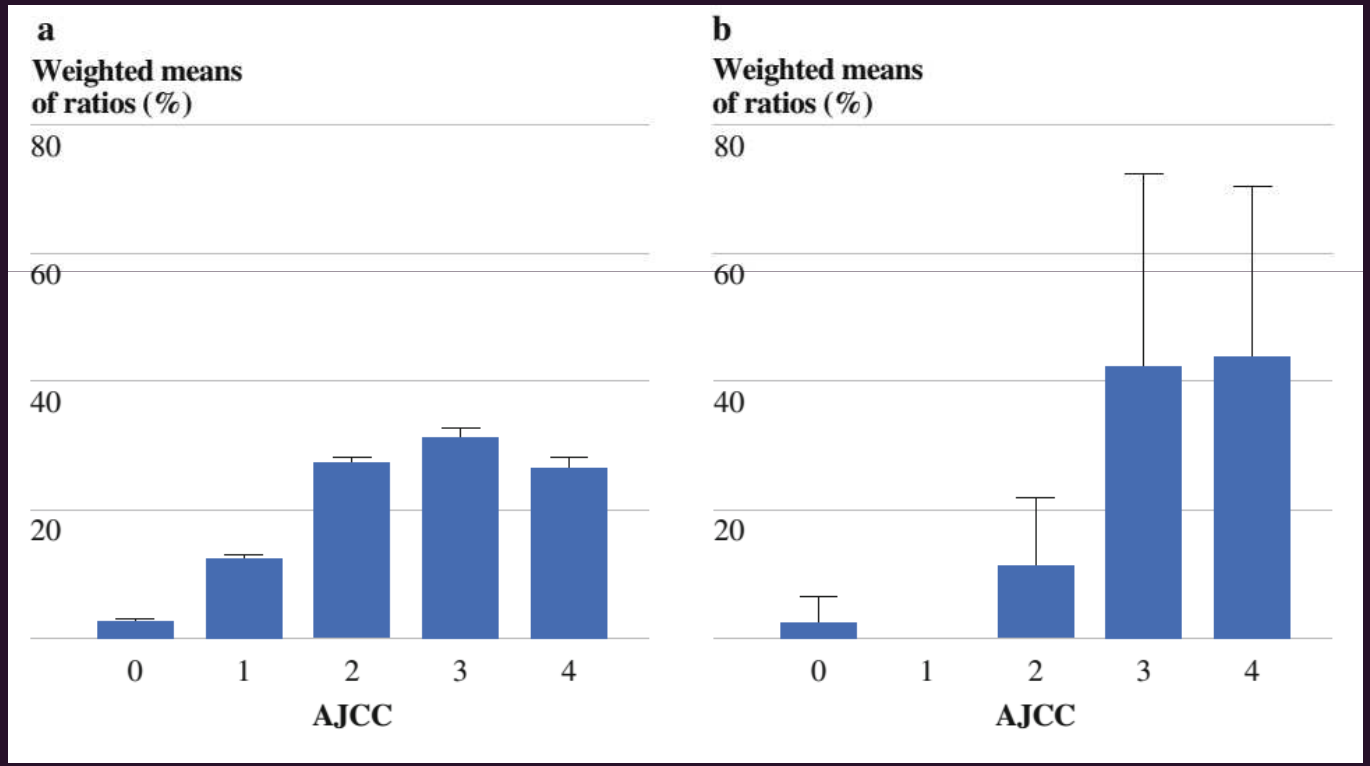
Reference (year)	Definition of IPN	Level of evidence[a]	Methodological quality[b]
Brent[18]	NS	2c	+
Cho[19]	<5 mm in size and no calcification	4	+
Phillips[25]	NS	4	−
Choi[26]	≤2 nodules, <6 mm in size, no calcification and no prior CT available	2c	++
Christoffersen[17]	NS	4	+
Grossmann[5]	NS	2c	+
Walter[27]	NS	2c	+
Quyn[32]	Soft tissue opacity and no calcification	2c	+
Restivo[31]	NS	2c	++
McQueen[28]	NS	4	+
Pomerri[29]	Rounded opacity and ≤30 mm in size	4	+
Varol[30]	<15 mm in size	4	+

Lung mets on MDCT

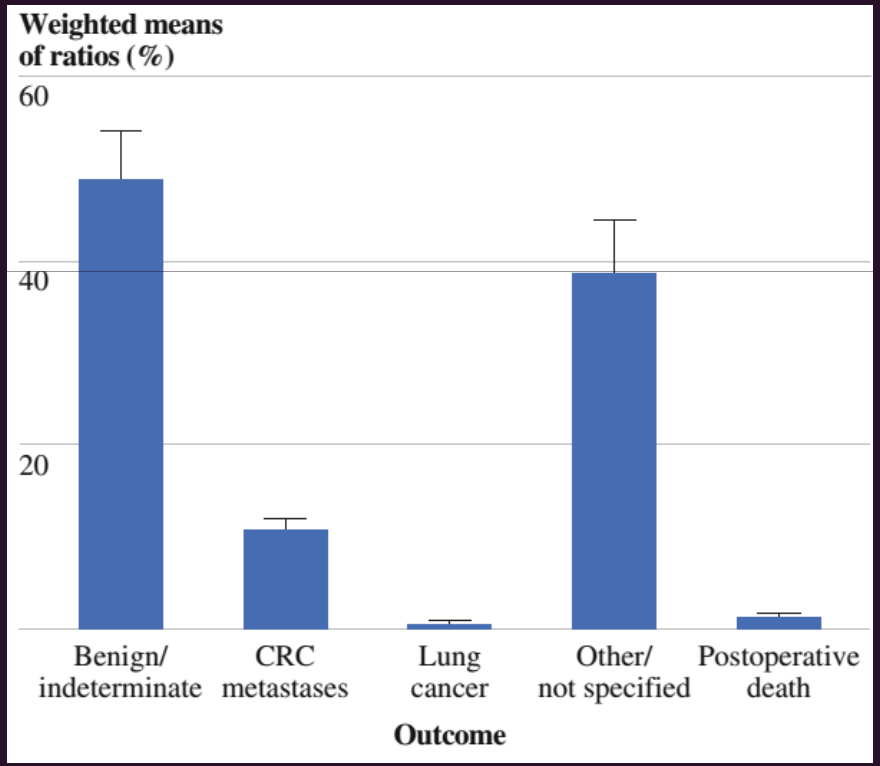


Preoperative chemotherapy and lung metastatectomy

Stage distribution vs stage distribution of IPN



Outcomes of IPN



Risk factors for IPN being malignant

Reference (year)	Characteristics for prediction of malignancy	Level of significance	Statistical analysis	Conclusion
Brent[18]	Positive nodal status	NS	NS	Few IPN progressed to metastatic disease. IPN should not delay surgery for CRC
Phillips[25]	Multiple/bilateral IPN Positive nodal status Distant metastases	NS	NS	Malignant progression of IPN is associated with multiple/bilateral lesions and nodal/ distant metastases. Targeted surveillance is recommended in this high-risk group
Choi[26]	Positive nodal status	NS	NS	Follow-up CT-scans recommended at 3- to 6-month intervals when IPN are detected preoperatively in patients with positive nodal status
Christoffersen[17]	Positive nodal status Elevated postoperative CEA	$P = 0.047$ $P = 0.02$	χ^2, Mann-Whitney, and log-rank test	Close follow-up with repeated CT scans is advisable, especially in patients with nodal disease and postoperatively elevated CEA
Quyn[32]	≥4 IPN Positive nodal status	$P < 0.01$ NS	χ^2 NS	Surveillance guidelines for IPN should include tumor stage and size and number of IPN
Pomerri[29]	>5 mm in size Irregular margin Calcification[a]	$P = 0.02$ $P = 0.02$ $P = 0.04$	Multivariate logistic regression	Follow-up CT-scan for 3–6 months after baseline staging of noncalcified IPN with irregular margins and >5 mm in size
Varol[30]	Multiple IPN Rectal cancer Calcification[a] Parenchymal location Irregular margin	$P = 0.006$ $P = 0.037$ $P = 0.026$ $P = 0.016$ $P = 0.002$	χ^2, Mann-Whitney, and multivariate logistic regression	Multiple IPN with an irregular border in a parenchymal location more likely to represent metastatic disease

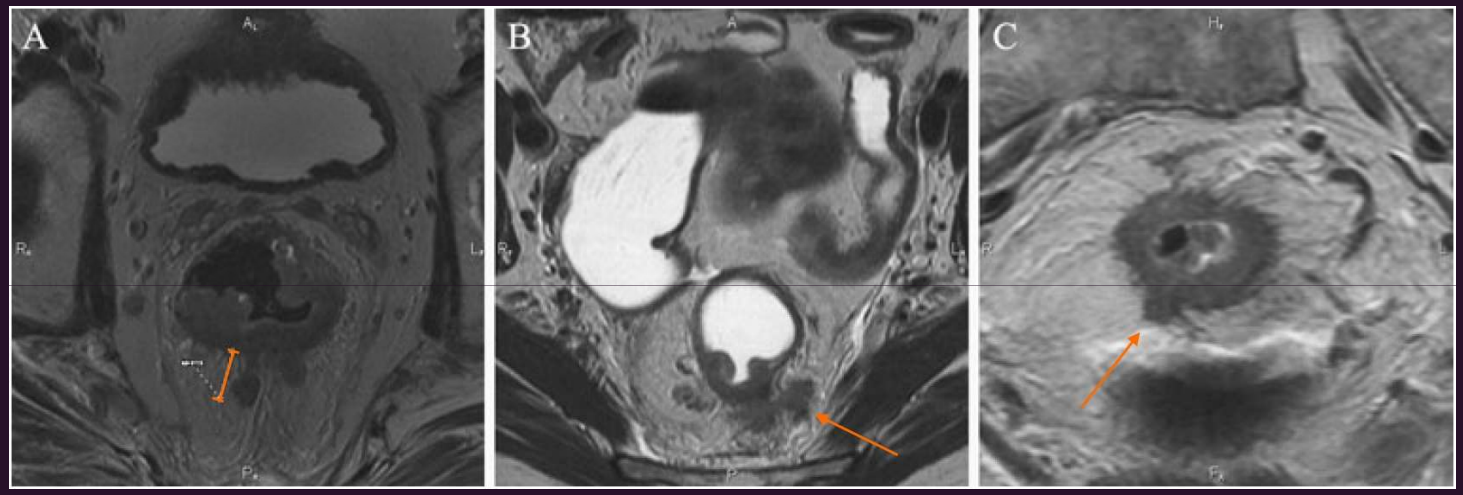
Pulmonary nodules that are likely to be malignant:

- >5mm in diameter
- Irregular bordered rather than malignant
- Lack of calcification
- Multiple rather than single
- CEA elevated post op

Suggested algorithm for IPN

- Pulmonary nodule and no previous imaging to compare:
  - High risk primary: compare against post op/postRx CT
    - If enlarging refer for VATS/metastatectomy after 1st line metastatic chemotherapy
    - If no change but post op CEA elevated, check PET-CT, surveillance CT after completion of adjuvant chemotherapy
  - Low risk/postop CEA normal: consider additional surveillance CT, likelihood of malignancy is low
- Consider possibility of synchronous lung primary in low risk colorectal cancer

Collaborative Study with McGill University



A - 15mm of extramural spread

B - involved circumferential resection margin

A-C - evidence of extramural venous invasion

Hunter *et al*. (2012) Ann Surg Oncol 19(4): 1199-1205.

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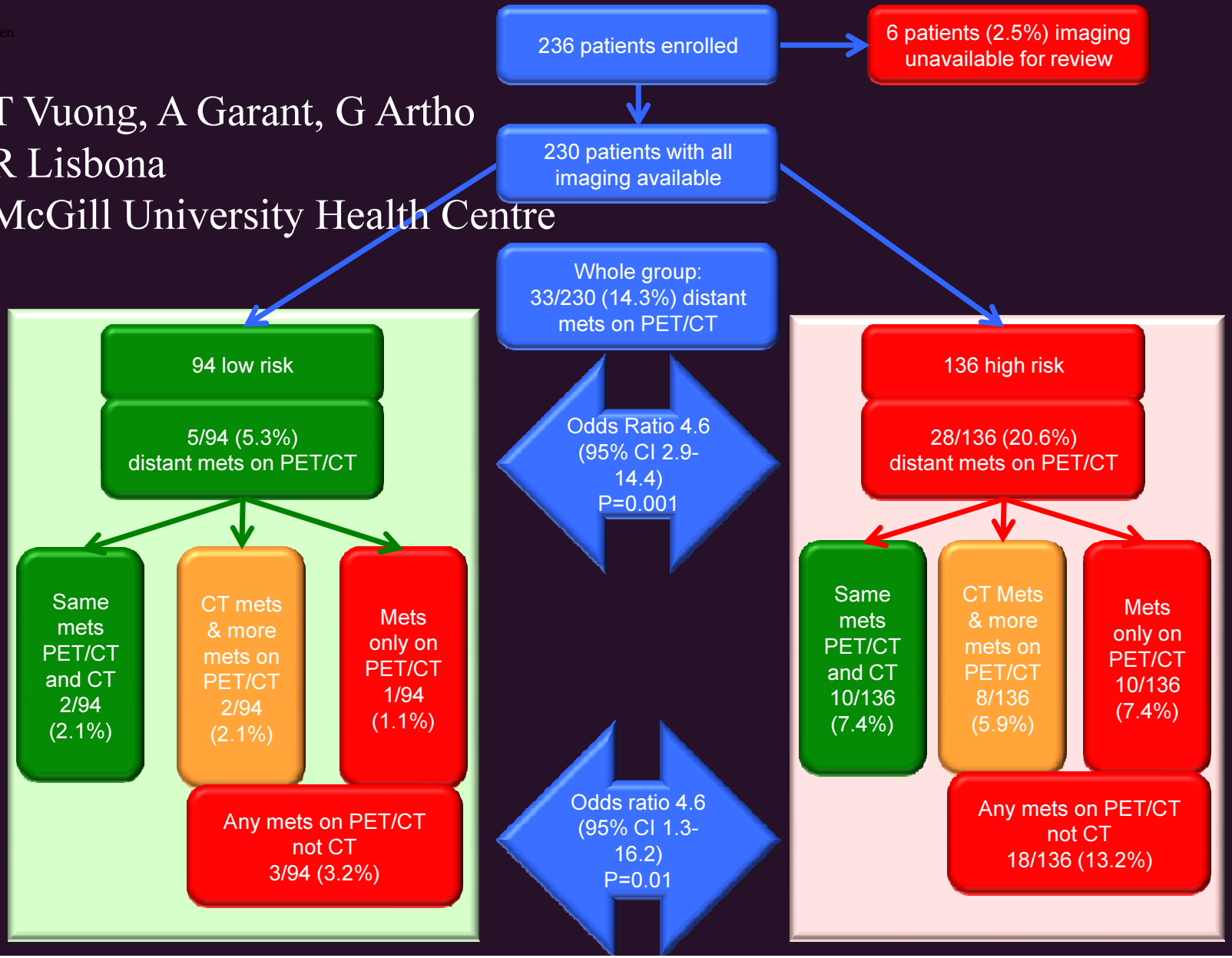
T Vuong, A Garant, G Artho
R Lisbona
McGill University Health Centre



Synchronous liver metastases

- Approx 13% of all rectal cancers
- Hunter *et al* (2012)
  - ⇧ risk rectal cancer = ⇧ synchronous liver metastases
  - High risk vs low risk – 20.7% vs 4.2% ($p<0.001$)

The Royal Mars

Variable	Synchronous Group	Metachronous Group	Control Group	P-Value
Gender	96M:47F[a]	18M:14F[a,b]	60M:59F[b]	0.022
Age, mean years, (95% CI)	64.41 (62.33-66.50)	63.13 (60.12-66.13)	63.27 (61.07-65.48)	0.71
Primary tumour site:				
Colon	80 (55.9)	19 (59.4)	57 (47.9)	0.32
Rectum	63 (44.1)	13 (40.6)	62 (52.1)	
Radiological T-stage:				
T1-2	5 (3.5)[a]	4 (13.3)[b]	19 (17.1)[b]	0.001
T3-4	138 (96.5)[a]	26 (86.7)[b]	92 (82.9)[b]	
Radiological T3-stage				
T3a-b	18 (19.1)[a]	4 (30.8)[a,b]	21 (53.8)[b]	<0.001
T3c-d	76 (80.9)[a]	9 (69.2)[a,b]	18 (46.2)[b]	
Radiological lymph node status				
N0	31 (25.2)[a]	12 (40.0)[a,b]	45 (38.1)[b]	0.001
N1	41 (33.3)[a]	8 (26.7)[a]	53 (44.9)[a]	
N2	51 (41.5)[a]	10 (33.3)[a]	20 (16.9)[b]	
Radiological EMVI status				
EMVI +ve	120 (88.9)[a]	13 (61.9)[b]	32 (52.5)[b]	<0.001
EMVI -ve	15 (11.1)[a]	8 (38.1)[b]	29 (47.5)[b]	
Primary tumour length				
≤ 40 millimetres	46 (35.7)	8 (40.0)	21 (33.3)	0.86
> 40 millimetres	83 (64.3)	12 (60.0)	42 (66.7)	

NHS

Imper
Lond

The Royal Marsden

Variable	Synchronous Group	Metachronous Group	Control Group	P-Value
Histopathology				
T-stage:				
T1-2	2 (2.3)[a]	3 (9.7)[a,b]	23 (23.2)[b]	<0.001
T3-4	85 (97.7)[a]	28 (90.3)[a,b]	76 (76.8)[b]	
Lymph node status:				
N0	21 (24.1)[a]	14 (45.2)[a, b]	49 (50.5)[b]	0.003
N1	35 (40.2)[a]	10 (32.3)[a]	32 (33.0)[a]	
N2	31 (35.6)[a]	7 (22.6)[a, b]	16 (16.5)[b]	
EMVI status				
EMVI +ve	53 (63.9)[a]	10 (37.0)[b]	24 (28.6)[b]	<0.001
EMVI -ve	30 (36.1)[a]	17 (63.0)[b]	60 (71.4)[b]	
Radiological metastatic characteristics				
Number of liver metastases:				
Solitary	48 (33.6)	19 (59.4)	--	0.007
Multiple	95 (66.4)	13 (40.6)	--	
Size of liver metastases:				
≤ 50 millimetres	72 (50.7)	23 (71.9)	--	0.03
> 50 millimetres	70 (49.3)	9 (28.1)	--	
Distribution of metastases:				
Unilobar	56 (39.4)	22 (68.8)	--	0.003
Bilobar	86 (60.6)	10 (31.3)	--	

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Univariate and multivariate logistic binary regression model for radiological predictors of synchronous disease.

Variable	Univariable Odds Ratio (95% CI)	*P*	Multivariable Odds Ratio (95% CI)	*P*
Site of primary tumour				
Colon	1.25 (0.80-2.00)	0.34	--	--
Rectum	Ref			
Radiological T-stage				
T1/T2	Ref		Ref	
T3	5.00 (1.82-13.65)	0.02	2.32 (0.65-8.34)	0.20
T4	7.00 (2.33-21.05)	0.01	3.72 (0.84-16.43)	0.083
Radiological primary tumour length	1.00 (0.98-1.01)	0.43	--	--
Radiological EMVI status				
EMVI positive	6.58 (3.30-13.13)	<0.001	4.74 (2.06-11.00)	<0.001
EMVI negative	Ref		Ref	
Radiological lymph node status				
N0	Ref		Ref	
N1	1.24 (0.69-2.23)	0.48	0.70 (0.31-1.56)	0.40
N2	3.13 (1.67-5.86)	<0.001	1.08 (0.46-2.55)	0.87

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Variable	Univariable Odds Ratio (95% CI)	P	Multivariable Odds Ratio (95% CI)	P
Age	1.04 (1.001-1.07)	0.05	1.02 (0.99-1.057)	0.30
Gender Male Female	 2.76 (1.13-6.73) Ref	 0.03	 2.12 (0.92-4.87)	 0.14
Site of primary tumour Colon Rectum	 1.61 (0.75-3.48) Ref	 0.30		
Radiological T-stage T2/T3a T3b T3c T3d T4	 0.62 (0.13-2.90) 0.96 (0.16-5.64) 0.57 (0.13-2.55) 0.47 (0.10 – 2.17) Ref	 0.54 0.10 0.50 0.33		
Radiological primary tumour length	0.99 (0.97-1.01)	0.40		
Radiological EMVI status EMVI positive EMVI negative	 2.56 (0.69-9.37) Ref	 0.20		
Number of liver metastases >1 metastasis 1 metastasis	 0.99 (0.42-2.33) Ref	 1.00		
Liver segmental sparing < 3 segments ≥ 3 segments	 2.03 (0.94-4.37) Ref	 0.07	1.34 (0.62-2.88)	0.53
Pre-operative CEA ng/ml	1.00 (1.00-1.00)	1.00		
Histology Lymph node +ve Lymph node –ve EMVI +ve EMVI –ve	 1.30 (0.47-3.66) Ref 1.50 (0.58-3.89) Ref	 0.70 0.50		
Radiofrequency ablation RFA No RFA	 1.24 (0.57-2.68) Ref	 0.70		
Management Upfront primary resection Neo-adjuvant therapy	 6.78 (3.33-13.78) Ref	 < 0.001	 5.67 (2.71-11.79)	 < 0.001

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MRI liver imaging protocol

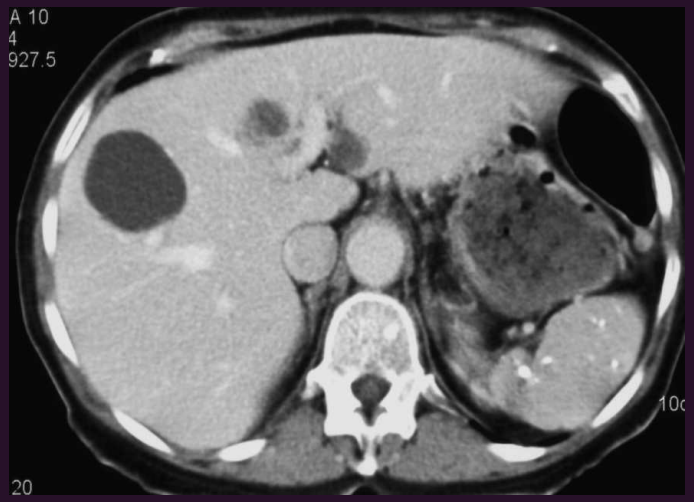
Lesion characterisation

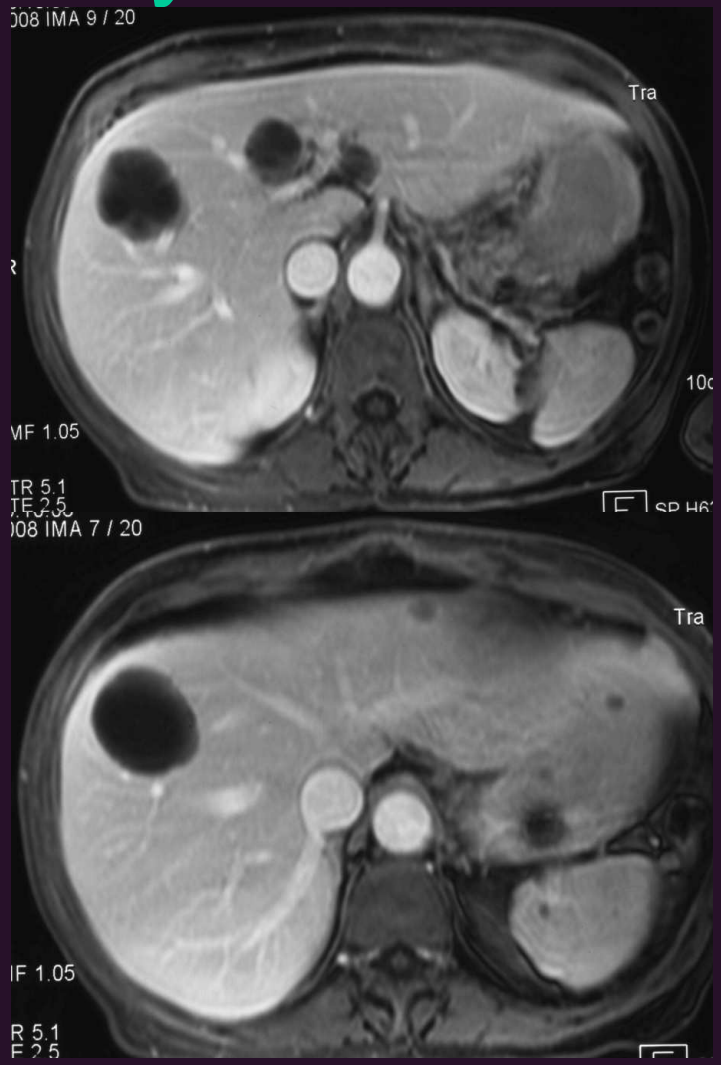
1. T1 breath-hold 3D volume unenhanced
2. T1 in and out of phase axial
3. T2W axial liver (triggered)
4. Heavily T2 weighted Long TE, TR>6000 (triggered)
5. T1 dynamic contrast IV gadolinium

Lesion mapping

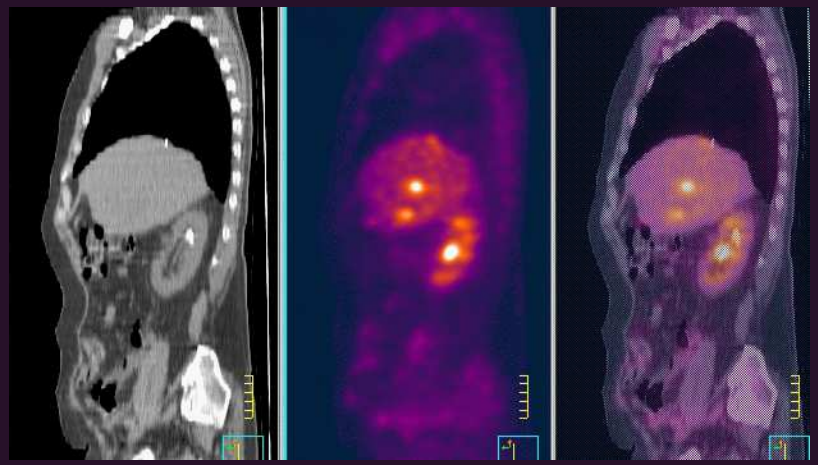
- Liver specific agent e.g.Gd BOPTA immediate and delayed 20min scan

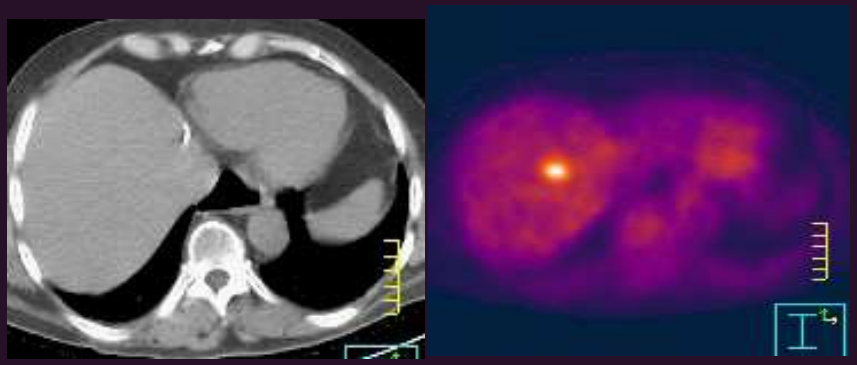
Just simple cysts?



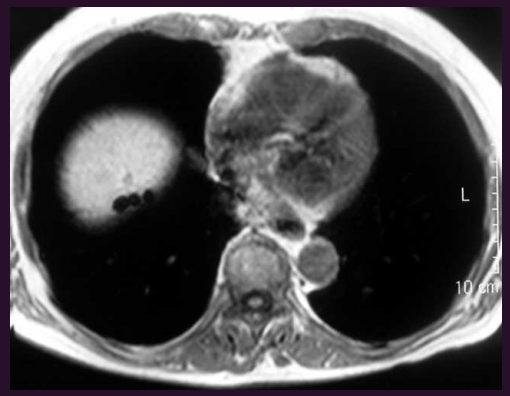


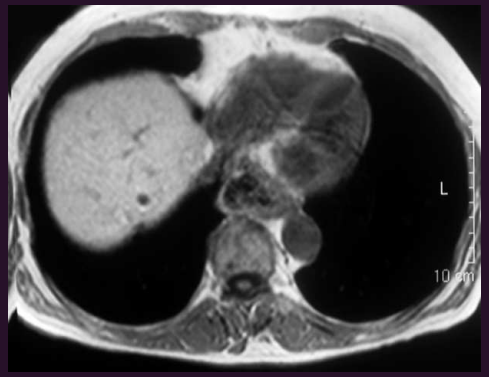
PET-CT – 3 lesions

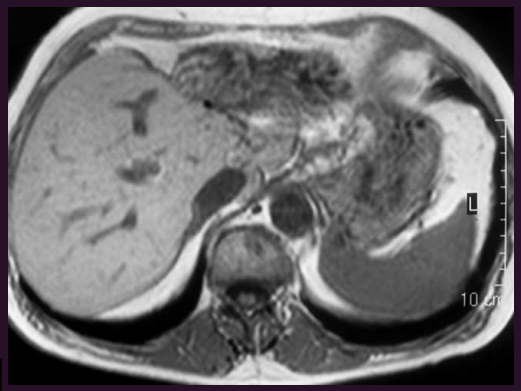


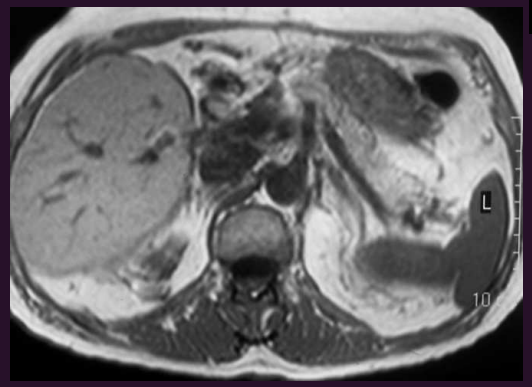


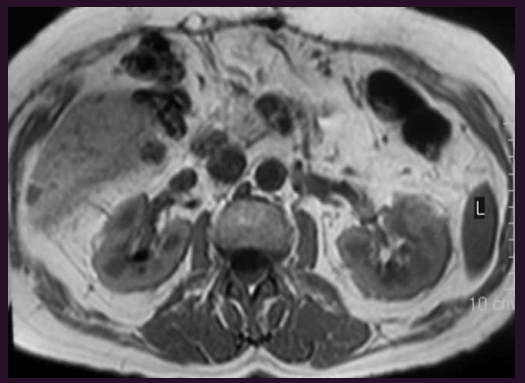
MRI - 5 lesions



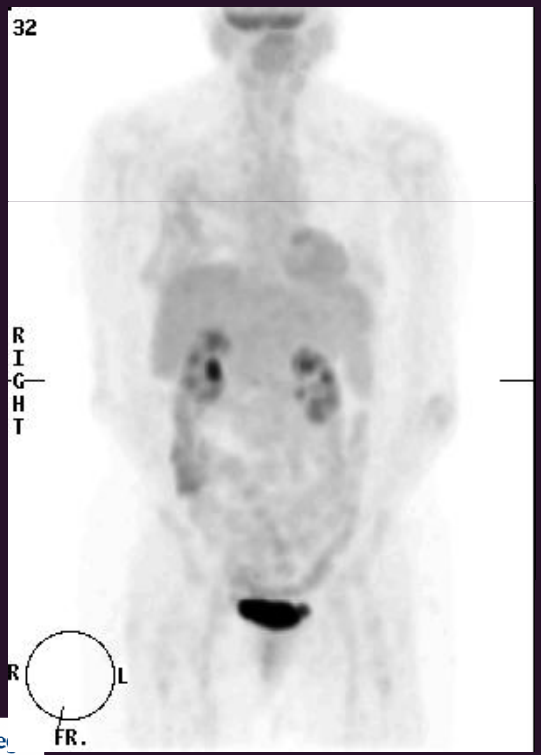


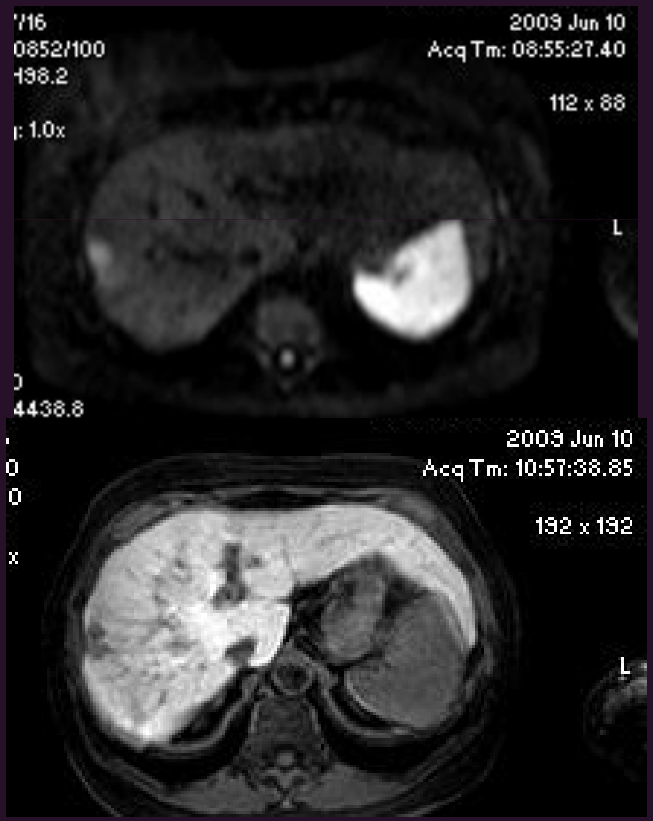






False negative PET - if suspicious about liver metastasis – must do an MRI





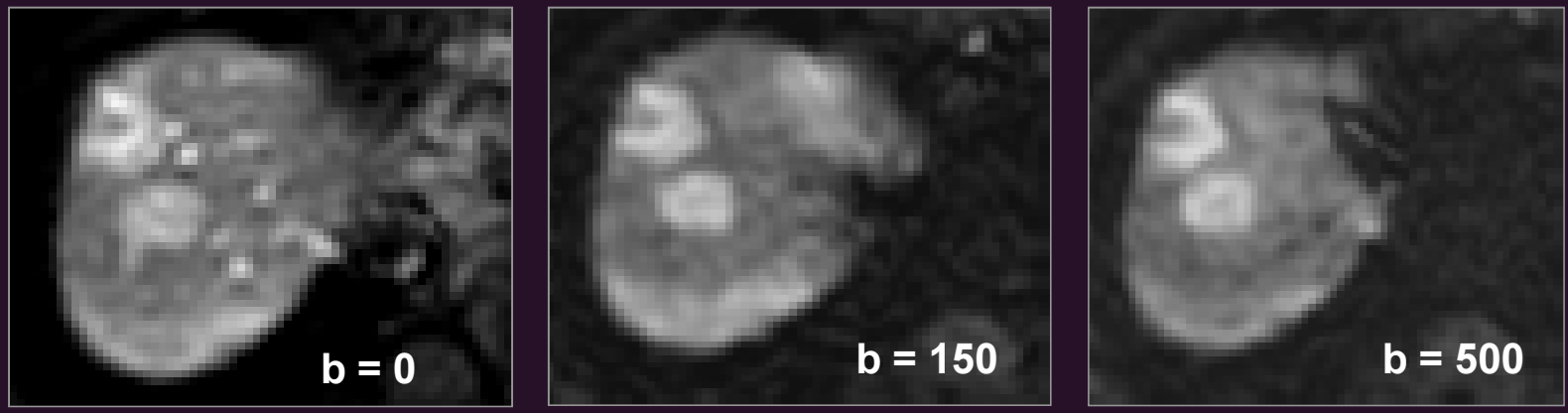
PET-CT vs MRI in detecting liver lesions

- On a per-lesion basis, PETCT and MRI were discordant in 15% (10/66 scans).
- MRI correctly identified more sub-centimetre metastases in eight scans.
- PETCT correctly identified more metastases in one case and confirmed disease in one equivocal MRI. Kong et al 2008 Eur J Nucl Med Mol Imaging.
- lesion detection reduces below 1 to 1.5 cm Park et al 2001

Diffusion-weighted MRI (DWI)

Features of colorectal metastases:

- High signal (restricted diffusion)



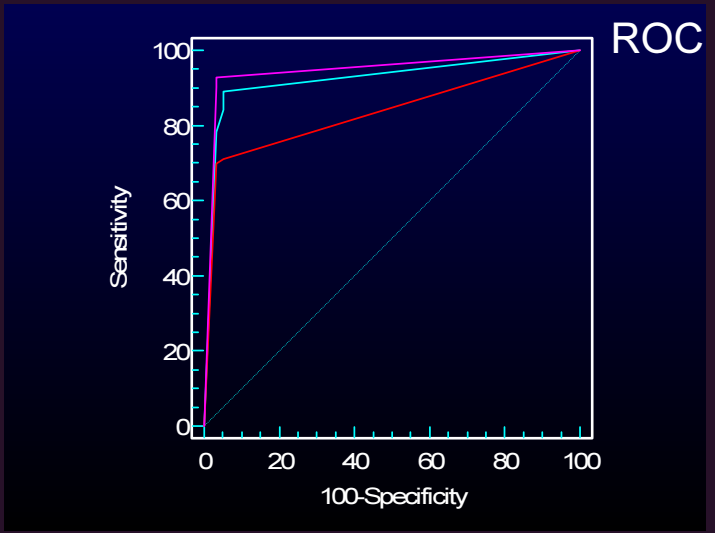
Koh, Riddell, Brown, Scurr et al ERad 2007

Results

Reader 1

Experienced in MnDPDP MRI

- Az = 0.92 (95% CI 0.86 - 0.96)
- Az = 0.83 (95% CI 0.76 – 0.89)
- Az = 0.94 (95% CI 0.89 – 0.97)



	Sensitivity*	Specificity*
MnDPDP MRI	84% (95% CI 76 – 92%)	95% (95% CI 89 – 100%)
DWI	70% (95% CI 60 – 80%)	96% (95% CI 91 – 100%)
MnDPDP + DWI	92% (95% CI 86 – 97%)	96% (95% CI 91 – 100%)

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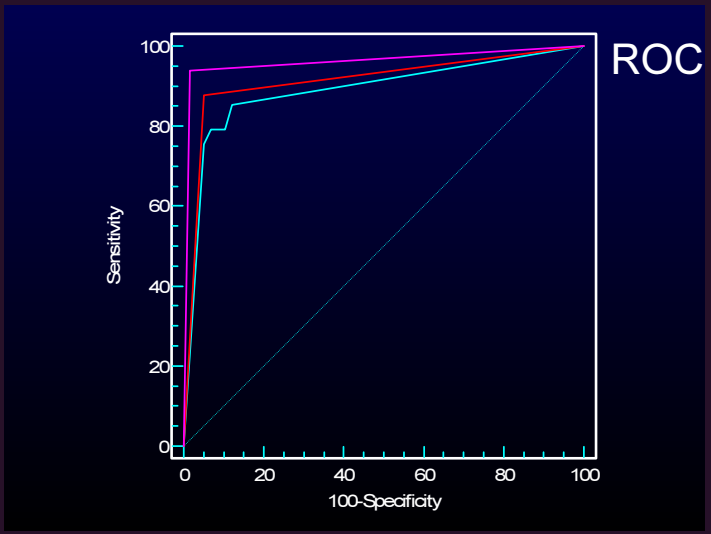
Results

Reader 2

Less experienced in MnDPDP MRI

- Az = 0.89 (95% CI 0.82 - 0.93)
- Az = 0.91 (95% CI 0.85 – 0.95)
- Az = 0.96 (95% CI 0.91 – 0.99)



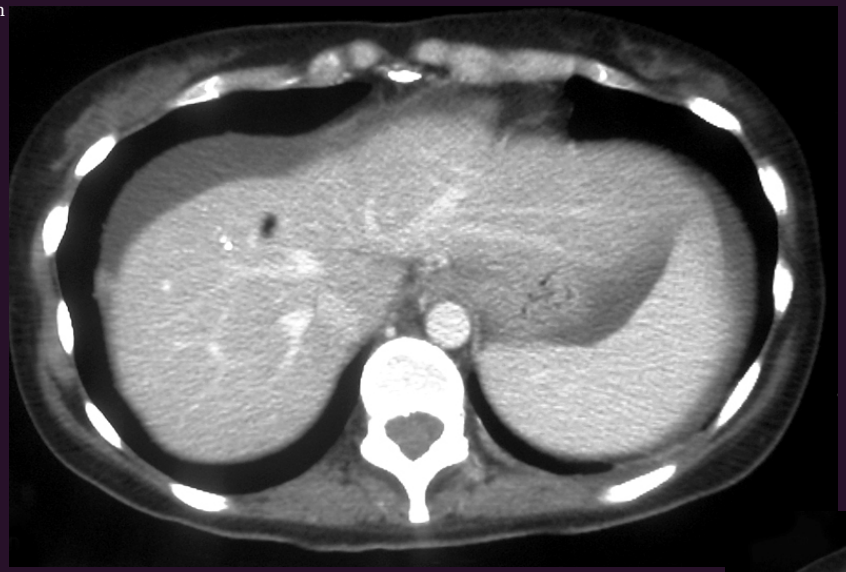
	Sensitivity*	Specificity*
MnDPDP MRI	78% (95% CI 69 – 87%)	93% (95% CI 87 – 99%)
DWI	86% (95% CI 79 – 94%)	94% (95% CI 89 – 100%)
MnDPDP + DWI	93% (95% CI 87 – 98%)	98% (95% CI 94 – 100%)

*Score of 4 or > indicates metastasis

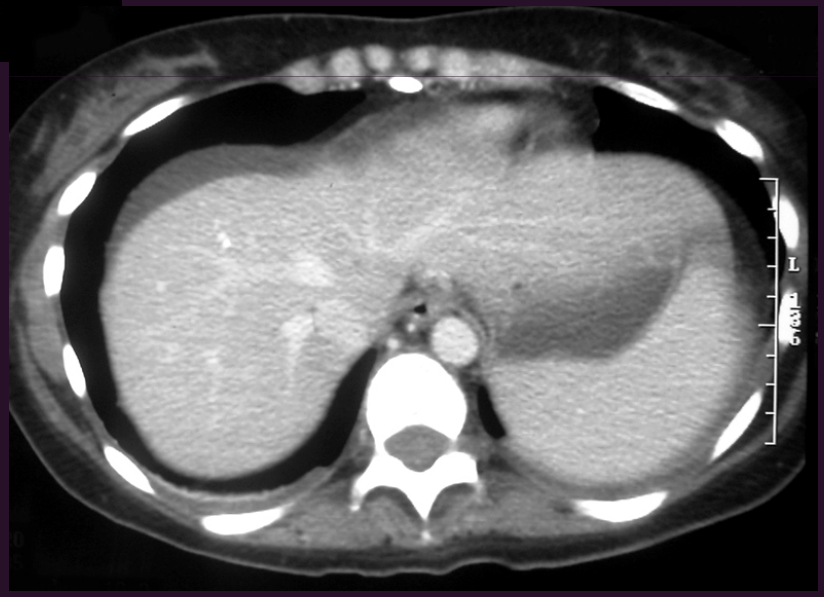
Detecting extrahepatic disease

- PETCT identified unexpected extrahepatic disease not detected on CT, leading to change in surgical management in 17%.
- There were three false-positive cases on PETCT.

Kong et al 2008

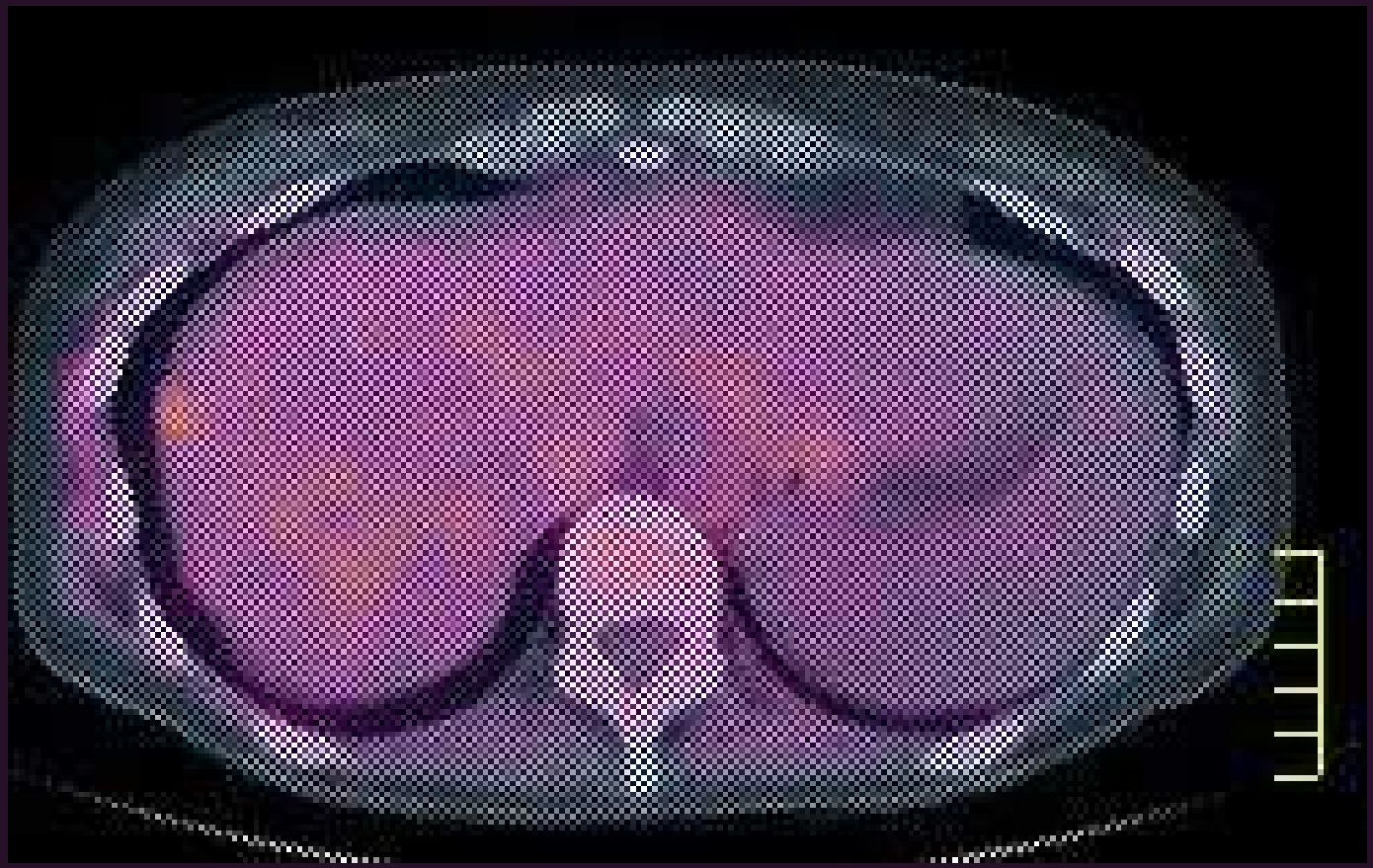


10/5/04



7/4/04

PET-CT extra information



The Royal Marsden

Survival outcomes for patients with equivocal ^{18}FDG-PET CT scan for extrahepatic disease prior to liver resection for metastatic CRC

- Patients included if they had Liver Resection and a PET prior to LR.
- PETs were coded as no EHD and “possible EHD”.
- Of the 2,480 patients on the registry, 273 had had Liver resection.
- Of these, 183 (67.0%) had a PET
- 137/183 – 75% had no EHD
- 46/183 – 25% had possible EHD on PET-CT / normal CT.

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J Clin Oncol 31, 2013 (suppl; abstr 1581)

	No EHD	PET-CT detected EHD (normal CT)
age	66.7 yrs	68.4 yrs
male	61.3%	63.0%
KRAS wildtype	11.0%	16.3%,
stage IV disease at initial diagnosis	49.6%	54.3%
colonic primary	74.4%	65.2%
one Liver resection	82.5%	89.1%
one line of chemotherapy	52.4%	48.6%
well-moderate tumour differentiation	85.7%	86.4%

Outcomes for PET-CT detected EHD

- The OS for no EHD vs possible EHD at 1-year was 98.5%-vs-93.5%
- 2-years OS was 87.6%-vs-88.0%
- 5-years OS was 61.5%-vs-59.4%.

On adjustment for age, gender, stage at diagnosis, primary site, number of LRs, lines of chemotherapy and tumour differentiation, the hazard ratio remained non-significant; HR=0.76 (95% CI 0.37–1.59, *P*-value = 0.47), for possible EHD.

Clinical Oncology

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Guidelines

Evidence-based Guideline Recommendations on the use of Positron Emission Tomography Imaging in Colorectal Cancer

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Abstract

Aims: To provide evidence-based practice guideline recommendations on the use of fluoro-2-deoxy-D-glucose positron emission tomography (PET) for diagnosis, staging, assessing treatment response, liver metastasis and restaging or recurrence of colorectal cancer.
Materials and methods: A systematic review by Facey *et al.* (*Health Technology Assessment* 2007;11(44):iii–iv, xi–267) was used as the evidence base for recommendation development. As the review was limited to August 2005, the evidence base was updated to May 2010 using the same search strategies for MEDLINE and EMBASE used in the original review. The authors of the current systematic review drafted recommendations, which were reviewed, adapted and accepted by consensus by the Ontario provincial Gastrointestinal Disease Site Group and a special meeting of clinical experts.
Results: The results from the Facey *et al.* review for colorectal cancer included three other systematic reviews and 24 primary studies. The 2005 to 2010 updated search included 10 additional systematic reviews and 28 primary studies. Recommendations were developed based on this evidence and accepted by consensus.
Conclusions: The routine use of PET is not recommended for the diagnosis or staging of clinical stage I–III colorectal cancers. PET is recommended for determining management and prognosis if conventional imaging is equivocal for the presence of metastatic disease. PET is also not recommended for routine surveillance in patients with colorectal cancer treated with curative surgery at high risk for recurrence. It is recommended to determine the site of recurrence in the setting of rising CEA when conventional work-up fails to unequivocally identify metastatic disease. Finally, PET is recommended in the preoperative assessment of colorectal cancer liver metastasis before surgical resection.

Key words: Colorectal cancer; diagnosis; FDG-PET; liver metastases; recurrence; staging

Introduction

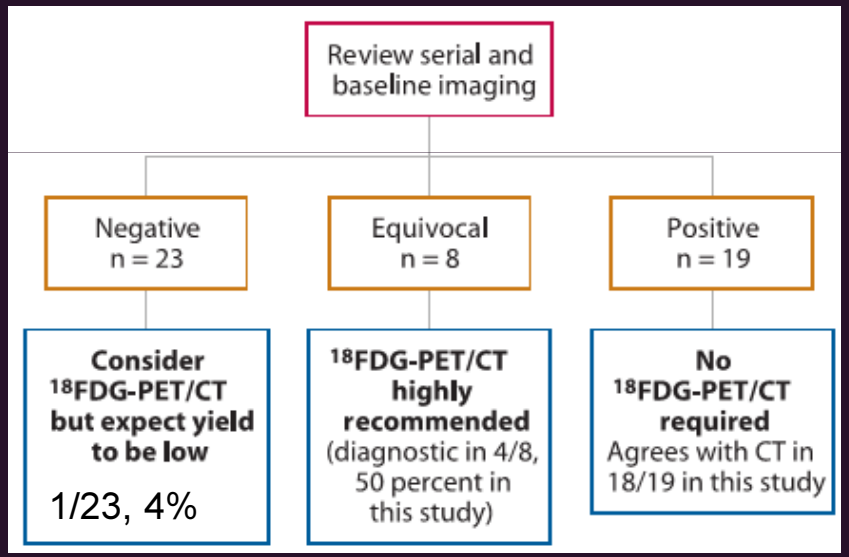
Colorectal cancer (CRC) is the third most common cancer, with an estimated 22,500 new cases and 9100 deaths for 2010 in Canada [1]. According to Canadian cancer statistics [1] for 2010, CRC is the second cause of death from cancer among both men and women. The mortality due to CRC in

mortality since 1986 has been attributed to the treatment of the cancer through chemotherapy.

The use of positron emission tomography (PET) as a major diagnostic imaging tool for cancer is on the increase in the USA, Canada, Europe and parts of Asia. Different studies have suggested that PET may perform better than other technological imaging modalities like X-ray, computed tomography (CT) and magnetic resonance

- 37/50 (74%) patients undergoing FDG-PET/CT were being investigated for an apparently unexplained elevated CEA or equivocal CT or MRI studies.
- Careful review of serial imaging studies, using the defined reporting protocol, enabled a definitive diagnosis to be made in 24/37 (65%) patients.

Relative contributions of PET-CT after review of imaging



APPENDIX 1. Codings and definitions for imaging findings on proformas

Nodes (by site)	
1	No node
2	Enlarged node/equivocal
3	New node/definite metastasis
Liver	
1	No liver lesion
2	Indeterminate lesion
3	Definite metastasis (new/rim enhancing lesion)
Lungs	
1	No pulmonary abnormality
2	Indeterminate changes/pulmonary lesions
3	Definite new/enlarging nodules
Peritoneal deposits	
1	No abnormality
2	Stranding/streaking
3	Measurable nodules
Pelvis	
1	Normal
2	Indeterminate
3	New/enlarging mass

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Rising CEA

Review SERIAL CT TAP IMAGING

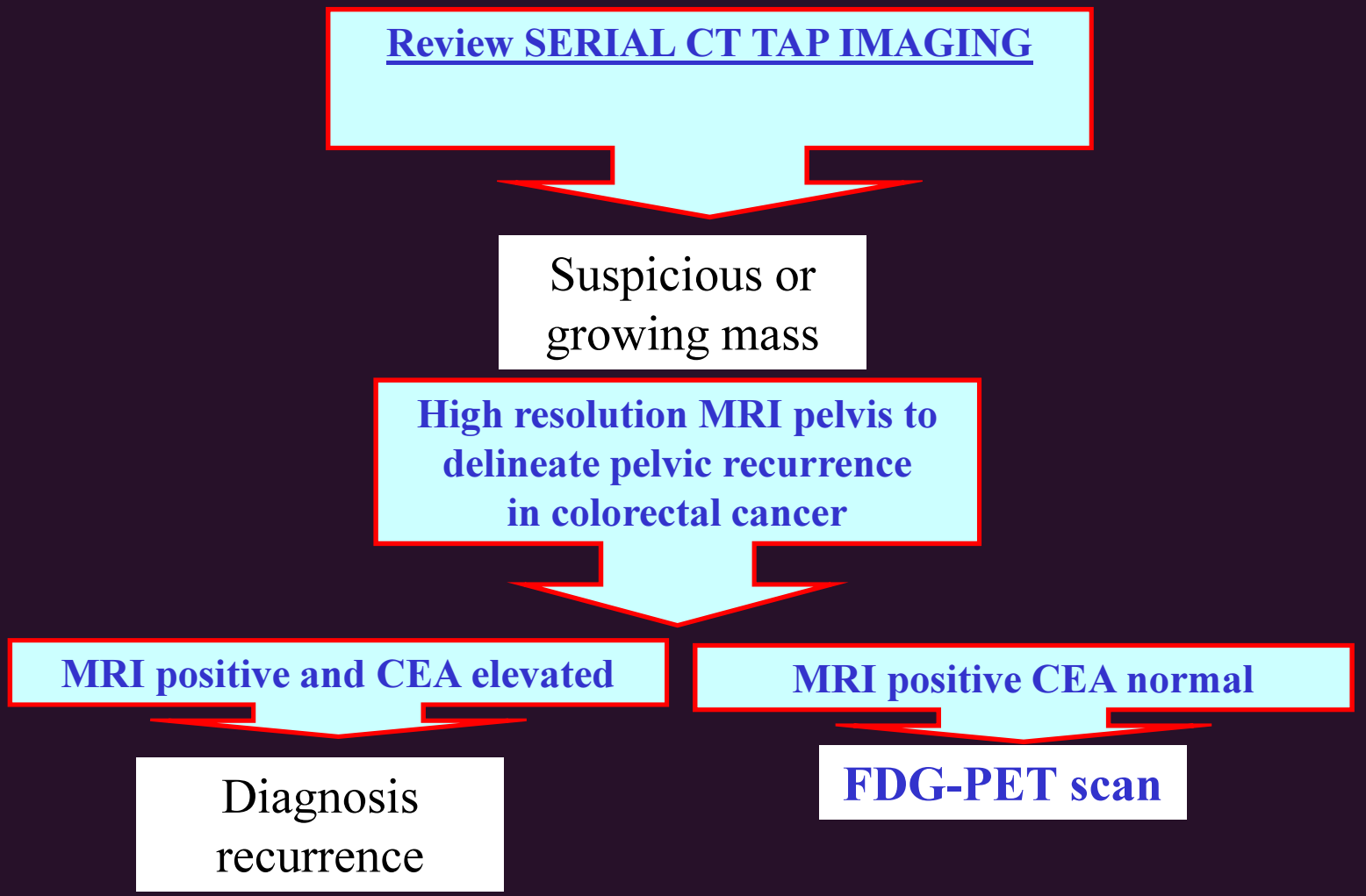
If negative

High resolution MRI pelvis to exclude pelvic recurrence in colorectal cancer

FDG-PET scan

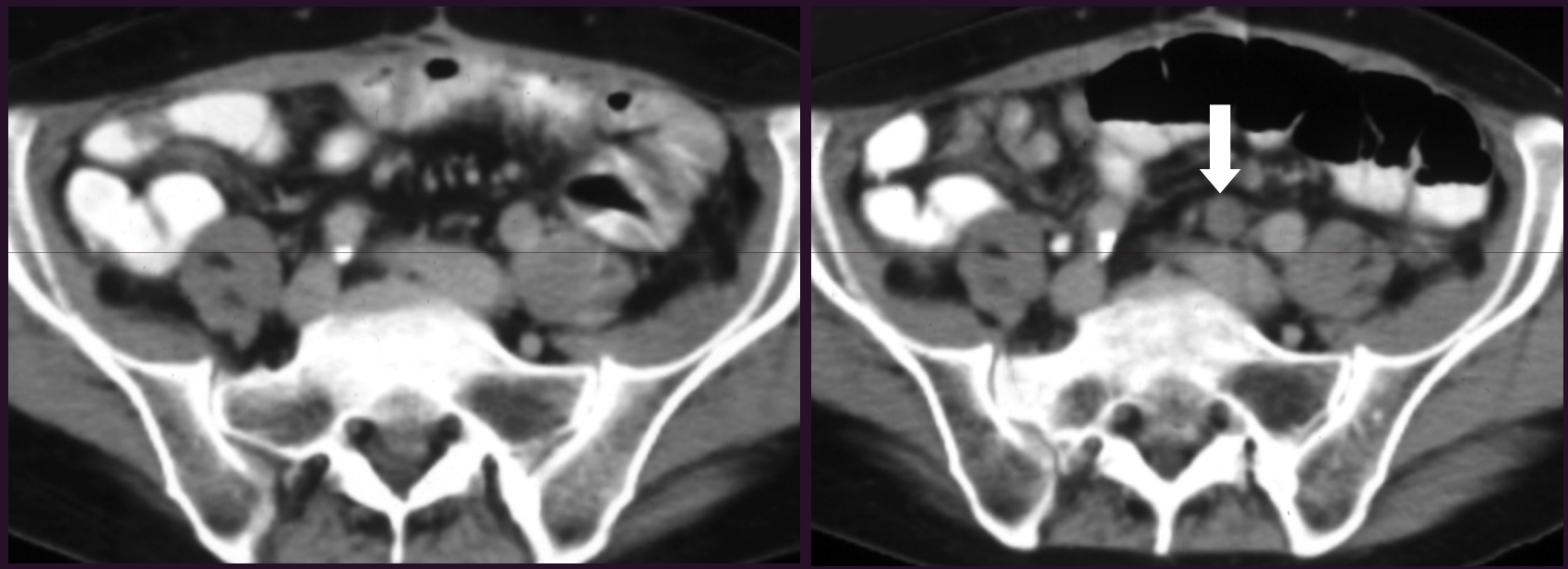
Liver MRI with liver specific contrast

Suspected recurrence

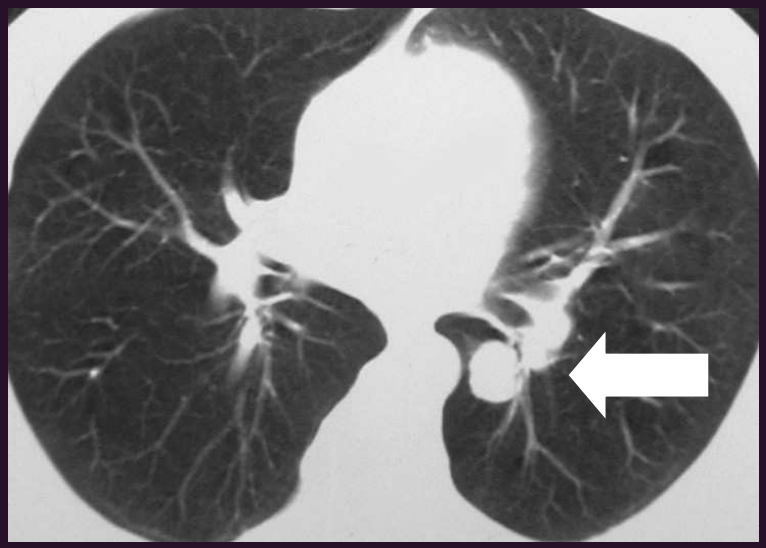


Examples of reporting criteria

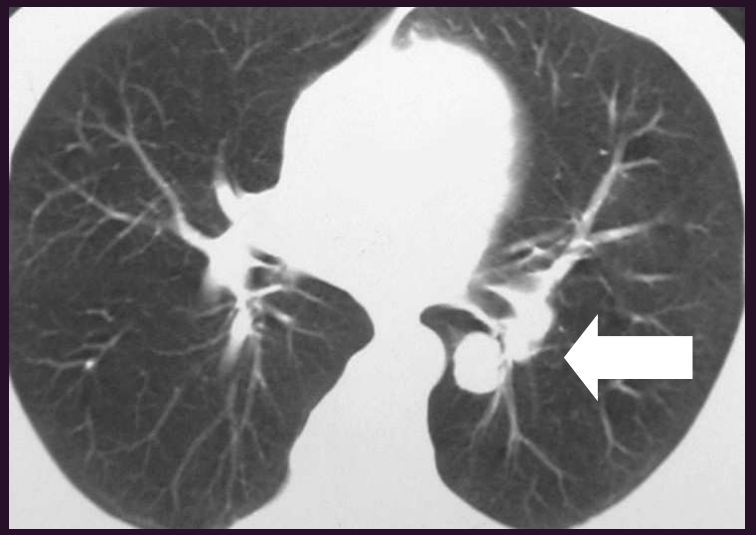
New Mass



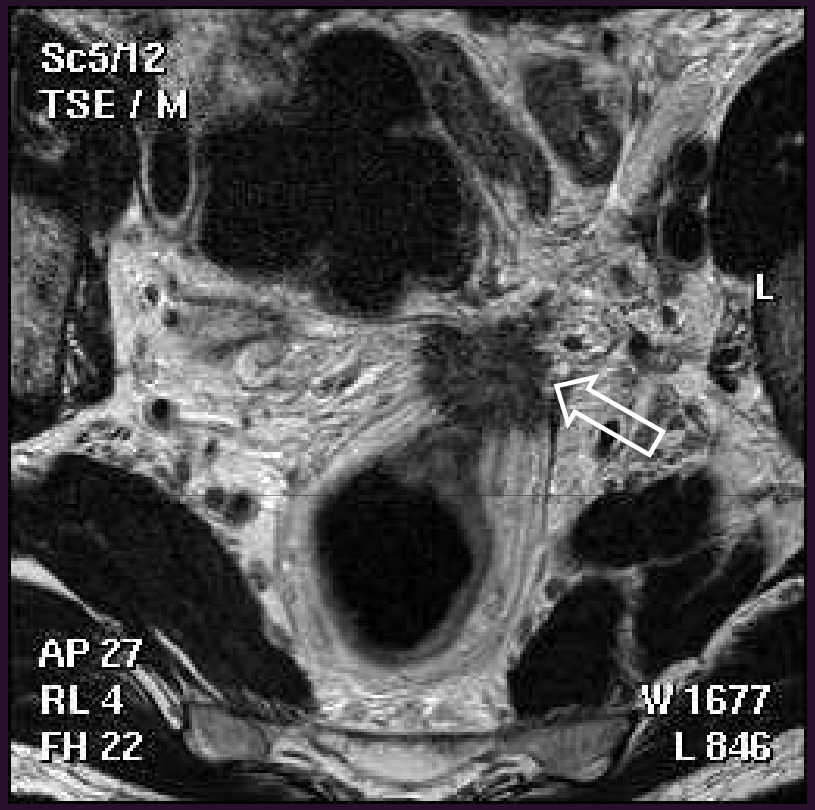
Importance of baseline review

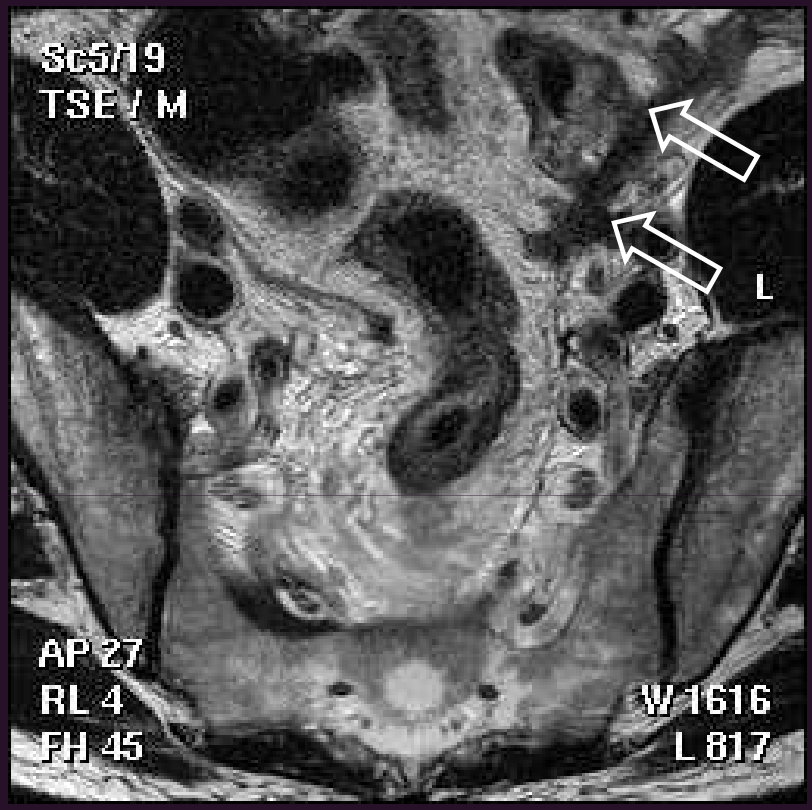


2004



2000





Peritoneal pelvic recurrence

Take home messages:

- Primary tumour assessment of T substage and EMVI on imaging is a strong predictor for synchronous metastatic disease
- Liver only is dominant site of spread and MRI should be undertaken at baseline to assess resectability
- Pulmonary nodules should fulfil criteria for malignancy – irregular, >5mm and multiple (otherwise routine follow up)
- PET-CT is indicated for patients with metastatic disease diagnosed on CT/MRI or unexplained rising CEA
- Caution when PET-CT identifies extrahepatic metastatic disease – as outcome data suggests this may not be prognostic, when conventional imaging is negative

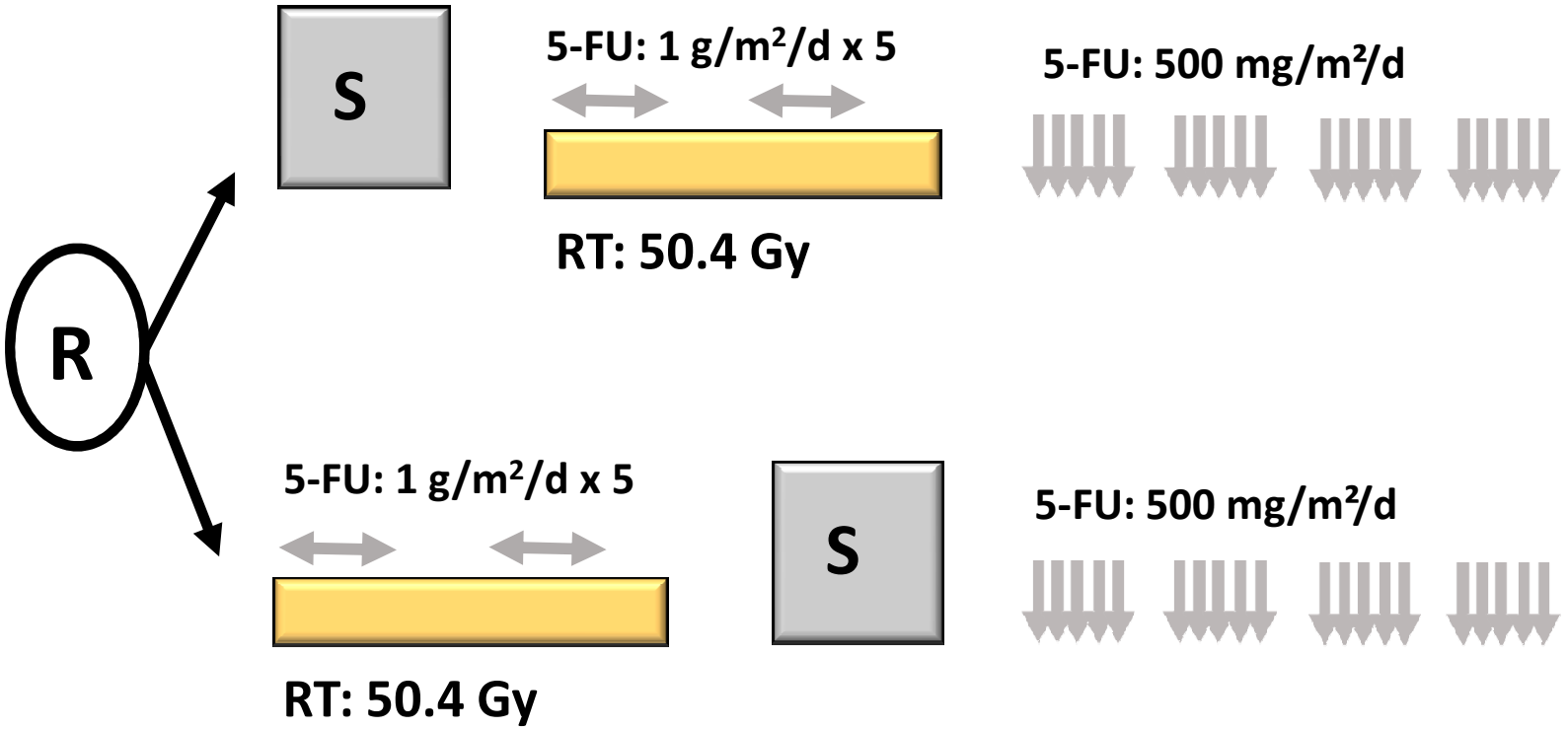
What is considered standard of care? Pivotal Trials and Guidelines: Radiotherapy

Claus Rödel
Department of Radiotherapy
University of Frankfurt
Germany

Where do we come from?

Three pivotal European clinical trials
(...and oncological principles)

CAO/ARO/AIO-94



Sauer R. et al., N Engl J Med 2004

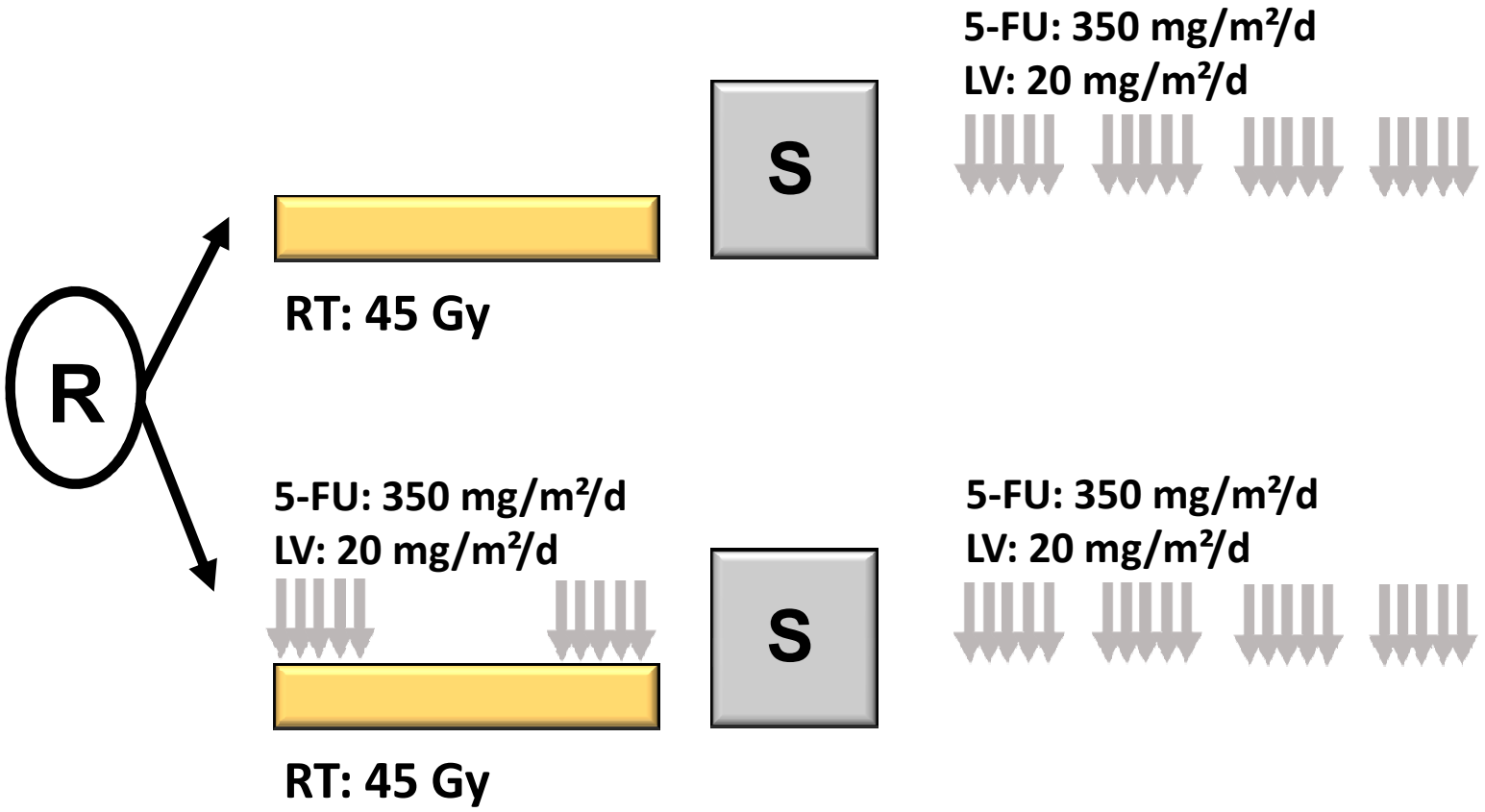
CAO/ARO/AIO-94

5-year Outcome	Postoperative CRT	Preoperative CRT	p
Local recurrences	13%	6%	.006
Sphincter preservation*	19%	39%	.004
Acute toxicity grade 3-4	40%	27%	.001
Distant recurrences	38%	36%	.84
Overall survival	76%	74%	.80

*Deemed to require APR

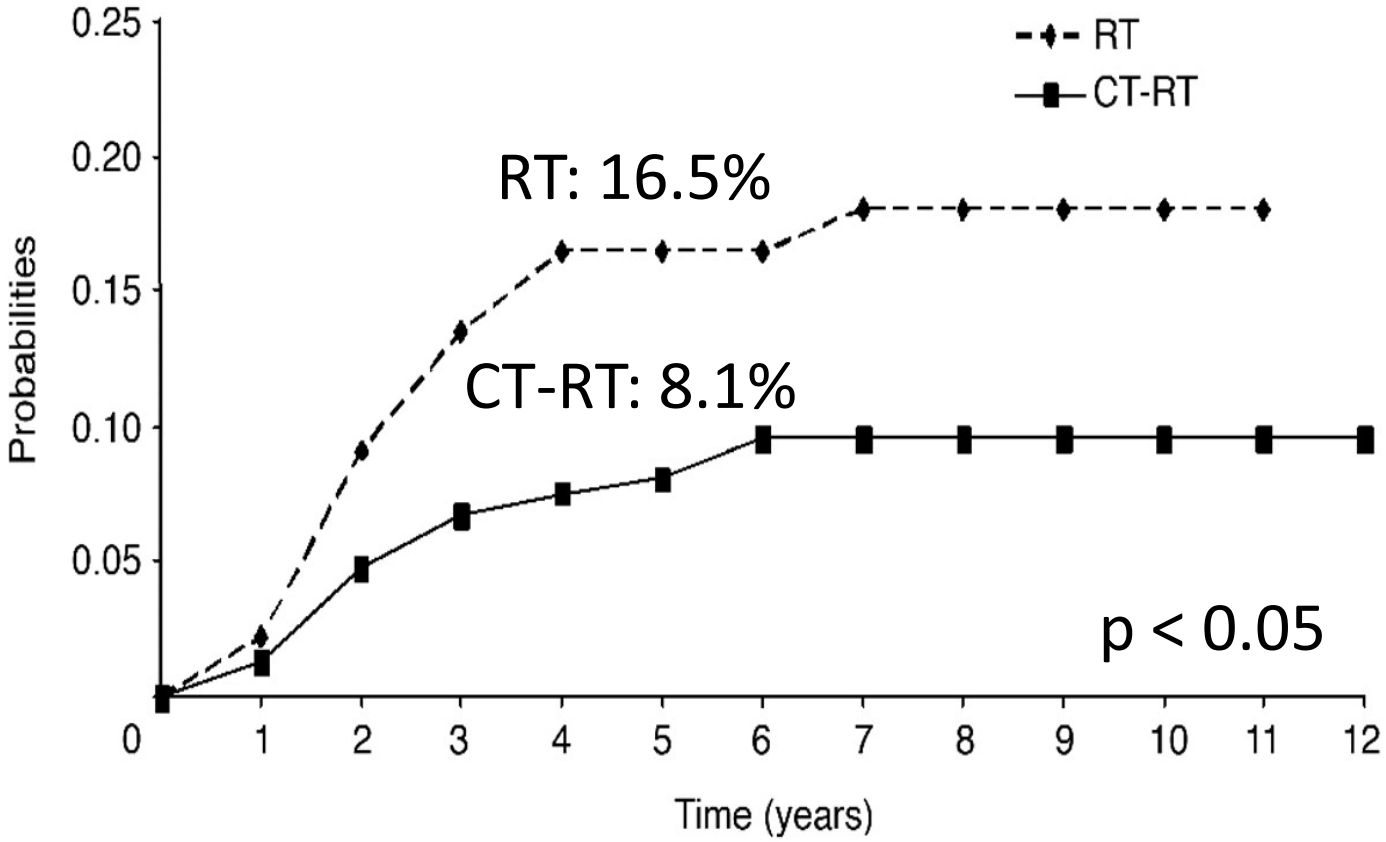
Sauer R. et al., N Engl J Med 2004

FFCD 9203-Trial



Gérard JP. et al., J Clin Oncol 2006

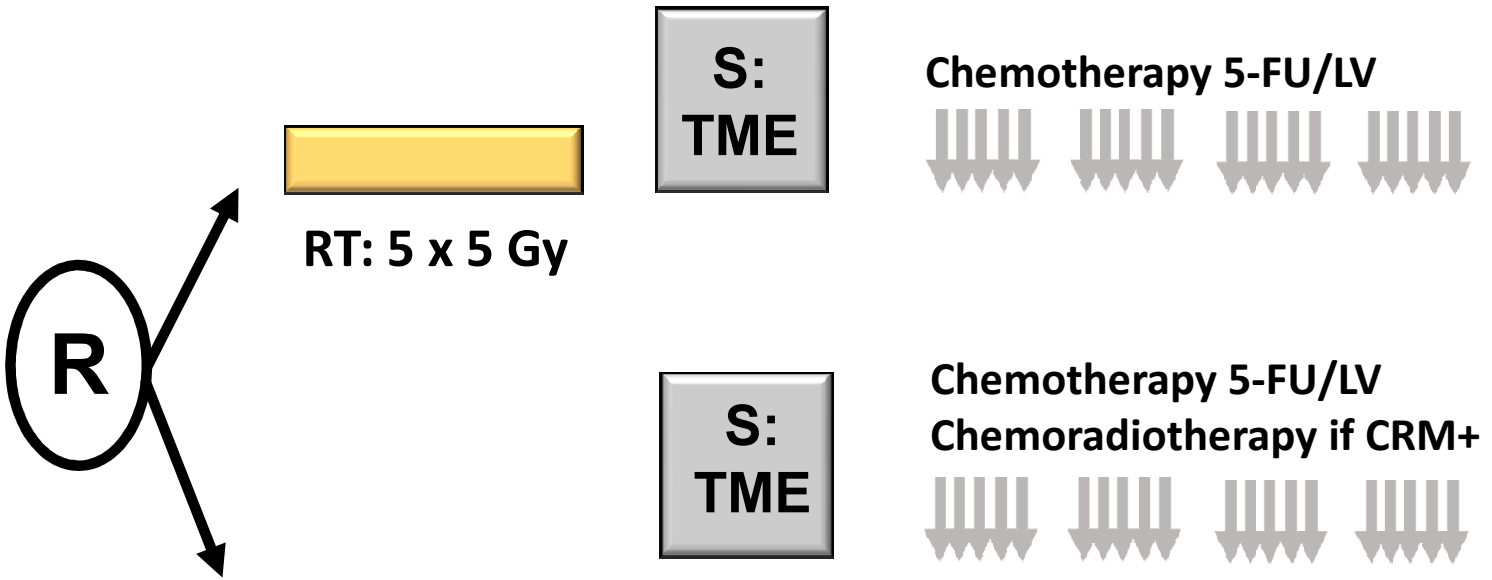
FFCD 9203 – Local Recurrences



Gérard JP. et al., J Clin Oncol 2006

Similar results: EORTC 22921; Bosset JF et al. N Engl J Med 2006

Dutch TME-Trial and MRC CR07



Kapiteijn E, N Engl J Med 2001
Sebaq-Montefiori D. et al., Lancet 2009

MRC-CR07 – Local Recurrences

TME-Quality	Local Recurrence Rate (3y)			
	N	RT + TME	TME	HR
„Poor“ Defects to Muscularis propria	154 (13%)	10%	16%	2.0
„Moderat“ Intra-mesorectal excision	398 (34%)	4%	10%	2.8
„Optimal“ Mesorectal excision	604 (52%)	1%	7%	4.5

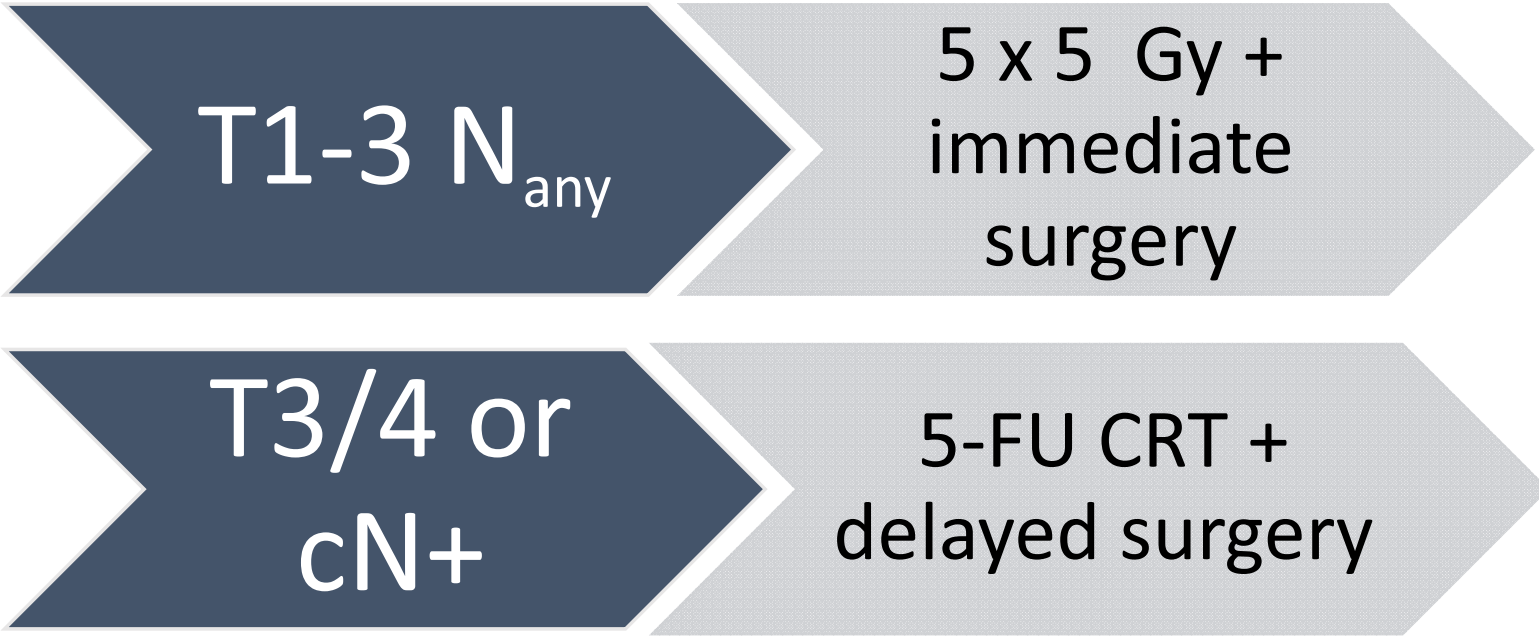
Sebaq-Montefiori D. et al., Lancet 2009

Similar results: Dutch TME Trial, Kapiteijn E, N Engl J Med 2001

What have we learned?

- ***Sequence RT, Chemo, S matters*** ***(CAO/ARO/AIO-94)***
- ***Synergy RT – 5-FU Chemo*** ***(FFCD 9303, EORTC 22921)***
- ***RT - optimized S complementary*** ***(Dutch Trial, MRC CR07)***

5 x 5 Gy or Chemoradiation?



T1-3 N_{any} **5x5 Gy** + Surg *vs* Surg alone

Swedish Trial
n=1168

Local Recurrences @ 13 years
9% vs 26%
(p<.001)

Overall Survival (13y)
38% vs 30%
(p=.008)

Fokesson et al., J Clin Oncol 2005

Dutch Trial
n=1861

Local Recurrences @ 10 years
5% vs 11%
(p<.001)

Overall Survival (10y)
48% vs 49%
(n.s.)

van Gijn et al., Lancet Oncol 2011

British Trial
n=1350

Local Recurrences @ 5 years
5% vs 12%
(p<.001)

Overall Survival (5y)
70% vs 68%
(n.s)

Sebag-Montefiore et al., Lancet 2009

T3/4 or N+ — **5-FU CRT** + Surg *vs* ...

German Trial
n=823

Local Recurrences (10y)
pre CRT vs post CRT
7% vs 10%
(p=.04)

Overall Survival (10y)
60% vs 60%
(n.s.)

Sauer et al., J Clin Oncol 2012

French Trial
n=762

Local Recurrences (10y)
pre CRT vs pre RT
8% vs 16%
(p<.05)

Overall Survival (10y)
68% vs 67%
(n.s.)

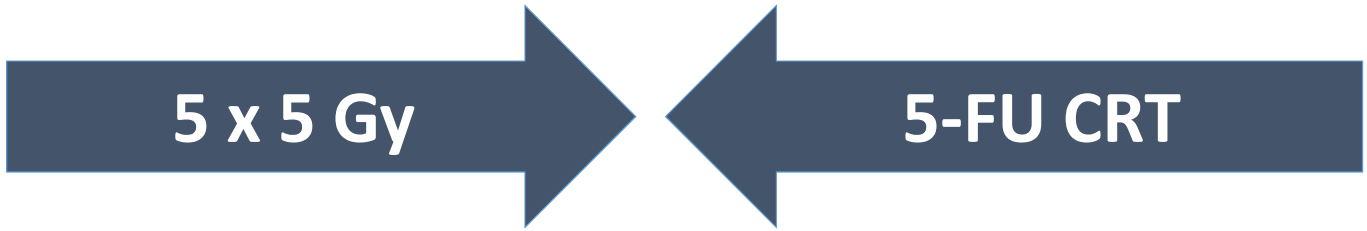
Gerard et al., J Clin Oncol 2006

EORTC Trial
n=1011

Local Recurrences (10y)
pre CRT vs pre RT
12% vs 22%
(p<.001)

Overall Survival (10y)
51% vs 49%
(n.s)

Bosset et al., Lancet Oncol 2014



Polish Trial
n=312

Inclusion (DRE)
Low T3-4 Nany

Primary Endpoint
Sphincter Preservation
(15% difference)

Trans-Tasman
n=326

Inclusion (ERUS;MRI)
T3 Nany

Primary Endpoint
Local Recurrences
(10% difference at 3y)

Polish Trial	5x5 Gy	CRT	P value
Acute Tox (Grade 3-4, %)	3	18	<.001
pCR (%)	1	16	<.001
CRM + (%)	13	4	0.02
Sphincter Preservation (%)	61	58	n.s.
Local Recurrences (4y, %)	11	16	n.s.
Overall Survival (4y, %)	67	66	n.s.
Late Tox (Grade 3-4, %)	10	7	n.s.

Med. F/U: 48 months

Bujko et al., Radiother Oncol 2004
Buiko et al., Br J Surg 2006
Pietrzak et al. Radiother Oncol 2007

Trans-Tasman	5x5 Gy	CRT	P value
Acute Tox (Grade 3-4; %)	2	28	<.001
ypT0 (%)	1	15	<.001
Sphincter Preservation (%)	63	69	0.22
Local Recurrences (3y, %)*	**7.5**	**4.4**	**0.24**
Overall Survival (5y, %)	74	70	0.62
Late Tox (Grade 3-4, %)	5.8	8.2	0.53

Med. F/U: 5.9 years

*< 5 cm from AV: 6/48 *vs* 1/31 pts (p= 0.21)

Ngan SY et al., J Clin Oncol 2012

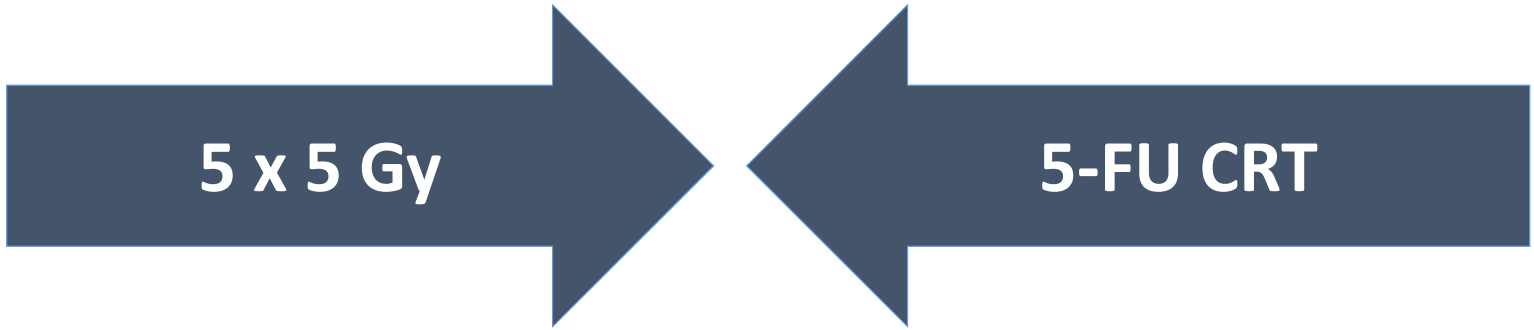
Limitations and Critical Points

Polish Trial

- Small (powered for 15% diff.)
- **Sphincter Preserv. dependent on surgical commitment**
- Poor compliance of CRT (69%)
- Imbalance in adjuvant CTx (46 vs 30% after CRT)
- No central quality control

Trans-Tasman

- Small
- **Local control: 10 % difference?**
- MRI staging not mandatory
- Lack of info on MRF
- Lack of info on TME, CRM
- Imbalance in tumor location (10% more low tumors in SCRT)



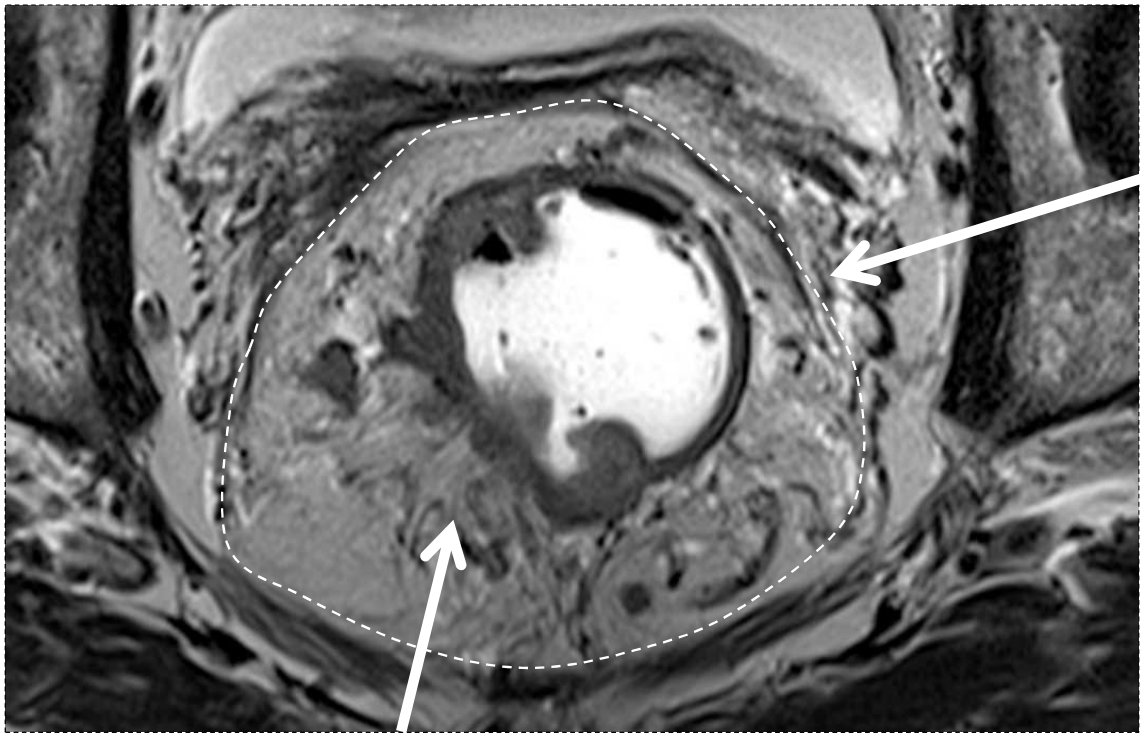
- Less acute tox
- Patient covenience
- Lower cost

- Better downsizing
- Lower surgical morbidity
- Ability to safely combine with chemo

„The lines were drawn, alliances formed, and we sat at different dinner tables at the ASCO GI Cancers Symposium“

Bruce D. Minsky, Editorial, J Clin Oncol 2012

Where are we now?

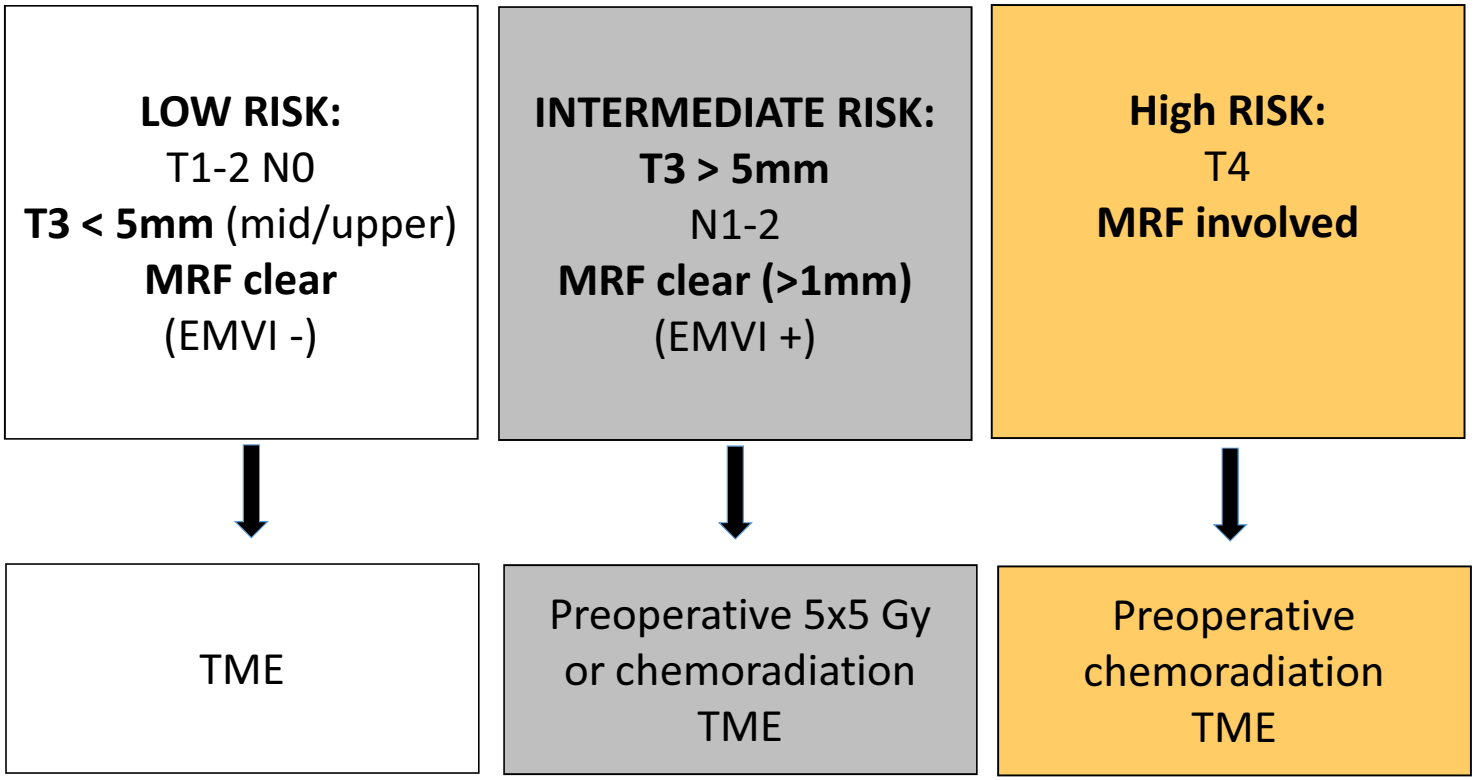


Mesorectal Facia (MRF)

Infiltration of perirectal fat (in mm)

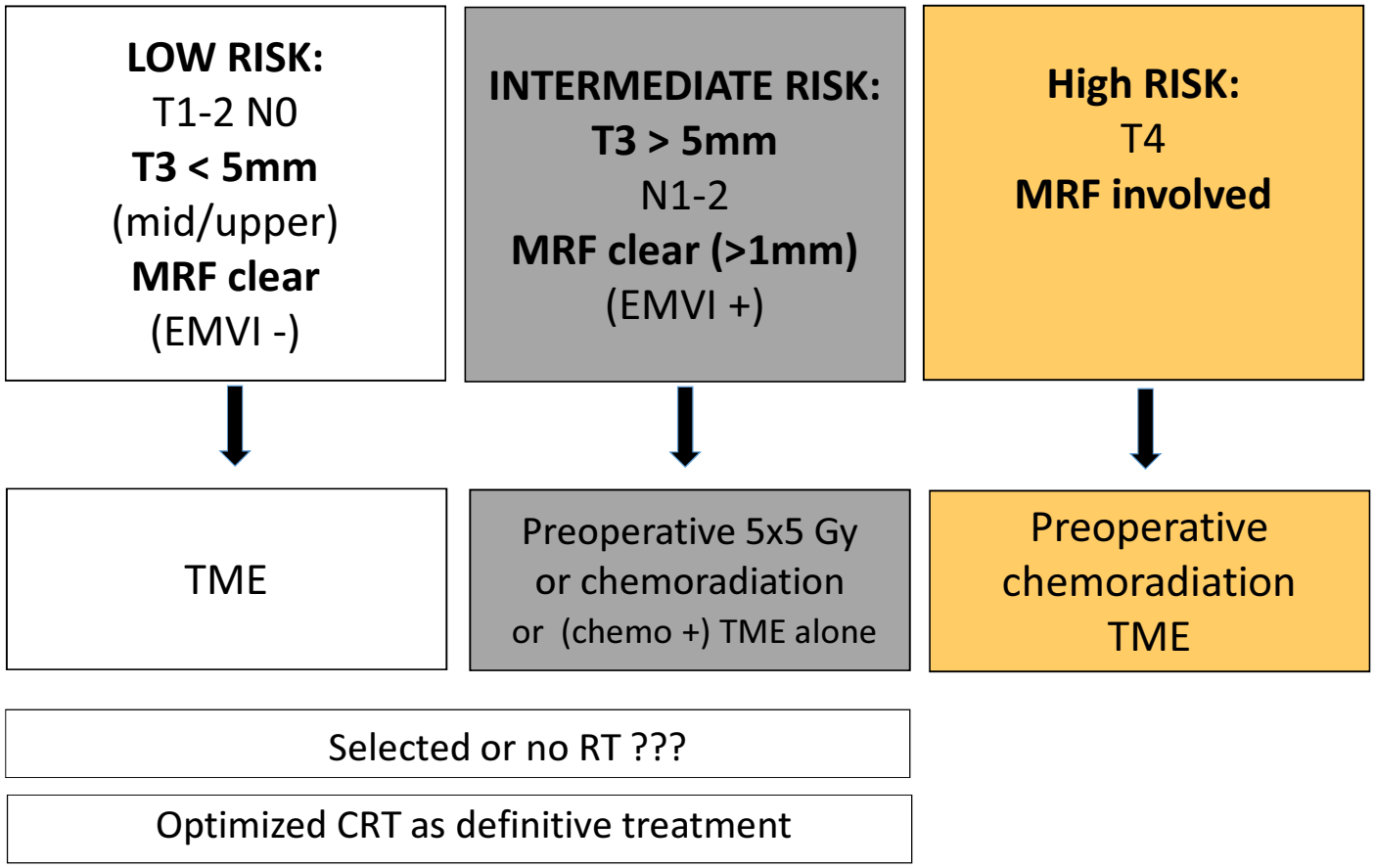
European Model of Stratification

based on MRI risk categorization



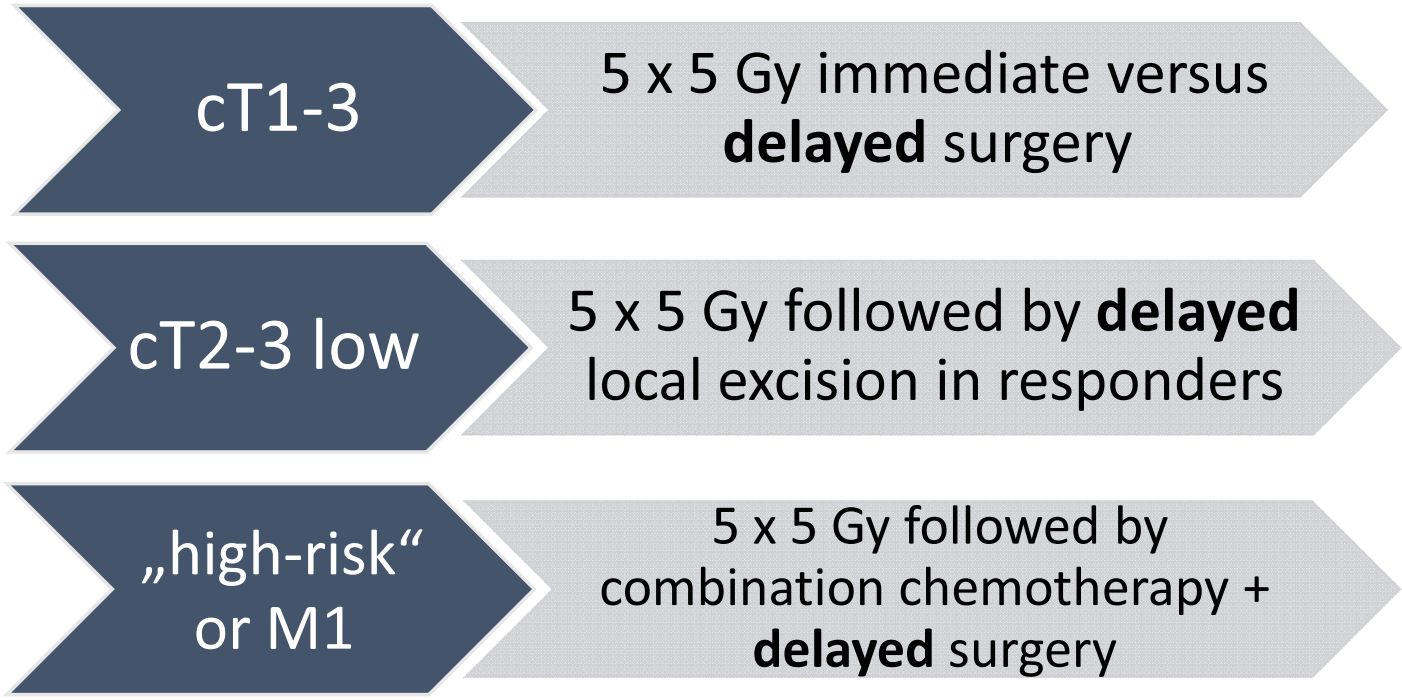
European Model of Stratification

based on MRI risk categorization



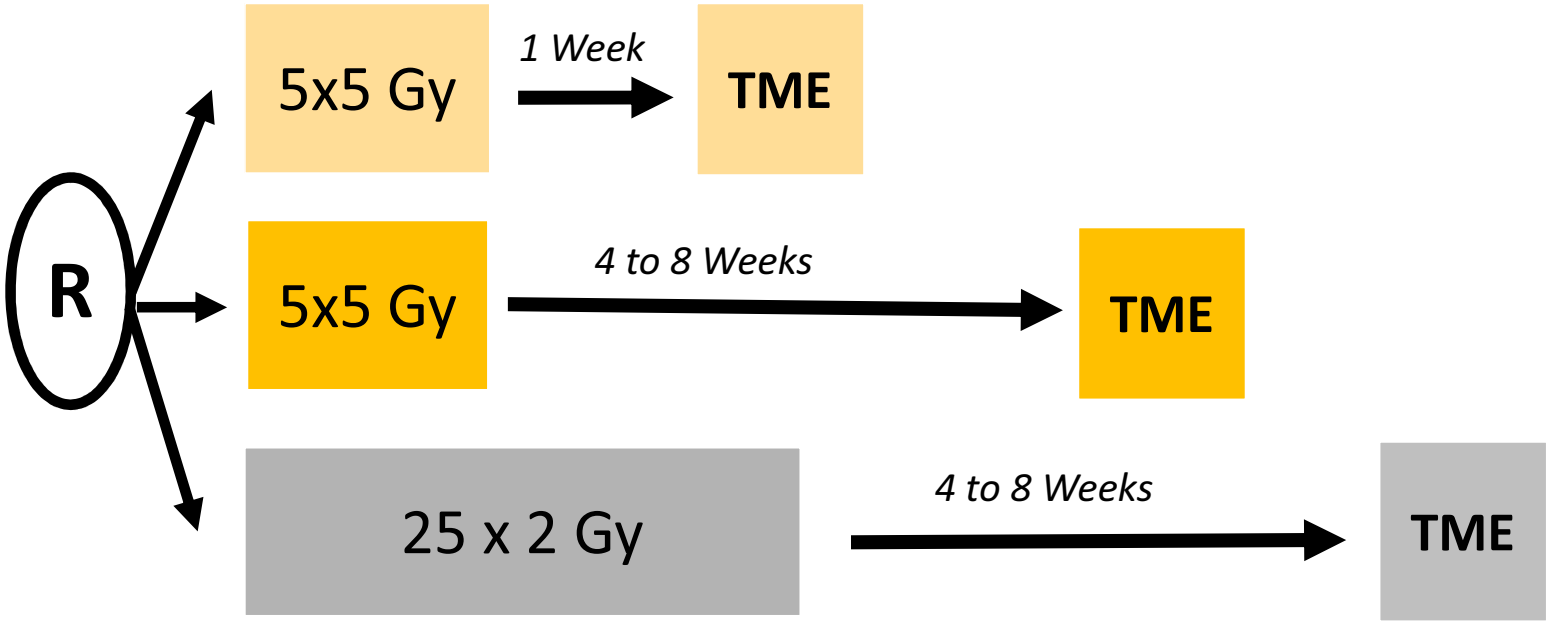
Where do we go from here?

Current trials with 5 x 5 Gy



Stockholm III Trial

Inclusion Criteria: clinically resectable RC < 15 cm from AV



Primary endpoint: Time to local recurrence, 840 pts to show equality (15% @ 5y, power 80%)
Secondary: acute, late tox, QoL, overall survival

Stockholm III Trial

First interim analysis after 300 pts (1998-2005)	**5x5 Gy immediate TME**	**5x5 Gy delayed TME**	**25x2 Gy delayed TME**
Number of pts	**118**	**120**	**65**
Severe RT-induced Tox (hospital admission, %)	**0**	**4.2**	**5**
Postop. Complications (%) **Reoperations (%)** **Anastomotic leak (%)**	**47** **10** **13**	**40** **11** **11**	**32** **5** **4**

Petterssons et al., Br J Surg 2010

Stockholm III Trial

Second interim analysis after 500 pts in 5x5 Gy arms (1998-2010)	**5x5 Gy immediate TME**	**5x5 Gy delayed TME**
Number of pts	**234**	**228**
ypT0 (%) **ypN0 (%)**	**2.1** **63.7**	**11.8** **71.5**
CRM + (%)	**11**	**9**
Abdominoperineal Resection (%)	**33**	**38**

Petterssons et al., Br J Surg 2015

Polish prospective multicenter study: n= 64

ypT0-1: 67%; Local recurrence (2y) 12%

Bujko et al., Radiother Oncol 2013

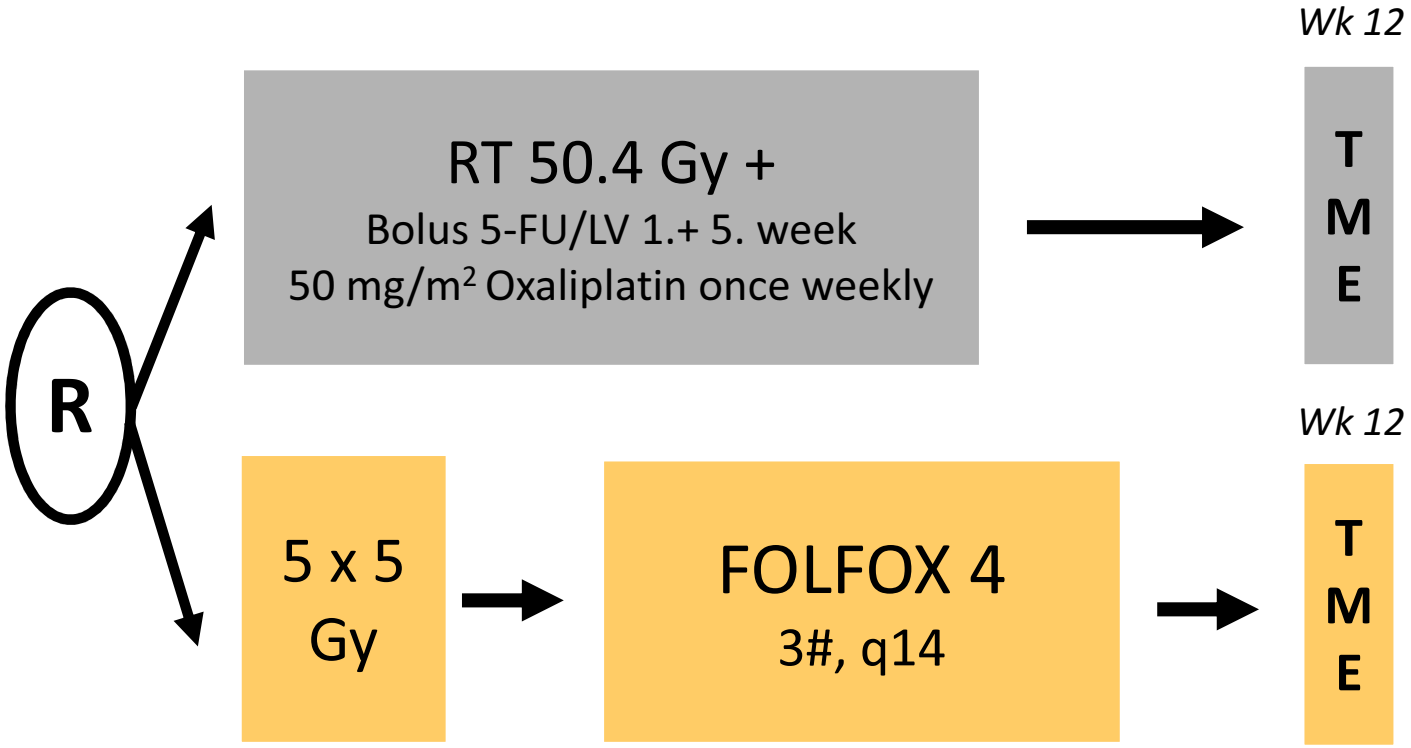
Dutch M1-trial: n= 50

pCR 26%, radical operation/ablation of all tumor sites (R0) in 72%

Van Dijk et al., Ann Oncol 2013

Polish II – Trial (randomized phase III)

High-risk criteria: fixed T3 or T4 („nonresectable“)



Primary endpoint: R0 resection rate (75% > 85%), 540 pts. required

Polish Trial II

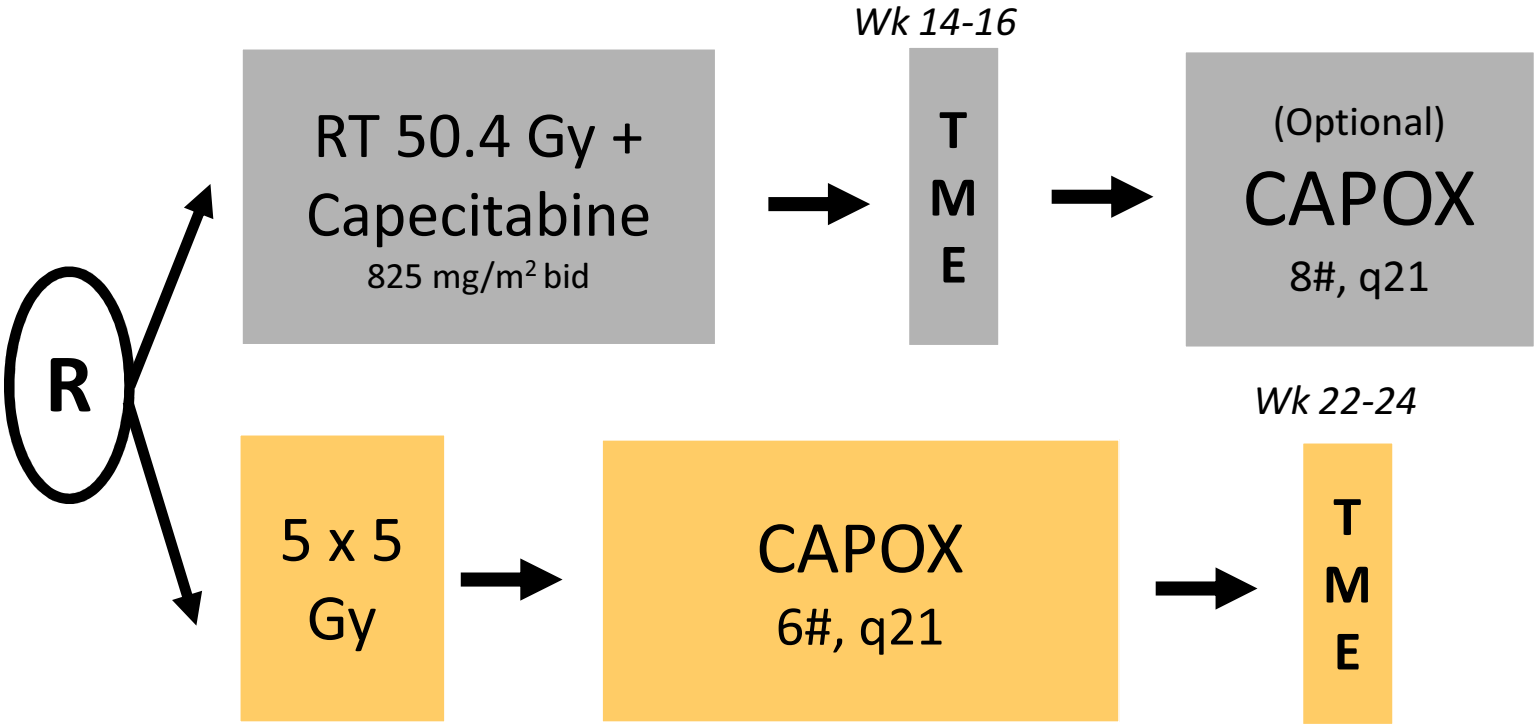
	50.4 Gy 5-FU/Ox	5x5 Gy FOLFOX	P-value
Number of pts	254	261	
R0 resection (%)	**71**	**77**	**.07**
pCR (%)	12	16	.21
Acute tox grade 1+2/ 3+4 / 5	50 / 21 / 3	60/ 23 / 1	.006
Postop complication	25	29	.18
Local Failure @3y (%)	21	22	.82
Disease-free Survival @ 3y (%)	52	53	.85
Overall Survival @ 3y (%)	65	73	.046

Med. F/u: 35 mo

Bujko et al., ASCO GI 2016

RAPIDO-Trial (randomized phase III)

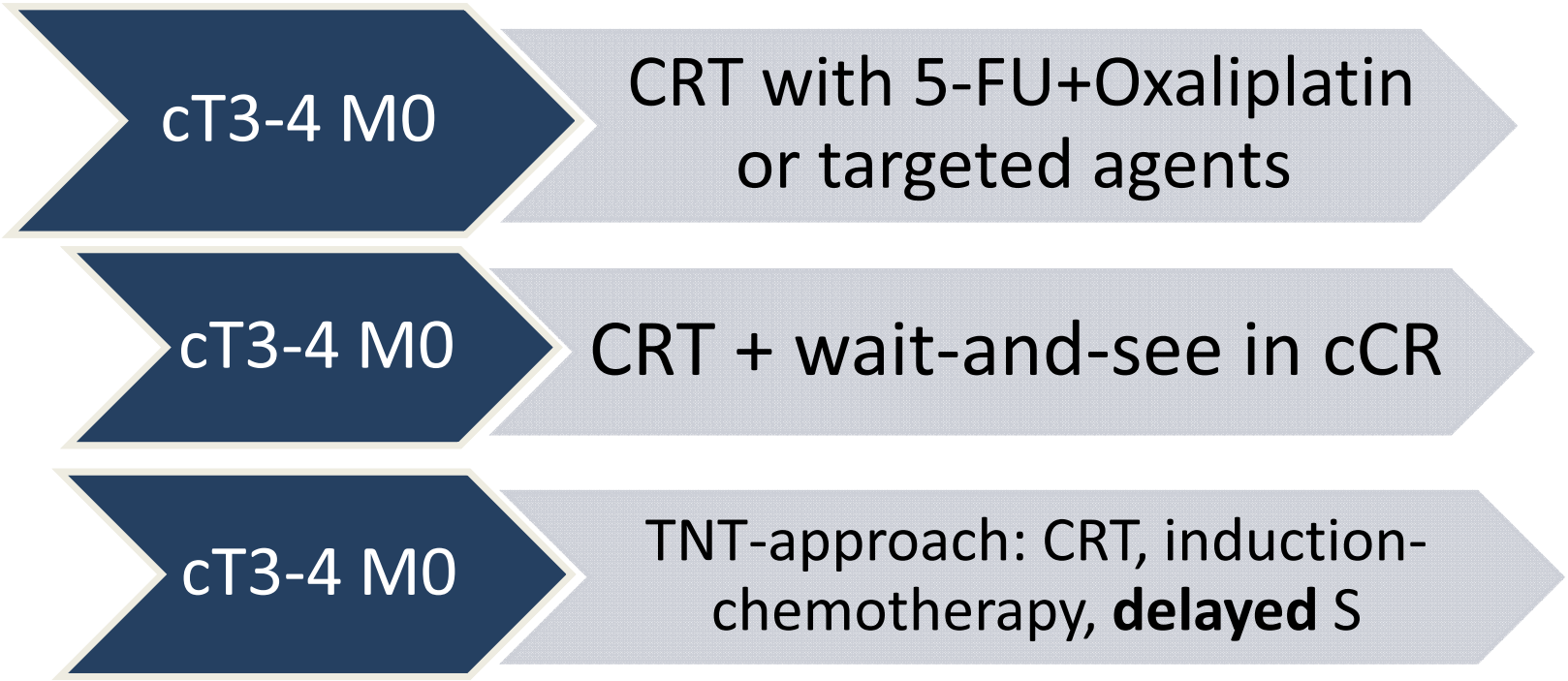
MRI-defined high-risk criteria:
cT4 or MRF+ or N2 or lateral N+ or EMVI+



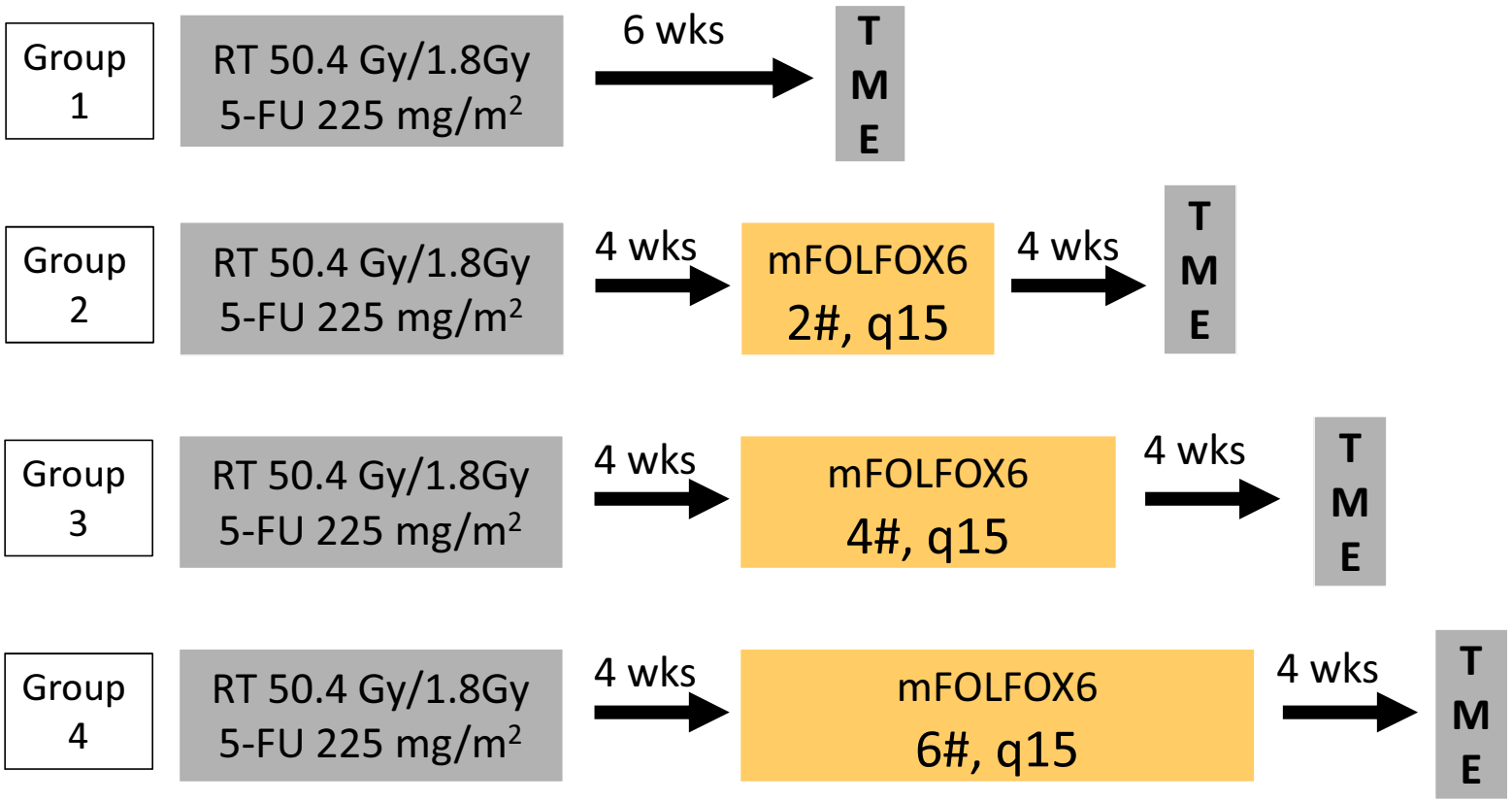
Primary endpoint: 3y-DFS (50% > 60%), 885 pts. required

Where do we go from here?

Current Trials with CRT



The TIMING Trial



Garcia-Aquilar J et al, Lancet Oncol 2015

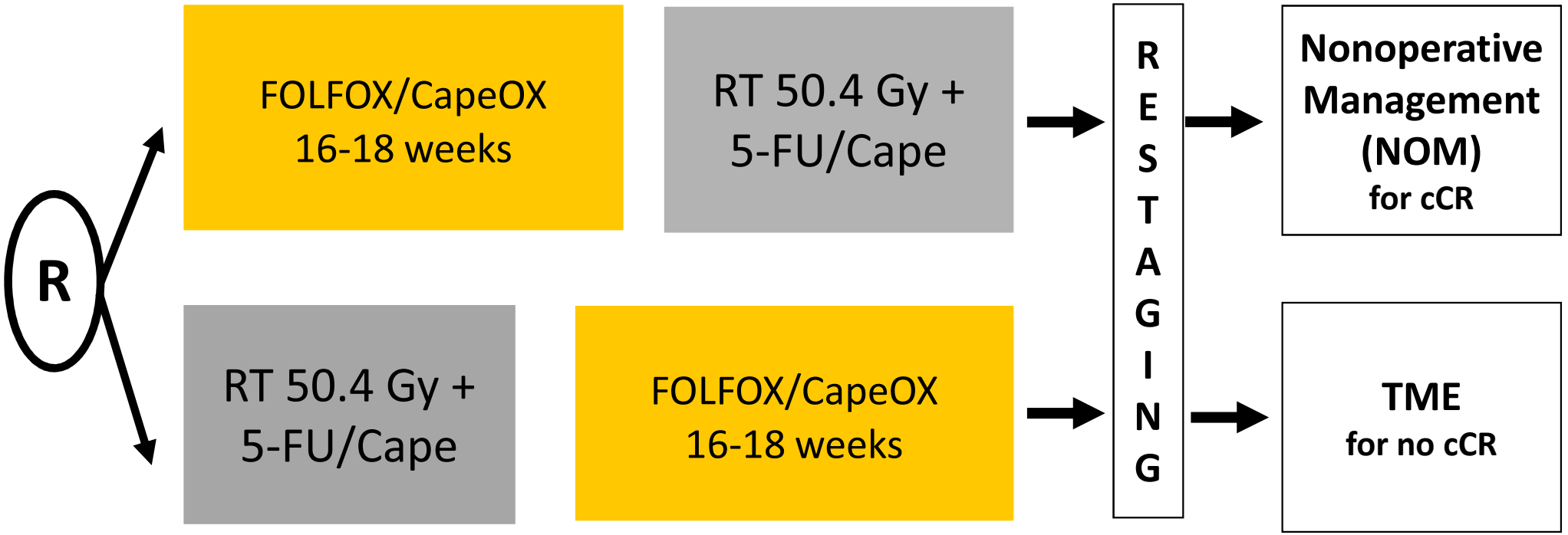
The TIMING Trial

cT3/4 or N+	G 1	G 2	G 3	G 4	p
Number of pts	60	67	67	65	
ypT0N0 (%)	18	25	30	38	.004
Pelvic Fibrosis (mean) (scale 1-10)	2.4	3.9	4.4	3.9	.0001
Surgical technical difficulty (scale 1-10)	4.5	4.9	5.1	4.8	.80

Garcia-Aquilar J et al, Lancet Oncol 2015

US - Rectal Cancer Consortium (randomized phase II)

MRI-defined T2-3 N0 or T_{any} N1,2



Primary endpoint: 3-year DFS

Conclusions (I)

What have we learned?

- ***Sequence RT, Chemo, S matters*** *(CAO/ARO/AIO-94)*
- ***Synergy RT – 5-FU Chemo*** *(FFCD 9303, EORTC 22921)*
- ***RT - optimized S complementary*** *(Dutch Trial, MRC CR07)*
- ***Interval between RT + S matters*** *(TIMING; Stockholm III)*
- ***Compliance RT + Chemo matters*** *(CAO/ARO/AIO-04)*

Conclusions (II)

What have we learned?

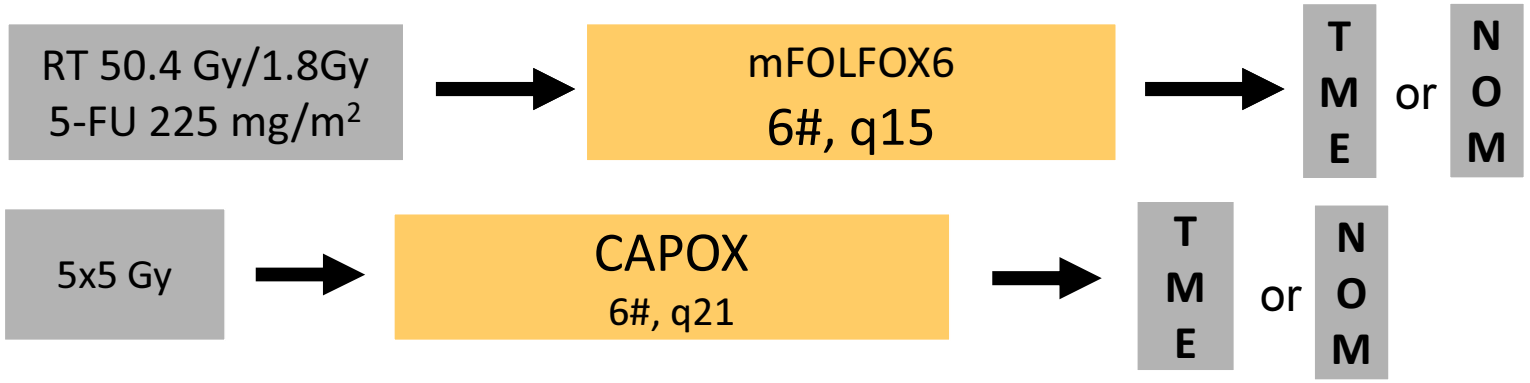
5x5 Gy + immediate S vs CRT + delayed S

- *Equally effective for SP, LC, OS, late tox (Polish, Trans-Tasman)*
- *Downsizing: CRT preferred for T4, MRF+, low RC (?)*
- *May be revised for SCRT and delayed S (Stockholm III, Polish II, RAPIDO)*

Conclusions (III)

Where do we go from here (with both concepts)?

- ***T**otal**N**eoadjuvant**T**reatment - **S** postponed/avoided*

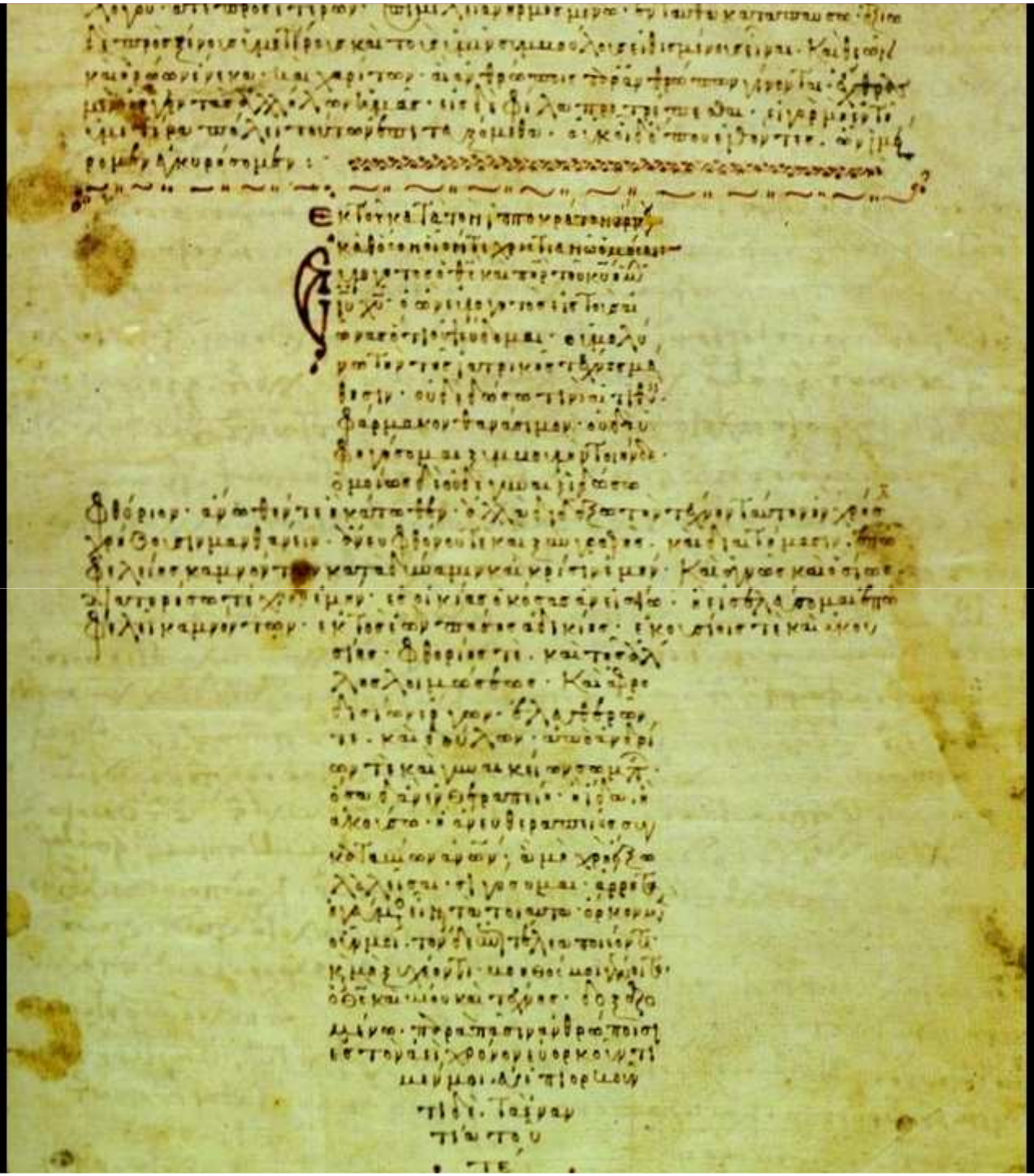


- ***Selection and monitoring by modern imaging!***

Current (European) Guidelines:
What is considered standard of care for concurrent and adjuvant chemotherapy ?

Rob Glynne-Jones
Mount Vernon Cancer Centre
on behalf of NCRI anal cancer subgroup

ESTRO School



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Rectal Cancer

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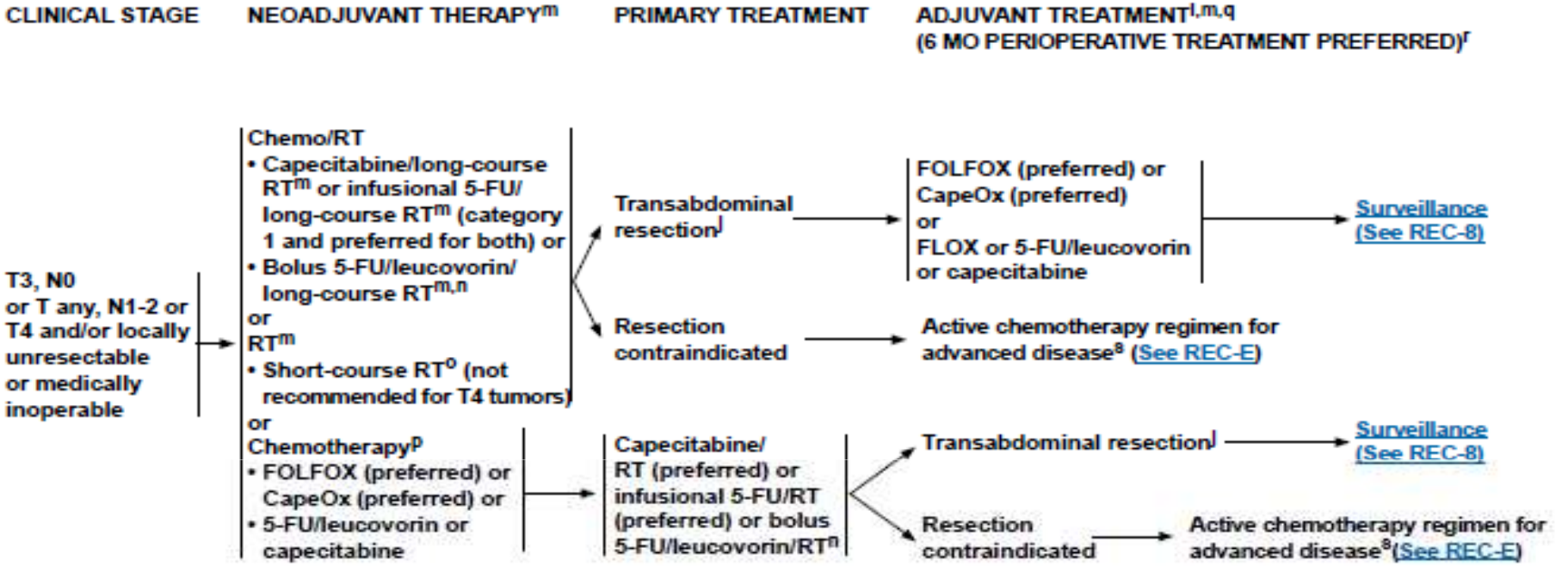

[j]See Principles of Surgery (REC-B).
[l]See Principles of Adjuvant Therapy (REC-C).
[m]See Principles of Radiation Therapy (REC-D).
[n]Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[o]Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for down-staging and the possibility of long-term toxicity.
[p]Fernandez-Martos C, Pericay C, Aparicio J, et al: Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010;28:859-865.

Cercek A, Goodman KA, Hajj C, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Canc Netw 2014;12:513-519.
[q]Postoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results.
[r]Total duration of perioperative chemotherapy, inclusive of chemotherapy and radiation therapy, should not exceed 6 months.
[s]FOLFOXIRI is not recommended in this setting.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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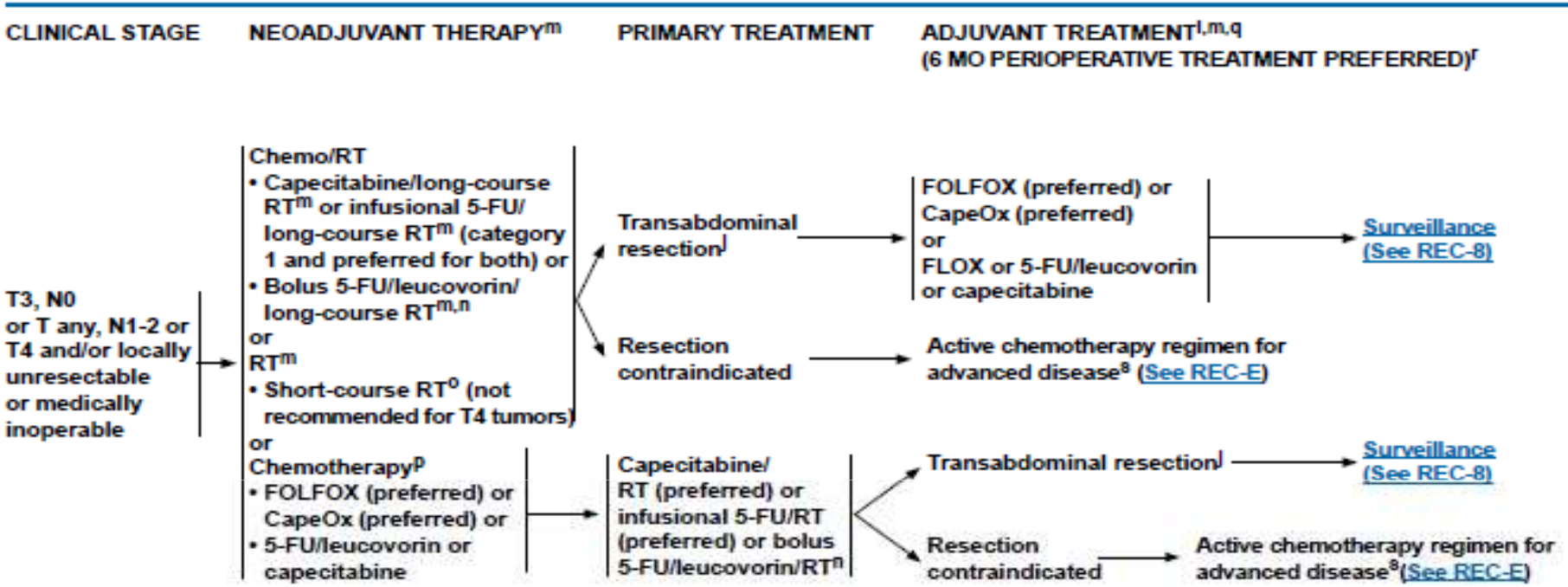

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School

Current ESMO Guidelines

- **Glimelius** B, Tiret E, Cervantes A, Arnold D; ESMO Guidelines Working Group.
- Ann Oncol. 2013 Oct;24 Suppl 6:vi81-8

Risk group	TN substage	Therapeutic options
Very early	*c*T1 sm1 (-2?) N0	Local excision (TEM). If poor prognostic signs (sm ≥ 2, high grade, V1), resection (TME) (or possibly CRT)
Early (good)	*c*T1-2; *c*T3a (b) if middle or high, N0 (or cN1 if high), mrf-, no EMVI	Surgery (TME) alone. If poor prognostic signs (crm+, N2) add postop CRT or CT[a]. (CRT with evaluation, if cCR, wait-and-see, organ preservation)
Intermediate (bad)	*c*T2 very low, *c*T3mrf- (unless cT3a(b) and mid- or high rectum, N1-2, EMVI+, limited *c*T4aN0	Preop RT (5 × 5 Gy) or CRT followed by TME. (if CRT and cCR, wait-and-see in high risk patients for surgery)
Advanced (ugly)	*c*T3mrf+, *c*T4a,b, lateral node+	Preop CRT followed by surgery (TME + more extended surgery if needed due to tumour overgrowth). 5 × 5 Gy with a delay to surgery in elderly or in patients with severe comorbidity who cannot tolerate CRT

- To my mind muddied by watch and wait

Guidelines for Postoperative adjuvant chemotherapy

Poulsen et al Acta Oncol 2015

Table I. International and national guidelines on postoperative adjuvant chemotherapy for rectal cancer.

	ESMO	NCCN	Norway	Sweden	Finland	Denmark	Spain	Dutch	NICE
Year	2013 [22,23]	2012 [2]	2013 [24]	2014 [25]	2009 [26]	2013 [27]	2013 [28]	2014 [29]	2011 [30]
RC High-risk stage II	FU/5FU	5FU/Ox#	No	5FU	5FU-Ox§	5FU(+ Ox)	Yes*	No	Yes
RC stage III	FU/5FU	5FU/Ox	No	5FU(+ Ox)	5FU-Ox	5FU(+ Ox)	Yes*	No	Yes
After preop. CRT**	n.s.	Yes	No	No	n.s.	Yes	No	No	n.s.

ONLY ESMO GUIDELINES state level of evidence supporting the recommendations

ESTRO School

The European Society for Medical Oncology rectal cancer guidelines 2013 state

"Standard preoperative chemoradiotherapy means a dose of 45-50.4 Gy, 1.8 Gy/fraction, or alternatively 50 Gy, 2 Gy/fraction together with a fluoropyrimidine"

Evidence base for the 2 Options for radiotherapy in locally advanced rectal cancer

- **Preoperative long course chemoradiotherapy CRT (25-28 X 1.8Gy Gy)**

- **(Post-op CRT as adjuvant)**

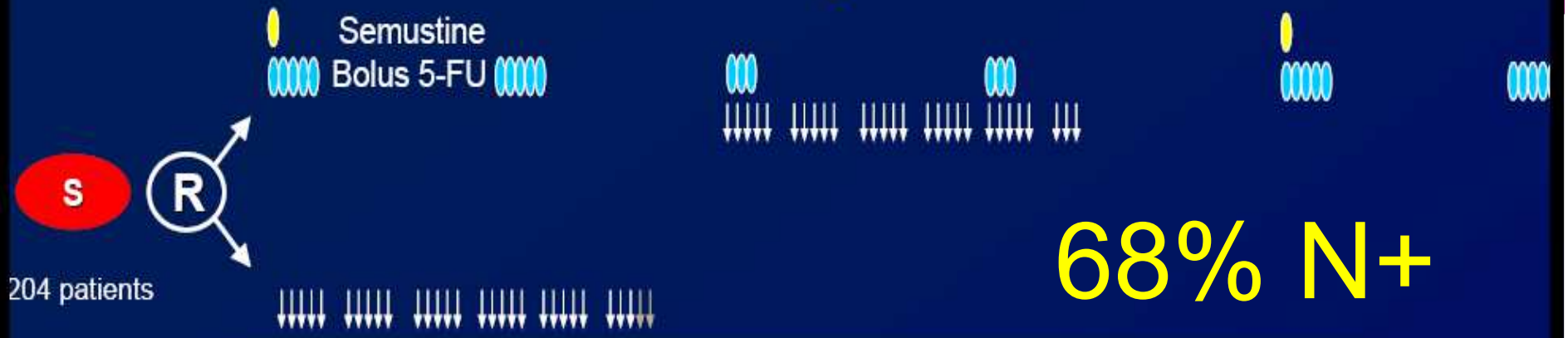
Postoperative Trials : Rectal Cancer

Randomised Trials of post-op CRT

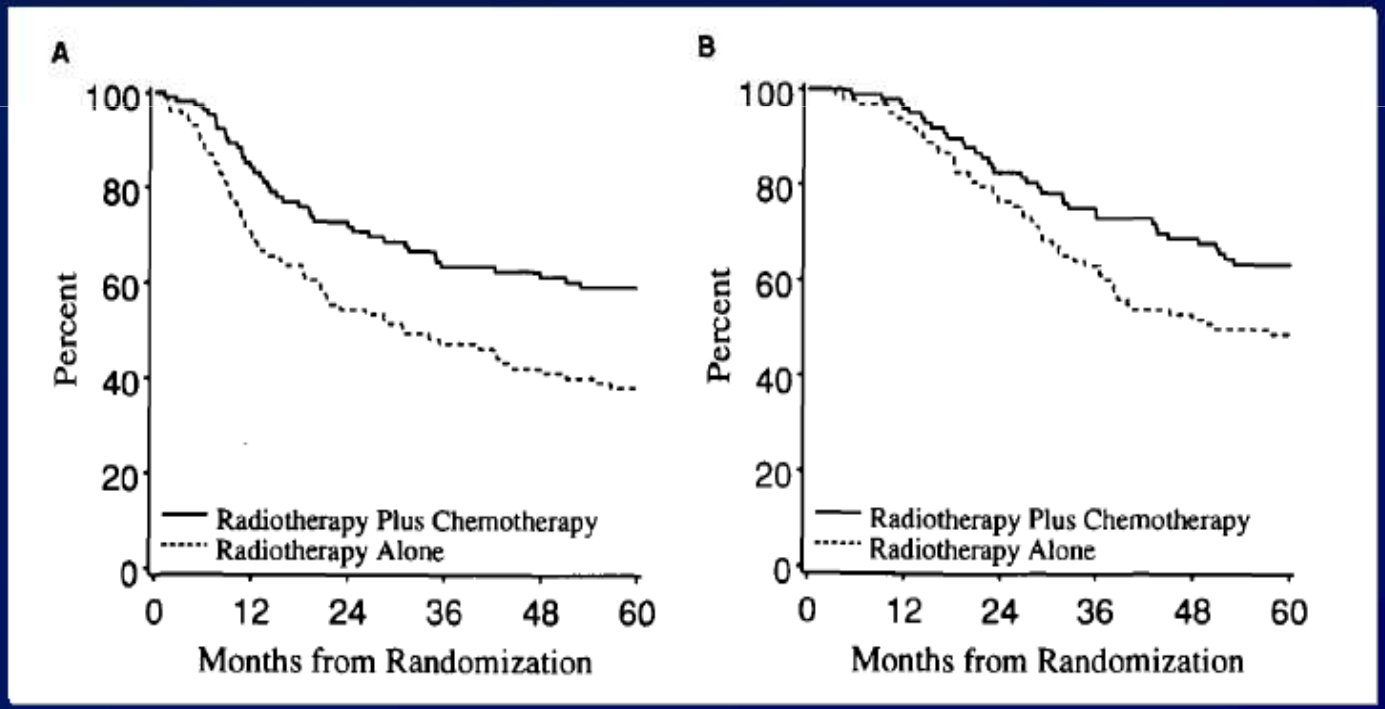
- GITSG
- NCCTG (Krook et al 1991)
- NSABP R02
- Intergroup (Infusional 5FU)

Further Intergroup studies

NCCTG/Mayo 794751



68% N+

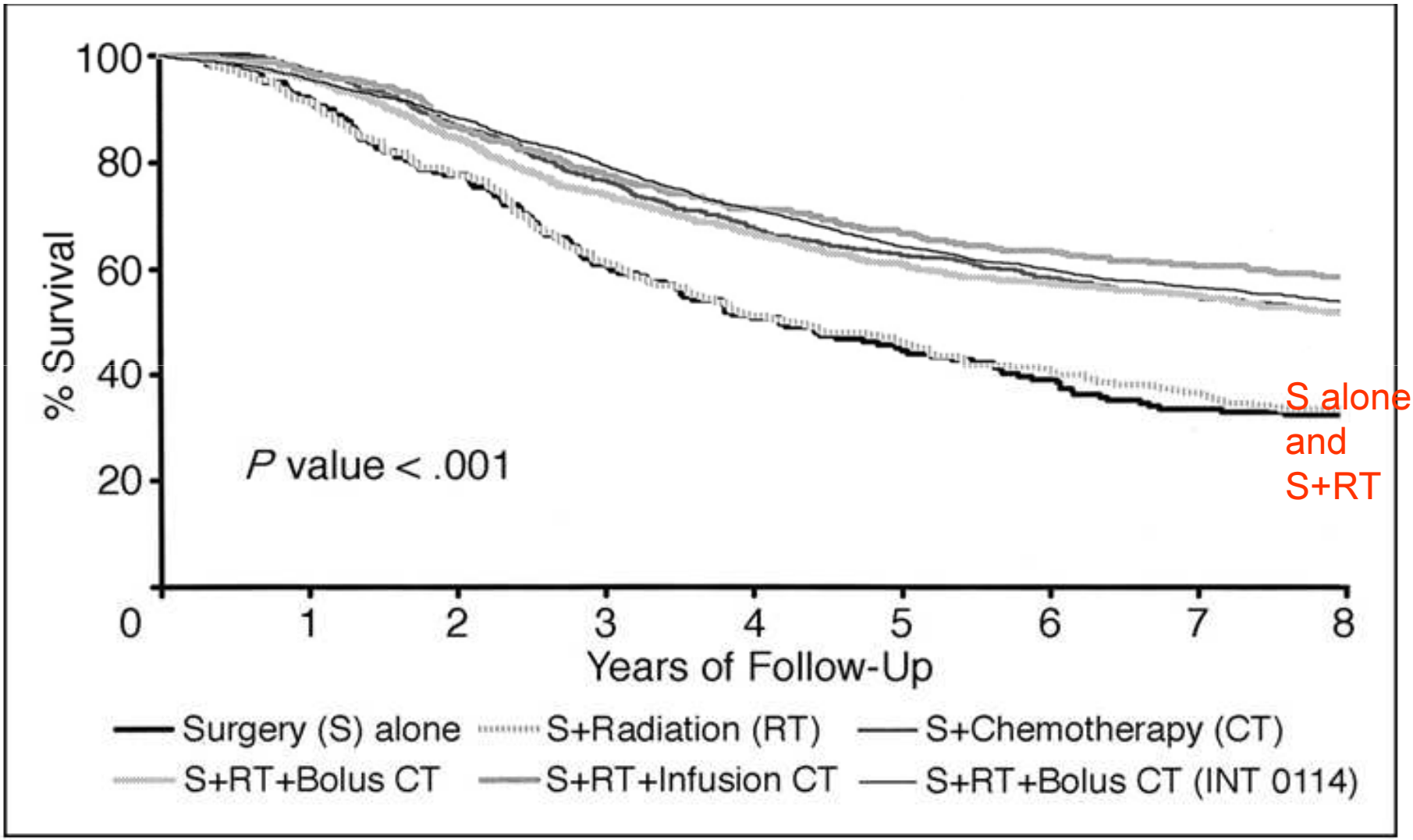


Disease-free survival

Overall survival

Krook et al. N Eng J Me 1991

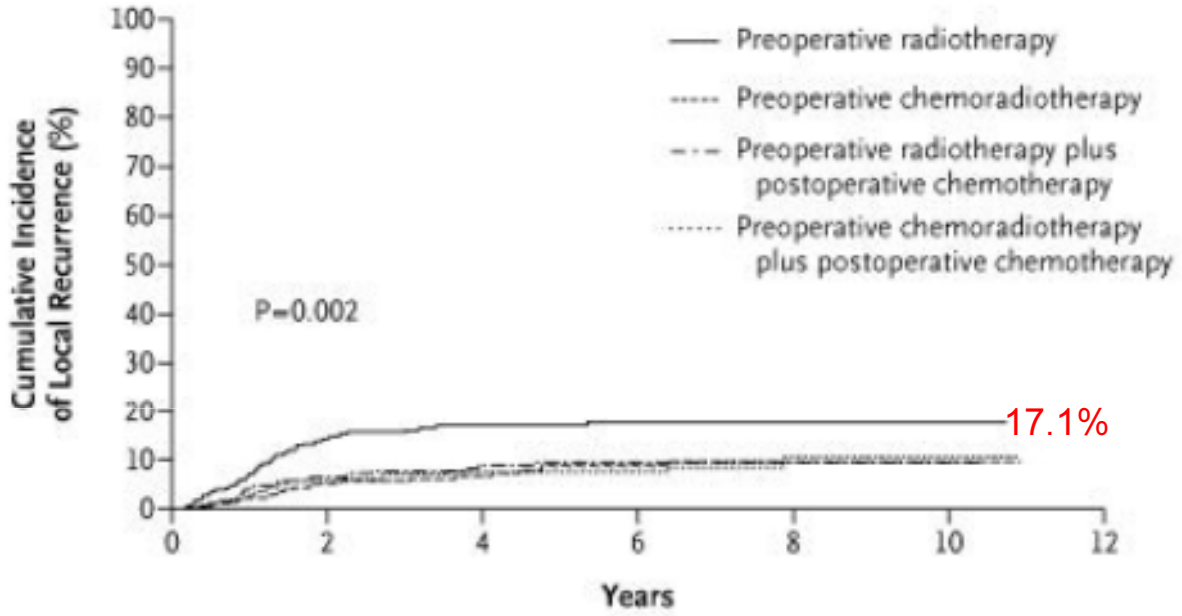
Impact on overall survival of 6 methods of treatment in rectal cancer pooled analysis



Gunderson, L. L. et al. J Clin Oncol; 22:1785-1796 2004

EORTC 22921 Trial

Local recurrence as a first event at 5 years was **17.1%** in the preoperative-radiotherapy group vs 8.7%, 9.6% and 7.6% in the group receiving preoperative chemoradiotherapy and postoperative chemotherapy.



No. at Risk						
Preoperative radiotherapy	252	147	87	60	24	6
Preoperative chemoradiotherapy	253	165	99	52	22	5
Preoperative radiotherapy plus postoperative chemotherapy	253	156	103	65	29	6
Preoperative chemoradiotherapy plus postoperative chemotherapy	253	159	113	59	20	3

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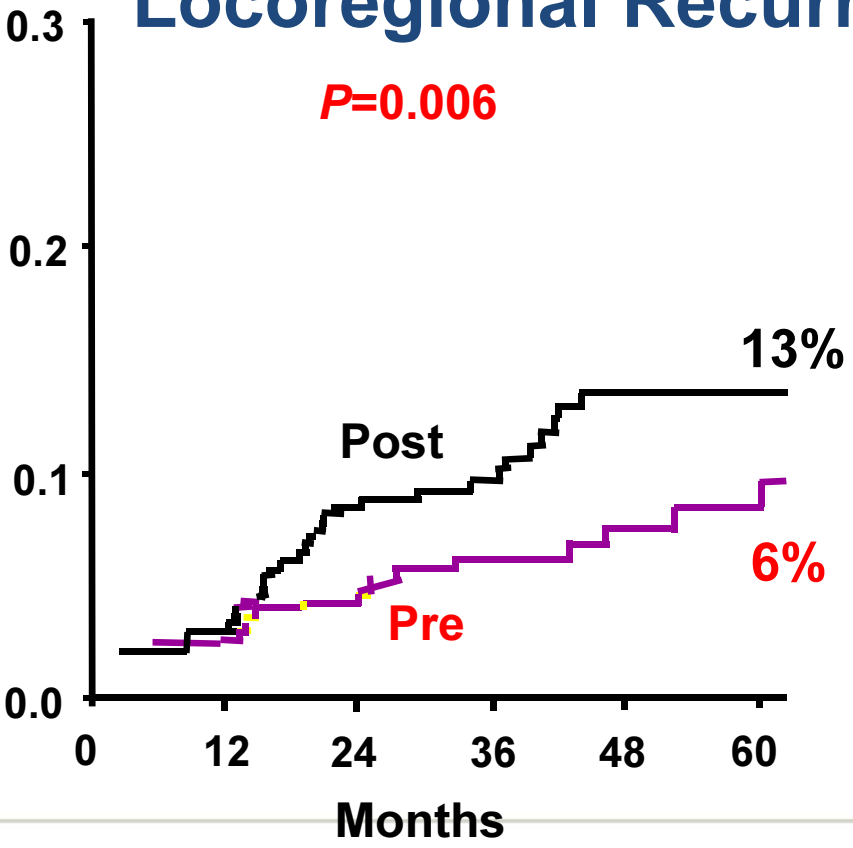
So you need chemotherapy in there somewhere!

(but I will come back to this)

Pre- vs post-operative chemoradiation CAO/ARO/AIO-94

Locoregional Recurrences

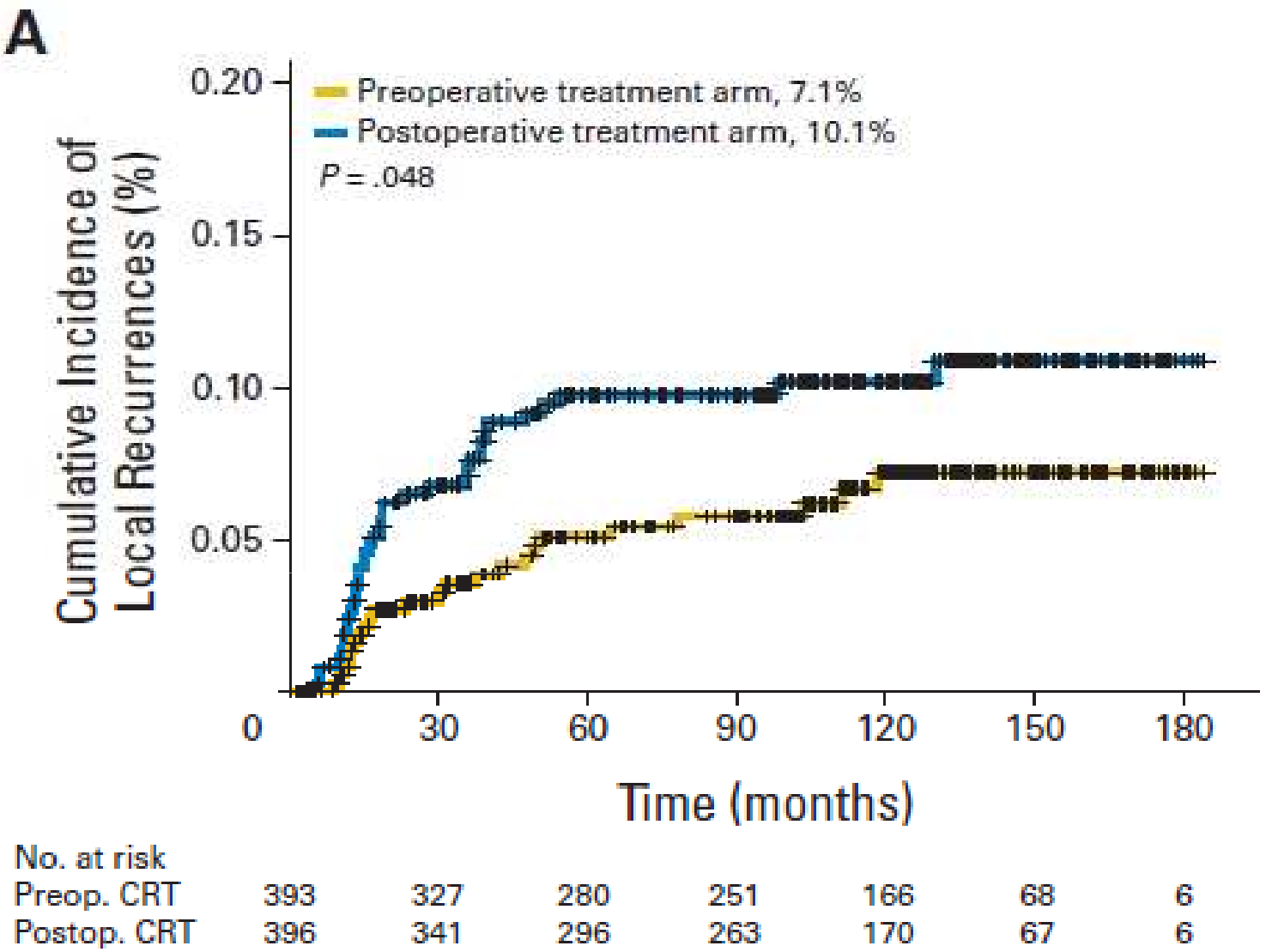


Acute G3/4 adverse events
27% vs 40% (p=0.001)

Long-term G3/4 adverse events
14% vs 24% (p=0.01)

There is a standard for chemoradiation

Sauer R. et al., N Engl J Med 2004;351: 1731-39



Long-term data on LOC REC from German study – 5/22 local recurrences ie 23% after 5 years (not like CR07)

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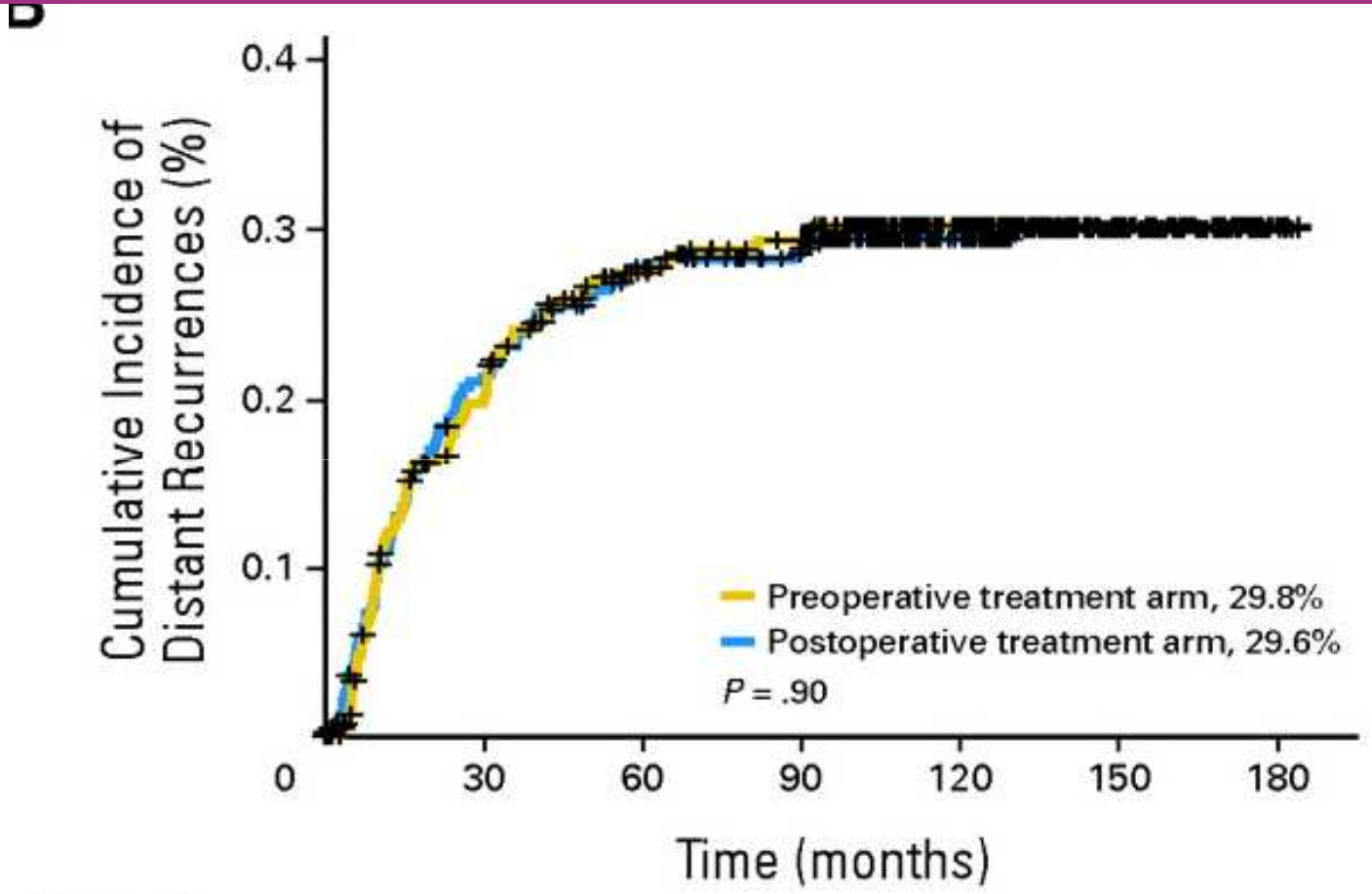
Pre- vs post-operative chemoradiation CAO/ARO/AIO-94



No. at risk							
Preop. CRT	393	295	262	241	158	60	5
Postop. CRT	396	310	267	246	162	63	6

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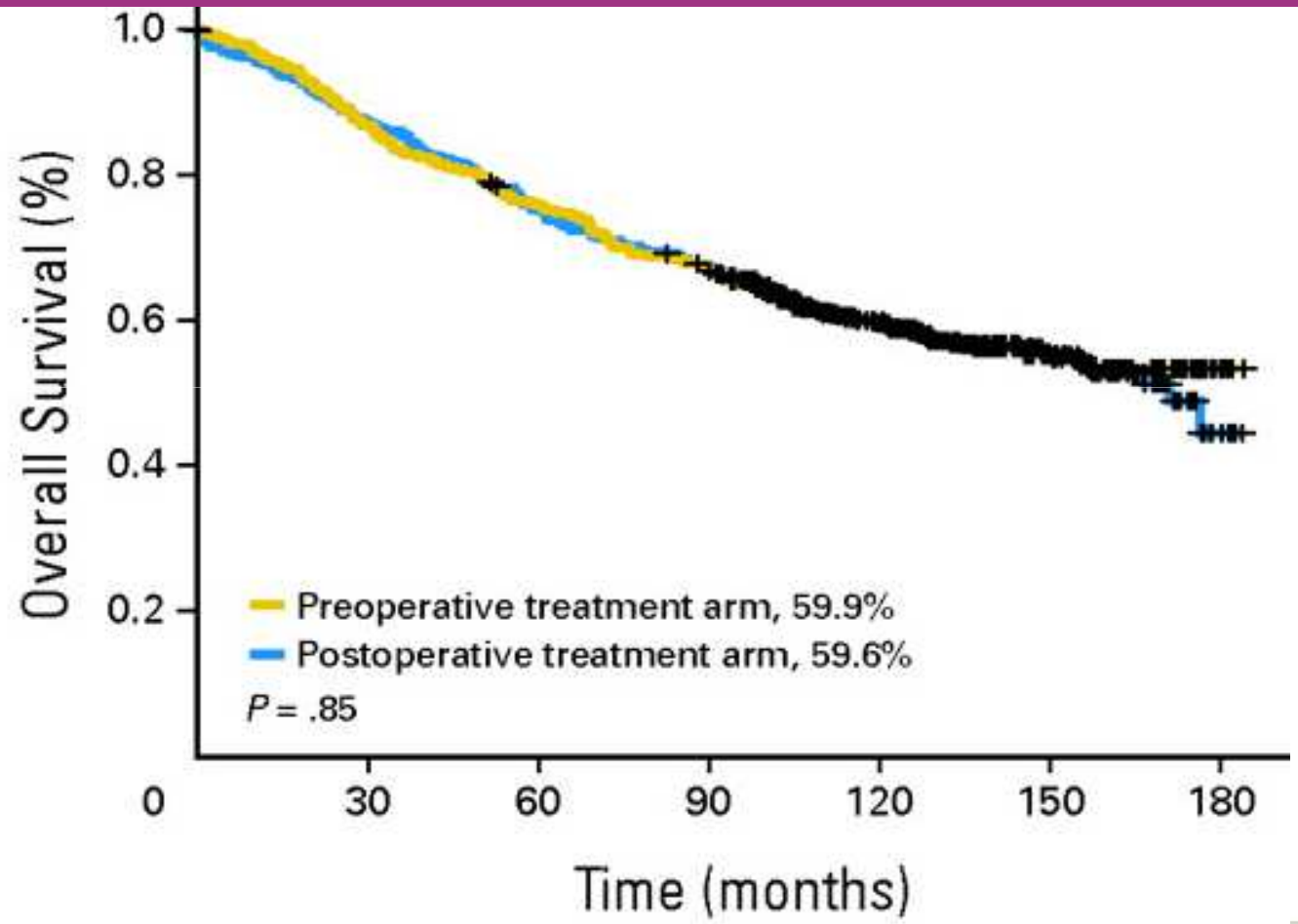
Pre- vs post-operative chemoradiation CAO/ARO/AIO-94



No. at risk							
Preop. CRT	404	351	305	268	174	67	6
Postop. CRT	395	342	295	262	172	70	6

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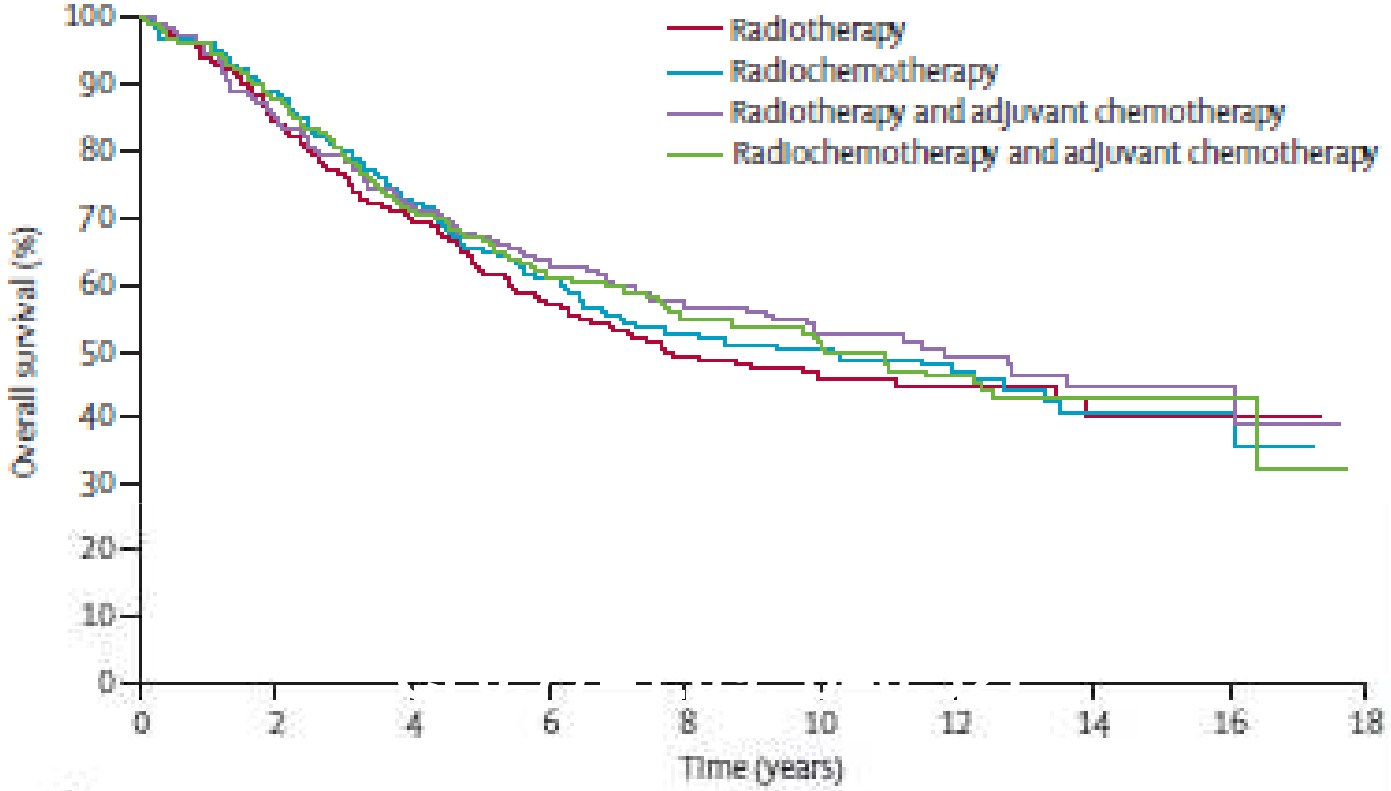
EORTC 22921 – Overall Survival



Number at risk									
Radiotherapy	252	208	165	129	98	62	32	15	5
Radiochemotherapy	253	223	173	135	96	66	41	19	9
Radiotherapy and adjuvant chemotherapy	253	212	171	140	102	69	42	18	8
Radiochemotherapy and adjuvant chemotherapy	253	221	174	143	108	77	44	18	4

So why have post-op CRT studies shown an improvement in survival

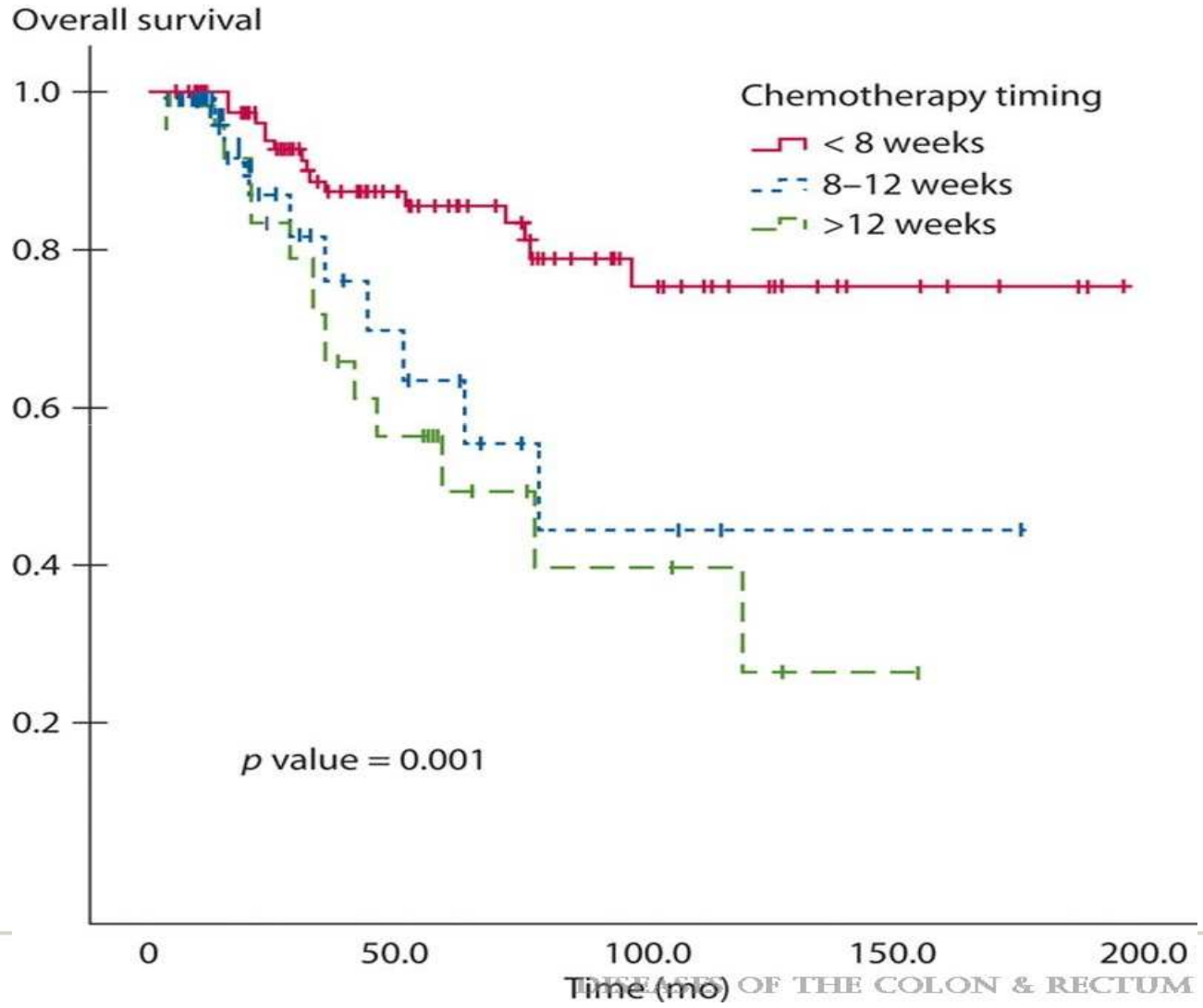
whereas preop CRT has not?

Suggests that in the trials

50-60% cN0

Compliance to postoperative adjuvant chemotherapy approx 50%

Timing of start of Adjuvant Postoperative Chemotherapy:

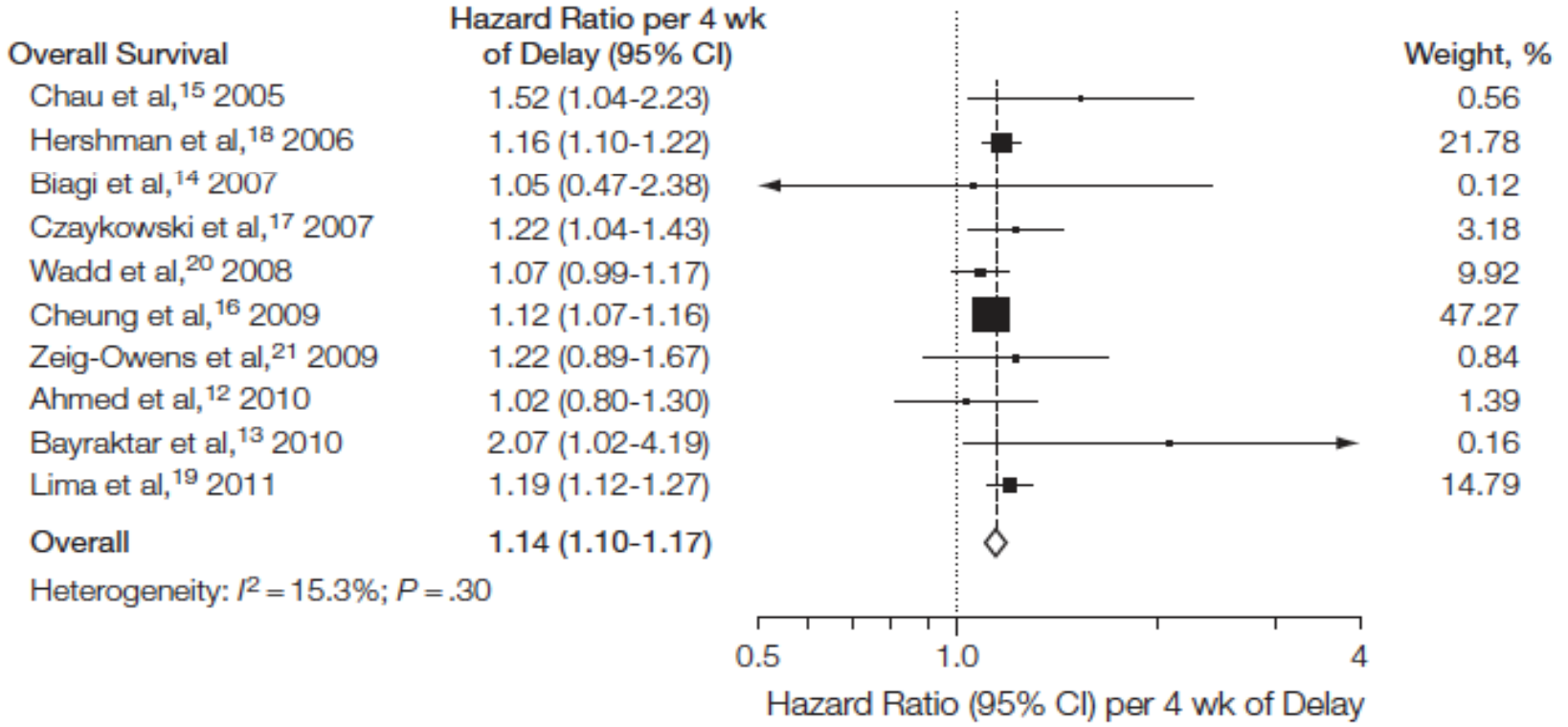


Tevis et al, DCR 2013

Association Between Time to Initiation of Adjuvant Chemotherapy and Survival in Colorectal Cancer

A Systematic Review and Meta-analysis

Increase in interval to start Adjuvant Chemotherapy
was associated with a **decrease in overall survival**



Biagi JJ et al., JAMA 2011 Jun 8;305(22):2335-42

Champalimaud Foundation

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So - What about?

- Oxaliplatin
- Irinotecan
- Biologicals

So what have the trials shown us?

All 5 Oxaliplatain trials used low dose oxaliplatin as a radiosensitizer with CRT

2 trials mandated oxaliplatin also as postoperative adjuvant (so if benefit which component?)

Some of the 5 trials did not mandate TME (NB the German trial did)

Phase III trials – Investigating

Trial	Eligibility	Fluoropyrimidine Platform
CAO/ARO/AIO-04	<12cm from anal verge T3/T4 cN0/N+ TRUS, CT and/or MRI	5FU 1000mg/2 X 5 days 1-5 + 29-33
NSABP R04 N=1606	<12cm; resectable stage II, III TRUS or MRI – CT if T4/ N1-2	PVI 5FU vs Capecitabine
FFCD N=598	Palpable; resectable; T3/4 N0-2; T2 distal anterior	Capecitabine in both arms
STAR – 01 N=747	Resectable stage II, III (c stage) <12cm from anal verge	PVI 5FU in both arms
PETTAC 6 N=1090	Stage II or III resectable or expected to become resectable <12cm from anal verge	Capecitabine in both arms

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Phase III: CAO/ARO/AIO-04

Best arm of CAO/ARO/AIO-94:

RT 50.4 Gy + 5-FU
1000 mg/m² days 1-5 + 29-33
623 patients

From Phase I/II Studies:

RT 50.4 Gy + 5-FU/OX
Ox: 50 mg/m² d 1, 8, 22, 29
5-FU: 250 mg/m² d 1-14 + 22-35

Note: Chemo gap 3rd week of RT !

613 patients

T

M

E

5-FU
500 mg/m² d 1-5, q29
4 cycles (4 months)

mFOLFOX6
Oxaliplatin: 100 mg/m² d1,q15
Folinic Acid: 400 mg/m² d1
5-FU: 2400 mg/m² d1-2
8 cycles (4 months)

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Endpoint	STAR-01	ACCORD 12/0405	CAO/ARO/ AIO-04	NSABP R-04	PETACC-6
PCR	16% both arms	14% vs 19%	12.8% vs 16.5% (p=0.038)	19% vs 21%	11.5% vs 13%
CRM	4% vs 7%	8% vs 13%	5% vs 6%	No data	2% vs 2%

Oxaliplatin Phase III trials: Control arm in red

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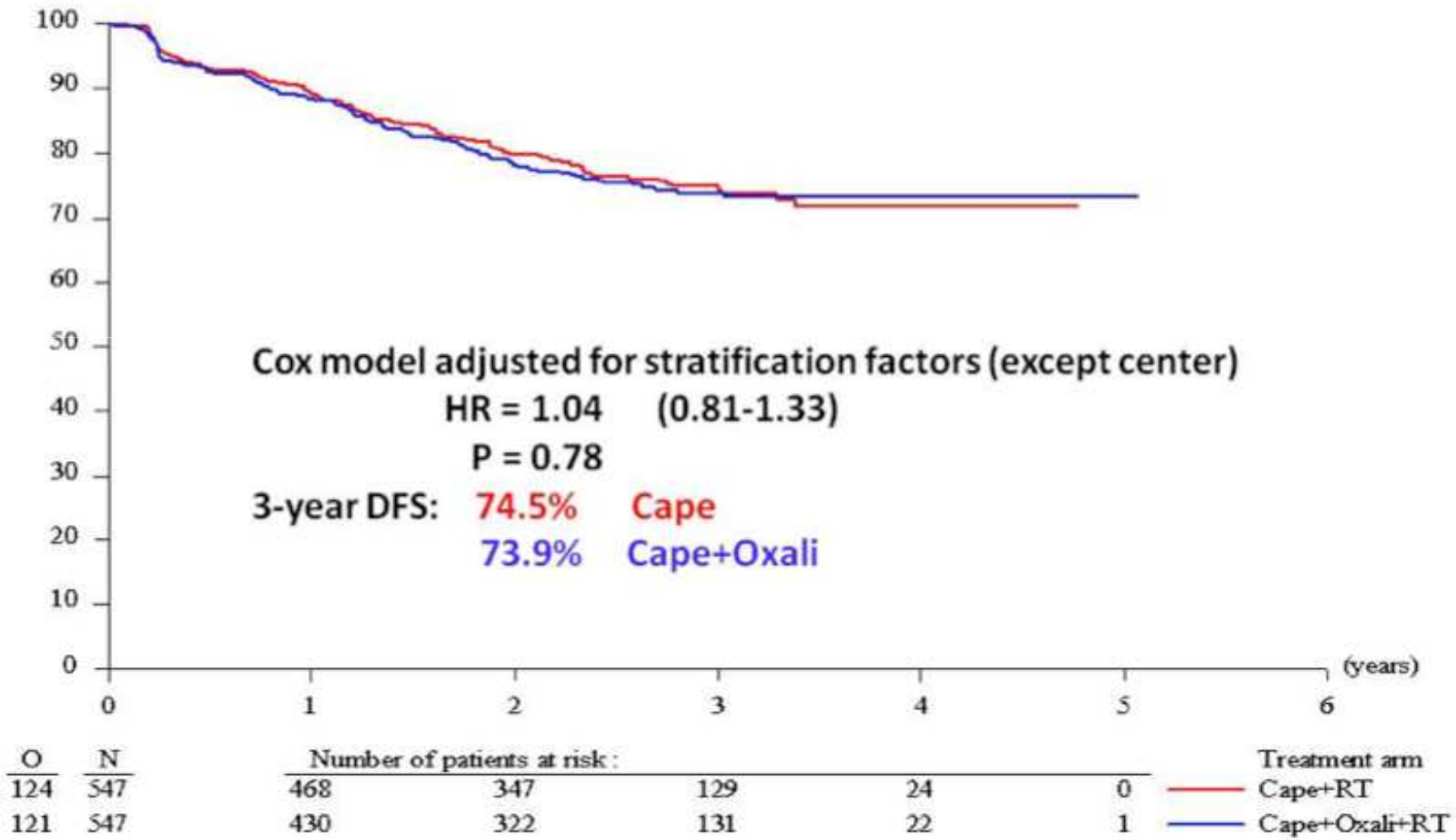
PETACC-6



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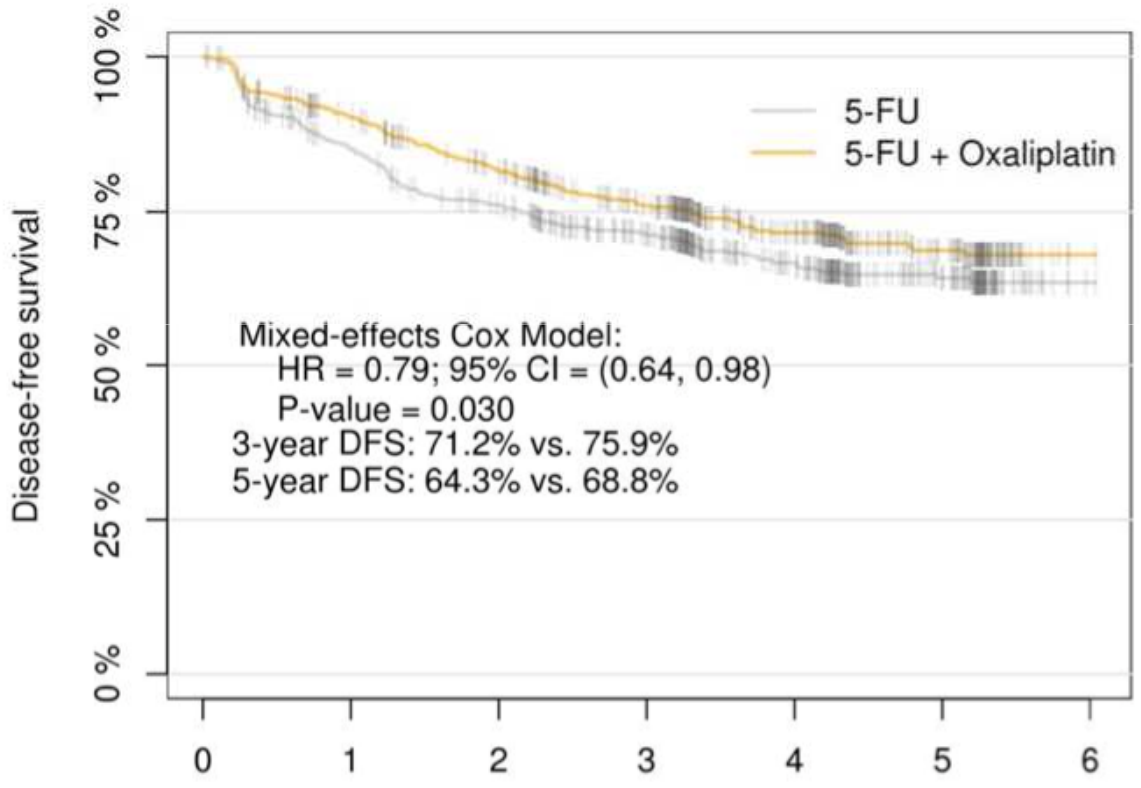
CAO/ARO/AIO-04 Trial



N at risk							
5-FU	623	509	441	363	233	114	1
5-FU/OX	613	522	447	364	230	110	1

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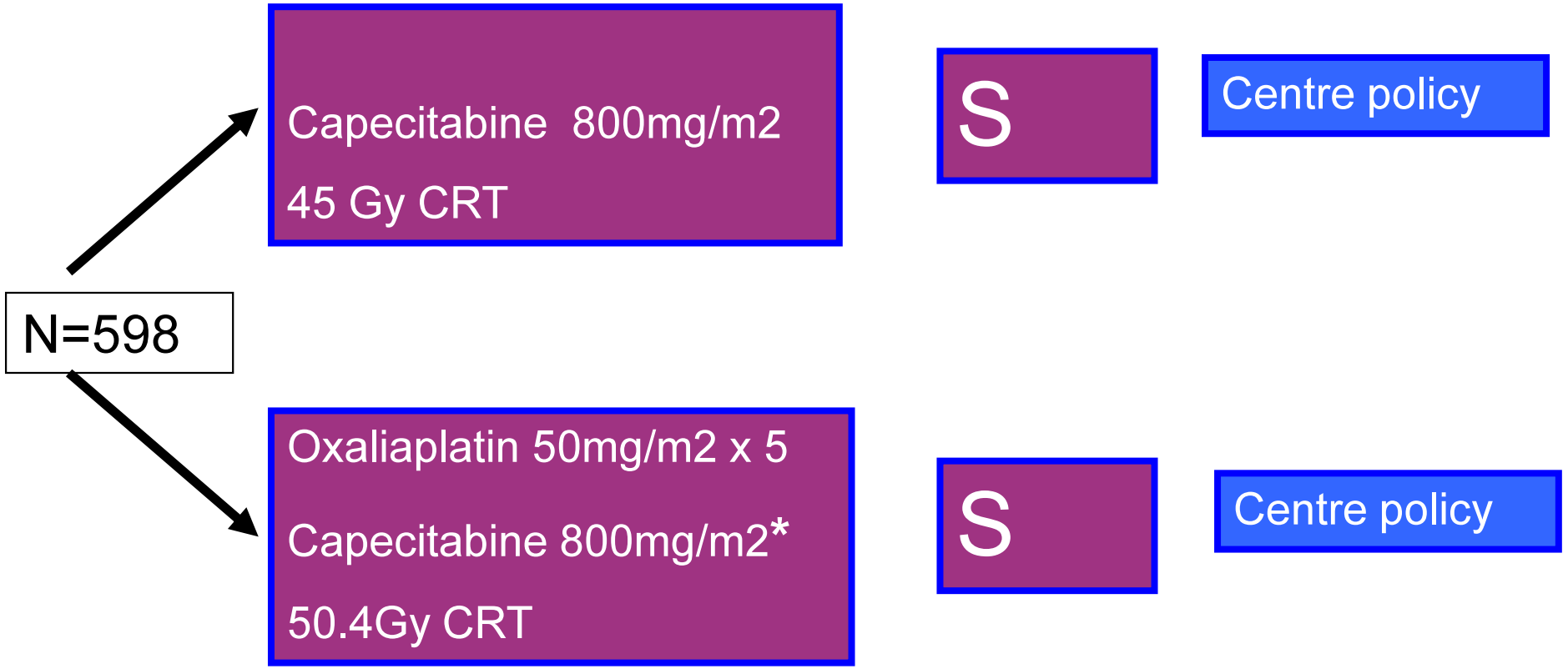
Prodige/ACCORD 12/0450 trial

Staging :- Evaluated by TRUS and/or MRI



Primary end point- pCR 11% - 20% 85% power

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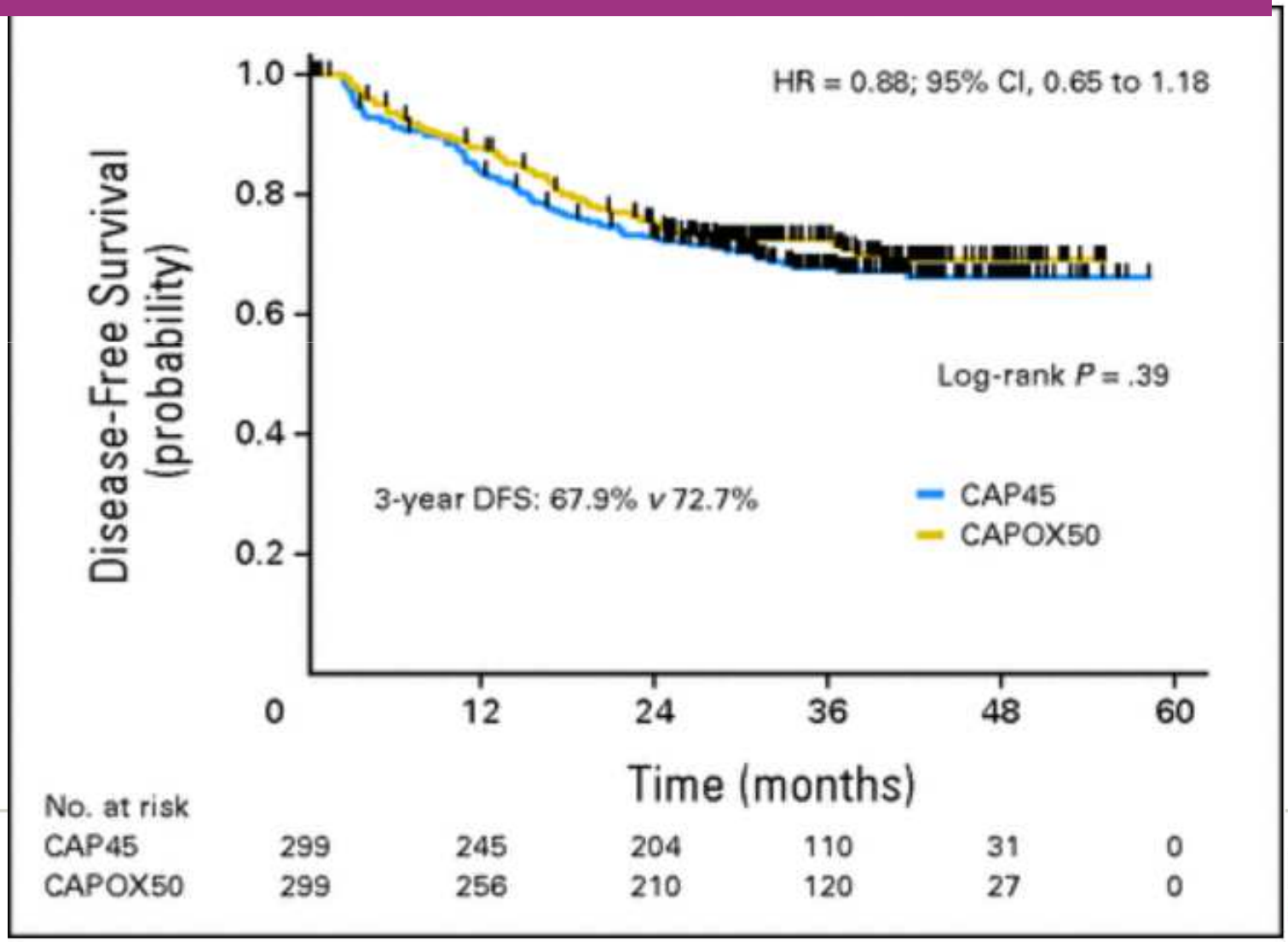
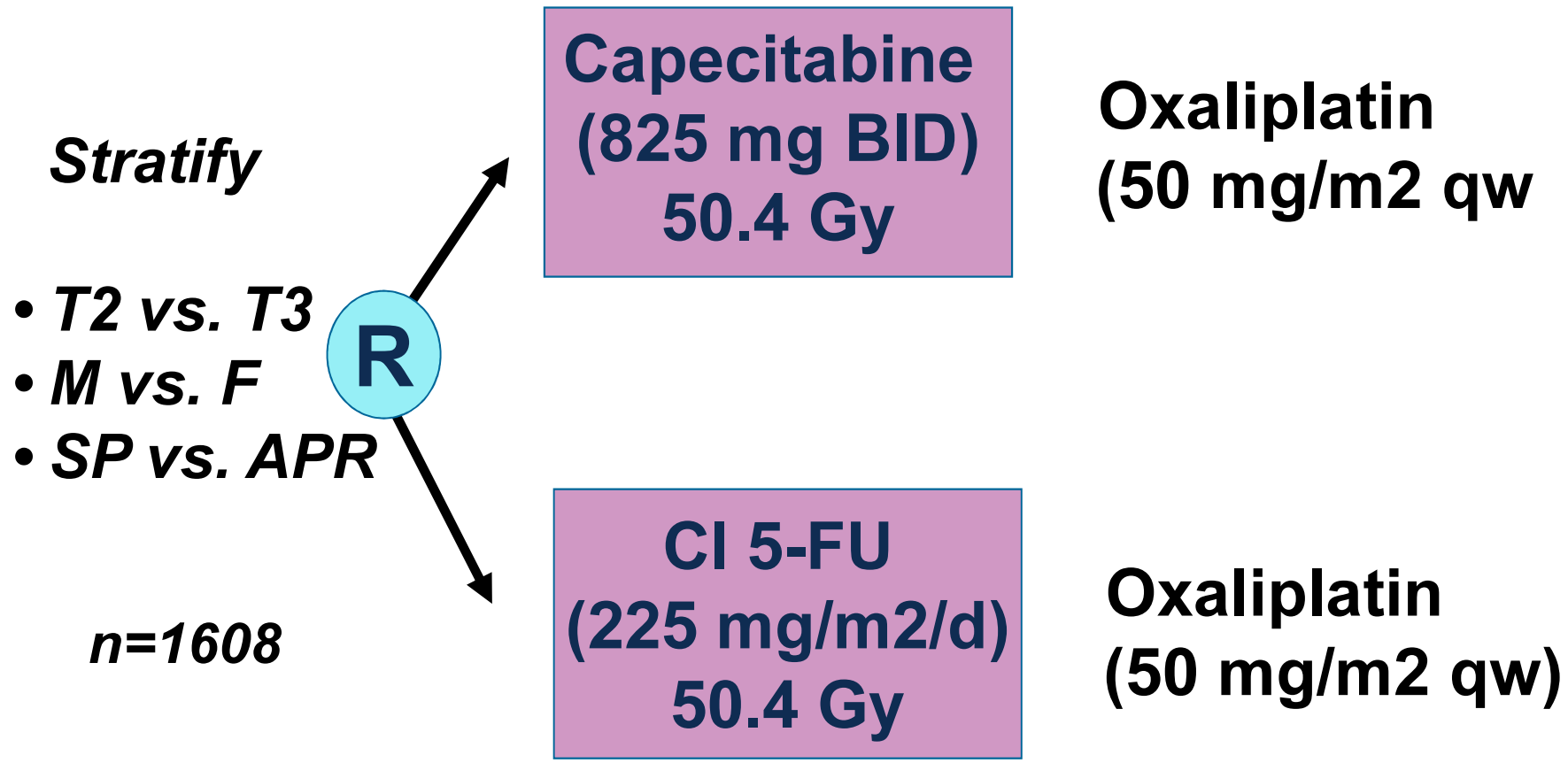
DFS: ACCORD 12/0405 PRODIGE 2



"50Gy and capecitabine is a new standard"

5-FU = Cape in Pre-op Rectal Cancer: NSABP R-04



NSABP R-04, Allegra et al; ASCO GI

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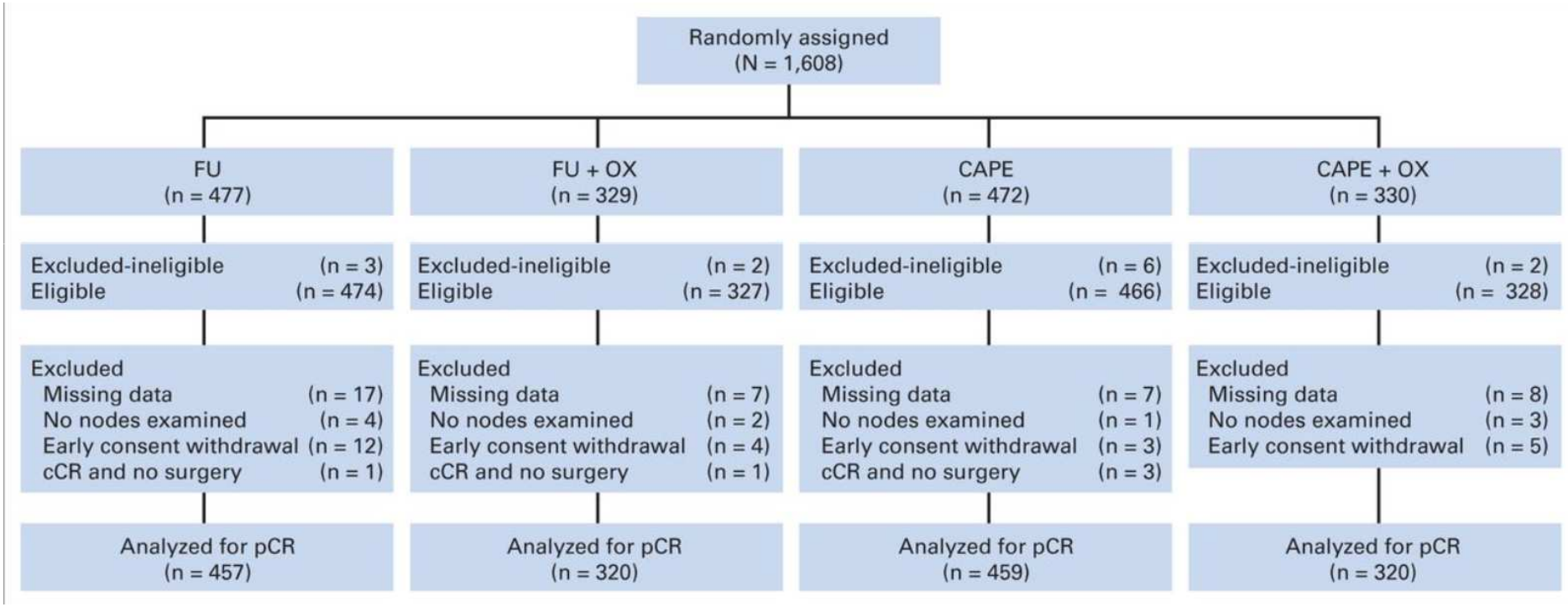
NSABP R-04



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NSABP R-04 establishes capecitabine as standard of care

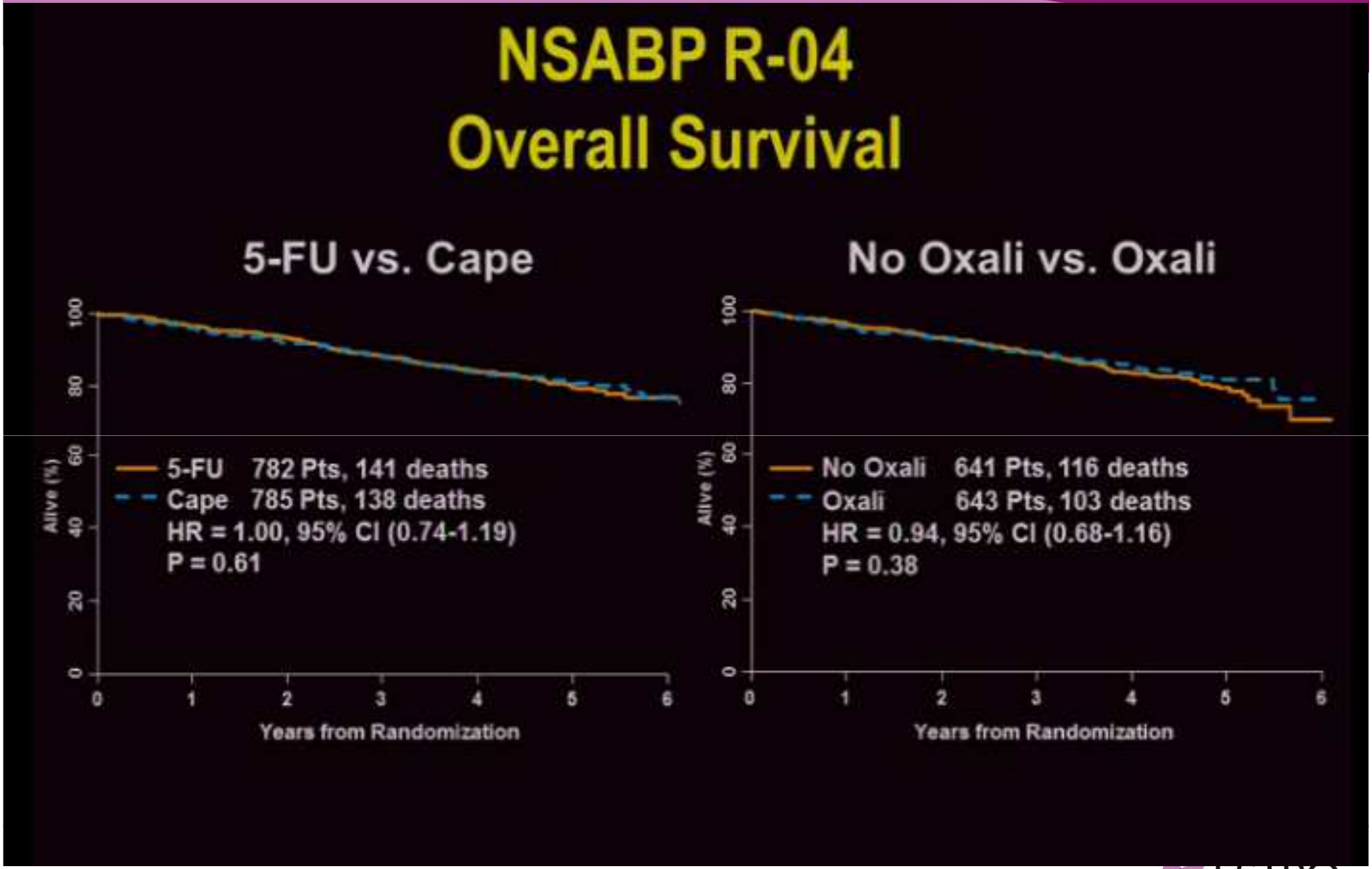
5-FU vs capecitabine

3-year local-regional tumour event rates (11.2% vs 11.8%),

5-year DFS (66.4% vs 67.7%)

5-year OS (79.9% vs 80.8%);

NSABP R-04
Overall Survival



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So what about postoperative adjuvant chemotherapy after Chemoradiation?

clinical practice guidelines

Annals of Oncology 24 (Supplement 6): vi81–vi88, 2013
doi:10.1093/annonc/mdt240

Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

B. Glimelius[1], E. Tiret[2], A. Cervantes[3] & D. Arnold[4], on behalf of the ESMO Guidelines Working Group*

[1]Dept of Radiology, Oncology and Radiation Science, Akademiska sjukhuset, Uppsala University, SE-751 85 Uppsala, Sweden; [2]2AP-HP, Hôpital Saint-Antoine, Pierre et Marie Curie University, Paris 6, France; [3]Department of Hematology and Medical Oncology, INCLIVA, University of Valencia, Valencia, Spain; [4]Klinik fuer Tumorbiologie, Freiburg, Freiburg, Germany

These Clinical Practice Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO)

" As in colon cancer stage III (and 'high-risk' stage II), adjuvant chemotherapy can be given, even if the level of scientific evidence for sufficient benefit is much lower than in colon cancer [33, 34, 35] [II, B]."

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Adjuvant chemotherapy in Colon Cancer

Good evidence for fluoropurimidines

Definite Benefit in Stage III (stage II QUASAR)

Good evidence for **Oxaliplatin** stage III

?Small benefit for 5FU in stage II

? Benefit Stage II for oxaliplatin

? Benefit over 70 years

Meta-analysis - reduction in risk of disease recurrence (25%) with adjuvant chemotherapy compared to observation (**HR=0.75,** CI: 0.68-0.83).

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Postoperative adjuvant chemotherapy in rectal cancer operated for cure.

Sune Høirup Petersen[1,*], Henrik Harling[2], Lene Tschemerinsky Kirkeby[3], Peer Wille-Jørgensen[4], Simone Mocellin[5]

Database Title

The Cochrane Library

Editorial Group: Cochrane Colorectal Cancer Group

Published Online: 14 MAR 2012

Assessed as up-to-date: 31 JAN 2012

DOI: 10.1002/14651858.CD004078.pub2

Only 1/21 trials received preoperative CRT

Only 2/21 received SCPRT

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Evidence in order of strength

Specific randomised trials (Quasar, EORTC 22921, Sainato, SCRIPT, Chronicle, ADORE)

Composite trials (PETACC-6 and German trial)

Individual patient Meta-analyses (often selected – some used retrospective data)

Pooled analyses

Systematic reviews

Nomograms based on randomised trials -Valentini

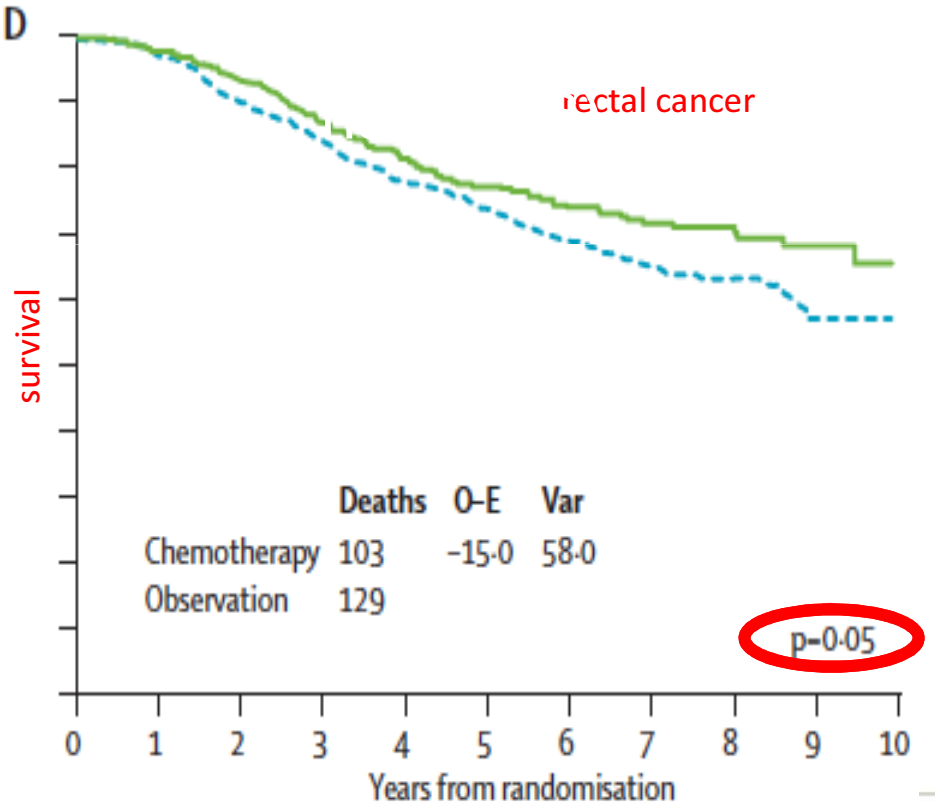
SCPRT 5x5Gy in Red

Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study

QUASAR Collaborative Group*

Colon 71% / **Rectal 29%**
Stage II 91% / Stage III 8%

	Chemotherapy (n=1622)	Observation (n=1617)
Stage		
I	8 (0·5%)	8 (0·5%)
II	1483 (91%)	1480 (92%)
III	131 (8%)	129 (8%)
Site		
Colon	1148 (71%)	1143 (71%)
Rectum (or both)	474 (29%)	474 (29%)



Lancet 2007; 370: 2020–29

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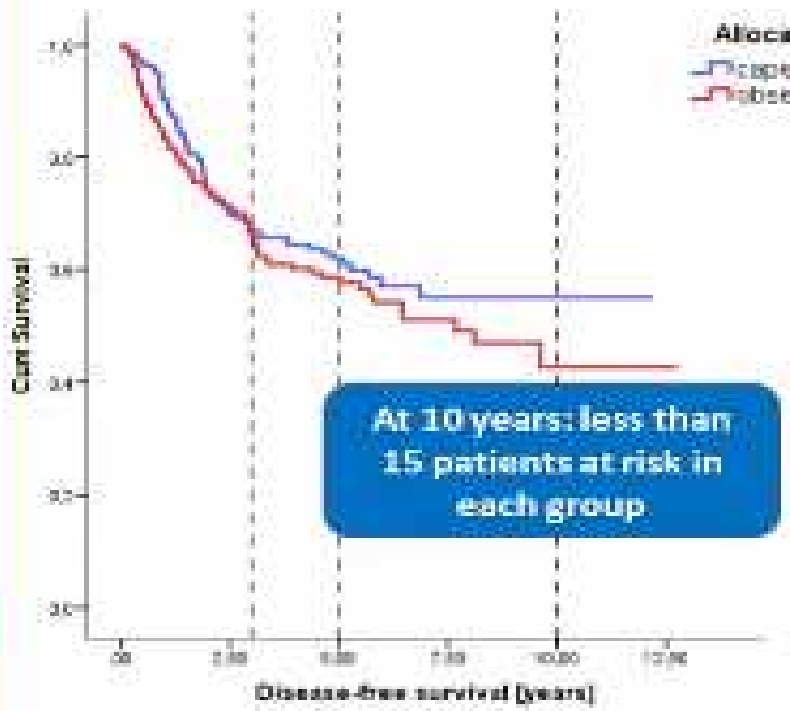
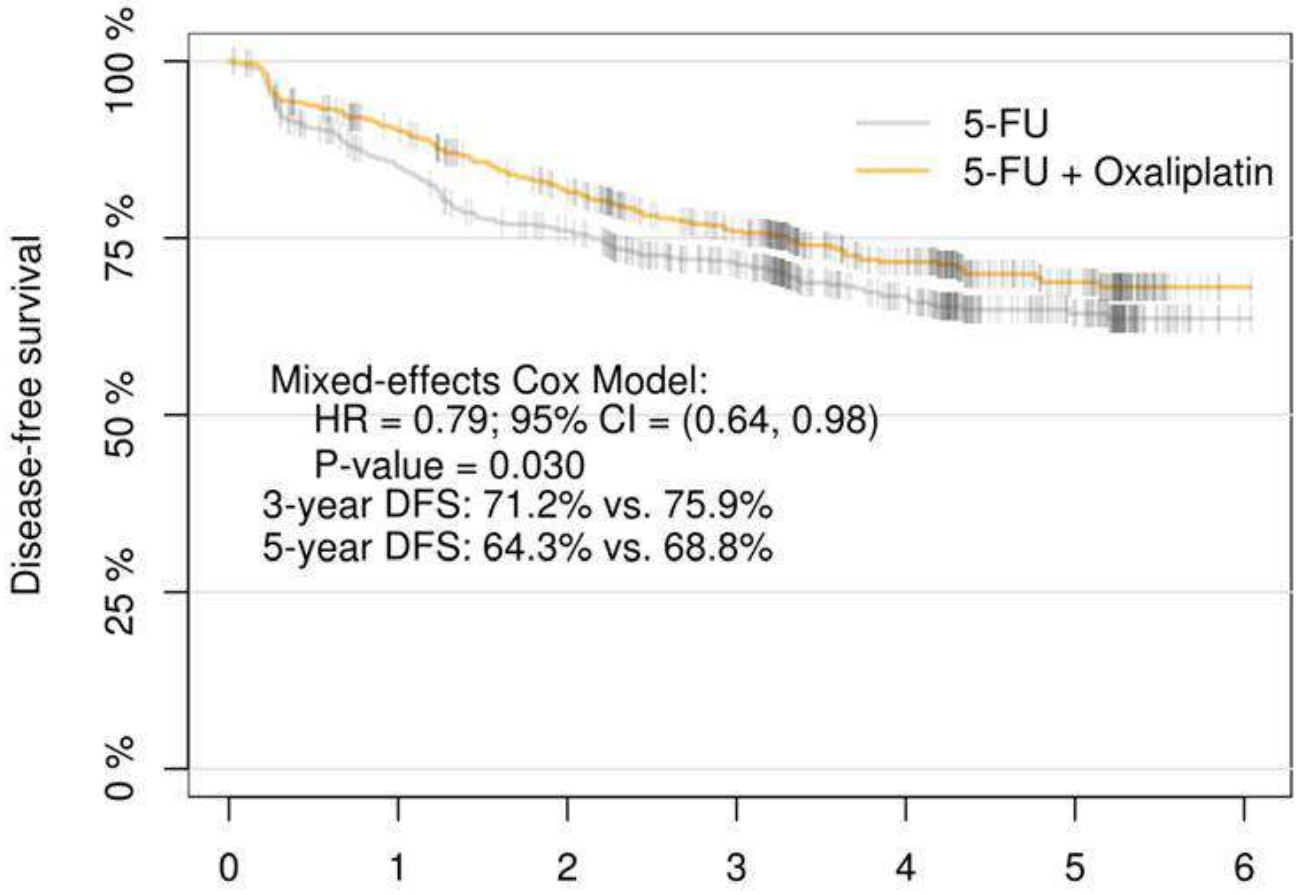
SCRIPT study

Results - Disease-free Survival



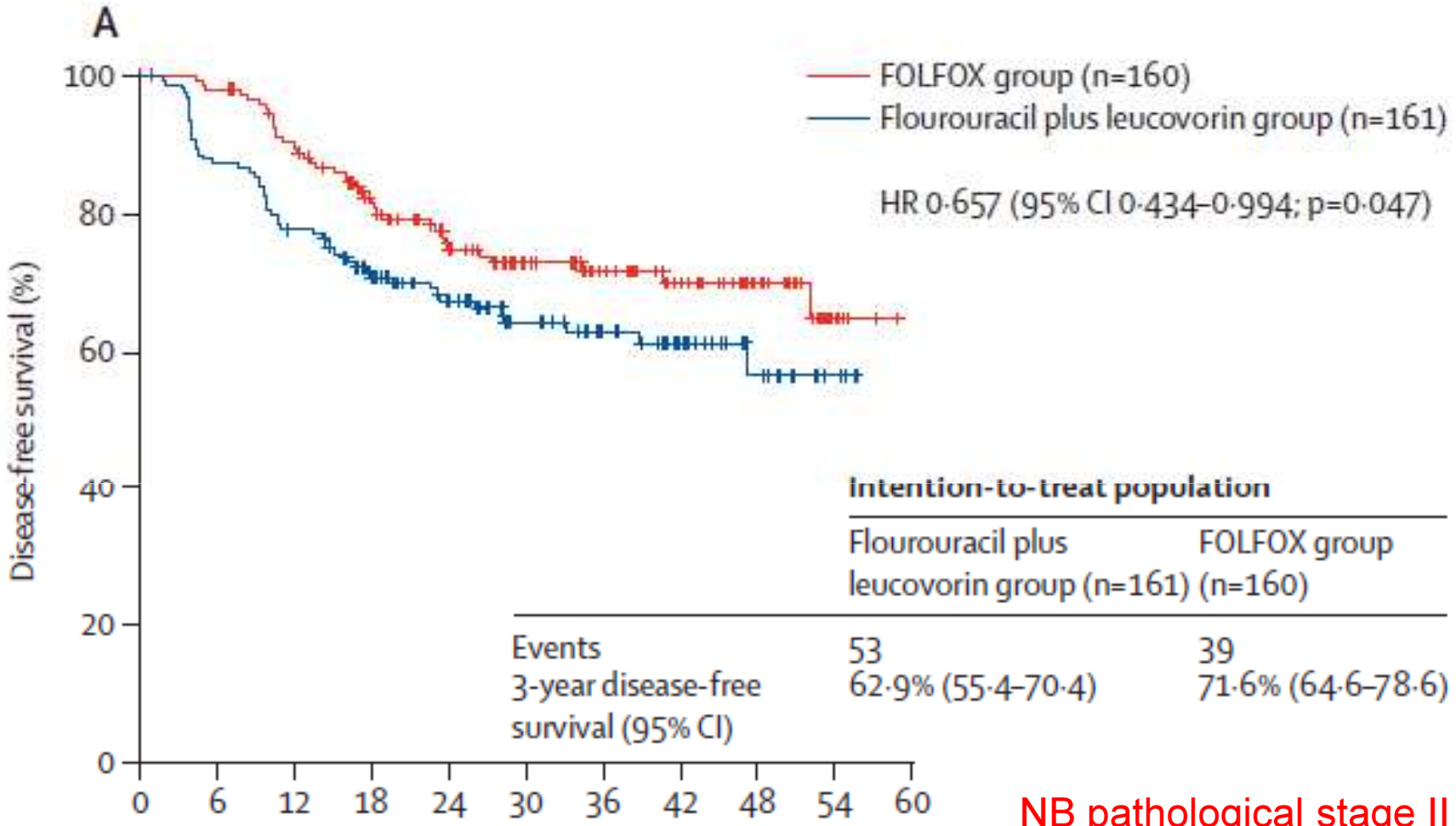
- p = 0.246
- 3-year DFS
  - Chemotherapy 67.4%
  - Observation 66.1%
- 5-year DFS
  - Chemotherapy 62.0%
  - Observation 58.4%
- 10-year DFS
  - Chemotherapy 55.6%
  - Observation 43.5%

Disease-free Survival: Intention-to-treat analysis



N at risk							
5-FU	623	509	441	363	233	114	1
5-FU/OX	613	522	447	364	230	110	1

THE ADORE PHASE II TRIAL : Disease Free Survival



Intention-to-treat population	Flourouracil plus leucovorin group (n=161)	FOLFOX group (n=160)
Events	53	39
3-year disease-free survival (95% CI)	62·9% (55·4–70·4)	71·6% (64·6–78·6)

Number at risk											
Flourouracil plus leucovorin group	161	129	114	95	76	53	41	27	12	3	0
FOLFOX group	160	143	128	105	83	64	50	38	23	5	0

NB pathological stage II
no significant difference

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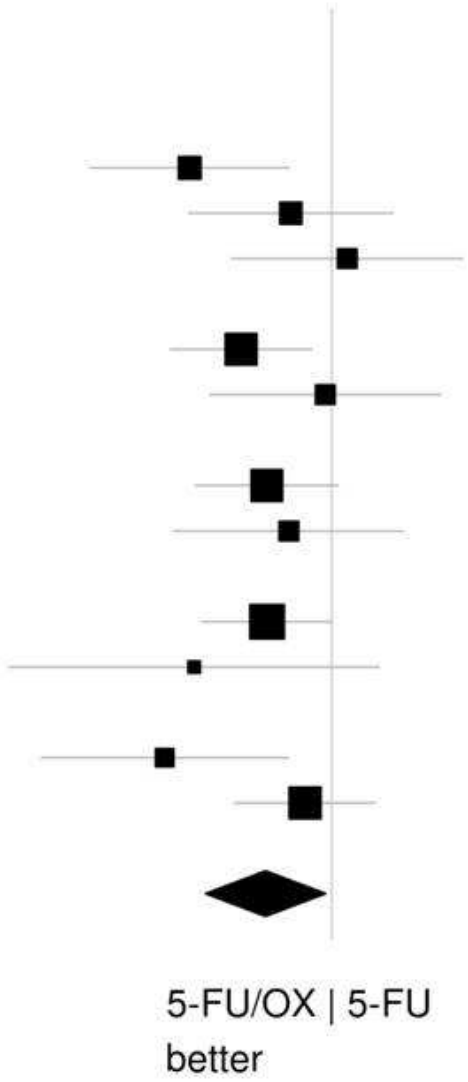
Subgroup Analysis of DFS: Pretreatment factors

Intention-to-treat

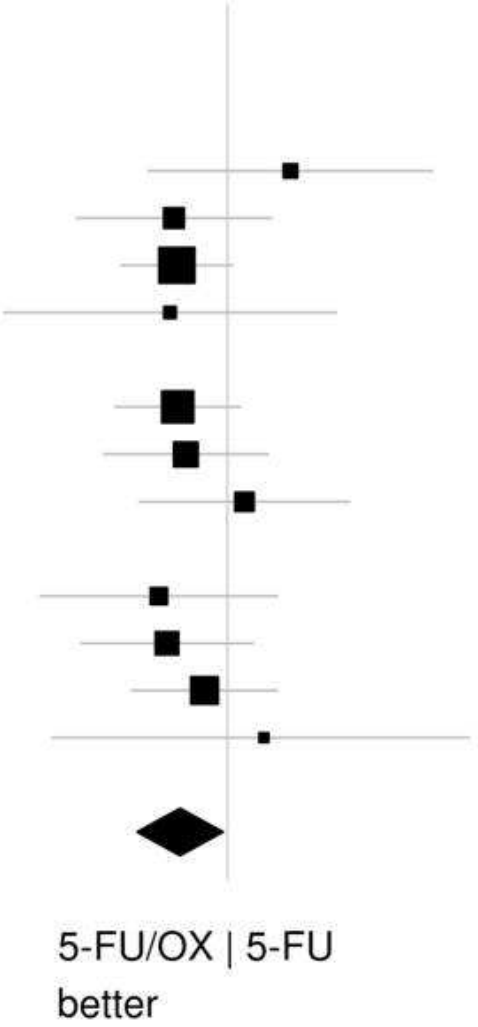
Variable	5-FU Events/n	5-FU/OX Events/n	HR 95% CI
Age, years			
< 61	84/241	52/230	0.61 (0.43, 0.86)
61-70	64/233	58/238	0.87 (0.61, 1.24)
> 70	50/149	49/145	1.06 (0.71, 1.58)
Gender			
Male	149/440	112/434	0.73 (0.57, 0.93)
Female	49/183	47/179	0.98 (0.65, 1.46)
ECOG, PS			
0	136/475	115/483	0.80 (0.62, 1.02)
1-2	58/141	43/123	0.86 (0.58, 1.28)
cT-category			
cT3	164/537	139/549	0.80 (0.64, 1.00)
cT4	27/50	14/41	0.62 (0.32, 1.18)
cN-category			
cN0	58/159	33/146	0.56 (0.36, 0.86)
cN+	134/451	123/452	0.91 (0.71, 1.16)
Total			
all	**198/623**	**159/613**	**0.79 (0.64, 0.98)**



Subgroup Analysis of DFS: Pathological factors

Intention-to-treat

Variable	5-FU Events/n	5-FU/OX Events/n	HR 95% CI
ypT-category			
ypT0-1	13/122	21/153	1.36 (0.68, 2.72)
ypT2	41/183	29/160	0.77 (0.48, 1.24)
ypT3	120/278	92/260	0.78 (0.60, 1.03)
ypT4	17/26	9/17	0.76 (0.34, 1.70)
ypN-category			
ypN0	94/423	75/416	0.78 (0.58, 1.06)
ypN1	53/131	45/133	0.82 (0.55, 1.22)
ypN2	44/60	30/42	1.09 (0.65, 1.81)
TNM stage			
Stage I	30/176	19/148	0.72 (0.40, 1.28)
Stage II	48/148	40/154	0.74 (0.49, 1.13)
Stage III	71/169	57/154	0.89 (0.63, 1.28)
ypT0ypN0	6/81	9/104	1.19 (0.43, 3.36)
Total			
all	**198/623**	**159/613**	**0.79 (0.64, 0.98)**



Trials randomising up front before CRT

The majority of patients are over-staged and probably Stage II

Compliance is poor in timing to start and doses received

Other trials randomising after CRT

TRIAL	Patient number	Primary endpoint	OS	DFS	HR for DFS
QUASAR (92% stage II)	3239 overall 968 rectal 203 preop RT	all-cause mortality.	80% versus 83.4%	Not stated	0.78 CI [0.44-1.22] (p=0·004)
PROCTOR SCRIPT	437	OS	5-year-OS 79·2% vs 80·4% (HR 0·93)	5-year-DFS 55·4%vs62·7 %(HR0·80)	0.80 CI [0.60-1.07] (p=0·13).
GERCOR	357 69% preop RT	DFS	OS HR =0.87	5-year DFS 58% vs 63%	0.80, (p=0.154)
Chronicle	113	DFS	3-year-OS 89% vs 88% (HR 1·18)	5-year DFS 71% vs 78%	0.80 (p=0.50)
ADORE	321	DFS	3-year-OS 86%vs95% (HR 0·46)	3-year DFS 63% vs 72%	0.63 (p=0.03)

So consider postop histology

Factors to consider 2

The type and quality of surgery are major (non-randomized) prognostic factors

Poor compliance may compromise the activity of adjuvant chemotherapy

After preoperative chemoradiation and surgery, time to start adjuvant chemotherapy is probably too long

Any benefit from 5FU may be achieved by the preop 5FU ie pCR

Conclusions

1. 5FU-based CRT (45-50Gy) more effective (downsizing) than RT but no improvement in SpS, DFS or OS
2. Capecitabine is an equivalent option
3. Watch and wait remains experimental
4. Radio-sensitizing 5FU-based CRT not improved by additional oxaliplatin ?
5. Biologicals have not yet delivered
6. Postop adjuvant chemotherapy after SCPRT or CRT remains of unproven benefit


Thank you for listening

- Whenever we proceed from the known into the unknown we may hope to understand, but we may have to learn at the same time a new meaning of the word 'understanding.”
  — Werner Heisenberg, *Physics and Philosophy: The Revolution in Modern Science*

Surgery and neoadjuvant radiotherapy: principles and prejudices

Chris Cunningham

Oxford UK

Surgical considerations in rectal cancer

Tumour location and stage

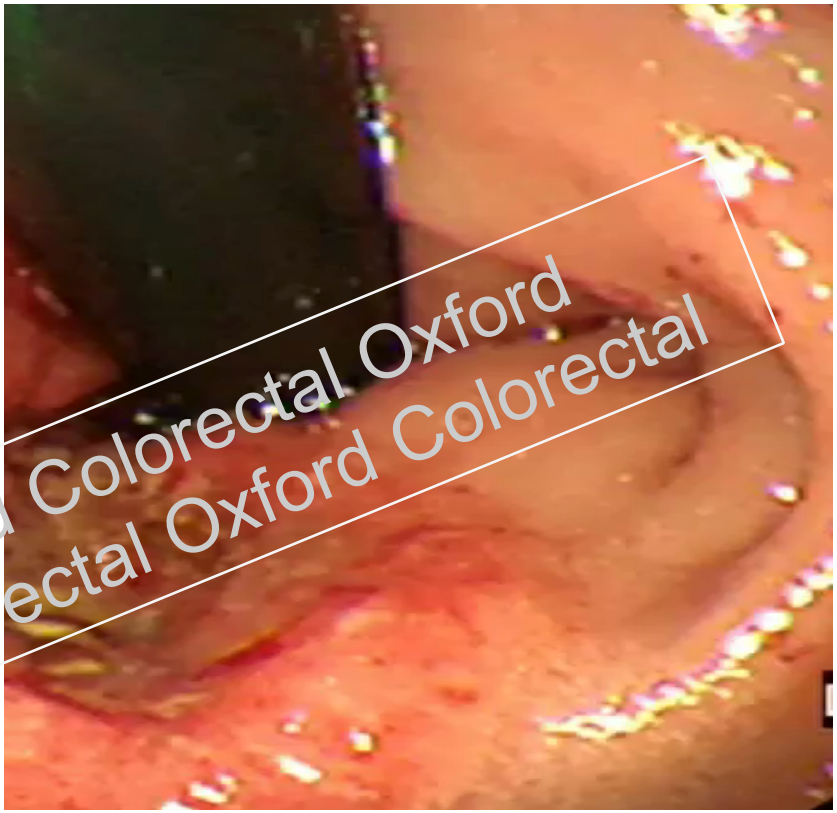
Desire to avoid permanent stoma

Baseline pelvic floor function

-continence

Comorbidity

Lifestyle



Surgical considerations in rectal cancer

Tumour location and stage

Desire to avoid permanent stoma

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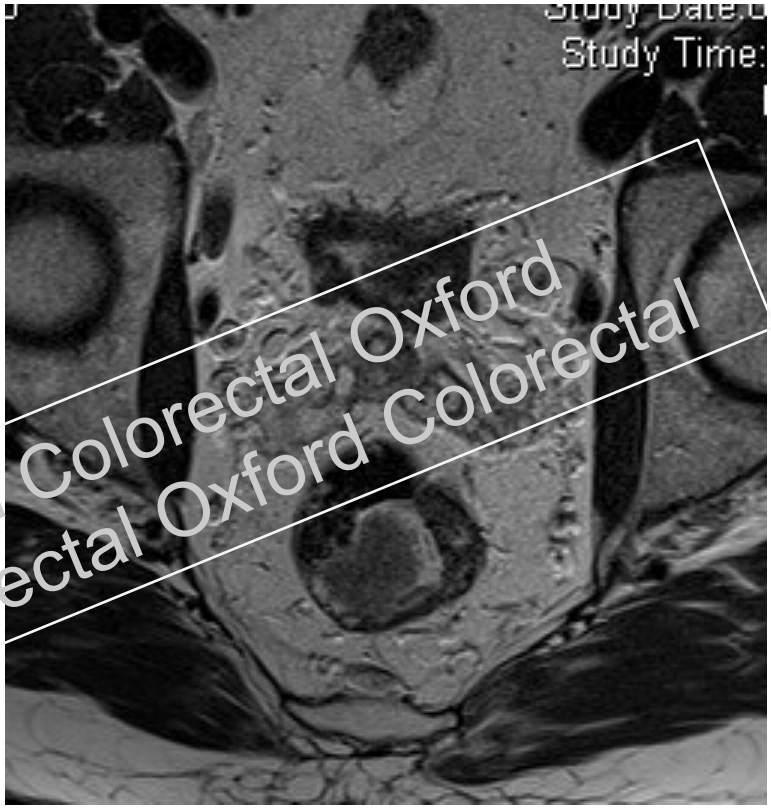
Comorbidity

Lifestyle



Surgical considerations in rectal cancer

Tumour location and stage

Desire to avoid permanent stoma

Baseline pelvic floor function

-continence

Comorbidity

Lifestyle

Surgical considerations in rectal cancer

Tumour location and stage

Desire to avoid permanent stoma

Baseline pelvic floor function

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Comorbidity

Lifestyle

Surgical considerations in rectal cancer

Tumour location and stage

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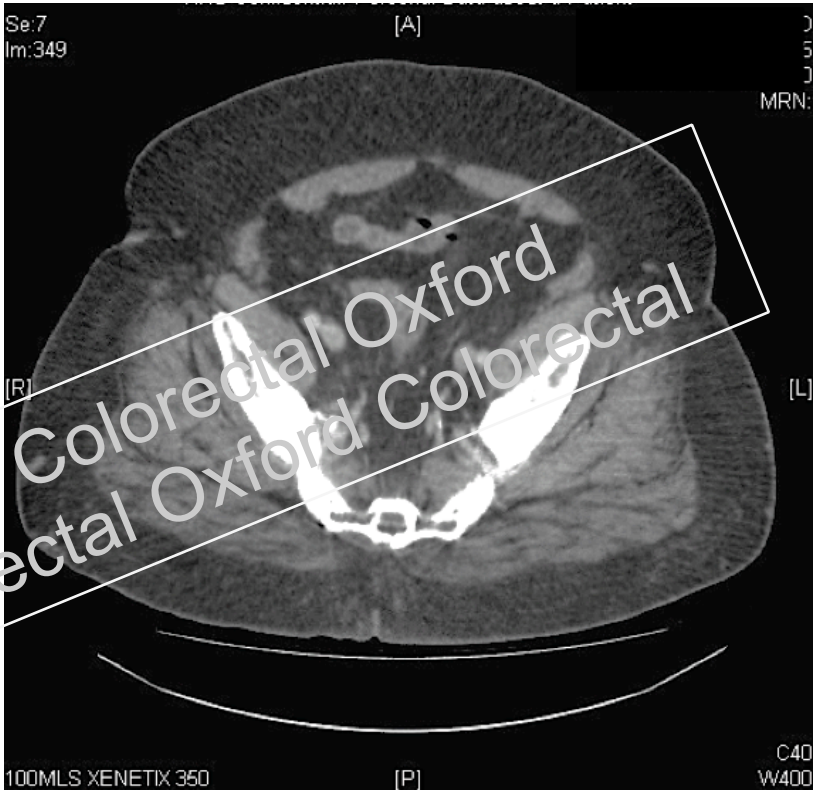


Surgical considerations in rectal cancer

Can we achieve R0 resection?

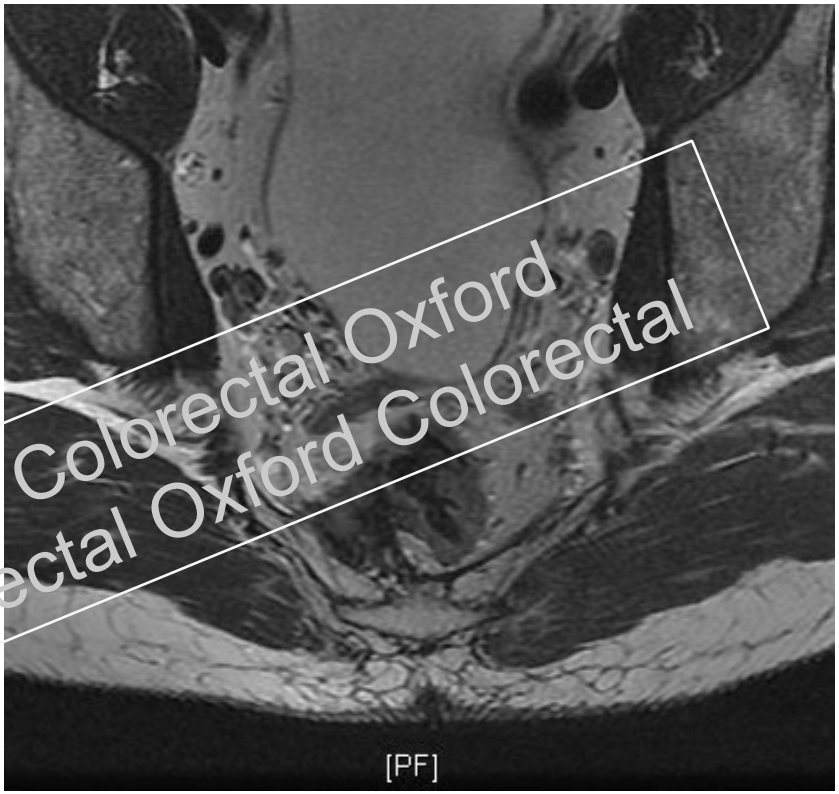
Can we do it safely?

Risk assessment:

- -CR-Possum
- -ACPGBI prediction

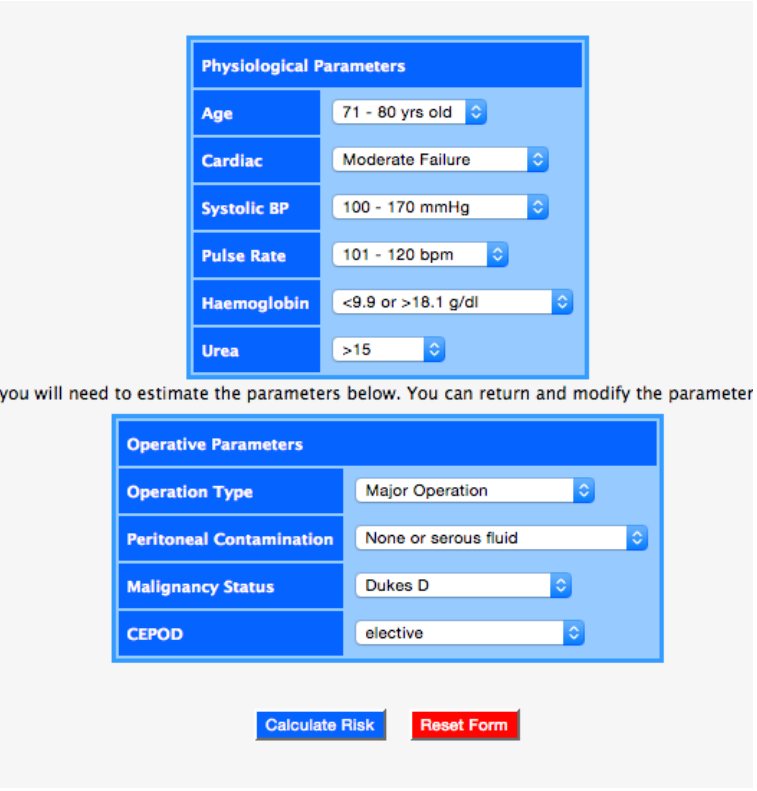
What can we do to make it safer?

- -CPET and optimization



Peri-operative risk (www.riskprediction.org.uk)

CR-POSSUM



Physiological Parameters	
Age	71 - 80 yrs old
Cardiac	Moderate Failure
Systolic BP	100 - 170 mmHg
Pulse Rate	101 - 120 bpm
Haemoglobin	<9.9 or >18.1 g/dl
Urea	>15

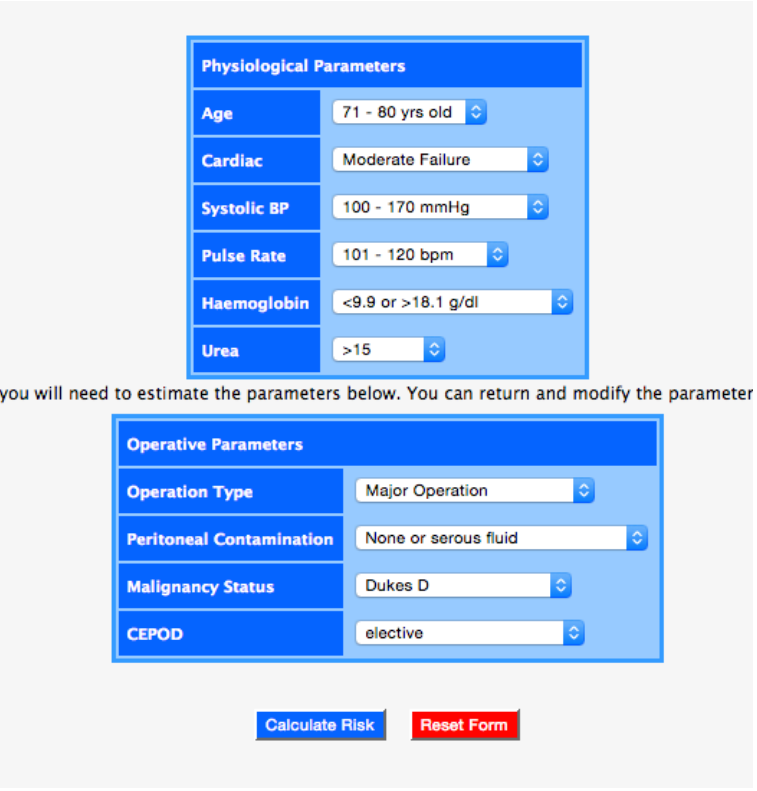
you will need to estimate the parameters below. You can return and modify the parameter

Operative Parameters	
Operation Type	Major Operation
Peritoneal Contamination	None or serous fluid
Malignancy Status	Dukes D
CEPOD	elective

Calculate Risk Reset Form

Peri-operative risk (www.riskprediction.org.uk)

CR-POSSUM



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Operative Parameters	
Operation Type	Major Operation
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Malignancy Status	Dukes D
CEPOD	elective

Calculate Risk | Reset Form

Physiology Score	Operative Severity Score	Mortality (%)
15	9	21.0

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Peri-operative risk (www.riskprediction.org.uk)

Risk Prediction in Surgery

ACPGBI Colorectal Cancer Model — **Jason J Smith & Paris P Tekkis**

Calculate an ACP Score - Original Model

Choose a value in **each** category that matches your patient from the drop down lists in both the physiological and operative parameters tables below. Default values (the commonest national value) are shown for each category.

Questions? - contact the Webmaster

Parameters	
Age	85 - 94 yrs old
Cancer Resection Status	(•) cancer resected ( ) cancer NOT resected
ASA Status	ASA II
Cancer Staging	Dukes C
Operative Urgency	Elective

Calculate Risk | Reset Form

Calculate an ACP Score - New Model (unpublished)

Choose a value in **each** category that matches your patient from the drop down lists in both the physiological and operative parameters tables below. Default values (the commonest national value) are shown for each category.

Parameters	
Age	75 - 84 yrs old
ASA Status	ASA II
Cancer Staging	Dukes B
Operative Urgency	Elective
Operative Procedure	Anterior Resection

Calculate Risk | Reset Form

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Peri-operative risk (www.riskprediction.org.uk)

Risk Prediction in Surgery

ACPGBI Colorectal Cancer Model — **Jason J Smith & Paris P Tekkis**

Calculate an ACP Score - Original Model

Choose a value in **each** category that matches your patient from the drop down lists in both the physiological and operative parameters tables below. Default values (the commonest national value) are shown for each category.

Questions? - contact the Webmaster

Parameters	
Age	85 - 94 yrs old
Cancer Resection Status	cancer resected / cancer NOT resected
ASA Status	ASA II
Cancer Staging	Dukes C
Operative Urgency	Elective

Calculate Risk | Reset Form

ACPGBI CRC Score	Mortality (%)
2.3	7.182

Calculate an ACP Score - New Model (unpublished)

Choose a value in **each** category that matches your patient from the drop down lists in both the physiological and operative parameters tables below. Default values (the commonest national value) are shown for each category.

Parameters	
Age	75 - 84 yrs old
ASA Status	ASA II
Cancer Staging	Dukes B
Operative Urgency	Elective
Operative Procedure	Anterior Resection

Calculate Risk | Reset Form

ACPGBI CRC Score	Predicted 30-day Mortality (%)
1.442	2.458

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Surgical considerations in rectal cancer

Can we cure this patient?

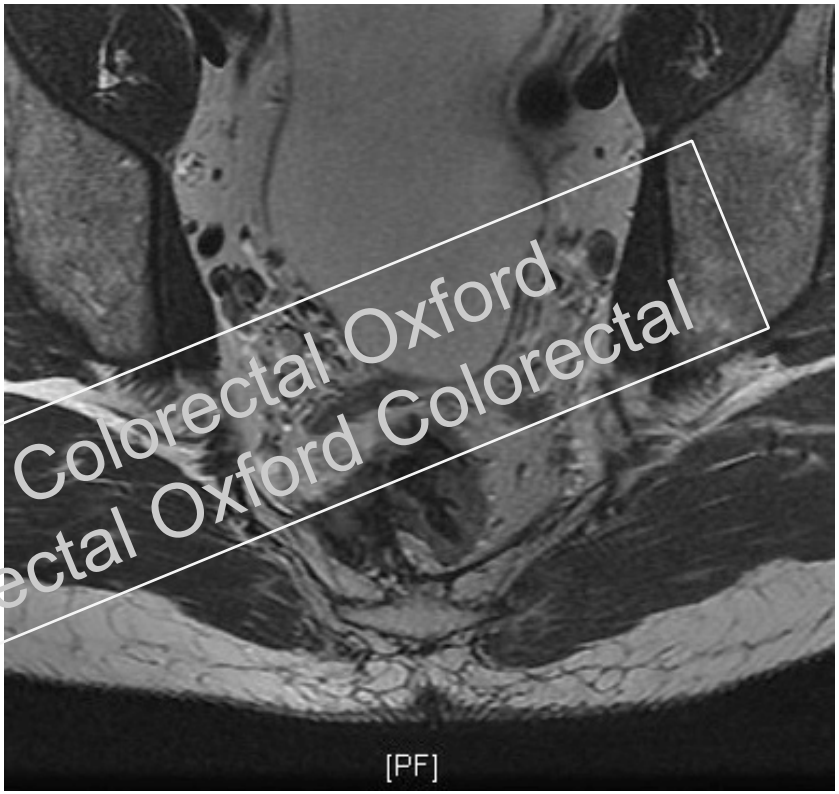
Can we do it safely?

Risk assessment:

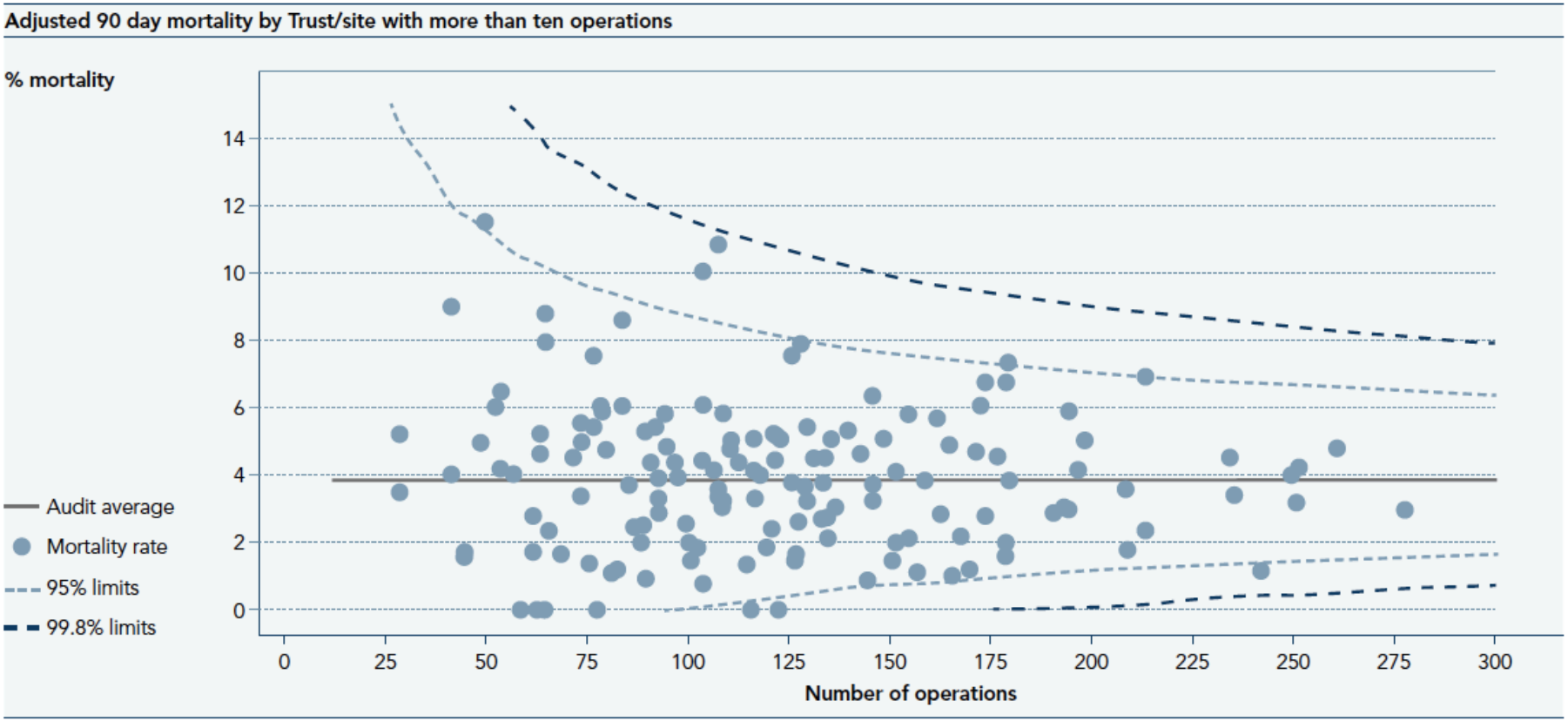
- -CR-Possum
- -ACPGBI prediction

What can we do to make it safer?

- -CPET and optimization



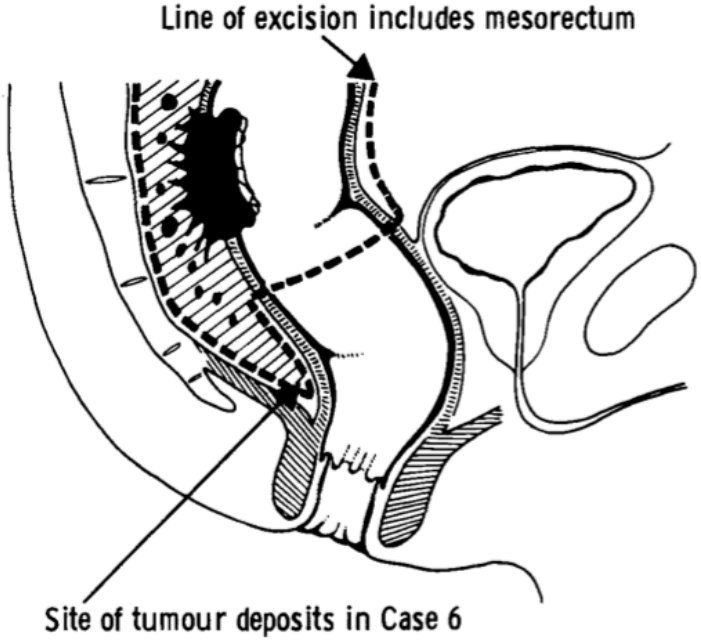
Managing peri-operative risk, reducing mortality



What operation should be considered in low rectal cancer?

Br. J. Surg. Vol. 69 (1982) 613–616 Printed in Great Britain

The mesorectum in rectal cancer surgery—the clue to pelvic recurrence?



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Surgical strategies?

ORIGINAL CONTRIBUTION

Low Rectal Cancer: Classification and Standardization of Surgery

Eric Rullier, M.D.[1,2] • Quentin Denost, M.D.[1,2] • Véronique Vendrely, M.D.[2,3]
Anne Rullier, M.D., Ph.D.[2,4] • Christophe Laurent, M.D., Ph.D.[1,2]

1 Surgery Department, CHU Bordeaux, Saint-Andre Hospital, Bordeaux, France
2 Bordeaux Segalen University, Bordeaux, France
3 Radiotherapy Department, CHU Bordeaux, Haut-Leveque Hospital, Pessac, France
4 Pathology Department, CHU Bordeaux, Pellegrin Hospital, Bordeaux, France

Table 1. Surgical classification of low rectal cancer

Classification	*Definition*	*Surgical procedure*
Type I	Supra-anal tumor > 1 cm from anal ring	CAA
Type II	Juxta-anal tumor < 1 cm from anal ring	pISR
Type III	Intra-anal tumor Internal sphincter invasion	tISR
Type IV	Transanal tumor External sphincter invasion	APR

Type IVa includes the levator ani muscles; IVb, external sphincter; IVc, Levator ani muscles and external sphincter.
CAA = conventional coloanal anastomosis; pISR = partial intersphincteric resection; tISR = total intersphincteric resection; APR = abdominoperineal resection.

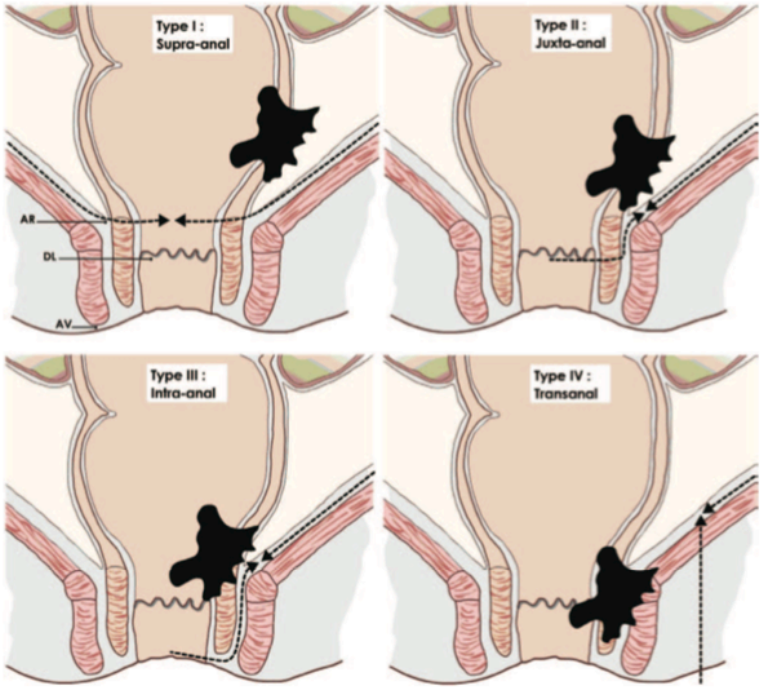

FIGURE 1. Surgical classification of low rectal cancer. Type I are supra-anal tumors (> 1 cm from the anal sphincter) and treated by conventional coloanal anastomosis; type II are juxta-anal tumors (< 1 cm from the anal sphincter) treated by partial intersphincteric resection; type III are intra-anal tumors (internal sphincter invasion) treated by total intersphincteric resection; and type IV are transanal tumors (external sphincter invasion) treated by APR. AR = anal ring, DL = dentate line; AV = anal verge. The dotted line represents the surgical dissection plane.

Rullier et al Diseases of the Colon & Rectum. 2013;56(5):560-7.

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Surgical strategies?

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4 Pathology Department, CHU Bordeaux, Pellegrin Hospital, Bordeaux, France

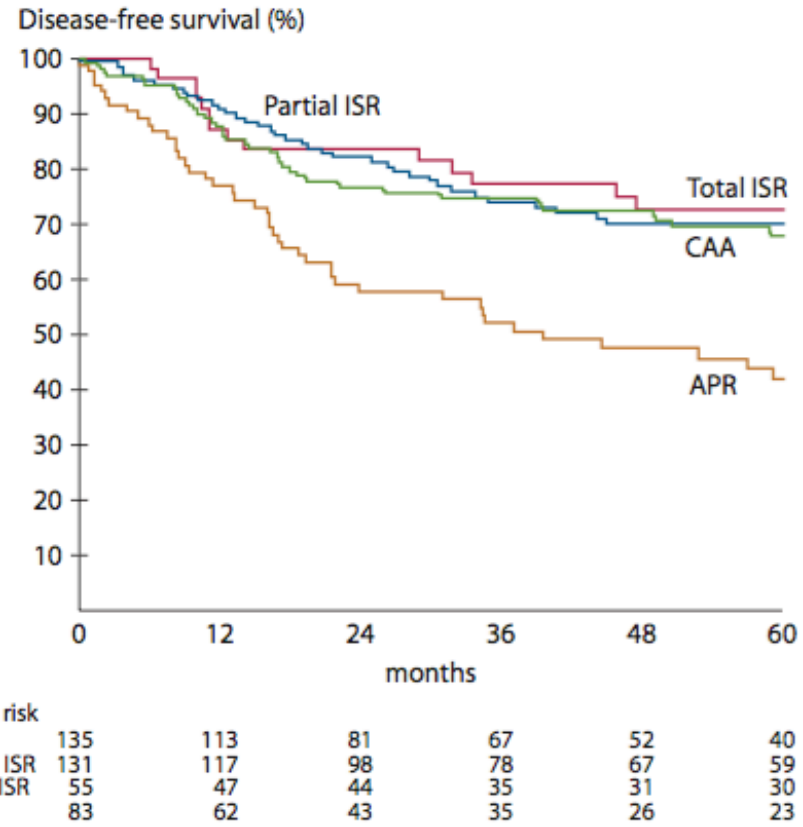
404 patients with low cancer

T3 51%

CRT in 85%

R1 10%

PCR 5%



No at risk						
CAA	135	113	81	67	52	40
Patial ISR	131	117	98	78	67	59
Total ISR	55	47	44	35	31	30
APR	83	62	43	35	26	23

Figure 2. Disease-free survival according to type of surgery. APR = abdominoperineal resection; CAA = coloanal anastomosis; ISR = intersphincteric resection.

Rullier et al Diseases of the Colon & Rectum. 2013;56(5):560-7.

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Does extreme resection need radiotherapy?

Ann Surg Oncol (2016) 23:S249–S256
DOI 10.1245/s10434-015-4461-z

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

CrossMark

ORIGINAL ARTICLE – COLORECTAL CANCER

Risk Factors for Anastomotic Leakage After Intersphincteric Resection Without a Protective Defunctioning Stoma for Lower Rectal Cancer

Motoi Koyama, MD, Akihiko Murata, MD, Yoshiyuki Sakamoto, MD, Hajime Morohashi, MD, Tatsuya Hasebe, MD, Takeshi Saito, MD, and Kenichi Hakamada, MD

Department of Gastroenterological Surgery, Hirosaki University Graduate School of Medicine, Hirosaki, Aomori, Japan

135 patients over

1995-2012

T3 60%

No preoperative RT

No stoma

Anastomotic leak rate 17%

On multivariate analysis AL

associated with:

partial ISR (OR 6.701; P = 0.001)

straight join (OR 5.552; P = 0.002)

Koyama et al Ann Surg Oncol. 2016;23(2):249-56.

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APR or low anterior resection?

N. S. WILLIAMS AND
D. JOHNSTON

University Department of Surgery, The General Infirmary, Leeds.

Br. J. Surg. Vol. 70 (1983) 460–462 Printed in Great Britain

The quality of life after rectal excision for low rectal cancer

The quality of life for patients with carcinoma of the lower two-thirds of the rectum (5–12 cm from the anal verge) treated by abdominoperineal resection (APER, n = 38) was compared with that of a similar group of patients treated by low sphincter saving resection (SSR, n = 40). Assessment was by questionnaire conducted a minimum of one year after operation. Thirty patients (75 per cent) after SSR were entirely continent and ten patients (25 per cent) had occasional episodes of incontinence. Each patient with a colostomy was incontinent and 25 (66 per cent) had leaks from their appliance (12 frequent; 13 occasional). Patients after APER avoided more items in the diet and took more medication to control their bowel habit than patients after SSR. Fifteen of the 18 patients (83 per cent) who were employed before SSR returned to work after operation; only 6 of 15 patients (40 per cent) returned to work after APER ($P<0{\cdot}05$). Sexual function was impaired in 6 of 20 men (30 per cent) after SSR and in 12 of 18 men (67 per cent) after APER ($P<0{\cdot}06$). Depression was significantly more prevalent after APER than after SSR. Patients with low rectal cancer who are treated by modern sphincter saving resection have a quality of life superior to those who are treated by APER.

'Thus, provided it is technically feasible and compatible with complete eradication of the disease, every effort should be made to conserve the anal sphincter with low rectal cancer'

ORIGINAL ARTICLE

Comparative Effectiveness of Sphincter-Sparing Surgery Versus Abdominoperineal Resection in Rectal Cancer

Patient-Reported Outcomes in National Surgical Adjuvant Breast and Bowel Project Randomized Trial R-04

Marcia M. Russell, MD,† Patricia A. Ganz, MD,*‡ Samia Lopa, MS,*§ Greg Yothers, PhD,*§ Clifford Y. Ko, MD,*‖ Amit Arora, MD,*¶ James N. Atkins, MD,*** Nathan Bahary, MD,*†† Gamini S. Soori, MD,*‡‡ John M. Robertson, MD,*§§ Janice Eakle, MD,*‖‖ Benjamin T. Marchello, MD,*¶¶ Timothy F. Wozniak, MD,**** Robert W. Beart, Jr, MD,*††† and Norman Wolmark, MD*‡‡‡*

FACT-C

EORTC QLQ-CR38

Baseline and 1 year

576 APER versus 926 SS

FACT-C total and subscale scores were not statistically different by surgery at 1 year

EORTC QLQ-CR38 totals were not different at 1 year but significant differences in domains

Ann Surg 2015;261:144–148

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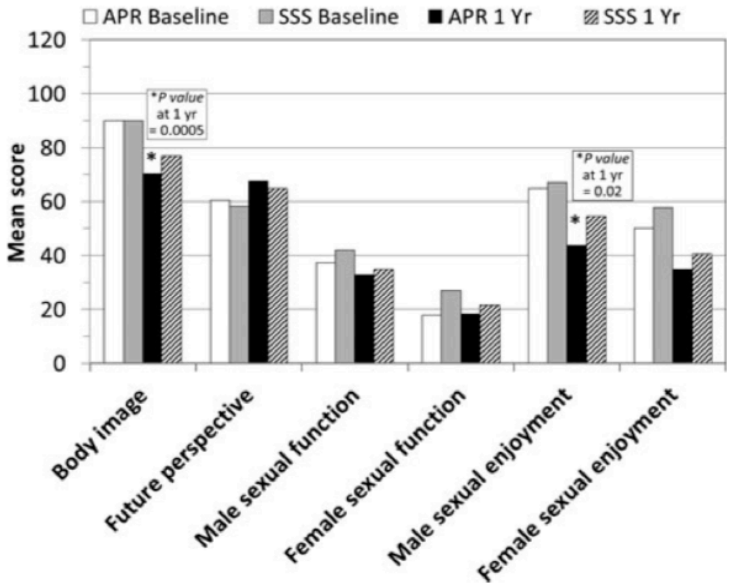

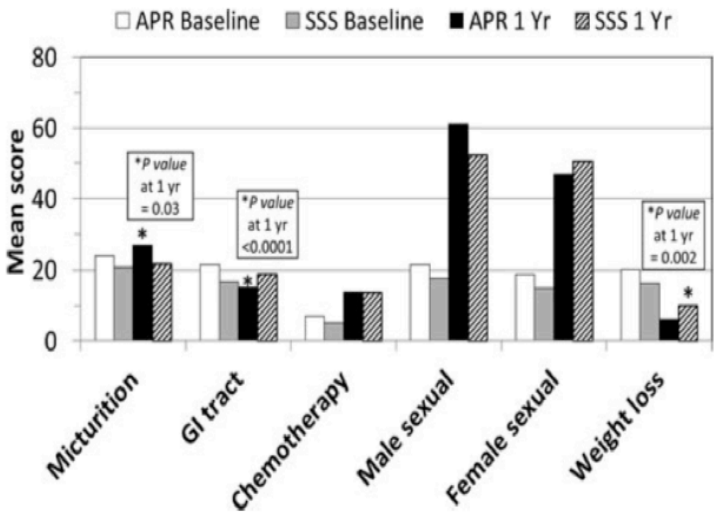

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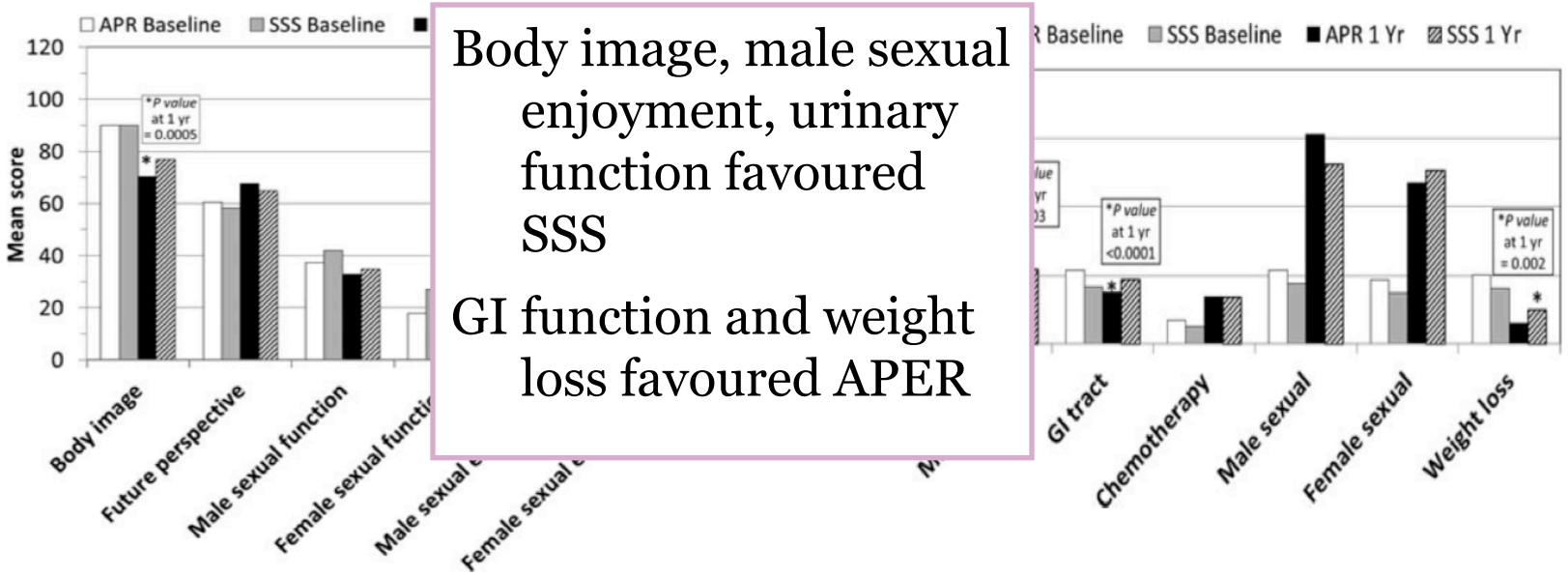

Body image, male sexual enjoyment, urinary function favoured SSS

GI function and weight loss favoured APER

Ann Surg 2015;261:144–148

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ORIGINAL ARTICLE

Comparative Effectiveness of Sphincter-Sparing Surgery Versus Abdominoperineal Resection in Rectal Cancer

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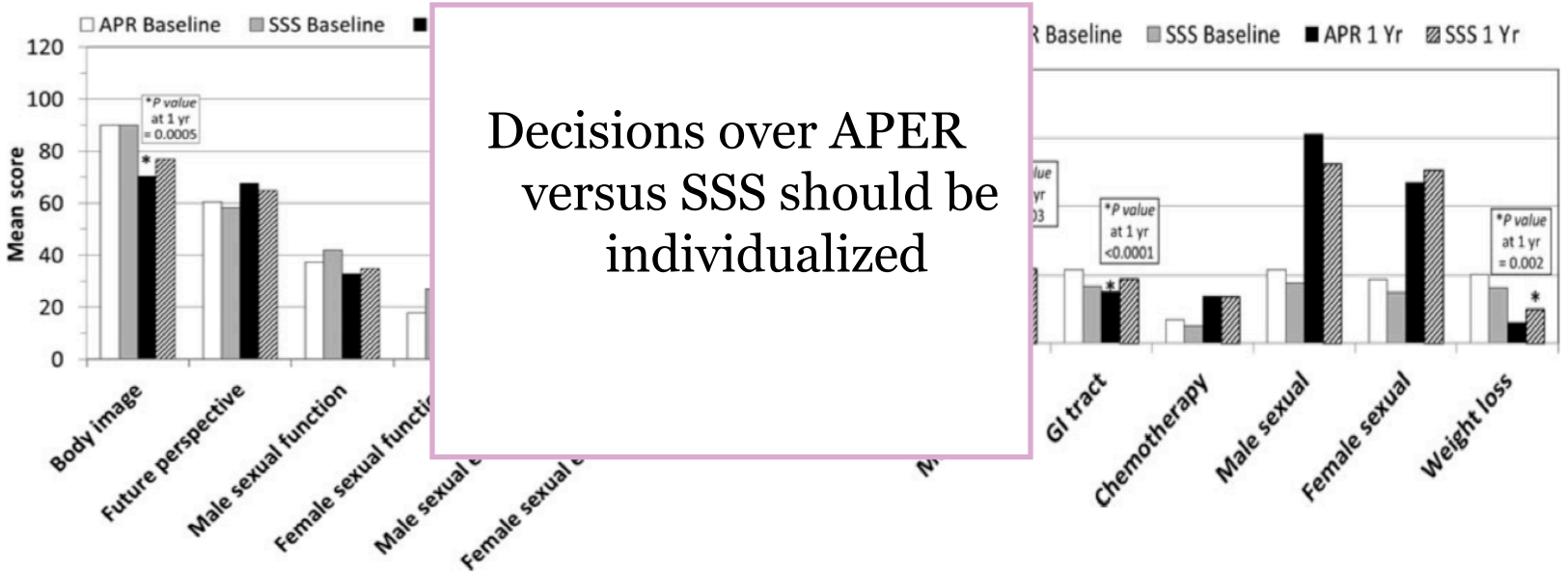

Decisions over APER versus SSS should be individualized

Ann Surg 2015;261:144–148

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How far do we go to pursue R0 margin?

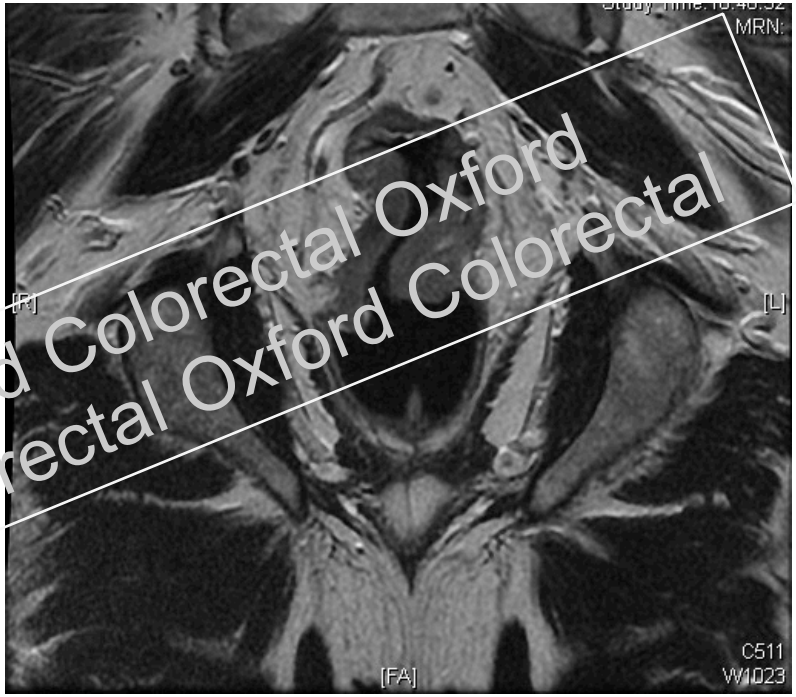
Beyond TME….

Pelvic lymphadenectomy

Sacrectomy

Cysto-prostatectomy

Outcomes favourable if Ro achieved



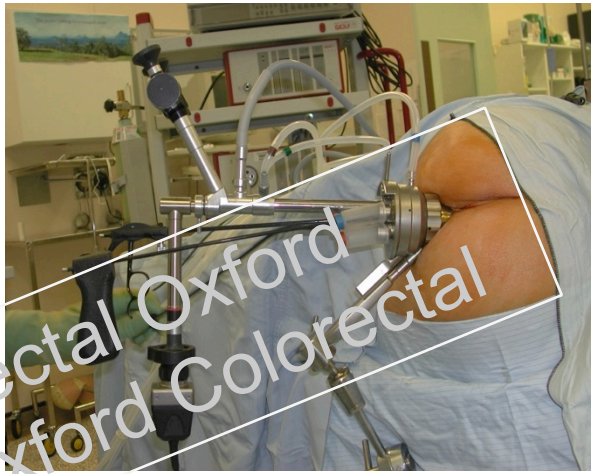
Is it suitable for local excision?

Usually not!

If complete response, best to observe

If suspected residual cancer in comorbid patient LE may have a role

If initially T3/4, N+, unlikely to be improved by LE

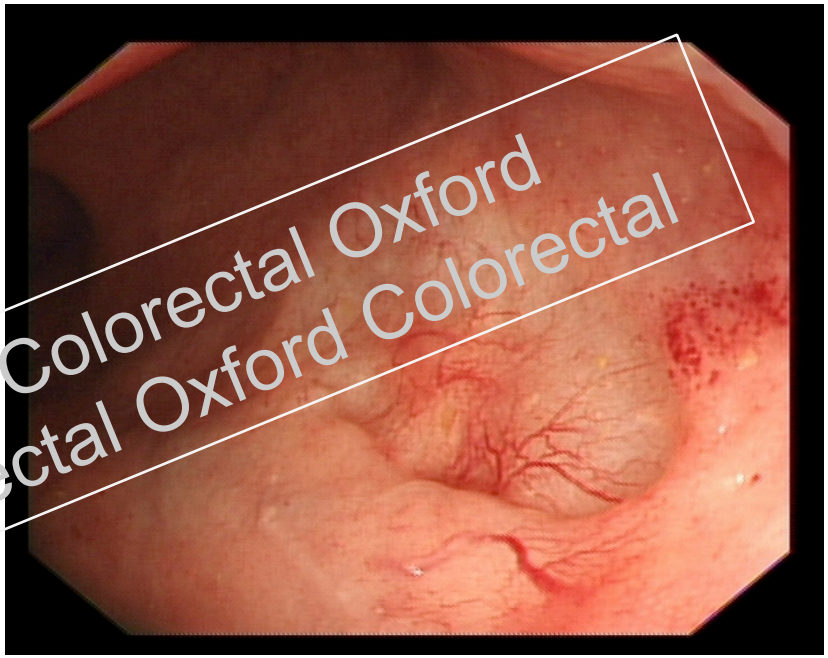


Avoid Surgery: Watch and wait approach

Attractive in elderly and comorbid patients

Needs infrastructure and engagement of patient and MDT

Should be considered in all patients?



Summary

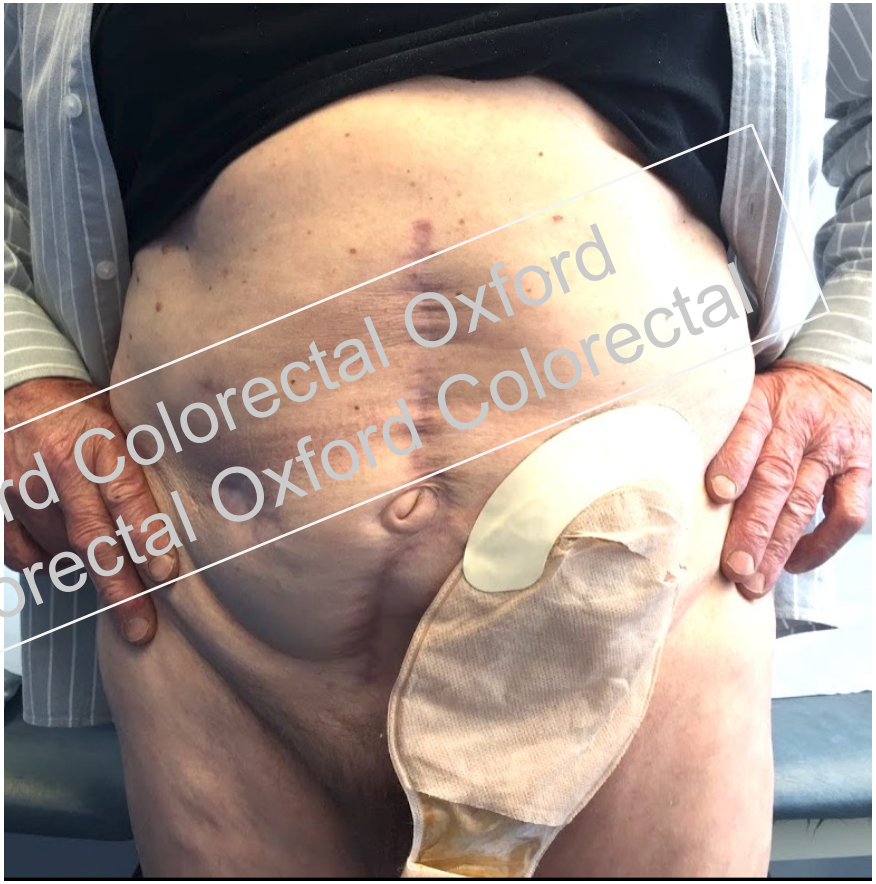
Surgical decision-making is complex in rectal cancer

Patient centred

What is possible technically may not be best for the patient

Complex physical, psychological and cultural considerations

One value of CRT is the decision may be deferred



What does the surgeon want from the radiotherapist?

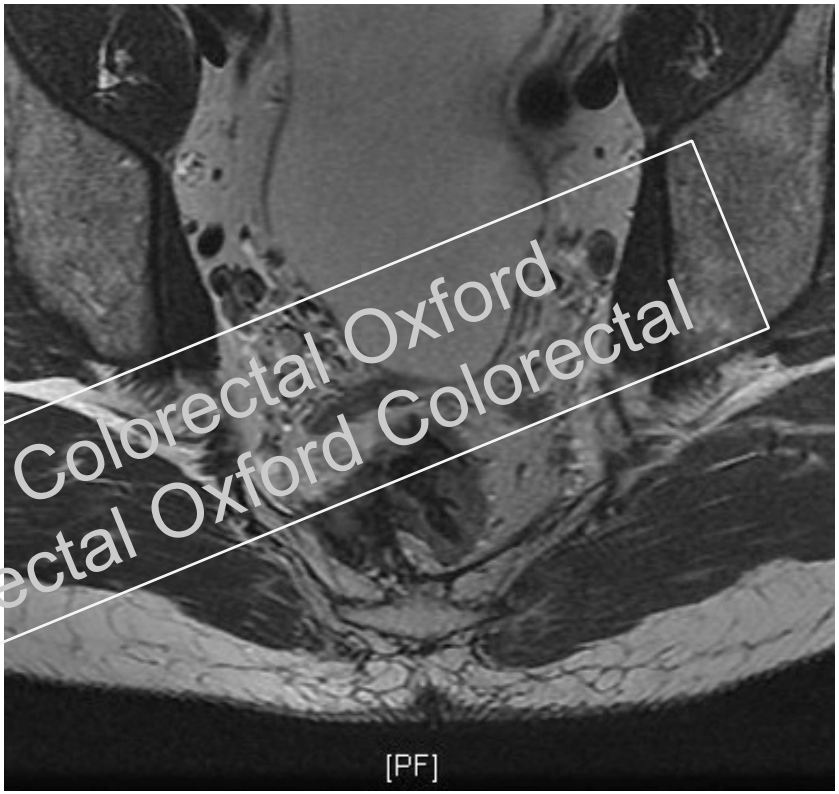
Improve outcomes!

Reduced R1 rates

Increase sphincter preservation

Minimal impact on complications

Minimal impact on patient QoL



A simple surgeon's view of radiotherapy and rectal cancer

Original article

doi:10.1111/j.1463-1318.2010.02360.x

Changes in the management and outcome of rectal cancer over a 10-year period in Oxford

W. Chambers, L. Hancock, R. McKenzie, O. Buchel, I. Lindsey, C. Cunningham, B. George and N. Mortensen

Department of Colorectal Surgery, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, UK

Received 25 January 2010; accepted 4 May 2010; Accepted Article online 1 July 2010

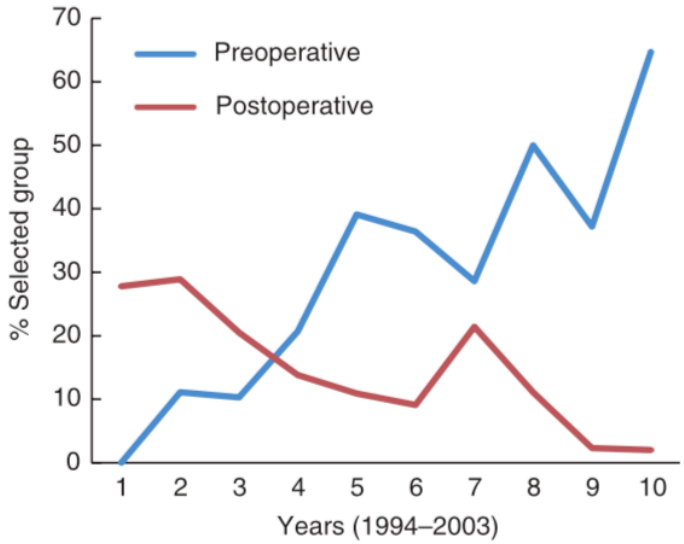


Figure 4 Changes in rates of preoperative and postoperative adjuvant therapy for selected group 1994–2003.

Chambers W et al. Colorectal 2011,13 :1004-8.

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A simple surgeon's view of radiotherapy and rectal cancer

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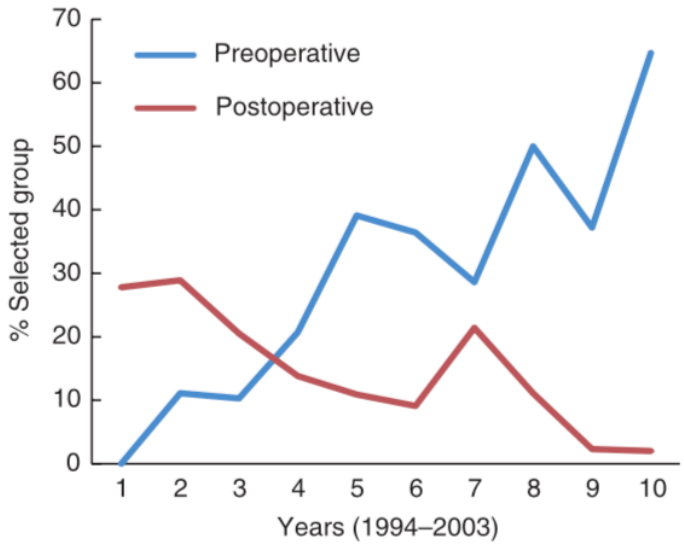

Figure 4 Changes in rates of preoperative and postoperative adjuvant therapy for selected group 1994–2003.

No change in survival

No significant change in LR

Leak rate increased from 2.6% to 9.6%

Chambers W et al. Colorectal 2011,13 :1004-8.

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Does radiotherapy improve outcomes?

Survival

The TME Trial After a Median Follow-up of 6 Years

Increased Local Control But No Survival Benefit in Irradiated Patients With Resectable Rectal Carcinoma

Koen C.M.J. Peeters, MD, Corrie A.M. Marijnen, MD, PhD,†‡ Iris D. Nagtegaal, MD, PhD,§ Elma Klein Kranenbarg, MSc,* Hein Putter, MD,‖ Theo Wiggers, MD, PhD,¶ Harm Rutten, MD, PhD,# Lars Pahlman, MD, PhD,** Bengt Glimelius, MD, PhD,††§§ Jan Willem Leer, MD, PhD,‖‖ and Cornelis J.H. van de Velde, MD, PhD,* for the Dutch Colorectal Cancer Group*

Local recurrence

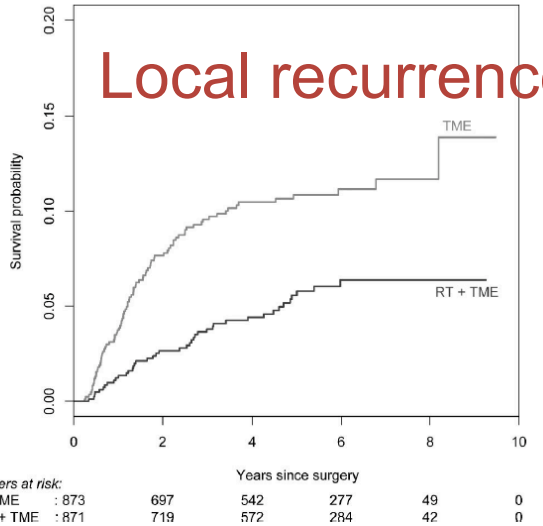


FIGURE 2. Rates of local recurrence among 1748 eligible patients who underwent macroscopically complete local resection, according to randomization.

Survival

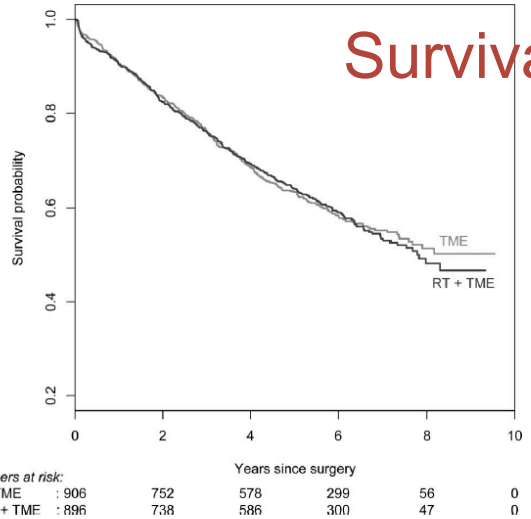


FIGURE 4. Rates of overall survival among 1805 eligible patients according to randomization.

Peeters et al. Annals of surgery, 2007; 246:693-701.

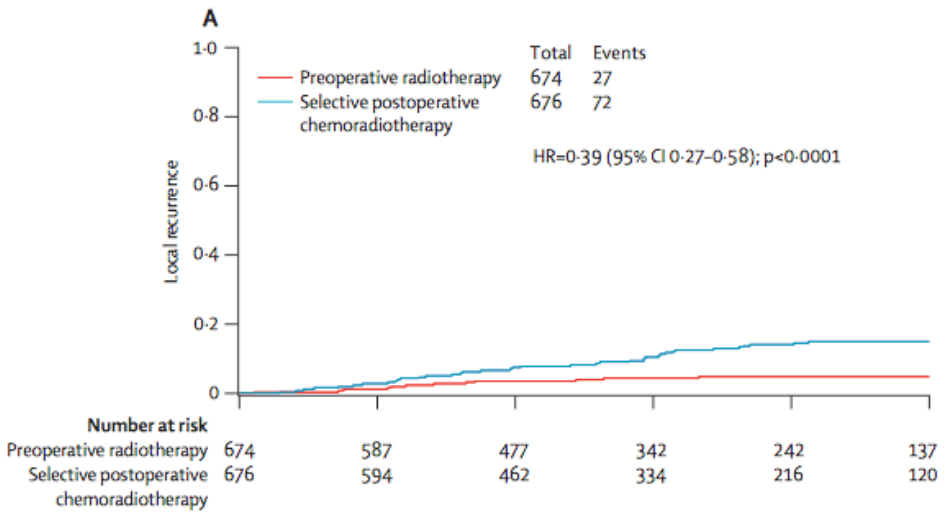
ESTRO School

Survival

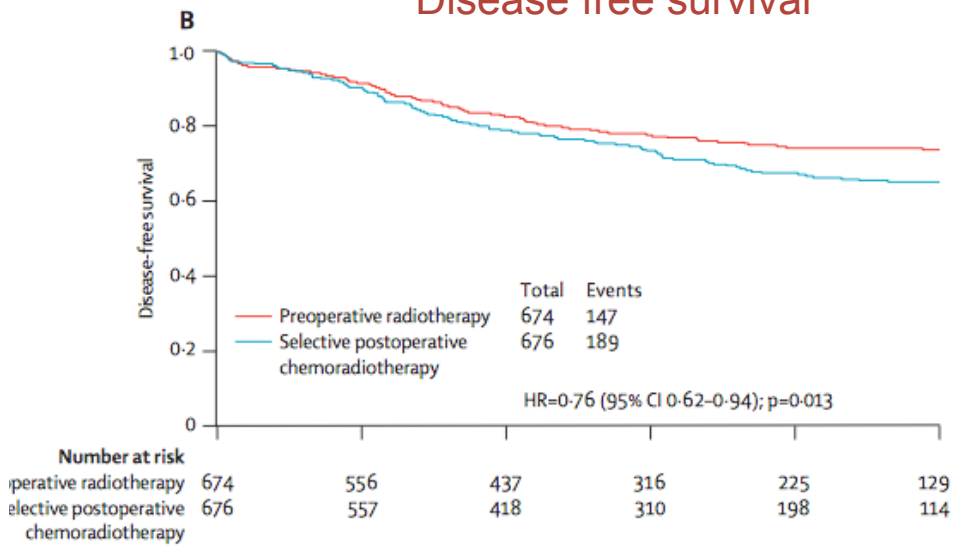
Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial

*David Sebag-Montefiore, Richard J Stephens, Robert Steele, John Monson, Robert Grieve, Subhash Khanna, Phil Quirke, Jean Couture, Catherine de Metz, Arthur Sun Myint, Eric Bessell, Gareth Griffiths, Lindsay C Thompson, Mahesh Parmar, on behalf of all the trial collaborators**

Local recurrence



Disease free survival



Sebag-Montefiore et al, The Lancet. 2009;373:811-20

ESTRO School

Reducing R1 rates?

Original article

Tumour regression in the randomized Stockholm III Trial of radiotherapy regimens for rectal cancer

D. Pettersson[1], E. Lörinc[2], T. Holm[1], H. Iversen[1], B. Cedermark[1], B. Glimelius[2,3] and A. Martling[1]

Departments of [1]Molecular Medicine and Surgery, and [2]Oncology and Pathology, Karolinska Institute, Stockholm, and [3]Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden

Correspondence to: Dr D. Pettersson, Department of Surgery, Norrtälje Hospital, Box 905, SE-761 28 Norrtälje, Sweden
(e-mail: david.pettersson@tiohundra.se)

Reports on 462 patients with resectable rectal cancer <15cm from AV

234 SRT immediate surgery

228 SRT and delayed surgery 4-8 weeks

Pettersson et al. British Journal of Surgery. 2015;102(8):972-8

ESTRO School

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Original article

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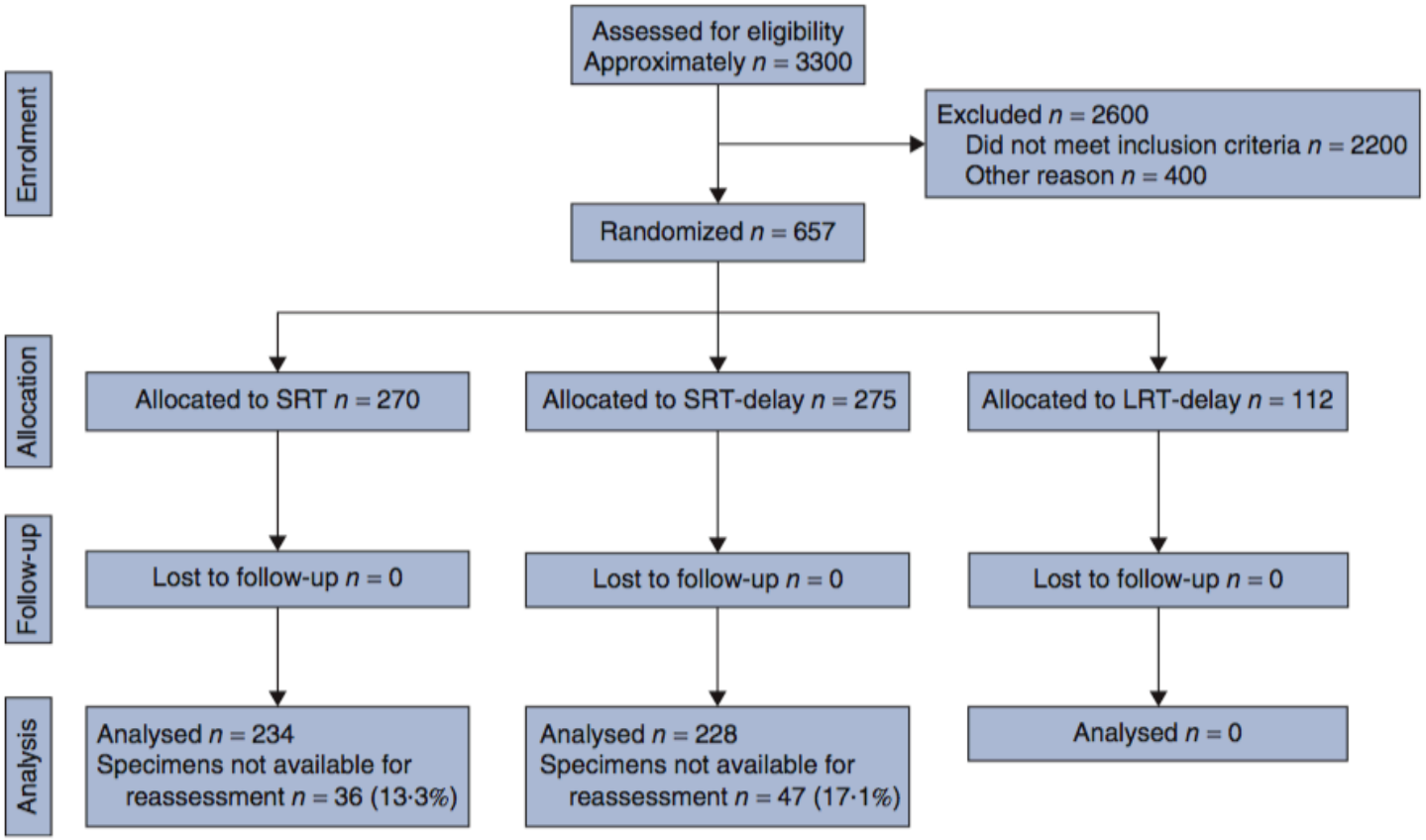
(e-mail: david.pettersson@tiohundra.se)



Pettersson et al. British Journal of Surgery. 2015;102(8):972-8

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Correspondence to: Dr D. Pettersson, Department of Surgery, Norrtälje Hospital, Box 905, SE-761 28 Norrtälje, Sweden (e-mail: david.pettersson@tiohundra.se)

Delay associated with:

Down-staging of T and N

Tumour regression

pCR rate of 11.8 vs 1.7%

Table 2 Pathological outcomes

	SRT ($n=234$)	SRT-delay ($n=228$)	P¶
Tumour stage			0·001
ypI	4 (1·7)	27 (11·8)	
ypI	69 (29·5)	76 (33·3)	
ypII	71 (30·3)	53 (23·2)	
ypIII	74 (31·6)	55 (24·1)	
ypIV	5 (2·1)	6 (2·6)	
ypx†	11 (4·7)	11 (4·8)	
Tumour category			<0·001
ypT0	5 (2·1)	27 (11·8)	
ypT1	12 (5·1)	27 (11·8)	
ypT2	74 (31·6)	60 (26·3)	
ypT3‡			
ypT3ab	88 (37·6)	67 (29·4)	
ypT3cd	41 (17·5)	26 (11·4)	
ypT3x	3 (1·3)	1 (0·4)	
ypT4‡			
ypT4a	1 (0·4)	5 (2·2)	
ypT4b	3 (1·3)	3 (1·3)	
ypTx†	7 (3·0)	12 (5·3)	
Node category			0·059
ypN0	149 (63·7)	163 (71·5)	
yp N1	52 (22·2)	41 (18·0)	
ypN2	28 (12·0)	19 (8·3)	
ypNx†	5 (2·1)	5 (2·2)	
Tumour regression*			<0·001
Grade 0	17 (7·3)	15 (6·6)	
Grade 1	165 (70·5)	104 (45·6)	
Grade 2	41 (17·5)	64 (28·1)	
Grade 3	2 (0·9)	11 (4·8)	
Grade 4	4 (1·7)	23 (10·1)	
Grade x†	5 (2·1)	11 (4·8)	
Circumferential resection margin§	$n=170$	$n=150$	1·000#
Positive (≤ 1 mm)	11	9	
Negative (> 1 mm)	159	141	

Pettersson et al. British Journal of Surgery. 2015;102(8):972-8

ESTRO School

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Correspondence to: Dr D. Pettersson, Department of Surgery, Norrtälje Hospital, Box 905, SE-761 28 Norrtälje, Sweden (e-mail: david.pettersson@tiohundra.se)

Delay associated with:

Down-staging of T and N

Tumour regression

pCR rate of 11.8 vs 1.7%

No difference in R0 rate (6.3%)

Table 2 Pathological outcomes

	SRT ($n = 234$)	SRT-delay ($n = 228$)	P¶
Tumour stage			0·001
ypT0	4 (1·7)	27 (11·8)	
ypI	69 (29·5)	76 (33·3)	
ypII	71 (30·3)	53 (23·2)	
ypIII	74 (31·6)	55 (24·1)	
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Grade x†	5 (2·1)	11 (4·8)	
Circumferential resection margin§	$n = 170$	$n = 150$	1·000#
Positive (≤ 1 mm)	11	9	
Negative (> 1 mm)	159	141	

Pettersson et al. British Journal of Surgery. 2015;102(8):972-8

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ORIGINAL CONTRIBUTION

Distribution of Residual Cancer Cells in the Bowel Wall After Neoadjuvant Chemoradiation in Patients With Rectal Cancer

Marjun P. Duldulao, M.D.[1] • Wendy Lee, B.A.[1] • Leanne Streja, Dr.P.H.[2]
Peiguo Chu, M.D.[3] • Wenyan Li, B.A.[1] • Zhenbin Chen, Ph.D.[1]
Joseph Kim, M.D.[1] • Julio Garcia-Aguilar, M.D., Ph.D.[4]

Cancer does not “implode” on response but leaves islands of cells

Reducing R1 rates?

J Gastrointest Surg (2015) 19:1676–1683
DOI 10.1007/s11605-015-2861-9

ORIGINAL ARTICLE

The Impact of Preoperative Radiation Therapy on Locoregional Recurrence in Patients with Stage IV Rectal Cancer Treated with Definitive Surgical Resection and Contemporary Chemotherapy

Bindu V. Manyam[1] · Ismail H. Mallick[2] · May M. Abdel-Wahab[1] · Chandana A. Reddy[1] · Feza H. Remzi[2] · Matthew F. Kalady[2] · Ian Lavery[2] · Shlomo A. Koyfman[1]

109 stage IV rectal cancer patients

64 peri-op chemotherapy, 45 CRT

R1 rates lower (10.9 vs 20%) in those with CRT

CRT may enhance pathologic down-staging

Manyam et al J Gastrointest Surg. 2015;19(9):1676-83.

ESTRO School

Does radiotherapy increase complications?

Leak rates and radiotherapy

Original article

Risk factors for anastomotic leakage after anterior resection of the rectum

P. Matthiessen*, O. Hallböök†, M. Andersson*, J. Rutegård* and R. Sjödahl†

Departments of Surgery, *University Hospital Örebro, Örebro, and †Linköping University Hospital, Linköping, Sweden

Received 18 December 2003; accepted 20 April 2004

432 patients having anterior resection in Sweden

Leak rate 12%, increased with:

-Male sex

-Anastomosis <6cm

-Pre-operative radiation

Matthiessen et al Colorectal Disease. 2004;6(6):462-9.

Leak rates and radiotherapy

Original article

Anastomotic leakage following routine mesorectal excision for rectal cancer in a national cohort of patients

M. T. Eriksen*‡, A. Wibe†, J. Norstein‡, J. Haffner* and J. N. Wiig§, on behalf of the Norwegian Rectal Cancer Group

*Department of Surgery, Buskerud Hospital, Drammen, †Department of Surgery, St. Olav's Hospital, Trondheim, ‡The Cancer Registry of Norway, Oslo, §Department of Surgery, The Norwegian Radium Hospital, Oslo, Norway

1958 patients

1993-1999

Anastomotic leak in

- 11.6%

Multivariate analysis AL increased with

- Male sex
- Pre-op RT
- Ileostomy protective for anastomosis <6cm

Eriksen et al Colorectal Disease. 2005;7(1):51-7.

Perineal wound healing and radiotherapy

CURRENT STATUS

Perineal Wound Healing After Abdominoperineal Resection for Rectal Cancer: A Systematic Review and Meta-analysis

Gijsbert D. Musters, M.D. • Christianne J. Buskens, M.D., Ph.D.
Willem A. Bemelman, M.D., Ph.D. • Pieter J. Tanis, M.D., Ph.D.

Department of Surgery, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Perineal wound breakdown increased with radiotherapy, OR 2.22

Independent of APER type

Standard vs ELAPE

Musters et al. Diseases of the colon and rectum. 2014;57:1129-39

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Article in Press

Neoadjuvant Radiotherapy: A Risk Factor for Short-Term Wound Complications after Radical Resection for Rectal Cancer?

Presented at the 96th Annual Meeting of the New England Surgical Society, Newport, RI, September 2015.

Stefan D. Holubar, MD, MS, FACS, FASCRS, Rachel K. Brickman, BA, Spencer W. Greaves, BS,

2,476 patients 39%

having RT

preoperatively within

90 days of surgery

No difference in rates of:

APER vs SSS

Wound or overall complications

Return to theatre

Length of stay

Holubar et al Journal of the American College of Surgeons 2016 in press

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Improving quality of life with radiotherapy?

Improving Quality of life?

VOLUME 23 · NUMBER 9 · MARCH 20 2005

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Impac… …on
Health… …ning in
Prima…
Rando…

Corrie A.M… …elis P. Maas, Hendrik M… …r, and Anne …

Sexual dysfunction

VOLUME 28 · NUMBER 27 · SEPTEMBER 20 2010

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Impact of Short… …
Rectal Cancer o…
Medical Researc… …te
of Canada Clini…
Clinical Trial

Richard J. Stephens, Lindsay …, Gareth O. Griffiths, and David Sebag-Montefiore

Faecal incontinence

ESTRO School

Saving more sphincters?

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 44, No. 5, pp. 1027–1038, 1999

0360-3016/99/$–see front matter

PII S0360-3016(99)00099-1

CLINICAL INVESTIGATION **Gastrointestinal**

TUMOR DOWNSTAGING AND SPHINCTER PRESERVATION WITH PREOPERATIVE CHEMORADIATION IN LOCALLY ADVANCED RECTAL CANCER: THE M. D. ANDERSON CANCER CENTER EXPERIENCE

NORA A. JANJAN, M.D.,* VINCENT S. KHOO, M.D.,* JAMES ABBRUZZESE, M.D.,†
RICHARD PAZDUR, M.D.,† RONELLE DUBROW, M.D.,‡ KAREN R. CLEARY, M.D.,§
PAMELA K. ALLEN, M.P.H.,* PATRICK M. LYNCH, M.D.,‖ GARY GLOBER, M.D.,‖
ROBERT WOLFF, M.D.,† TYVIN A. RICH, M.D.,¶ AND JOHN SKIBBER, M.D.#

Departments of *Radiation Oncology, †Medical Oncology, ‡Diagnostic Radiology, §Pathology, ‖Gastrointestinal Oncology and Digestive Diseases, and #Surgical Oncology, The University of Texas, M.D. Anderson Cancer Center, Houston, TX, and the ¶Department of Radiation Oncology, University of Virginia Health Science Center, Charlottesville, VA

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Saving more sphincters?

Int. J. Radiation Oncology Biol. Phys., Vol. 44, No. 5, pp. 1027–1038, 1999

0360-3016/99/$–see front matter
PII S0360-3016(99)00099-1

CLINICAL INVESTIGATION — Gastrointestinal

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Departments of *Radiation Oncology, †Medical Oncology, ‡Diagnostic Radiology, §Pathology, ‖Gastrointestinal Oncology and Digestive Diseases, and ¶Surgical Oncology, The University of Texas, M.D. Anderson Cancer Center, Houston, TX, and the #Department of Radiation Oncology, University of Virginia Health Science Center, Charlottesville, VA

Tumor down-staging occurred in 72 (62%) cases

Pathological complete response (CR) in 32 (27%) of patients

In cancers < 6cm from AV, sphincter preservation was performed in 9 of the 17 (53%) CRs but only 20 of 52 patients (38%) when residual disease present

ESTRO School

Saving more sphincters?

Int. J. Radiation Oncology Biol. Phys., Vol. 44, No. 5, pp. 1027–1038, 1999

0360-3016/99/$–see front matter
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In cancers < 6cm from AV, sphincter preservation was performed in 9 of the 17 (53%) CRs but only 20 of 52 patients (38%) when residual disease present

Impact of RT seems to be for population with probable CCR

Conclusion

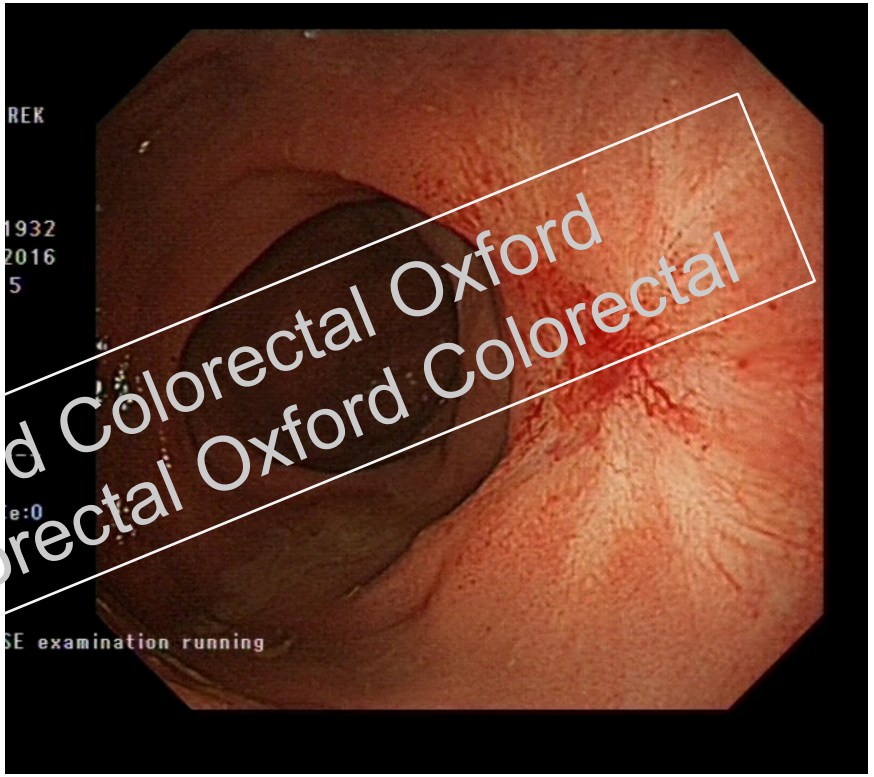
Radiotherapy offers value in advanced disease and will reduce R1 rate

Role of radiotherapy in surgically resectable disease yet to be defined

Most benefit from RT comes from those with complete response

-Increase sphincter preservation

-Avoid radical surgery

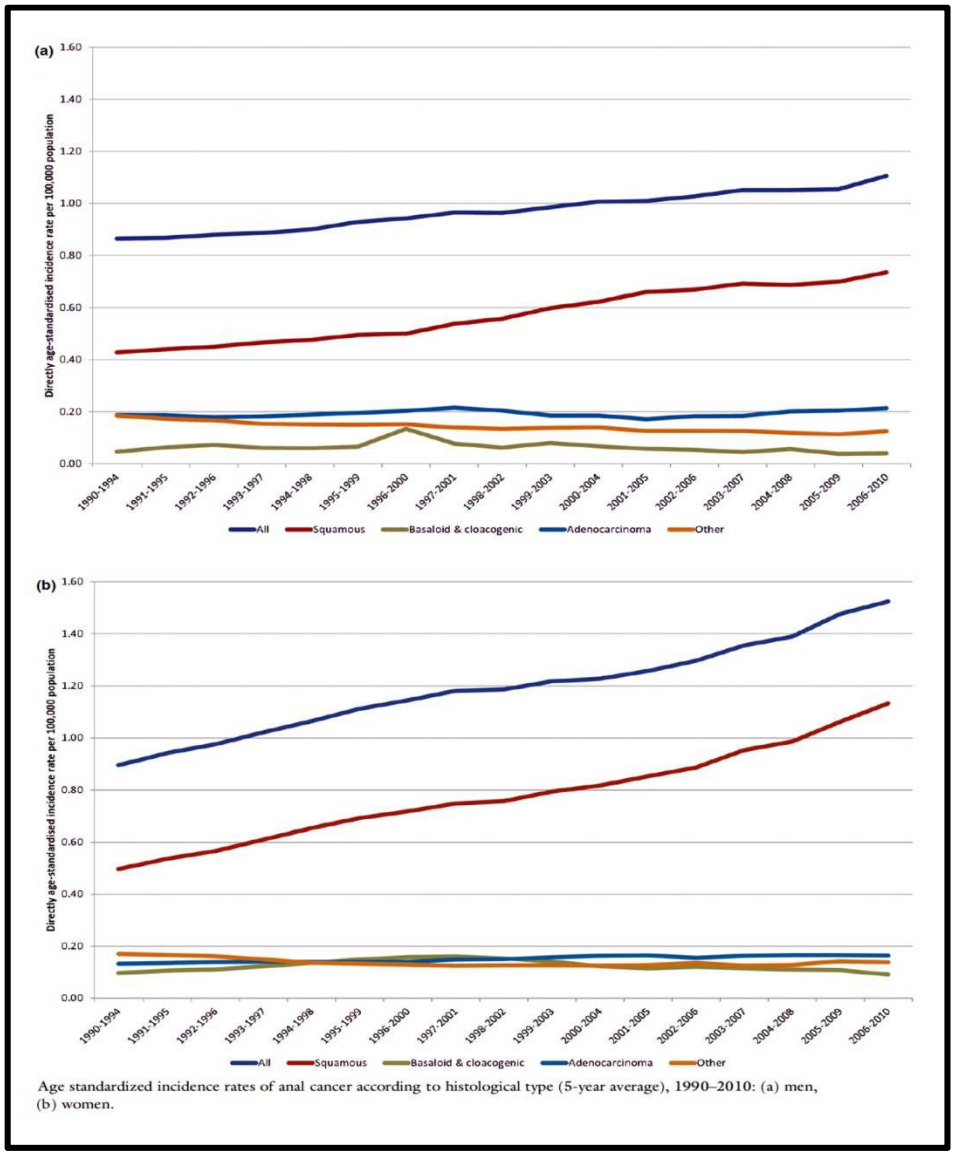


Prognostic Factors in Anal Cancer

ESTRO LOWER GI COURSE :

Technical & Clinical Challenges for Radiation Oncologists

Anal cancer – Increasingly Common

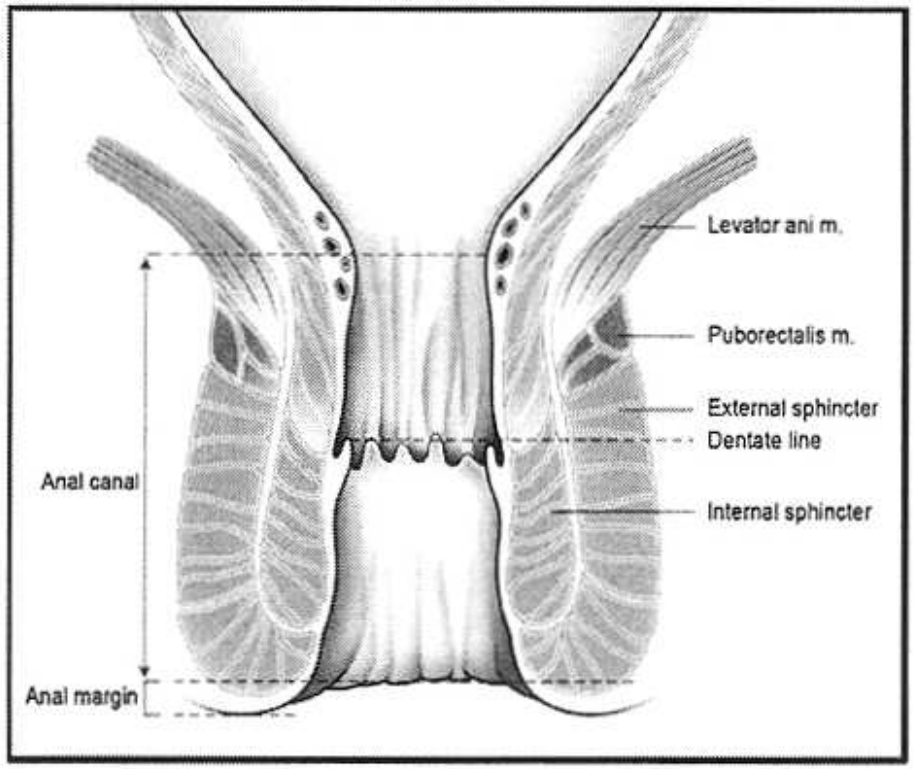


Age standardized incidence rates of anal cancer according to histological type (5-year average), 1990–2010: (a) men, (b) women.

- **English National Cancer Data Repository 1990 – 2010 (all anal cancers diagnosed in England)**
- **69 % increase in age standardised incidence for SCC in men from 0.43 per 100,000 to 0.73 per 100,000**
- **126 % increase for women from 0.5 per 100,000 to 1.13 per 100,000**
- **No change in incidence of anal adenocarcinoma**
- **Similar changes reported in Scotland, Denmark, Sweden, Australia and the USA**

(Wilkinson et al 2014)

Anal cancer – Anal Canal & Anal Margin



Most Anal tumours arise in the Anal Canal

- The anal margin is defined as the area of pigmented skin around the anal orifice - extending laterally to a radius of 5cm
- Anal margin tumours are staged as cutaneous SCCs

ANAL CANCER : UICC TNM STAGE

T STAGE

- **TX** - tumor cannot be assessed
- **T0** - no primary tumor
- **Tis** - AIN 2 & 3 ; high grade SIL
- **T1** - tumor < 2cm maximum diameter
- **T2** - tumor > 2cm & < 5cm
- **T3** - tumor > 5cm
- **T4** - tumor of any size invading adjacent organs eg. vagina, urethra,bladder (excludes rectum, peri-anal skin & sphincter muscle)

N STAGE

- **NX** - nodes cannot be assessed
- **N0** – no node metastasis
- **N1** – metastasis in peri-rectal nodes
- **N2** – metastasis in unilateral internal iliac and/or inguinal nodes
- **N3** – metastasis in peri-rectal & inguinal nodes or bilateral internal iliac node involvement or bilateral inguinal node involvement

- **any tumor between rectum and peri-anal skin**
- **anal margin tumors classified as skin cancers**

Anal Cancer : TNM stage & Outcome

- **US GI Intergroup RTOG 98-11 phase 3 anal cancer trial**
- **RCT of RT + 5FU/MMC versus RT + 5FU/CDDP & indictin chemotherapy with 5FU/CDDP**
- **T2 – T4 +/- LN metastases (excludes T1 N0-3 and M1 disease)**
- **N = 620 patients**

	No.	5yr Local Failure	5yr DM	3yr Colostomy failure	5yr DFS	5yr OS
T2 N0	323	17 %	10 %	11 %	72 %	82 %
T3 N0	96	18 %	14 %	13 %	61 %	74 %
T4 N0	31	37 %	21 %	26 %	50 %	57 %
T2 N1-3	99	26 %	27 %	11 %	57 %	70 %
T3 N1-3	46	44 %	24 %	27 %	38 %	57 %
T4 N1-3	25	60 %	24 %	24 %	31 %	42 %
T2 or 3 N0	419	17 %	11 %	11 %	70 %	80 %
T4N0 or T2-4 N1-3	201	36 %	25 %	19 %	49 %	62 %

(Gunderson et al 2013)

Anal Cancer : the importance of tumour size

- **Das et al (2007) : 167 patients treated with CRT**
- **3 yr locoregional control :**
- **T1/Tx 90 % (76 – 100)**
- **T2 86 % (76 – 96)**
- **T3 77 % (61 – 93)**
- **T4 63 % (41 – 86)**

T stage a significant independent predictor of loco-regional failure on multivariate analysis (HR 1.71)

- **Ajani et al (2009 & 2010) : RTOG 98-11 trial of RT + 5FU/MMC versus RT + 5FU/cisplatin**
- **Tumour diameter > 5cm associated with a greater risk of colostomy, worse 5 yr DFS & 5 yr OS (p = 0.0003) compared with smaller tumours**

Anal Cancer : the importance of nodal metastasis

- Das et al (2007) : 167 patients treated with CRT

	3 yr locoregional control	3 yr distant control
N0	85 %	94 %
N1	88 %	79 %
N2	84 %	75 %
N3	39 %	76 %

- N stage an independent predictor of loco-regional failure, distant metastasis and OS on multivariate analysis !

- Ajani et al (2010) : RTOG 98-11 trial
- Clinically positive nodes associated with worse 5 yr DFS and 5 yr OS ($p < 0.0001$)

Other Prognostic Factors

- **Male gender**

- **EORTC 22861 :**
- **local control p= 0.0028**
- **overall survival p=0.0034**

- **RTOG 98-11 :**
- **disease free survival p = 0.02**
- **overall survival p=0.016**

- **ACT 1 Trial :**
- **Loco-regional failure HR 1.6 (1.03-2.49) p=0.036**
- **Anal cancer death HR 1.8 (1.03-3.16) p=0.039**
- **Overall survival HR 1.56 (1.12 – 2.17) p=0.008**

Other Prognostic Factors

- **ACT 1 trial :**

➢ **low Hb associated with increased anal cancer death (p=0.008)**

- **EORTC 22861 :**

➢ **skin ulceration associated with loco-regional failure (p=0.003) and overall survival(p=0.005)**

ANAL CARCINOMA : HISTOLOGICAL CLASSIFICATION

- **SQUAMOUS CELL CARCINOMA NOS (80 - 90%)**
  - size of neoplastic cell
  - basaloid morphology
  - keratinization
  - presence of mucinous microcysts
  - degree of differentiation
  - presence of adjacent AIN

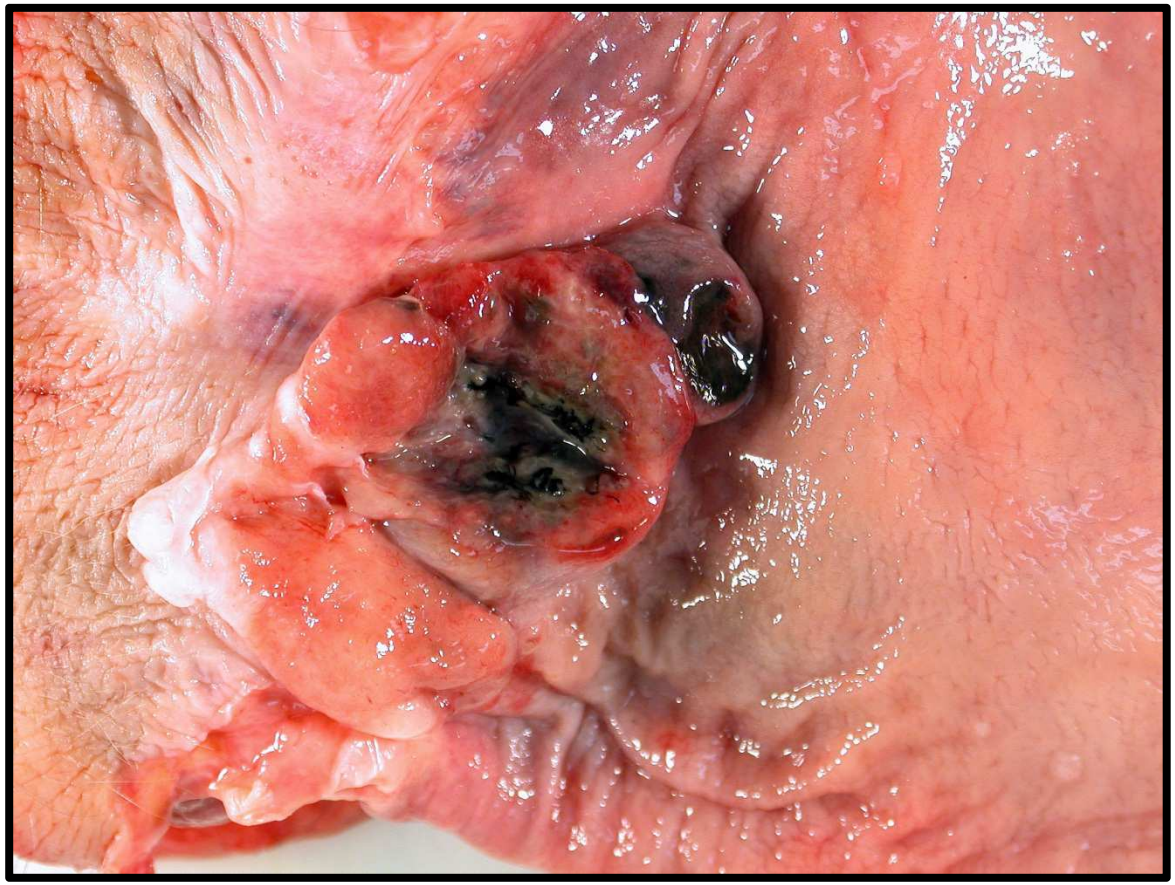
WHO 2nd Edition.
large cell keratinizing
large cell non-keratinizing
Basaloid (cloacogenic)

- **VERRUCOUS CARCINOMA (GIANT CONDYLOMA OF BUSCHKE-LOWENSTEIN) (< 1 %)**

- **ADENOCARCINOMA (anal gland, mucinous – fistula related, rectal type) (10 – 15 %)**
- **NEUROENDOCRINE CARCINOMA (large cell & small cell type) (< 2 %)**

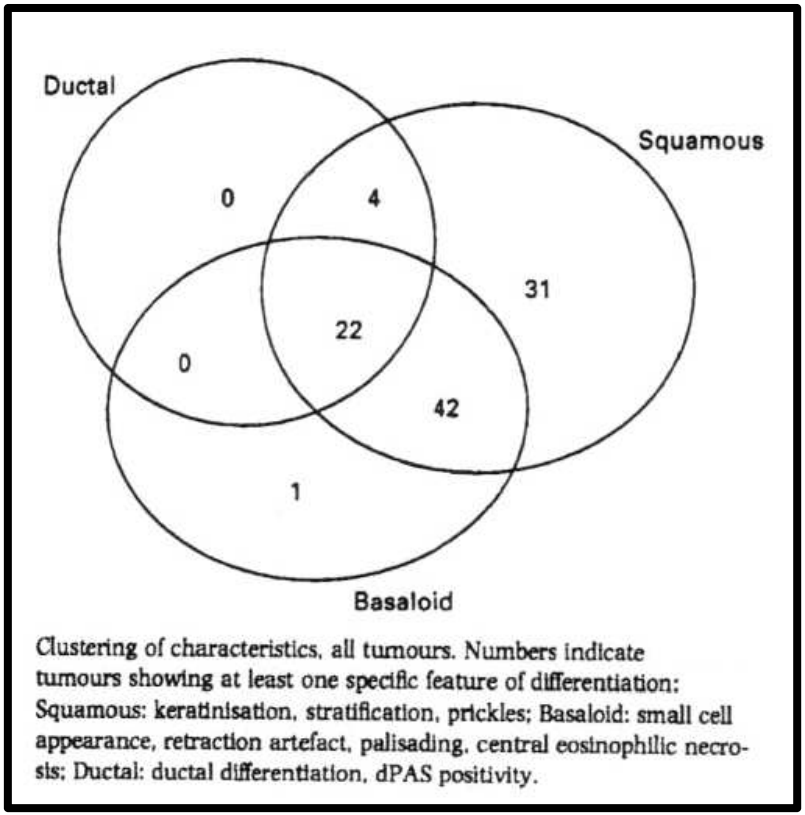
Other Cancers

- **Malignant Melanoma (< 2 %)**



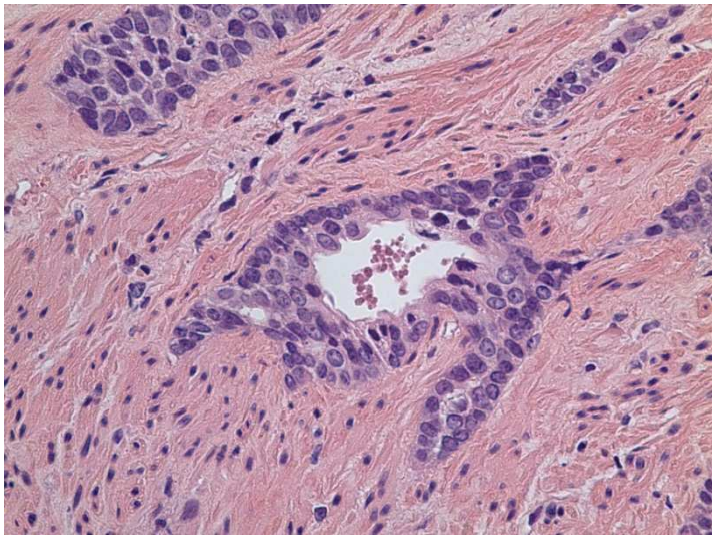
- **Lymphoma**
- **Sarcoma**

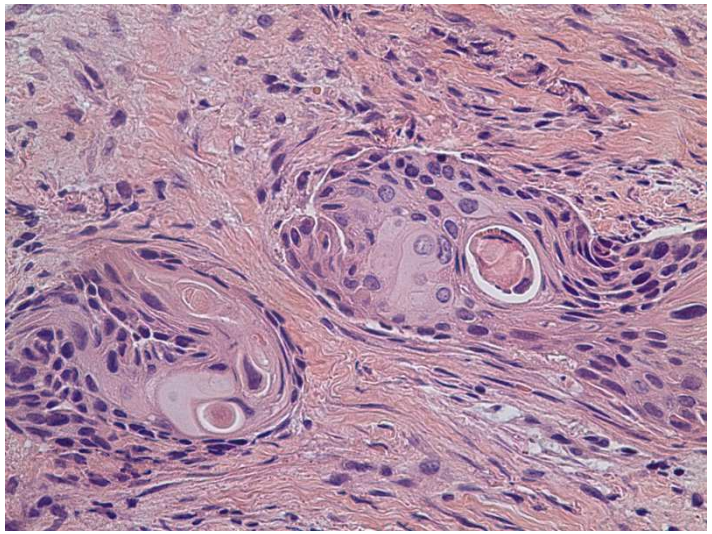
SCC of the Anal Canal : Overlap of Histological Types

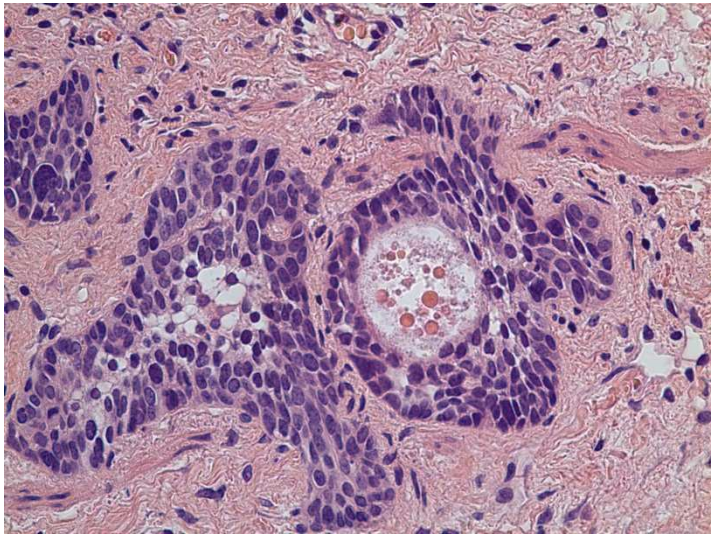


Clustering of characteristics, all tumours. Numbers indicate tumours showing at least one specific feature of differentiation: Squamous: keratinisation, stratification, prickles; Basaloid: small cell appearance, retraction artefact, palisading, central eosinophilic necrosis; Ductal: ductal differentiation, dPAS positivity.

(Williams & Talbot 1994)

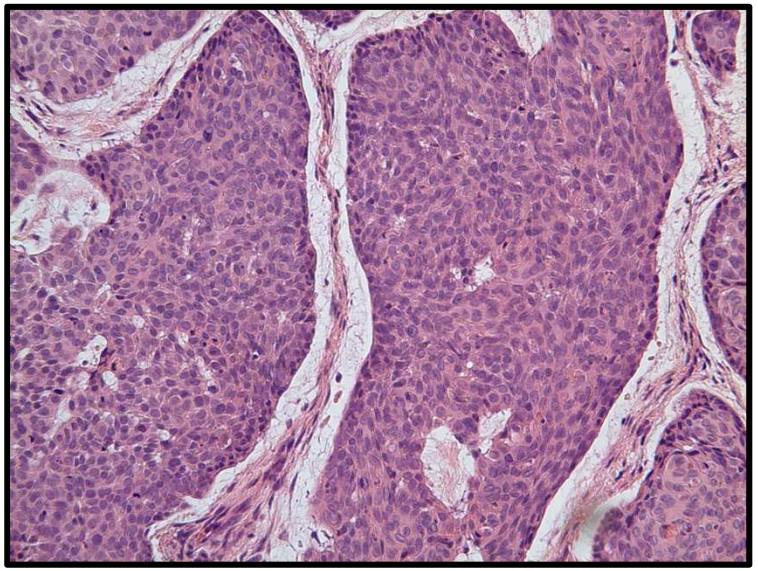


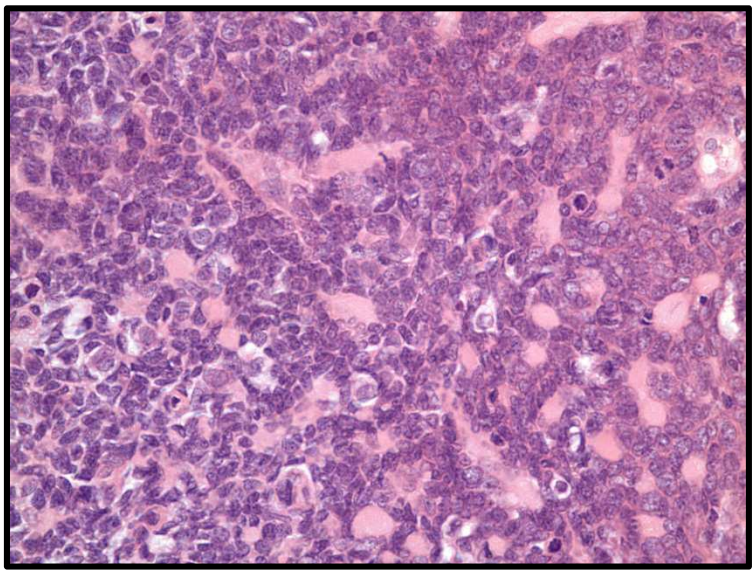


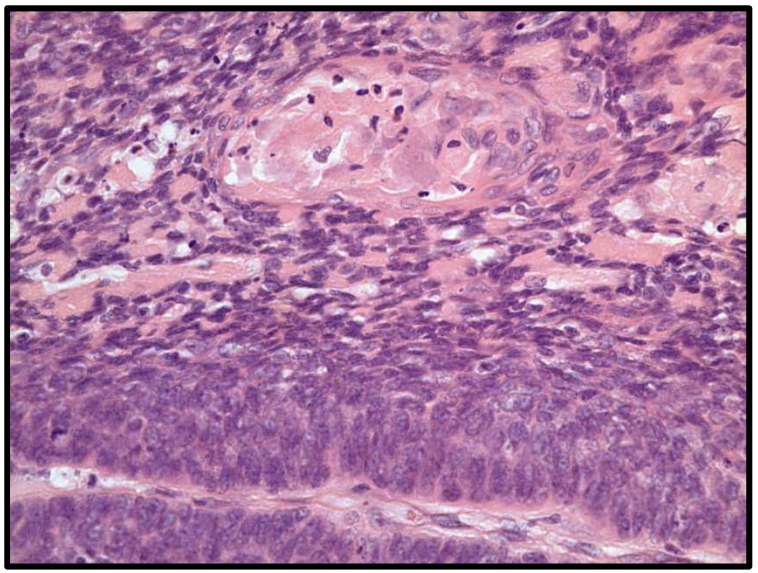


Basaloid Variant SCC

Bonnen et al (1984)	61/160	(38 %)
Dougherty et al (1984)	11/79	(13.9 %)
Shepherd et al (1989)	60/166	(36 %)

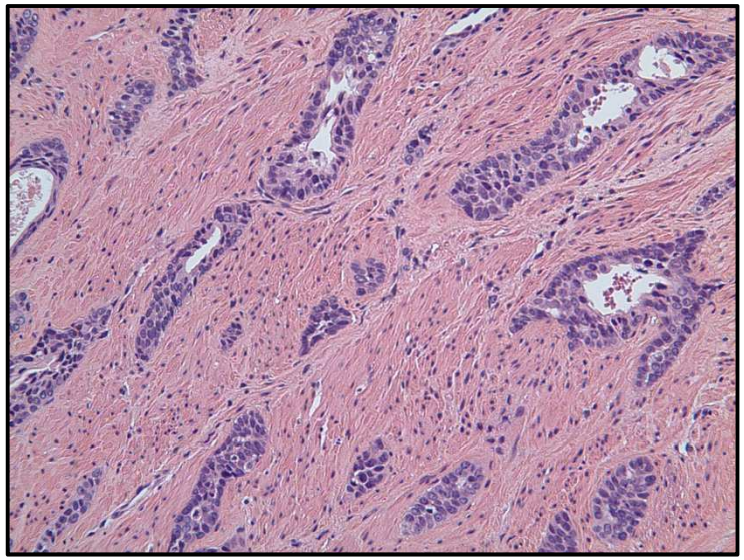


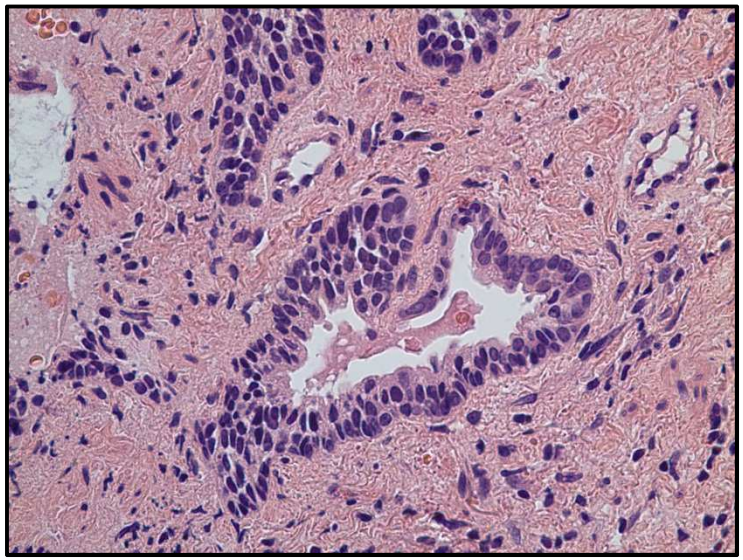


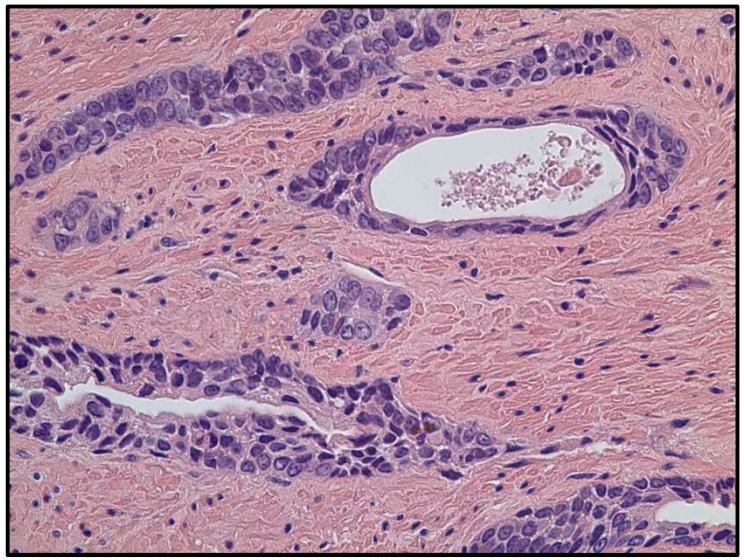


Squamous Cell Carcinoma with Mucus Microcysts (“Mucoepidermoid carcinoma of the anus”)

Morson et al (1963)	21/178	(11.8 %)
Dougherty et al (1984)	6/79	(7.6 %)
Shepherd et al (1989)	10/235	(4.3 %)







study	No.	Time period	treatment	outcome
Boman et al (1984) SCC – grades 1 to 4 Basaloid type SCC	188	1950-1976	Surgery	Grade & type correlated with stage. No significant correlation with survival after adjusting for stage.
Dougherty et al (1984) Keratinizing SCC Non-keratinizing SCC Basaloid SCC SCC with microcysts	79	Pre 1978	Surgery	No correlation of histologic type with depth of invasion or node metastasis. No correlation with survival.
Shepherd et al (1989) SCC Basaloid type Mixed type	235	1948-1985	Surgery	Histologic type not predictive of survival in multivariate analysis.
Bartelink et al (1997) SCC versus other types Histologic grade	110	1987-1994	RT & CRT	Neither type nor grade predicted local control or survival.
Myerson et al (2001) SCC – low & high grade Basaloid type	106	1975-1997	Mainly CRT	Borderline significant improved 5yr DFS for basaloid type. No effect of tumour grade.
Das et al (2007) SCC grades 1 to 3 Basaloid type	167	1992-2004	CRT	Basaloid type associated increased risk of Distant Metastasis (HR 4.23). No correlation type or grade with loco-regional failure or survival.

Biomarkers in Anal Carcinoma – Much Ado About Nothing

- **p53 : 8 studies 1996 – 2009 (n = 14 – 214)**

- immunohistochemistry used in all studies
- 34% – 100 % cancers positive (34-60% in 6/8 studies)
- All cancers treated with CRT
- **No prognostic significance in 6/8 series** ; reduced DFS in 2/8

- **p21 : 3 studies 2001 – 2006 (n = 94 – 215)**

- immunohistochemistry used in all studies
- 65 % – 71 % cancers showed positive staining
- **absent expression associated with reduced OS in one study and a trend towards reduced DFS in the other two** ; significant association with loco-regional failure in one out of three.

- **EGFR : 3 studies 2005 – 2009 (n = 21 – 38)**

- immunohistochemistry used in all 3 series
- EGFR expression seen in 55 % – 100 % of cancers
- **NO prognostic significance found**

(Lampejo et al 2010)

Biomarkers in anal Carcinoma – Much Ado About Nothing

- **BCL – 2 : 3 studies 2003 – 2009 (n = 21 – 98)**

- immunohistochemistry in all 3 studies
- BCL 2 expressed in 24 – 58 % of cancers
- associated with reduced local control and DFS in one study ; no prognostic significance in the other two

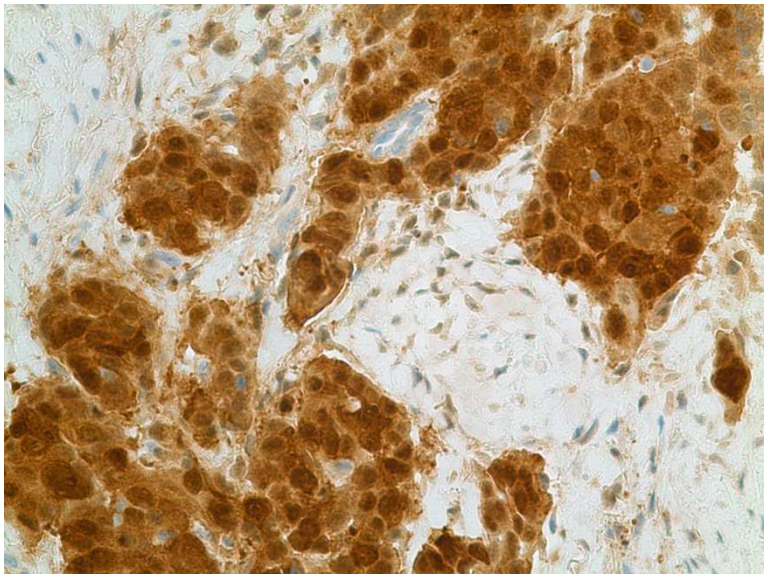
- **Ki67 : 4 studies 1998 – 2009 (n = 31 – 62)**

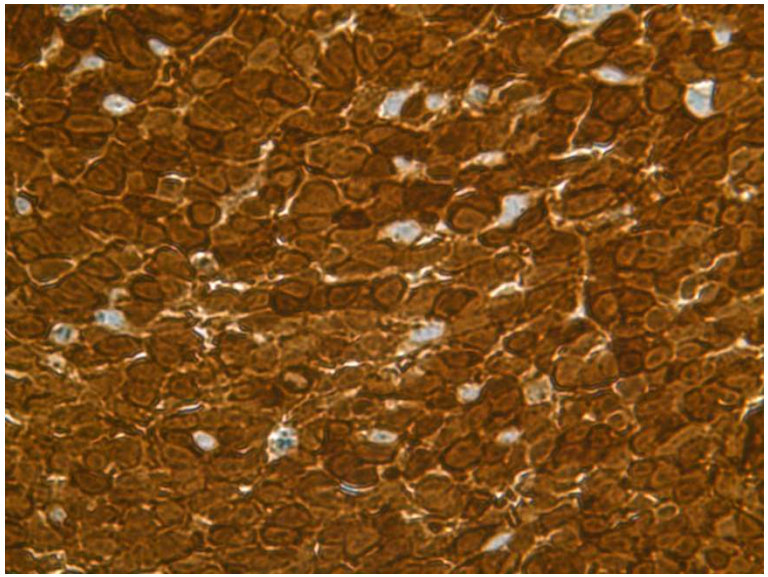
- Immunohistochemistry (MIB1) used in all studies
- No prognostic significance in 2 out of 4 studies ; elevated Ki67 associated with longer DFS in one study and improved colectomy free survival in a second study.

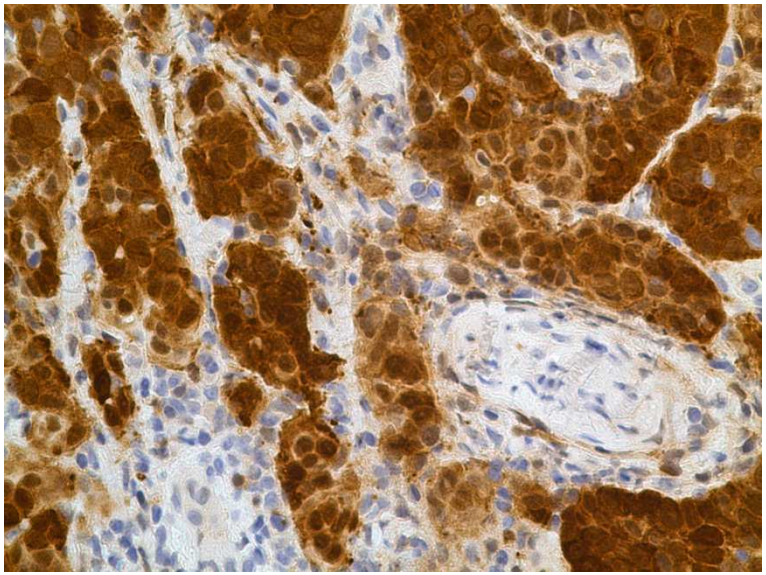
- **Others : VEGF - no prognostic significance**
  MVD - no prognostic significance
  PCNA - no prognostic significance
  Cyclins - no prognostic significance in 3 out of 4 studies

(Lampejo et al 2010)

p16 – a promising biomarker in Anal Cancer







p16 – ink4a
Chromosome 9p21
Inhibits entry into S phase of the cell cycle
Binds CDK4/6 inhibiting formation of the cyclin-CDK4/6 complex
HPV E7 protein binds Rb releasing E2F transcription factor leading to increased p16 expression

p16 overexpression in anal cancer is a useful surrogate marker of high risk HPV infection !!!

Human Papilloma Virus & Anal Carcinoma

- Vuyst et al (2009) – meta-analysis of 29 international studies between 1986 – 2008

➢ Overall prevalence of HPV in AIN = **92.7 %** (1280 cases)

➢ Overall prevalence of HPV in anal carcinoma = **84.3 %** (955 cases)

	All types	HPV 16	HPV18	Multiple types
AIN 1	91.5 %	37.2 %	21.3 %	54.4 %
AIN 2 & 3	93.9 %	59.8 %	17.4 %	
SCC	84.3 %	73.4 %	5.2 %	6.8 %

- ? HPV more common in basaloid variant SCC (> 95 %)
- ? HPV associated lower T stage & N stage at diagnosis

HPV & ANAL CANCER

- **143 stage I – III anal SCCs (2000 – 2010)**
- **Single centre in Denmark**
- **52 % treated with RT ; 48 % treated with CRT**
- **Median F.U 51.2 months**
- **Recurrent disease in 23 %**
- **87.6 % HPV + (79.6% HPV16)**
- **92.9 % p16 +**

	Overall Survival	Disease Specific Survival
HPV +	74 %	84 %
HPV -	52 %	52 %
p16 +	76 %	85 %
p16 -	30 %	30 %

(Serup-Hansen et al 2014)

HPV associated Anal Cancer is genetically distinct

- Meulendijks et al (2015)
- 138 anal SCC

	No.	% p53 I/C +	% p53 disruptive mutations	3 yr loco-regional control	3yr OS
HPV+ p16+	93	10% (9/93)	6 % (1/18)	82 %	87 %
HPV- p16+	4		33 % (1/3)	75 %	75 %
HPV- p16-	10	50% (5/10)	80 % (8/10)	15 %	35 %

No difference in T or N stage between HPV+ and HPV - cancers

HIV & ANAL CANCER

Historically (pre-HAART) anal carcinoma treatment in HIV positive patients associated with lower response rate and reduced survival

Radiotherapy and chemotherapy poorly tolerated with more toxicity and breaks in treatment

More recent studies (post HAART) suggest outcomes equivalent to non-HIV+ patients

Is the prognosis of Anal cancer worse in HIV infected patients ?

- **Oehler – Janne et al (2008)**
- **40 consecutive HIV(+) patients from 4 centres in Switzerland, France & Canada treated with CRT between 1997-2006**
- **Compared with 81 HIV(-) patients**
- **98 % SCC**

	HIV (+)	HIV (-)
cCR	92%	96%
5 yr local control	38%	87%*
5 yr sphincter preservation	38%	74%**
5 yr DM free survival	91%	84%
5 yr DSS	68%	85%***
5 yr OS	61%	65%
Acute G3/4 toxicity	48%	31%
Severe skin toxicity	35%	17%
Severe haematologic toxicity	33%	12%

- **poorer local control experienced by HIV(+) group with significantly higher colostomy rate**
- **Higher treatment related toxicity**
- **Less use of MMC in HIV(+) group**
- **Longer duration of RT in HIV(+) group (? more treatment breaks)**

(* P = 0.008 ; **p = 0.035 ; *** p = 0.09)

HIV & ANAL CANCER

- **Wexler et al (2007)**
- 32 HIV+ patients treated with CRT (5FU+MMC) between 1997 and 2005
- Median tumour size 2.8 % ; **44% cT1 cN0**
- 5 yr actuarial risk of local failure = 16 %
- 3 / 32 developed distant metastases
- 5 yr overall survival = 65 %
- 5 yr cancer specific survival = 75 %
- **Fraunholz et al (2011)**
- 25 HIV + patients and 45 HIV – patients
- No difference in T or N stage at diagnosis (all M0)
- More young males in the HIV+ group
- No difference in RT dose delivered
- 72 % HIV+ received full dose of chemotherapy cf. 91 % HIV- group

	CR at 8 wks	5 yr local control	5 yr metastasis free survival	5 yr overall survival
HIV +	**84 %**	**65 %**	**86 %**	**71 %**
HIV -	**93 %** pNS	**78 %** pNS	**91 %** pNS	**77 %** pNS

SCC of the Anal Margin

- 5 – 10x less common than anal canal tumours
- more often well differentiated & keratinizing
- less often hrHPV positive (80% in women & 28% in men – Frisch et al 1999)
- Small well differentiated tumours < 2cm can be treated by local excision +/- adjuvant radiotherapy
- Larger tumours that are poorly differentiated or metastatic to inguinal lymph nodes (15 – 20 % of patients) are treated with radiotherapy or CRT

SCC of the Anal Margin

- Risk of lymph node metastasis is related to tumour size:

Tumour size	% Node Metastasis Papillon & Chassard (1992)	% Node Metastasis Cummings et al (1986)
< 2cm	0 %	0 %
2 – 5 cm	24 %	
> 5cm	67 %	25 %

SCC of the Anal Margin : Results of Radiotherapy

	number	5 yr LRC	5 yr OS	Sphincter preservation
Chapel et al 2006	26	61 %	71 %	65 %
Cummings et al 1986	29	72 %	NS	NS
Papillon et al 1992	57	88 %	59 %	90 % (in cured patients)
Touboul et al 1995	17	86 %	82 %	82 %
Bieri et al 2001	24	70 %	56 %	67 %
Peiffert et al 1997	31	77 %	67 %	84 %
Khanfir et al 2008	45	78 %	55 %	80 %

SCC of the Anal Margin : Prognostic Factors

- Anal margin tumours have been reported to have both a better and worse prognosis than anal canal lesions – ACT 1 trial found no effect for LRF or OS.
- Studies of prognostic factors specific to anal margin tumours are lacking and reported series are small

➢ Chapet et al (2007) - 26 patients treated with primary EBRT or adjuvant RT after local excision : cancer specific survival related to age, tumour differentiation, T stage & N stage

Tumour diffn	5 yr CSS
Well diffn	85 %
Mod diffn	67 %
Poor diffn	50 %

T stage	5 yr CSS
T1	100 %
T2	92 %
T3	37 %
T4	0 %

N stage	5 yr CSS
N0	93 %
N1	67 %
N2	33 %

➢ Khanfir et al (2008) – 45 patients with primary EBRT or adjuvant RT after local excision : no factors (T stage, N stage, histological grade or age) were predictive of loco-regional control

Prognostic Factors in Anal Cancer

- Tumour size
- T stage
- N stage
- Distant Metastasis
- ? Histological type (probably not !)
- ? Histological grade (probably not !)
- Presence of skin ulceration (EORTC 22861)
- Male sex (ACT 1, EORTC 22861 & RTOG 98-11)
- Low Haemoglobin (ACT 1)
- HIV status (not so important post HAART)
- HPV status & p16 immunohistochemistry

The ROYAL MARSDEN
NHS Foundation Trust

Rectal Carcinoma: staging the bad tumours

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Royal Marsden Hospital
Imperial College, London

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The Royal Marsden

Cuthbert Dukes 1932: Nodes as a prognostic factor

- *A cases* - carcinoma is limited to the wall of the rectum, no extension into the extra-rectal tissues and no metastases in lymph nodes.
- *B cases* - carcinoma has spread by direct continuity to the extra-rectal tissues but has not yet invaded the regional nodes,
- *C cases* - metastases are present in the regional lymph nodes.
- system predicted **prognosis** and became a gold standard: Three-year survival after surgery was 80%, 73% and **7%** for A,B and C respectively.

NHS

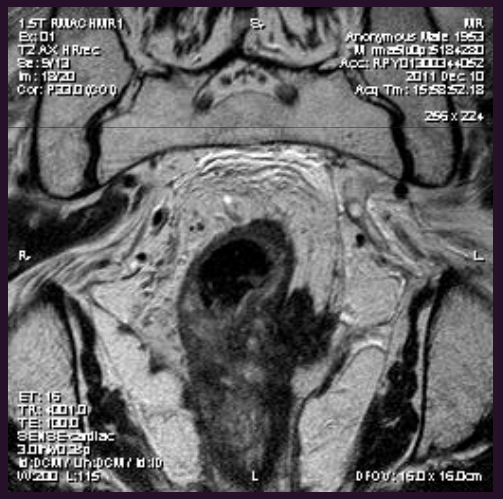
There are big problems with the current TNM system and preoperative staging rectal cancer…..

The problems with TNM

- T3 category is enormous and survivals range from 90% (same as Dukes A) to 25%
- Stage III classification is too heterogenous
- TNM does not take into account CRM status
- TNM does not take into account extramural vascular invasion
- TNM does not take into account low rectal cancer stage system
- Using T and N staging does not perform adequately in the assessment following neoadjuvant therapy

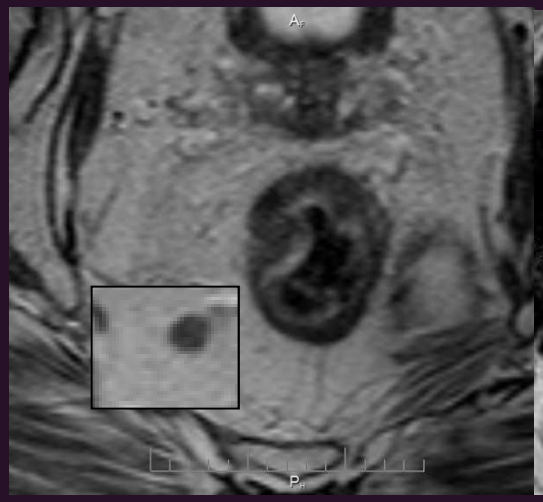
These tumours have entirely different prognostic outcomes

Stage II (T3N0)



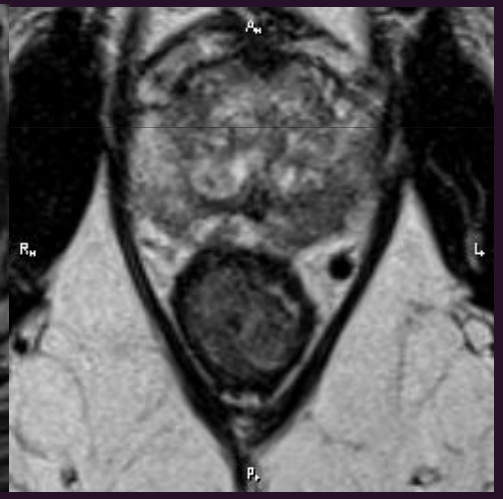
mrT3dN0EMVI pos
CRM+:CRT+chemo +
beyond TME surgery

Stage III (T3N1)

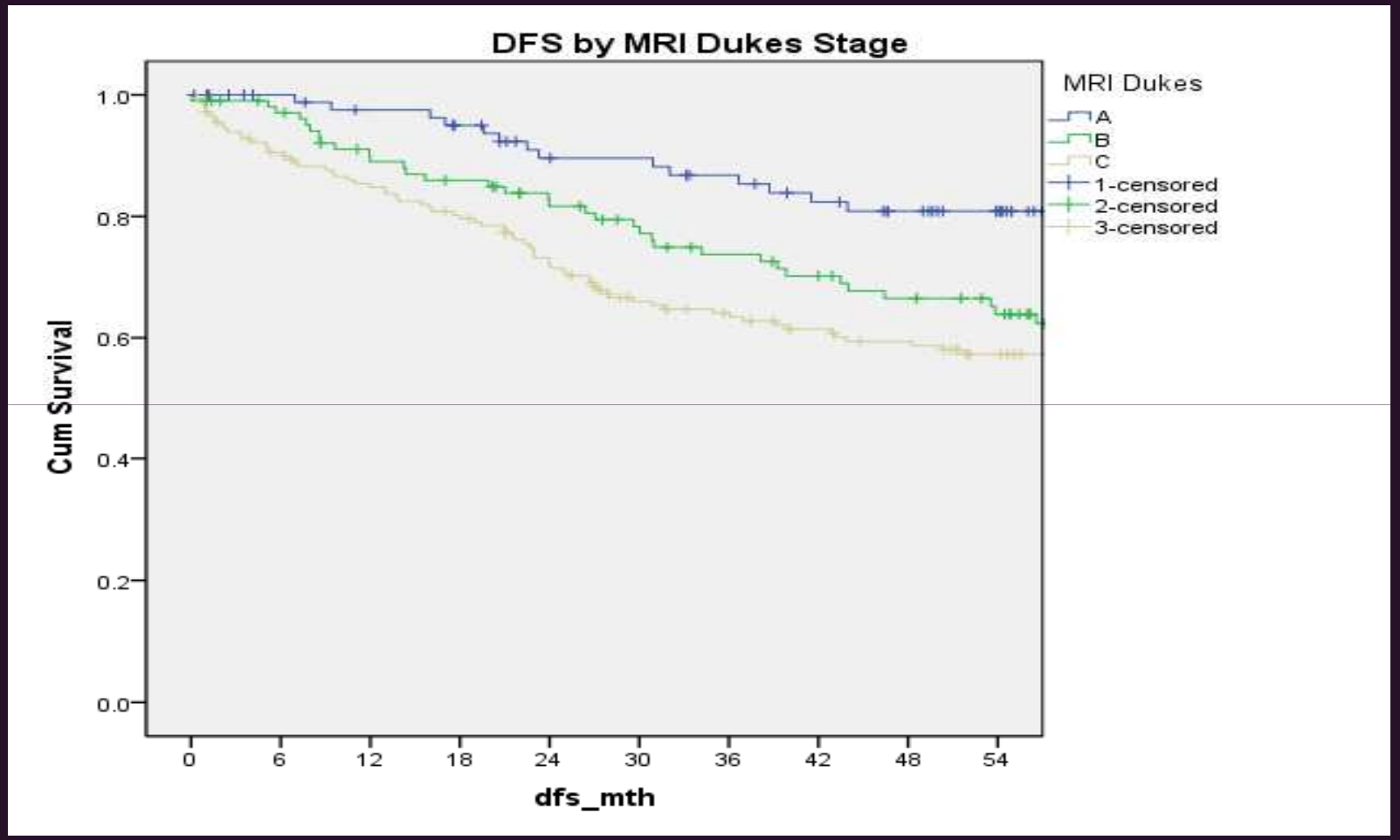


mrT3aN1CRM-ve
Primary TME surgery

Stage I (T1N0)



mrT1 EMVI deposit,
CRM+ve, Preoperative CRT
and ELAPE


DFS by MRI Dukes Stage
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
6
12
18
24
30
36
42
48
54
dfs_mth
MRI Dukes
A
B
C
1-censored
2-censored
3-censored

Current evidence base for preoperatative local staging assessment using MRI

#1. Identifying patients at risk of Local Recurrence

Published Ahead of Print on November 25, 2013 as 10.1200/JCO.2012.45.3258
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2012.45.3258

Firs
M

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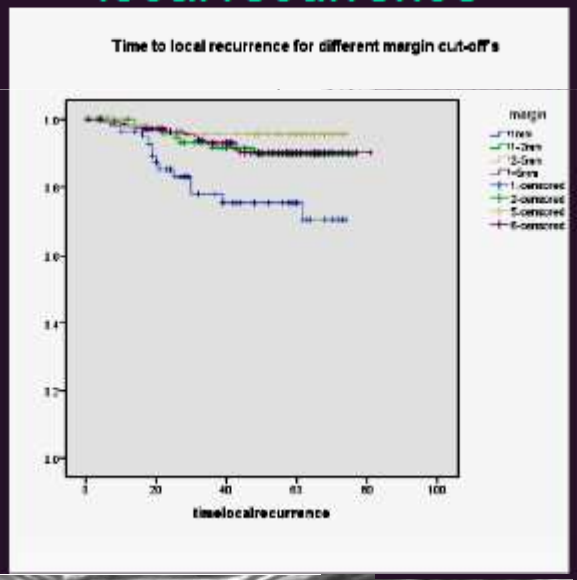
REPORT

Conclusion
High-resol
criteria for
associatec
treatment

J Clin Onc

only 1mm cut-off on MRI predicts local recurrence



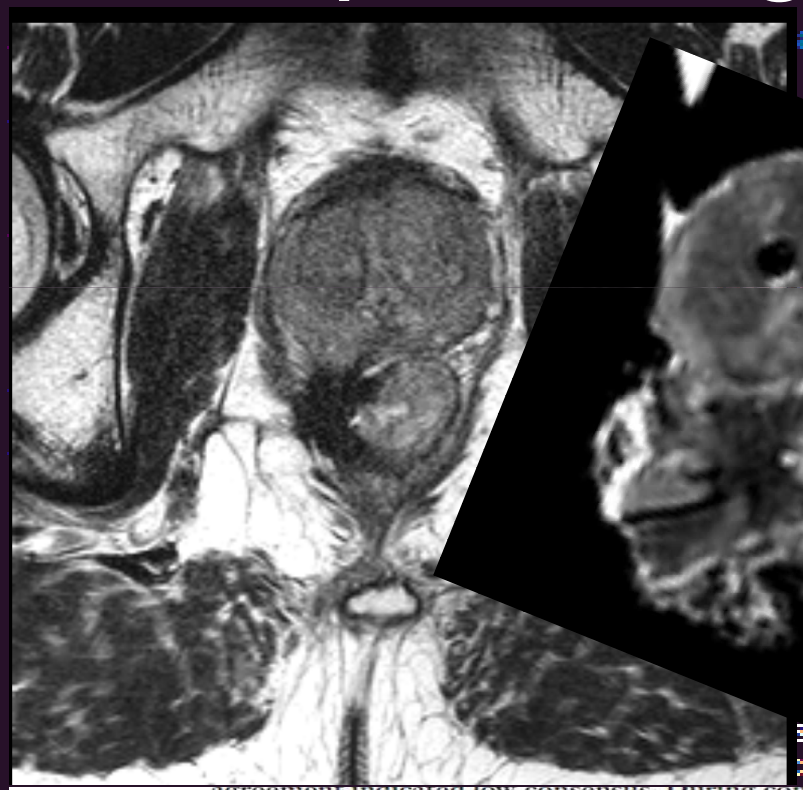
l multidisciplinary team
treatment strategy: the
eliminate positive
erential margins?

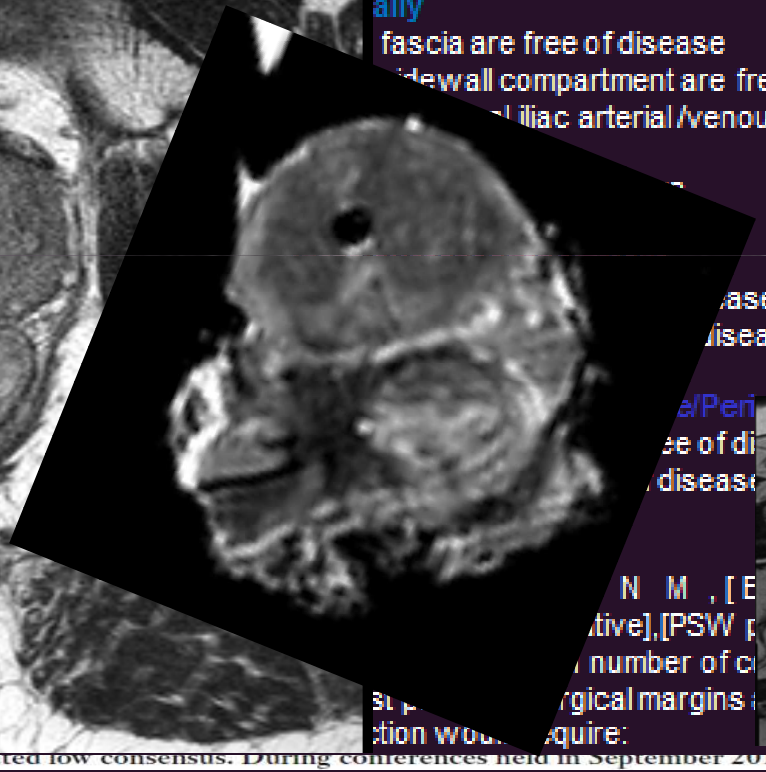
involvement of margins when
ssion of MRI scans compared with
tive discussion takes place

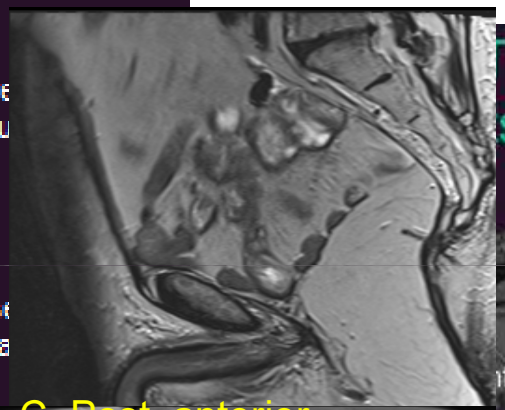
ion of preoperative MRI scans
, positive CRM rate is now 2-3%
G, Daniels IR, Norman AR, Mason B,
ancer. 2006 Feb 13;94(3):351-7.

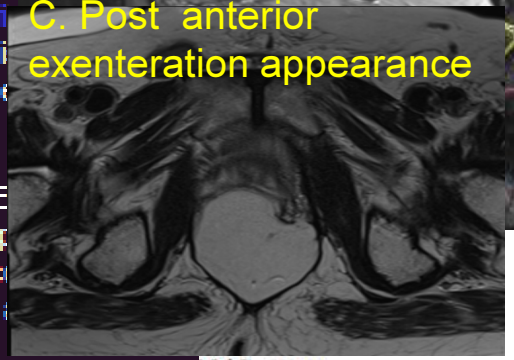
NHS

#2. Identifying patients who require surgery beyond TME







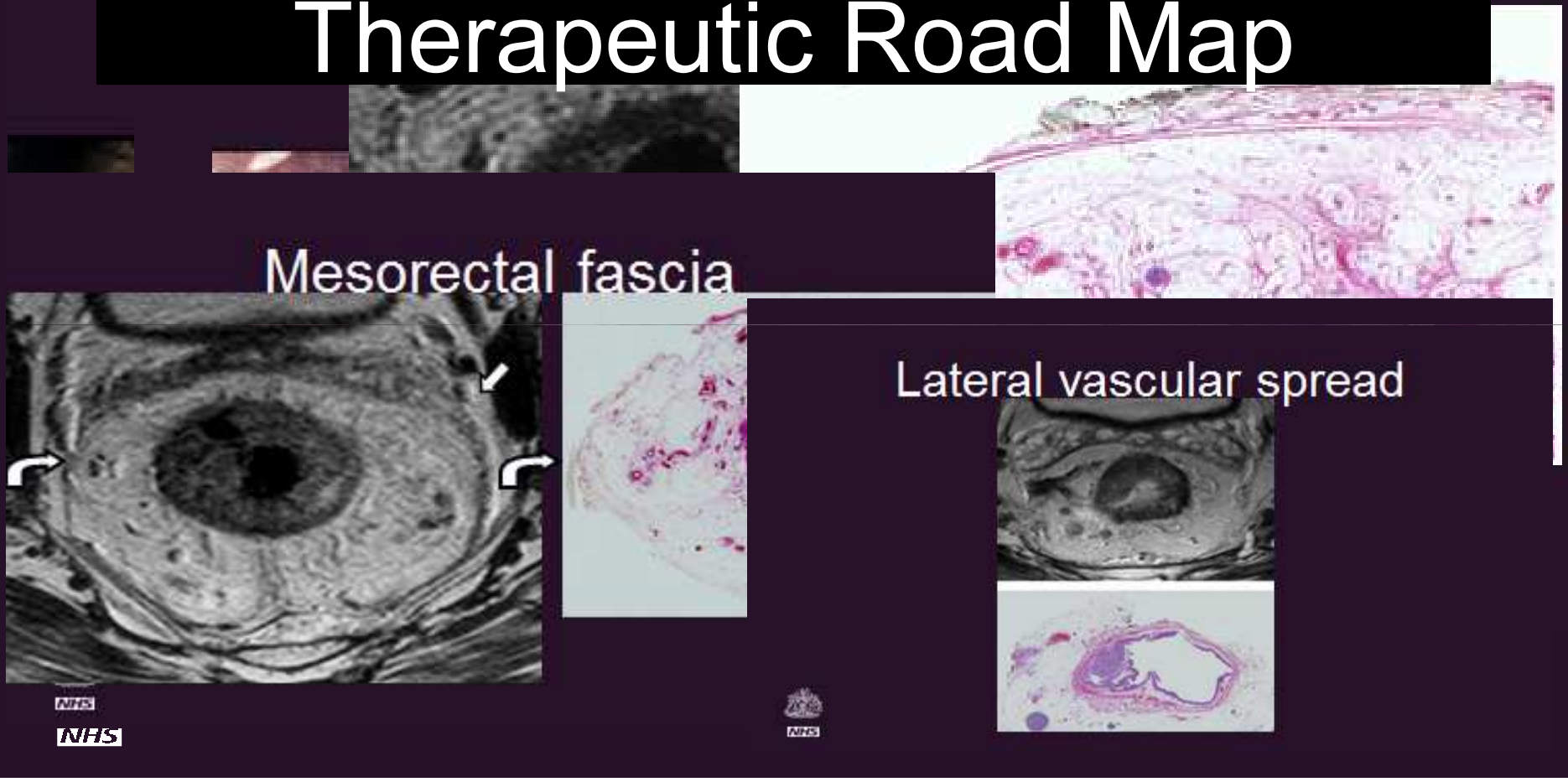


C. Post anterior exenteration appearance

ally
fascia are free of disease
idewall compartment are fre
iliac arterial/venou
ase
disea
e/Peri
ee of di
disease
N M , [E
tive],[PSW p
number of c
rgical margins
ction wou quire:

agreement indicated low consensus. During conferences held in September 2011 and March 2012, open

#3. Anatomic Surgical and Therapeutic Road Map



#4. Staging and assessment of low rectal cancer

rates of 30%.

– Patients with no adverse MRI features and a "safe" mrLRP underwent sphincter preserving surgery without preoperative radiotherapy, resulting in a 1.6% pCRM rate.

Battersby, N. J., How, P., Moran, B., Stelzner, S., West, N. P., Branagan, G. et al. MERCURY II Study Group. (2015).
Prospective Validation of a Low Rectal Cancer Magnetic Resonance Imaging Staging System and
Development of a Local Recurrence Risk Stratification Model: The MERCURY II Study. *Ann Surg*. 2015

#5. MRI assessment of depth of tumour spread gives the most accurate prognostic information

mrT3<5mm h

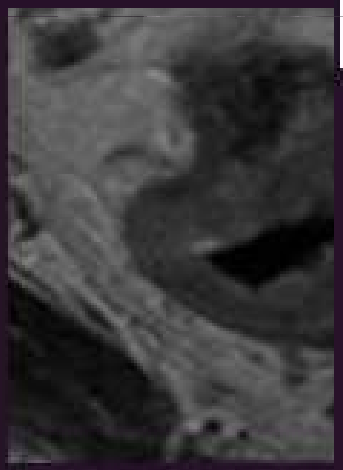
if mrC

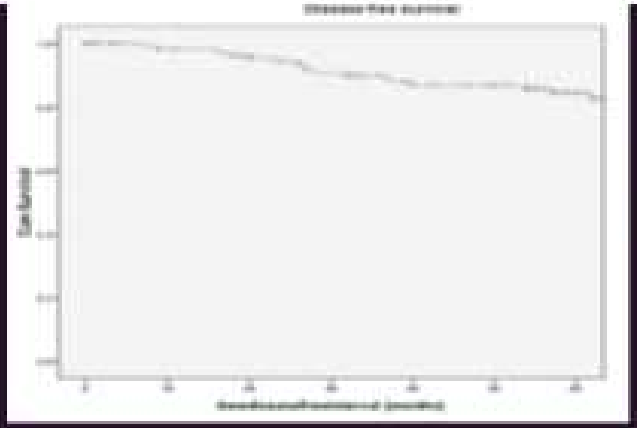
l

Outcomes for MRI good prognosis rectal cancers: regardless of N stage

TABLE 3. Outcomes for MRI-predicted Good Prognosis Patients and Effect of Univariate and Multivariate Analysis Local Recurrence, 5-year Overall Survival and Disease-free Survival

MERCURY—MRI-predicted Good Prognosis Patients	Local Recurrence	5-Year Overall Survival	5-Year Disease-free Survival
Total patients (n = 122)	3.3%	68.2% (95% CI, 60.2%–7.0%)	84.7% (95% CI, 76.0%–90.4%)
T3a/b N0, N1, and N2 (n = 58)	1.7%	67.9% (95% CI, 53.9%–78.5%)	81% (95% CI, 66.1%–89.8%)
T1,2, or, 3b, N positive disease (n = 22)	0%	81% (95% CI, 48.7%–78.2%)	95% (95% CI, 69.5%–99.3%)

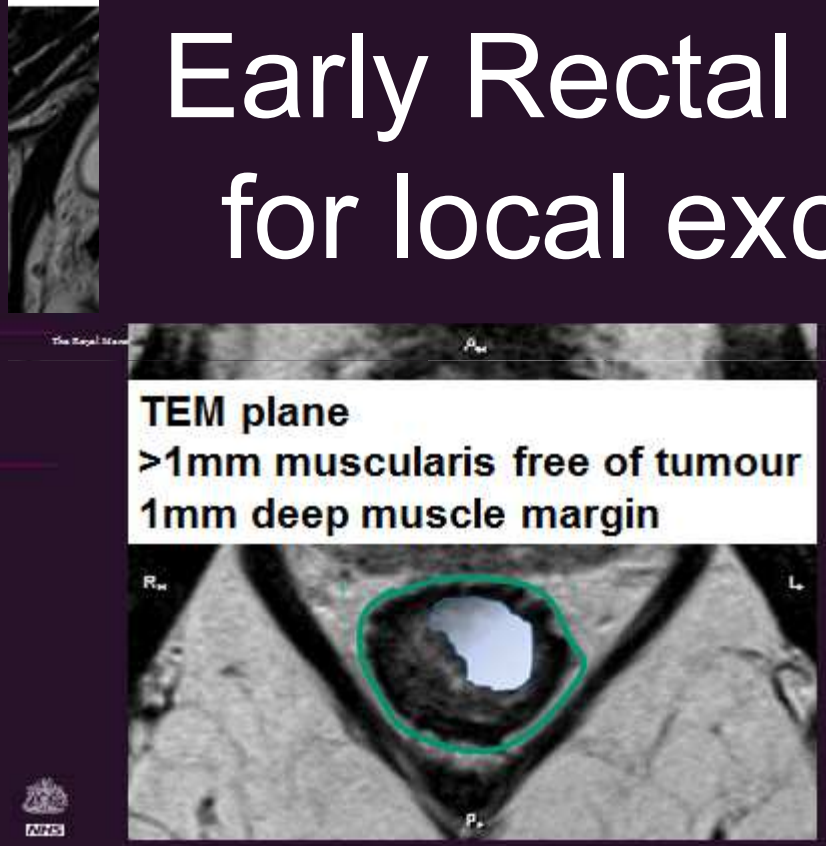




Taylor et al, MERCURY
Annals of Surgery 2011

equivalent to within 0.5 mm (6K). *Radiology 2007*

#6 An opportunity to identify Early Rectal Lesions suitable for local excision approach



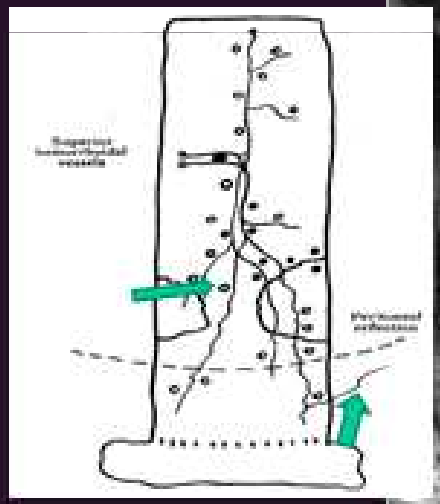
#7 MRI identification of EMVI

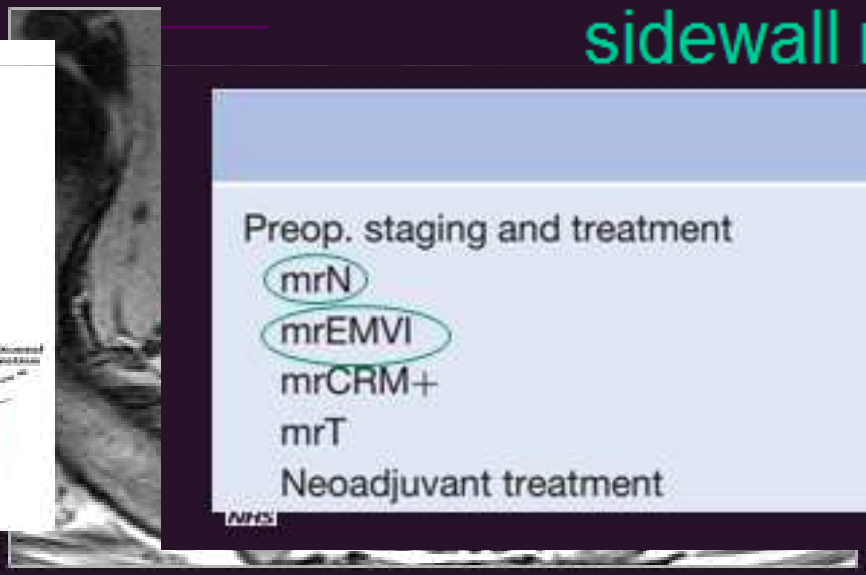
TABLE 4. Univariate and Multivariate Analysis (Cox Proportional Hazards for DFS) by Clinical, Preoperative MRI and Postoperative Histopathology Characteristics

Variables		Group	Patient Numbers	Univariate Analysis HR	95% CI	P	Multivariate Analysis HR	95% CI	P
Patient characteristics	Sex	Female	67	Ref			Ref		
		Male	121	1.093	0.625–1.912	0.756	0.93	0.53–1.68	0.832
	Height	Upper/mid	119	Ref			Ref		
		Low	69	1.369	0.815–2.298	0.235	1.46	0.869–2.68	0.223
Baseline MR staging	mrT stage	Good	51	Ref			Ref		
		Poor	137	1.187	0.638–2.206	0.588	1.12	0.51–2.43	0.782
	mrN stage	Negative	65	Ref			Ref		
		Positive	123	1.196	0.691–2.071	0.523	1.72	0.99–3.28	0.199
	mrEMVI	Negative	0	Ref			Ref		
		Positive	188	0.902	0.527–1.544	0.706	0.89	0.42–1.89	0.078
	mrCRM	Negative	107	Ref			Ref		
		Positive	81	0.846	0.497–1.441	0.539	0.85	0.44–1.62	0.617
Post-CRT preoperative MR staging	ymrT stage	Good	116	Ref			Ref		
		Poor	72	1.218	0.723–2.052	0.459	1.01	0.54–1.89	0.984
	ymrN stage	Negative	104	Ref			Ref		
		Positive	84	1.179	0.701–1.982	0.534	0.431	0.21–0.91	0.206
	ymrEMVI	Negative	80	Ref			Ref		
		Positive	96	1.987	1.237–4.323	0.004	1.97	1.01–3.90	0.044
	ymrCRM	Clear	148	Ref			Ref		
		Involved/threatened	40	1.26	0.674–2.354	0.469	1.16	0.59–2.67	0.729
Final pathology staging	ypT	Good	68	Ref			Ref		
		Poor	124	1.125	0.695–1.279	0.534	0.99	0.31–8.62	0.994
	ypN	Negative	118	Ref			Ref		
		Positive	70	2.912	1.724–4.878	<0.001	3.41	0.91–12.82	0.069
	ypEMVI	Negative	142	Ref			Ref		
		Positive	46	3.889	2.008–6.281	<0.001	2.39	1.11–5.14	0.026
	ypCRM	Negative	178	Ref			Ref		
		Positive	10	3.352	1.421–7.907	0.006	1.32	1.24–2.38	0.032

#8.Lateral Pelvic Tumour Spread

mrEMVI is as
sidewall t





Preoperative risk factors associated with MRI pelvic sidewall nodes

	Odds ratio	*P*
Preop. staging and treatment		
mrN	3·64 (1·67, 7·94)	0·032
mrEMVI	2·48 (1·08, 5·69)	0·001
mrCRM+	0·85 (0·33, 2·17)	0·738
mrT	1·14 (0·64, 2·01)	0·663
Neoadjuvant treatment	1·72 (0·77, 3·86)	0·190

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How do we find tumours that require neoadjuvant therapy?

- Definition of mrCRM at risk
- Importance of mrT substage rather than stage
- The importance of MRI detected EMVI as a gold standard
- Prognostic importance of assessment of height and MRI low rectal stage
- Prognostic relevance of mrTRG
- Prognostic relevance of mucinous tumours
- examples of how MRI is being used for treatment stratification in clinical surgical and oncological trials

NHS

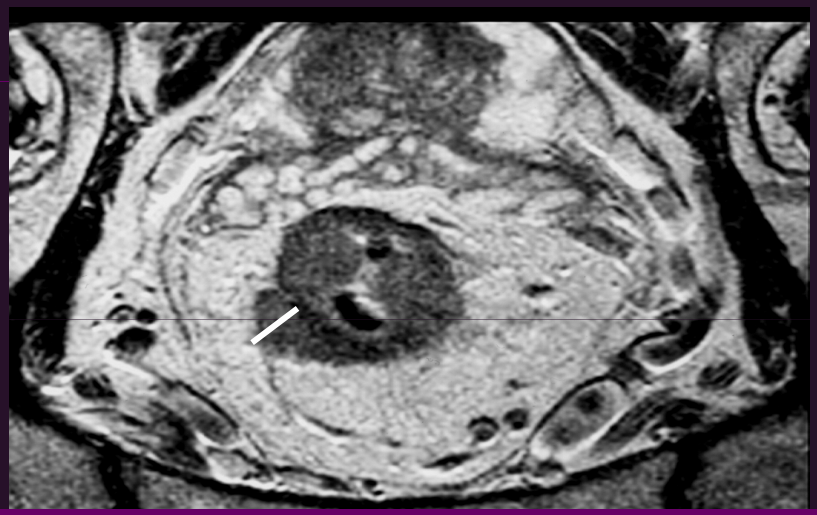
1958 – to present

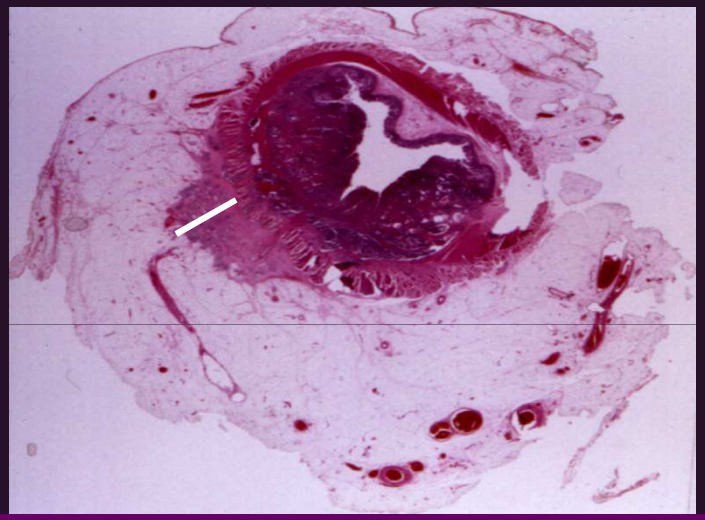
- Jass (St Marks, UK) : increasing depth of spread – independent prognostic significance
- Harrison (Tennessee, USA): prognostic score use depth of spread in mm
- Cawthorne (Guildford, UK): depth of spread significance
- Merkel and Hermanek (Erlangen, Germany) :
  - T3 subclassification
    - T3a <1mm
    - T3b>1-5mm,
    - T3c>5-15mm
    - T3d>15mm (TNM staging system 1993 supplement)

Extramural depth of spread is an equally important prognostic factor as node status

NHS

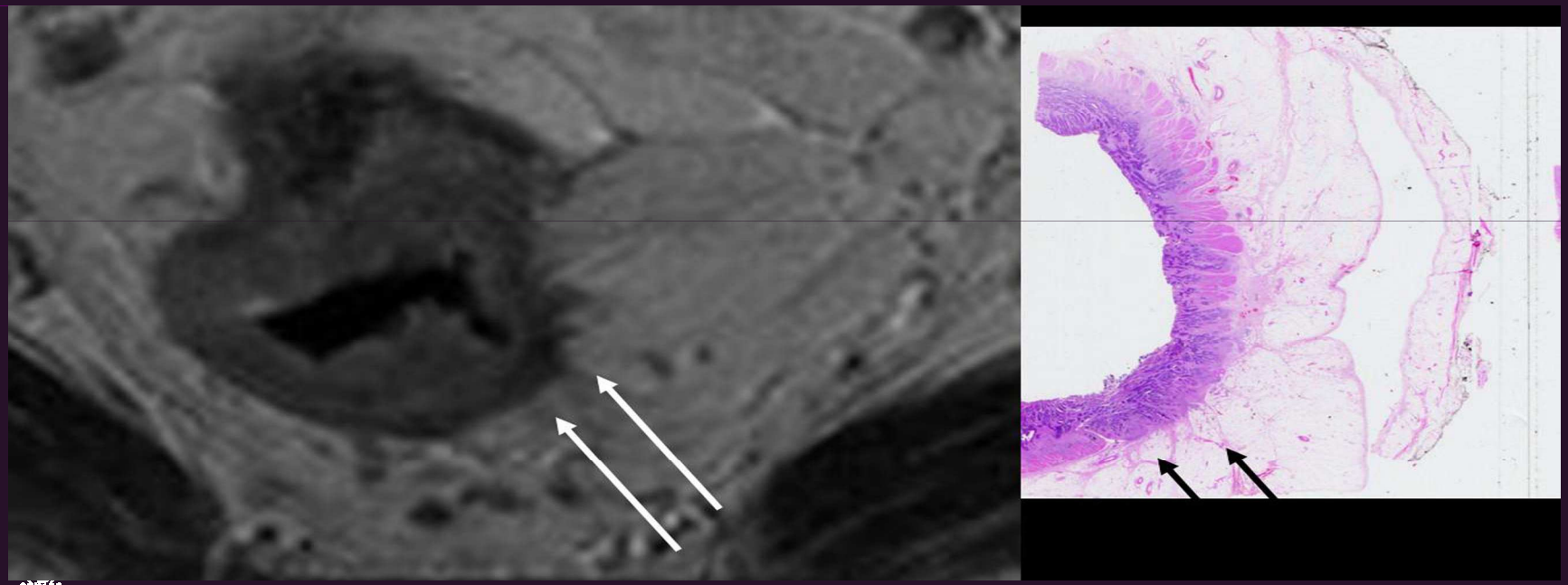
“measuring depth is the least subjective and most reliable of all the observations by a radiologist”

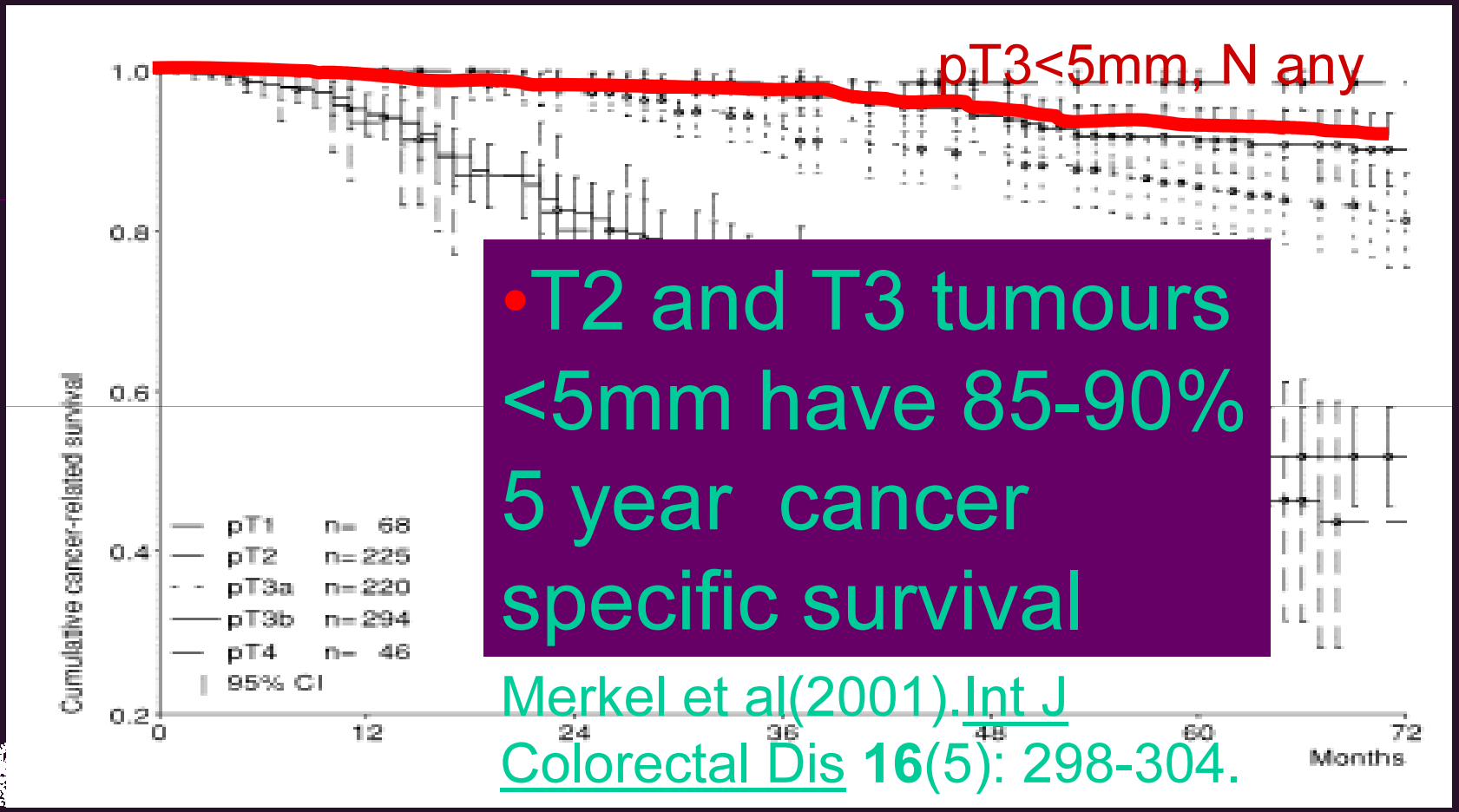




295/311 (95 %) patients who underwent primary surgery.
The mean difference between MRI and histopathology assessment of tumor EMD was -0.046 mm, SD = 3.85 mm, the 95 % CI was -0.487 to 0.395 mm.
MRI and histopathology assessment of tumor spread are considered equivalent to within 0.5 mm (θR). ***Radiology 2007***

Does it matter if this tumour is T3a or T2? Prognosis is identical…





- T2 and T3 tumours <5mm have 85-90% 5 year cancer specific survival

Merkel et al(2001).Int J Colorectal Dis **16**(5): 298-304.

NHS

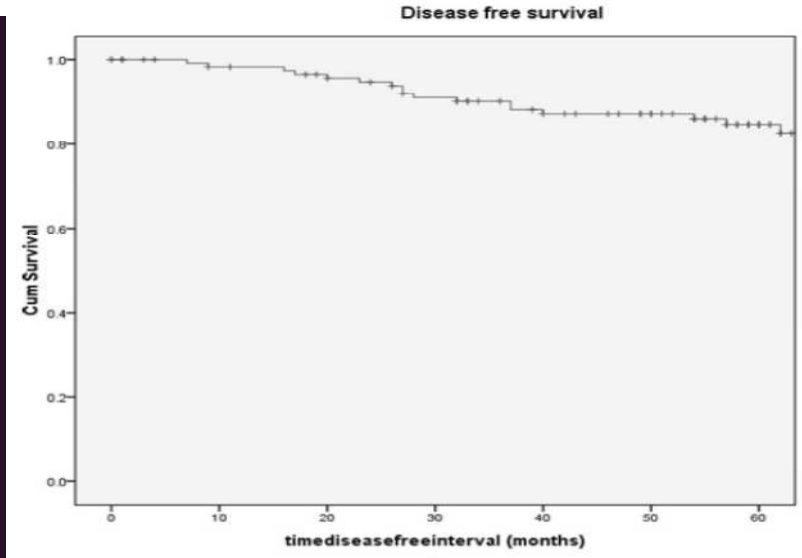
MERCURY trial

- 2002-2003
- 11 international centres (30 radiologists)
- 295 patients undergoing primary surgery
- Policy to avoid radiotherapy for mrCRM clear, mrEMVI negative, T3b or less rectal cancers, regardless of N stage

NHS

Outcomes for MRI good prognosis rectal cancers: regardless of N stage

MERCURY—MRI-predicted Good Prognosis Patients	Local Recurrence
Total patients (n = 122)	3.3%
T3a/b N0, N1, and N2 (n = 58)	1.7%
T1,2, or, 3b, N positive disease (n = 22)	0%



5-Year Disease-free Survival
84.7% (95% CI, 76.0%–90.4%)
81% (95% CI, 66.1%–89.8%)
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Taylor et al, MERCURY
Annals of Surgery 2011

MERCURY experience
MRI “good prognosis tumours”

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If a radiologists calls all patients with <5mm spread node negative, the pre-test probability for the node negative status to be correct is 82%, the risk of local recurrence for patients with path node positive in patients mrTR3b or less, mrCRM clear and EMVI negative is 0% . For the whole MRI “good prognosis” group – risk is 3.3%

Therefore overcalling nodes in patients with low risk features results in overtreatment and more harm than benefit.

The Royal Marsden

What is the risk of local recurrence for node positive vs negative if CRM is clear

- For a good quality TME CRM-ve – no difference – CR07 5-6% LR (Quirke et al Lancet Oncology) rates irrespective of node status
- OCUM trial follow up data...

NHS

Canadian “Quicksilver Trial”

- Prospective trial testing avoidance of CRT in MRI defined good risk tumours
  - T3b or less N stage any
  - EMVI negative
  - CRM and low rectal plane safe

Variable	Categories	Overall survival		Disease-free survival		Time till local recurrence (Stratified on UICC)	
		HR (95% CI); P-value		HR (95% CI); P-value		HR (95% CI); P-value	
		Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
Age	<65 years	1	1	1	1	1	1
	≥65 years	1.90 (1.36-2.66)***	1.91 (1.37-2.68)***	1.03 (0.73-1.45)	1.04 (0.73-1.47)	0.92 (0.48-1.77)	0.98 (0.50-1.89)
Sex	Male	1	1	1	1	1	
	Female	0.65 (0.46-0.9)*	0.70 (0.50-0.98) *	0.6 (0.41-0.87)*	0.64 (0.44-0.94)*	0.52 (0.25-1.08)	0.57 (0.27-1. 2)
Treatment	LCRT	1	1	1	1	1	
	SCRT	0.82 (0.46-1.46)	1.14 (0.62-2.10)	0.6 (0.31-1.16)	0.87 (0.43-1.77)	0.29 (0.06-1.38)	0.63 (0.12-3.2)
	Chemo & RT	1.07 (0.63-1.83)	1.29 (0.74-2.24)	1.1 (0.62-1.89)	1.45 (0.82-2.60)	1.33 (0.51-3.5)	2.20 (0.82-5.89)
	Surgery only	0.75 (0.48-1.17)	0.99 (0.57-1.71)	0.68 (0.42-1.09)	1.31 (0.73-2.38)	0.55 (0.23-1.3)	1.98 (0.66-5.91)
Height from anal verge	>5cm	1	1	1	1	1	
	≤5cm	0.90 (0.64-1.27)	0.87 (0.60-1.25)	1.27 (0.89-1.81)	1.35 (0.92-1.99)	1.97 (1.03-3.8)*	2.15 (1.06-4.37)
MRI AJCC	MRI Stage I	1	1	1	1	1	
	MRI Stage II	1.13 (0.73-1.76)	0.90 (0.57-1.44)	2.23(1.23-4.06)**	2.01(1.09-3.71) *	1.87(0.58-6.07)	1.37(0.40-4.69)
	MRI Stage III	1.13 (0.76-1.69)	0.91(059-1.40)	2.69(1.54-4.68)***	2.42(1.36-4.32) *	2.8(0.98-8.2) P=0.054	2.08(0.68-6.37)
MRI CRM	Negative	1	1	1	1	1	1
	Positive	1.99 (1.39-2.89)***	1.97 (1.27-3.04)*	1.96 (1.31-2.94)* *	1.65 (1.01-2.69) *	3.9 (1.99-7.62)***	3.50 (1.53-8.00)*

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Questions to think about regarding mrEMVI

1. MRI does not always agree histopathology at detecting vascular invasion by tumour especially after CRT
2. MRI detected EMVI is a stronger predictor for distant metastatic disease and pelvic recurrence than MRI assessment of nodal involvement
3. Is more prevalent than nodal metastatic disease in patients with rectal cancer

NHS

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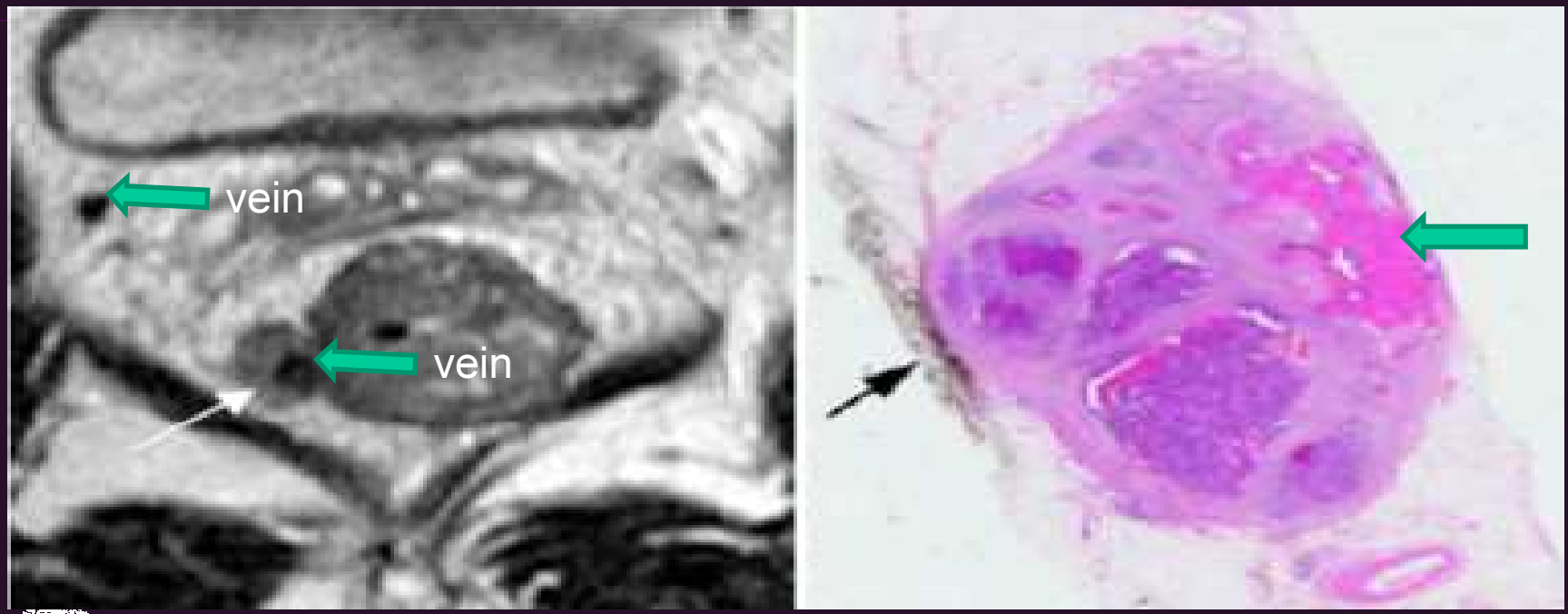
Reference:

- Chand, M., Evans, J., Swift, R. I., Tekkis, P. P., West, N. P., Stamp, G., . . . Brown, G. (2014). The Prognostic Significance of Postchemoradiotherapy High-Resolution MRI and Histopathology Detected Extramural Venous Invasion in Rectal Cancer.. *Ann Surg*. doi:10.1097/SLA.0000000000000848

The Royal Marsden

When is a node not a node?



Detection of venous invasion

- The search for vessel invasion as recommended by Brown and Warren.
- At least three sections of the tumor were taken in each case and stained with Masson's aniline blue trichromestain to emphasize the smooth muscle wall of the small veins.

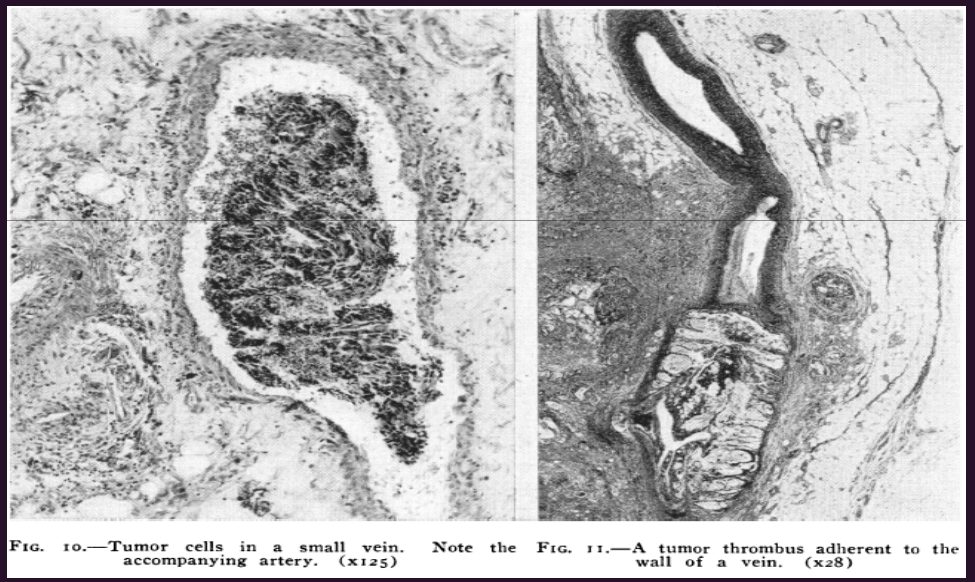


FIG. 10.—Tumor cells in a small vein. Note the accompanying artery. (x125)

FIG. 11.—A tumor thrombus adherent to the wall of a vein. (x28)

Vascular Invasion

- Brown and Warren Surg Obstet Gynaecol1938
- 170 rectal cancer post mortem examinations majority palliative colostomy/ no surgery/ immediate postoperative death.
- histological evidence of tumour invasion of veins in 61% of 165 rectal adenocarcinomas
- 67 of the 100 patients with venous invasion were found to have visceral metastases, mostly liver.
- Only one case of metastasis in the absence of any vascular invasion was found

Venous invasion important

"as far as the prediction of visceral metastases in rectal carcinoma from the local growth and nodes is concerned, the presence of intravascular tumour means as much from the prognostic standpoint as neoplastic nodes, and their absence means much more"

Brown and Warren 1938

THE LYMPHATIC AND VENOUS SPREAD OF CARCINOMA OF THE RECTUM*

ROBERT S. GRINNELL, M.D.

NEW YORK, N. Y.

FROM THE DEPARTMENT OF SURGERY, PRESBYTERIAN HOSPITAL, AND THE SURGICAL PATHOLOGY LABORATORY COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK, N. Y.

AN UNDERSTANDING of the spread of carcinoma of the rectum is essential for the treatment of the disease. Four main routes are possible: (1) By direct extension; (2) by the lymphatics; (3) by the blood stream; and (4) by transplantation through the peritoneal cavity. The second and third routes of spread are the subjects of this report.

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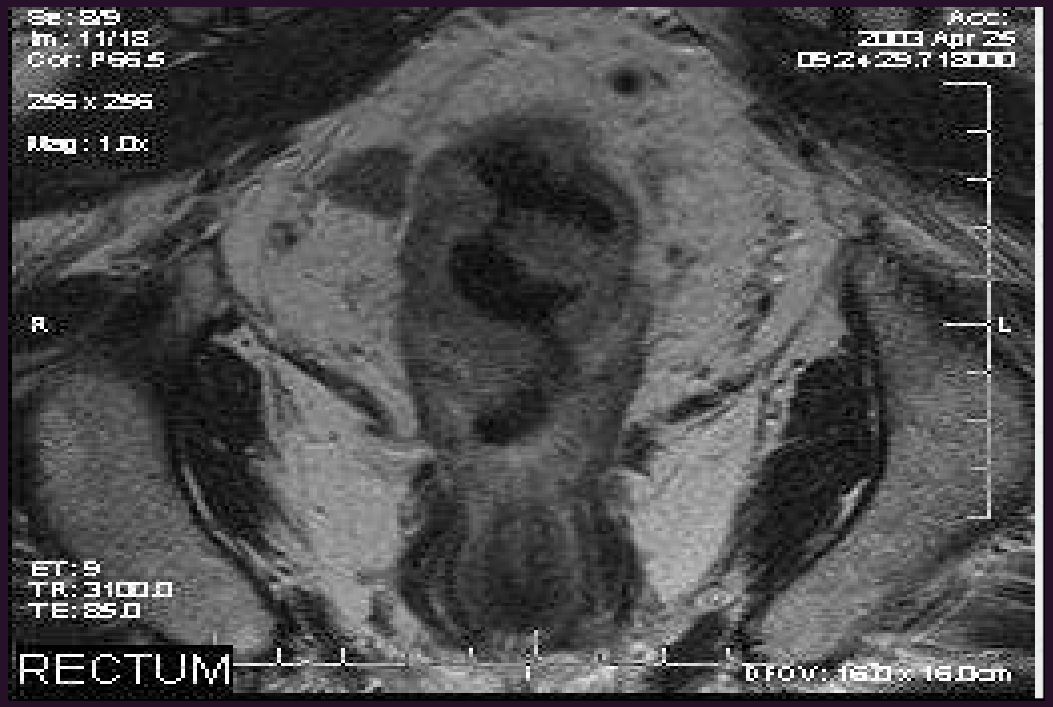
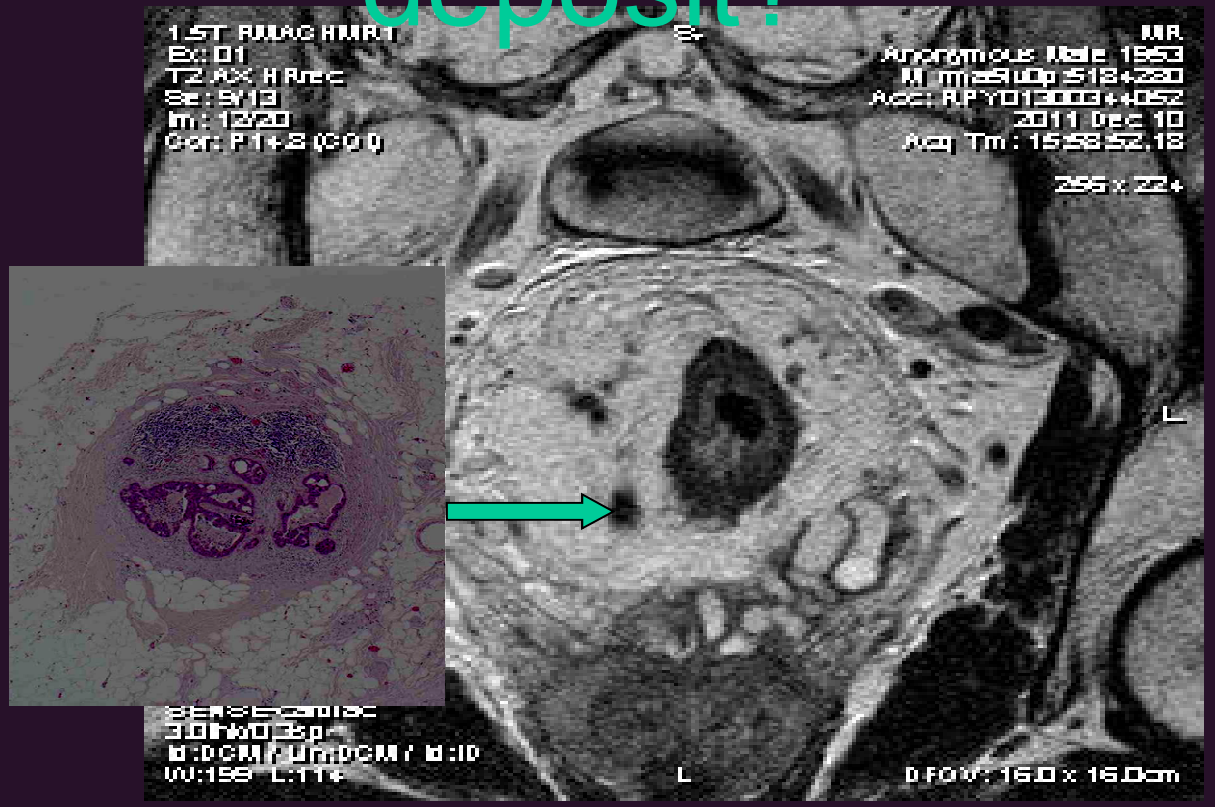
Is this is a venous deposit or a Lymph node?



The Royal Marsden

Lymph node or venous deposit?

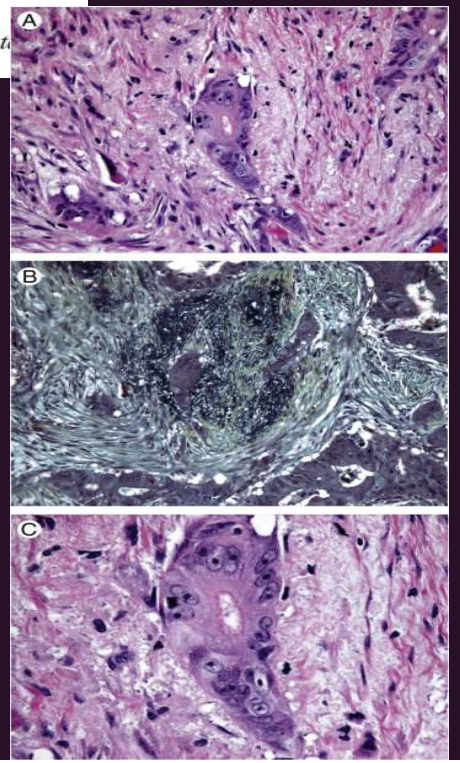


Developments in the assessment of venous invasion in colorectal cancer: implications for future practice and patient outcome

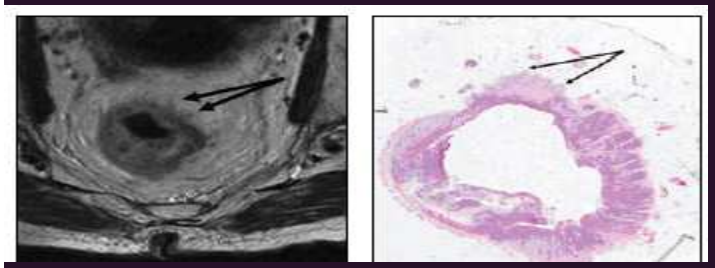
David E. Messenger MBChB[a], David K. Driman MBChB[b,*], Richard Kirsch MBChB, PhD[c]

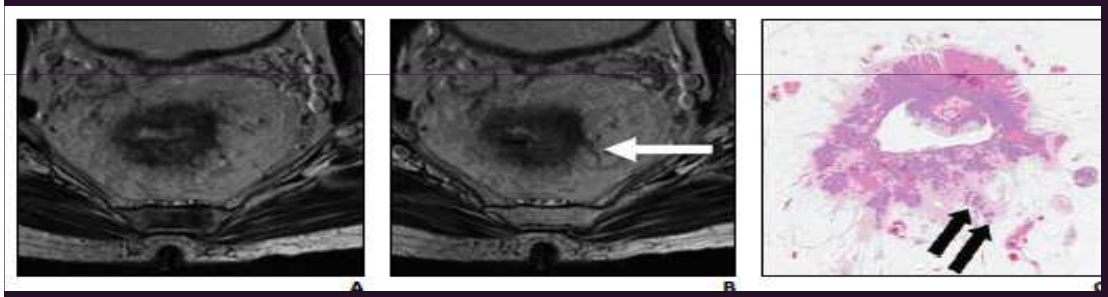
[a]Division of General Surgery, Royal United Hospital NHS Trust, Bath, BA1 3NG, UK
[b]Department of Pathology, London Health Sciences Centre and University of Western Ontario, London, Ontario, Canada N6A 5A5
[c]Departments of Pathology and Laboratory Medicine, Mount Sinai Hospital and University of Toronto, Toronto, Ont Canada M5G 1X5

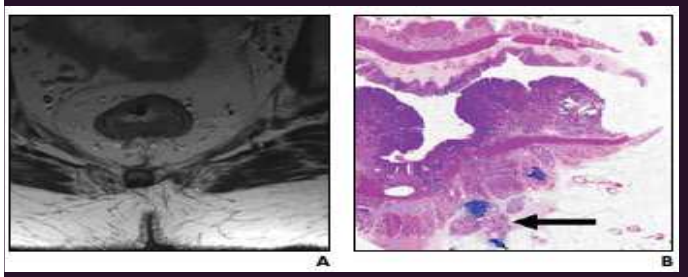
- Poor interobserver agreement for EMVI
- Large variations in reporting rates 10% -50% - underreporting widespread
- Lack of agreement of definitions



Characteristic features of EMVI





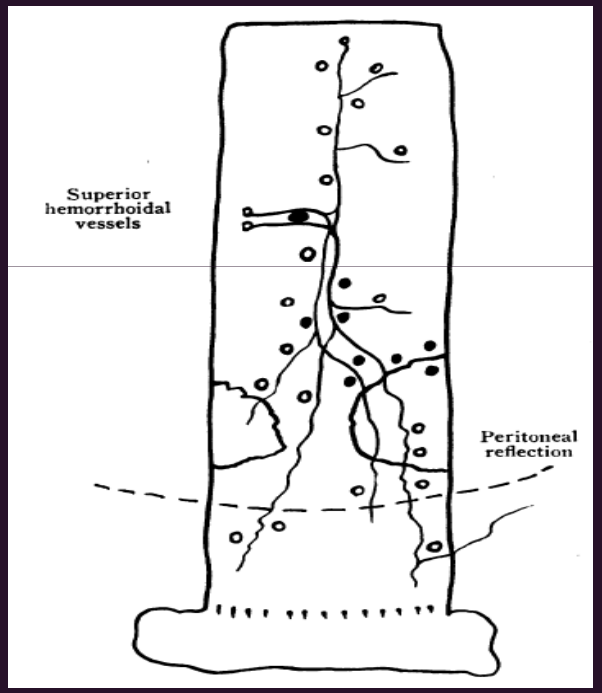


- Expansion of extramural vessels by tumour
- Serpiginous / tubular extension of tumour signal

MRI for detection of extramural vascular invasion in rectal cancer.
AJR Am J Roentgenol **191**(5): 1517-1522.

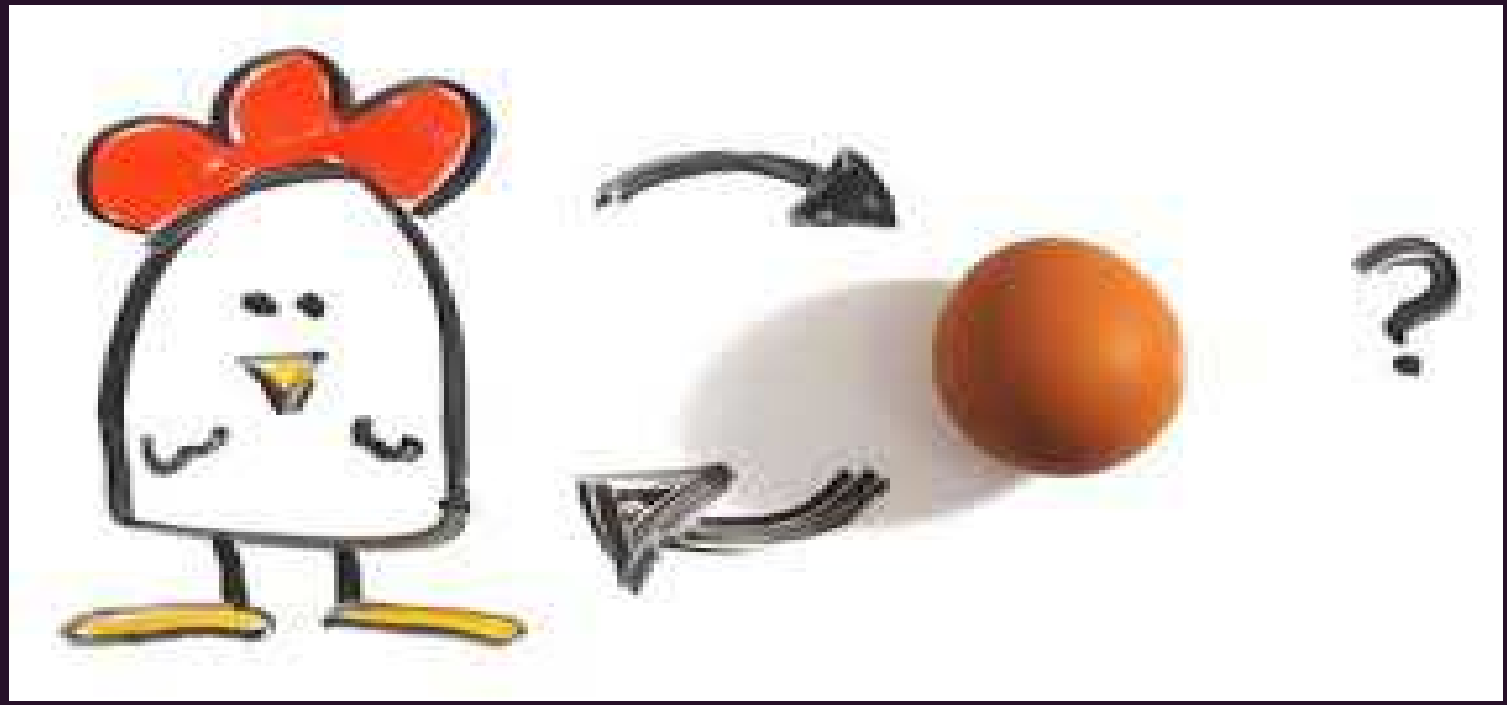
The Royal Marsden

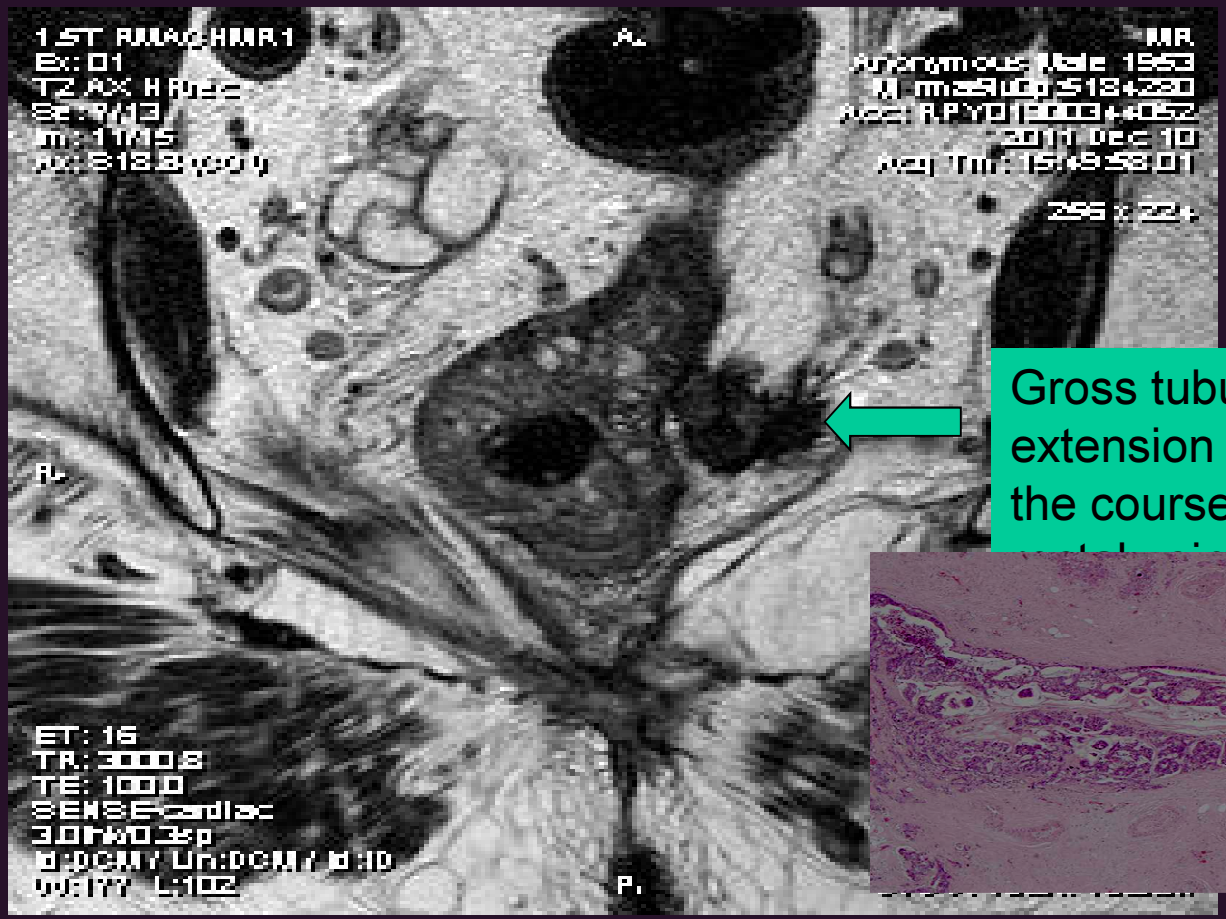
Grinnell – mapping of nodes along lymphovascular channels



NHS

Which came first the vascular invasion or the lymph node metastasis?




Gross tubular
extension along
the course of lateral

The Royal Marsd

Predictive factors of positive circumferential resection margin after radiochemotherapy for rectal cancer: The French randomised trial ACCORD12/0405 PRODIGE 2

Anne Rullier [a,*], Sophie Gourgou-Bourgade [b], Marta Jarlier [b], Frédéric Bibeau [b], Catherine Chassagne-Clément [c], Christophe Hennequin [d], Laurent Tisseau [e], Agnès Leroux [f], Francette Ettore [g], Michel Peoc'h [h], Marie-Agnès Diebold [i], Yves-Marie Robin [j], Isabelle Kleinclaus [k], Laurent Mineur [l], Christophe Petitjean [m], Jean-François Mosnier [n], Isabelle Soubeyran [o], Norbert Padilla [p], Anne-Isabelle Lemaistre [q], Jocelyne Bérille [r], Bernard Denis [k], Thierry Conroy [f], Jean-Pierre Gérard [g]

	Stepwise model			Selected model		
	OR	95% CI	*p*	OR	95% CI	*p*
Dworak-modified tumour response			0.005			0.003
Major/complete response	1			1		
No/partial response	8.73	1.92–39.69		9.01	2.06–39.30	
Surgery			0.006			0.004
Sphincter-saving resection	1			1		
Abdominoperineal resection	3.18	1.40–7.20		3.24	1.44–7.27	
Vascular invasion			0.023			0.026
No	1			1		
Yes	2.92	1.16–7.37		2.78	1.12–6.88	
Gender			0.094			
Male	1					
Female	1.96	0.89–4.31				
Treatment Arm			0.122			
Cap 45	1					
Capox 50	0.52	0.23–1.19				

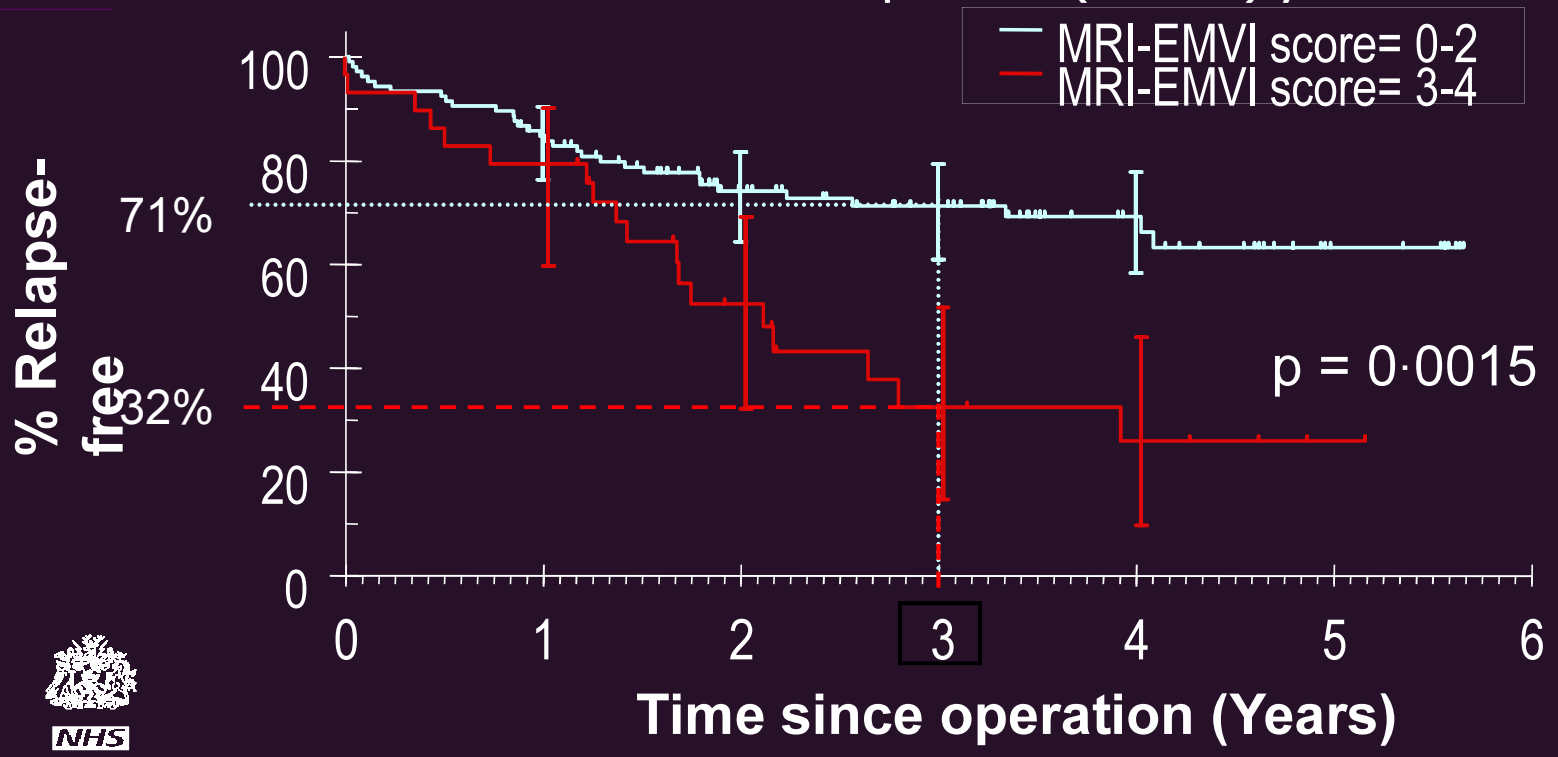
NHS

Vascular invasion is an independent risk factor for CRM invovlement

Smith et al. "Prognostic significance of MRI-detected Extramural Vascular Invasion." BJS. 2008

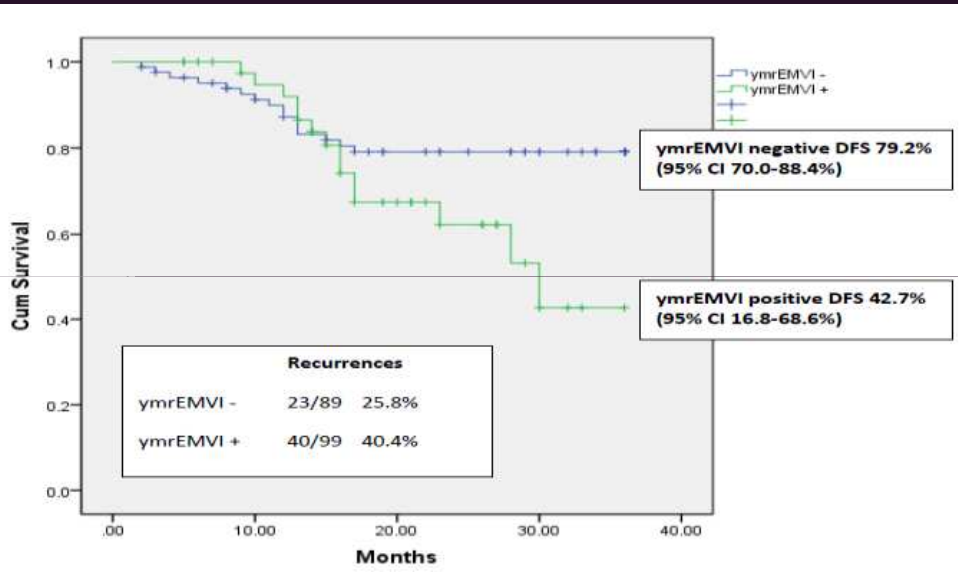
MRI-EMVI score & Outcome

n=135. Median follow-up=3·12 (0·9-5·7) years.



MRI detected more persistent EMVI post CRT than pathology

Group	Local/distant Recurrence		p-v
ypEMVI -	34/142	23.9%	
ypEMVI +	20/46	43.5%	<0.05
ymrEMVI -	23/89	25.8%	
ymrEMVI +	40/99	40.4%	<0.05



Chand M, Evans J, Swift RI, et al. Prognostic Significance of Postchemoradiotherapy High-Resolution MRI and Histopathology Detected Extramural Venous Invasion in Rectal Cancer. Ann Surg. 2014.

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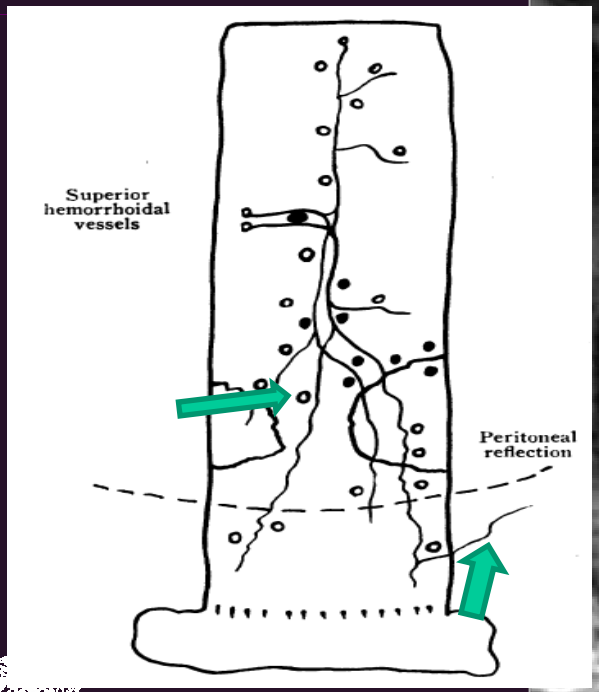
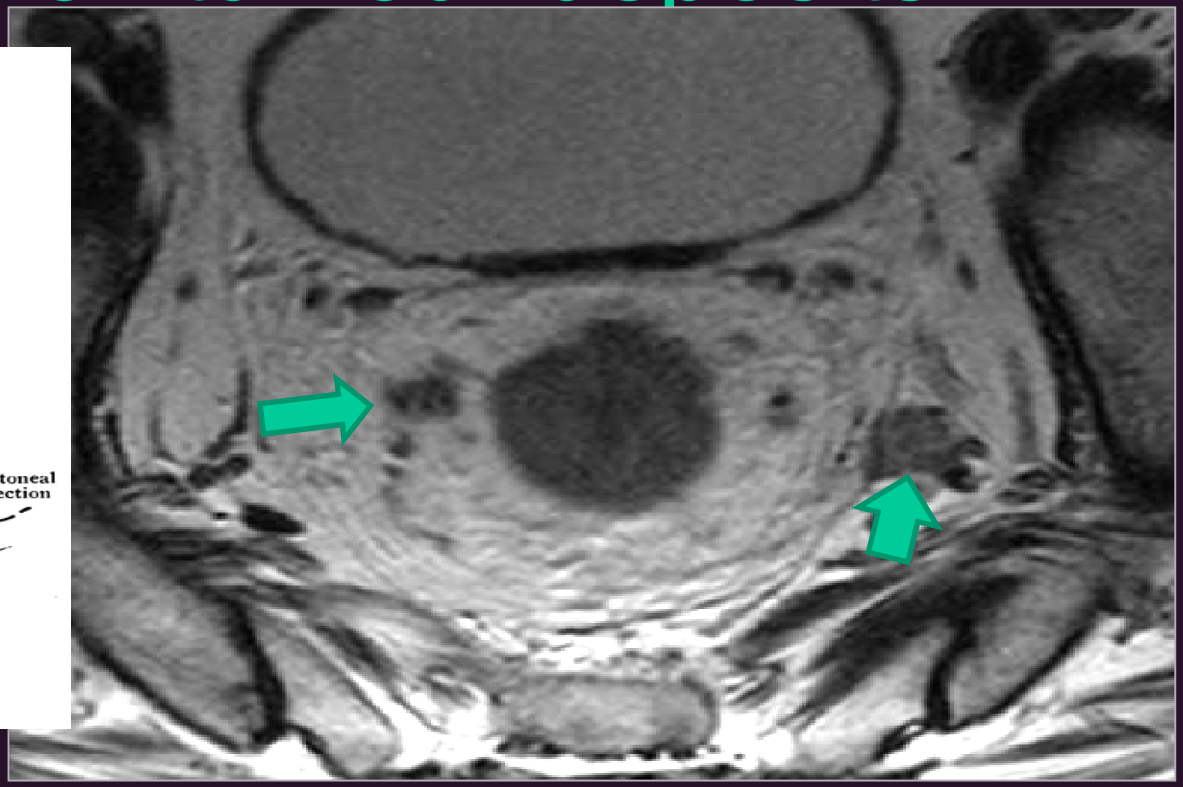
mrEMVI is associated with pelvic sidewall tumour deposits





NHS

Preoperative risk factors associated with MRI PSW nodes

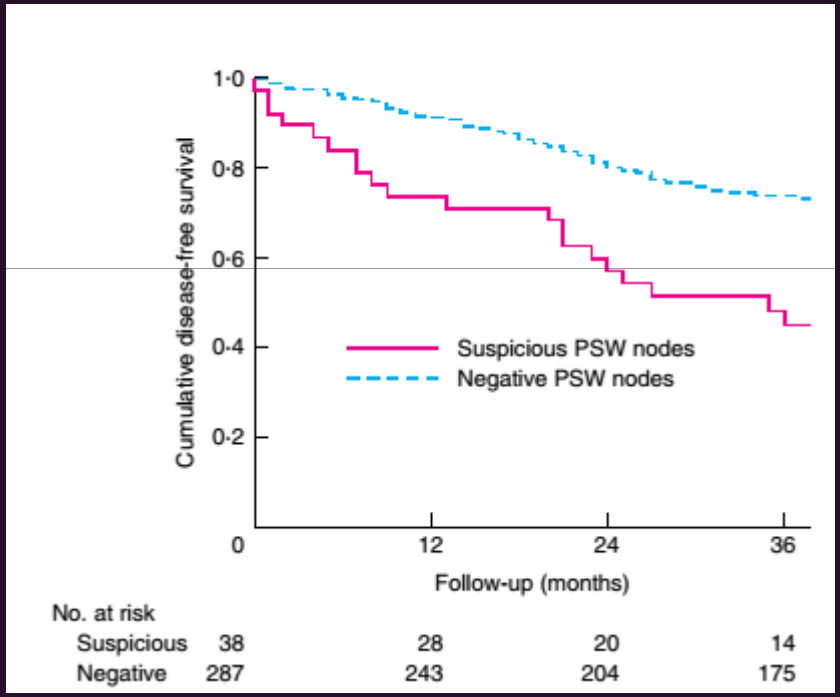
	Odds ratio	*P*
Preop. staging and treatment		
mrN	3·64 (1·67, 7·94)	0·032
mrEMVI	2·48 (1·08, 5·69)	0·001
mrCRM+	0·85 (0·33, 2·17)	0·738
mrT	1·14 (0·64, 2·01)	0·663
Neoadjuvant treatment	1·72 (0·77, 3·86)	0·190

What is the relevance of MRI detected PSW nodes?

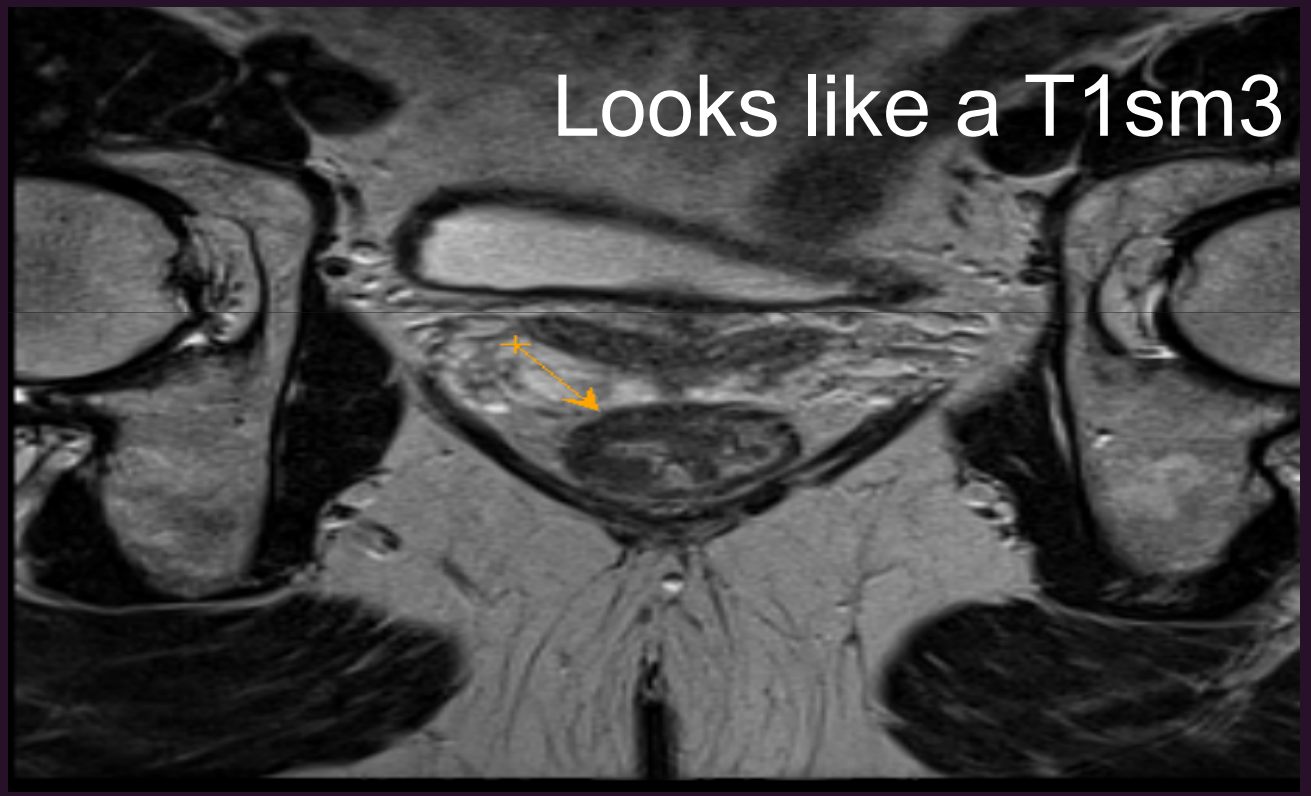
- 325 patients, 38 (11.7%) had MRI-identified suspicious PSW nodes on baseline MRI scans
- The size of pelvic nodes was not a factor
- PSW nodes with either mixed signal or capsular irregularity were considered to have a high suspicion of malignancy, whereas those with neither feature were considered negative for malignancy – irrespective of size

Outcomes for PSW

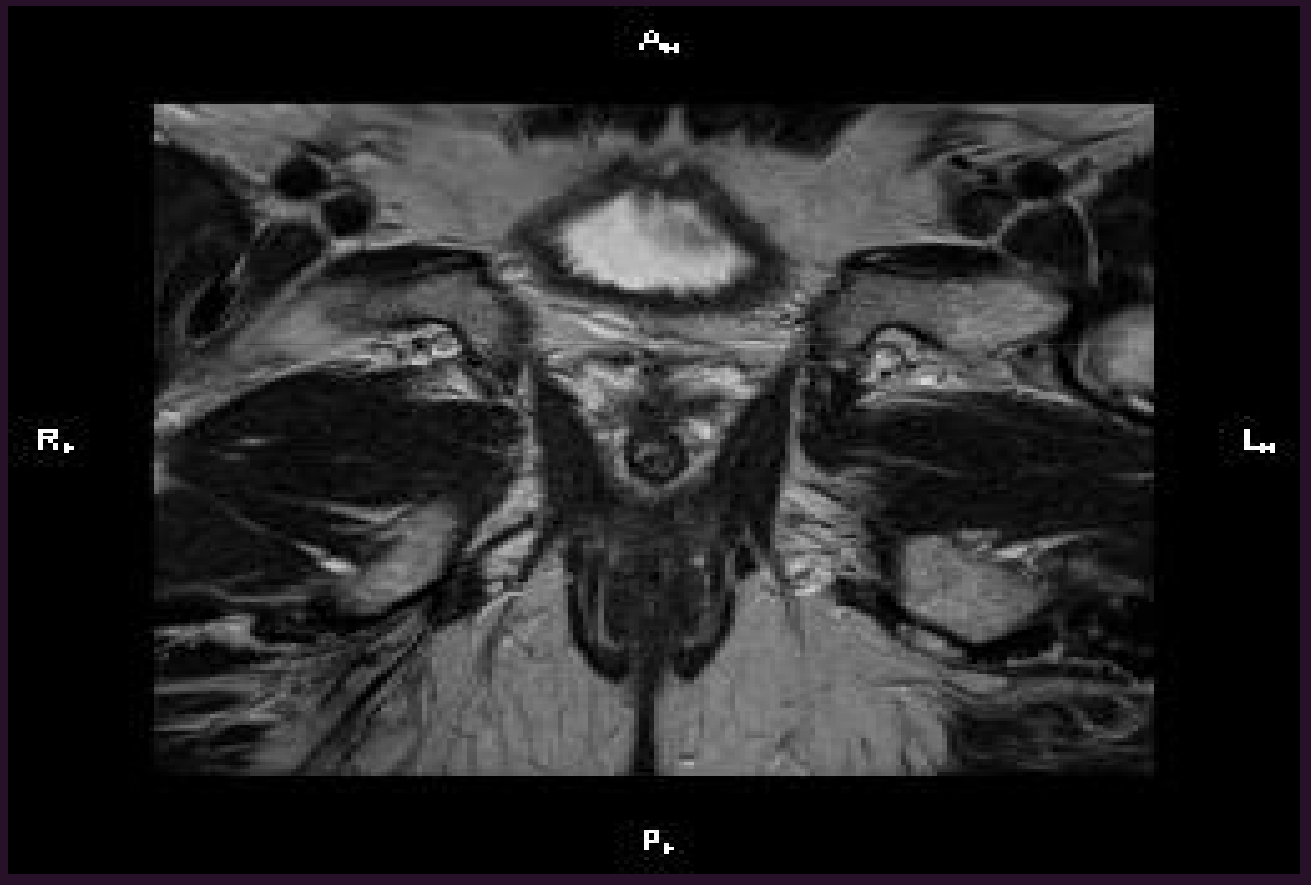
- 5-year DFS of patients with suspicious PSW nodes on MRI was significantly worse than that of patients without suspicious nodes: 42% versus 70·7% (P<0·001).



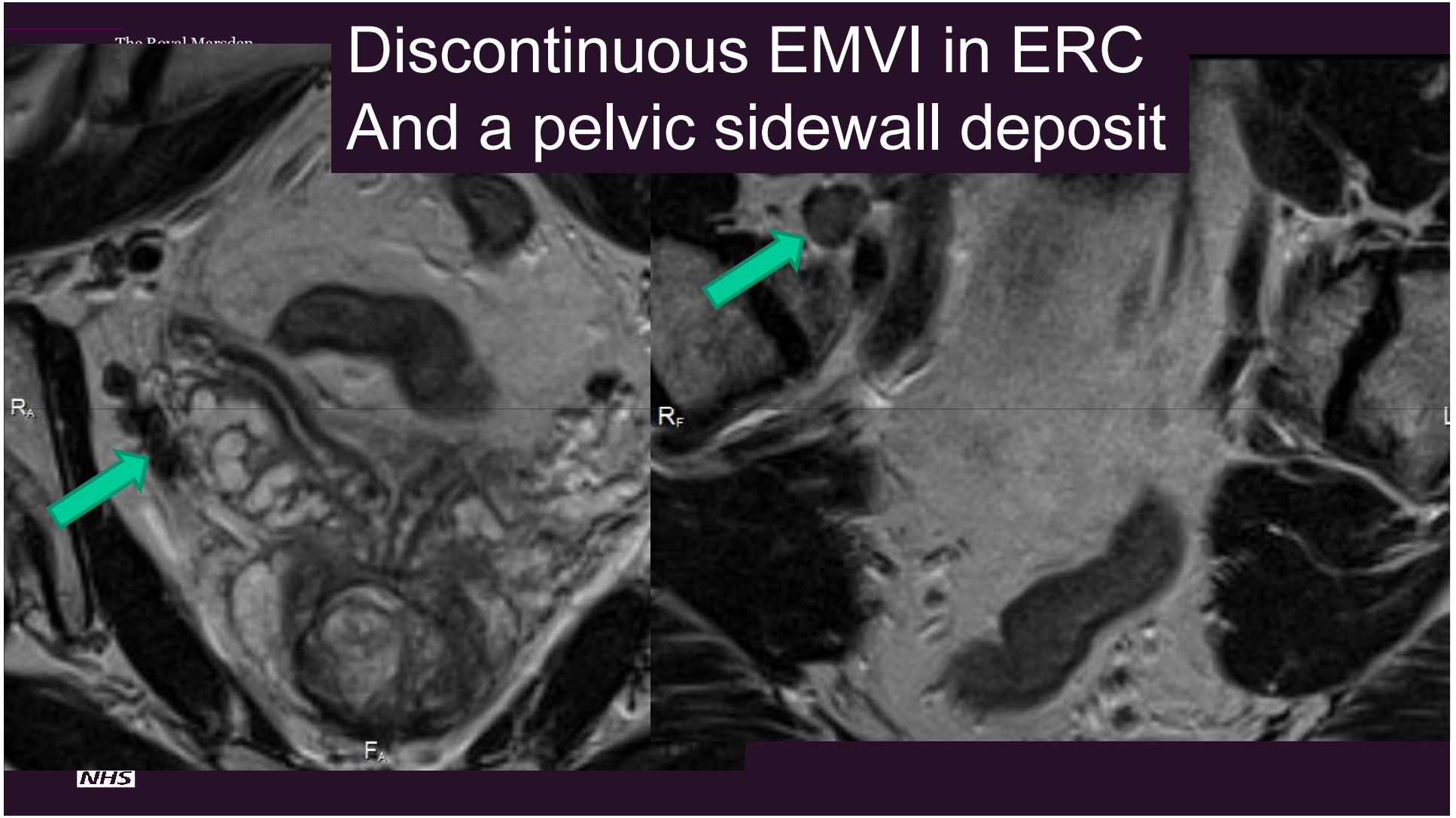
A good prognosis tumour?

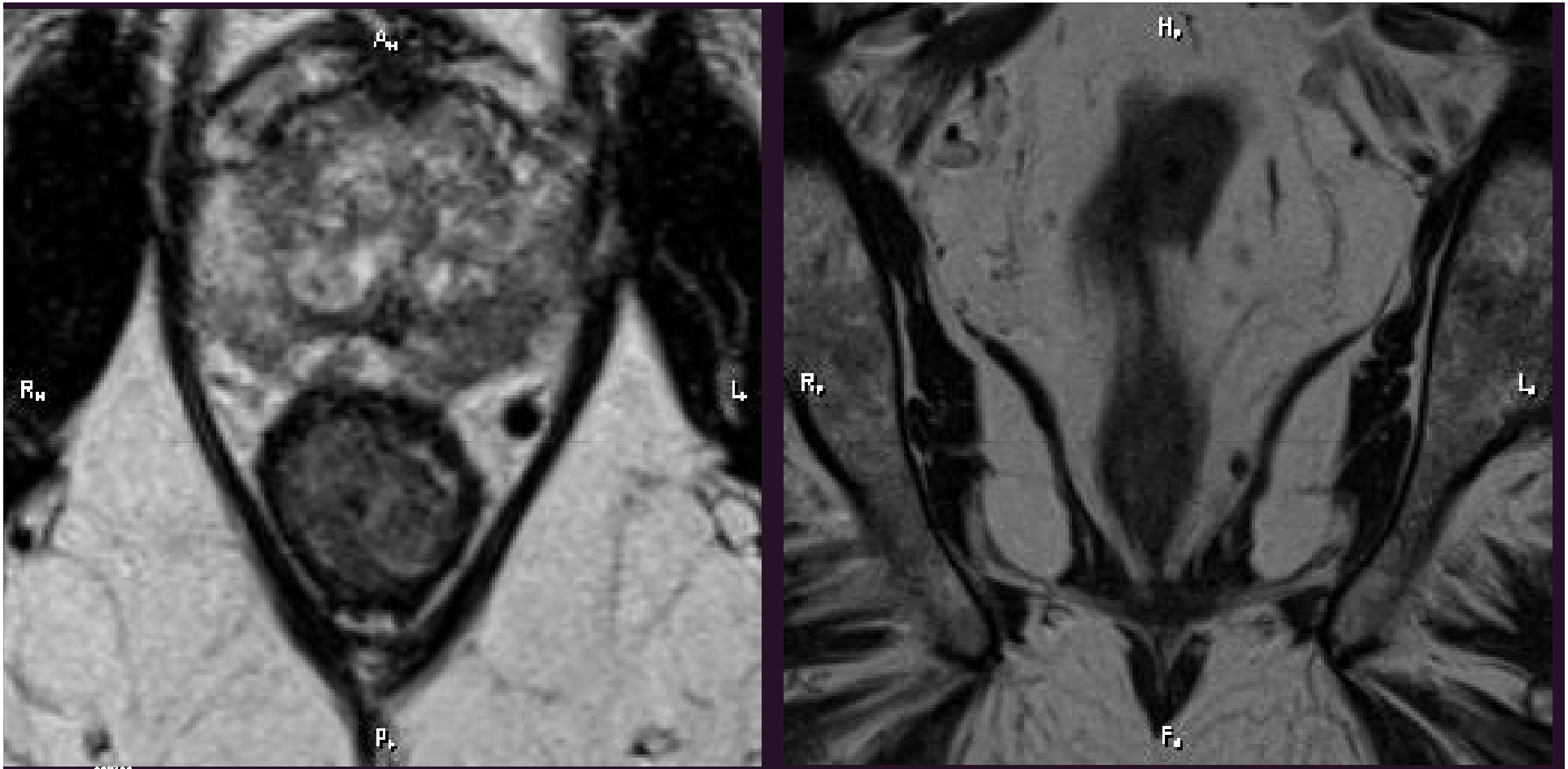


Discontinuous EMVI in low rectal cancer



Discontinuous EMVI in ERC
And a pelvic sidewall deposit

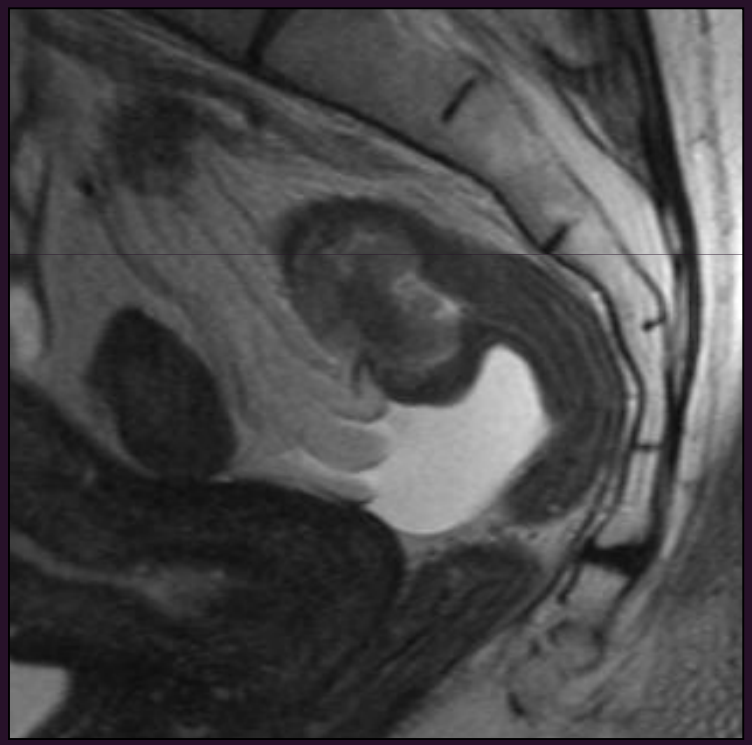




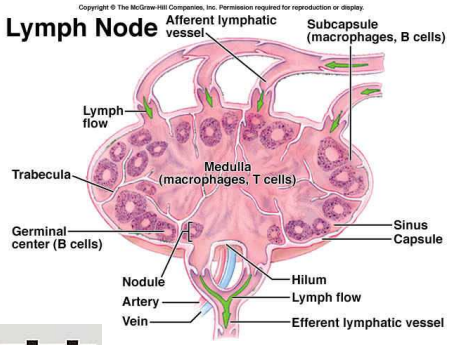
Discontinuous extramural venous spread – a poor prognostic factor

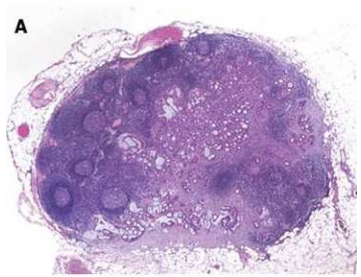
mrEMVI

- mrEMVI seen in 40% of rectal cancers
- Detected more readily than by pathology
- Independent risk factor for CRM involvement, local and distant recurrence

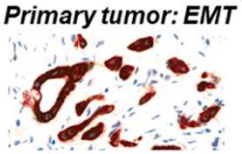


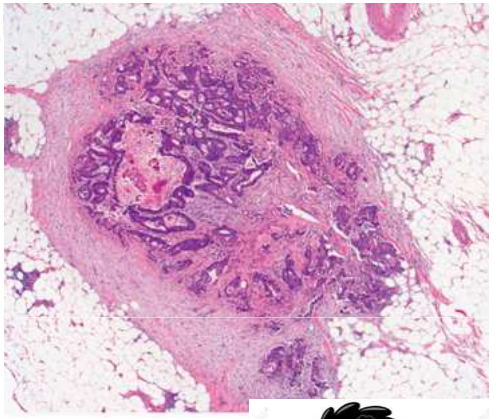
Lymph nodes versus extranodal deposits



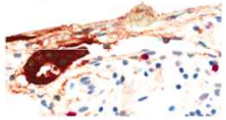


Tumor Budding

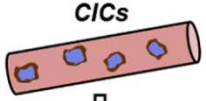




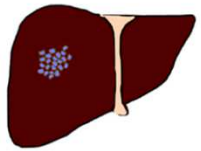
Angioinvasion

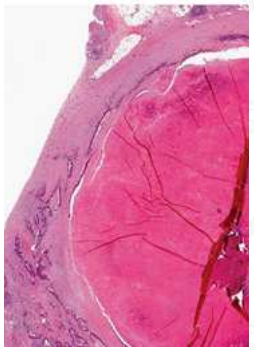


Systemic spread

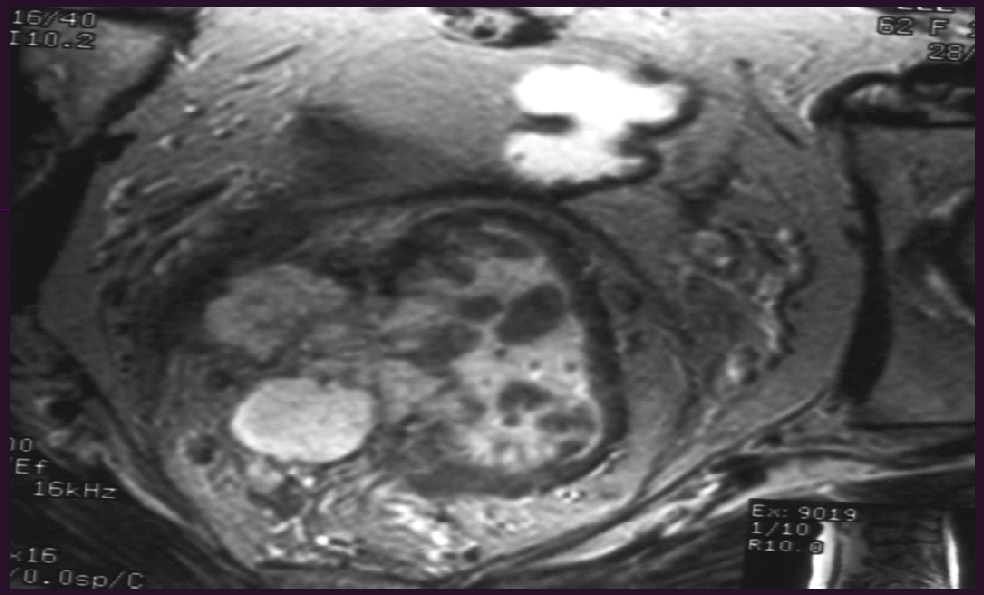


Distant metastasis





The Royal Marsden



Mucinous carcinoma

Poor prognosis

MRI more likely to diagnose mucinous subtype

- diagnostic odds ratio MRI vs biopsy = 4.67, $p < 0.05$.
- All 60 (100%) patients undergoing surgery for mrMucinous tumours were confirmed as such on final histopathology.

Yu SKT, Tait DM, Chand M, Brown G. Magnetic resonance imaging defined mucinous rectal carcinoma is an independent imaging biomarker for poor prognosis and poor response to preoperative chemoradiotherapy. European Journal of Cancer 2014

NHS

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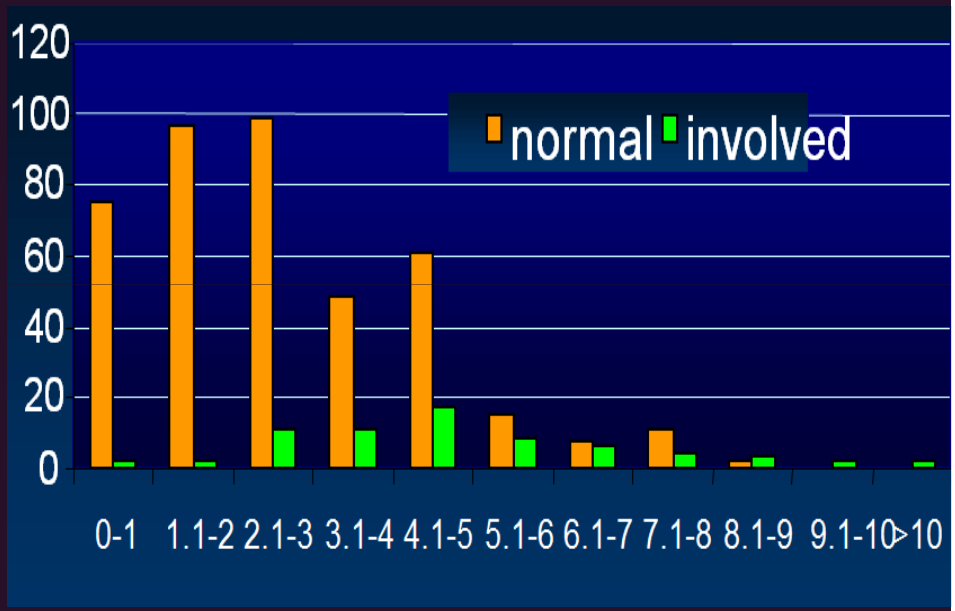
Measuring size of nodes worsens results – overstaging and overtreatment of low risk patients

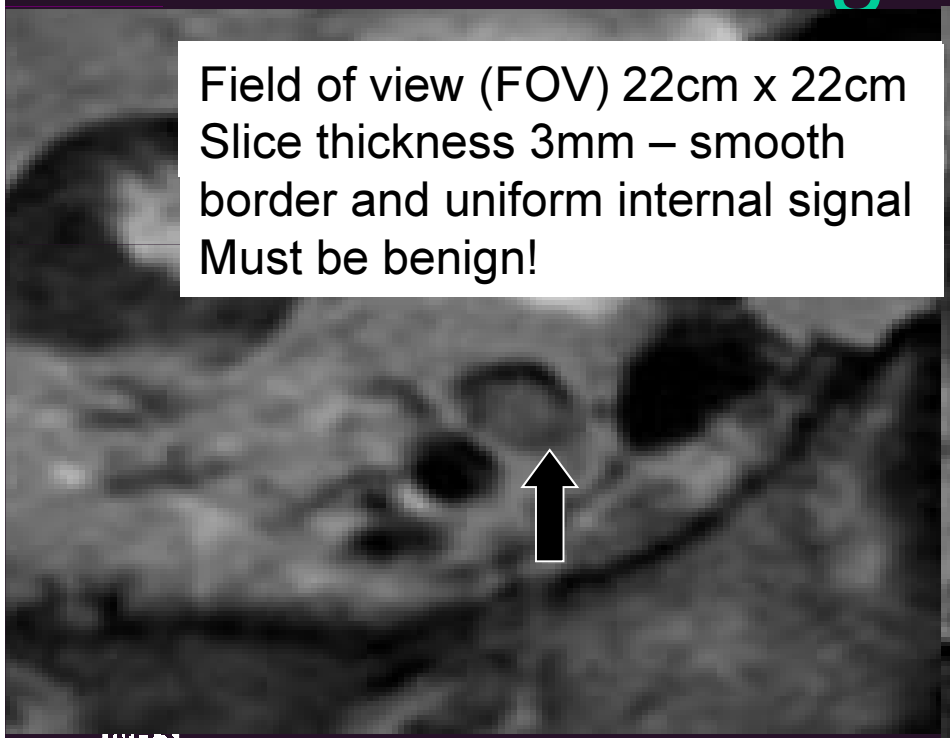
- node positive if either irregular border or mixed signal intensity.
- Metastases demonstrated in 51/56 nodes (91%, 95% CI 81% to 96%) with either an irregular border or a mixed intensity signal.
- only 9/225 nodes (4%, CI 2.1% to 7.4%) with smooth borders and a uniform signal contained metastases irrespective of size.
- Size of node bears no relationship to malignant risk

Brown et al Radiology 2003

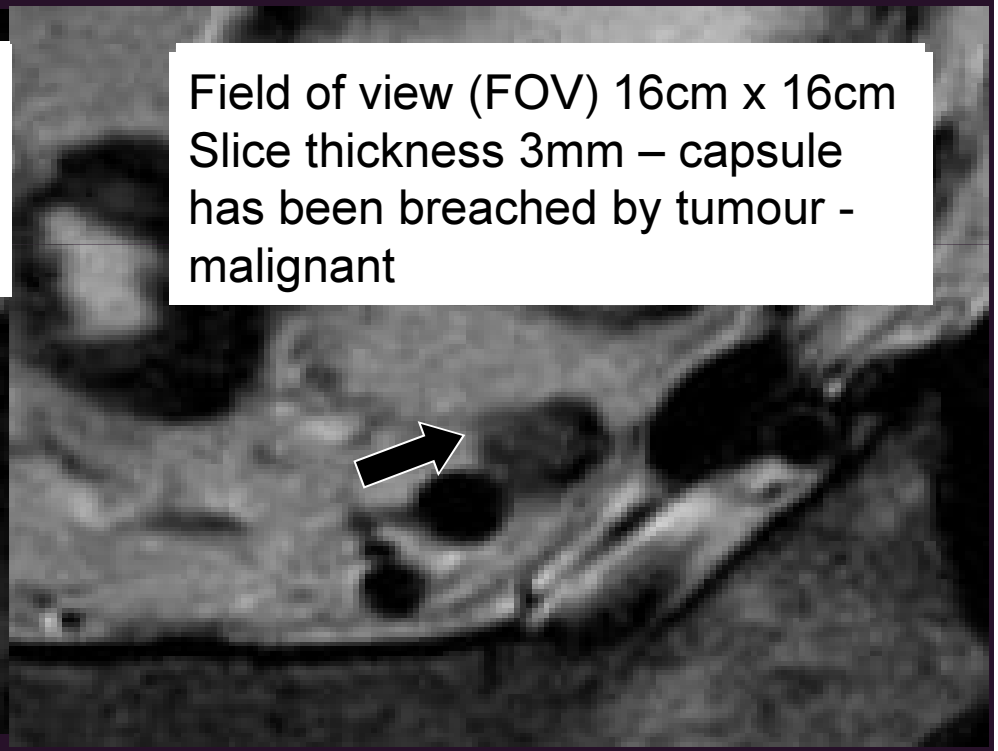


NHS

Is this a benign or malignant node?



Field of view (FOV) 22cm x 22cm
Slice thickness 3mm – smooth border and uniform internal signal
Must be benign!



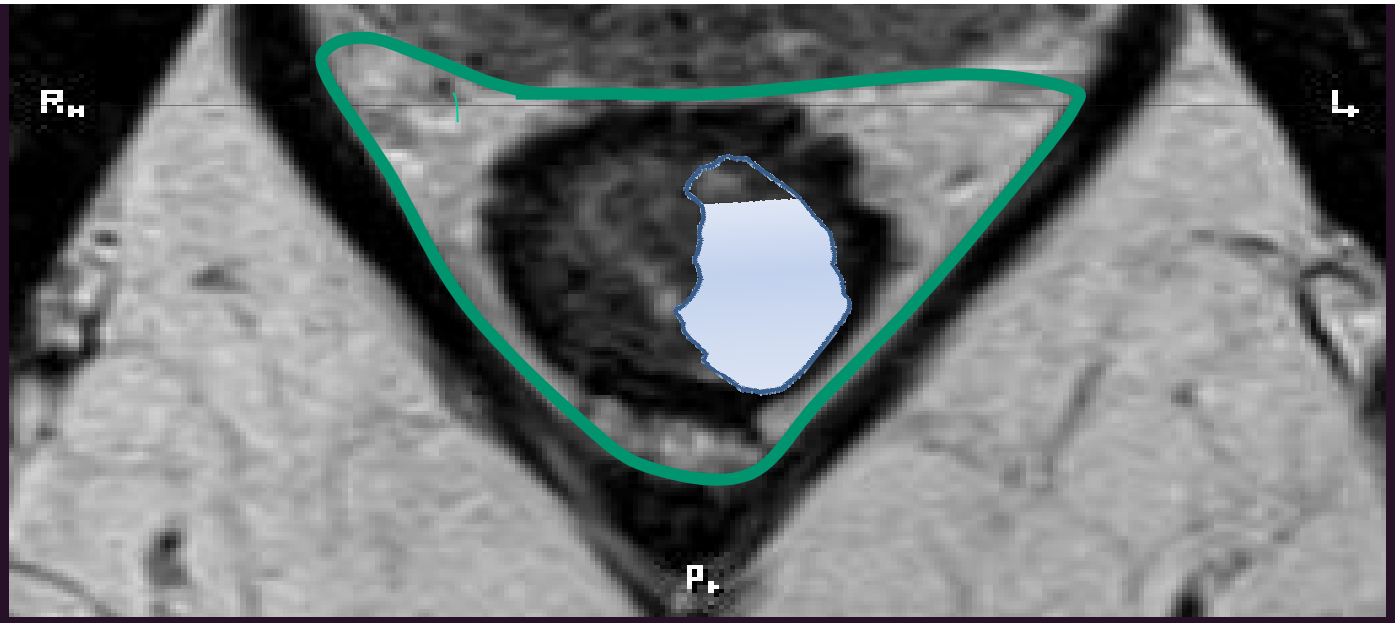
Field of view (FOV) 16cm x 16cm
Slice thickness 3mm – capsule has been breached by tumour - malignant

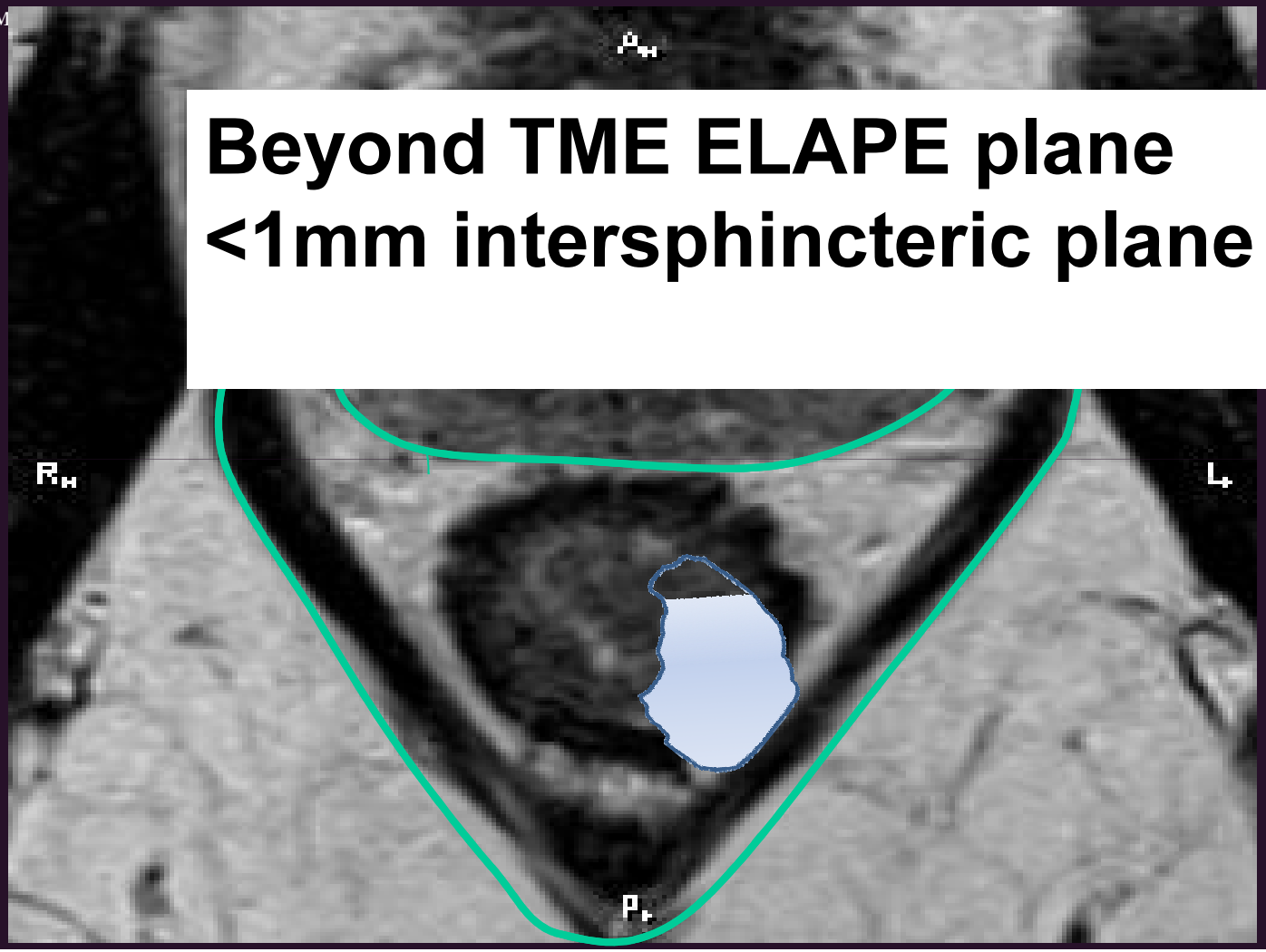
MRI detected **Lymph Nodes** close to the mesorectal fascia are not associated with pCRM involvement (Shihab et al, BJS 2010)

- Involvement of CRM by lymph node metastases alone is uncommon (1.3% of all patients in MERCURY series).
- Caution when recommending neoadjuvant therapy based solely on an MRI-detected lymph node close to the mesorectal fascia.

NHS

TME Mesorectal plane
For coloanal anastomosis/ intersphincteric
>1mm of intersphincteric plane clear





Beyond TME ELAPE plane
<1mm intersphincteric plane clear

NHS

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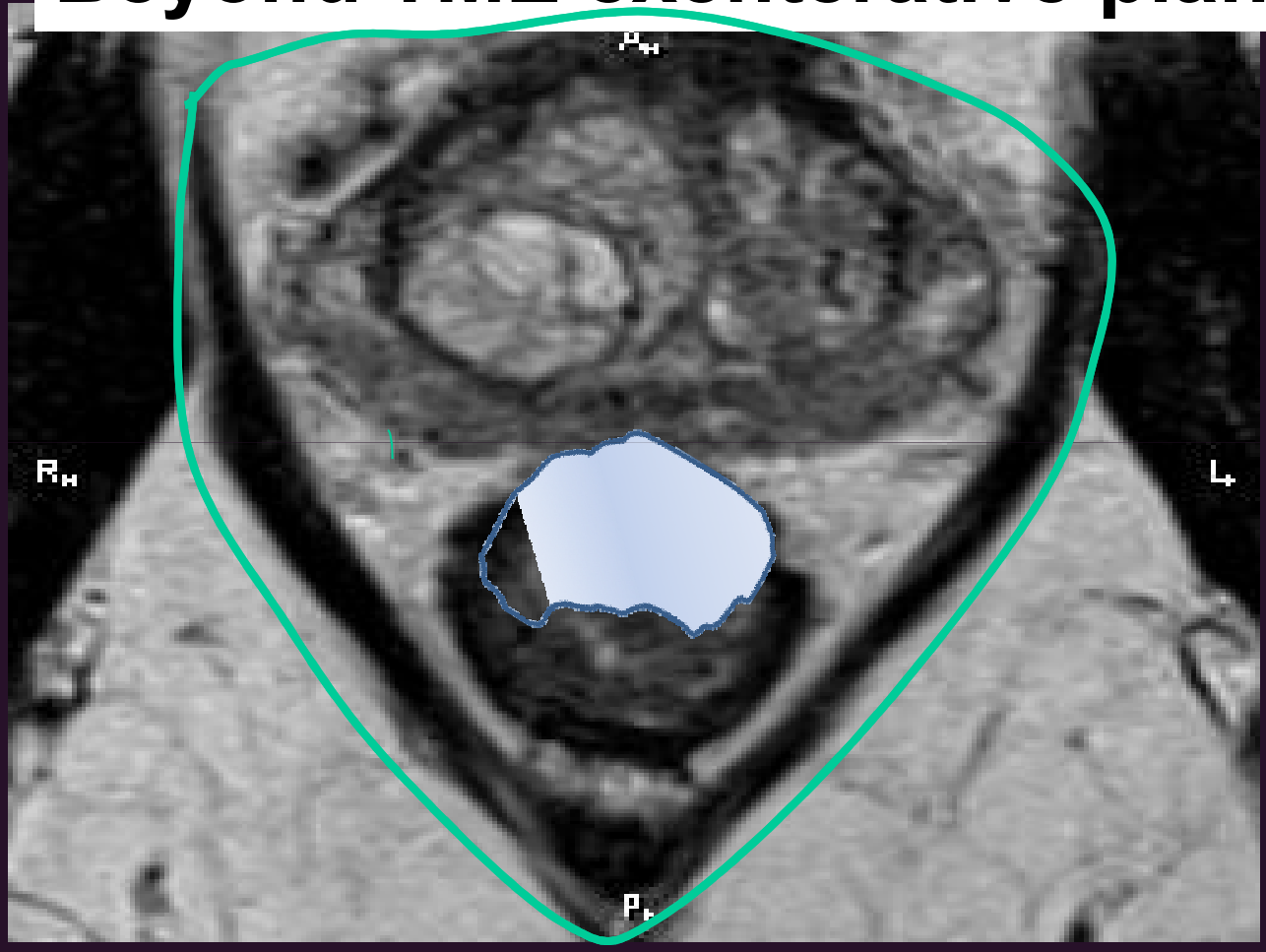
Beyond TME exenterative planes



The tumours that require preoperative therapy because of poor prognosis:

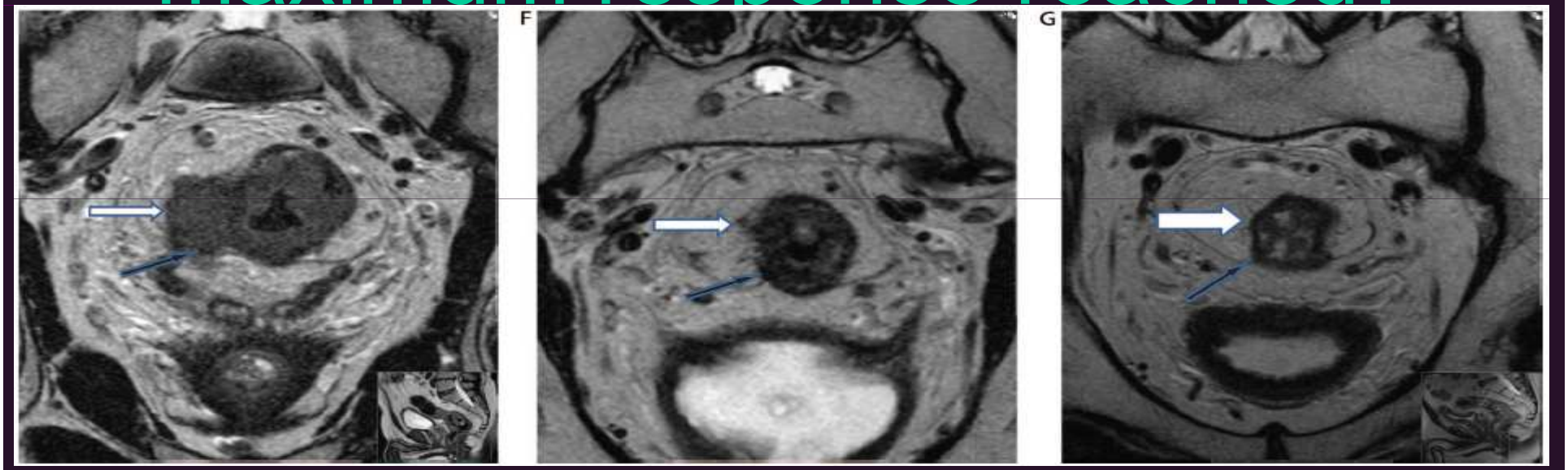
- TME plane CRM involvement
- Depth of extramural spread >5mm risk factor for poor DFS
- Presence of MRI detected venous invasion – risk factor for local and distant recurrence and seen more frequently than path EMVI
- MRI detected mucinous tumours
- MRI Nodal involvement in the absence of any of the above does not confer any significant additional risk of either local or distant relapse

Assessing response

Method	Prospectively validated against DFS outcomes
MRI DWI	No – many retrospective quantitative cut-offs and qualitative assessments – none prospectively validated
DCE-MRI	No – many retrospective values proposed – none validated
PET-CT	No – but retrospective SUV cut-offs proposed – unverified prospectively
mrVolume assessment	Yes: >80% volume reduction
mrTRG	Yes : TRG1-5 validated prospectively and against outcomes
mrT and mrN stage	validated prospectively and against outcomes

The Royal Marsden

Timing after CRT? When is maximum response reached?



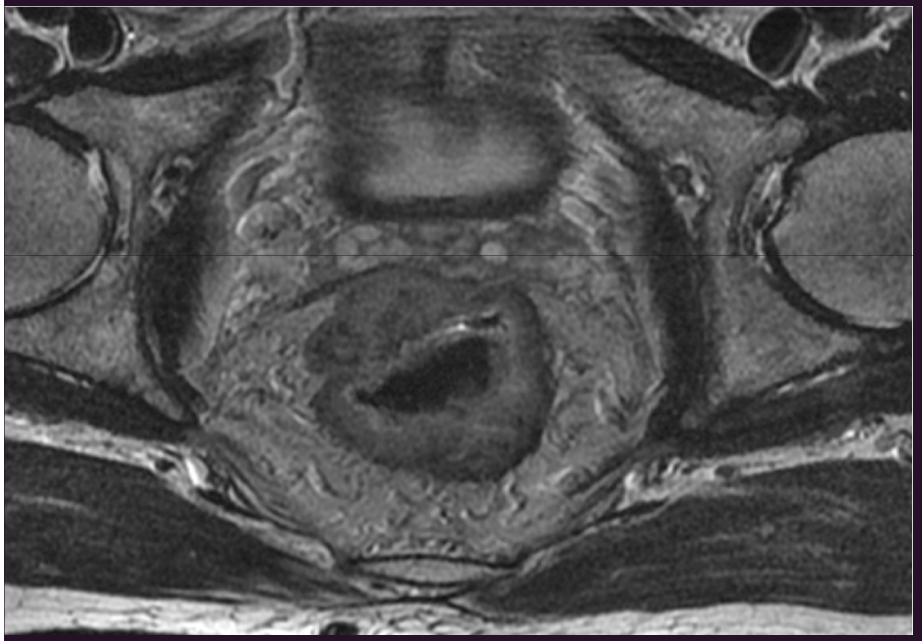
Baseline
mrT4

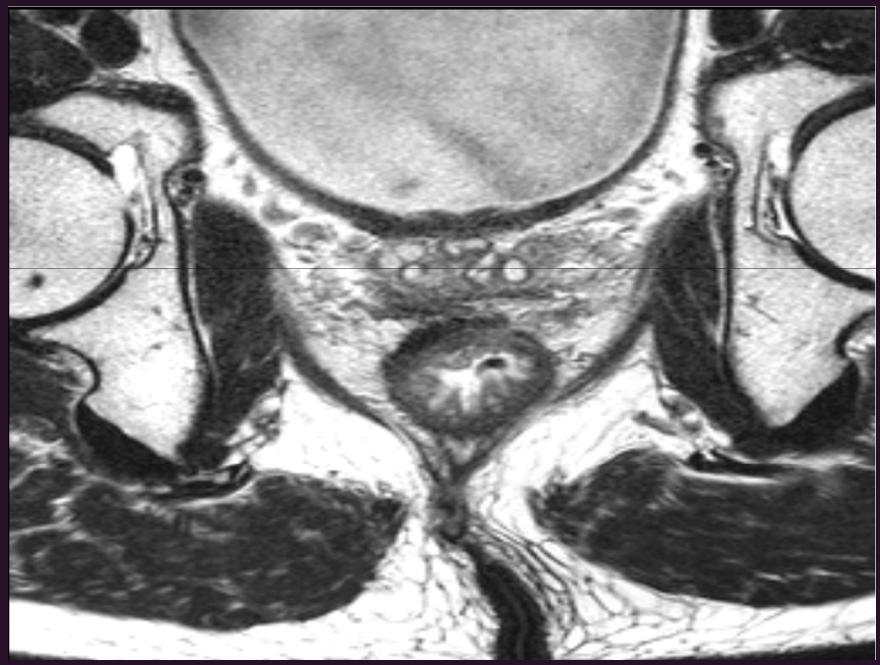
6 weeks
ymrT3b

12 weeks
ymrT2

Final Pathology: ypT2N0

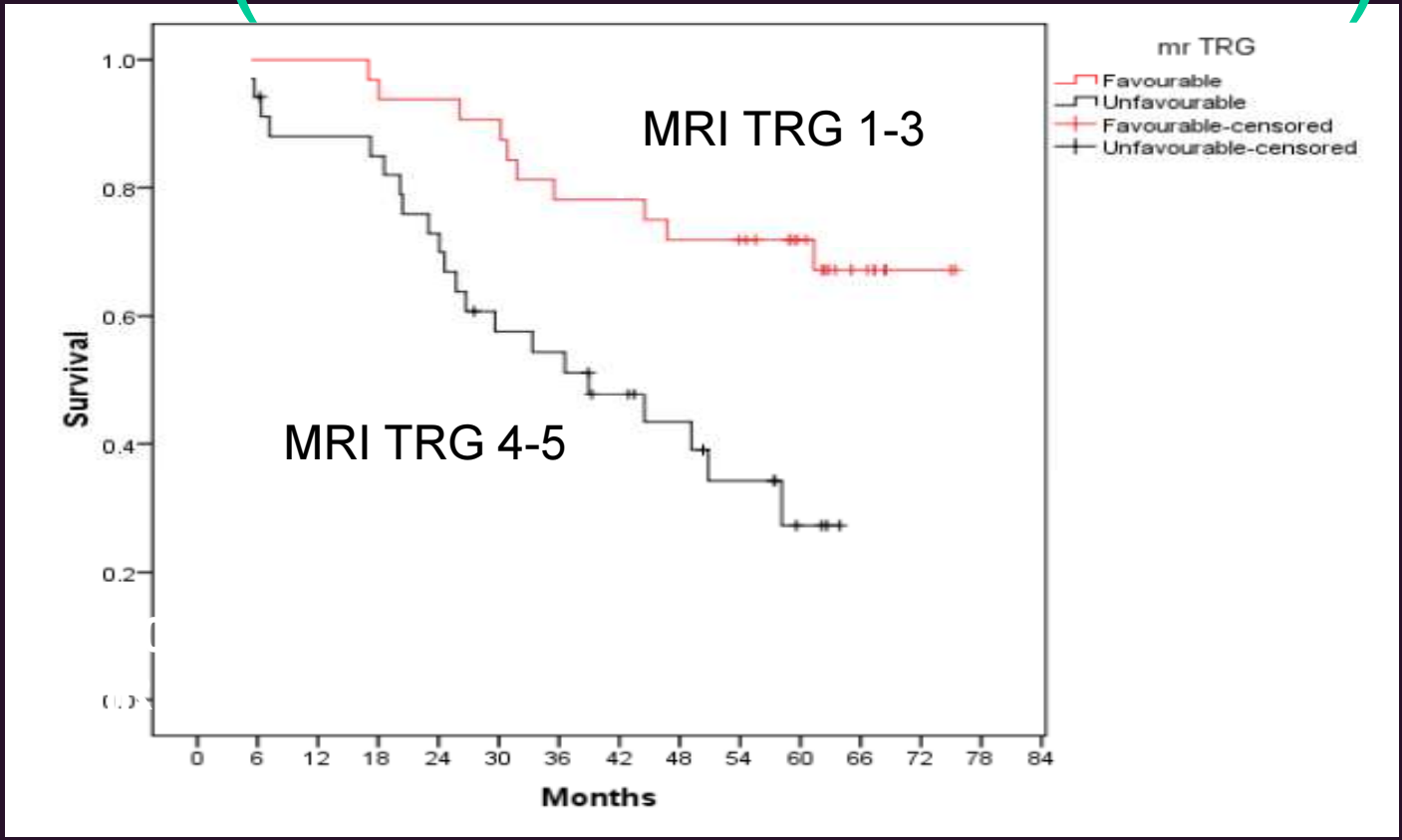
MR TRG





The Royal Marsden

TRG and Survival (Patel et al JCO 2011)



MRI assessment

		Post Rx mr T stage				Post Rx mr Node stage				mr TRG stage				Post Rx mr CRM			
		os	dfs	lr		Os	dfs	lr		os	Dfs	lr		os	dfs	lr	
MRI Variable	ymrT good	1	1	1	MR N-	1	1	1	MR TRG good	1	1	1	MR CRM-	1	1	1	
	ymrT poor	2.27	1.82	0.91	MR N+	1.75	1.98	1.16	MR TRG poor	4.40** (1.65-11.7)	3.28* (1.22-8.80)	3.71	MR CRM+	1.76	1.08	4.25††† (1.45-12.51)	
Age	<65 years	1	1	1	<65 years	1	1	1	<65 years	1	1	1	<65 years	1	1	1	
	≥65 years	1.48	0.88	0.59	≥65 years	1.75	1.11	0.87	≥65 years	1.46	0.98	0.65	≥65 years	1.57	0.93	1.10	
Sex	Male	1	1	1	Male	1	1	1	Male	1	1	1	Male	1	1	1	
	Female	0.88	0.59	0.931	Female	0.81	0.54	1.01	Female	0.70	0.67	0.80	Female	0.76	0.46† (0.24-0.89)	1.16	
Treatment	Chemo & RT	1	1	1	Chemo & RT	1	1	1	Chemo & RT	1	1	1	Chemo & RT	1	1	1	
	LCRT	0.98	0.93	0.99	LCRT	1.08	0.99	0.95	LCRT	0.69	0.69	0.41	LCRT	0.86	0.89	0.51	
Operation	Anterior Resection	1	1	1	Anterior Resection	1	1	1	Anterior Resection	1	1	1	Anterior Resection	1	1	1	
	AP excision	1.36	0.85	2.69	AP excision	1.24	0.81	2.25	AP excision	0.81	0.58	1.69	AP excision	0.99	0.56	2.05	
Height from anal verge	*>5cm*	1	1	1	*>5cm*	1	1	1	*>5cm*	1	1	1	*>5cm*	1	1	1	
	≤5cm	0.92	1.37	0.95	≤5cm	0.93	1.34	1.28	≤5cm	1.05	1.19	0.99	≤5cm	0.73	1.30	1.08	

NHS

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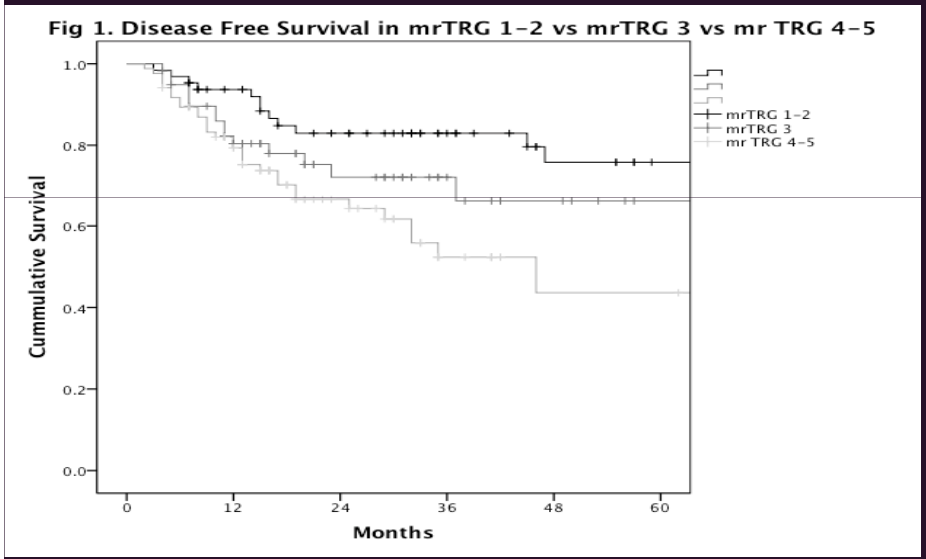
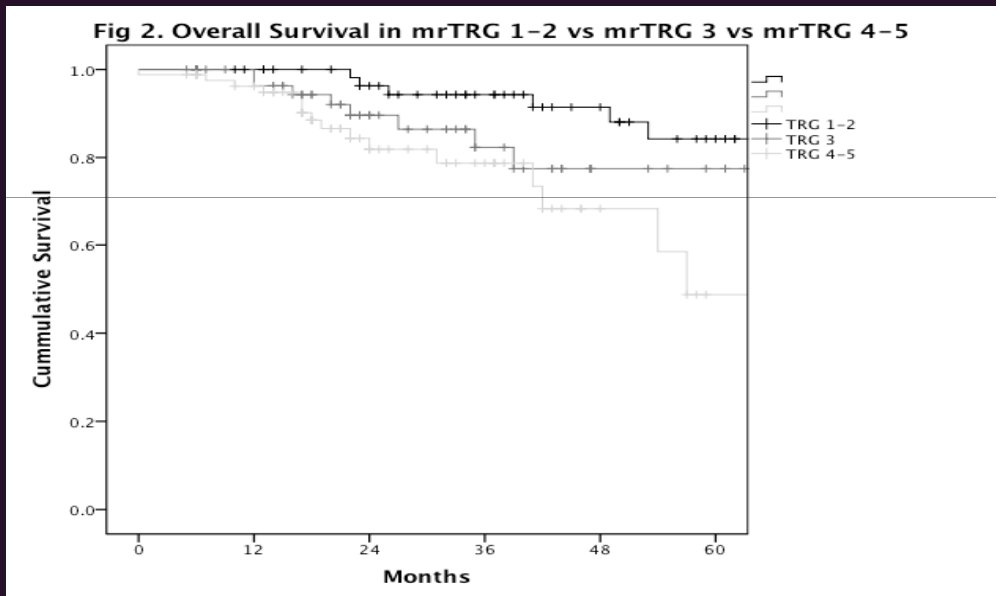
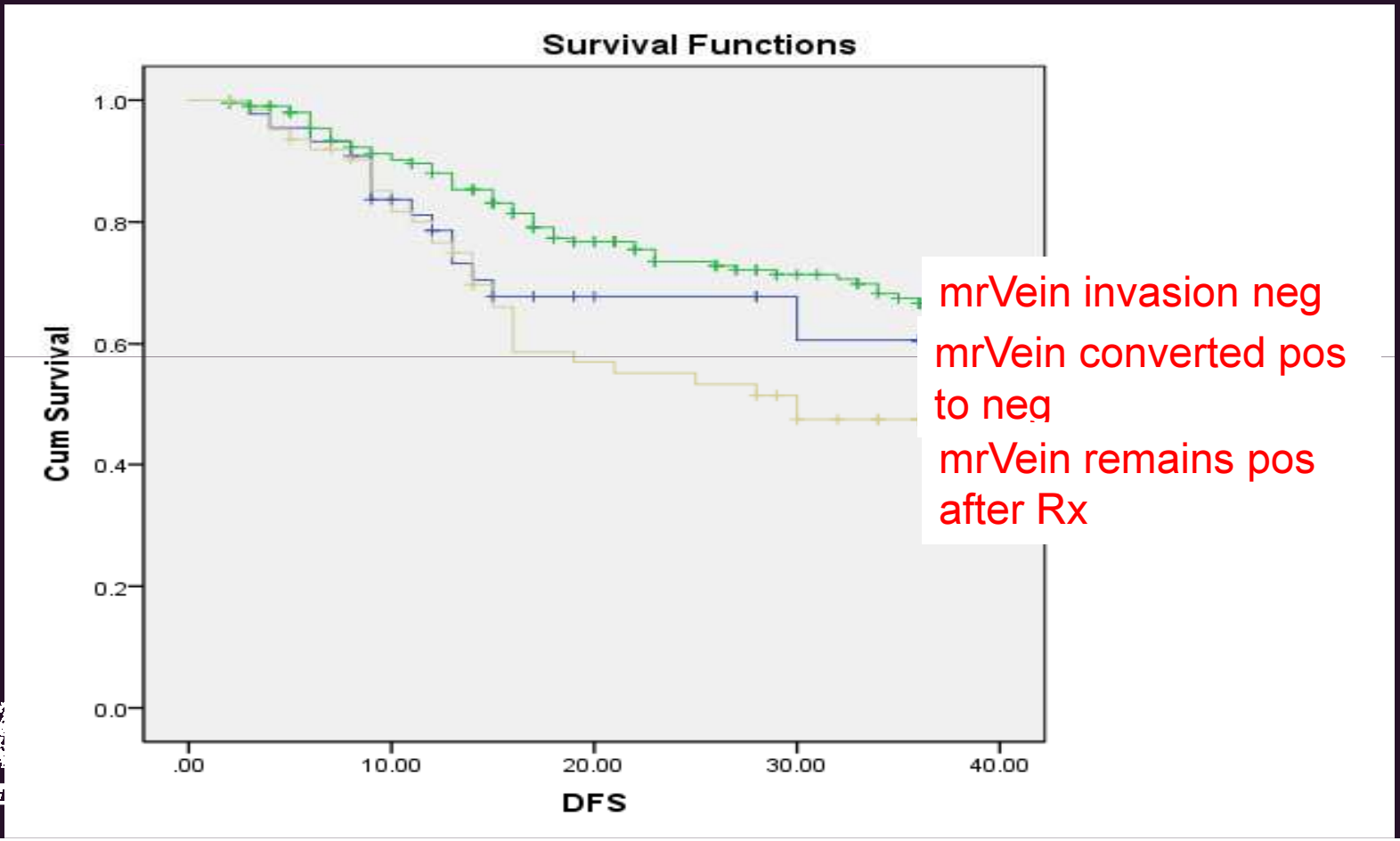
Royal Marsden n=208 patients





Yu et al , ESMO World GI Congress, Barcelona 2015

Post CRT effect on EMVI – 3-year DFS



mrTRG is a prognostic (and predictive) biomarker

- Shows good interobserver radiology agreement and reproducibility
  - MERCURY trial (JCO 2011 – multiple radiologists)
  - EXPERT-C trial
  - GEMCAD study (17 radiologists)
  - CORE study (interobserver agreement)
  - MERCURY 2 trial – risk factor for CRM involvement
- In EXPERT C trial identified 40% of patients with mrTRG1/2 – 89.8% overall survival. Compared with only 15% pathologic CR rate (90% survival).
- Therefore mrTRG could be justified as a more clinically relevant endpoint

NHS

Prognostic/predictive item	Validation by modality?	
	EUS	MRI
T substage rather than T stage	no	yes
Detection of EMVI rather than N stage	no	yes
CRM status – should be a staging item	no	yes
Assessment of low rectal plane	no	yes
Reassessment after CRT	no	yes
Effective treatment stratification?	no	yes

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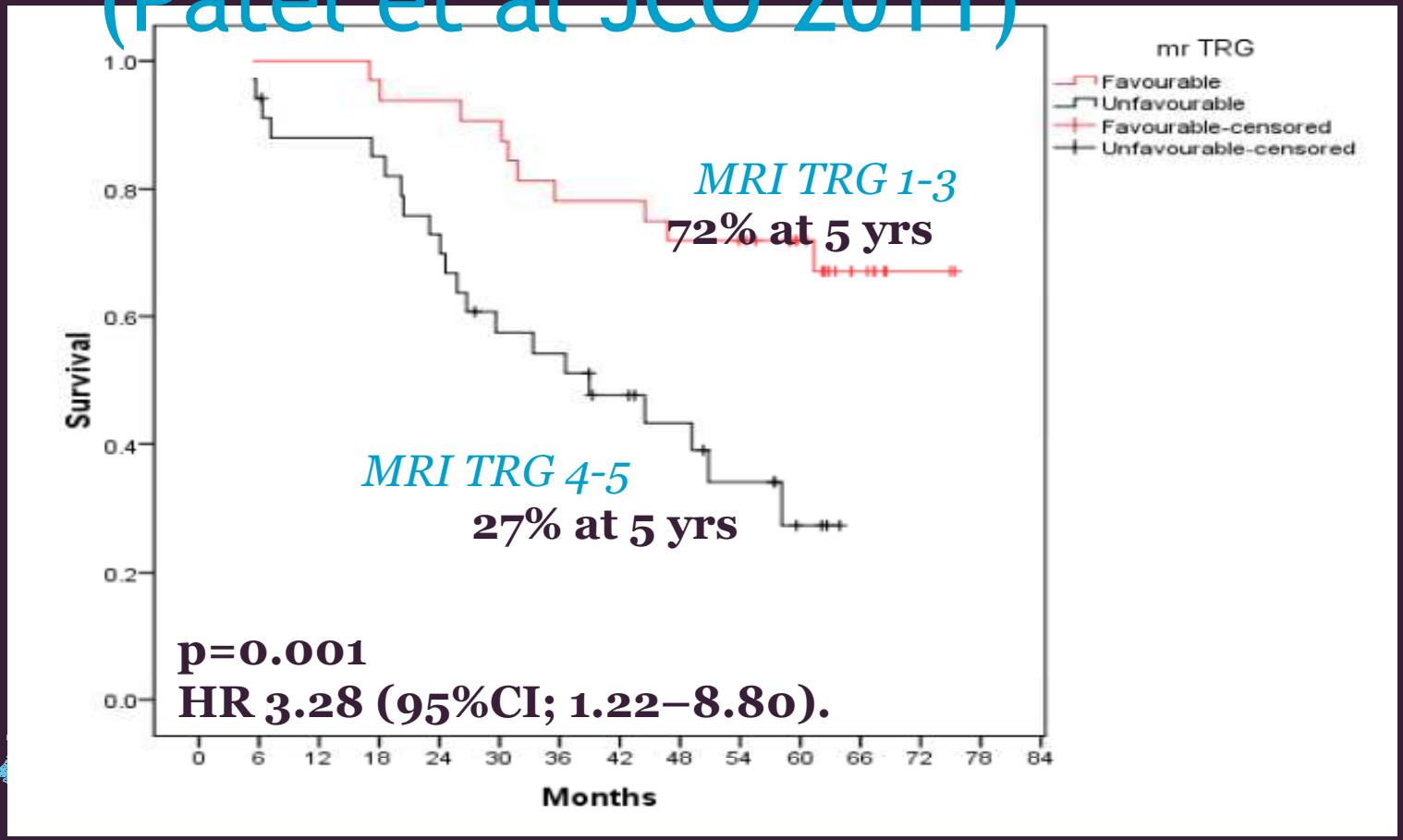
MRI reassessment after CRT

- Philosophy of avoiding APE surgery if patient has had a good response to treatment
- mrTRG 1-3 - used to identify patients suitable for deferral (many are falsely positive on biopsy, DWI and PET-CT)
- Serial imaging – decision for deferral is not based on a single scan – uses the advantage of high resolution MRI monitoring
- Employing serial MRI monitoring - gives opportunity to delay surgery until there is evidence of tumour regrowth rather than biopsy of tumour cells which are of uncertain viability

NHS

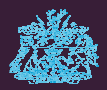
TRG and Survival (Patel et al JCO 2011)



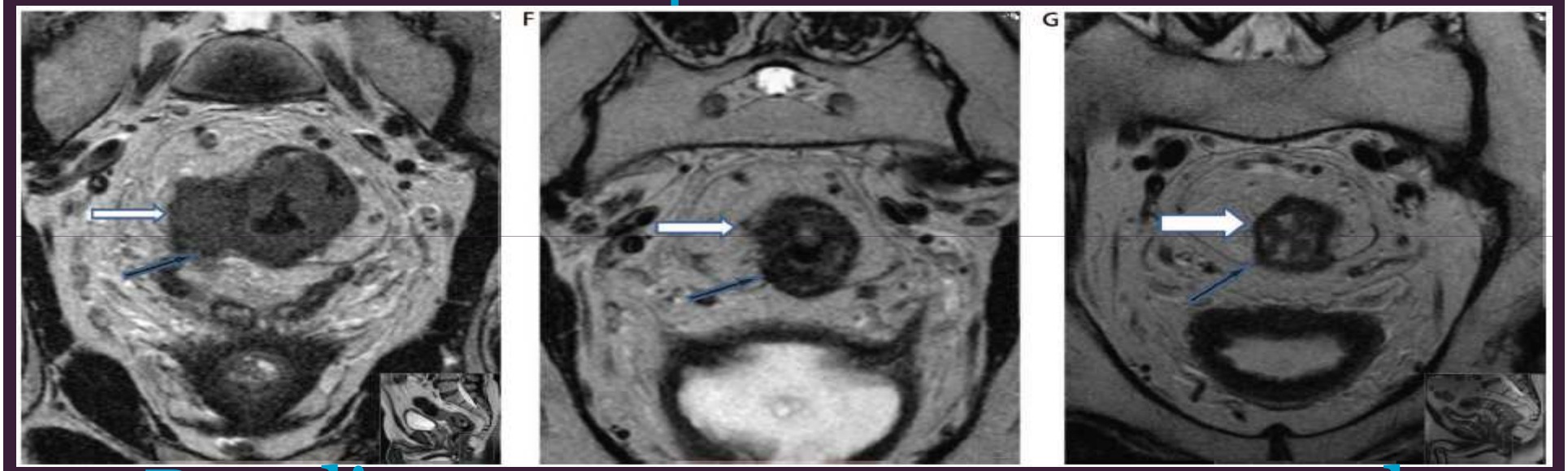
Timing of Surgery after Radiotherapy – Prospective Randomised Study

– Hypothesis

Greater downstaging and tumour regression is observed when surgery is delayed to 12 weeks after completion of CRT compared to 6 weeks.



Timing after CRT? When is maximum response reached?



Baseline
mrT4

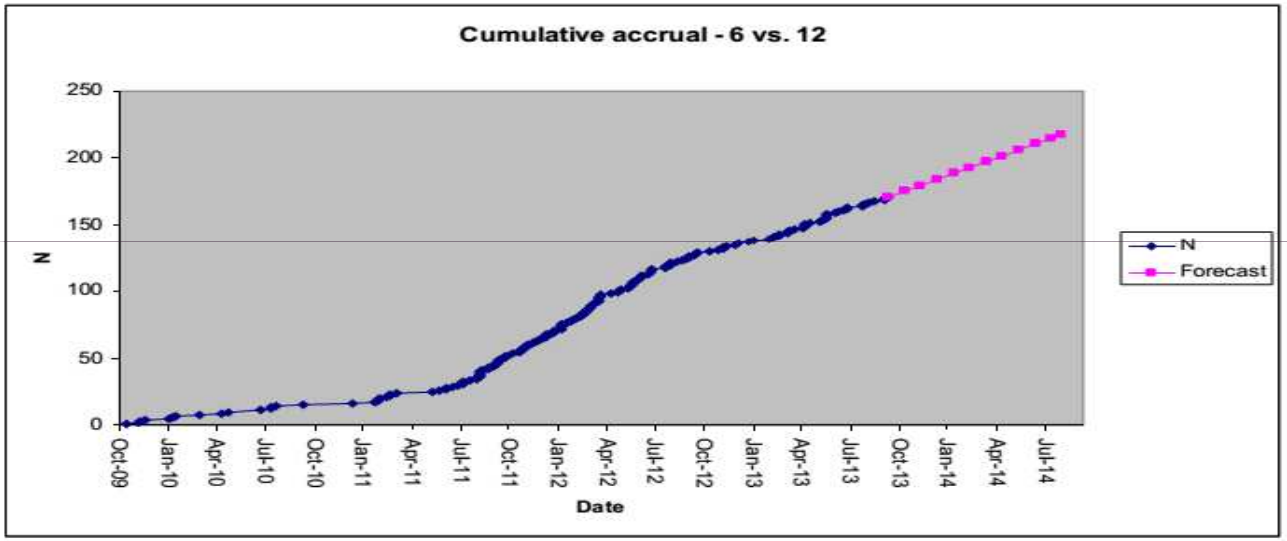
6 weeks
mrT3b

12 weeks
mrT2

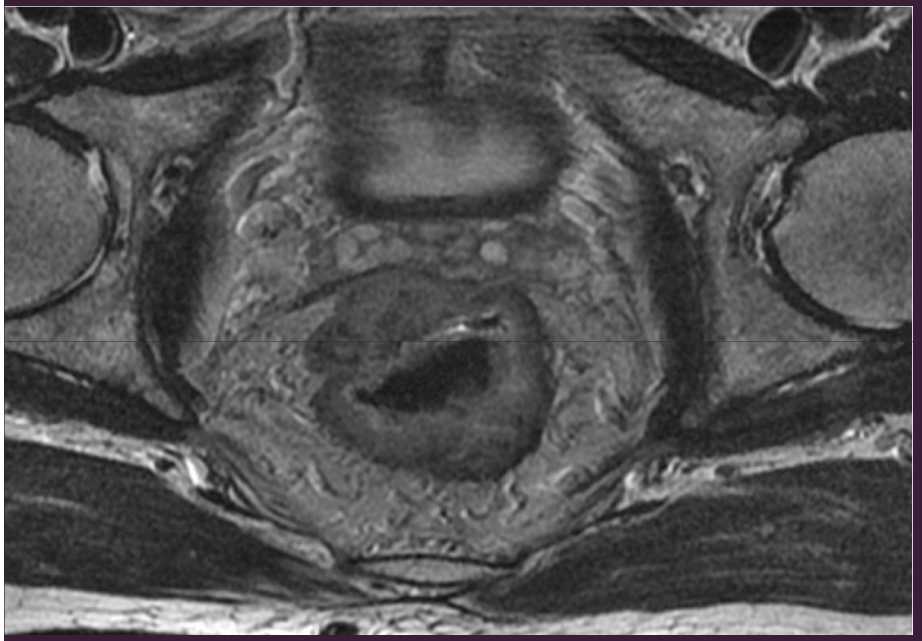
Final Pathology: ypT2N0

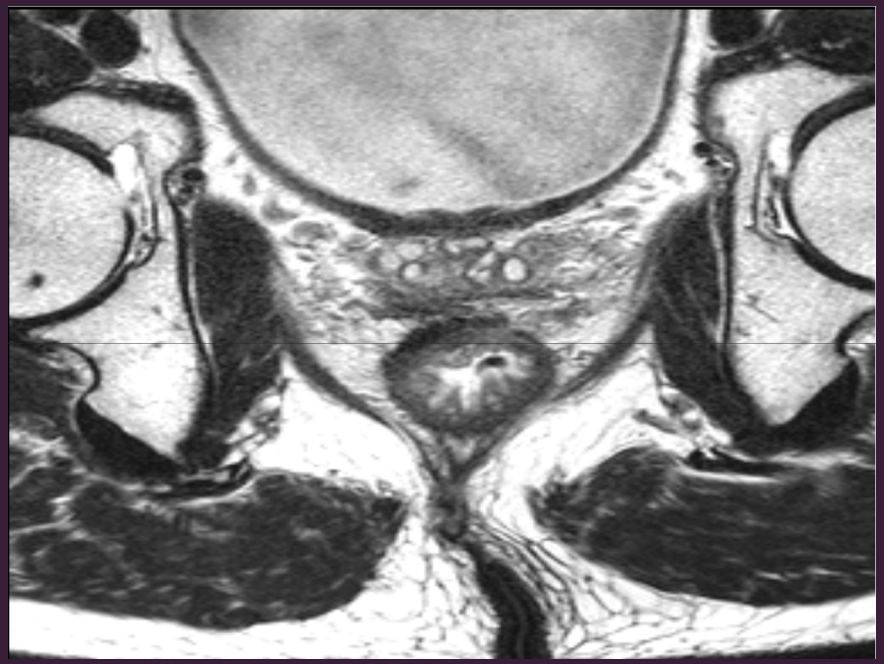
Accrual now complete: analysis and report of 6 vs 12 trial in 2015

Centre	Total	Percent
Bath	11	6%
Birmingham	12	7%
Brazil	6	4%
Canada	8	5%
Chichester	6	4%
Colchester	19	11%
Cyprus	13	8%
Dorset	4	2%
Great Yarmouth	3	2%
Medway	1	1%
Mid Yorkshire	2	1%
North Durham	1	1%
North Tees	2	1%
Northwick Park	1	1%
Poole	5	3%
Portsmouth	10	6%
Royal Marsden Hospital	63	37%
St Barts	1	1%
St Georges	3	2%
Grand Total	171	100%



MR TRG





MRI assessment, MERCURY follow up: JCO 2011

		Post Rx mr T stage				Post Rx mr Node stage				mr TRG stage				Post Rx mr CRM			
		os	dfs	lr		Os	dfs	lr		os	Dfs	lr		os	dfs	lr	
MRI Variable	ymrT good	1	1	1	MR N-	1	1	1	MR TRG good	1	1	1	MR CRM-	1	1	1	
	ymrT poor	2.27	1.82	0.91	MR N+	1.75	1.98	1.16	MR TRG poor	4.40** (1.65-11.7)	3.28* (1.22-8.80)	3.71	MR CRM+	1.76	1.08	4.25††† (1.45-12.51)	
Age	<65 years	1	1	1	<65 years	1	1	1	<65 years	1	1	1	<65 years	1	1	1	
	≥65 years	1.48	0.88	0.59	≥65 years	1.75	1.11	0.87	≥65 years	1.46	0.98	0.65	≥65 years	1.57	0.93	1.10	
Sex	Male	1	1	1	Male	1	1	1	Male	1	1	1	Male	1	1	1	
	Female	0.88	0.59	0.931	Female	0.81	0.54	1.01	Female	0.70	0.67	0.80	Female	0.76	0.46† (0.24-0.89)	1.16	
Treatment	Chemo & RT	1	1	1	Chemo & RT	1	1	1	Chemo & RT	1	1	1	Chemo & RT	1	1	1	
	LCRT	0.98	0.93	0.99	LCRT	1.08	0.99	0.95	LCRT	0.69	0.69	0.41	LCRT	0.86	0.89	0.51	
Operation	Anterior Resection	1	1	1	Anterior Resection	1	1	1	Anterior Resection	1	1	1	Anterior Resection	1	1	1	
	AP excision	1.36	0.85	2.69	AP excision	1.24	0.81	2.25	AP excision	0.81	0.58	1.69	AP excision	0.99	0.56	2.05	
Height from anal verge	*>5cm*	1	1	1	*>5cm*	1	1	1	*>5cm*	1	1	1	*>5cm*	1	1	1	
	≤5cm	0.92	1.37	0.95	≤5cm	0.93	1.34	1.28	≤5cm	1.05	1.19	0.99	≤5cm	0.73	1.30	1.08	

mrTRG 1 -2 and nodal status when surgery performed at 6-8 weeks after CRT

	pCR patients (frequency / %)	Non pCR patients (frequency / %)	ypN0 status (%)	Total
mrTRG 1	18 / 95%	1 /5%	19 (100%)	19
mrTRG 2	16 / 39%	25 / 61%	39 (95%)	41
mrTRG 3	9 / 14%	54 / 86%	18 (43%)	63
mrTRG 4	8 / 10%	69 / 90%	33 (53%)	77
mrTRG 5	0 / 0%	8 / 100%	1 (13%)	8
Total	51	157	109	208

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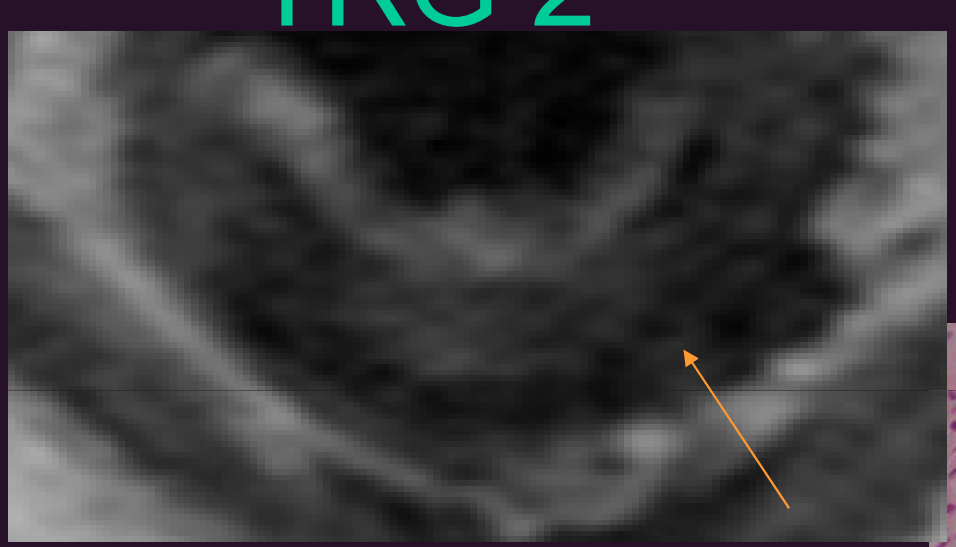
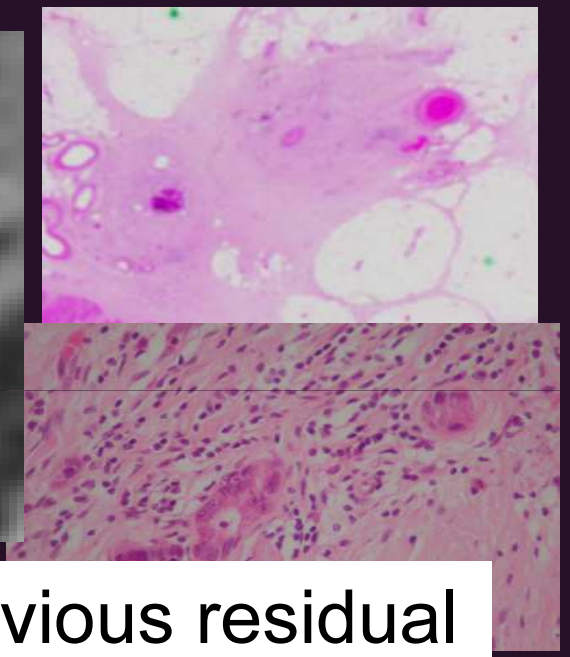
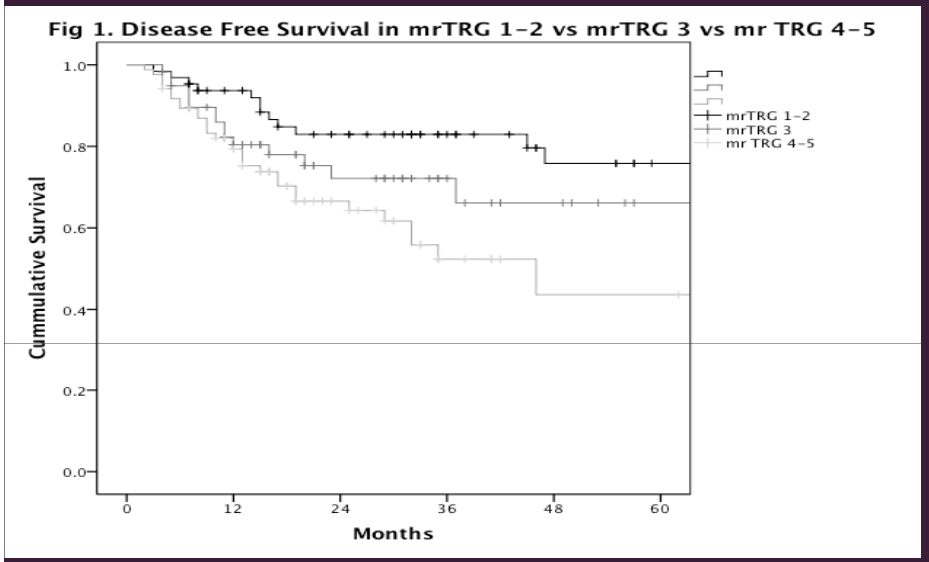
TRG 2

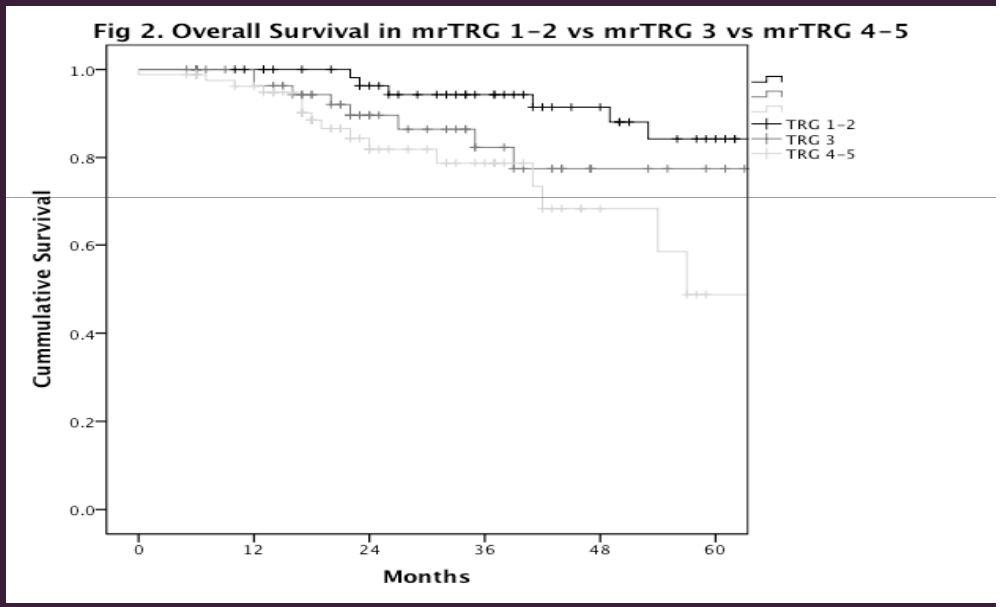




Good response :dense fibrosis; no obvious residual tumour, signifying microscopic residual disease only and on continued surveillance may become TRG1 no viable tumour

Royal Marsden database n=208 irradiated patients





EXPERT C trial for patients at high risk of local and distant failure

- Tumors within 1 mm of mesorectal fascia (ie, potential circumferential resection margin involvement)
- T3 c (extramural spread 5-15 mm) and T3 d (extramural spread >15 mm), regardless of N stage
- MRI T4a or T4b disease regardless of N stage
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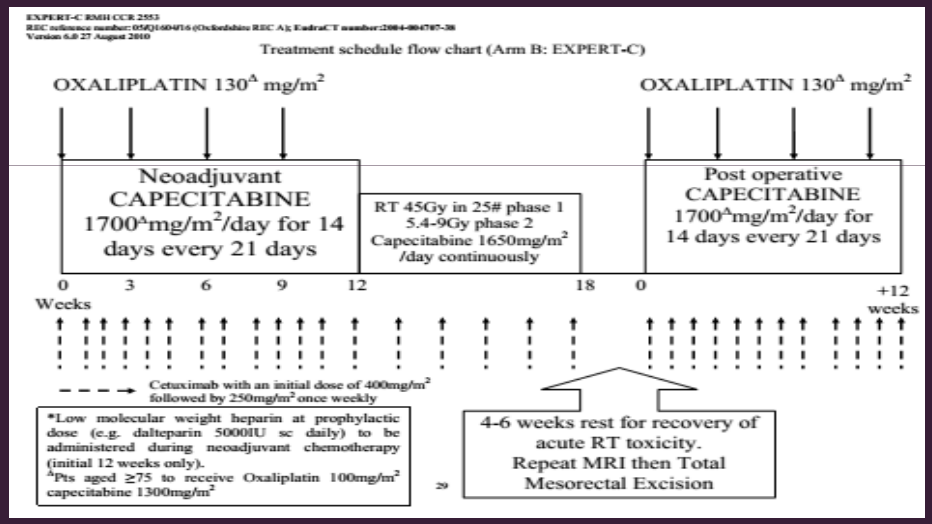
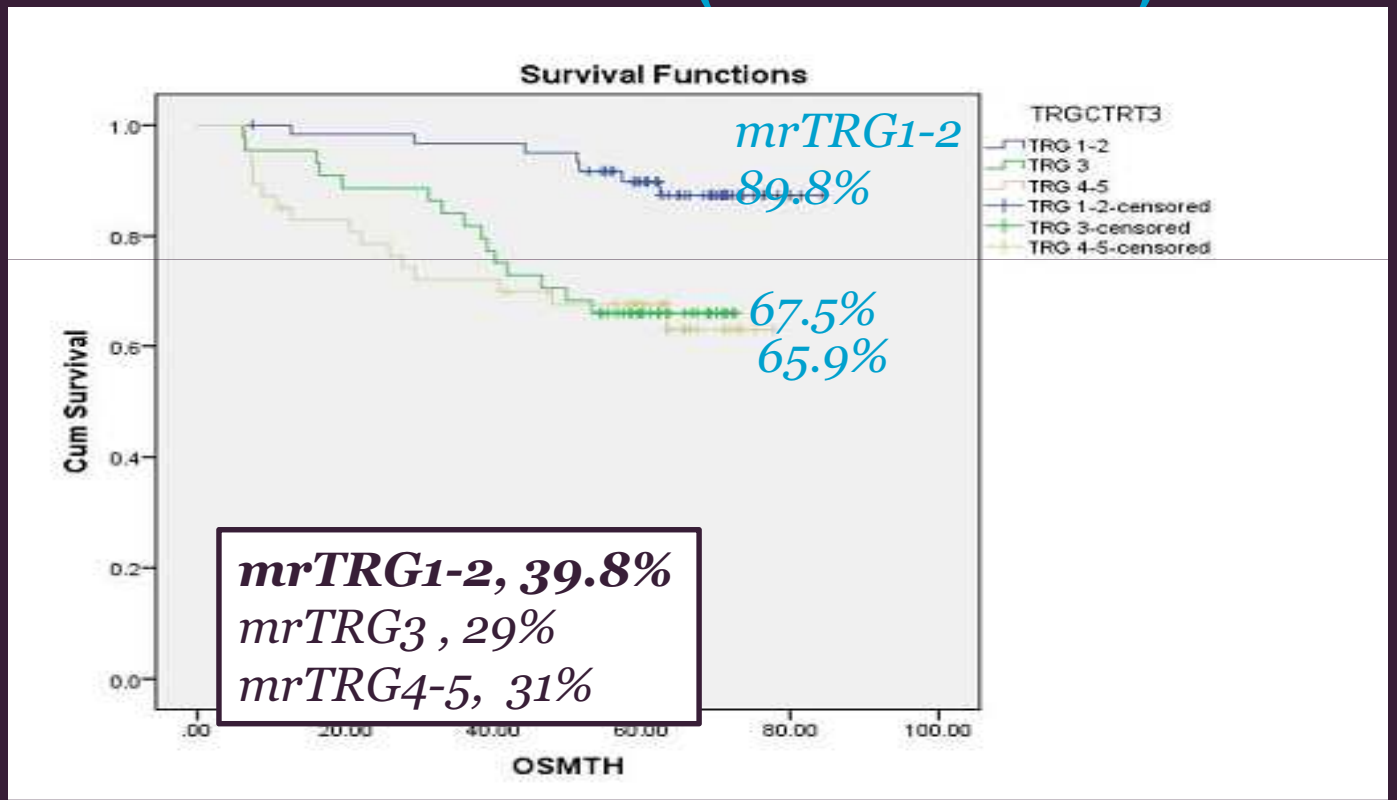


Overall Survival by TRG (1-2 v 3 v 4-5) after Chemo-Radiotherapy in EXPERT-C trial (both arms)



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- Identified 40% of patients with mrTRG1/2 – 89.8% overall survival. Compared with only 8.8% patients with pathologic CR.
- Therefore mrTRG could be justified as a more clinically relevant endpoint

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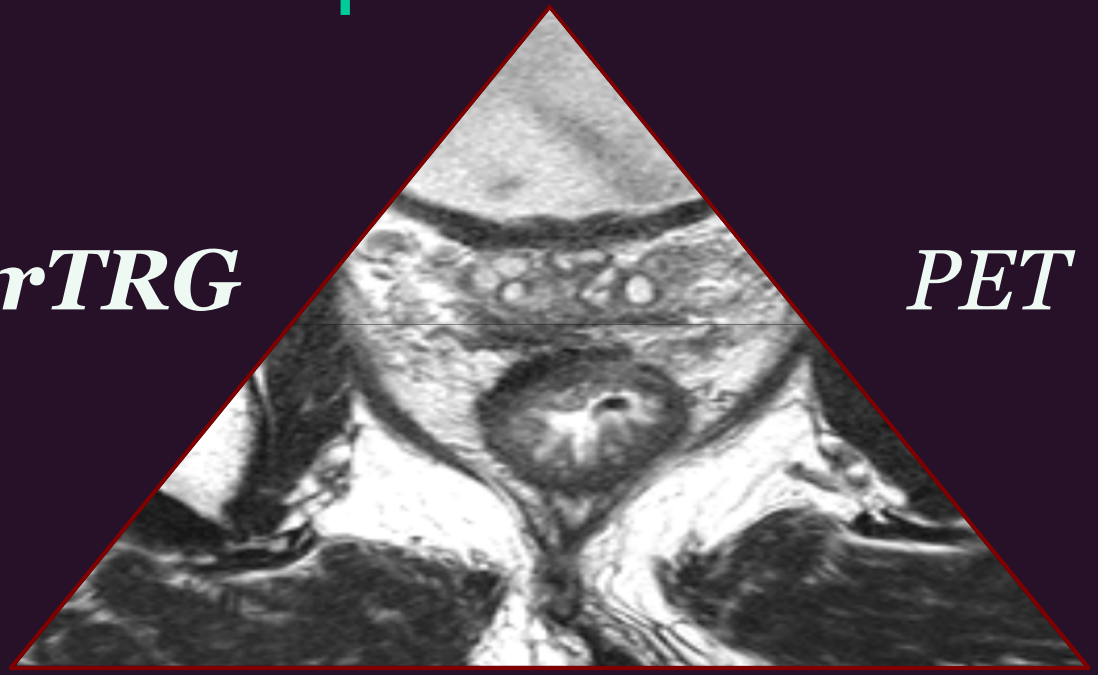
SELECTING PATIENTS FOR DEFERRAL

How are the patients identified?



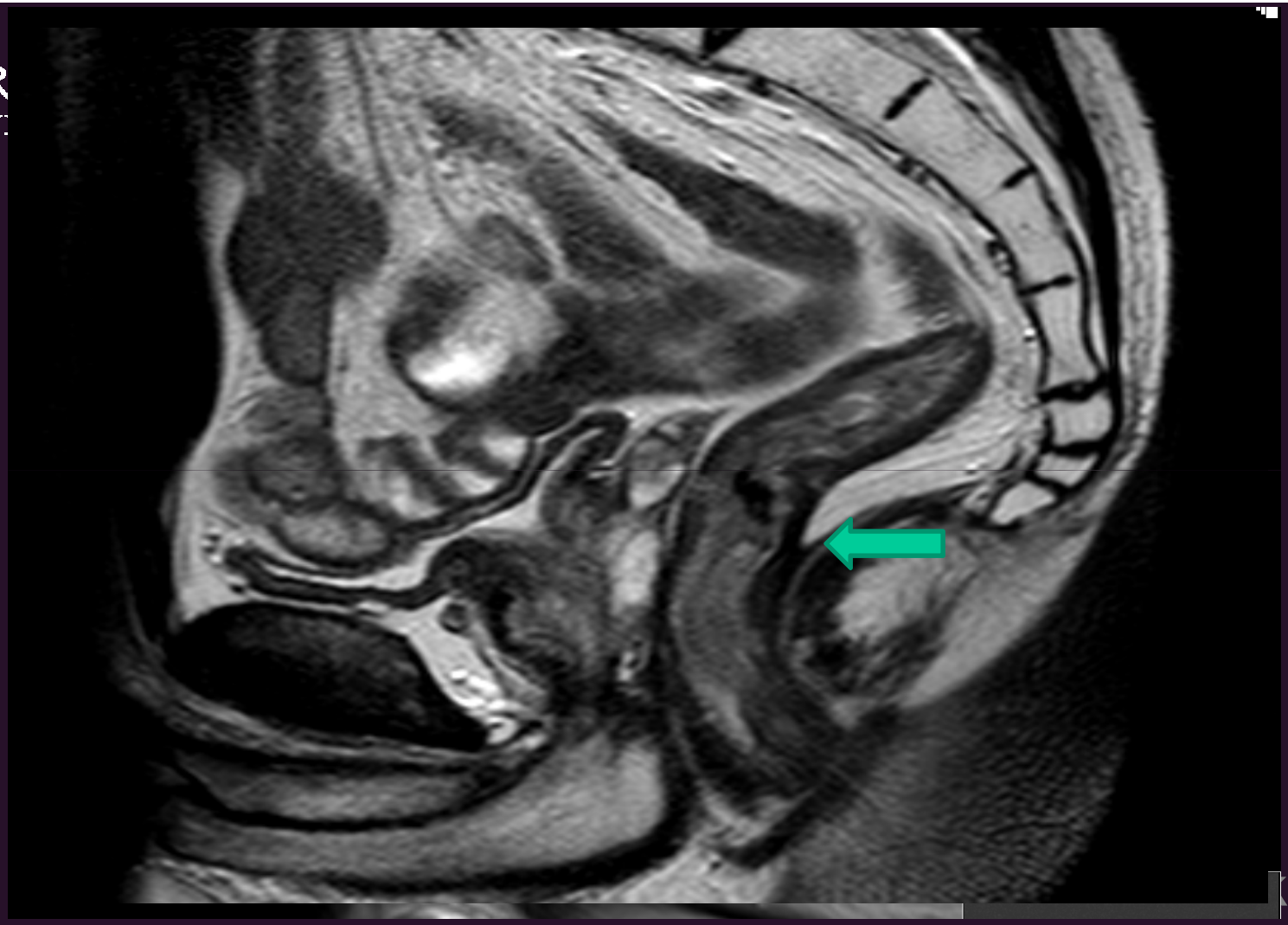
mrTRG

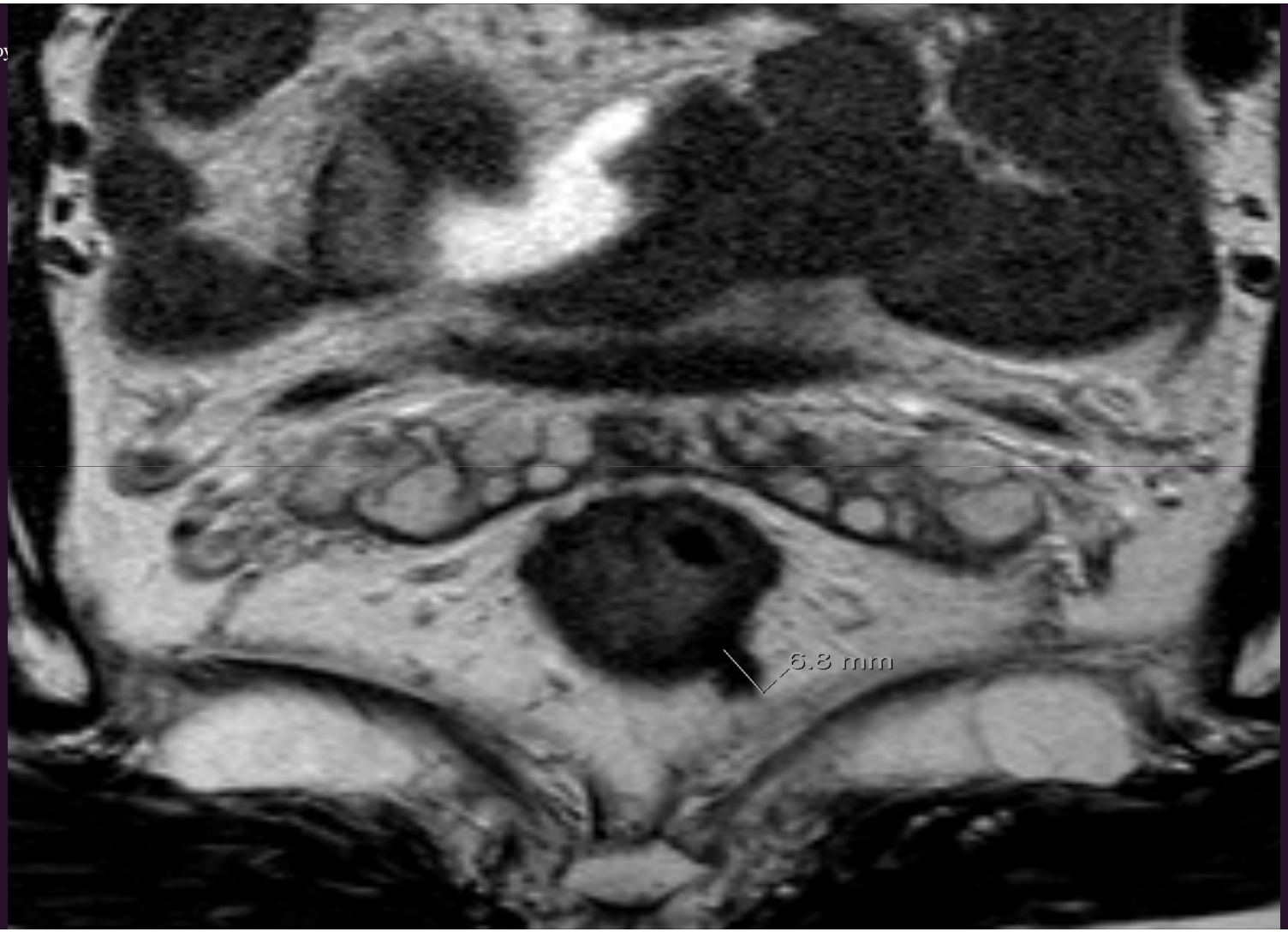
PET

Clinically - DRE
+/- biopsy

The R

N




6.8 mm

Enrolment

mrTRG1 -2 @4-6 weeks post CRT → no viable disease
(low signal intensity fibrotic scar tissue only)
confirmed by MRI @ 8-12 weeks

mrTRG3 @ 4-6 weeks post CRT → a good partial response
Continued incremental response on MRI @ 8-12 weeks

NOT INITIALLY EXCLUDED EVEN IF:

- DRE - Thickening of rectal wall or clinically palpable tumour
- Endoscopically – mucosal abnormality
- Pathology - Biopsy positive

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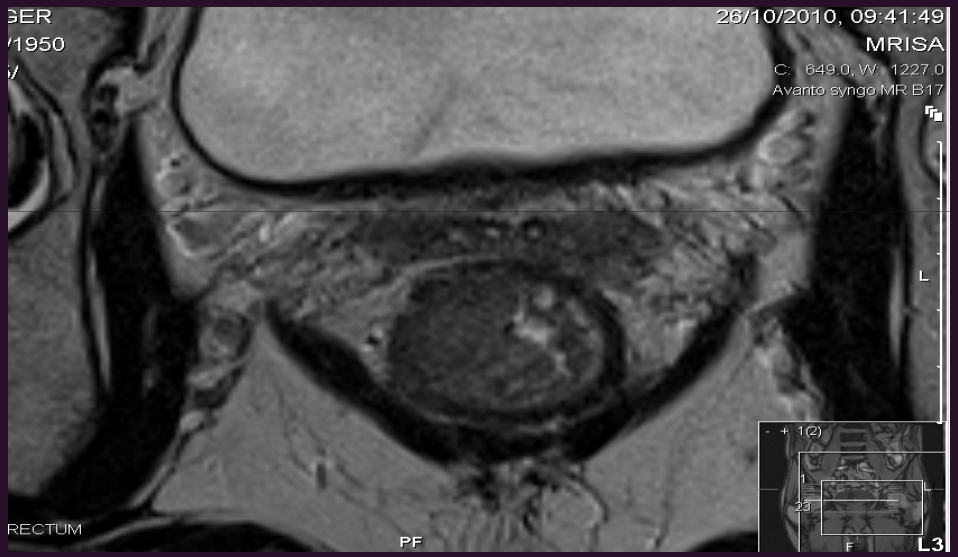
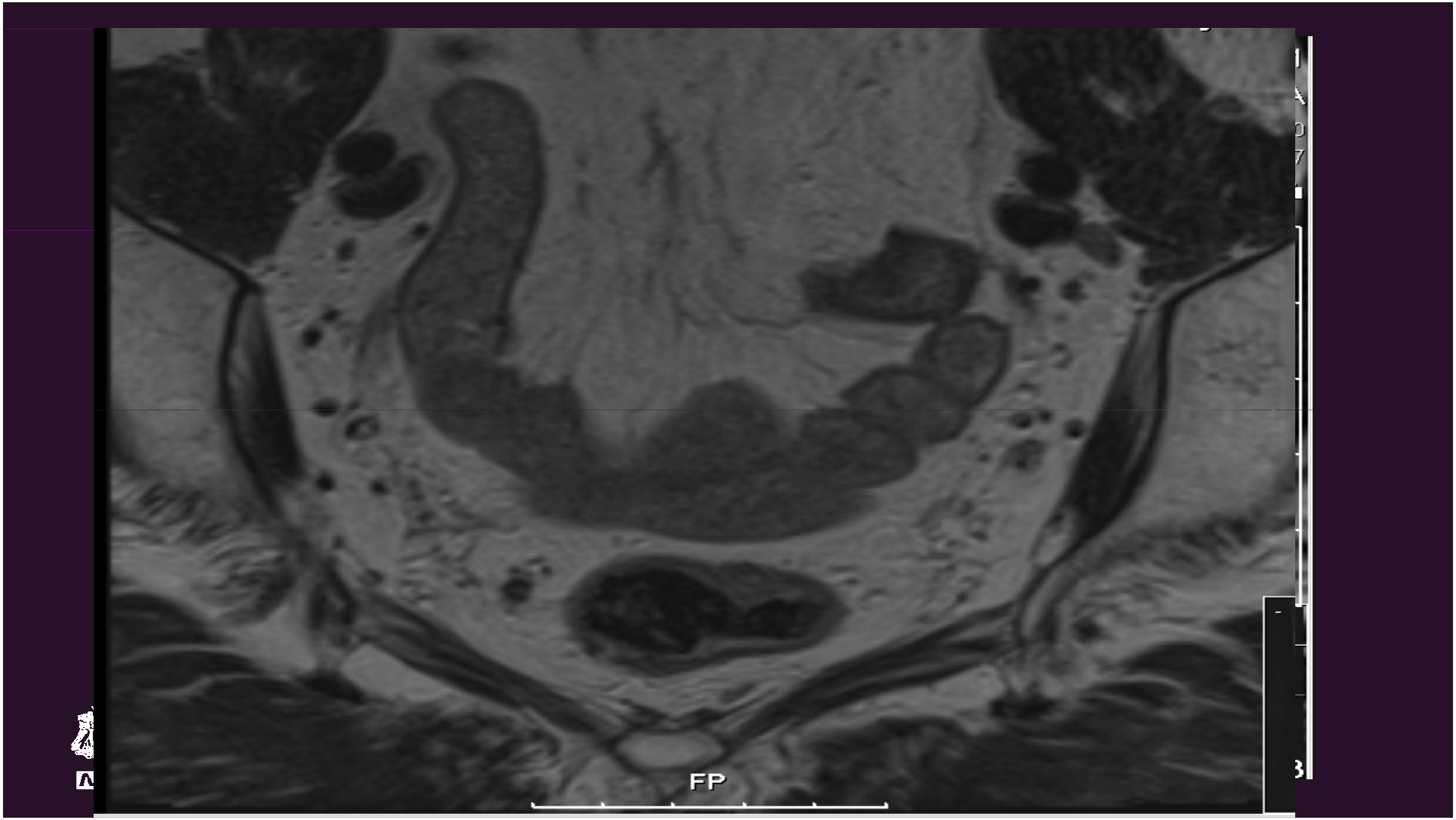
MDT options: MRI T1sm3N1



- Primary surgery : abdominoperineal excision, permanent stoma
- Local excision and chemoradiotherapy
- Preoperative Chemoradiotherapy


FP

Royal Marsden Criteria

1. MRI defined complete response: mrTRG1-2 : low signal intensity fibrotic scar tissue only seen at MRI performed 4 weeks after long-course CRT, confirmed at 8-12 week MRI.

Biopsy positive disease not an initial exclusion criterion

Thickening of rectal wall – not an exclusion

Abnormality on endoscopy – not an exclusion

Clinically palpable tumour – not an exclusion

PET-CT positivity not an initial exclusion

Persistent DWI signal – not an initial exclusion

Patients deferring surgery

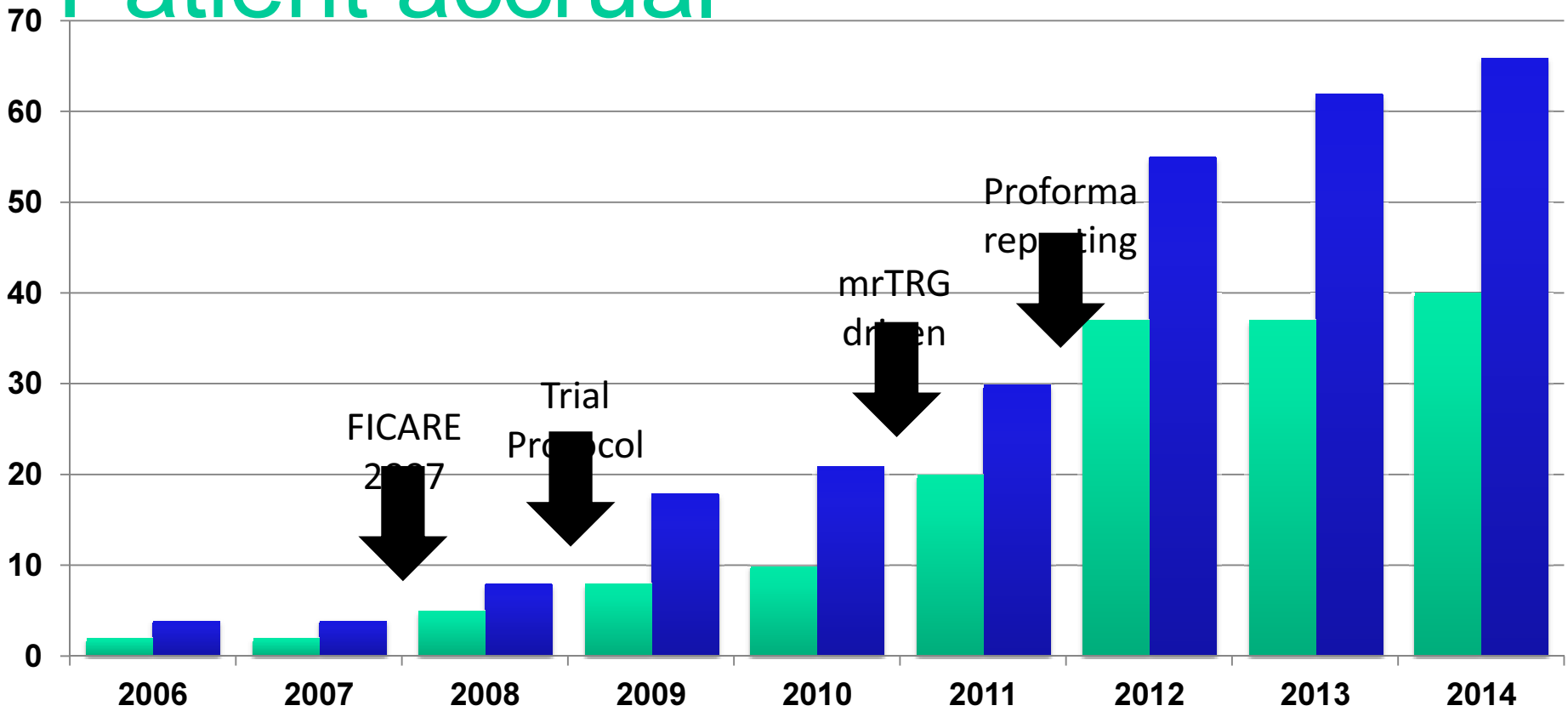
Follow-up Schedule

The ROYAL MARSDEN NHS Foundation Trust

TIME	Year 1							Year 2				Year 3		Year 4		Year 5		Yr 6
	1	2	3	4	6	9	12	15	18	21	24	30	36	42	48	54	60	72
DRE	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CEA	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
MRI	x	x	x	x	x	x	x		x		x		x		x		x	x
PET		x		x			x											
CT							x				x		x					
Sigmoid /Colon			S		S	S	C		S		S		S		S		C	S

Clinical Follow-up	1M, 2M, 3Mly – 1-2yrs, 6Mly – 3-4yrs, then Annually
MRI	1M, 2M, 3Mly – 1st Yr, 6Mly - 2nd Yr, Annually
PET	2M, 4M, 1yr
Sigmoidoscopy	3Mly – Yr 1, 6Mly – Yr 2, Annually
CT & Colonoscopy	as per current NICE guidelines.

Patient accrual



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Proforma reporting

Post Treatment Assessment MRI Rectal Cancer

Comparison is made with the previous examination of:

- The treated tumour: shows no fibrosis,TRG5
- Less than <25% fibrosis, predominant tumour signal, TRG4
- 50% tumour/fibrosis, TRG 3
- >75% fibrosis, minimal tumour signal intensity,TRG2
- low signal fibrosis only no intermediate tumour signal TRG1

The distal edge of the luminal tumour arises at a height of [ ] mm from anal verge:
The distal edge of the tumour lies [ ]mm [Above, at, below] the top of the puborectalis sling compared with []mm previously
The tumour extends craniocaudally over a distance of [ ] mm compared with [ ]mm previously
The proximal edge of tumour lies [above at below] the peritoneal reflection
The invading edge of treated tumour extends from [to] O'clock
Tumour signal is [Confined to / Extends through the muscularis propria.]
Fibrotic signal is [Confined to / Extends through muscularis propria.]
Extramural spread: [ ]mm for tumour signal [ ]for fibrotic stroma

yMR T stage: • T1 • T2 • T3a • T3b • T3c • T3d •T4 visceral •T4 peritoneal

Treated tumour [is/ is not] present at or below the puborectalis sling
- tumour signal/fibrosis extends into the submucosal layer/part thickness of muscularis propria : intersphincteric plane/mesorectal plane is safe intersphincteric APE or ultra low TME possible, CRM is safe
- tumour signal/fibrosis extends through the full thickness of muscularis propria : intersphincteric plane/mesorectal plane is unsafe, for extralevator APE.
- tumour signal/fibrosis extends into external sphincter : intersphincteric plane/mesorectal plane is unsafe:for extralevator APE
- tumour signal/fibrosis extends into beyond external sphincter into [prostate/vagina] : intersphincteric plane / mesorectal plane is unsafe, for extralevator APE.

Additional comments:

Lymph nodes:
- None /Only benign reactive [N0]
- Present number mixed signal/irregular border [N1/N2]

Extramural venous invasion: [• No evidence • Evidence]
[• Small • Medium • Large]

CRM
Closest circumferential resection margin: [ ]O'clock
Closest CRM is from [Direct spread of tumour • Extramural venous invasion • Tumour deposit]
Minimum tumour distance to mesorectal fascia: [ ]mm [• CRM clear • CRM involved]

Peritoneal deposits: [• No evidence • Evidence]

Pelvic side wall lymph nodes: • None • Benign • Malignant
[Location: Obturator fossa • R •L . External Iliac Nodes •R •L. Inf Hypogastric •R •L]

Summary: y MRI Overall stage ymrT ymr N M , TRG
- Good prognosis, CRM clear, TRG 1-3, EMVI negative
- Poor prognosis, CRM pos or TRG4/5 or EMVI positive

TRG1-2 low tumour – eligible for consideration for deferral of surgery

NHS

The Endpoint

Local Failure

- Powered for unacceptable failure rate – 80% power <15% local recurrence at 2 years.
- STOPPING RULE - ≥5 regrowth resulting in positive pathologic CRM – trial ends

Safe deferral

- 90% power - ≥10% defer - expected to be at least 25%
- ✓ success ≥ 11 of 59 patients safely defer surgery at 2yrs

NHS

Secondary endpoints

1. Time to local re-growth.
2. Time to maximal tumour response after CRT
3. Time to local pelvic relapse, pre or post surgery.
4. Time to metastatic relapse, pre or post surgery.
5. Percentages of positive margins, and sphincter-preservation rates in patients who have had surgery. Pathology T N stage.
6. Progression-free and overall survival
7. Quality of Life including long-term bowel and urinary function
8. Probability of detecting early re-growth on MRI at 16 weeks, 24 weeks and 9 months.
9. Report on proportion of patients eligible at 12 weeks compared to eligible at 6 weeks.
10. Frequency of local re-growth detected outside scheduled imaging/endoscopic timepoint by DRE/CEA.

RMH Deferral Trial Entry Criteria

1. MRI defined complete response: mrTRG1-2 : low signal intensity fibrotic scar tissue only seen at MRI performed 4 weeks after long-course CRT, confirmed at 8-12 week MRI.

Biopsy positive disease not an initial exclusion criterion

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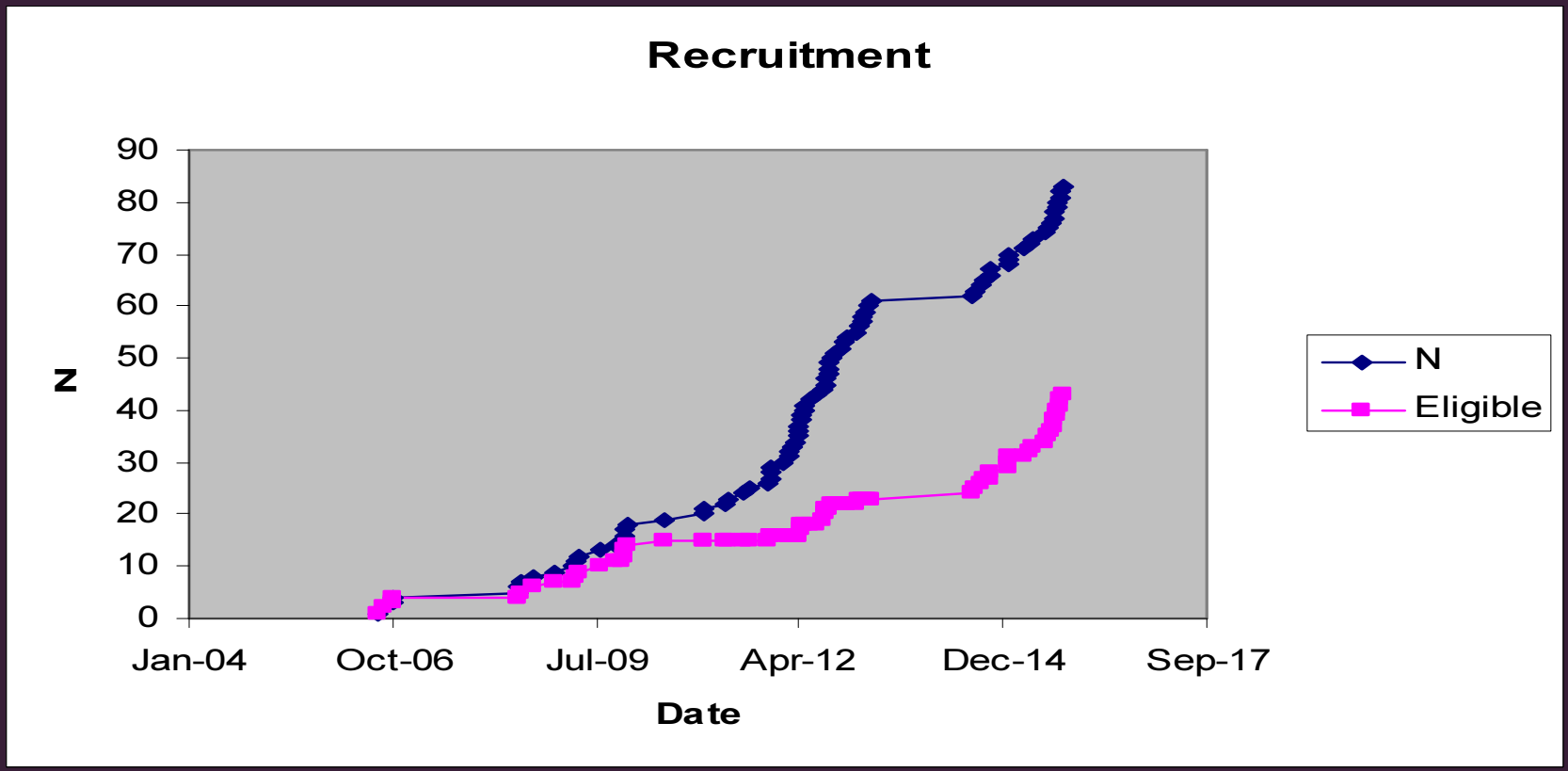
59 patients enrolled in 3 years


Recruitment
90
80
70
60
50
40
30
20
10
0
N
Jan-04
Oct-06
Jul-09
Apr-12
Dec-14
Sep-17
Date
N
Eligible

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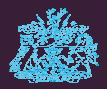
Magnetic Resonance Tumour Regression Grade (mrTRG) Directed Management Of Good And Poor Responders To Chemoradiotherapy in Rectal Cancer: A Multicentre Randomised Control Trial

Life demands excellence

objectives

- A feasibility trial for locally advanced rectal cancer investigating whether response to chemotherapy and radiotherapy can be assessed with a novel MRI technique
- Can (mrTRG), MRI directed management improve patient outcomes



Inclusion criteria

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- T3 c (extramural spread 5-15 mm) and T3 d (extramural spread >15 mm), regardless of N stage
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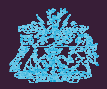

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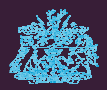
TRIGGER trial

Life demands excellence

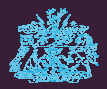
Objectives of trial

- recruit patients and stratify treatment using mrTRG directed management. The ‘good responders’ (mrTRG1&2) often have no evidence of tumour and it may be possible to avoid surgery in this group (deferral of surgery).
- The ‘poor responders’ (mrTRG3-5) are at high risk of poor oncological outcomes and additional therapy before surgery may improve prognosis.



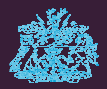
Phase III

- the phase III trial will be designed to detect an improvement in 3 year DFS in the intention to treat population from 74% to 82% (i.e. a hazard ratio of 0.66) with 80% power and a 5% 2- sided level of statistical significance.
- 633 patients over 3-5 years – recruitment rate 5-11 patients (total from all sites) randomised per month



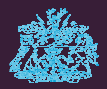
Radiology support and training

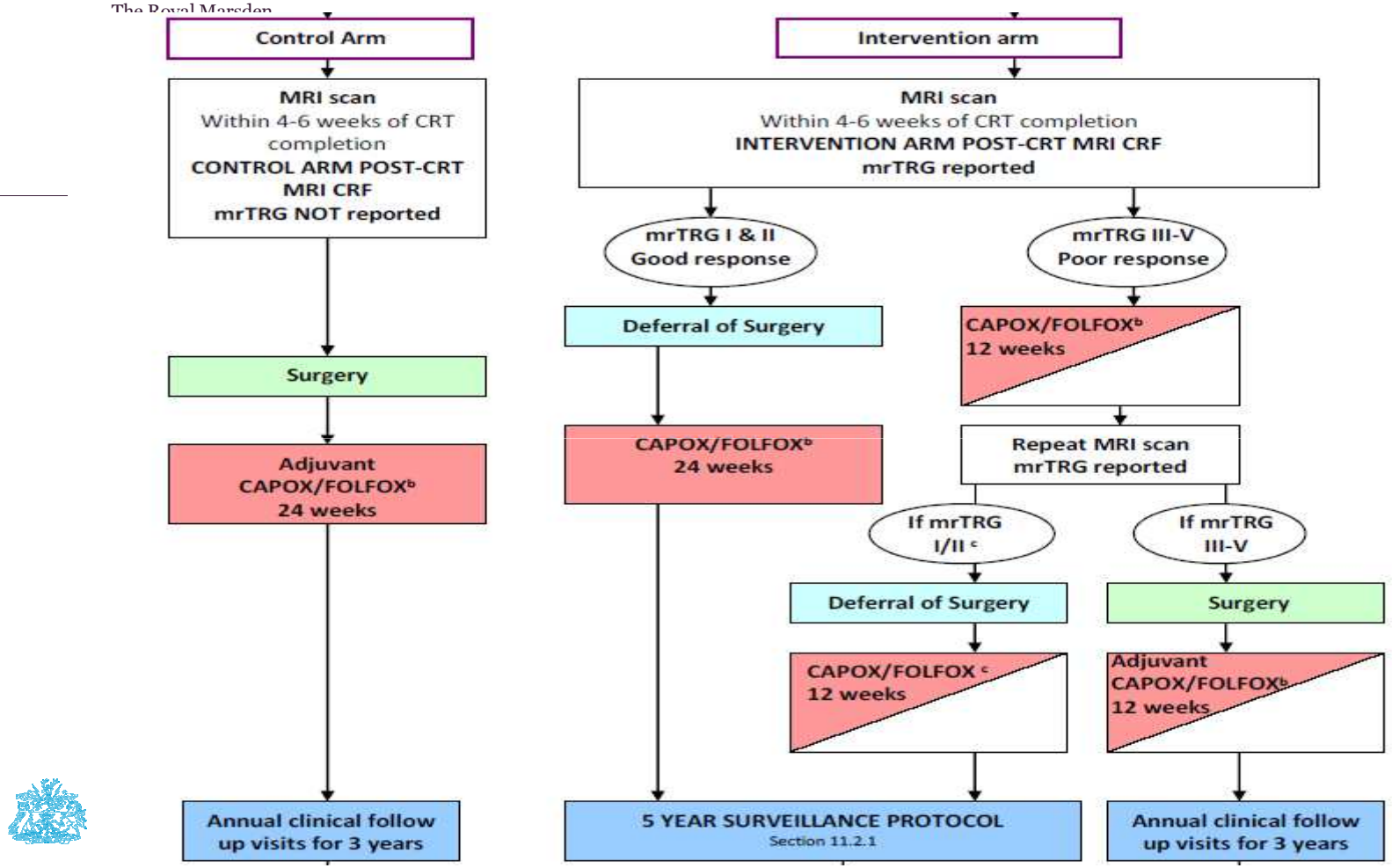
- To ensure consistency, a nominated study GI radiologist will be asked to participate in an CME-accredited trial-specific MRI reporting workshop/webinar.
- A site will not be able to open until the allocated radiologist has achieved mrTRG competency (mrTRG kappa ≥ 0.7). But training and support will be available to enable all radiologists to achieve this.



Feasibility secondary endpoints

- Assess response rates by comparing the reported mrTRG in the control and intervention arm
- Evaluate the reproducibility of mrTRG by recruiting radiologists
- To evaluate safety by assessing acute drug toxicity and 30 day surgical morbidity
- pCRM involvement rate in the control versus intervention arm
- Quality of surgery in control vs intervention arms



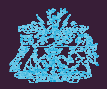

Control Arm
MRI scan
Within 4-6 weeks of CRT completion
CONTROL ARM POST-CRT MRI CRF
mrTRG NOT reported
Surgery
Adjuvant CAPOX/FOLFOX[b] 24 weeks
Annual clinical follow up visits for 3 years
Intervention arm
MRI scan
Within 4-6 weeks of CRT completion
INTERVENTION ARM POST-CRT MRI CRF
mrTRG reported
mrTRG I & II Good response
mrTRG III-V Poor response
Deferral of Surgery
CAPOX/FOLFOX[b] 24 weeks
CAPOX/FOLFOX[b] 12 weeks
Repeat MRI scan mrTRG reported
If mrTRG I/II [c]
If mrTRG III-V
Deferral of Surgery
Surgery
CAPOX/FOLFOX [c] 12 weeks
Adjuvant CAPOX/FOLFOX[b] 12 weeks
5 YEAR SURVEILLANCE PROTOCOL
Section 11.2.1
Annual clinical follow up visits for 3 years

Conclusions restaging MRI - prognostic and predictive imaging biomarkers for DFS

- Persistent ymrEMVI seen twice as frequently as ypEMVI and independent risk factor for poor DFS
- mrTRG 1-2 has similar DFS and OS as pCR but seen 4 times more frequently than pCR (prospective randomised trial data)
- mrTRG1-2 represents a population of patients highly likely to have no viable tumour hence suitable for MRI monitoring in deferral of surgery trial
- Patients will be randomised to have an mrTRG defined treatment strategy in the TRIGGER trial – do please join us!

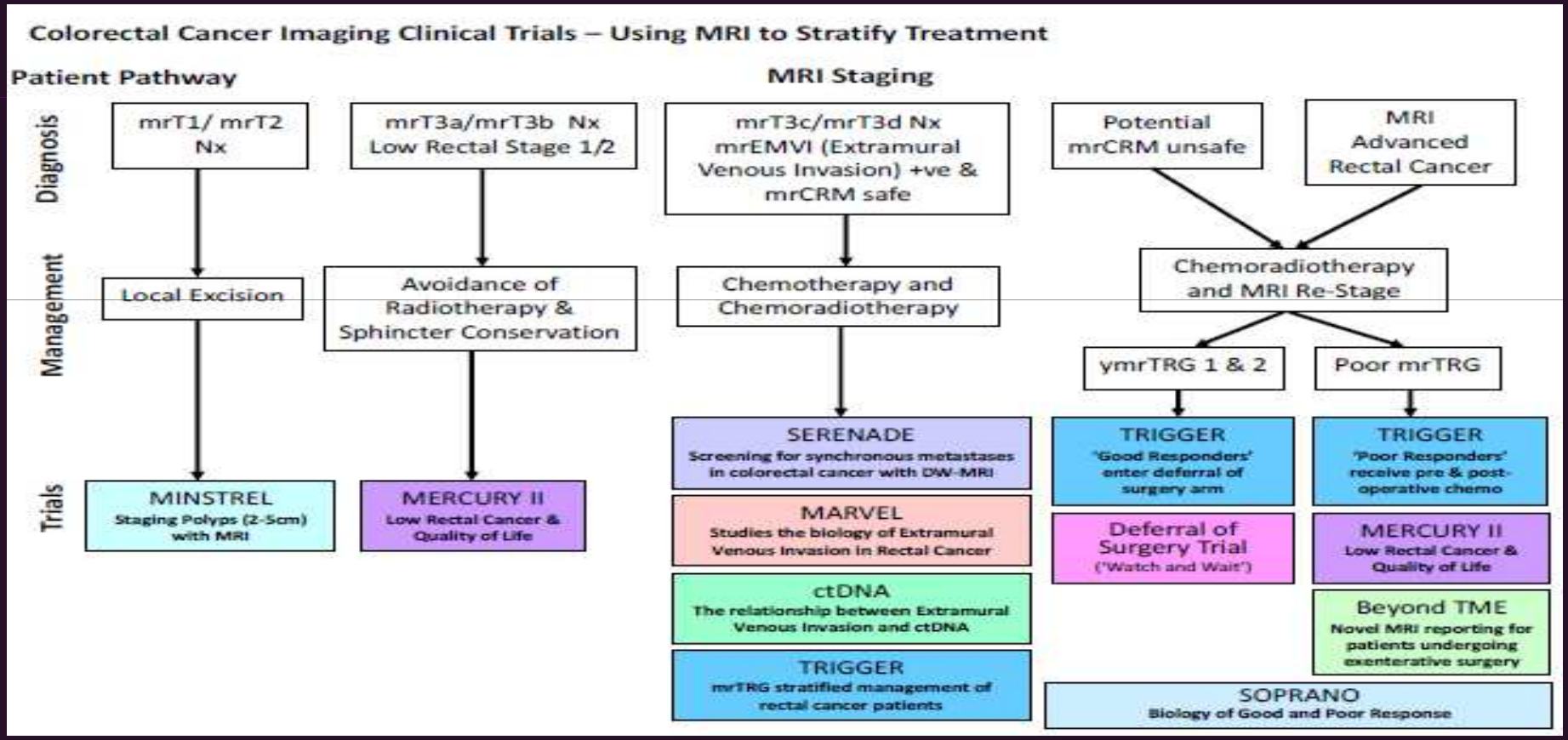
Acknowledgements

- Uday Patel, Stanley Yu, Manish Chand, Nicholas Battersby: Research Fellows
- Deferral of Surgery Trial. RJ Heald, P. Tekkis, D Cunningham, D Tait, A Wotherspoon, G Stamp, I Chau.
- MERCURY trial investigators, Pelican Cancer Foundation
- EXPERT-C trial: A Dewdney, D. Cunningham, J Tabernero, J Capdevila, B Glimelius, A Cervantes, D Tait, AWotherspoon, Y Chua, R Wong and I Chau
- CORE Trial investigators: Rutten H, Rullier E, Quirke P,West N, Sebag-Montefiore D, Peeters M, Van Cutsem E , Ricci S , Van de Velde C, Glynne-Jones R.



The Royal Marsden

MRI Trials and the Colorectal Patient Pathway



www.slideshare.net/ginabrown3

- MRI reporting templates
- MRI high resolution technique
- How to identify mrEMVI
- Details of workshops for surgeons, oncologists and radiologists

Reporting Minimum Standards

Baseline assessment of Rectal cancer MRI report
Primary tumour
The primary tumour is demonstrated as an [Annular | Semi-annular | Ulcerating | | Polypoidal | Mucinous] mass with a [nodular / smooth] infiltrating border.

The distal edge of the luminal tumour arises at a height of [ ] mm from anal verge:
The distal edge of the tumour lies [ ]mm [Above,at, below] the top of the puborectalis sling
The tumour extends craniocaudally over a distance of [ ] mm
The proximal edge of tumour lies [above at below] the peritoneal reflection
Invading edge of tumour extends from [to] O'clock
Tumour is [confined to] [extends through] the muscularis propria:
Extramural spread is [ ] mm
mrT stage: [T1] [T2] [T3a] [T3b] [T3c] [T3d] [T4visceral] [T4 peritoneal]

Tumour is [present] [not present] the level of the puborectalis sling at this level:
[Tumour is confined to the submucosal layer/part thickness of muscularis propria indicating that the intersphincteric plane/mesorectal plane is safe and intersphincteric APE or ultra low TME is possible]
[Tumour extends through the full thickness of the muscularis propria : intersphincteric plane/mesorectal plane is unsafe, Extralevator APE. is indicated for radial clearance]
[Tumour extends into the intersphincteric plane : intersphincteric plane/mesorectal plane is unsafe, therefore an extralevator APE. is indicated for radial clearance]
[Tumour extends into the external sphincter : intersphincteric plane/mesorectal plane is unsafe.]
[Tumour extends into adjacent [prostate/vagina/bladder/sacrum] : exenterative procedure will be required

Additional comments:

.

Lymph node assessment
Only benign reactive and no suspicious nodes shown [N0]
[ ] mixed signal/irregular border nodes [N1/N2]
Extramural venous invasion: [No evidence] [Evidence]
[ ] Small [ ]Medium [ ]Large vein invasion is present
CRM
The closest circumferential resection margin is at o'clock
The closest CRM is from [Direct spread of tumour] [Extramural venous invasion] [Tumour deposit]
Minimum tumour distance to mesorectal fascia: mm [CRM clear] [CRM involved]
Peritoneal deposits: [No evidence] [Evidence]
Pelvic side wall lymph nodes:
[None] [Benign] [Malignant mixed signal/irreg border]
Location: [Obturator fossa • R •L] . [External Iliac Nodes • R •L] .[Internal iliac • R •L]

Summary: MRI Overall stage: T N M [CRM clear] , [CRM involved] , [EMVI positive] [EMVI negative],[PSW positive] [PSW negative]
No adverse features eligible for primary surgery
High risk safe margins for preoperative therapy : eligible for Serenade, Marvel
Poor prognosis unsafe margins eligible for preoperative chemoradiotherapy: eligible for 6 vs 12 trial
Low Rectal <6cm – eligible for the Low Rectal Study.

Reporting Template Post Treatment

Post Treatment Assessment MRI Rectal Cancer
Comparison is made with the previous examination of:
• The treated tumour: shows no fibrosis,TRG5
• Less than <25% fibrosis, predominant tumour signal, TRG4
• 50% tumour/fibrosis, TRG 3
•>75% fibrosis, minimal tumour signal intensity,TRG2
•low signal fibrosis only no intermediate tumour signal TRG1

The distal edge of the luminal tumour arises at a height of [ ] mm from anal verge:
The distal edge of the tumour lies [ ]mm [Above, at, below] the top of the puborectalis sling compared with []mm previously
The tumour extends craniocaudally over a distance of [ ] mm compared with [ ]mm previously
The proximal edge of tumour lies [above at below] the peritoneal reflection
The invading edge of treated tumour extends from [to] O'clock
Tumour signal is [Confined to / Extends through the muscularis propria.]
Fibrotic signal is [Confined to / Extends through muscularis propria.]
Extramural spread: [ ]mm for tumour signal [ ]for fibrotic stroma

yMR T stage: • T1 • T2 • T3a • T3b • T3c • T3d •T4 visceral •T4 peritoneal

Treated tumour [is/ is not] present at or below the puborectalis sling
• tumour signal/fibrosis extends into the submucosal layer/part thickness of muscularis propria : intersphincteric plane/mesorectal plane is safe intersphincteric APE or ultra low TME possible, CRM is safe
• tumour signal/fibrosis extends through the full thickness of muscularis propria : intersphincteric plane/mesorectal plane is unsafe, for extralevator APE.
• tumour signal/fibrosis extends into external sphincter : intersphincteric plane/mesorectal plane is unsafe:for extralevator APE
•tumour signal/fibrosis extends into beyond external sphincter into [prostate/vagina] : intersphincteric plane / mesorectal plane is unsafe, for extralevator APE.

Lymph nodes:
• None /Only benign reactive [N0]
• Present number mixed signal/irregular border [N1/N2]

Extramural venous invasion: [• No evidence • Evidence]
[• Small • Medium • Large]
CRM
Closest circumferential resection margin: [ ]O'clock
Closest CRM is from [Direct spread of tumour • Extramural venous invasion • Tumour deposit]
Minimum tumour distance to mesorectal fascia: [ ]mm [• CRM clear • CRM involved]

Peritoneal deposits: [• No evidence • Evidence]

Pelvic side wall lymph nodes: • None • Benign • Malignant
[Location: Obturator fossa • R •L . External Iliac Nodes •R •L. Inf Hypogastric •R •L]

Summary: y MRI Overall stage ymrT ymr N M , TRG
• Low/intermediate risk, CRM clear, TRG 1-2, EMVI negative
• High prognosis, CRM pos or TRG4/5 or EMVI positive

TRG1-2 low tumour – eligible for consideration for deferral of surgery

Prognostic Factors in Rectal Cancer after Chemo-Radiotherapy

ESTRO Lower GI Course:

Technical & Clinical Challenges for Radiation Oncologists

RECTAL CANCER AUDIT 1997 - 2013

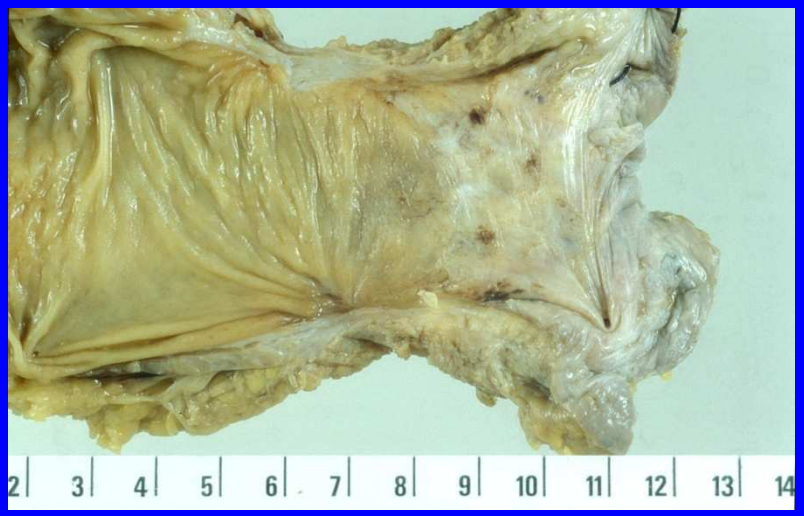
	No. of resections	% RT or CRT	Median LNs
1997	28	0 %	12
1998	34	3 %	14
1999	36	14 %	18.5
2000	28	32 %	19
2001	25	48 %	17
2002	29	41 %	18
2003	29	48 %	18.5
2004	17	71 %	15
2005	24	54 %	18
2006	39	59 %	19
2007	41	51 %	17
2008	40	33 %	16
2009	62	55 %	14
2010	44	57 %	18
2011	21	48 %	21
2012	74	65 %	15

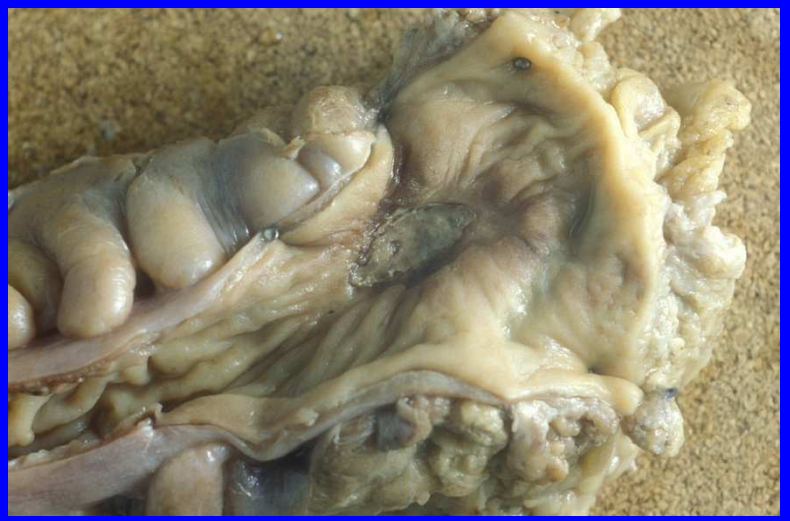
- downstage advanced tumours prior to surgery
- reduce CRMI
- reduce local recurrence
- ? increase sphincter preservation
- ? allow organ-sparing approaches in selected patients

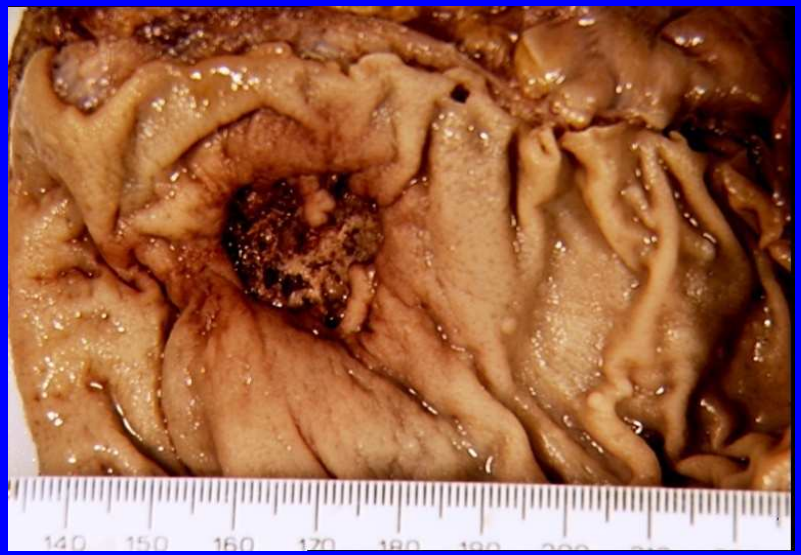
Examining the Rectal Cancer Specimen after Chemo-Radiotherapy

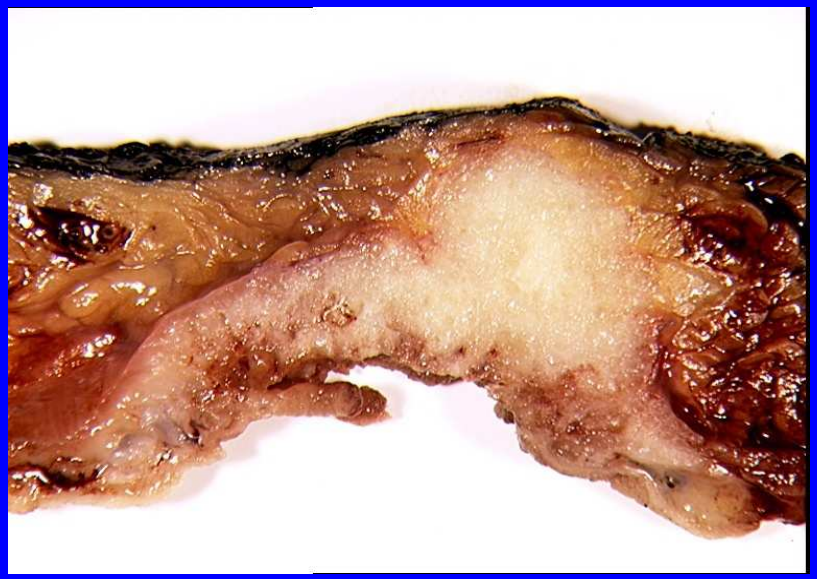
- Determine prognosis : predict local recurrence and distant metastasis
- Assess response of the tumour to radiotherapy / chemotherapy
- Audit surgical technique
- Audit the quality of imaging

MACROSCOPIC APPEARANCE OF LARC POST CHEMO-RADIOTHERAPY









Tumour Regression after Neoadjuvant Therapy

	ypT0 N0
• short course radiotherapy : 5x5 Gy (surgery within 1 week)	**< 1 %**
• short course radiotherapy with delay: (5x5 Gy – surgery after 4-8 weeks)	**13 %**
• long course radiotherapy eg. 25x2 Gy	**5 – 14 %**
• long course combined CRT	**10 – 30 %**

pCR after CRT for LARC – Evidence for a Better Outcome.

- Maas et al (2010) : pooled analysis of 3105 patients undergoing surgery after CRT for LARC (17 datasets ; 27 published articles)
- **pCR** – 484/3105: **16 %**
- median follow-up : **48 months** (0 – 277)

- 5 yr crude DFS : pCR **83.3 %**
  non-pCR **65.6 %**

- Adjusted HRs after multivariate analysis:
- **DFS** **0.54** (0.4 – 0.73)
- **Local recurrence** **0.41** (0.21 – 0.81)
- **Distant metastasis free survival** **0.49** (0.34 – 0.71)
- **OS** **0.65** (0.47 – 0.89)

"Colloid Response" – Acellular Mucin Pools after Radiotherapy

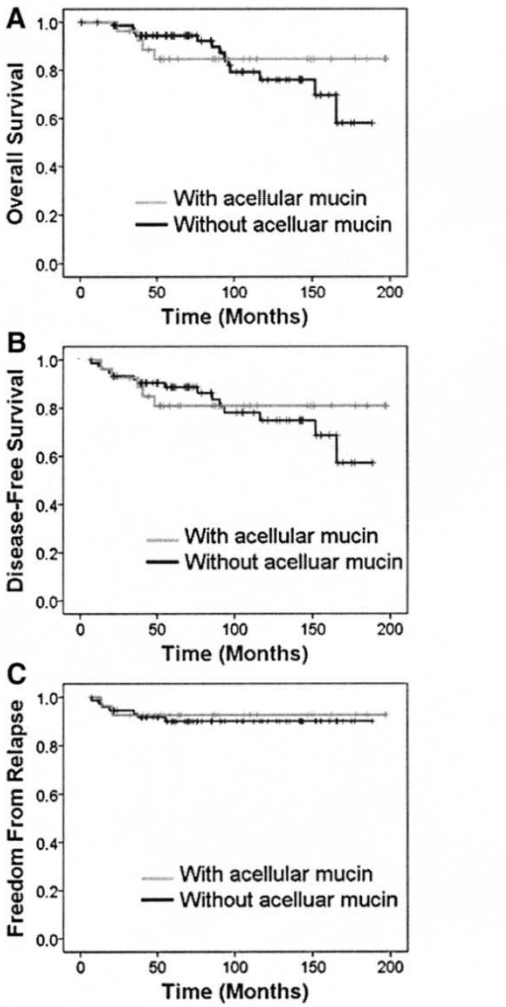
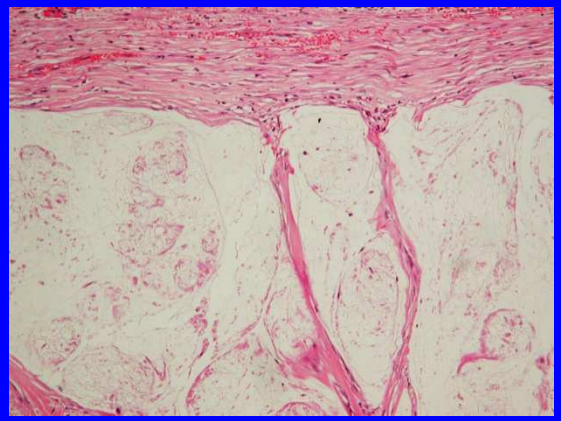
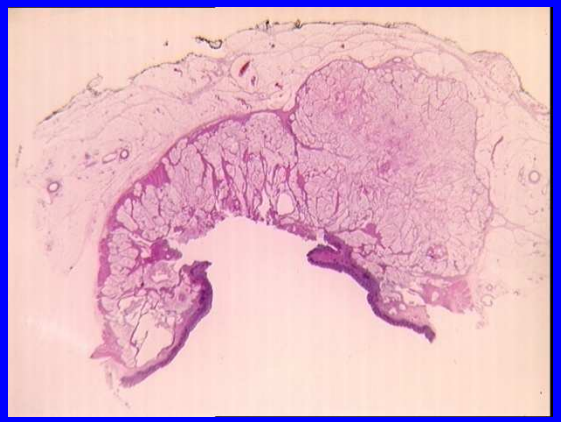


FIGURE 2. Kaplan-Meier survival curves for (A) overall survival, (B) disease-free survival, and (C) freedom from relapse.

- **prevalence : 16 % – 27 % of all pCR**
- **may be present in lymph nodes as well as bowel wall**
- **positive association with:**
  - **mucinous ca / signet ring ca in pre-op bx (approx. 10%)**
  - **male gender**
- **most studies show NO impact on disease recurrence or survival**





"Colloid Response" – Acellular Mucin Pools in Rectal Cancer Post-Radiotherapy ?

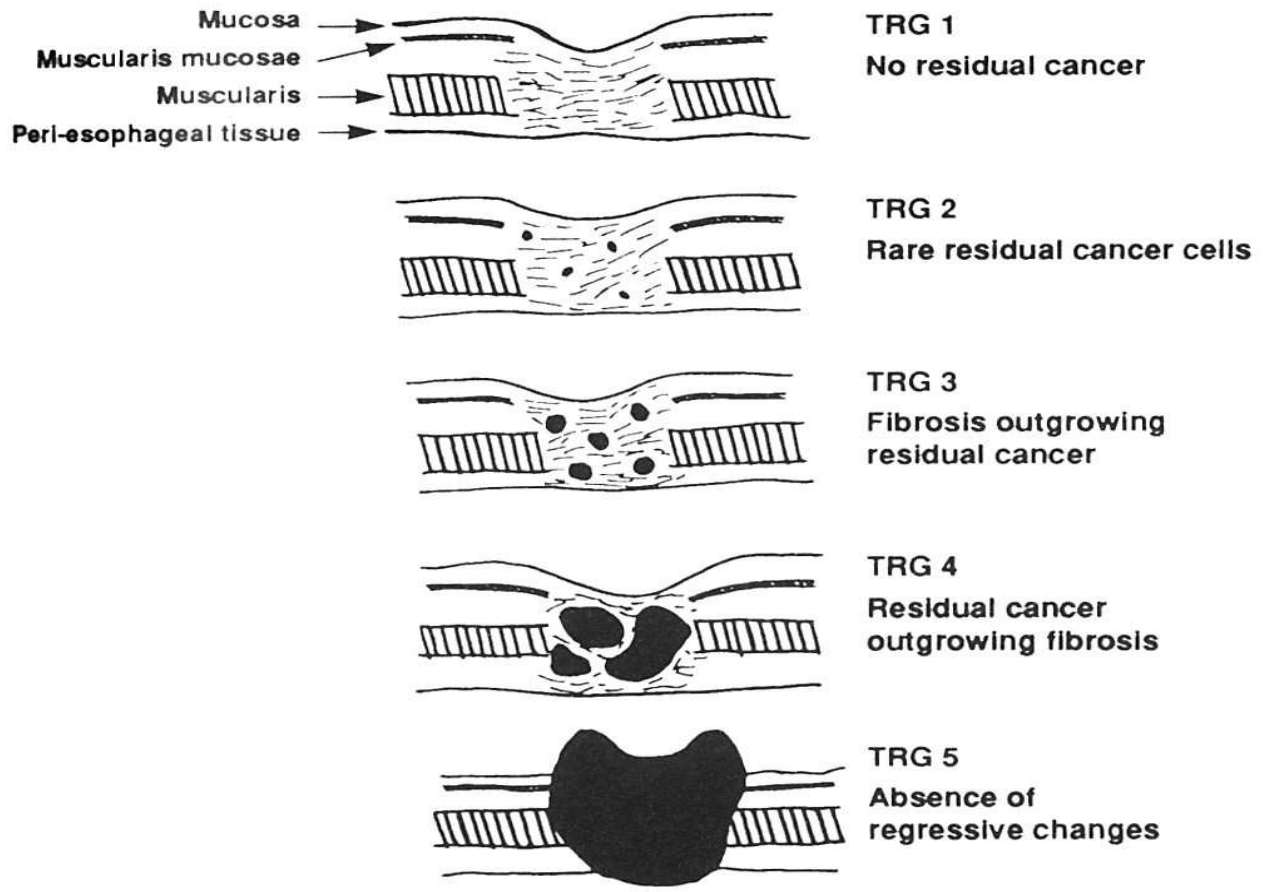
	group	No.	LR	Distant metastasis	3yr RFS	3yr OS	7yr OS
Smith et al 2010	pCR mucin	27	0 %	7 %			85 %
	pCR No mucin	73	1 %	8 %			92 %
Shia et al 2011	pCR Mucin	12			100%		
	ypT0 or ypT1	21			94%		
Campos-Lobato et al 2011	pCR Mucin	11	0%	21%		83%	
	pCR No mucin	47	0%	5%		95%	
Lim et al 2013	pCR Mucin	35				97%	
	pCR No mucin	182				96%	

Measuring Tumour Response to Neoadjuvant therapy

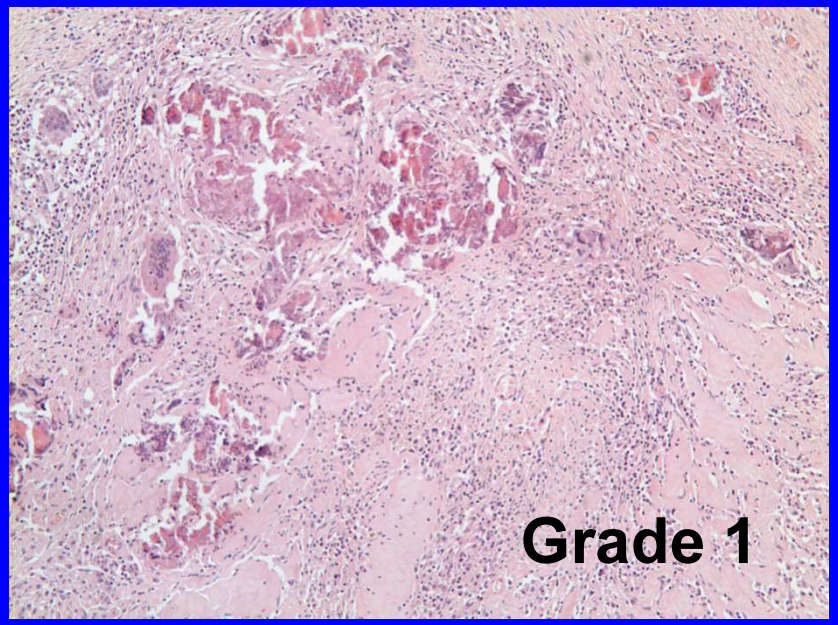
- Tumour downstaging : comparison of pre-treatment clinical stage (cT cN) with post-treatment pathological stage (ypT ypN)
- pCR rate : frequency of ypT0 ypN0
- Regression Grading

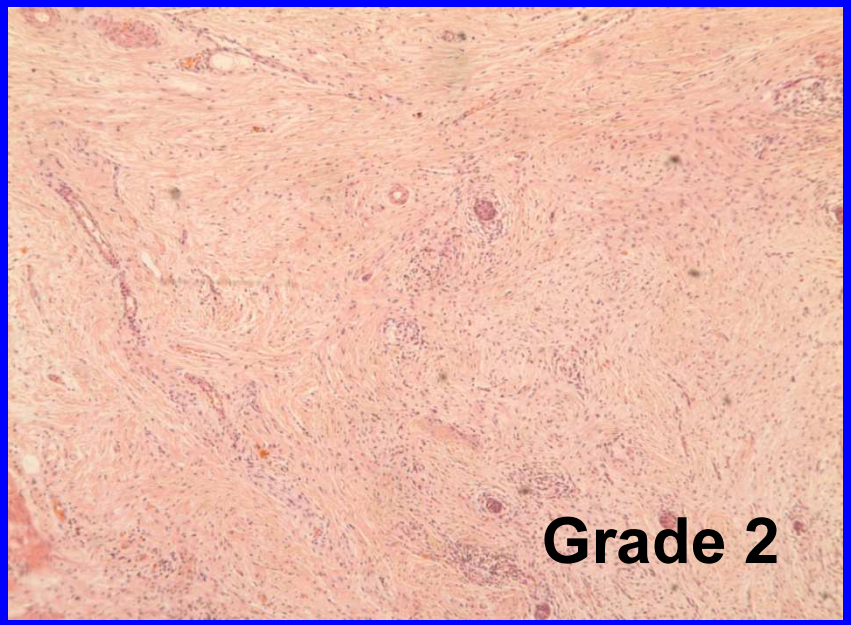
TUMOUR REGRESSION GRADING

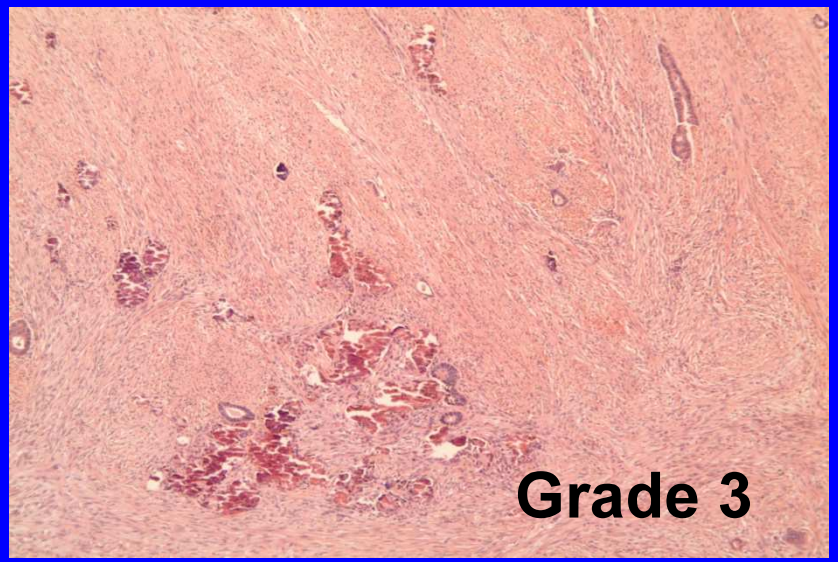
- Mandard et al. 1994
- Dworak et al. 1997
- Wheeler et al. 2002
- Royal College of Pathologists 2007
- Beddy et al. 2008

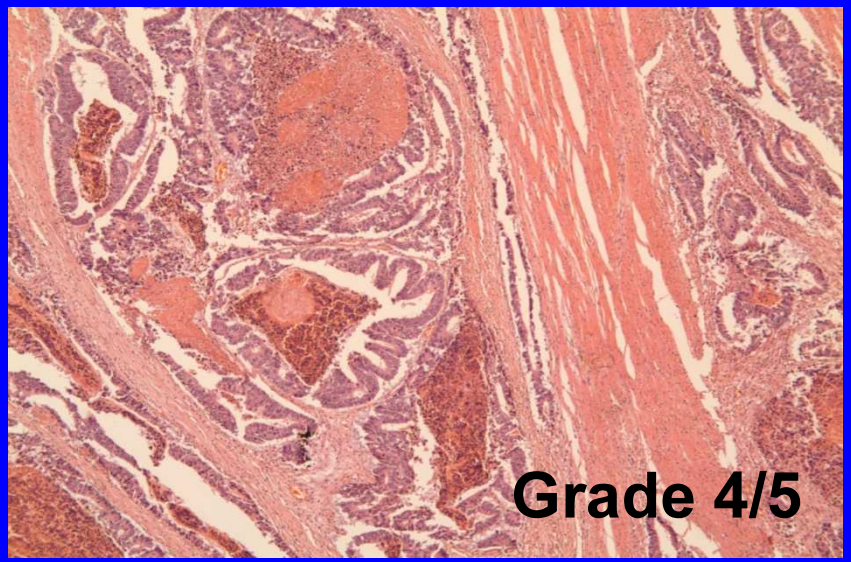

Mucosa
Muscularis mucosae
Muscularis
Peri-esophageal tissue
TRG 1
No residual cancer
TRG 2
Rare residual cancer cells
TRG 3
Fibrosis outgrowing residual cancer
TRG 4
Residual cancer outgrowing fibrosis
TRG 5
Absence of regressive changes
RESIDUAL CANCER CELLS
SCAR

MANDARD GRADING









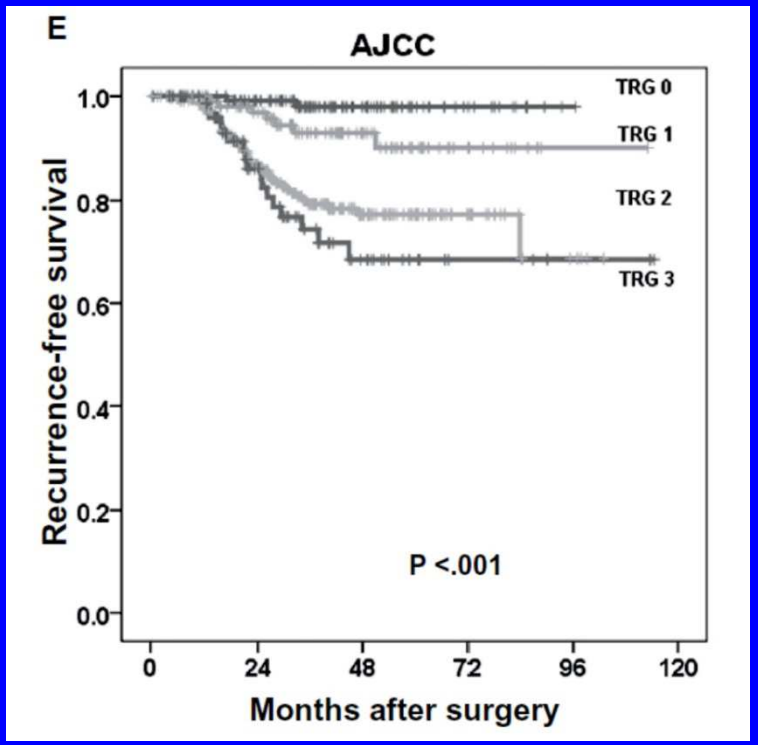
TRG : WHICH IS BEST ?

- Trakarnsarga et al (2014)
- 563 rectal cancers : cT3/4 or N+ : 1998 – 2007
- CRT : 50.4 Gy plus 5FU based chemotherapy
- TME after 6 – 8 weeks
- Median F.U. 39 months
- pCR = 21 % ; LR = 2 %; DM = 17 %
- TRG determined by expert GI pathologists
  - Mandard (5 & 3 tier)
  - Dworak / Rodel (5 & 3 tier)
  - MSKCC
  - AJCC / CAP

TRG : WHICH IS BEST ?

- All TRGs predicted recurrence free survival (univariate analysis)
- No benefit from 5 tier system over 3 tier system
- Concordance index highest for AJCC (= 0.694)

AJCC TRG	5yr recurrence free Survival
TRG 0	98 %
TRG 1	90 %
TRG 2	73 %
TRG 3	68 %



Trakarnsarga et al 2014

TRGs : A TRANSATLANTIC CONSENSUS ?

Tumor Regression Grade (modified from Ryan et al[29])

Description	Tumor Regression Grade
No viable cancer cells	0 (Complete response)
Single cells or small groups of cancer cells	1 (Moderate response)
Residual cancer outgrown by fibrosis	2 (Minimal response)
Minimal or no tumor kill; extensive residual cancer	3 (Poor response)

Tumor regression should be assessed only in the primary tumor; lymph node metastases should not included in the assessment.

College of American Pathologists AJCC 2013

d) Response to pre-operative therapy

There is evidence that patients with completely excised rectal carcinomas who have received pre-operative chemoradiotherapy, which has resulted in complete or marked regression, have a better prognosis than those without significant regression.[15,16,80,81] However, there is no consensus over how lesser degrees of regression are estimated histologically.[82] Despite this, an indication of regression is regularly sought by oncologists at MDTM and therefore it is recommended that the degree of tumour regression following pre-operative therapy is recorded as a core data item. A descriptive four-tier system is recommended, similar to that described by Ryan *et al*:[66,83]

- no viable tumour cells (fibrosis or mucus lakes only)
- single cells or scattered small groups of cancer cells
- residual cancer outgrown by fibrosis
- minimal or no regression (extensive residual tumour).

Royal College of Pathologists 2014

TRG , ypT & ypN stage

• 131 resectable cT3/T4 rectal carcinomas treated with CRT (polish RCT of SCRT versus pre-op CRT)

- TRG 0 : no cancer cells present
- TRG 1 : a few cancer foci (< 10% of tumor mass)
- TRG 2 : residual cancer representing 10 – 50 % of tumor mass
- TRG 3 : residual cancer representing > 50 % of tumor mass

	ypT0	ypT1	ypT2	ypT3		ypN0	ypN1/2
TRG 0	**22** (100%)					**20** (95%)	**1** (5 %)
TRG 1		**7** (17%)	**25** (63 %)	**8** (20 %)		**31** (77 %)	**9** (23 %)
TRG 2		**1** (3 %)	**13** (32 %)	**26** (65 %)		**22** (55 %)	**18** (45 %)
TRG 3		**4** (14 %)	**10** (34 %)	**15** (52 %)		**15** (54 %)	**13** (46 %)

- ypT stage best predictor of nodal status in multivariate analysis :

OR 4.66 for ypT2 & 12.06 for ypT3 versus ypT0/1.

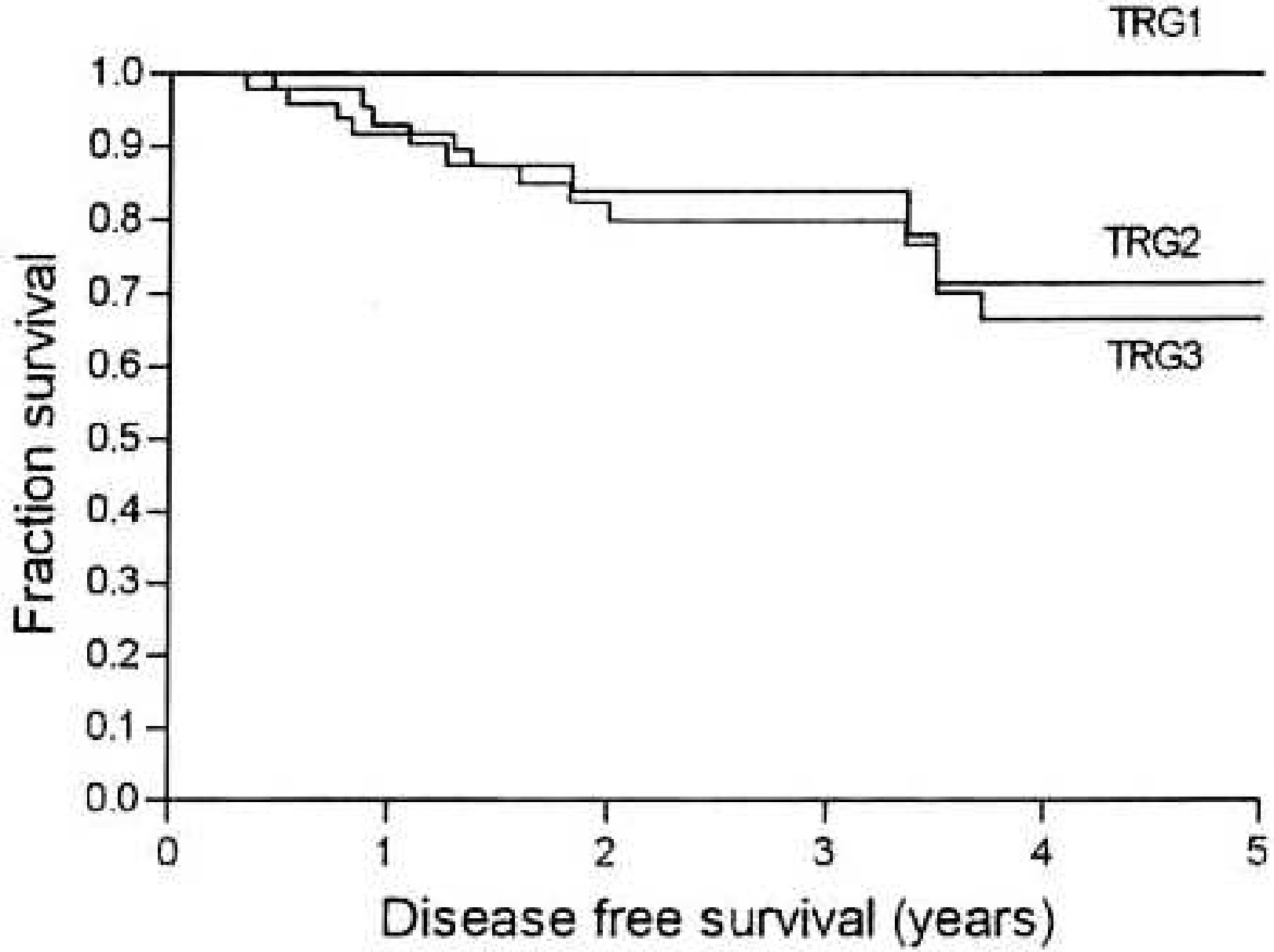
(Bujko et al 2010)

TRG & SURVIVAL AFTER CHEMORADIOTHERAPY

- 126 patients 1997 – 2007 with cT3-4 or cN1/2 disease treated with 45-50 Gy plus 5FU prior to surgery
- Mandard grades used with simplification to 3 categories : mandard 1 & 2 = TRG 1
  mandard 3 = TRG 2
  mandard 4 & 5 = TRG 3

➢ Tumour downstaged in 60 % cases
➢ TRG 1 : 21 % TRG 2 : 39 % TRG 3 : 40 %
➢ Local recurrence rate all cases : 7 %
➢ 5 yr disease free and overall survival all cases : 72 % and 63 %

Beddy et al 2008


TRG1
TRG2
TRG3
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Fraction survival
0
1
2
3
4
5
Disease free survival (years)

Prognostic Value of TRG after CRT for Rectal Cancer : CAO/ARO/AIO-94 TRIAL

	N	Node pos	5yr LR	5yr met free Survival	5yr DFS
TRG 0 + 1	75	41%	6%	66%	63%
TRG 2 + 3	229	32%	4%	75%	75%
TRG 4	40	10%	0%*	86%**	86%**

* p = 0.33
** p = 0.009
*** p = 0.006

TRG 0: no regression
TRG 1: fibrosis < 25% tumor mass
TRG 2: fibrosis 25-50% tumor mass
TRG 3: fibrosis > 50% tumor mass
TRG 4: complete regression

ypT & ypN stage still most important prognostic factors for DFS on multivariate analysis !

Rodel et al 2005

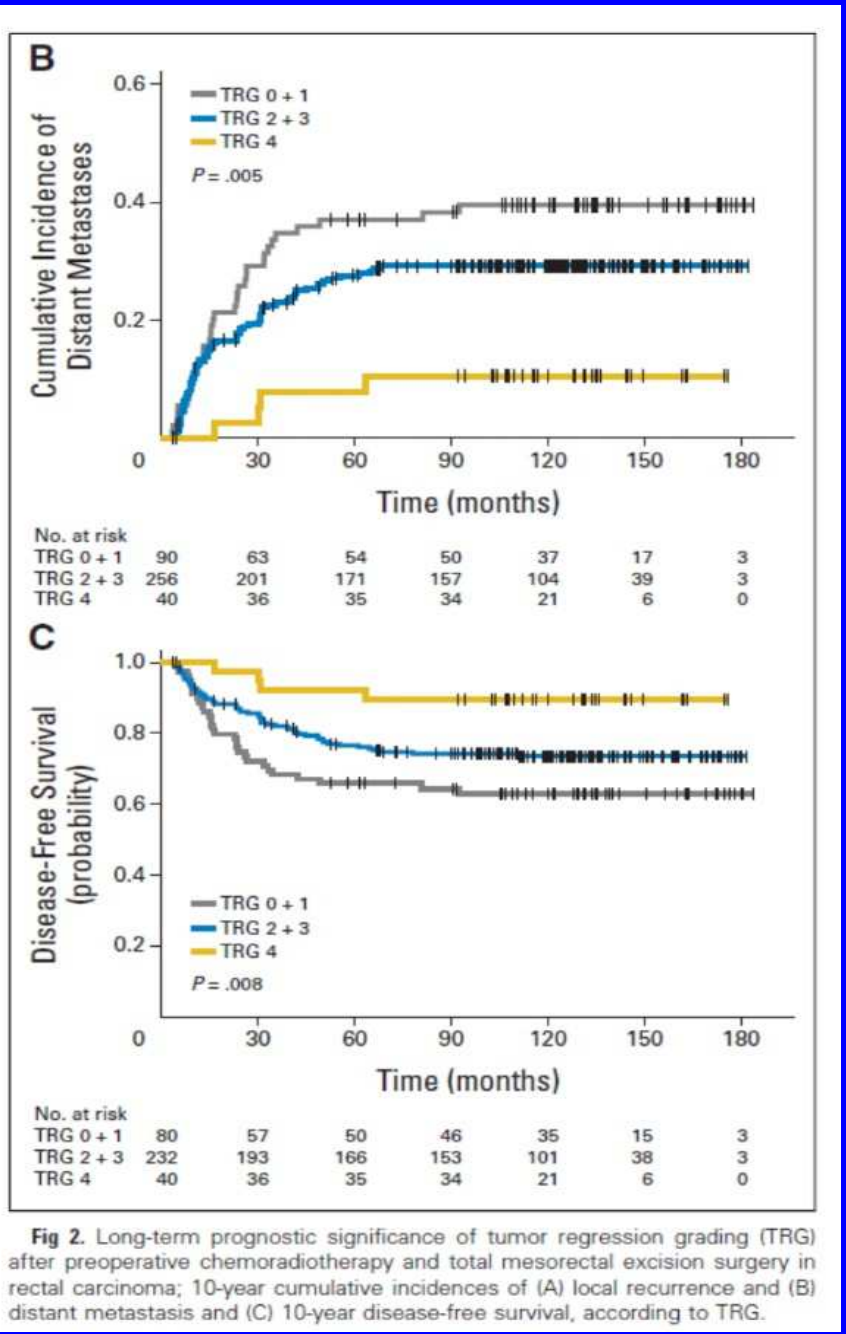


Fig 2. Long-term prognostic significance of tumor regression grading (TRG) after preoperative chemoradiotherapy and total mesorectal excision surgery in rectal carcinoma; 10-year cumulative incidences of (A) local recurrence and (B) distant metastasis and (C) 10-year disease-free survival, according to TRG.

CAO/ARO/AIO-94 Trial

N = 386
Median F.U. 132 months

TRG	%	10 yr DM rate	10 yr DFS
TRG 0+1	23.3%	39.6%	63%
TRG 2+3	66.3%	29.3%	73.6%
TRG 4	10.4%	10.5%	89.5%

HR for TRG in multivariate analysis :
0.74 for DM
0.76 for DFS

$p < 0.04$

(Fokas et al 2014)

Lymph node harvest after neoadjuvant therapy

	Surgery only	Short course RT	Long course RT
Marijnen et al.2001	9.7	7.7	
Wichmann et al 2002	19		13
Wijesuriya et al 2005	9		4
Baxter et al 2004	10		7

(Numbers represent median or average no of nodes.)

	Median no of nodes	3 yr DFS	5 yr DFS	5 yr LR
Beresford et al (2005)*	5	< 3 nodes: 26% > 3 nodes: 58%		
Habr-gama et al (2007)	8		no nodes: 74% ypN0: 59% ypN+: 30%	
Rullier et al (2008)*	13 (mean)	No relationship between no of nodes and survival at any cut-off		
Govindarajan et al (2011)	10	No relationship between no of nodes and DSS at any cut-off		
De Campos-Lobato et al (2013)	15		<12 nodes: 77.1% >12 nodes: 75.2%	<12 nodes: 0% >12 nodes: 11%
Persiani et al (2014)	7	No relationship between no of nodes and survival using any cut-off between 8 - 12		

(* Node negative cases only)

Correlation between ypT & ypN stage following CRT for LARC

	ypT0	ypT1	ypT2	ypT3	ypT4	all ypT
Medich 2001	0 %	40%	41%	45%		**40%**
Read 2004	**2%**	**4%**	**23%**	**47%**	48%	**34%**
Bedrosian 2004	**9%**	20%	**23%**			**24%**
Stipa 2004	7%	8%	**22%**	**37%**	67%	**27%**
Rodel 2005	**10%**					
Bujko 2005	5%	8%	**26%**			
Hughes 2006	17%					
Kim 2006	**2.2 %**	7.7%	**17%**	**49%**	43%	**31%**
Mignelli 2010	**3.2 %**	11%	29%	37%	0%	**26%**
Smith 2012	3%	0%	**30%**	**46%**	59%	**36%**

numbers in bold = categories with > 40 cases .

Glynne-Jones 2008: 47 studies – 545 patients with ypT0 tumours:

36/545 ypN0 – 6.6%

TRG : local recurrence & survival

- 131 cT3/T4 rectal cancers resected after pre-op CRT (polish trial)
- median follow-up 4 years

	No.	5 yr LR	5 yr distant metastasis	4 yr DFS
TRG 0	**22**	**5 %**	**9 %**	**91 %***
TRG 1	**40**	**9 %**	**34 %**	**67 %**
TRG 2	**40**	**16 %**	**35 %**	**54 %**
TRG 3	**29**	**26 %**	**47 %**	**47 %**

(* P = 0.015)

- **NO significant difference in LR, distant recurrence or 4 yr disease free survival between TRG 1, 2 and 3 !!!**

(Bujko et al 2010)

Pathological stage and survival after pre-Operative Chemoradiotherapy for rectal cancer

- CRM positive in 4 %
- LR rate : 3 % ; distant metastases : 20 %.
- 5 yr disease free survival : 74 %
- Best predictor of DFS was pathological stage :

	concordance index*
➢ Pre-treatment clinical stage	**0.5**
➢ Pathological stage	**0.75**
➢ % tumour response	**0.65**

* ability to predict disease recurrence

Quah et al 2008

Causes of CRMI following pre-op Chemo-Radiotherapy

- Advanced Tumour Stage
- Inadequate Mesorectal Excision
  (poor surgery)
- Radiotherapy & Chemotherapy resistance
  (aggressive tumour biology)

Prognostic Significance of CRM involvement after Chemo-Radiotherapy for LARC

	CRM	2yr LR	2yr OS	5y OS	5yr DFS	5yr LR free survival	5yr DM free survival
Gosens et al 2007 n = 201 cT3/T4	Neg	8%	80%				
	Pos	43%*	58%*				
Rullier et al 2010 n = 292 uT3/T4	Neg			80%			
	Pos			30%*			
Kim et al 2009 n = 420 cT3/T4	Neg				78%		
	Pos				44%*		
Trakarnsanga et al 2013 n = 563 cT3/T4	> 1mm					98 %	
	< 1mm					66 %	
	> 2mm						78 %
	< 2mm						41 %*

* = significant in multivariate analysis

CRMI is a better predictor of Local Recurrence after Neo-adjuvant Radiotherapy

- Nagtegaal & Quirke (2008) :
- Literature review – prognostic significance of CRMI in publications between 1985 – 2006
- Data available on 17,500 patients

➢ Predictive value of CRMI for local recurrence after multi-modality treatment greater than after surgery alone:

➢ HR for LR after neo-adjuvant therapy : **6.3** (3.7 – 16.7)

➢ HR for LR after surgery : **2.0** (1.4 – 2.9)

Venous Invasion after CRT

		No.	%V1/2	10yr LR	10yr DM	10 yr DFS	3 yr DFS
Fokas et al 2014 CAO/ARO/A10-94	V0	386	4.7%	6.3%	28%	74.5%	
	V1/V2			9.1%	57.9%*	42.9%*	
Chand et al 2015	V0	188	19%				65.9%
	V1/V2						36.9%**

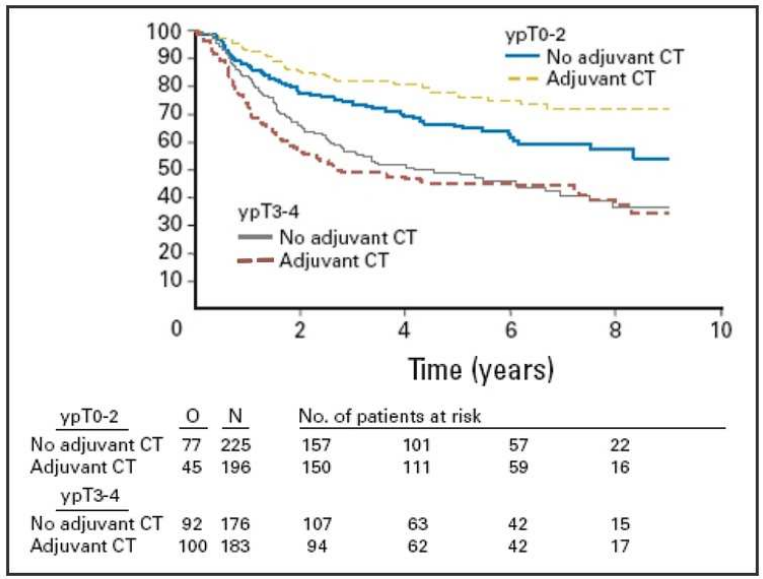
pEMVI is still a strong prognostic factor for DFS & the development of distant metastasis after pre-operative chemoradiotherapy !!

(* p < 0.002)

WHAT ARE THE MOST IMPORTANT PATHOLOGICAL PREDICTORS OF DISEASE CONTROL AFTER CRT & SURGERY ?

- ypT stage (especially ypT0)
- ypN stage
- CRM status
- ?? Tumour Regression Grade

Who should get adjuvant chemotherapy after pre-operative chemo-radiotherapy and surgery ?



	O	N	No. of patients at risk			
ypT0-2						
No adjuvant CT	77	225	157	101	57	22
Adjuvant CT	45	196	150	111	59	16
ypT3-4						
No adjuvant CT	92	176	107	63	42	15
Adjuvant CT	100	183	94	62	42	17

Fig 3. Kaplan-Meier curve of disease-free survival after surgery by adjuvant treatment and pathological down staging to ypT0-2. O, number of events; N, number of patients; CT, chemotherapy.

Collette et al 2007

EORTC trial 22921

Bosset et al 2014
EORTC trial 22921

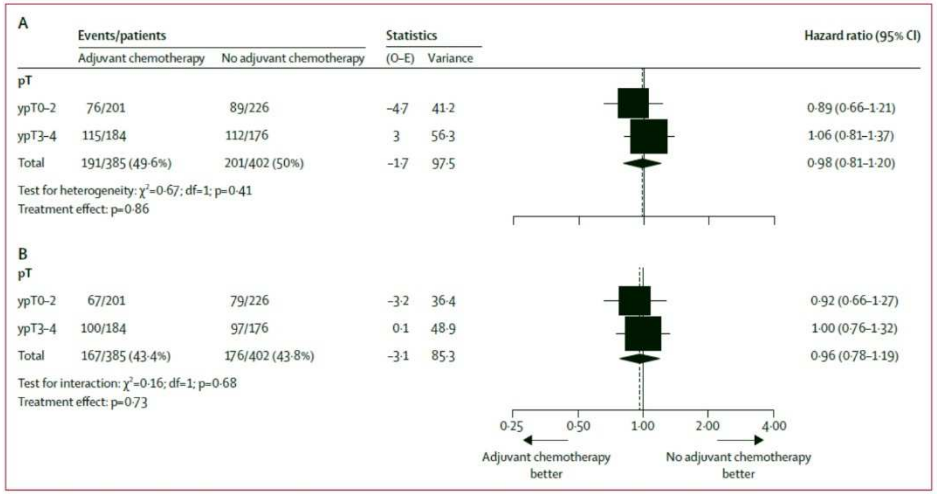


Figure 4: Effect of adjuvant treatment on (A) disease-free survival post-surgery and (B) overall survival post-surgery, by tumour pathological downstaging, in 787 eligible patients whose disease did not spread to distant sites before or at surgery and in whom a microscopically complete (R0) resection was done

ESTRO teaching course May Bruxelles 2016

RT-Dose/fractionation concepts
(5x5Gy, 1.8-2.0 Gy to 45/50 Gy or higher?)

Rob Glynne-Jones
Mount Vernon Cancer Centre

ESTRO School

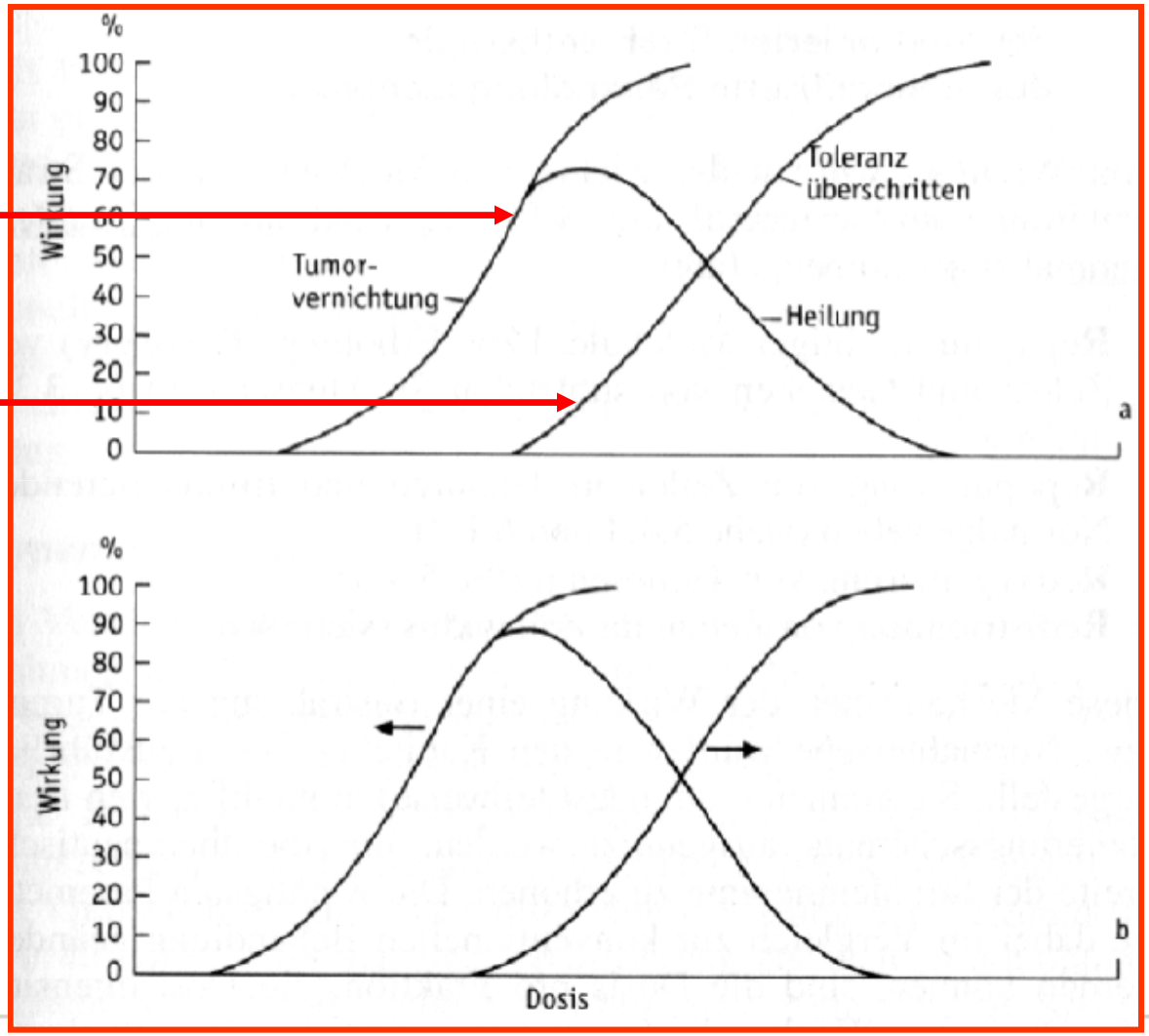
My thanks to

Rafal Dziadziuszko

Therapeutic window

TCP
= tumor control probability

NTCP
= normal tissue complication probability



Holthusen, *Strahlentherapie* 57: 254, 1936

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Therapeutic ratio (I)

$$P_+ = TCP \cdot (1 - NTCP)$$

- Easy to interpret: if TCP and NTCP are statistically independent, this is the probability of being cured without a complication
- Has been used in several published studies
- The same relative change in NTCP will have a much larger influence on P_+ for large NTCP relative to small NTCP
- Face validity for non-fatal complications?
  - A: TCP=40% and NTCP=40% ⇒ R=24%
  - B: TCP=60% and NTCP=60% ⇒ R=24%
  - ...but proportion of patients with tumor control AND side-effects is 16% with treatment A versus 36% with treatment B

Therapeutic ratio (II)

$$R = \frac{TCP}{NTCP}$$

- Easy to interpret: this is the cure rate in percentage point per percentage point patients with toxicity

- Very sensitive to statistical uncertainty for small values of NTCP

- Face validity?

  TCP=40% and NTCP=1% $\Rightarrow$ R=40

  TCP=80% and NTCP=2% $\Rightarrow$ R=40

There are 2 preoperative radiation regimens accepted as standard:

- Short course (5 X 5 Gy delivered over 1 week) with surgery performed ideally within the next 5 days
- conventionally fractionated chemoradiation 45-50.4Gy (25-30 fractions of 1.8 or 2 Gy over 5-6 weeks) with surgery performed 4 to 10 weeks after treatment completion.

- (Folkesson et al, JCO 23, 24: 5644 – 5650, Kapiteijn *et al*, NEJM, 345 (9), 638-646, 2001, David Sebag-Montefiore *et al,* Lancet. 2009 Mar 7;373(9666):811-20)

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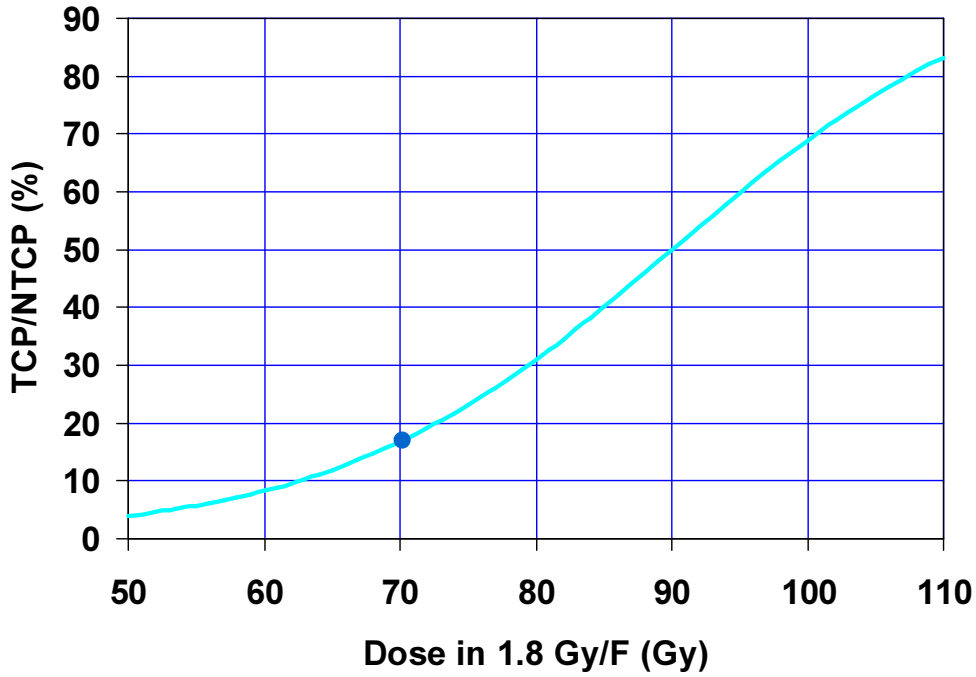
Dose equivalent of chemotherapy

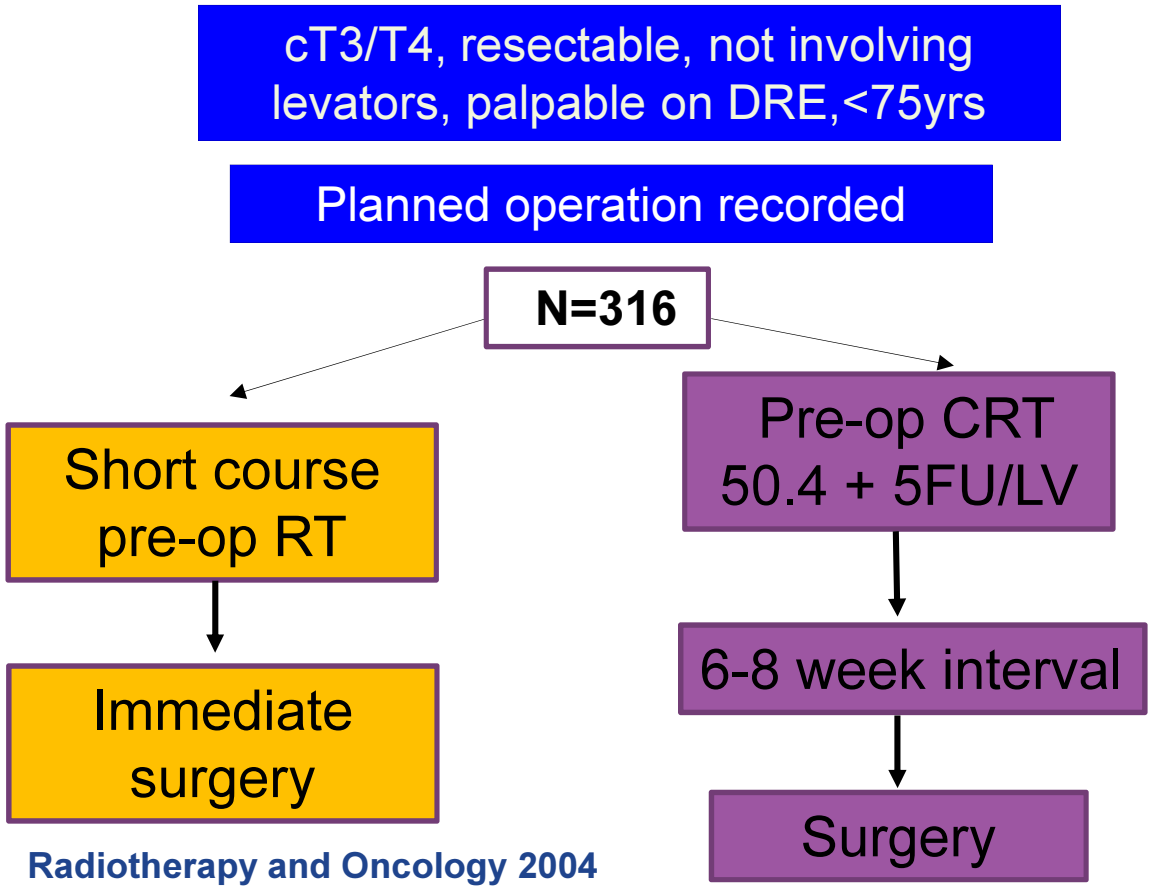


4 questions

- **5x5Gy or 1.8-2.0 Gy to 45/50 Gy?**
- **45 or 50 Gy?**
- **Or higher doses**

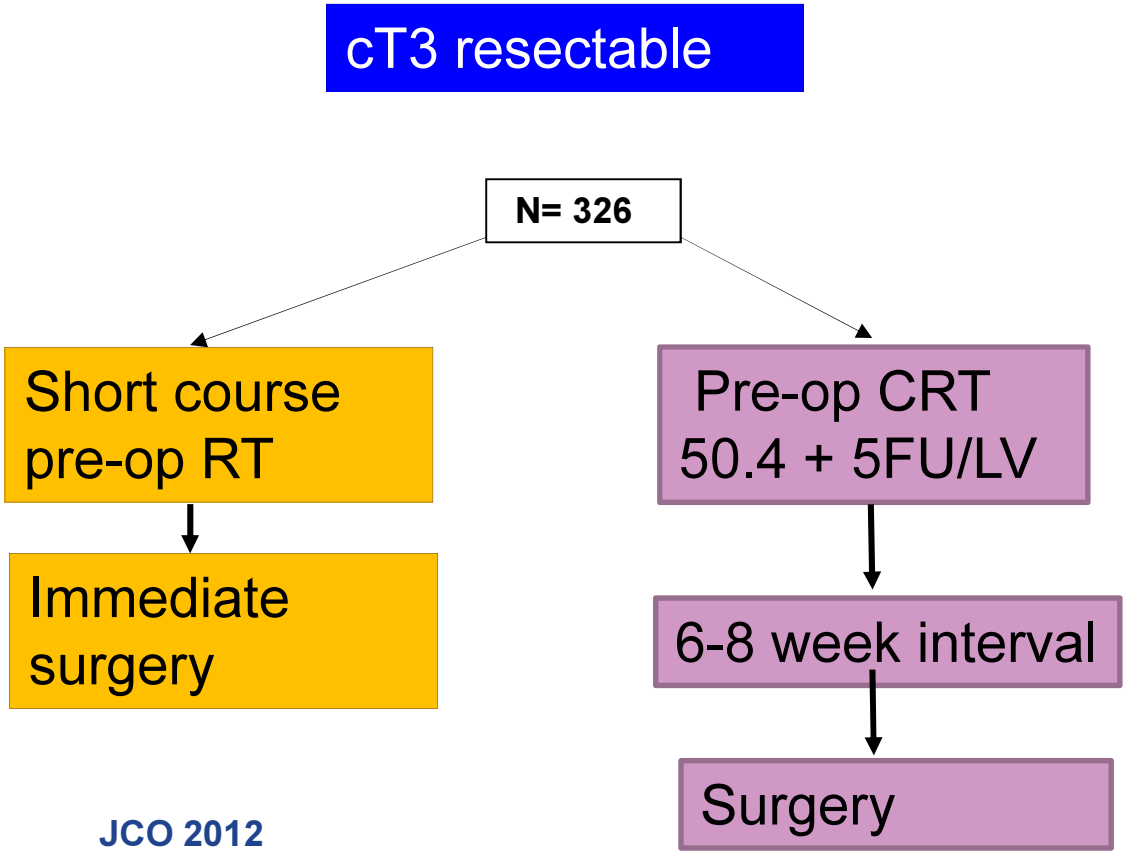
- **Implicit question – what is best?**

Polish trial Bujko et al.



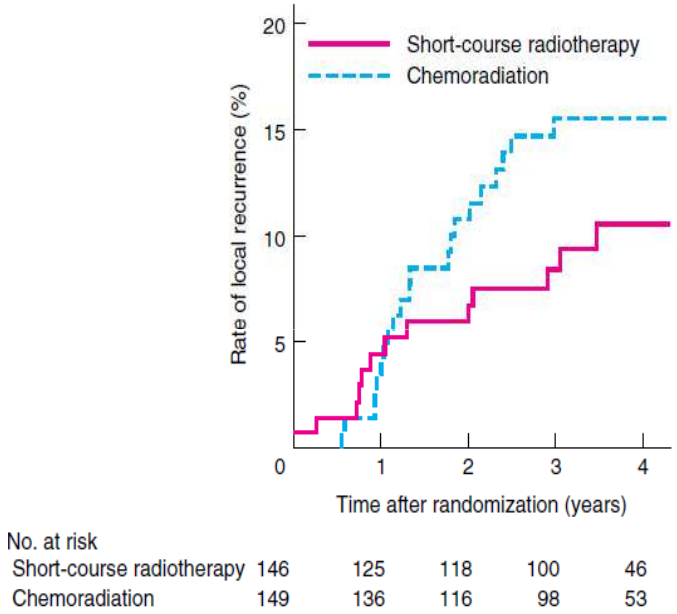
Radiotherapy and Oncology 2004

TROG 01-04 LSSANZ RACS trial Ngan et al.

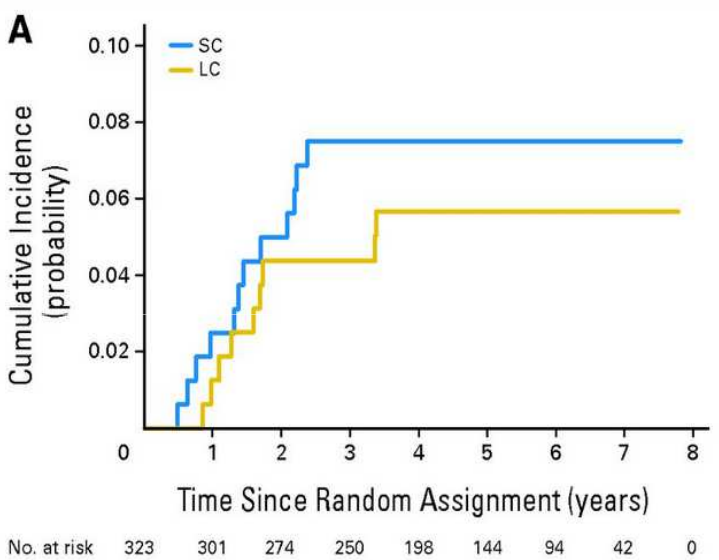


JCO 2012

SCPRT versus CRT : no difference in local control



Polish Trial (Bujko 2006)
Rate of Local Recurrence (LR)
14.4% vs 18.6%
P= 0.17



TROG-01 Trial (Ngan 2012)
Cumulative Incidence of LR
7.5% vs 4.4%
P = 0.24

SCPRT: Short course pre-operative radiotherapy
CRT: Chemoradiotherapy

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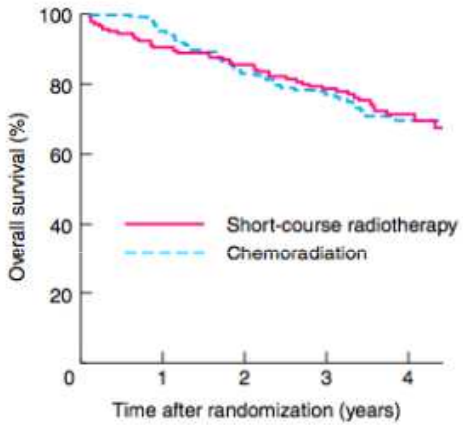
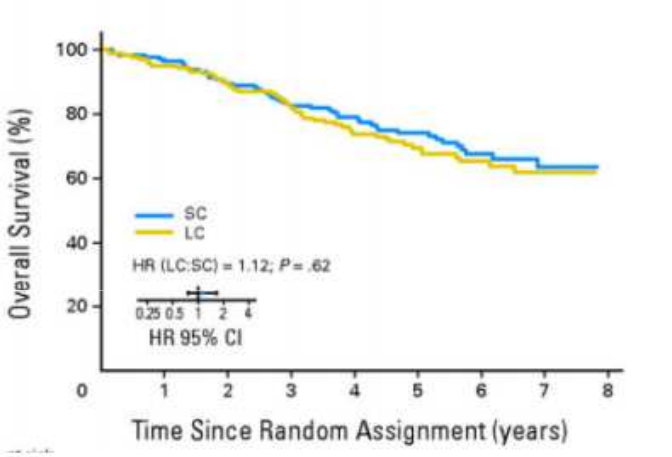
SCPRT versus CRT : No difference in overall survival



Polish trial (Bujko 2006)



Trans-Tasman trial (Ngan 2012)

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The ideal fractionation/dose

To reduce local recurrence prior to surgery

To combine with chemotherapy to achieve maximum down-staging

To avoid surgery (non-operative/organ sparing)

To fit with systemic chemotherapy (adjuvant, neoadjuvant or palliative

To minimise late effects

To produce the optimum immune effects

To reduce local recurrence

Who uses preoperative Chemoradiation?

45Gy?

50Gy?

Higher?

Locally advanced Rectal Cancer (LARC) 1:

- Low doses of RT are administered
- Chemoradiation and SCPRT are potentially curative treatments for locally advanced rectal adenocarcinoma.
- Not usually intended to be curative ‘per se’ (unless brachytherapy/Papillon boost)

Locally advanced Rectal Cancer (LARC) 2:

- However, only 10-25% achieve a pathological CR or CCR after definitive CRT
- Approx 30-40% of patients fail to respond
- Most patients will not achieve sustained local control unless surgery is added.
- Despite low dose - considerable late morbidity
- Late morbidity is contributed to (but not usually caused) by surgery.

Therefore if you are going to model

You have to know that you are comparing like with like

Therefore if you are going to model

You have to know that you are comparing like with like

Unless you control for the quality of surgery

then you simply cannot model RT dose and local control

Therefore if you are going to model

You have to know that you are comparing like with like

Unless you control for the quality of pathology

then you simply cannot model RT dose and local control

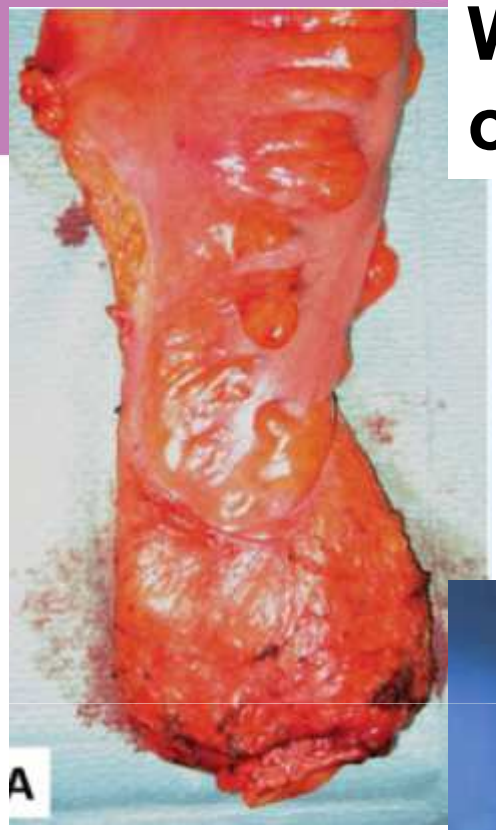
Randomised trials SCPRT (5x5Gy)

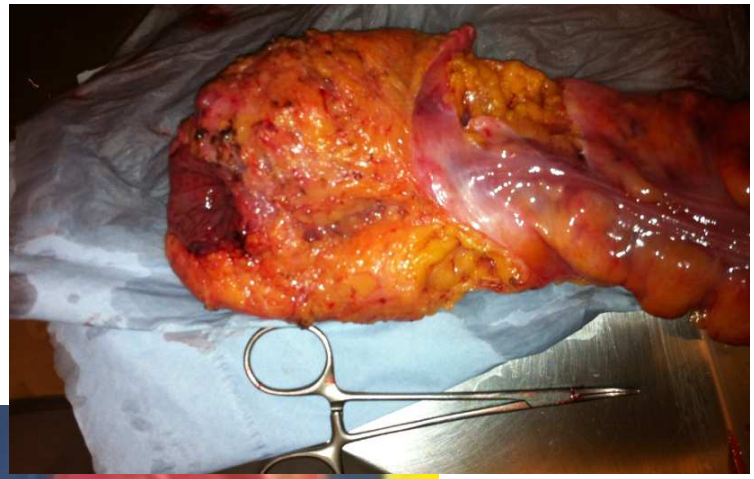
Trial	MRI mandated	EUS mandated	TME mandated	Good Quality TME	Median no of nodes resected
Swedish Rectal	No	No	No	?No	Not stated
Dutch TME	No	No	Yes	**50%**	7
Polish	No	No	?	?	9
CR07	No	No	No	**50%**	11
TROG-0104	If US not possible	Yes	No	?	Not stated

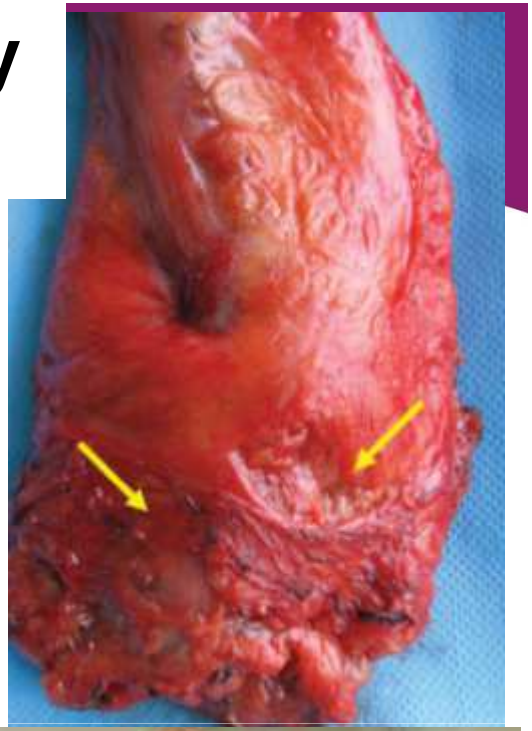
Randomised trials Preop CRT

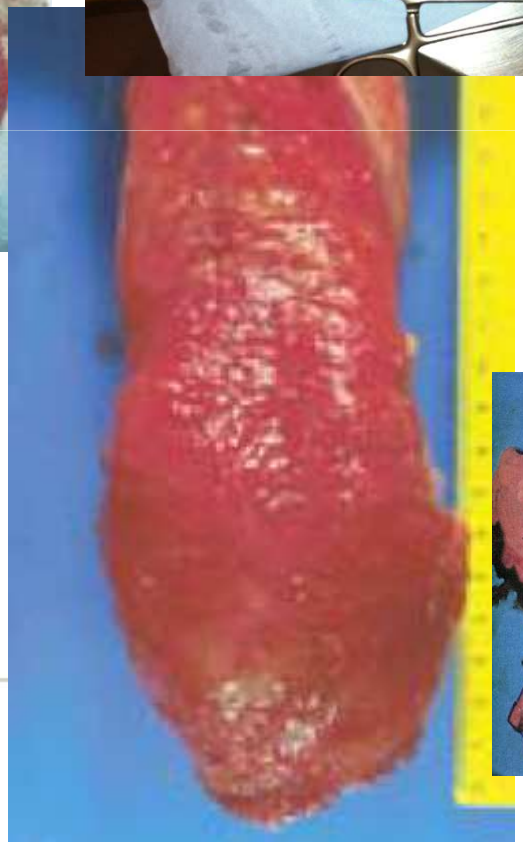
Trial	MRI mandated	EUS mandated	TME	Good Quality TME	Median no of nodes resected
German (Sauer 2004)	No	Yes	?	No data	Collected but not stated
EORTC 22921	No	No	**38%**	No data	7 after CRT
FFCD 9203	No	No	No data	No data	Not stated
NSABP R03	No	?	No	No data	Not stated
Polish	No	No	?	No data	8
TROG-0104	some	Yes	?	No data	Not stated

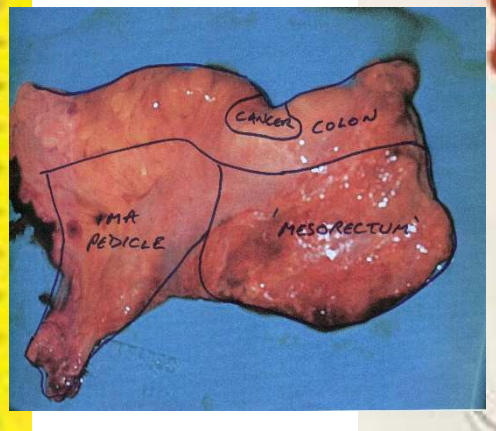
We can judge the quality of the Surgery

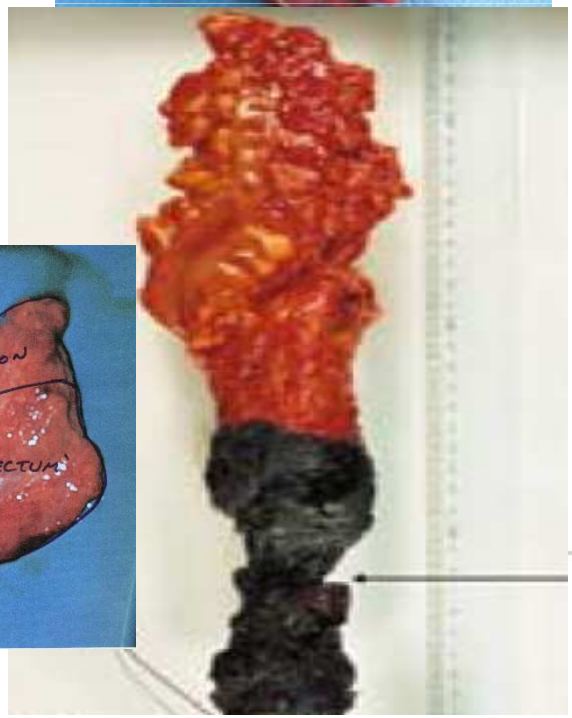


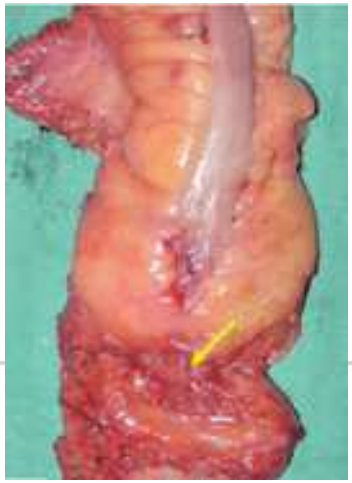












Aims from this session

Is there a standard ?

or

Can we select patients for short course/long course chemoradiation and total dose and fractionation

ie Risk adaptive/aims adaptive

Can we tailor the treatment to the individual patient?

Dose/ fractionation

Depends on what we are trying to achieve??

Aims of treatment: 1

- Radiotherapy to render unresectable/borderline resectable cancers (CRM+) resectable

Aims of treatment 2. Resectable cancers

- To reduce the risk of local recurrence
- To help to achieve sphincter/organ sparing?

ie Refuseniks/ frail, aged or unsuitable for radical surgery because co-morbidity

What is the mechanism of effect of preoperative CRT?

1. To prevent local recurrence by treating microscopic areas not seen and so not routinely removed by surgeon (discontinuous deposits etc ?
2. To prevent local recurrence by treating areas not routinely removed by surgeon (external iliac nodes/obturator nodes etc..) ?
3. To prevent local recurrence by countering spillage ie rendering cells non-viable with RT?
4. To prevent local recurrence by countering spillage growing ie tumour bed effect?
5. To prevent local recurrence by compensating for poor surgical technique?
6. To prevent local recurrence by immune effects?

So what is the optimum fractionation/dose?

Fluoropyrimidine based chemoradiation?

Fractionation 1.8Gy-2.0Gy conventional

more toxicity if combined with larger fractions

Reasonable to add Papillon/brachytherapy if surgery not intended

?evidence for EBRT dose escalation in randomised studies

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Impact of radiotherapy boost on pathological complete response in patients with locally advanced rectal cancer: A systematic review and meta-analysis

Johannes Peter Maarten Burbach [a,*,1], Annemarie Maria den Harder [b,1], Martijn Intven [a], Marco van Vulpen [a], Helena Marieke Verkooijen [c], Onne Reerink [a]

[a] Department of Radiation Oncology; [b] Department of Radiology; and [c] Trial Bureau Imaging Division, University Medical Center, Utrecht, The Netherlands

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ABSTRACT

Purpose: We conducted a systematic review and meta-analysis to quantify the pathological complete response (pCR) rate after preoperative (chemo)radiation with doses of $\geqslant$60 Gy in patients with locally advanced rectal cancer. Complete response is relevant since this could select a proportion of patients for which organ-preserving strategies might be possible. Furthermore, we investigated correlations

Conclusion

"Dose escalation above 60Gy for locally advanced rectal cancer results in high pCR-rates and acceptable early toxicity."

Randomised trials of Dose escalation of RT

Are there any trials?

Only 3 Randomised Trials

Publication	n	Regimens in trial	PCR in Control	PCR in Novel arm
RTOG 0012 J Clin Oncol 2006 T3/T4	106	PVI 5FU + 44.2Gy - 60Gy versus PVI 5FU + Irinotecan 50.4Gy -54Gy	26%	 26%
Jakobsen IJROBP 2012	248	50.4Gy + UFT versus 50.4Gy + UFT+ Brachytherapy	18%	 18%
Engineer IJCRD 2013	90	45Gy + Cape Versus 40Gy +20Gy RT alone	7%	 11%

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Jakobsen A 2012: endpoints

Endpoint	CRT +brachytherapy boost n=90	Standard CRT n= 92	P value
pCR	18%	18%	NS
R0 Resection	99%	90%	P= 0.03
Major response TRG 1 and 2	44% (35/80)	28% (23/82)	P= 0.04

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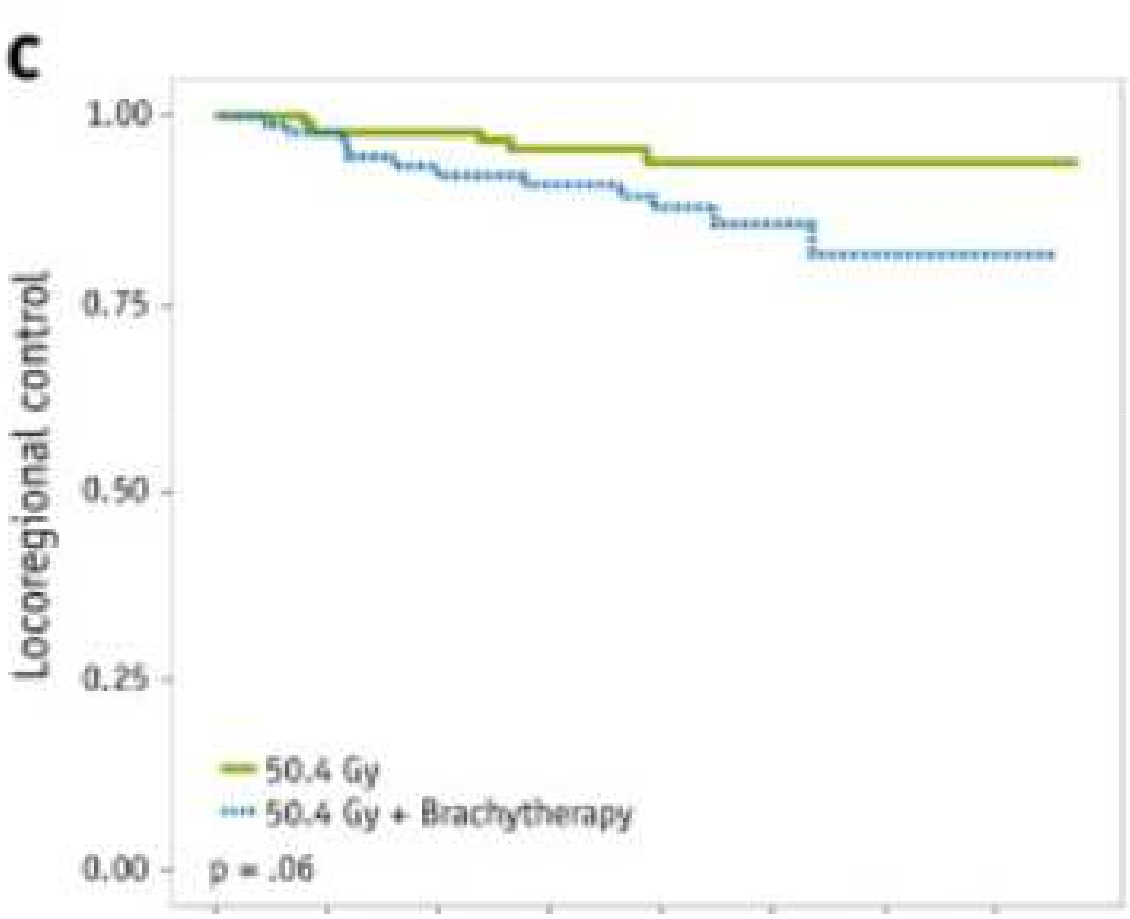
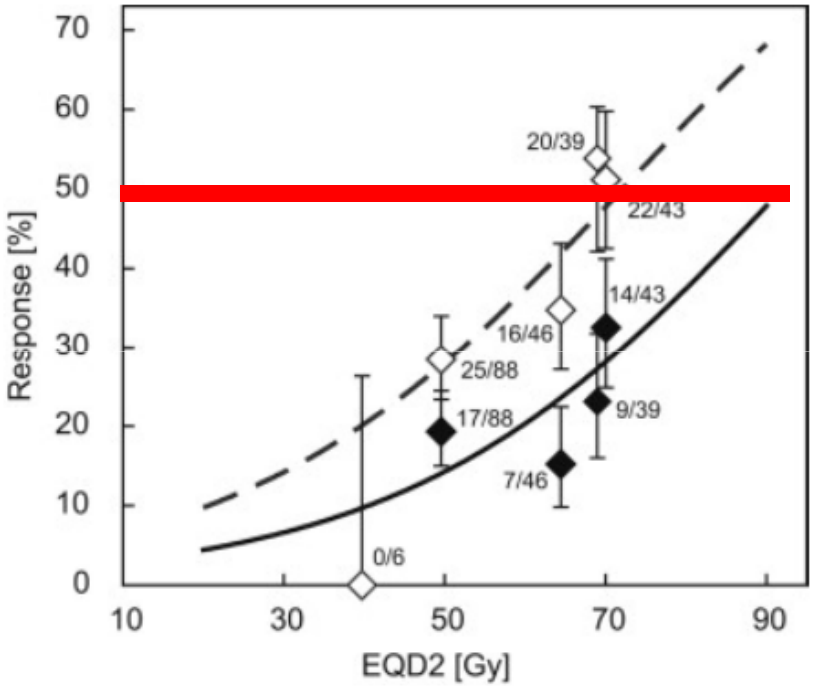
Locoregional control Appelt 2014



- Which begs the question regarding the mechanism of action for preventing local recurrence?

Ane Appelt dose response curve



Dose-response relationships for complete response (TRG1) (*solid line, filled squares*) and major response (TRG1-2) (*dashed line, open squares*) after preoperative chemoradiation therapy (CRT) for rectal cancer.

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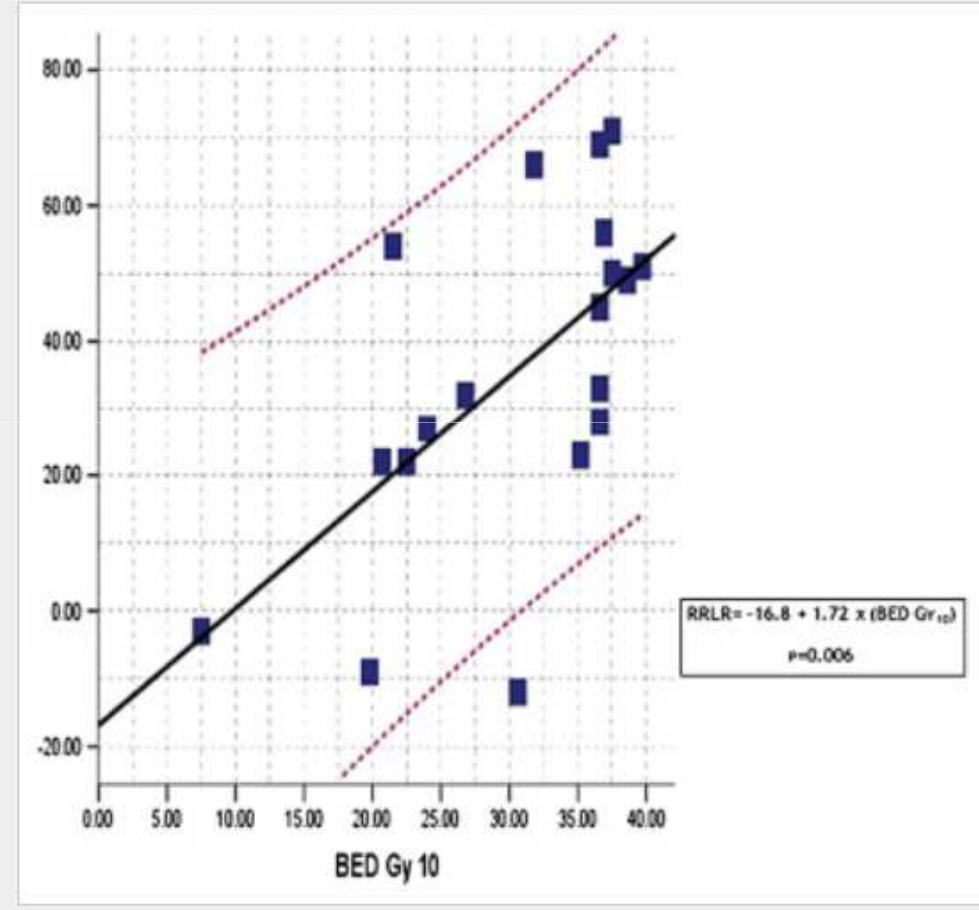
Viani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20.00
0.00
-20.00
0.00
5.00
10.00
15.00
20.00
25.00
30.00
35.00
40.00
BED Gy 10
RRLR= -16.8 + 1.72 x (BED Gy10)
p=0.006

Viani

- using this model, we could hypothetically predict that a BED of approximately 68.8 Gy_{10} would need to be delivered to patients with localized rectal cancer to achieve 100% local control with surgery

- using a high dose for fraction of 5 Gy to achieve a BED Gy_{10} of 68.8 would require nine fractions, resulting in a BED of 117 Gy_3.

Conclusions

Thank you

For optimum dose – we would need

Large randomised trials

Meta-analyses with large number of individual patient data

Controlled for quality of surgery/pathology

performed over a short time frame with little change in radiation delivery

The same field sizes

- Radiotherapy is generally regarded as a cell death inducing technique.

- Radiation also induces inflammatory or anti-inflammatory reactions depending on dose and fractionation

Reichl B, et al. DEGRO practical guidelines for radiotherapy of non-malignant disorders: Part I: physical principles,radiobiological mechanisms, and radiogenic risk. Strahlenther Onkol 2015;191(9):701-9.

Shahabi V, et al. Immune-priming of the tumor microenvironment by radiotherapy: rationale for combination with immunotherapy to improve anticancer efficacy. Am J Clin Oncol 2015;38(1):90-7.

PCR and CCR not the same (but some linkage)

small tumours show high rate of pCR and high rate of cCR (about 30- 40%)

and high rate of agreement between pCR and cCR (about 70%)

CCR evident within a few weeks

5x5Gy
Smart et al epub BJS 2016 (TREC)

No of patients	pCR	ypT1	ypT2	ypT3
62	20 (32%) 13/27 (48%) with uT0/uT1 disease 5/29 (17%) with uT2	23 (37%)	18 (29%)	1 (2%)

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Larger Tumours (T3/T4)

Lower rate of pCR (about 15%) and lower rate of cCR (about 5% in some studies at 6-8 weeks)

lower rate of agreement between pCR and cCR (ulceration and fibrosis may not mean tumour is present)

May need to wait much longer to assess CCR

Evidence Base:There is a systematic bias

Earlier historical trials

- Gave lower doses of RT
- Gave less effective chemotherapy
- Had shorter intervals to surgery
- Were not accurately staged
- Did not perform such good quality surgery
- Did not have good pathology (accurate pCR)

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Tumour control Probability (TCP)

- Appears different according to T stage (T1/T2 versus T3/T4)
- And nodal stage

- Local response is time dependent
- Local control may be blurred by the occurrence of metastases

NTCP

May be different according to

T stage (T1/T2 versus T3/T4)and nodal stage because may reflect field size

Modern more sophisticated and less toxic methods of radiotherapy delivery with IMRT

Different fractionation schedules

BASIS For Extrapolation

	All	pCR	No pCR	p value
Clinical T stage				<0·0001
T1	0% (12/2785)	2% (7/462)	58%	
T2	5% (145/2785)	9% (41/462)	28%	
T3	83% (2301/2785)	81% (374/462)	16%	
T4	12% (327/2785)	9% (40/462)	12%	
Missing	10% (320/3105)	5% (22/484)	11% (298/2621)	

Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data

Monique Maas, Patty J Nelemans, Vincenzo Valentini, Prajnan Das, Claus Rödel, Li-Jen Kuo, Felipe A Calvo, Julio García-Aguilar, Rob Glynne-Jones, Karin Haustermans, Mohammed Mohiuddin, Salvatore Pucciarelli, William Small Jr, Javier Suárez, George Theodoropoulos, Sebastiano Biondo, Regina G H Beets-Tan, Geerard L Beets

MRI FINDINGS				
T2, T3a, T3b <4mm CRM not threatened (predicted margin ≥2mm) N0 EMVI: Negative	T3b >4mm CRM not threatened (predicted margin ≥2mm) N1 EMVI: Negative	T3b >4mm T3c CRM not threatened (predicted margin ≥2mm) N2 EMVI: Positive	T3d >15mm, T4a (resectable) CRM not threatened (predicted margin ≥2mm) N: Any EMVI: Any	T3c,T3d, T4b CRM breached or threatened (predicted margin <1mm) N:Any EMVI: Any
MRI RISK STRATIFICATION				
LOW RISK		**INTERMEDIATE RISK**		**HIGH RISK**
Low risk local recurrence	Low risk local recurrence	Moderate risk of local recurrence	High risk of local recurrence	High risk local recurrence
Low risk of metastases	Moderate risk of metastases	High risk of metastases	High risk of metastases	High risk of metastases
MRI DIRECTED CLINICAL MANAGEMENT				
Surgery alone	If able to perform good quality R0 resection, RT may be omitted	SCPRT or CRT depending on whether shrinkage of tumour required	SCPRT or CRT depending on whether shrinkage of tumour required	CRT required or SCPRT + chemo

ACCORD 12/0405 PRODIGE 2

Increased both RT dose 45Gy to 50Gy

And added oxaliplatin

Primary endpoint pCR

ypCR rate was 13.9% with Cap 45 and 19.2% with Capox 50 (P = .09).

If ypCR was combined with yp few residual cells, the rate was respectively 28.9% with Cap 45 and 39.4% with Capox 50 (P = .008).

The rate of positive circumferential rectal margins (between 0 and 2 mm) was 19.3% with Cap 45 and 9.9% with Capox 50 (P = .02).

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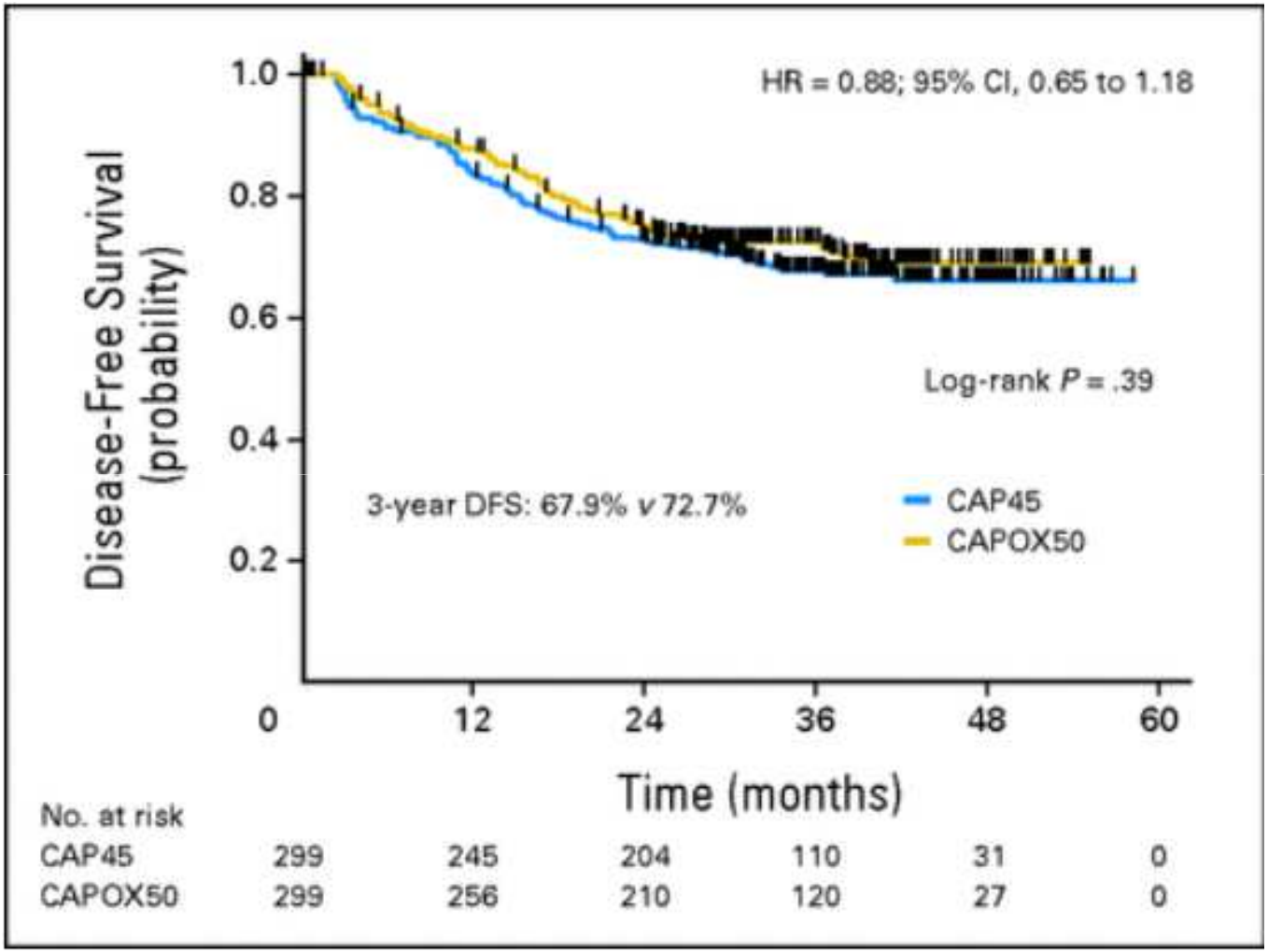
But…

More preoperative grade 3 to 4 toxicity occurred in the Capox 50 group (25 v 1%; P < .001).


HR = 0.88; 95% CI, 0.65 to 1.18
Log-rank P = .39
3-year DFS: 67.9% v 72.7%
CAP45
CAPOX50
Disease-Free Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
12
24
36
48
60
Time (months)
No. at risk
CAP45 299 245 204 110 31 0
CAPOX50 299 256 210 120 27 0

Selection/Risk adaptive according to

- Stage/radiological features
- CEA
- Molecular biology (EGFR, Ras, MSI, Braf…)
- Gene signatures
- MicroRNA
- Immune markers (PD-1, TILs)

Dose response for Radiotherapy depends on

T stage

Size of the tumour

N stage?

Histology (Mucinous/ signet ring)

? Site

And the tumour environment

Poor prognostic tumours 70% ≤ 1mm CRM

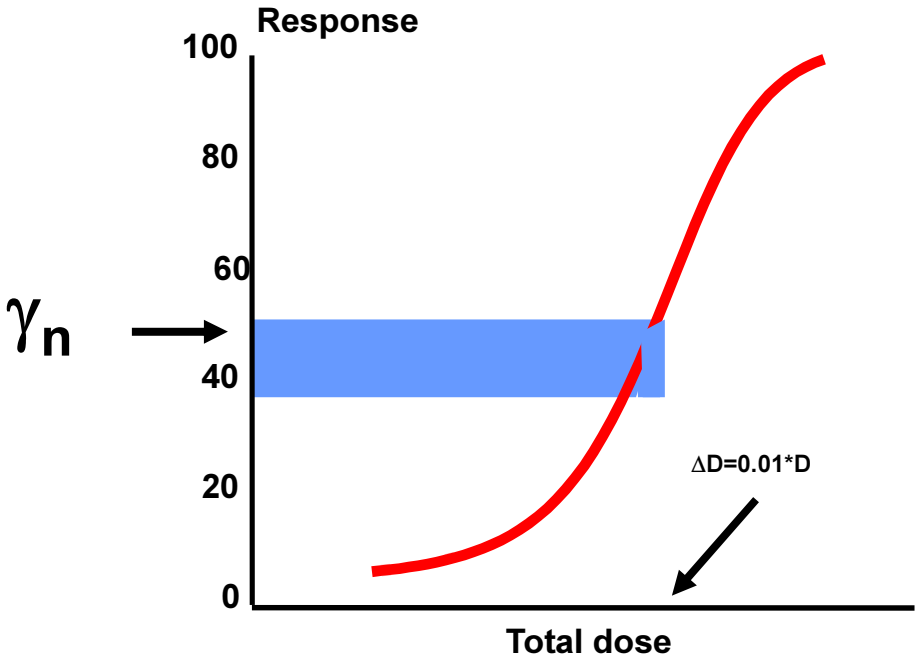
92% ≤ 2 mm CRM

Large tumours

Many patients clinically node positive

Pathology too soon – surgery 6-8 weeks

Jakobsen 2013



$$\gamma(D) \equiv D \cdot \frac{dP(D)}{dD}$$

Strategies to enhance pCR/CCR

Dose-escalation

EBRT (IMRT/IGRT)

Contact

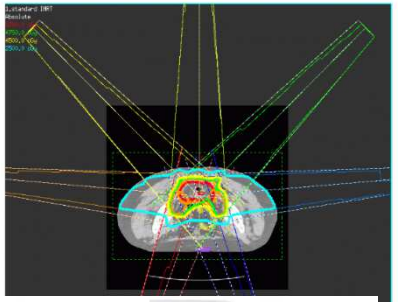
Brachytherapy

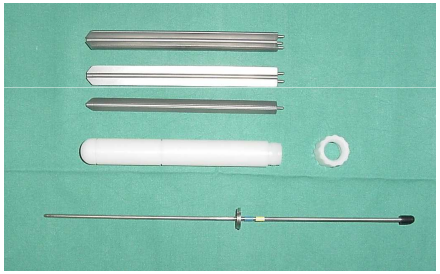
SABR

IMRT Rectum

Prone position
Seven 6 MV co-planer beams

Beam angles:
0°, 40°, 85°, 160°, 200°, 275°, 315°





Immobilisation/precision

Radiotherapy strategies

- Hyperfractionation

Hyperfractionation

RTOG 00-12

hyperfractionated CRT did not improve

the rate of pathologic complete response

or any clinical outcome (LC, DFS, OS)

Mohiuddin M, *et al*. Neoadjuvant chemoradiation for distal rectal cancer: 5-year updated results of a randomized phase 2 study of neoadjuvant combined modality chemoradiation for distal rectal cancer. Int J Radiat Oncol Biol Phys 2013: 86:523–528

Radiotherapy strategies

- Hyperfractionation
- Increase total dose

  Facilitated by improved technical delivery

  (IMRT/VMAT/IGRT)

What would you need for TCP/NTCP?

Brachytherapy for Rectal Cancer

Karin Haustermans on behalf of Corrie Marijnen

Department of Radiation Oncology

UZ Leuven

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Introduction

Surgery = mainstay of cure for rectal cancer

However:

- Serious adverse events possible[1-3]
- Postoperative mortality increases in the elderly:
  - 12% vs. 3-4%[4]

➔Radiotherapy with curative intent for a subgroup of patients

1. Peeters et al. J Clin Oncol 2005;23(25):6199-6206
2. Birgisson et al, J Clin Oncol 2005;23(34):8697-8705
3. Frykholm et al. Dis Colon Rectum 1993;36(6):564-572
4. Marijnen et al. J Clin Oncol 2002;20:817-825.

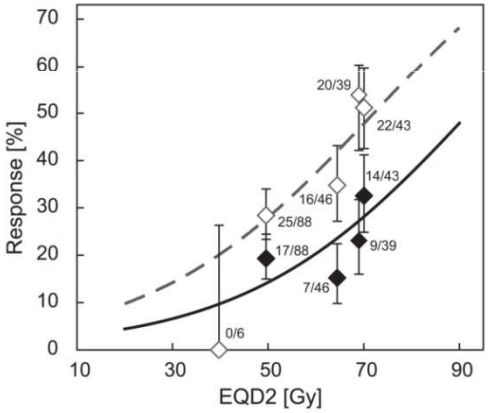
Dose escalation

- Dose response relationship in rectal cancer
- EBRT dose escalation leads to increased toxicity
- Other strategy is needed

➔ Intracavitary irradiation

→ Contact Therapy (Papillon)

→ Endoluminal Brachytherapy (EBT)



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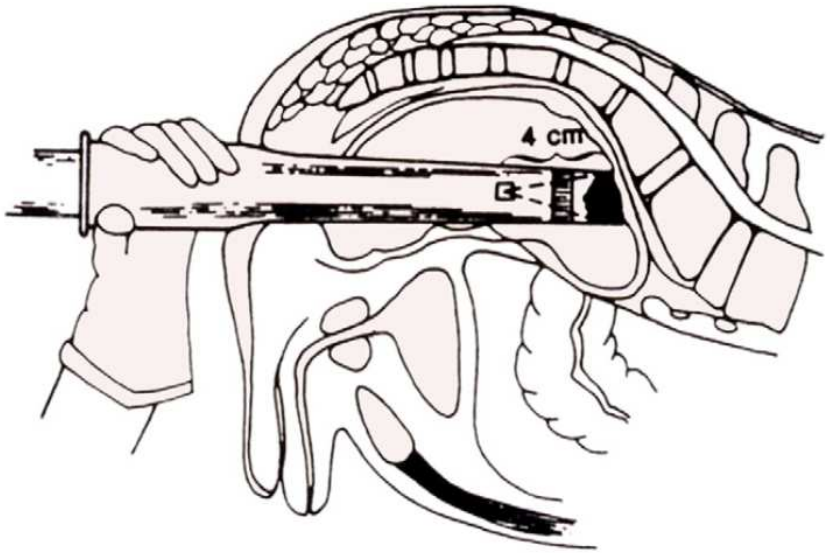
CONTACT THERAPY (PAPILLON)

Contact Therapy (Papillon)

- Jean Papillon (Lyon)
- 50 kV maximal energy X-ray beam
- Focal distance of 4 cm
- Applicator diameter of 20-30 mm
- Direct visual control
- Outpatient basis
- Output: 20 Gy/min
- Percentage depth dose:
  - 100% at surface
  - 44% at 5 mm
  - 10% at 20 mm



Gerard et al. Clin Oncol (R Coll Radiol) 2007;19(9):661–73.

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Contact therapy (Papillon)

- Dose prescribed at the surface of the tumor
- Steep fall-off of dose with depth

  44% at 5 mm

  25% at 10 mm
- Delivery of large doses per fraction (approximately 30 Gy per fraction)
- Gradual destruction of exophytic tumours layer per layer in a few fractions
  - 3-4 fractions (90-120 Gy)
  - 4-6 weeks overall treatment time

Gérard et al. Int J Radiat Oncol Biol Phys. 1996;34(4):775–83.
Papillon et al. Int J Radiat Oncol Biol Phys. 1989;17(6):1161-9
Coatmeur et al. Radiother Oncol 2004;70(2):177–82.

Contact therapy alone

Papillon:

- 312 patients between 1951 – 1984
- T1 and favorable T2 rectal adenocarcinoma
- 5Y local control: 90 %
- 5Y overall survival: 75 %
- Low morbidity

Mendenhall:

- Early stage rectal adenocarcinoma
- 20 patients contact therapy vs. 45 patients local excision +EBRT
- 5Y LC 80 vs. 86%

Papillon et al. Int J Radiat Oncol Biol Phys. 1989;17(6):1161-9
Mendenhall et al. J Clin Oncol 1997;15(10):3241-3248

Contact therapy alone

Coatmeur:

- 124 patients treated with contact therapy +/- interstitial brachytherapy
- Outcome was related to Dijon clinical staging (T1 < 3 cm; T2 > 3 cm)
- Average dose 95 Gy
- 10 patients interstitial brachytherapy 24 Gy
- 5Y LC: 83 % (T1) and 38 % (T2)
- 5Y OS: 62,4 %

Papillon, Mendenhall & Coatmeur:

→ **Local control rate for tumors < 3 cm is good**

→ **Contact therapy can be an alternative to surgery**

→ **Results not satisfactory for tumors > 3 cm**

Coatmeur et al. Radiother Oncol 2004;70(2):177–82.
Marijnen et al. Clin Oncol (R Coll Radiol) 2007;19(9):706–10.

Combined therapy

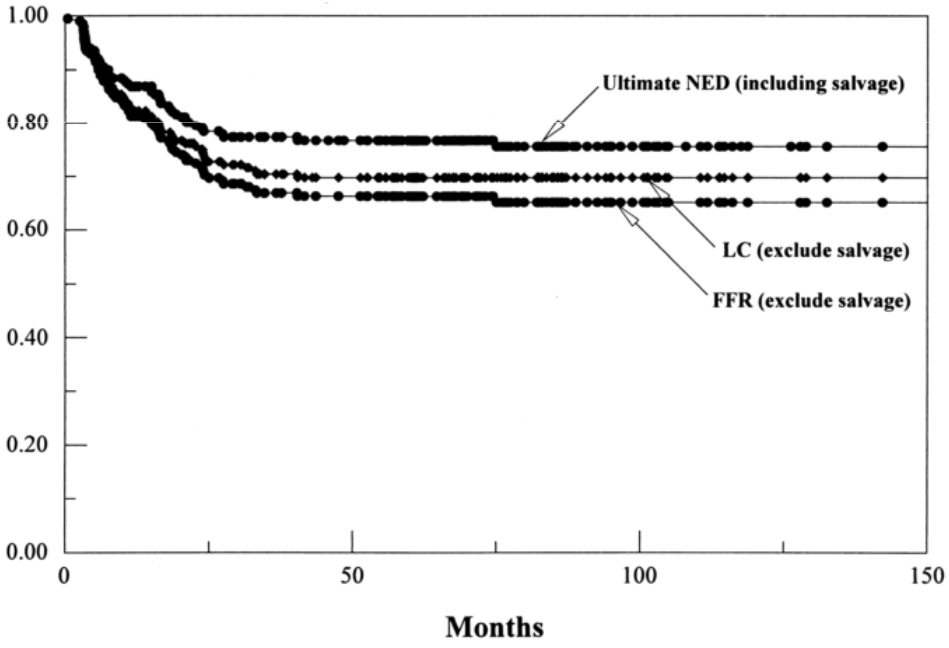
Aumock:

- 199 patients with local rectal cancer
- 77 cases staged by ERUS
- Contact therapy alone (n=21) or preceded by EBRT (45Gy/1,8Gy) (n=178)

- 71 % local control (141 patients)
- Significant factors for control:
  - Mobility on palpation
  - Use of EBRT
  - Pretreatment debulking
- LC 100% if uT1, 85% freely mobile uT2, 56% uT3 and immobile uT2

➔ **Excellent results for small tumors**

➔ **Reasonable results for larger tumors**



Aumock et al. Int J Radiat Oncol;51(2):363–70.

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Contact therapy - Conclusions

- Tumor < 3 cm: contact therapy is an alternative for surgery
  - T1 or early T2 (freely mobile)
  - No nodal involvement
- Tumor > 3 cm: combination with EBRT (39 – 45 Gy) or interstitial brachytherapy (20 – 30 Gy) and close follow-up is needed
- Local control 70 – 90 %
- Toxicity is acceptable
  - Acute: 10 – 40%, mainly mucositis, no grade 3 – 4 toxicity
  - Late: mainly rectal bleeding or ulceration
- **TWO DRAWBACKS:**
  - **Diameter of the proctoscope determines the maximal size of the tumor that can be treated (max. 4 – 5 cm)**
  - **Rapid dose fall-off hampers treatment of tumors invading mesorectal fat**

Gérard et al. Int J Radiat Oncol Biol Phys. 1996;34(4):775–83.
Papillon et al. Int J Radiat Oncol Biol Phys. 1989;17(6):1161-9
Coatmeur et al. Radiother Oncol 2004;70(2):177–82.
Aumock et al. Int J Radiat Oncol;51(2):363–70.

ENDOLUMINAL BRACHYTHERAPY

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1. HDR-EBT – Procedure

- HDR Brachytherapy
- Remote after-loading system using 192-Ir
- Most common: single source catheter
  → Dose prescription at 1 cm
- More recently: flexible catheter with 8 channels
  → Selective loading possible
  → Dose prescription at tumor radial margins (better dose penetration at the radial depth)
- Treatment time: 10 min per fraction
- Curative, adjuvant and palliative treatment possible

Vuong et al. Brachytherapy 2005;4:230e235.

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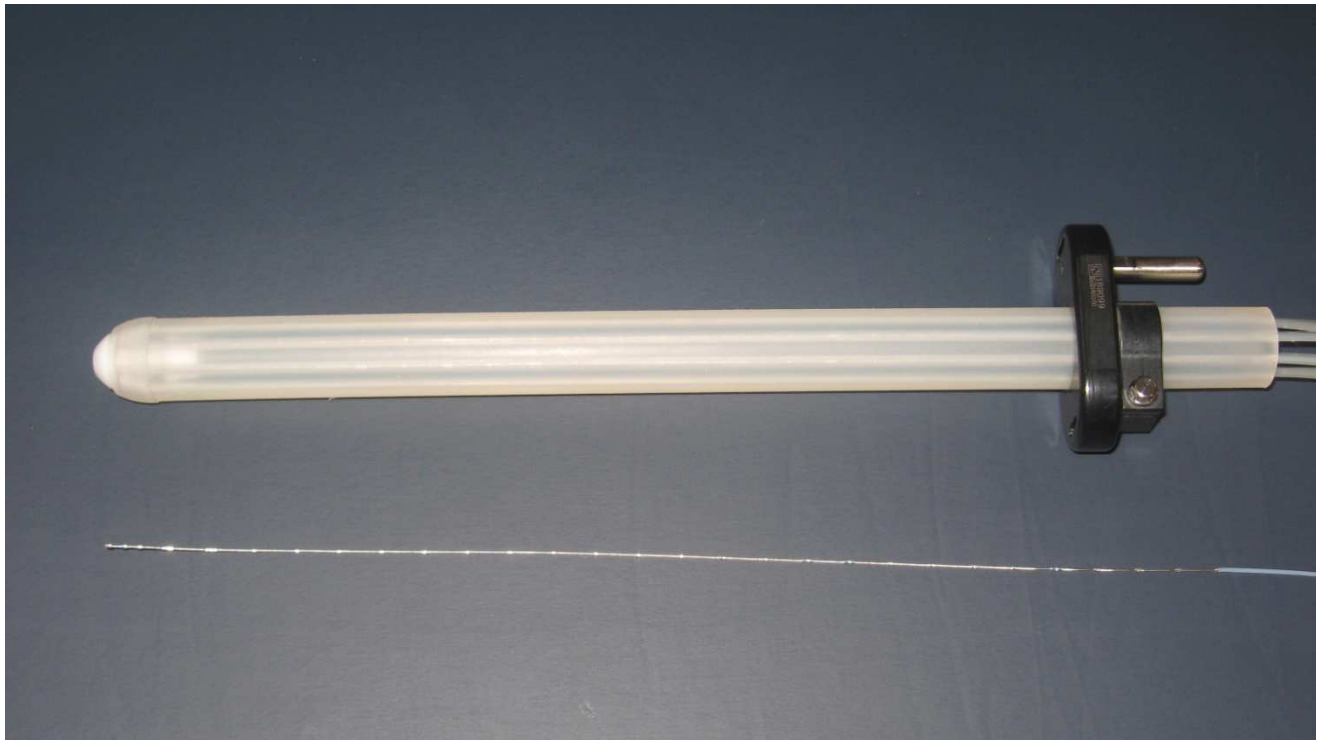
Flexible multi-channel rectal probe



1. HDR-EBT – Procedure

- MRI and EUS for staging
- Sigmoidoscopy to clip tumor
- Planning CT scan with applicator in situ
- Delineation of tumor on CT scan
- Optimizing dose with planning system
- HDR radiotherapy (consecutive days)
- Position verification with X-rays and clips

Vuong et al. Brachytherapy 2005;4:230e235.

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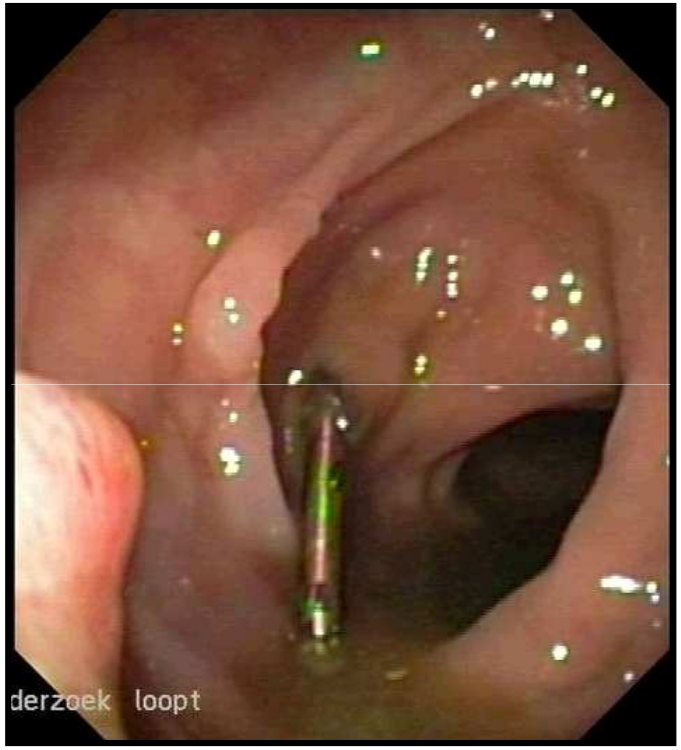
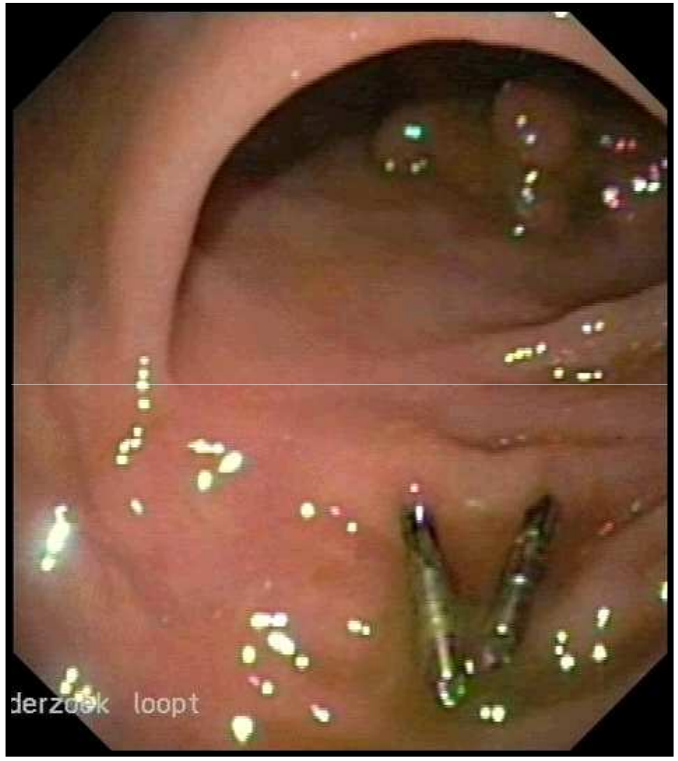
Sigmoidoscopy to clip tumor





Courtesy of Marijnen C., LUMC, Leiden, The Netherlands

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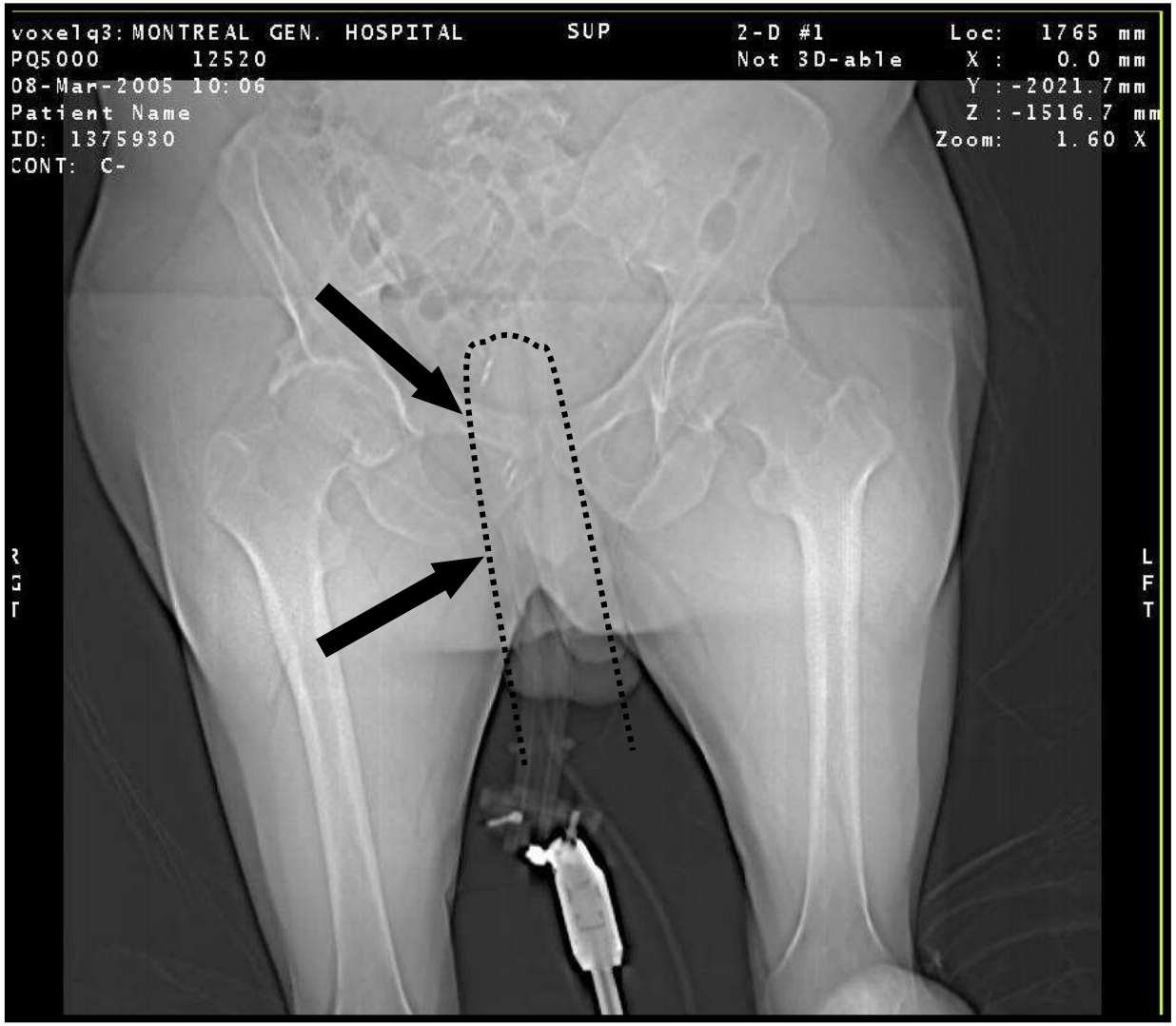
CT scanning with applicator in situ



Courtesy of Marijnen C., LUMC, Leiden, The Netherlands

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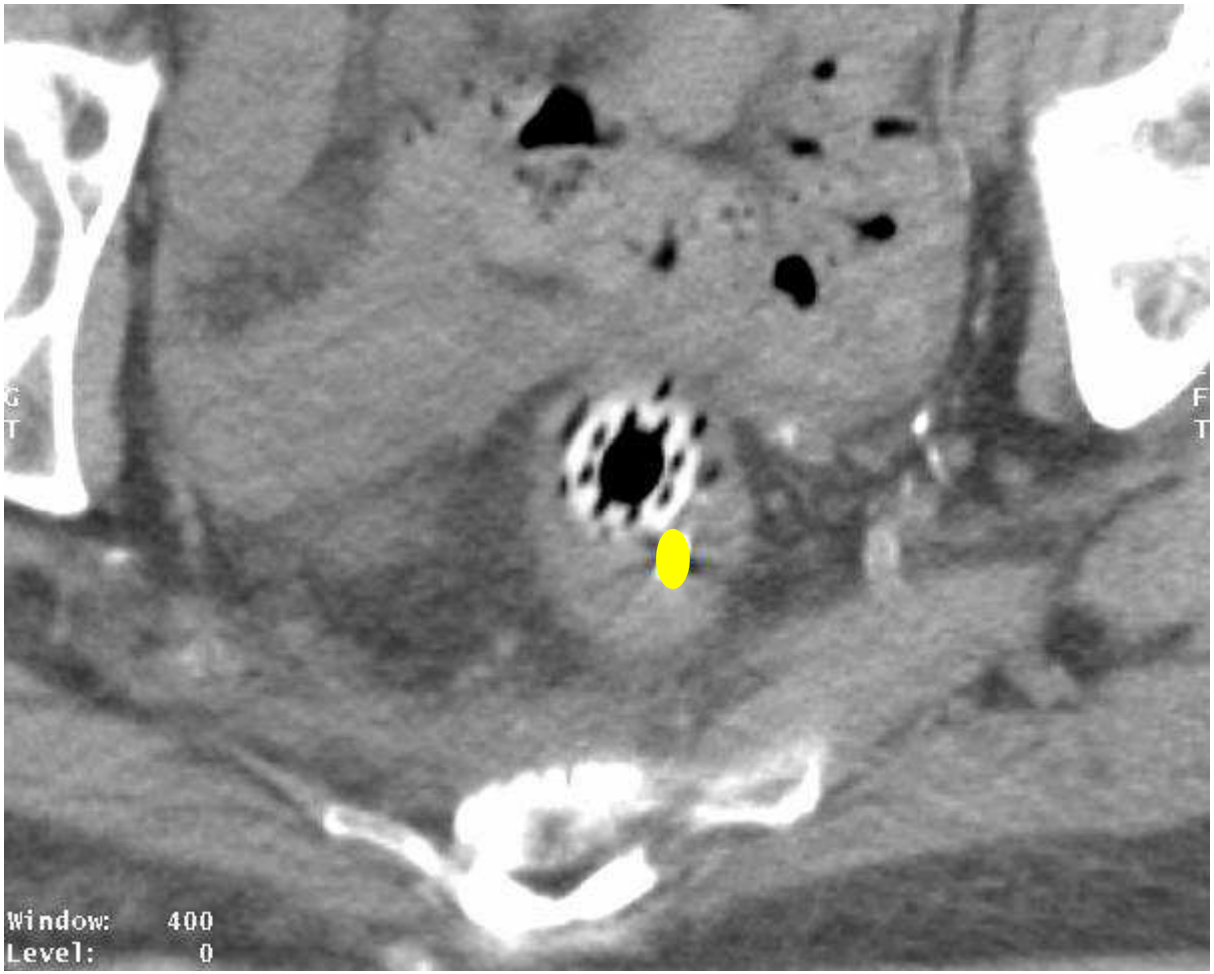
Outlining radiopaque clips



Courtesy of Marijnen C., LUMC, Leiden, The Netherlands

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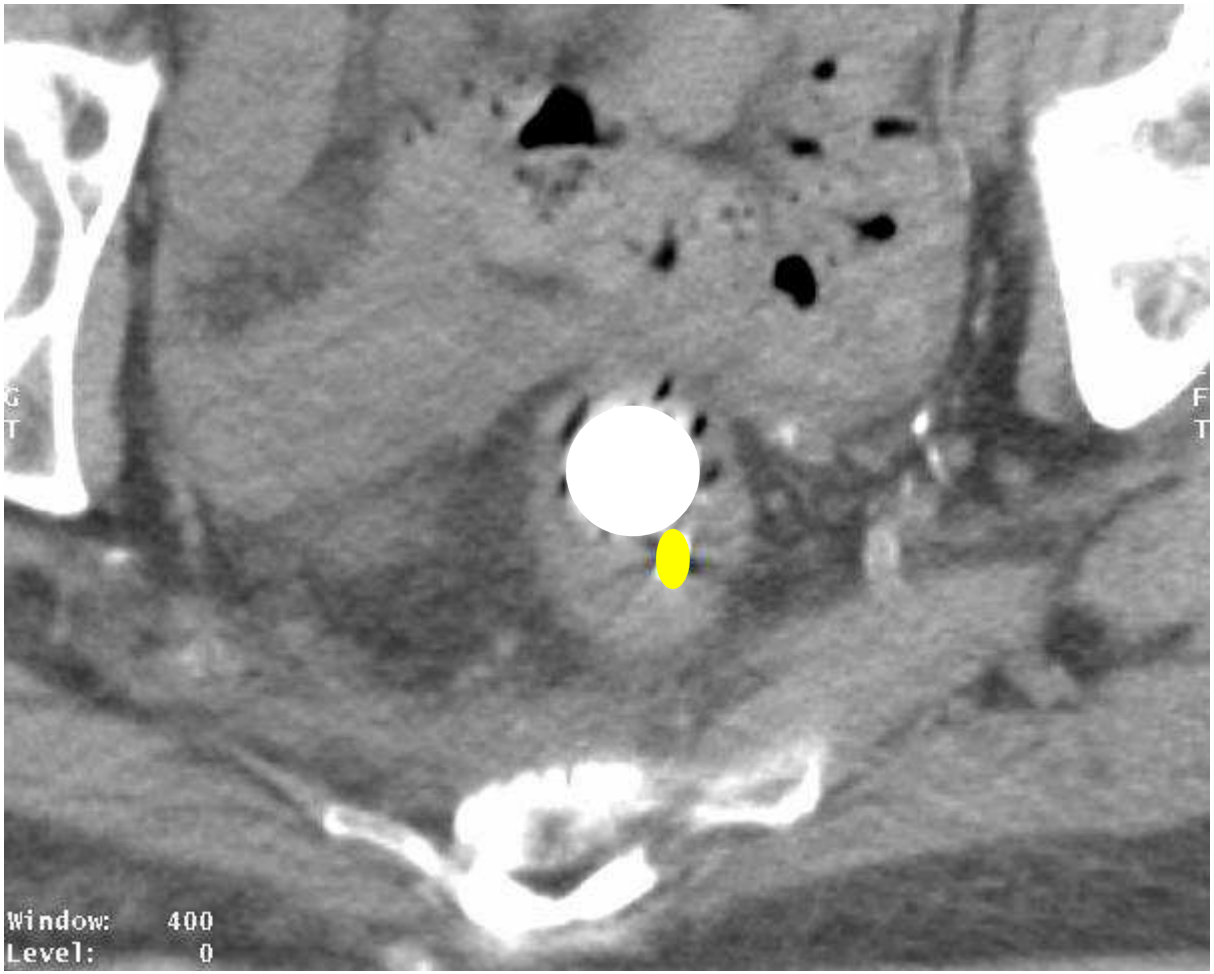
Outlining applicator



Courtesy of Marijnen C., LUMC, Leiden, The Netherlands

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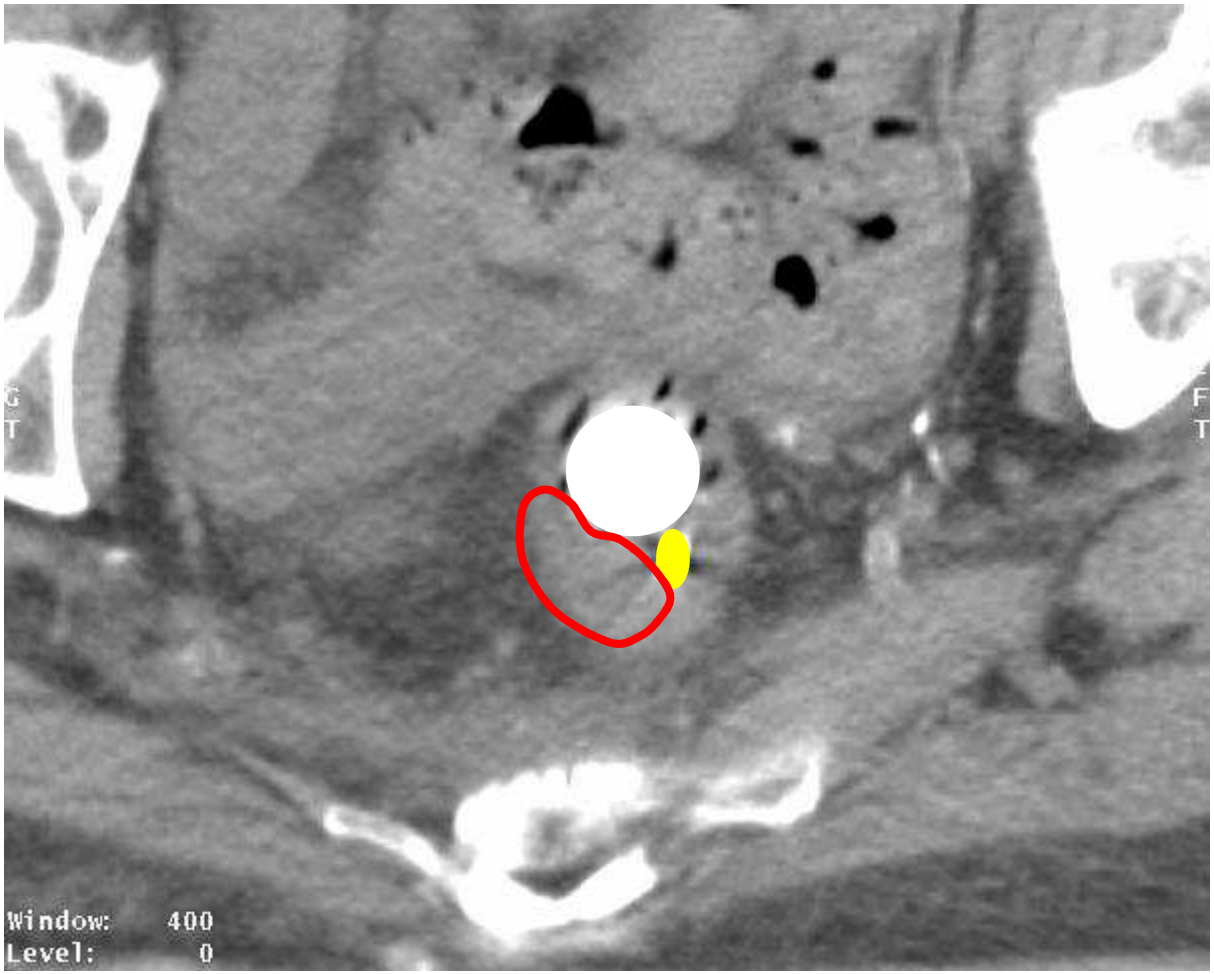
Outlining tumor



Courtesy of Marijnen C., LUMC, Leiden, The Netherlands

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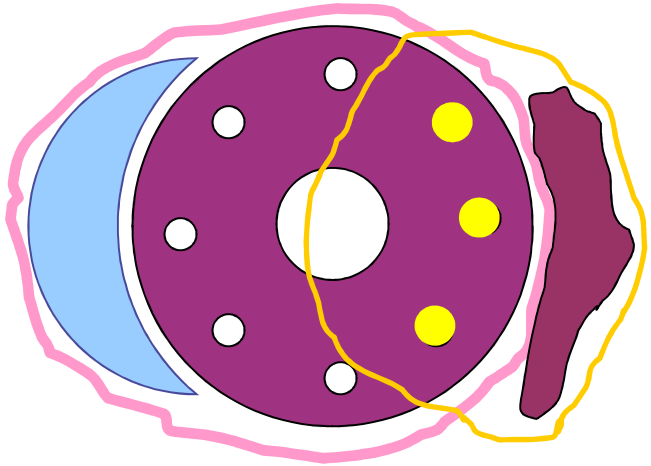
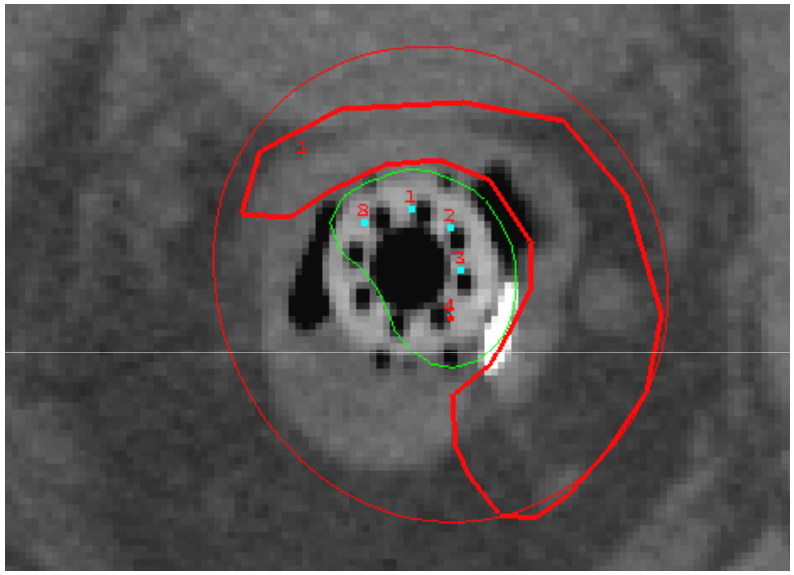
Catheter loading: conformal dose delivery





Asymmetrical catheter loading

Courtesy of Vuong T., McGill, Montreal, Canada

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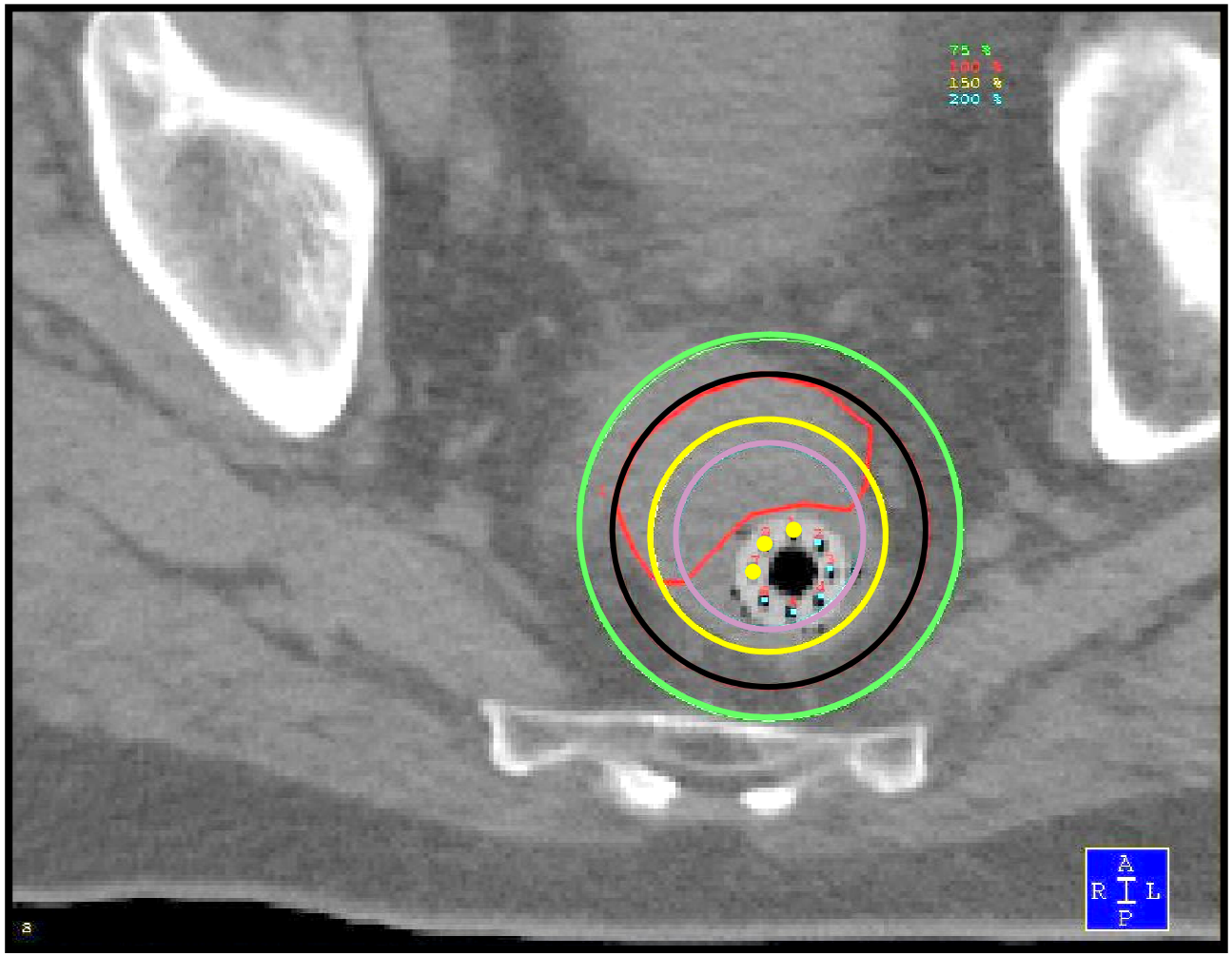
Dose conformity: 100% isodose around tumor

75 %

100 %

150 %

200 %



Courtesy of Marijnen C., LUMC, Leiden, The Netherlands

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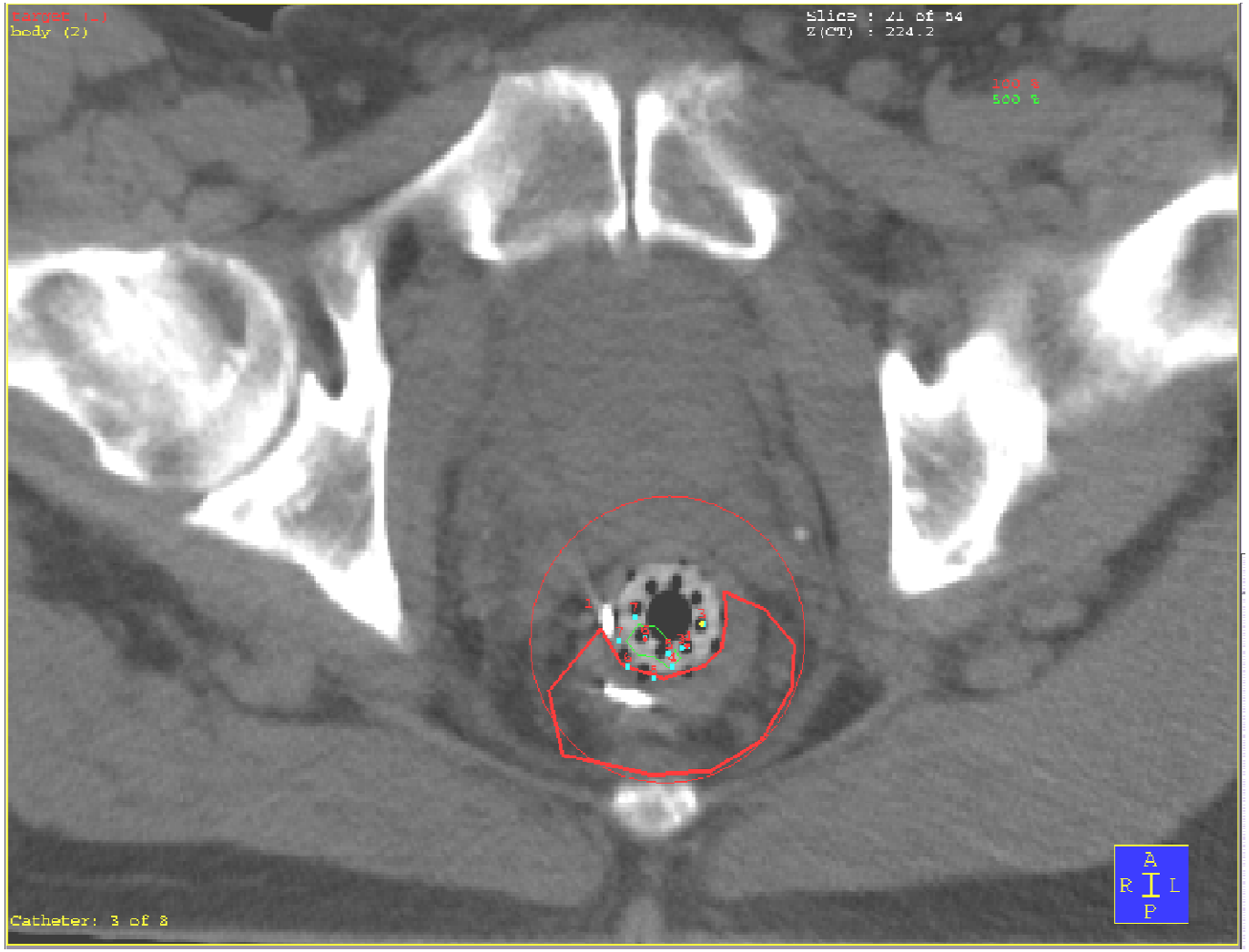
Nodes can be included



Courtesy of Marijnen C., LUMC, Leiden, The Netherlands

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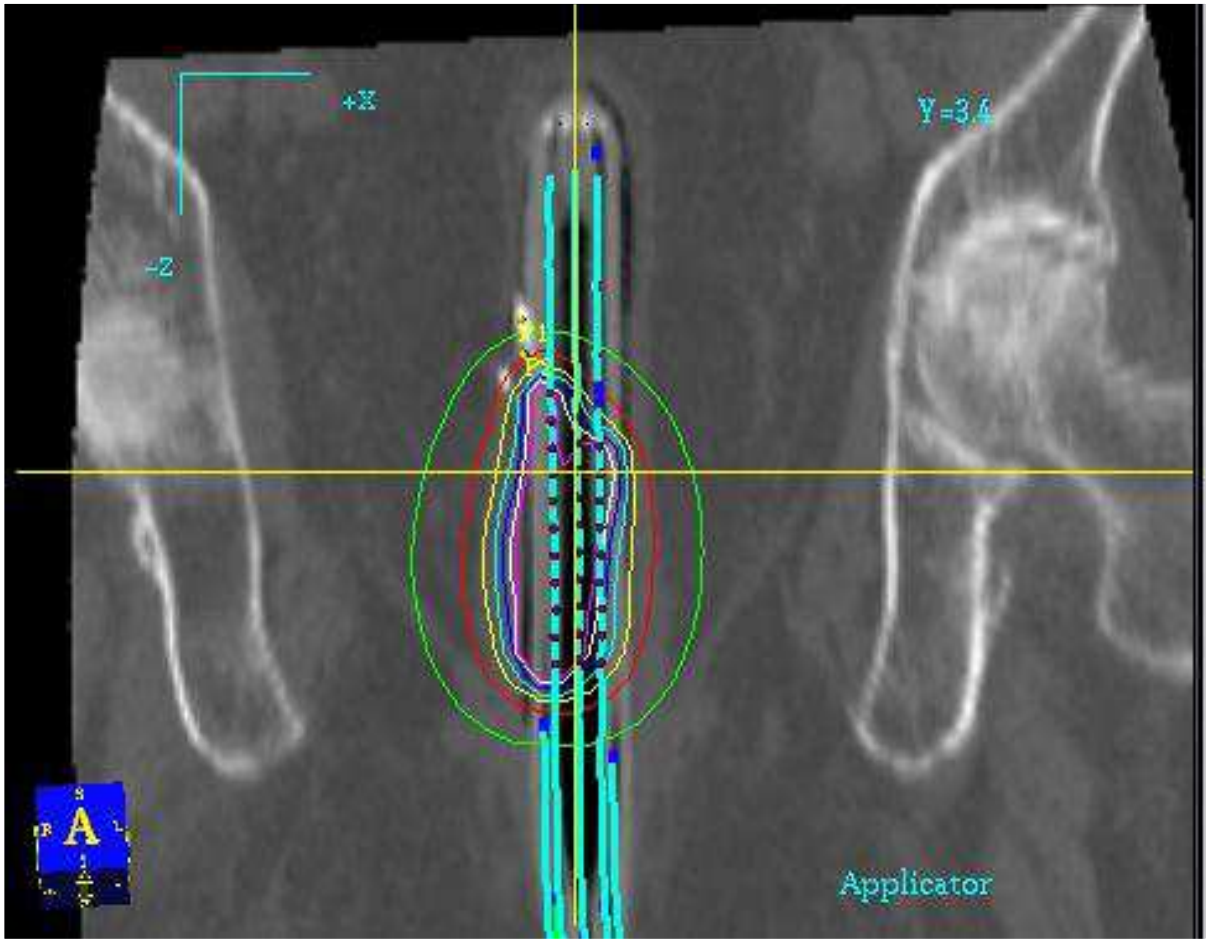
Isodose distribution



Courtesy of Marijnen C., LUMC, Leiden, The Netherlands

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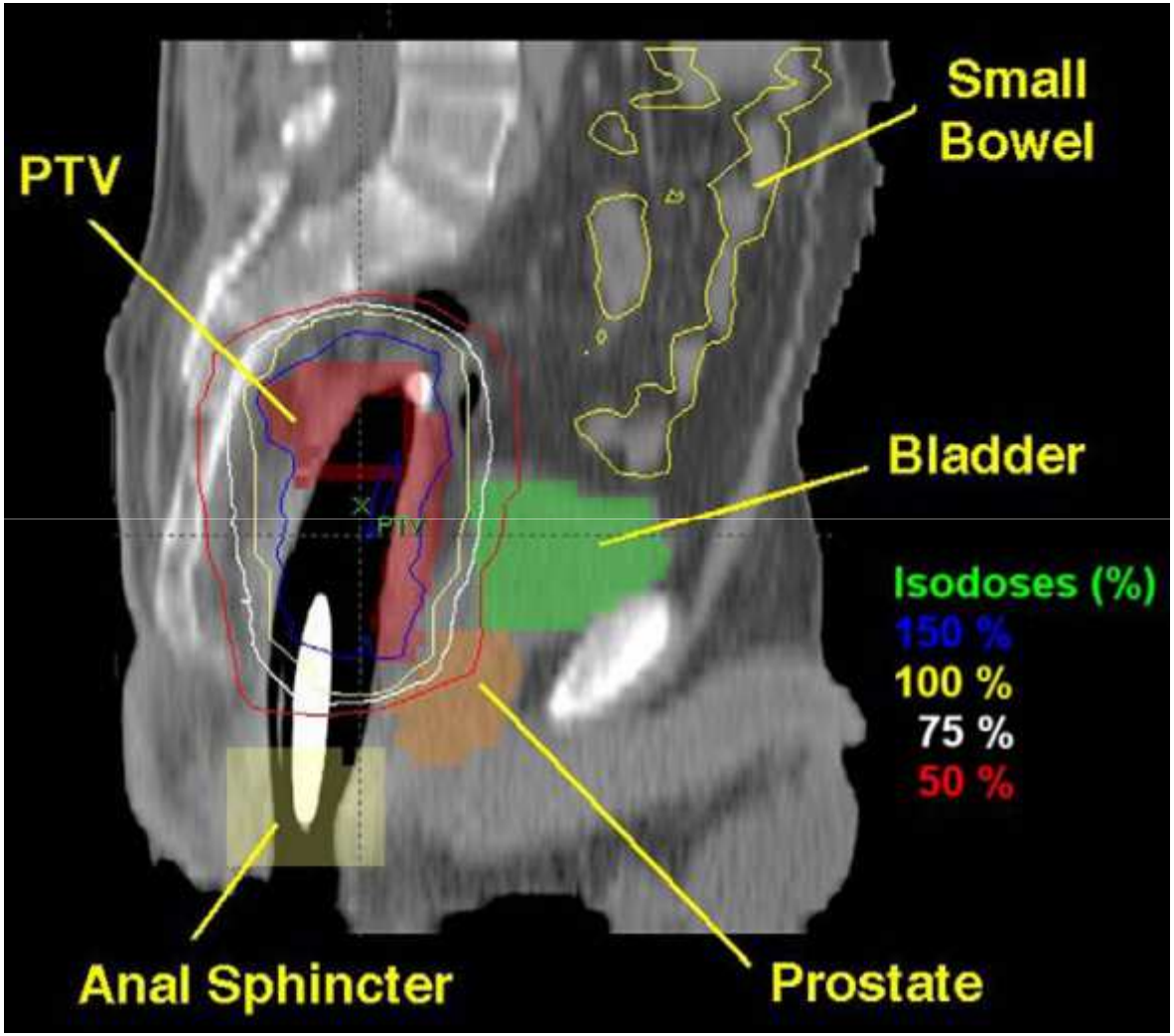
Isodose distribution



Vuong et al. Clin Oncol (R Coll Radiol) 2007;19(9):701–5.

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2. HDR-EBT – Alternative to EBRT

Hesselager:

- Resectable rectal cancer (T1, T2, T3)
- 318 patients: preoperative HDR-EBT (4x 6,5 Gy) → surgery after 4 – 8 weeks
- Matching with Swedish Rectal Cancer Registry:
  - 318 patients SCRT: 5x 5 Gy EBRT
  - 318 patients surgery only

- Purpose: to compare immediate postoperative outcome after EBRT with outcome after HDR-EBT

Hesselager et al. Color Dis. 2013;15(6):662–6.

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2. HDR-EBT – Alternative to EBRT

Variable	HDREBT (n = 318)	SCRT (n = 318)	RT- (n = 318)	P-value HDREBT/SCRT
Cardiovascular	30 (9.4%)	10 (3.1%)	23 (7.2%)	0.002
Infection	30 (9.4%)	26 (8.2%)	20 (6.3%)	0.2
Surgery-related overall	87 (27.4%)	87 (27.4%)	71 (22.3%)	0.3
Wound infection	29	39	19	0.25
Intra-abdominal infection	12	8	9	0.4
Anastomotic dehiscence	13	20	13	0.2
Wound dehiscence	9	8	5	0.4
Reoperation	13 (4.1%)	45 (14.2%)	39 (12.3%)	0.0005

Conclusion:

- **No major differences in postoperative complications when comparing HDR-EBT with SCRT or surgery only.**
- **HDR-EBT appears to be a safe alternative**

Hesselager et al. Color Dis. 2013;15(6):662–6.

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3. HDR-EBT – Boost after EBRT

Dose-Effect Relationship in Chemoradiotherapy for Locally Advanced Rectal Cancer: A Randomized Trial Comparing Two Radiation Doses

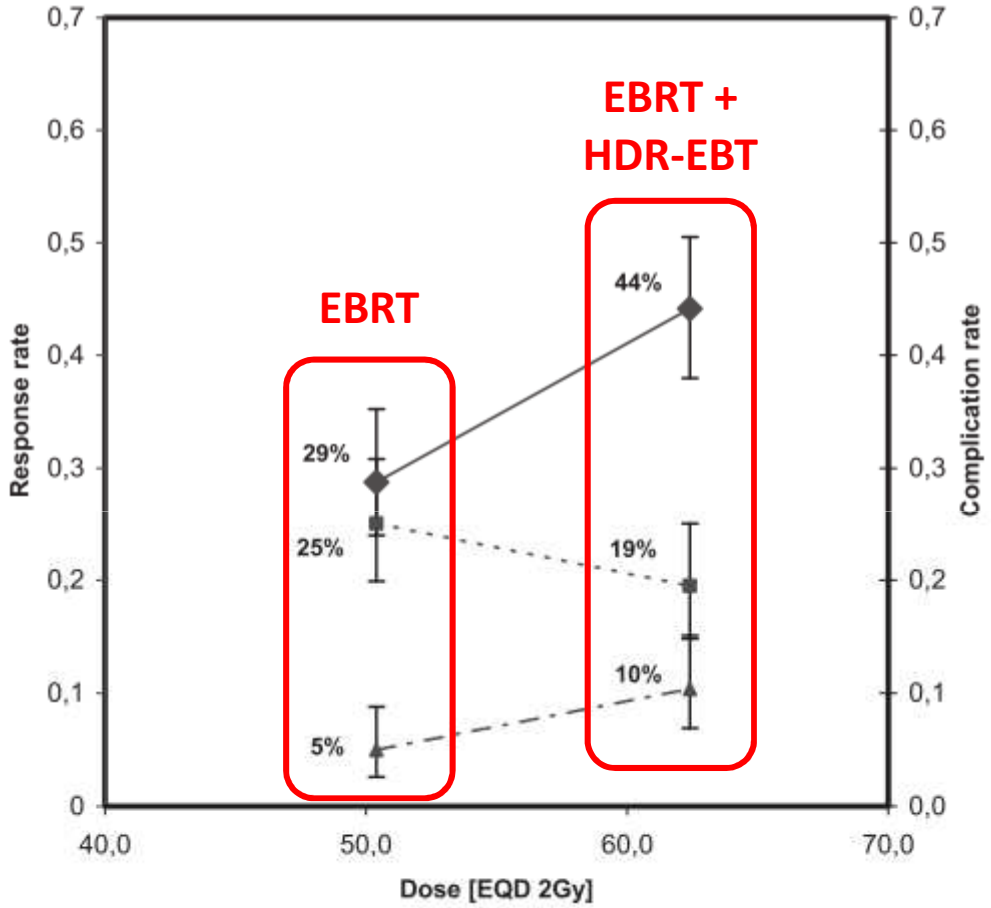
Anders Jakobsen, DMSc,*,† John Ploen, MD,† Té Vuong, MD,‡ Ane Appelt, MSc,*,† Jan Lindebjerg, MD,* and Soren R. Rafaelsen, MD*

- A dose-escalation phase III trial comparing 2 doses of radiation:
  - → 50,4 Gy in 28 fractions (n = 123)
  - → 50,4 Gy in 28 fractions + HDR-EBT boost 10 Gy in 2 fractions (n = 120)
- Both arms concomitant chemotherapy

- **Primary endpoint: pCR**
- Secondary endpoints:
  - → Tumor response
  - → Rate of complete resection

Jakobsen et al. Int J Radiat Oncol Biol Phys;84(4):949–54.

3. HDR-EBT – Boost after EBRT

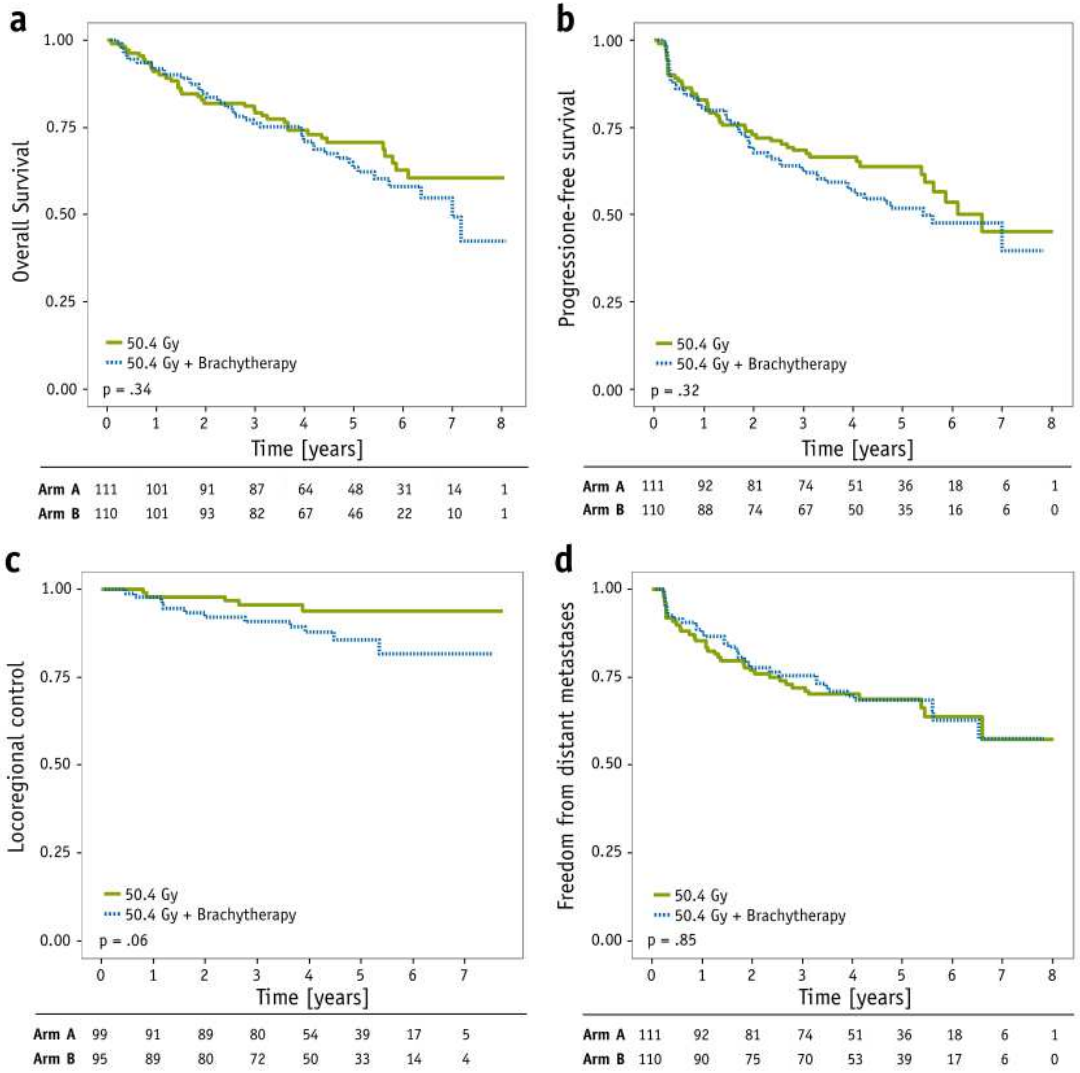


➔ **HDR-EBT boost is feasible without increase in toxicity**

Jakobsen et al. Int J Radiat Oncol Biol Phys;84(4):949–54.

ESTRO School

3. HDR-EBT – Boost after EBRT



Late results (published in 2014)

- No benefit on late outcome (OS, PFS, LC, distant mets)
- Improved tumor regression does not lead to relevant clinical benefit when high-quality surgery is performed

Appelt et al. Int J Radiat Oncol Biol Phys. 2014;90(1):110–8.

ESTRO School

4. HDR-EBT – Palliation

Hoskin:

- HDR-EBT with a single channel applicator
- 50 inoperable rectal cancer patients
  - → Palliation (n=22): HDR-EBT 1x10 Gy
  - → Unfit for surgery (n=26): radical treatment
    - HDR-EBT 6x6 Gy
    - HDR-EBT boost of 12 Gy after 45 Gy/1,8 Gy EBRT+CTx

Table 1
Patient details

Age	
Median	82.3 years
Range	35–91 years
Males	25
Females	25

Hoskin et al, Radiother Oncol 2004;73(2):195–8.

4. HDR-EBT – Palliation

- Local tumor response only available for 25 patients: median duration 7 months
  - 14/25 achieved complete remission
  - 7/25 achieved partial remission
  - 4/25 reached stable disease
- Limited toxicity

➔ **HDR-EBT:**

- **Simple outpatient procedure**
- **Minimal toxicity**
- **Important role in offering effective and durable palliation for the frail elderly**
- **Can be offered in combination with EBRT when surgery is contra-indicated**

Hoskin et al, Radiother Oncol 2004;73(2):195–8.

5. HDR-EBT – Definitive option

Herbert study (presented at ESTRO 2016)

- Dose-finding feasibility study of EBRT + HDR-EBT boost for patients unfit for surgery
- Rectal adenocarcinoma < 15 cm, < 2/3 of circumference, cT2-4 N0-1 M0-1
- Life expectancy ≥ 6 months

Marijnen C., Rijkmans E. LUMC, Leiden, The Netherlands.
Presented at ESTRO 2016

ESTRO School

HDR-EBT – Conclusions

1. **HDR-EBT delivers a high dose to the tumor and a limited dose to surrounding normal tissues**
2. **In resectable rectal cancer, HDR-EBT is a feasible and safe alternative to EBRT**
3. **HDR-EBT can be used as a boost technique after EBRT:**
   - **No increase in toxicity**
   - **No improved outcome (OS, PFS, LC, distant metastases)**
   - **However, higher tumor regression grade potentially interesting for organ preservation strategies**
4. **Effective palliation can be obtained with HDR-EBT, which is a simple outpatient procedure**
5. **In elderly inoperable patients, trials for EBRT + HDR-EBT as a definitive option are ongoing**

Dose constrains for organs at risk, acute/late toxicity, supportive treatment during RT

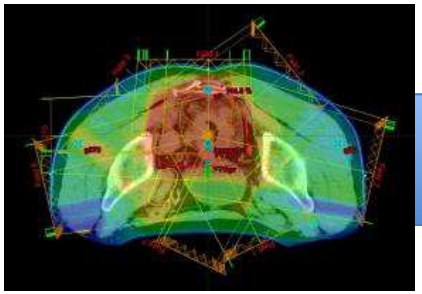
Maria Antonietta Gambacorta

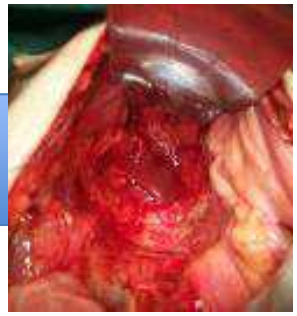
Radiotherapy Department

Fondazione Universitaria Policlinico A. Gemelli

Rectal cancer treatment options

25Gy

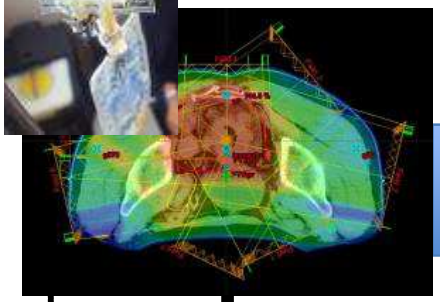


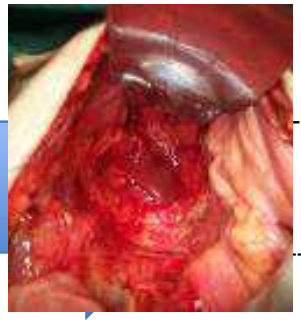


RISK FACTORS

Late toxicity

45- 55 Gy





RISK FACTORS

Acute toxicity

Late toxicity

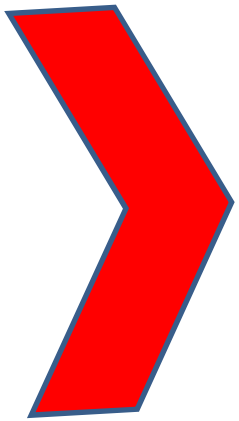
Contributing factors

Therapy's related

RT: Dose/volume, technique
Concomitant CT (5FU, capecitabine)
Surgery

Patient's related

Age, Sex (F>M)
Previous surgery
Comorbidities (diabetes, hypertension, vascular disease…)
Pelvic inflammatory disease
Genetic susceptibility
Behaviour: smoking



TOXICITY

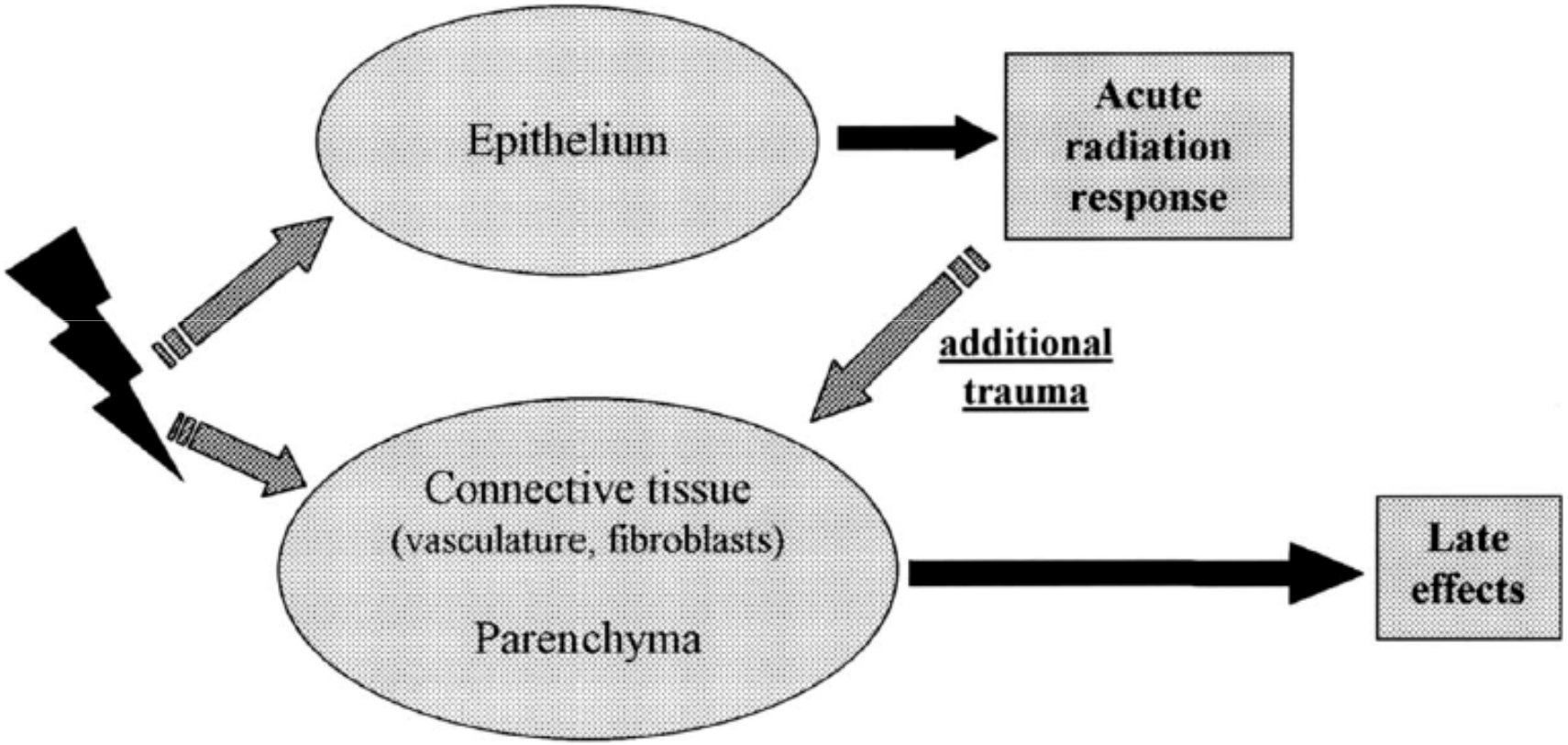
Tumor's related

Tissue distortion, Proteolitic enzymes, Cytokins

Stone HB et al. The Lancet Oncology 2003

Pathogenesis

ACUTE → inflammation, cell loss

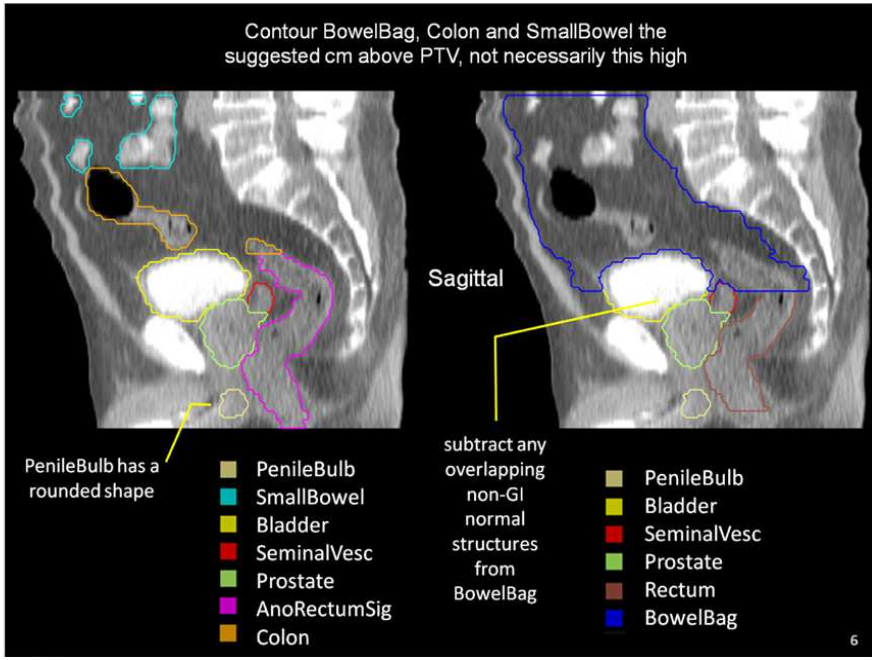


LATE → endoarteritis-hypoxia-fibrosis

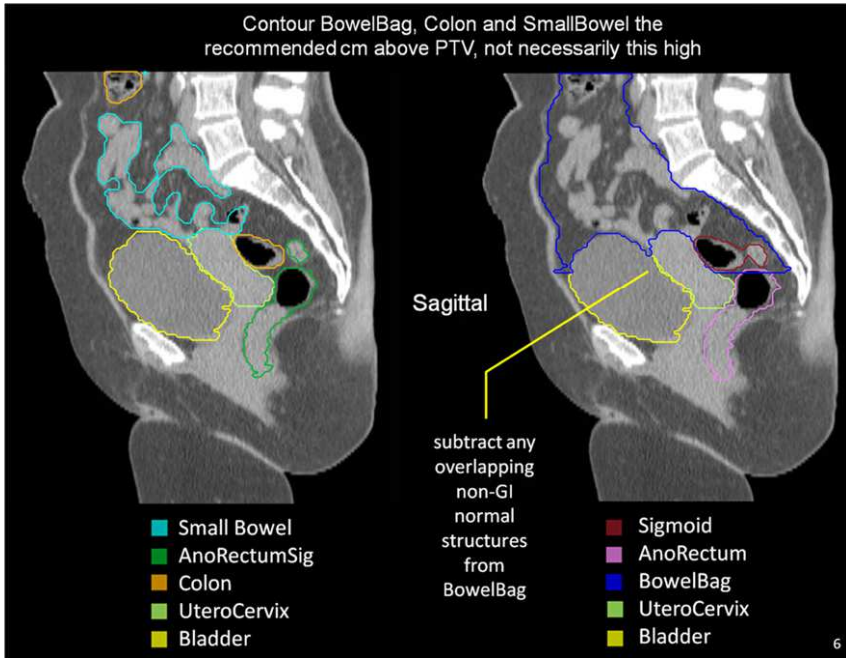
Joiner & van der Kogel: Basic Clinical Radiobiology-4° edition

Organ at Risk in rectal cancer

male



female



Gay HA et al. Int J Radiat Oncol Biol Phys, 2012

Small bowel enteritis

Small bowel Toxicity

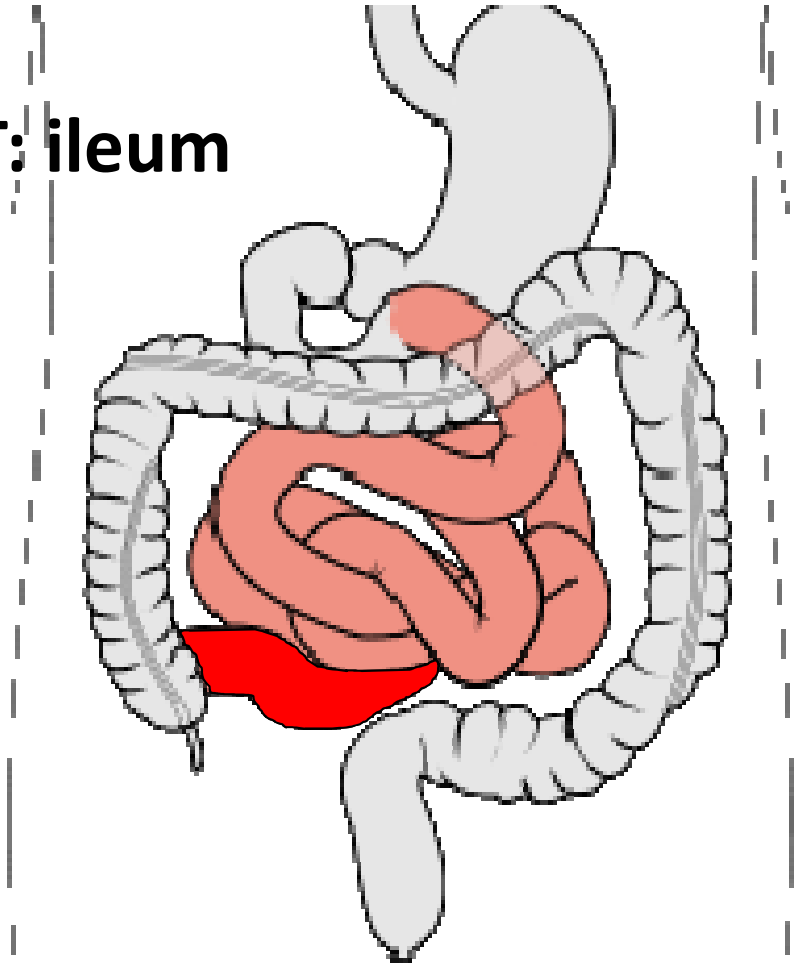
- **Acute SB toxicity**
  - Any grade **20-70%**

- **Late SB toxicity**
  - Any grade: **5-30%**
  - **65%** long survivor patients

Acute Small Bowel toxicity

@ the 2nd II week of treatment → month after treatment

Most frequent site in pelvic RT: ileum



Symptoms:

- Abdominal pain (cramps)
- Diarrhea
- Nausea
- Lack of appetite
- Weight loss

Andreyev HJ. Clin Oncol.2007 **Ruiz-Tovar.** J,Clin Transl Oncol 2009

Acute SB Toxicity: pathogenesis

DAMAGE

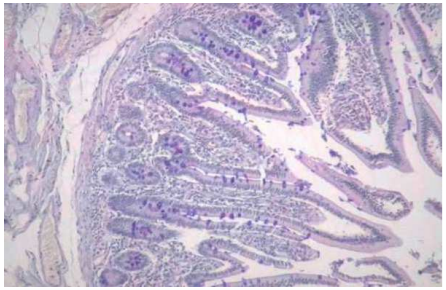
↓

ADSORPTION

↓

SYMPTOMS

Distortion of the villous → enzymatic deficit→ decreased capability to digest macromolecules in the intestinal lumen



Accumulation of **glucides e peptons** retains osmotically fluids in the bowel lumen. **Osmotic DIARRHEA**

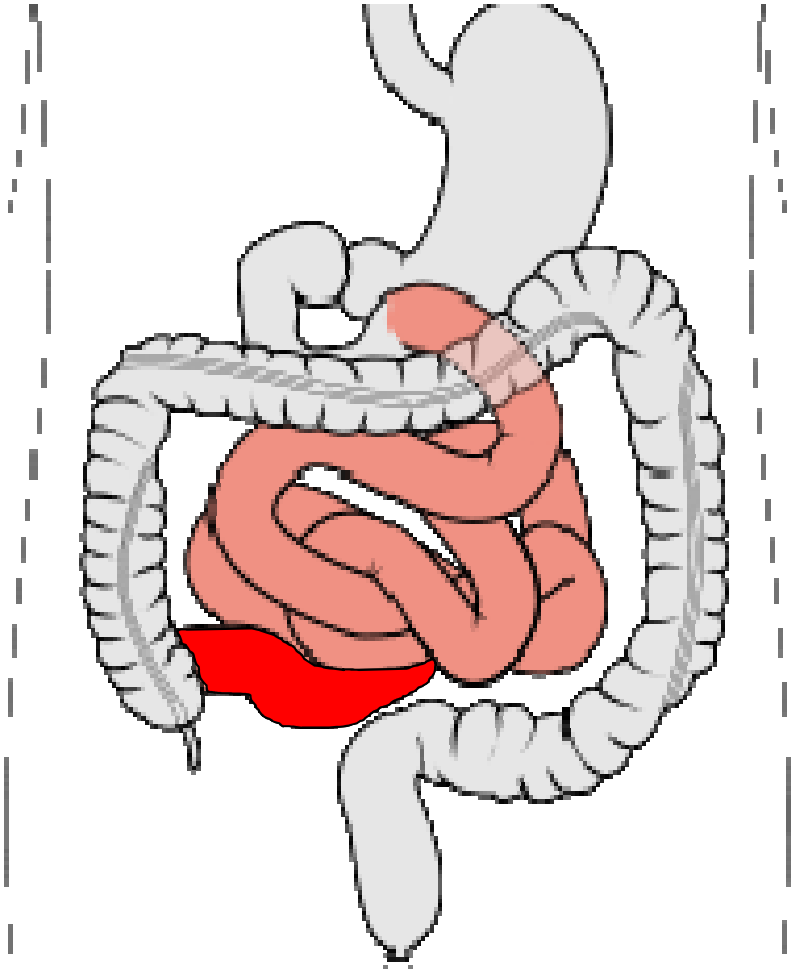
Increase of **organic residues** with **ph reduction** → reduced adsorbtion of electrolites, gas production, endotoxin secretion. **METHEORISM, CRAMPS, PAIN**

Increase of the intraluminal fats → decreased absorption of biliary salts→ Direct mucolytic action, increased cellular permeability and sodium trasudation
Hyperperistaltism → Reduction of the transit time
Increased pathogenic bacterial. Aqueous DIARRHEA

loss of appetite, weight loss, electrolyte imbalance…

Late Small Bowel toxicity

- **Time:** 18 mths - 6 yrs after treatment. Cases also after 15 yrs
- **Incidence:** increased with survival, reported 1/5 patients
- **Underestimated**
- **Cause:** RT dose and volumes.
- **Medical treatment**: 55% of symptomatic pts requires medical treatments



Game B. Aliment Pharmacol Ther 2003

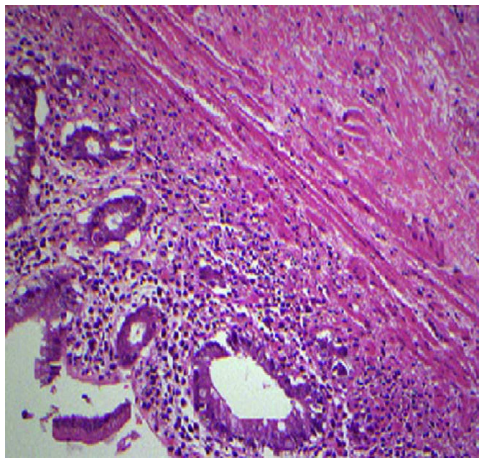
Late SB Toxicity: pathogenesis and symptoms

DAMAGE

- Vascular degeneration (endoarteritis)
- Collagen production/deposition
- Damage of the lymphatic vessels

- Ischemia
- Intestinal wall edema
- Mucosal ulcer
- Intestinal wall necrosis
- Hemorrages
- Strictures/Stenosis
- Adherences

SYMPTOMS



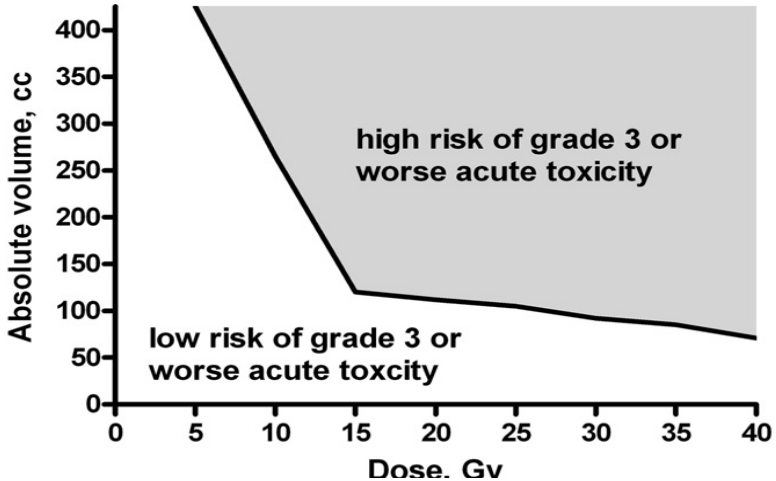
Sub-mucosal fibrosis, atipical fibrobasts, inflammatory infiltration, increased size of the endotelial cells

- Intestinal transit alterations: PAIN and CRAMPS
- Alternating STIPSIS and DIARRHEA
- Maladsorption syndrome, FOOD INTOLEREANCE
- Bleeding and anemia

Management during therapy
Acute enteritis

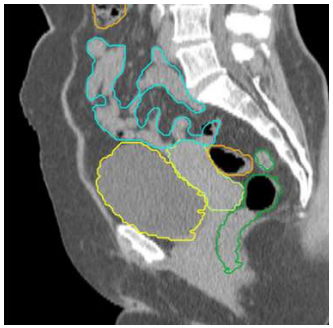
- **Prevention**
- **Therapy**

Prevention: Dose constraints



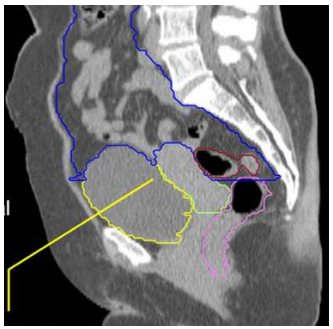
SET-UP

Bowel loops



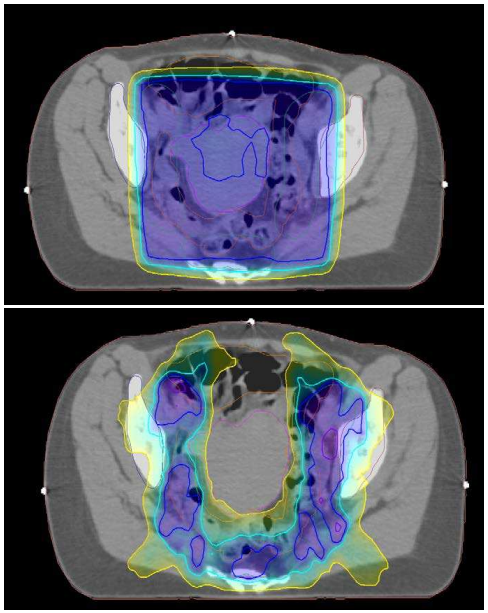
V15 = 120 cc

Bowel bag



V45 = 195 cc

Planning



Small bowel displacement

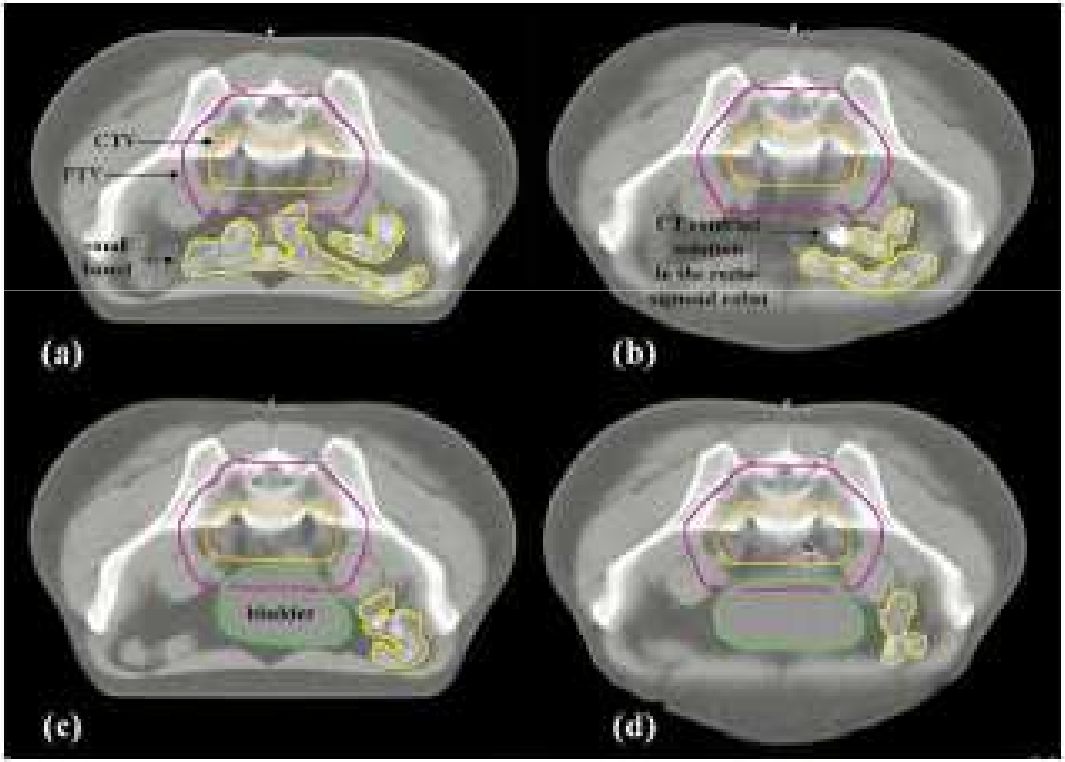
full bladder

belly board/false table-top

Displacement devices

belly board vs full bladder:

prone



BBD

FB

FB & BBD

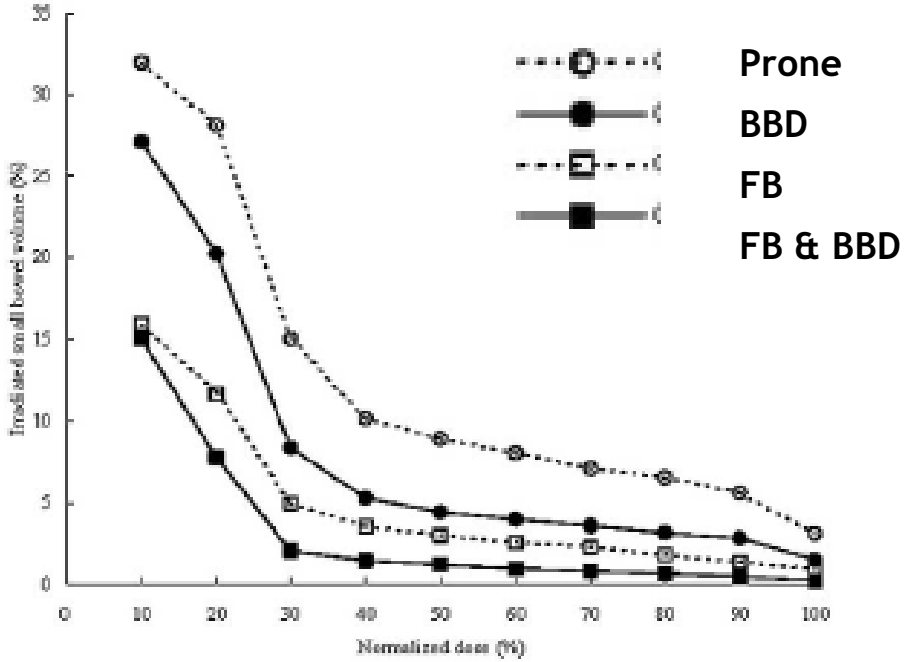
PRE-operative RT

Kim TH. IJROBP 2005

Displacement devices

belly board vs full bladder:

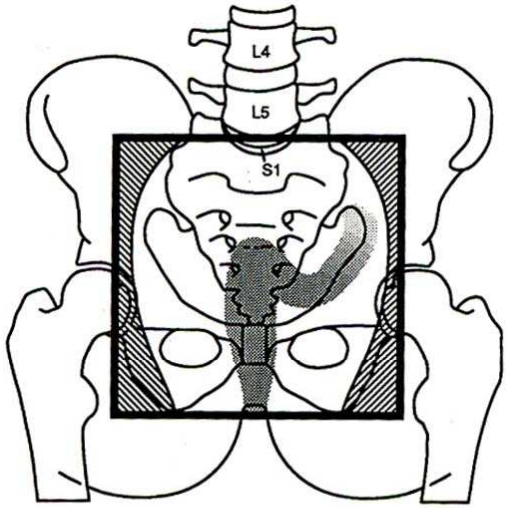
Belly-Board+Full-Bladder >Full-Bladder > Belly-Board

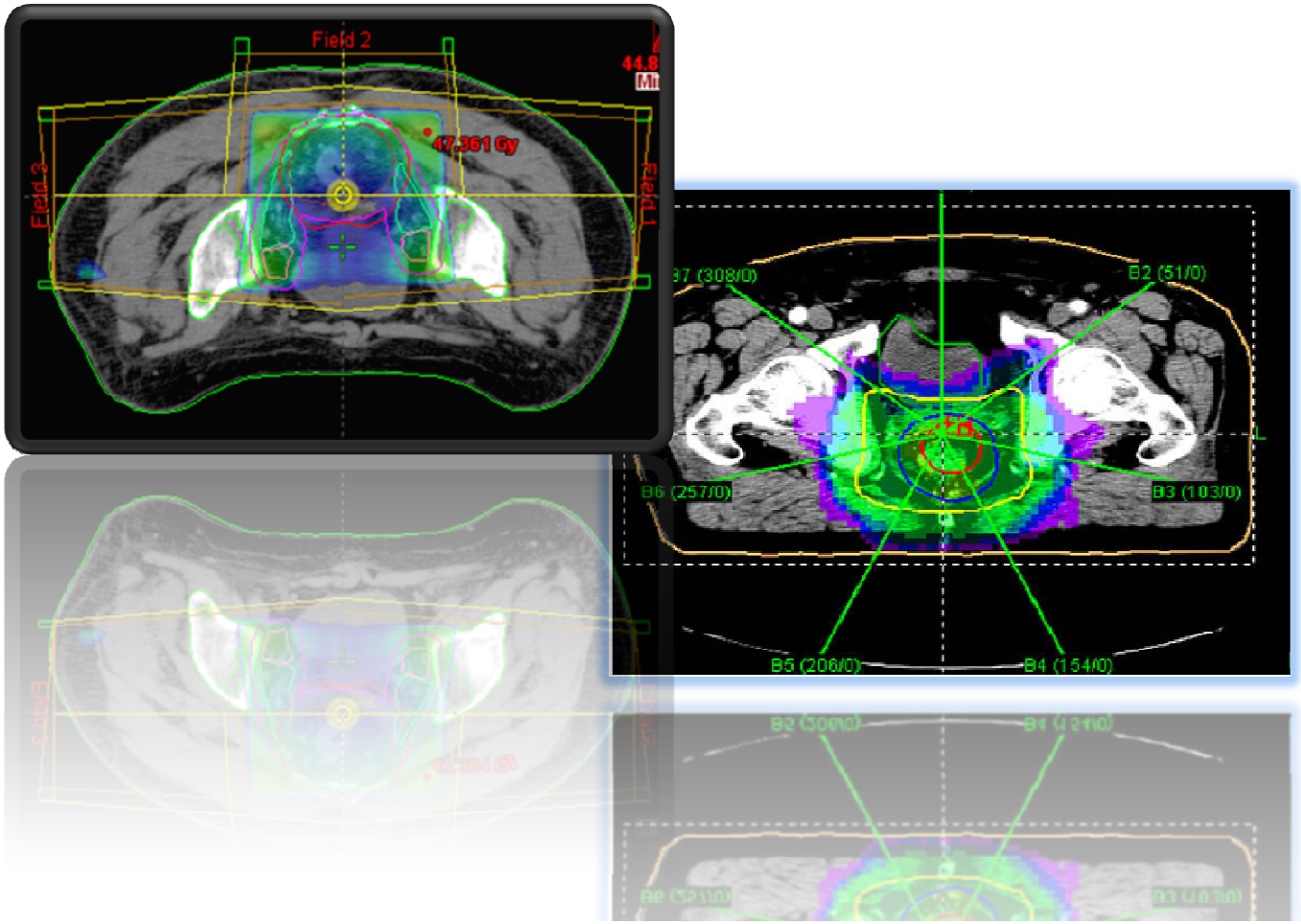


PRE-operative

Kim TH. IJROBP 2005

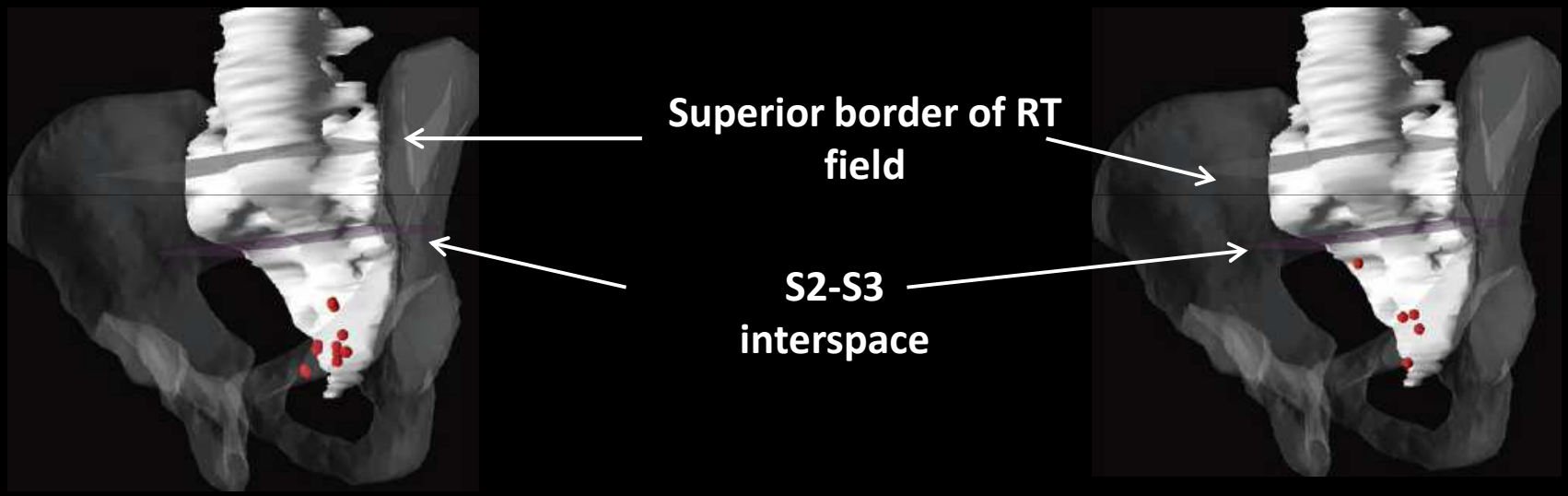
Technique


L4
L5
S1


Field 2
47.361 Gy
Field 3
Field 1
B2 (51/0)
B6 (257/0)
B3 (103/0)
B5 (206/0)
B4 (154/0)

CTV reduction

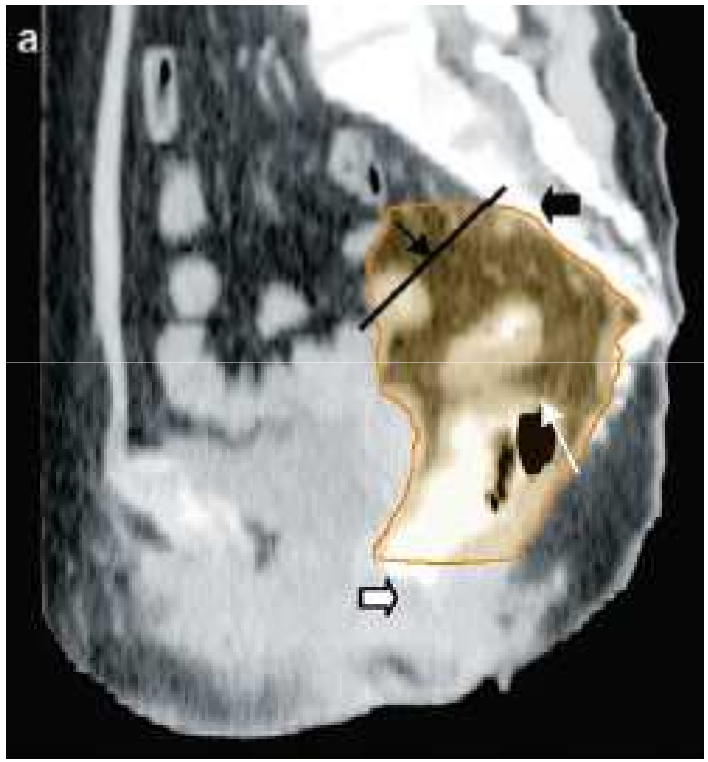
Local recurrences: 2/3 in the lower of the pelvis.
CRM- and NODE NEGATIVE: all LR below S2-3 interspace



Nijkamp et al IJROBP 2011

CTV reduction

cranial border to S2-S3 interspace → **reduction of 60% of SB exposure at doses 15-35 Gy**



Nijkamp et al IJROBP 2011

Prevention: Diet

AVOIDANCE

- Fibers → poorly adsorbed →laxative effect
- Lactose → villous damage → loss of lactase
- Fat → release bile salts→ damage

Liu L et al. Int J Radiat Oncol Biol Phys 1997

Wedlake L et al., Eur J Cancer 2008

Prevention: Diet

Metanalysis on 22 studies with 2246 pts 37% good qualiy studies

Table 1 | Summary of interventions and effects: RCT studies only

Reference	Study design: Intention RCT/CT	Quality Score	Intervention	Effect of intervention on GI toxicity end-points
Elemental formulae				
35	RCT Open-label: Preventative	7	Low-fibre diet vs. low-fibre diet plus elemental formula (900kcals/d)	No difference compared to low-fibre diet
36	RCT Open-label: Preventative	4	Standard diet vs. natural diet plus elemental formula (33% TE)	Improved outcomes compared to standard diet
37	RCT Open-label: Preventative	10	Normal diet vs. normal diet with elemental formula (33% TE)	No difference compared to normal diet
38	RCT Open-label: Preventative	7	Low-fibre diet vs. low-fibre diet plus elemental formula (900 kcals/d)	No difference compared to low-fibre diet
Low- or modified-fat diets				
21	RCT Open-label: Preventative	8	Normal diet vs. low-lactose low-fat diet (40 g/d)	Improved outcomes compared to normal diet
25	RCT Double-blind placebo: Therapeutic	12	Low-fat diet (40 g/d) plus placebo vs. low-fat diet (40 g/d) plus cholestyramine	Improved outcomes compared to placebo
41	RCT Open-label: Preventative	3	Low-fat diet (20 g/d) vs. low-fat diet (20 g/d) plus MCT supplement (50% TE)	Improved outcomes compared to normal diet
42	RCT Open-label: Preventative	13	Normal diet (LCT 40% TE) vs. Low-fat (LCT 20%) vs. Low-fat (LCT 20%) plus MCT (20%)	No difference compared to normal or MCT-supplemented diet
Low- or high-fibre diets				
43	RCT Open-label: Crossover: Therapeutic	9	Standard medication (codeine phosphate) vs. fibre supplement (psyllium)	Worse outcome for fibre supplement compared to medication
45	RCT Open-label: Preventative	8	Low-fibre and fat (LFF) diet vs. LFF diet plus fibre supplement (psyllium)	Improved outcomes compared to low-(dietary) fibre low-fat diet
Low-lactose diets				
48	RCT Open-label: Preventative	6	Normal lactose vs. low-lactose vs. normal lactose plus enzyme	No difference between groups
Probiotics and Synbiotics				
49	RCT Open-label: Preventative	5	Low-fibre, fat and lactose(LFFL) diet vs. LFFL diet plus synbiotic	Improved outcomes compared to LFFL diet alone
50	RCT Double-blind placebo: Therapeutic	14	Placebo vs. probiotic	No difference compared to placebo
51	RCT Double-blind placebo: Preventative	5	Placebo vs. probiotic	Improved outcomes compared to placebo
52	RCT Double-blind placebo: Preventative	12	Placebo vs. probiotic	Improved outcomes compared to placebo
53	RCT Double-blind placebo: Preventative	12	Placebo vs. probiotic	Improved outcomes compared to placebo

Elemental Formula : 1/4 positive

Low-fat diet: 3/4 positive

Fibers diet: 1/2 positive

Low lactose diet: 0/1 positive

Pro-biotics: 3/5 positive

Wedlake LJ et al. Aliment Pharmac Ther2012

Prevention: probiotics

PROBIOTICS:

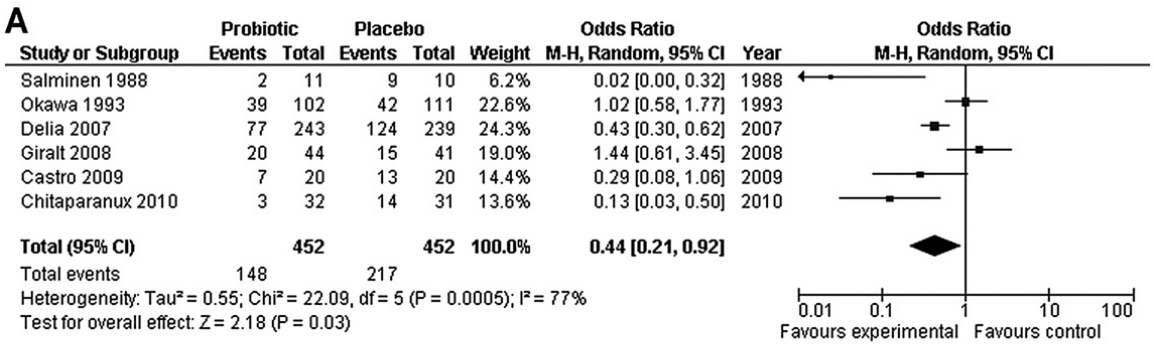
- live micro-organisms which when administrated in adequate amounts confer a health **benefit on the host**. They iclude LACTOBACILLI and BIFIDOBACTERIA

ACTION:

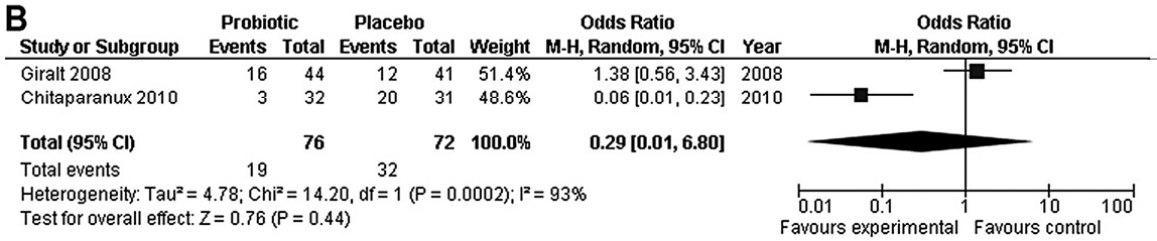
- inhibition of epithelial and **mucosal adherence of pathogens**
- induction of lower colonic pH favouring the **growth of non-pathogenic** species
- stimulation of **immunity**
- production of **antimicrobial substances**
- Enhance **barrier function/integrity**: mucous production-short fatty acid (butyrrate)

Hamaad A Clin Nutr 2013

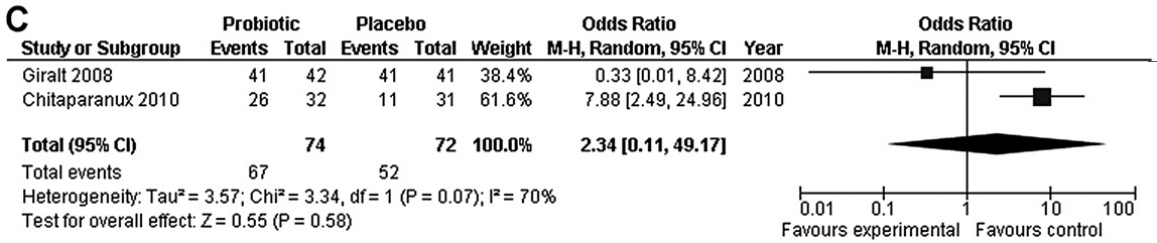
Prevention: probiotics



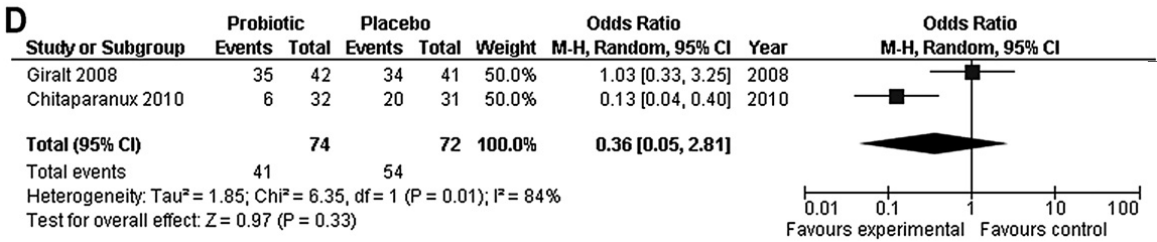
Diarrhea



Loperamide use



Soft stool



Watery loose

Hamaad A Clin Nutr 2013

Treatment of diarrhea

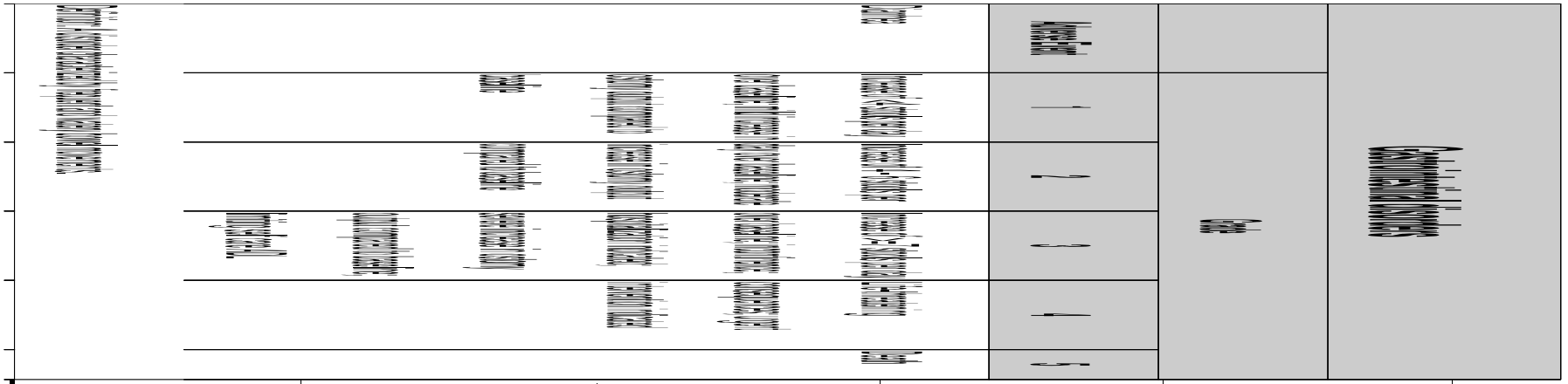
Rehydration: oral or i.v.

Loperamide: opioid with local action decreasing bowel motvements → intestinal transit, bile salt adsorpion→ diarrhea

Octreotide: somatostanine analogue inhibiting secreting diarreha

5-ASA (mesalazine): anti-inflammatory action

Antibiotics: doxicicline, metronidazole



Therapy	Probiotics and diet Monitor electrolytes	Probiotics and diet loperamide, mesalazine Monitor electrolytes, oral hydration	Probiotics, loperamide, mesalazine, antibiotics Monitor electrolytes, iv hydration	hospitalization

Rectum proctitis

Proctitis

RECTUM is a TARGET, NOT an OAR

ACUTE: 15-30%

CHRONIC: 2-20%

O'Brian PC et al. IJROBP 2004

Proctitis: symptoms

Swelling
Prolapse

Itch

Abdominal cramps

Burning Pain

Urgency
Incontinence

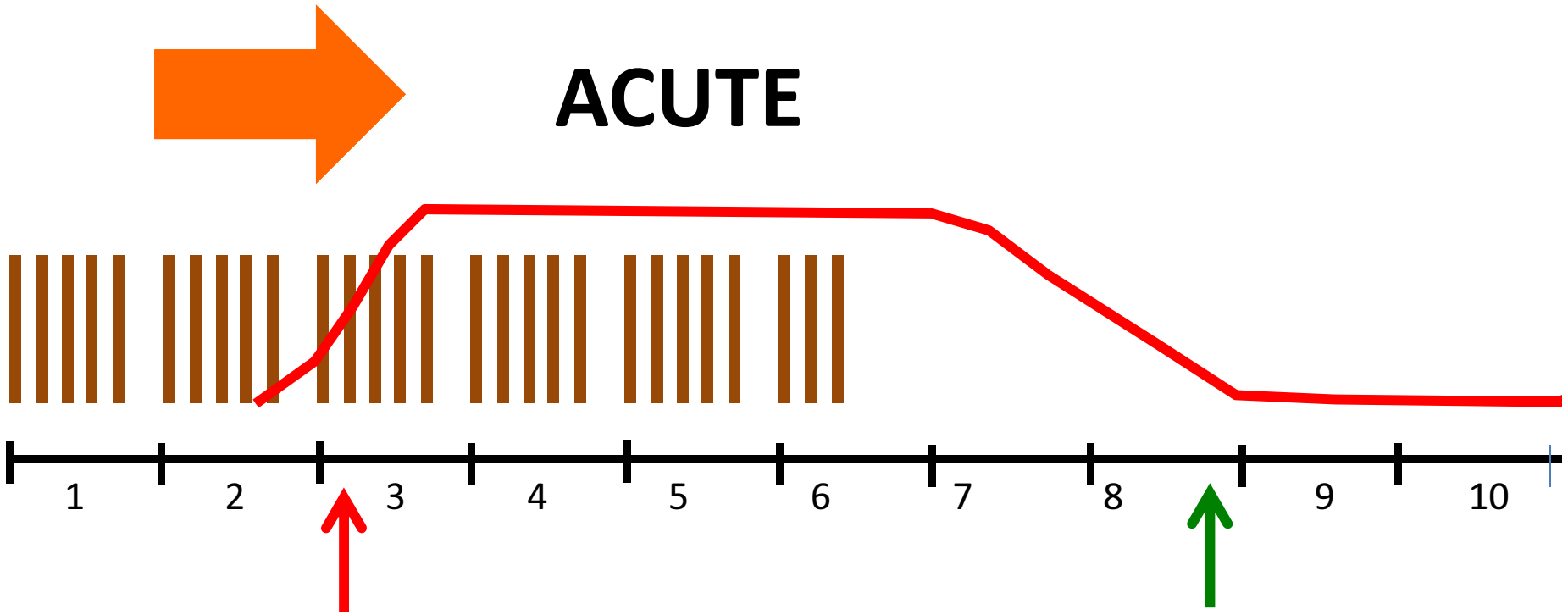
Mucous discharge

Soft stools
Diarrhea

Stipsis

Bleeding

Proctitis



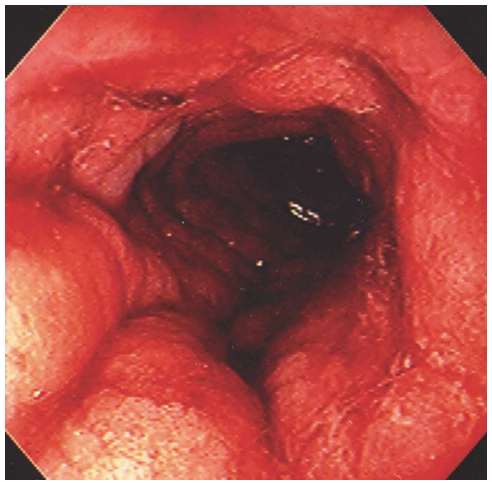
Onset: **2-4 wks** from the start of RT

Resolution: **1-2 wks from the end** of RT

Do NL et al. Gastroent. Res Pract 2011

proctitis

ACUTE



Endoscopic appearance

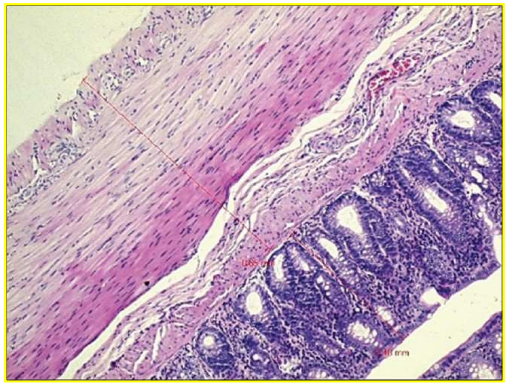
- ✓Edema
- ✓Erythema
- ✓Friability of the mucosa
- ✓Erosions

Courtesy Dott. G. FANELLO

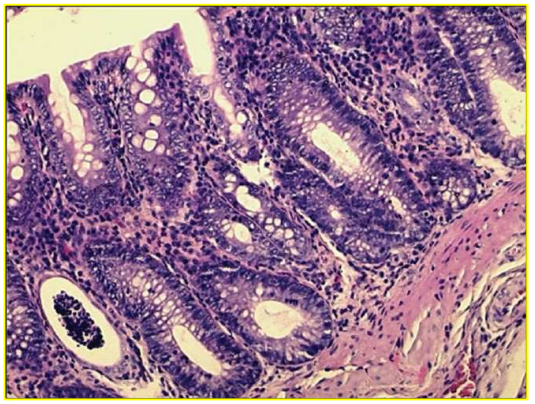
Proctitis

ACUTE

HISTOLOGICAL appearance



- Absence of mitotic activity
- Loss or architectural distortion of the microvilli
- Inflammatory Infiltration of the mucosa
- Cryptic abscesses
- Dilation of vessels



Courtesy Dott. G. FANELLO

Acute Proctitis management

Support Care Cancer (2013) 21:313–326
DOI 10.1007/s00520-012-1644-z

SPECIAL ARTICLE

Systematic review of agents for the management of gastrointestinal mucositis in cancer patients

Rachel J. Gibson · Dorothy M. K. Keefe · Rajesh V. Lalla · Emma Bateman · Nicole Blijlevens · Margot Fijlstra · Emily E. King · Andrea M. Stringer · Walter J. F. M. van der Velden · Roger Yazbeck · Sharon Elad · Joanne M. Bowen · For The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO)

- **Systematic Literature Review:** '251 Analyzed papers'
- **Type cancer therapy:** RT, CT, HDCT for TMO
- **Intervention goal:** prevention, therapy
- **Route of administration:** oral, topical, intravenous

Acute Proctitis: prevention

Hyaluronic Acid (component of the extracellular matrix, contributes to cell proliferation and migration) topical from the start of RT → **delay**

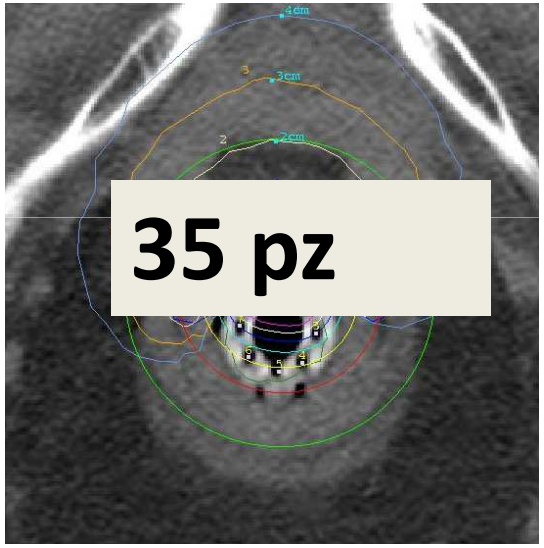
Amiphostine (free-radical scavenger) ev injection → **prevention**

Basalazide (anti-inflammatory) oral pro-drug converted in 5-ASA by the colonic bacteria: 5 days before therapy up to 2 wks after therapy → **reduction**

Gibson RJ et al. Supp Cancer Care 2013

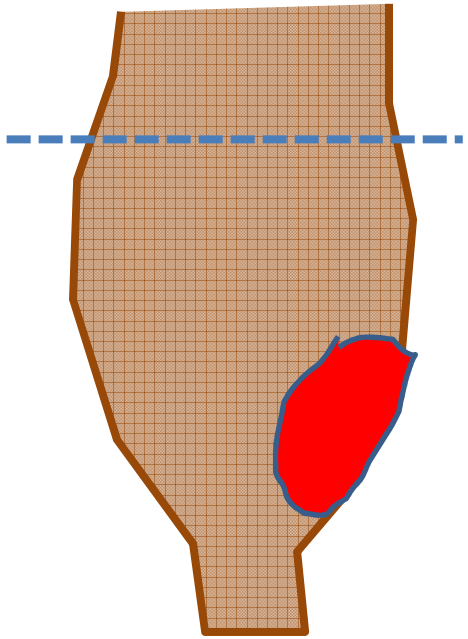
Acute Proctitis: prevention (HDR)

HDR preop RT

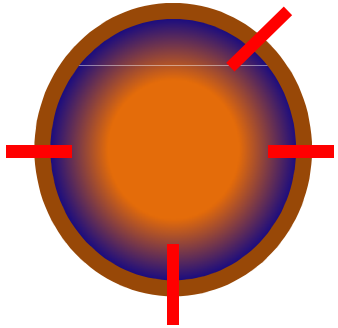


26 Gy 4 frx

Botox injection after last HDR



15 pz
BOTOX



dose escalation: 25 U; 50 U; 100 ; 150 U

Vuong T et al. IJROBP 2011

Acute Proctitis: prevention (HDR)

MTD: 100 U

Anal-pain score 1-10

Table 1. Anal pain score

Dose level (U)	Adjusted mean (SE)	Contrast
150	3.94 (0.67)	
100	1.26 (0.54)	<150 U ($p = 0.002$) <50 U ($p = 0.016$) <25 U ($p = 0.014$) <Control ($p = 0.078$)
50	3.35 (0.62)	
25	3.28 (0.62)	
Control	2.88 (0.26)	

Bowel frequency

Table 2. Bowel frequency

Dose level (U)	Adjusted Mean (STD)	Contrast
150	42.5 (4.7)	> Control ($p = 0.034$)
100	18.3 (3.4)	< 150 U ($p < 0.001$) < 50 U ($p = 0.006$) < 25 U ($p = 0.022$) < Control ($p = 0.016$)
50	34.9 (3.9)	
25	31.9 (3.9)	
Control	29.7 (2.3)	

Vuong T et al. IJROBP 2011

Proctitis toxicity scale CTCAE v.04

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
P R O C T I T I S	Rectal discomfort, intervention not indicated	Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Acute Proctitis: therapy

Topic steroids → RESOLUTION of ACUTE SYMPTOMS (burning, pain, mucous…)

Mesalazine (5-ASA) oral 3/day + topical 1/day

→ **REDUCTION** of hemorragic proctitis,

→ NO ACTION on pain, tenesmus or frequency of defecation

Sucralphate: Sucrose sulfate-aluminium complex that binds to the ulcer, creating a physical barriers

→ **ACTIVE** in chronic proctitis

→ **small**/no EFFECT in ACUTE proctitis

Sodium Butyrate: short chain fatty acid, produced by colon bacteria, increasing blood flow and mucosal integrity

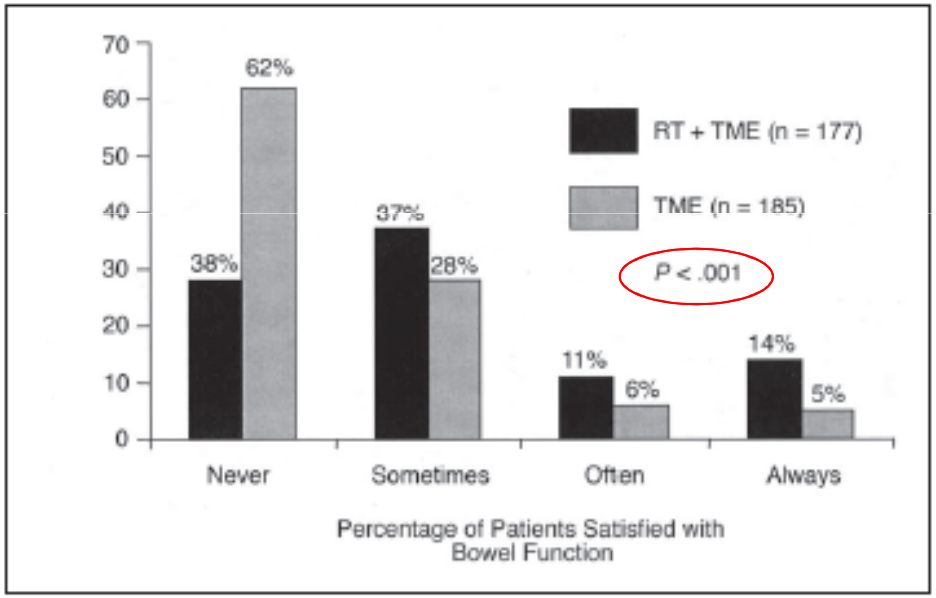
→ **small EFFECT** vs PLACEBO in ACUTE PROCTITIS

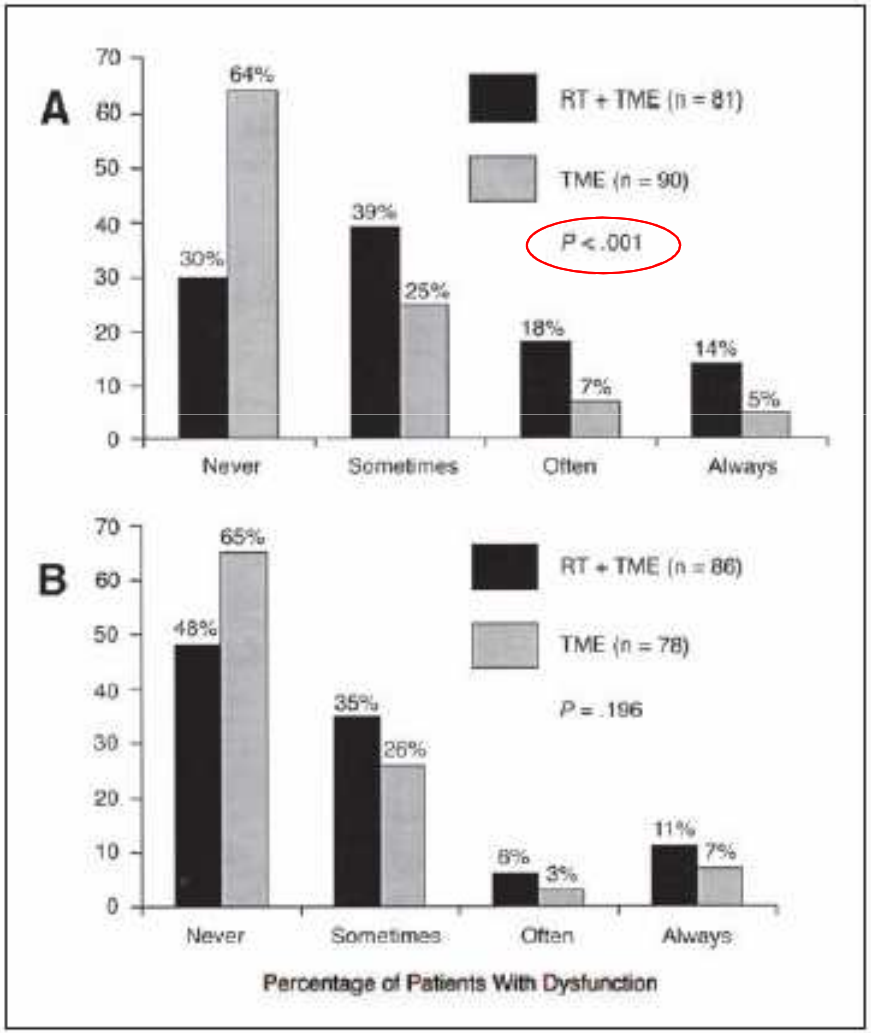
Gibson RJ et al. Supp Cancer Care 2013

INCONTINENCE

Bowel funtion: incontinence

Dutch Trial



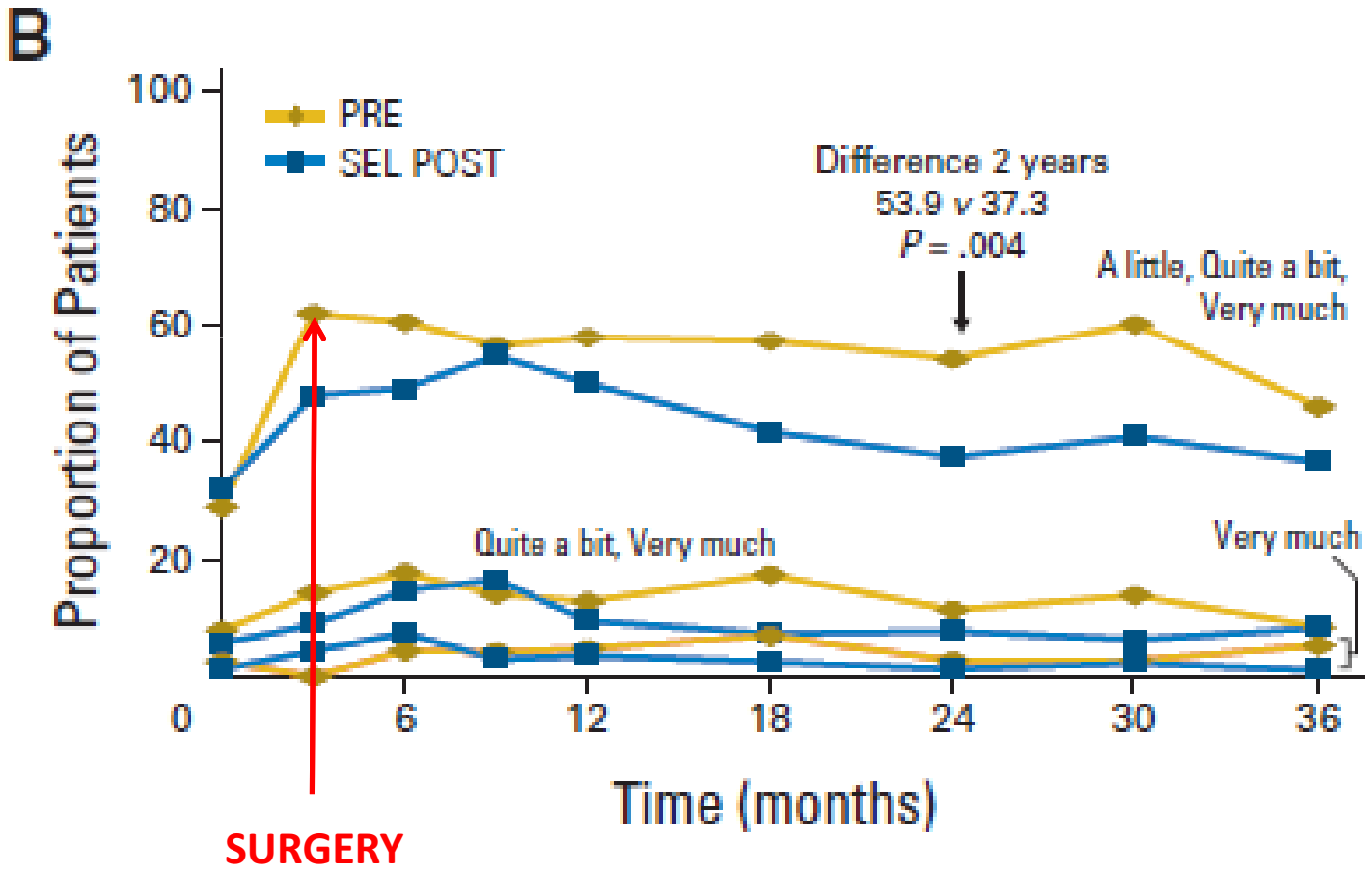


A: mid rectum (5-10 cm)
B: high rectum (10-15 cm)

Peeters et al JCO 2005

Unintentional release of stool

MRC-CR07 trial



Stephens et al JCO 2010

Bowel QLQ-C30 (no stoma)

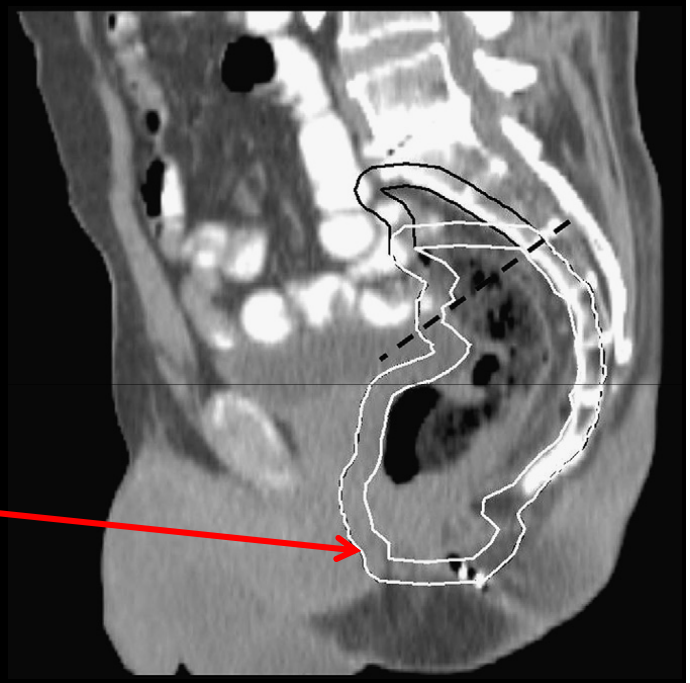
Treatment	Incontinence for liquid	Incontinence for gas
RT	38%	56%
RT-CT	58%	75%
Treatment	**Good function**	**P**
RT	30%	0.046
RTCT	11%	

Braendegen et al IJROBP 2011

CTV reduction: sphincter

Anal canal inclusion in CTV → incontinence

Anal canal in CTV	Y	N	p
incontinence	93%	65%	0.059



Inferior limit → avoid anal sphincter and IRF when not invaded

DISTAL MARGIN from the tumor
High → T + 4 cm margin of mesorectum
mid-low → entire mesorectum

Lange MM et al.Br J Surg 2007
Nijkamp et al IJROBP 2011
Bujiko *Multidisciplinary Management of Rectal Cancer 2012*

SEXUAL FUNCTION

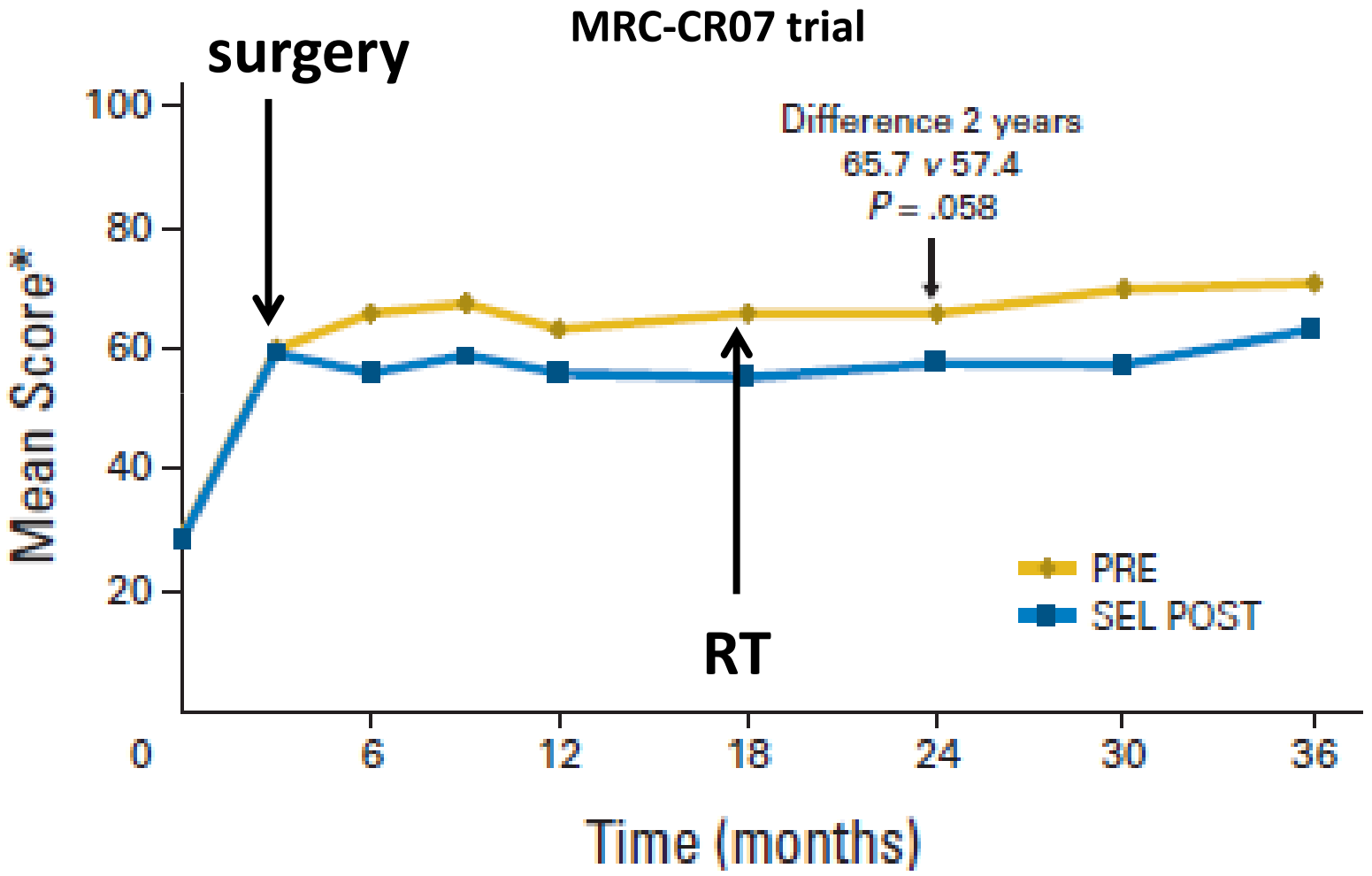
Sexual function: SC-RT

Dutch trial

SEXUAL ACTIVITY (pts active before therapy)	Sex	TME	RT-TME	p
	Male	76%	67%	0.06
	Female	90%	72%	0.01

Marijnen et al JCO 2005

Sexual function (male*)



*Only 11% of women completed the questionnaire at 2 yrs

Stephens et al JCO 2010

Male sexual function: IIEF (LC-RT)

	CRT ($n = 26$)	RT ($n = 18$)	Maximum points on IIEF questionnaire
Age (y)	66 (42–79)	64 (51–78)	
Erectile function*	6.9 (1–29)	10.4 (1–29)	30
Orgasmic function	2.6 (0–10)	3.9 (0–10)	10
Sexual desire	4.8 (2–8)	5.6 (2–9)	10
Intercourse satisfaction	2.7 (0–13)	4.2 (0–13)	15
Overall satisfaction	4.5 (1–9)	4.9 (1–9)	10

***1-10: severe dysfunction**

11-16: moderate dysfunction

17-21: mild to moderate dysfunction;

22-25: mild dysfunction;

26-30: no dysfunction

Braendegen et al IJROBP 2011

Female sexual function (LC-RT)

- < 50% sexually active during the last month
- vaginal dryness during intercourse
- Low interest in sex
- Sex doesn’t affect their life

Braendegen et al IJROBP 2011

CTV: sexual

Anterior limit

Exclude inferior part of the vagina (Bartolini glands)

Inferior limit: penile bulb

D 70	Erectile dysfunction
0-40 Gy	0%
40-70 Gy	80%
>70 Gy	100%

Fish et al Urology 2001

Bujiko *Multidisciplinary Management of Rectal Cancer 2012*

Conclusions

- Acute toxicity → treatment interruptions, QoL
- Late toxicity → Long survivors, QoL
- Medical therapy → symptomatic
- Prevention
  - Set-up → Belly board, bladder filling
  - IMRT → possibility of avoidance of OARs
  - Delineation of OAR → fundamental
  - CTV/field borders→ modulation according T stage
  - Medical prevention → not conclusive results

CYSTITIS

Cystitis

ACUTE: 25-30%

CHRONIC: 20%

(9% recurrent macro-ematuria)

Cystitis

Diyuria

Pollachiuria

Urgency

Burning

Incontinence

Pain

Obstruction

Bleeding

Acute cystitis: prevention

Crumberry
D – Mannose
Probiotics

- ✓ **E.Coli anti-adhesion**
- ✓ **Dose 300 mg/die (2juice glasses/day)**
- ✓ **Clinical benefit: hours**
- ✓ **Duration: 10 h**

Decrease use of antibiotics

Cowan CC et al. Clinical Oncol 2012

Acute cystitis: prevention

crumberry

RCT double blind

Group 1:
Crumberry *

Gruop 2:
PLACEBO

*juice twice a day

6 weeks

Evaluation

Diary of symptoms, urine samples

Cowan CC et al. Clinical Oncol 2012

Acute cystitis: prevention

Crumberry

128 pz

Patients in the compliant population who experienced an increase in urinary symptoms or d… infection at any time during treatment and follow-up

Increased urinary symptoms or Worst grade of urinary symptoms experienced during treatment and follo… Arm

Worst grade of urinary symptoms experienced during treatment and follow-up	Intention-to…		Compliant population			
	Arm		Arm			
		Placebo	Cranberry		Placebo	
		Count %	Count	%	Count	%
0	3.5%	6 10.5%	0	0.0%	1	7.1%
1	31 54.4%	20 35.1%	13	72.2%	7	50.0%
2	17 29.8%	17 29.8%	3	16.7%	3	21.4%
3	7 12.3%	14 24.6%	2	11.1%	3	21.4%
Total	57* 100.0%	57* 100.0%	18	100.0%	14	100.0%

Not significant!

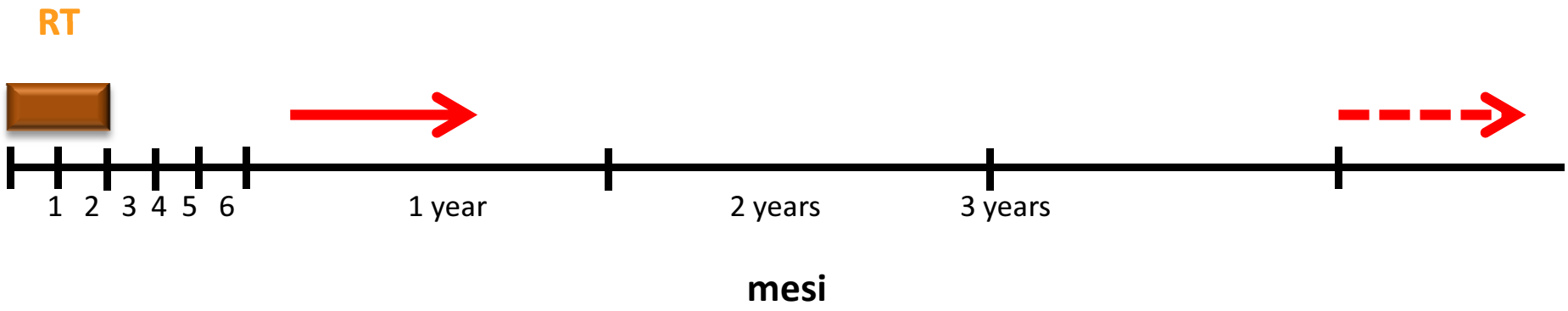
Cowan CC et al. Clinical Oncol 2012

Acute cystitis: therapy

Symptomatic

- ✓ **Phenazopyridine hydrochloride: pain, urgency**
- ✓ **Anticholinergic drugs: spams**
- ✓ **Flavoxate hydrochloride: muscle relaxant**
- ✓ **alpha1-adrenoreceptor blockade: smooth muscles relaxant**

Chronic cystitis

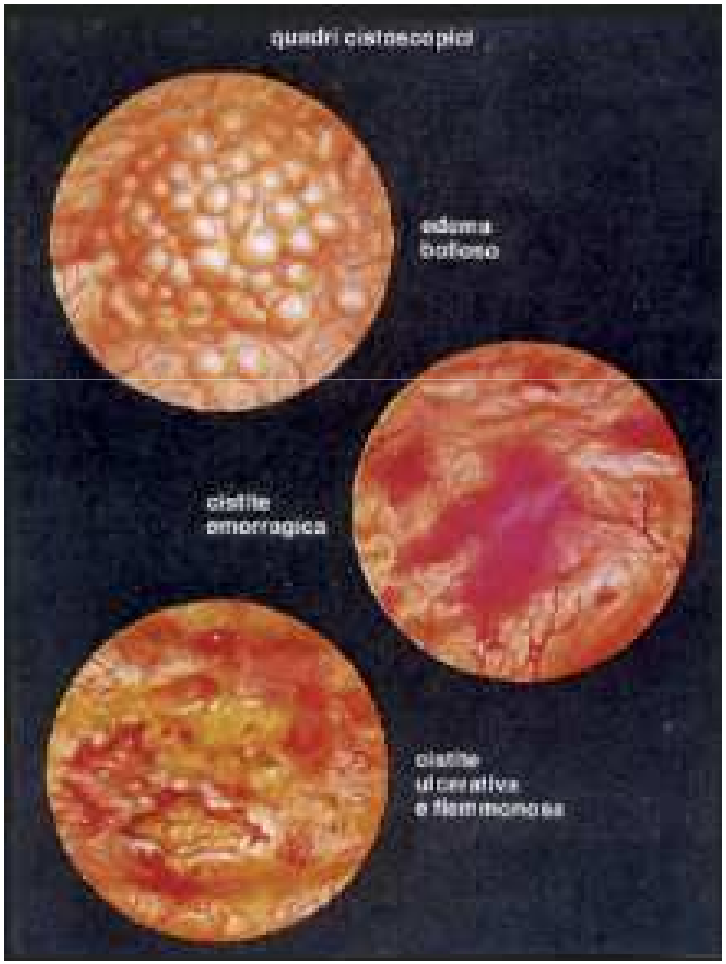


Onset : months7years from the end of RT

Chronic cystitis

Endoscopic changes

- ✓Edema
- ✓Eritema
- ✓Telenagectasia
- ✓Bleeding ulcer
- ✓Fistulae
- ✓Fibrosis
- ✓Volume reduction



Smit SG et al.. Nat Rev Urol. 2010

Chronic cystitis

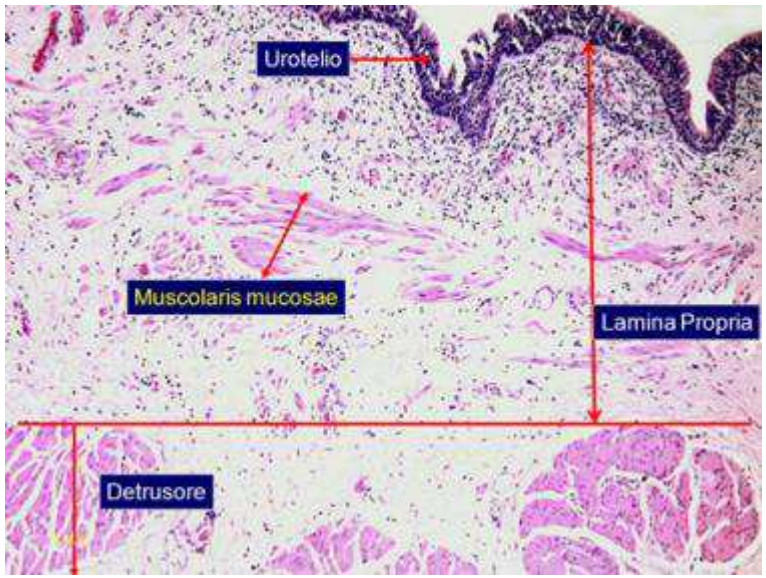
Hystologic changes

✓**Vascular changes** (iperplasia, occlusion, fibrosis)

✓**Muscles changes**

✓**Ischemia**

✓**Fibrosis**



Martinez-Rodriguez R et al. Acta Urol Esp 2010

Chronic cystitis

Practical treatment approach of radiation induced cystitis

R. Martínez-Rodríguez*, J. Areal Calama, O. Buisan Rueda, C. González Satue, J. Sanchez Macias, M. Arzoz Fabregas, J. Gago Ramos, S. Bayona Arenas, L. Ibarz Servio, and J.M. Saladié Roig

Urology Service, Hospital Germans Trias i Pujol, Badalona, Spain

Systemic: *estrogens, sodium polyphosfate, amonocaproic acid*

Intravescical: *hyaluronic acid, aluminium salt, formalin*

Physical: *Int Iliac Art embolization, Helmstein ballon distension, HyperBaric Oxigen, Cystectomy*

Martinez-Rodriguez R et al. Acta Urol Esp 2010

Conclusions

- Acute toxicity → treatment interruptions, QoL
- Late toxicity → Long survivors, QoL
- Medical therapy → symptomatic
- Prevention
  - Set-up → Belly board, bladder filling
  - IMRT → possibility of avoidance of OARs
  - Delineation of OAR → fundamental
  - CTV/field borders→ modulation according T stage
  - Medical prevention → not conclusive results

Treatment planning: state of the art I (rectal cancer)

C. Fiorino

Medical Physics

San Raffaele Institute, Milano, Italy

OSPEDALE SAN RAFFAELE

ESTRO School

Summary

Techniques for external beams optimization (mainly focused on long course…no bracky, no inoperable advanced disease):

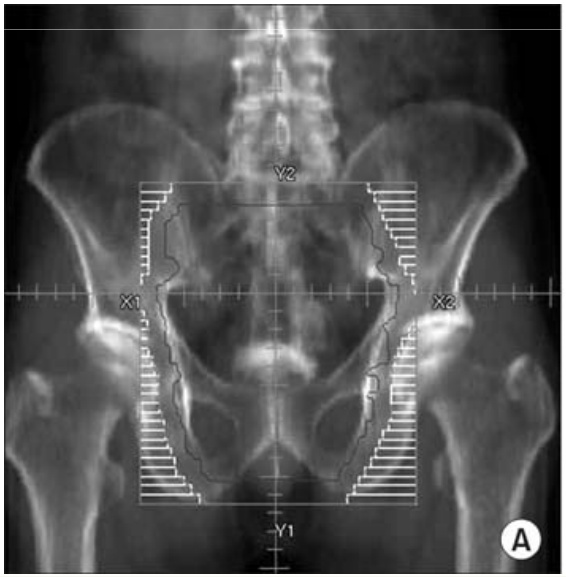
- 3DCRT
- IMRT (vs 3DCRT)
- Rotational techniques (IMAT/VMAT, Tomotherapy)
- Sequential and simultaneous boosting
- IGRT and potentials for plan adaptation

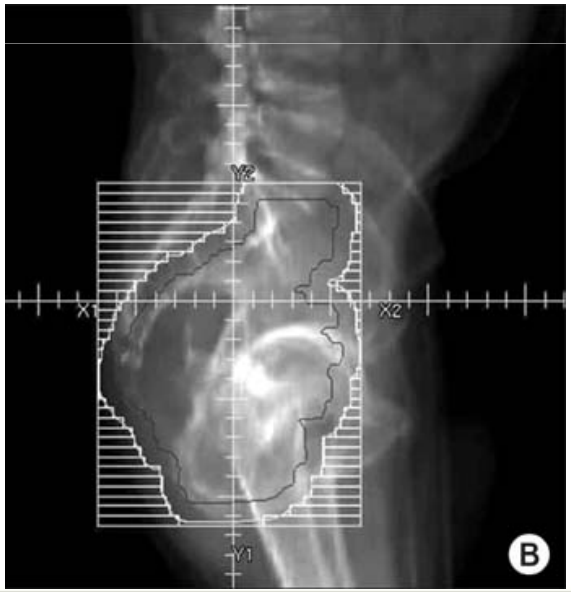
- Sparing bowel and bladder
- Sparing bone marrow (haematological tox)
- Sparing genitalia

- Conclusive remarks

3DCRT: robust conformal delivery

- (Favourable) geometry of irradiation
- Lateral BEV highly efficient in sparing bowel and bladder
- 3-4 field techniques mostly used (i.e.: PA±AP + R/L wedged)
- Prone vs supine (use of belly board, repeatibility…pre-IGRT)





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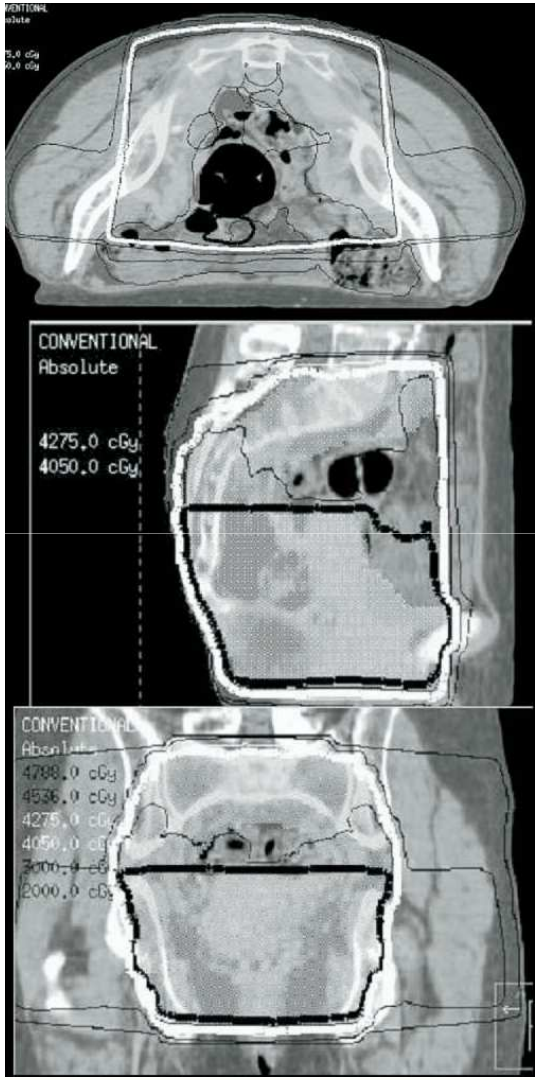
3DCRT: robust conformal delivery

- Limits in conformality (limited, but existing, concavity of PTV !)
- Treated volume (ICRU) much larger than PTV
- Dose to many structures not strictly «under control» (genitals, bones, bone marrow.....) and, in several cases, relevant (50-80%)



Guerrero-Urbano 2006

ESTRO School

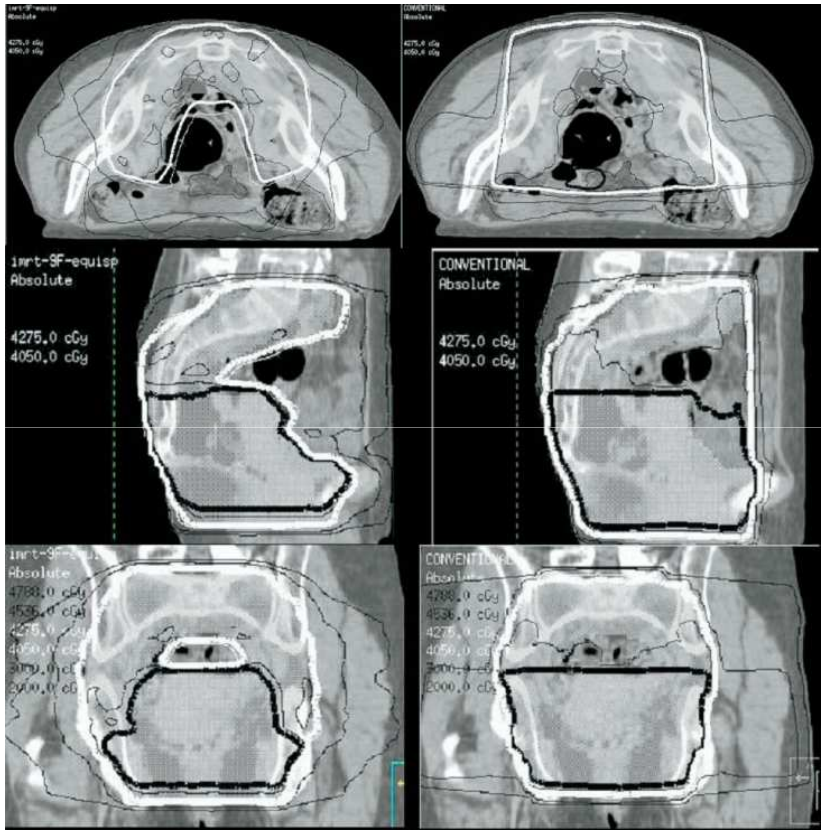
IMRT (vs 3DCRT)

- Better conformality (suggested ≥ 5 fields)
- Better sparing of bowel and bladder (high dose)

Table 4. Comparison of mean ± SD bladder dose statistics

	Conventional	3D-CRT	$IMRT_{3FFW}$	$IMRT_{9FEq}$	$IMRT_{7FEq}$	$IMRT_{5FEq}$	$IMRT_{5FCSS}$
Mean dose (Gy)	26.4 ± 7.2 ($p = 0.05$*)	41.1 ± 6.0 ($p = 0.03$*)	38.8 ± 5.6 ($p = 0.07$)	35.5 ± 3.3	35.0 ± 3.3 ($p = 0.5$)	35.8 ± 4.6 ($p = 0.7$)	37.0 ± 4.4 ($p = 0.1$)
V_{50} (%)	11.9 ± 14.3 ($p = 0.3$)	32.7 ± 18.43 ($p = 0.007$*)	21.7 ± 15.6 ($p = 0.01$*)	6.3 ± 6.8	6.4 ± 8.0 ($p = 0.8$)	5.4 ± 8.4 ($p = 0.4$)	3.2 ± 4.6 ($p = 0.05$*)
V_{40} (%)	19.3 ± 23.0 ($p = 0.3$)	65.1 ± 22.0 ($p = 0.007$*)	57.3 ± 20.5 ($p = 0.009$*)	31.9 ± 15.7	29.0 ± 13.0 ($p = 0.4$)	36.2 ± 21.0 ($p = 0.1$)	41.1 ± 22.5 ($p = 0.08$)

Abbreviations as in Tables 1 and 3.
* Statistical significance of all plans compared with $IMRT_{7FEq}$ plan using Student's paired t test.



Guerrero-Urbano 2006

ESTRO School

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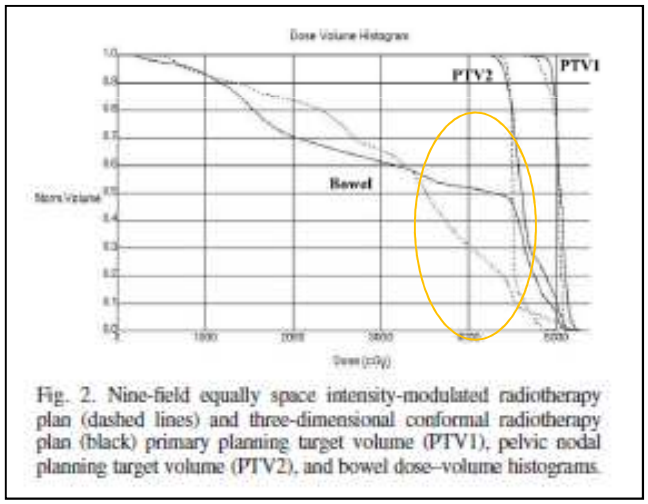
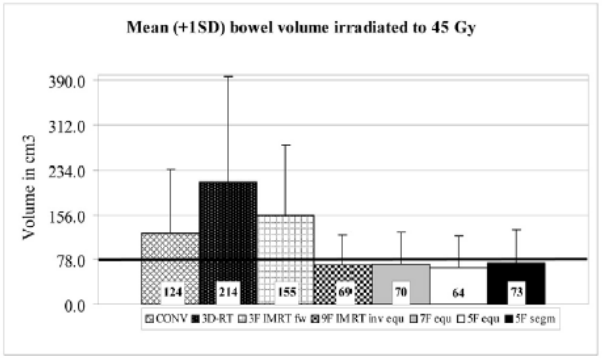


Fig. 2. Nine-field equally space intensity-modulated radiotherapy plan (dashed lines) and three-dimensional conformal radiotherapy plan (black) primary planning target volume (PTV1), pelvic nodal planning target volume (PTV2), and bowel dose–volume histograms.



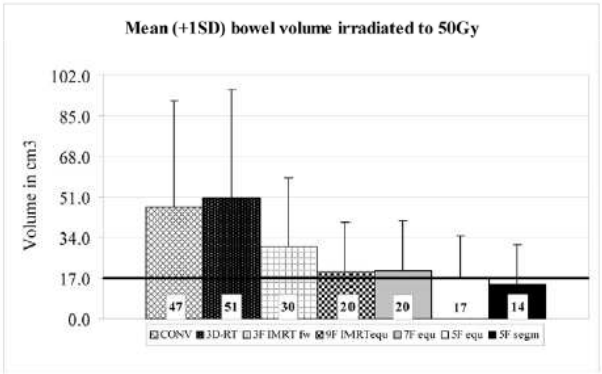


Fig. 3. Mean bowel volume (±SD) irradiated to 45 and 50 Gy. CONV = conventional radiotherapy plan; 3D-RT = three-dimensional conformal radiotherapy; 3F IMRT fw = three-field forward planned intensity-modulated RT; 9F IMRT inv equ, 7F equ, 5F equ = nine-field, seven-field, and five-field, respectively, equally spaced inverse planned IMRT; 5F segm = five-field segmented IMRT.

Guerrero-Urbano 2006

IMRT (vs 3DCRT)

- Is the sparing of bowel with IMRT clinically relevant ?
- Very few positive reports….(for instance: Samuelian 2012, Parekh 2013)

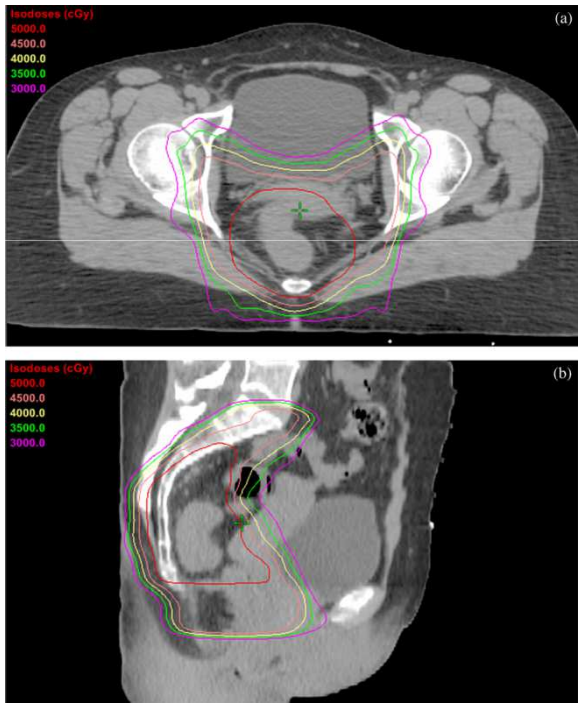


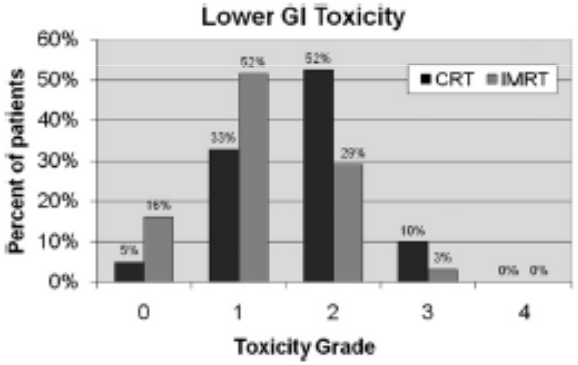
Table 1. Patient, tumor, and treatment characteristics

Characteristic	IMRT $n = 31$ (%)	CRT $n = 61$ (%)	p
Median age, y (range)	63 (26–75)	67 (38–86)	0.007
Sex			0.51
M	20 (65)	35 (57)	
F	11 (35)	26 (43)	
Tumor status*			0.36
T1–2	4 (13)	5 (8)	
T3	13 (42)	37 (61)	
T4	4 (13)	7 (11)	
Recurrent	10 (32)	12 (20)	
Nodal status			0.83
Positive	13 (42%)	27 (44%)	
Negative	18 (58%)	34 (56%)	
RT sequence			0.17
Preoperative	25 (81)	56 (92)	
Postoperative	6 (19)	5 (8)	
Median RT dose (range)	50 Gy (25.2–56)	50.4 Gy (25.2–54)	0.90
Concurrent chemotherapy			0.56
5-FU	13 (42)	27 (44)	
Capecitabine†	18 (58)	32 (53)	
None	0 (0)	2 (3)	
Treatment intent			
Curative	29 (94)	53 (87)	0.49
Noncurative	2 (6)	8 (13)	

Abbreviations: IMRT = intensity-modulated radiotherapy; CRT = conventional radiotherapy; 5-FU = 5-fluorouracil.

* Clinical stage (if treated preoperatively) or pathologic stage (if treated with initial surgery).

† Five patients in the CRT group received concurrent oxaliplatin and 2 patients also received leucovorin.



Samuelian 2012

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IMRT & GI toxicity

- But….negative report from a controlled trial
- NRG Oncology RTOG0822 study (IMRT to decrease acute GI tox 45Gy + boost 5.4Gy concomitant with Capecitabine/Oxaliplatin)
- Sampled to detect ≥12% reduction of acute grade 2-5 CTC_AEv.3.0 compared to RTOG0247
- Rate 51 % vs 40% (RTOG0247) vs 28% (provisional)
- Rate grade 3 diarrhea similar to studies using 3DCRT

Table 5 Grade ≥3 diarrhea in oxaliplatin chemoradiation arms from phase 3 studies

Study	n	Other chemotherapy agents in trial	No. of patients with grade ≥3 diarrhea (%)
STAR-01 (1)	353	5-FU	54 (15)
ACCORD 12/0405 PRODIGE 2 (2)	291	Capecitabine	36 (12.6)
NSABP R-04 (3)	644	5-FU or capecitabine	106 (16.5)
NRG Oncology RTOG 0822	68	Capecitabine	12 (17.6)

Abbreviations: 5-FU = 5-fluorouracil; RTOG = Radiation Therapy Oncology Group; STAR = Studio Terapia Adiuvante Retto; PRODIGE = Partenariat de Recherche en Oncologie Digestive; ACCORD = Action Clinique Coordonnees en cancerologie Digestive; NSABP = National Surgical Adjuvant Breast and Bowel Project.

Clinical Investigation

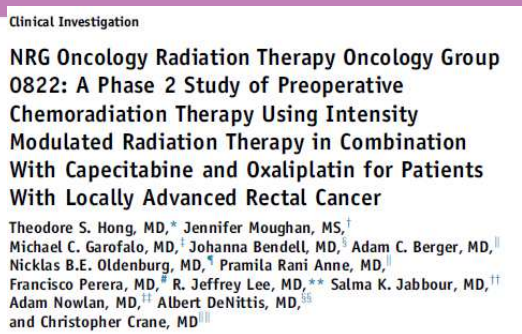
NRG Oncology Radiation Therapy Oncology Group 0822: A Phase 2 Study of Preoperative Chemoradiation Therapy Using Intensity Modulated Radiation Therapy in Combination With Capecitabine and Oxaliplatin for Patients With Locally Advanced Rectal Cancer

Theodore S. Hong, MD,* Jennifer Moughan, MS,† Michael C. Garofalo, MD,† Johanna Bendell, MD,§ Adam C. Berger, MD,‖ Nicklas B.E. Oldenburg, MD,¶ Pramila Rani Anne, MD,‖ Francisco Perera, MD,# R. Jeffrey Lee, MD,** Salma K. Jabbour, MD,†† Adam Nowlan, MD,†† Albert DeNittis, MD,§§ and Christopher Crane, MD‖‖

Hong 2015

IMRT & GI toxicity

- But….negative report from a controlled trial,



Clinical Investigation

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WHY ?

- Constraints V35<180 cc; V40<100 cc; V45<65 cc ?…they used «peritoneal space» as «small bowel» contour
- No sparing on V15-V20 ? (no !, they tested: V10-V45 not correlated..)
- Little portion of bowel to be spared compared to 3DCRT ?
- Major contribution from CHT and from rectum irradiation ?
- It is a question of CTV/PTV volumes ?
- Hot spots permitted in the PTV (V115%<5%) & no constraints on bowel >V45/Dmax

……Good to discuss bowel constraints….come back later !

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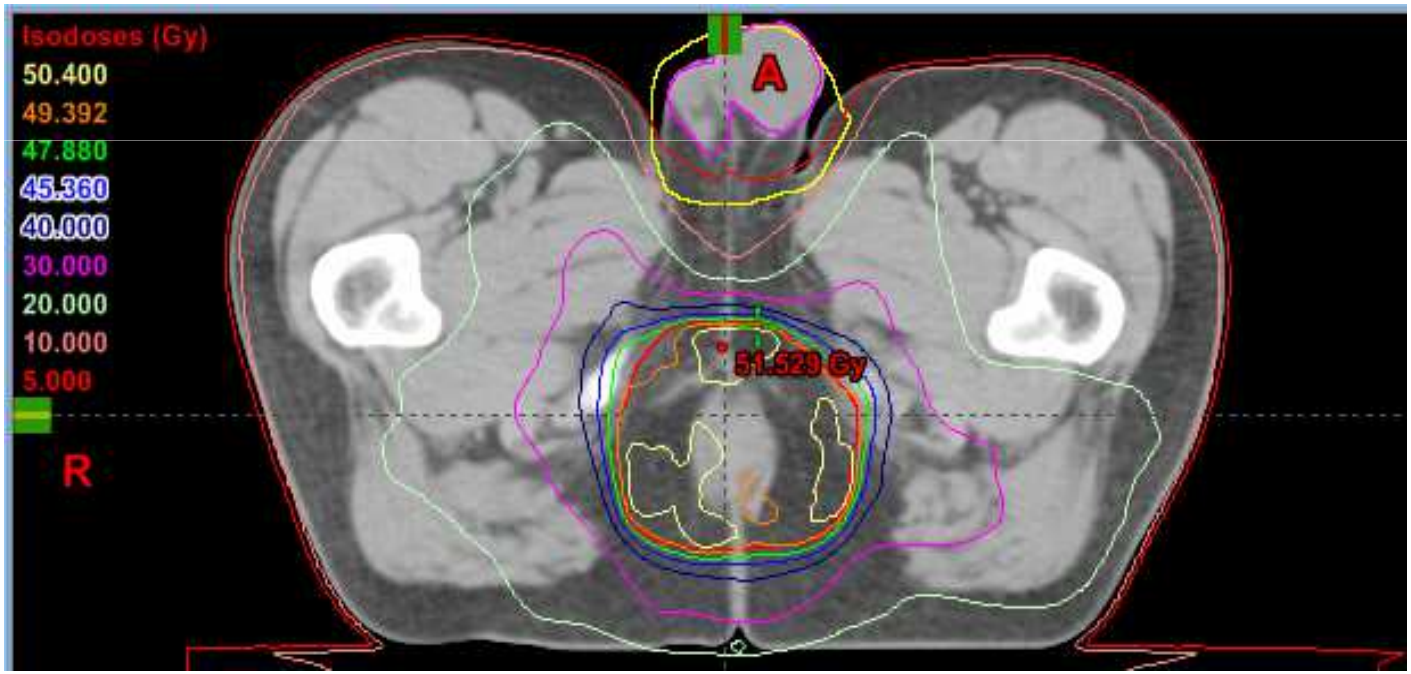
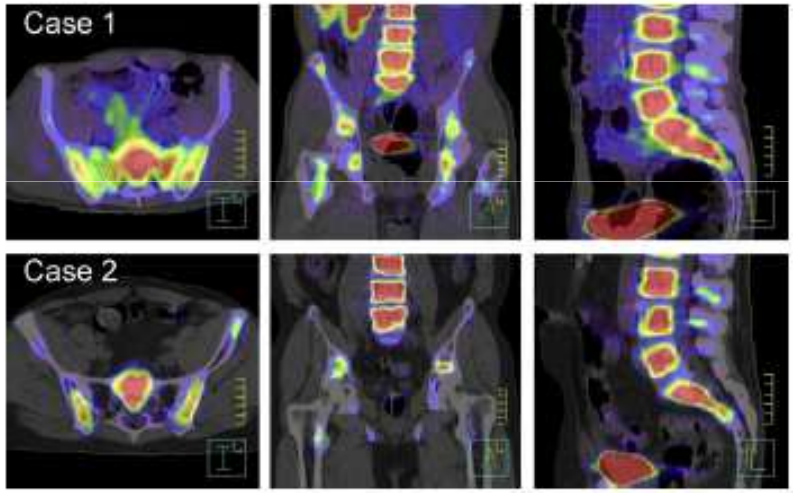
IMRT to spare genitalia

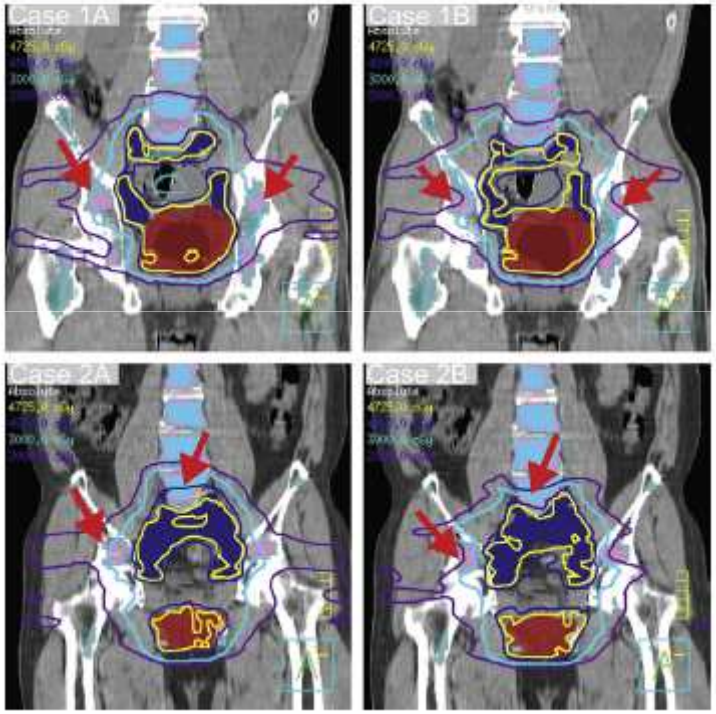
- Highly efficient in avoiding external genitals
- Role for sparing structures involved in erection (i.e.: penile bulb)
- Sparing Vagina (?)



IMRT to spare bone marrow ?

- Potentials for reducing the dose to bone marrow





McGuire 2011

Gyno patients ([18F]FLT_PET based planning)

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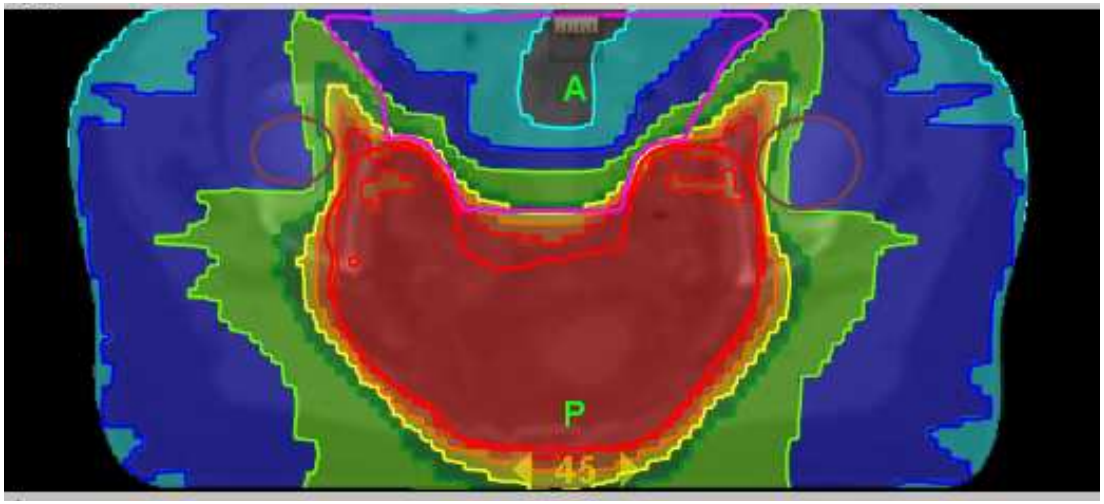
Rotational (intensity-modulated) techniques

- Cone-beam: IMAT, VMAT, RA…; Helical Tomotherapy (> degrees of freedom)
- Pro's: > conformality, > efficiency
- Con's (?)…low-dose bath (….may be controlled by using blocking options during planning optimization)
- Candidate to become «gold standard» …



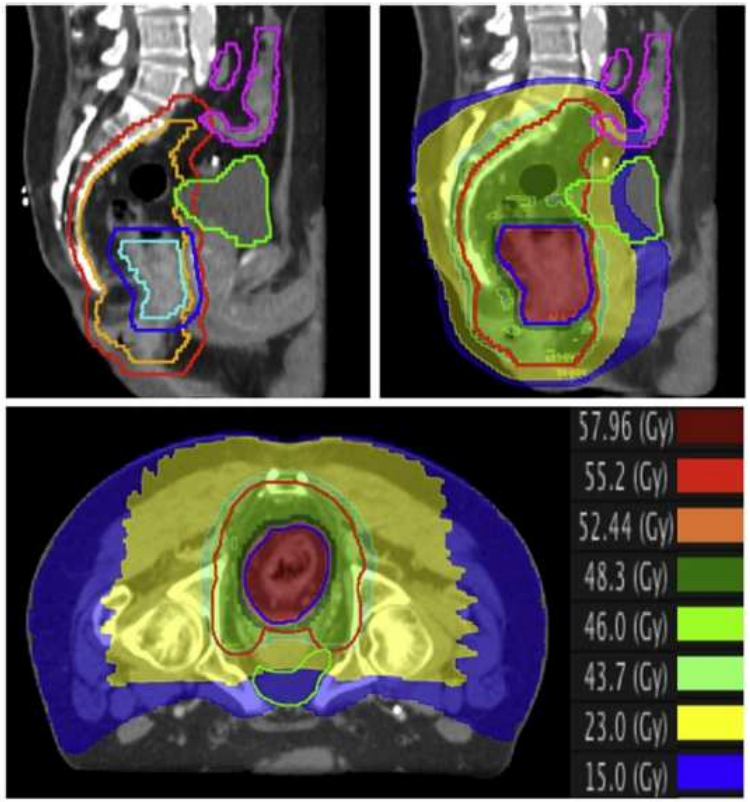
Passoni 2013 Tomotherapy planning

Sequential vs concomitant boosting

- Existence of a dose effect vs Major response/pCR….boosting GTV

- Seq. vs SIB: different radiobiology meaning
- SIB with conventional or moderate hypo
- IMRT better than 3DCRT
- From the point of view of plan optimization:

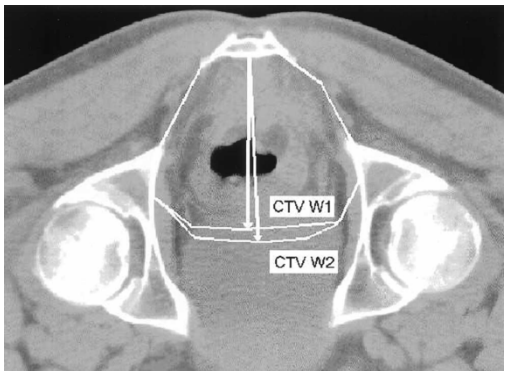
Concomitant boosting is more efficient: better control of the dose to OARs, better conformity index ansd dose homogeneity in PTVs



Engels 2013 46Gy/23fr, SIB 55.2Gy (no CHT)

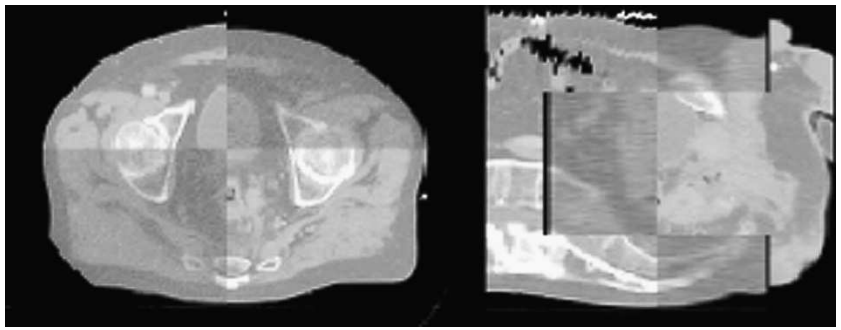
IGRT for rectal cancer

- Diagnostic kVCT
- CT in-room imaging, highly effective for image-guidance: CBCT, MVCT,…mesorectum is quite well visible
- Image-guidance during neo-adjuv/adjuv RT
- Only rigid correction !

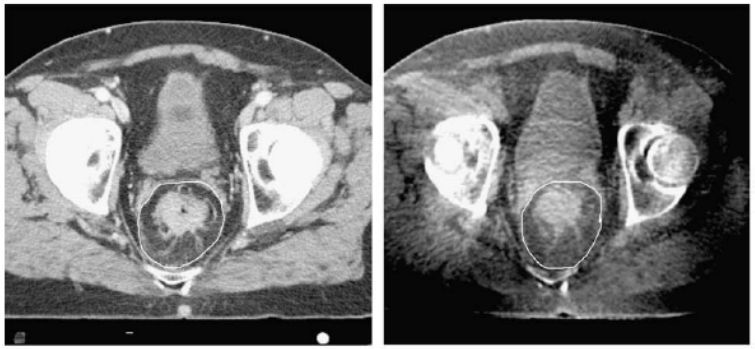


Nuyttens 2002 kVCT

Tournel 2008 MVCT Tomo



Niikamp 2009 CBCT



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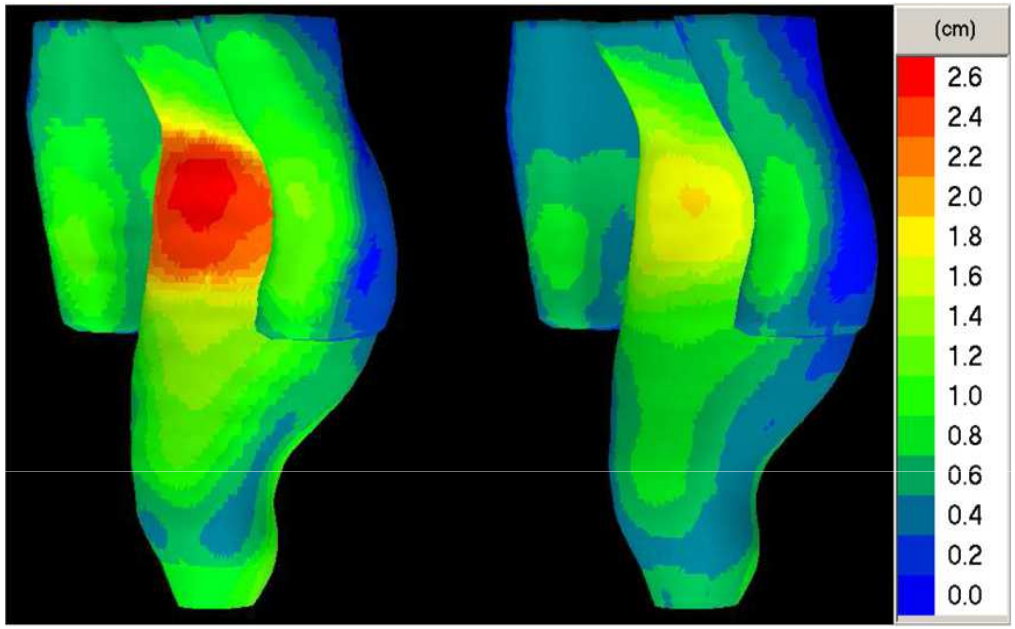
IGRT for rectal cancer

- Mesorectum reported to change in shape (correlated mainly with bladder and, secondarily, rectum motion)
- Main changes in ANT direction
- Larger impact for short-course, prone position and female pts
- Residual margins difficult to assess (local deformations, CTV contouring uncertainty)
- «Optimal» margins often not clinically feasible (Dmin>95%/90% pts too strict criterion? Contouring uncertainty too high..?)
- Issues concerning the real clinical impact in neo-adjuv RT(CHT)



Wout With daily correction

Njikamp 2012

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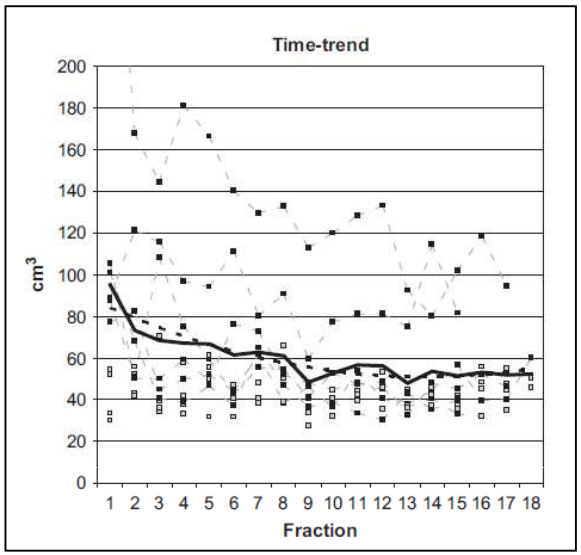
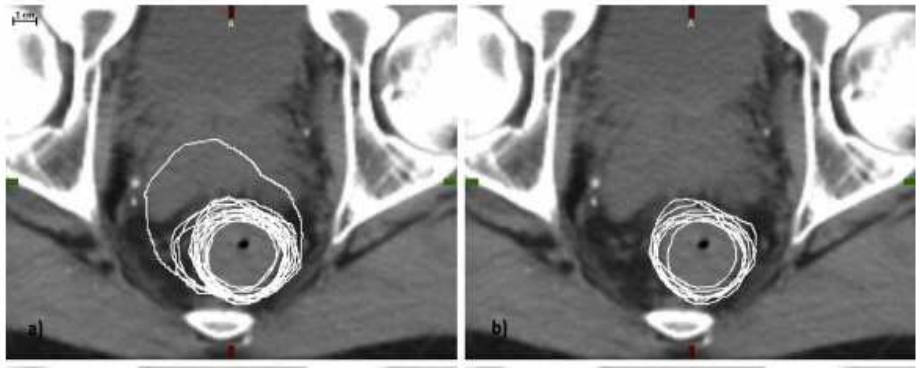
IGRT for rectal cancer: boost

- IGRT focused on the boost volume (simpler assessment of margins ?)
- Rectal motion as a surrogate of GTV/CTVboost
- Reported trend for rectal volume reduction and for shape variation (Njikamp 2012, Maggiulli 2012, Raso 2015)
- Residual deformation error after rigid correction: anisotropic, higher in the first few fractions
- Relatively small «optimal» margins reported (especially if excluding the first fractions)….mainly 5-15 mm
- Larger motion in female pts

Maggiulli 2012





Raso 2015

….to be better discussed later (IGRT & adaptive)

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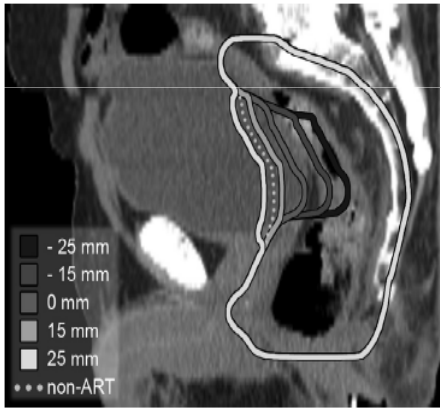
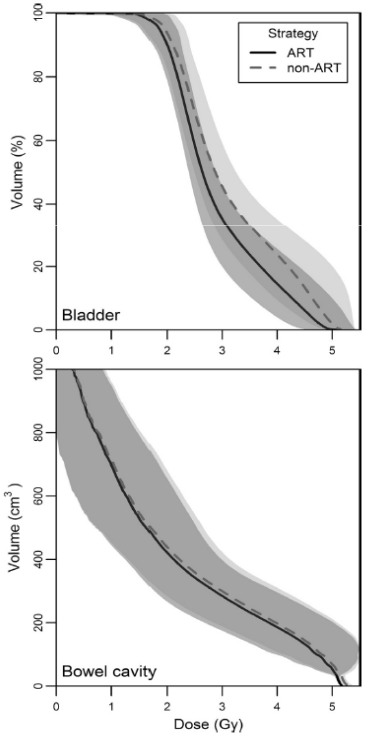
Adaptive planning

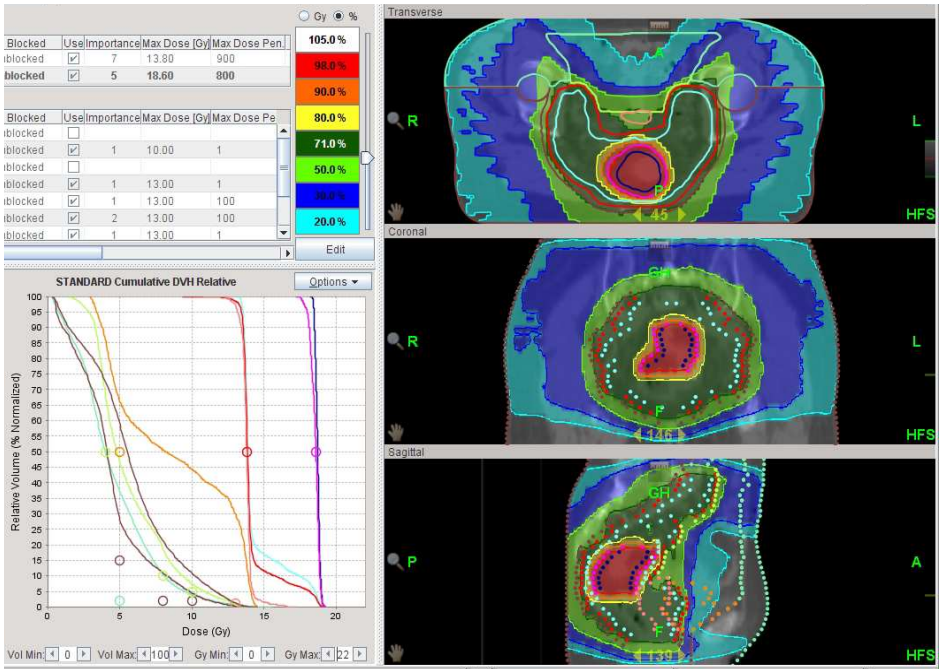
-Re-planning/plan of the day approach to take mesorectum changes into account, suggested but no clinical experiences (cost-benefit ?)





Lutkenhaus 2016

- Adaptive planning to boost the residual GTV after half-RT T regression (promising approach to escalate the dose to T)....to be better discussed later (IGRT & adaptive)



Passoni 2013

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Summary

Techniques for external beams optimization (mainly focused on long course…no bracky, no inoperable advanced disease):

- 3DCRT
- IMRT (vs 3DCRT)
- Rotational techniques (IMAT/VMAT, Tomotherapy)
- Sequential and simultaneous boosting
- IGRT and potentials for plan adaptation

- Sparing bowel and bladder
- Sparing bone marrow (haematological tox)
- Sparing genitalia

Short critical (rectal ca - oriented) summary, of pelvic OARs constraints

- Conclusive remarks

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Pelvic OARs constraints: Main References

Systematic review

Dose–volume effects for normal tissues in external radiotherapy: Pelvis

Claudio Fiorino [a,*], Riccardo Valdagni [b], Tiziana Rancati [b], Giuseppe Sanguineti [c]

[a] Medical Physics Department, San Raffaele Scientific Institute, Milan, Italy
[b] Prostate program, Scientific Directorate Fondazione IRCCS – Istituto Nazionale dei Tumori, Milan, Italy
[c] Radiotherapy Department, The John Hopkins University, Baltimore, MD, USA

Radiother. Oncol. 2009

QUANTEC, IJROBP 2010

QUANTEC: ORGAN-SPECIFIC PAPER **Pelvis: Rectum**

RADIATION DOSE–VOLUME EFFECTS IN RADIATION-INDUCED RECTAL INJURY

Jeff M. Michalski, M.D.,* Hiram Gay, M.D.,* Andrew Jackson, M.D.,† Susan L. Tucker, Ph.D.,† and Joseph O. Deasy, Ph.D.*

QUANTEC: ORGAN-SPECIFIC PAPER **Pelvis: Bladder**

RADIATION DOSE–VOLUME EFFECTS OF THE URINARY BLADDER

Akila N. Viswanathan, M.D., M.P.H.,* Ellen D. Yorke, Ph.D.,† Lawrence B. Marks, M.D.,† Patricia J. Eifel, M.D.,§ and William U. Shipley, M.D.¶

QUANTEC: ORGAN-SPECIFIC PAPER **Pelvis: Penile Bulb**

RADIATION DOSE–VOLUME EFFECTS AND THE PENILE BULB

Mack Roach, III, M.D., FACR,* Jiho Nam, M.D.,† Giovanna Gagliardi, Ph.D.,‡ Issam El Naqa, Ph.D.,§ Joseph O. Deasy, Ph.D.,§ and Lawrence B. Marks, M.D.†

Predicting toxicity in radiotherapy for prostate cancer

Valeria Landoni [a], Claudio Fiorino [b], Cesare Cozzarini [c], Giuseppe Sanguineti [d], Riccardo Valdagni [e,f,g], Tiziana Rancati [e,*]

[a] Medical Physics, Istituto Nazionale Tumori Regina Elena, Rome, Italy
[b] Medical Physics, Raffaele Scientific Institute IRCCS, Milan, Italy
[c] Radiotherapy, Raffaele Scientific Institute, Milan, Italy
[d] Radiotherapy, Istituto Nazionale Tumori Regina Elena, Rome, Italy
[e] Prostate Cancer Program, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[f] Radiation Oncology 1, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[g] Clinical Sciences and Community Health, University of Milan, Milan, Italy

Physica Medica (EJMP), Landoni et al. 32: 521-532, 2016 (update of the period 2009-2016)

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Pelvic OARs constraints: sparing the bowel

- Few evidence of quantitative dose-volume relationships (V5-V45)

Organ: Bowel; End-point: Moderate/severe acute toxicity

Ref.	No. of pts	Doses[a]	Suggested constraints	Definition of bowel/Comments
Baglan [122]	40	45 Gy	Grade 3 CTC 3.0: V15Gy < 150 cc (V40Gy < 125 cc)	Loops/four-fields technique; rectal patients; concomitant chemotherapy V5Gy–V40Gy correlated with toxicity
Roeske [123]	40	45 Gy	⩾ Grade 2 RTOG: V45Gy < 150–200 cc	Loops/IMRT; gynecological patients
Tho [126]	41	45 Gy	⩾ Grade 2 CTC 3.0: V15Gy < 100 cc (risk < 20%)	Loops/four-fields technique; rectal patients; concomitant chemotherapy V5Gy–V45Gy correlated with toxicity
Huang [125]	80	39.6–45 Gy	⩾ Grade 2 diarrhoea CTC 3.0: V16–18Gy and V40–45Gy independently predictive for pts without/with previous surgery, respectively	Loops/four-fields technique; gynecological patients
Robertson [127]	91	45 Gy	Grade 3 diarrhoea CTC 3.0: V15Gy < 120 cc V25Gy < 105 cc V40Gy < 71 cc	Loops/four-fields technique; rectal patients; concomitant chemotherapy; V5Gy–V40Gy correlated with toxicity
Sanguineti [124]	149	0/54 Gy[b]	⩾ Grade 2 CTC 2.0: V15Gy < 1186 cc	Intestinal cavity/IMRT; prostate patients; pooled patients with/without pelvis irradiation
Fiorino [128]	175	50.4–54 Gy	⩾ Grade 2 RTOG: Intestinal cavity outside PTV/Whole cavity V50Gy < 35 cc/100 cc V45Gy < 100 cc/250 cc V40Gy < 150 cc/350 cc V30Gy < 300 cc/500 cc	Intestinal cavity/four-fields technique and IMRT; prostate patients; V20Gy–V50Gy correlated with toxicity; V15Gy best predictor for non-IMRT patients

[a] To the pelvis, 1.8–2 Gy/fr.
[b] Pooling patients with/without pelvic nodes irradiation.

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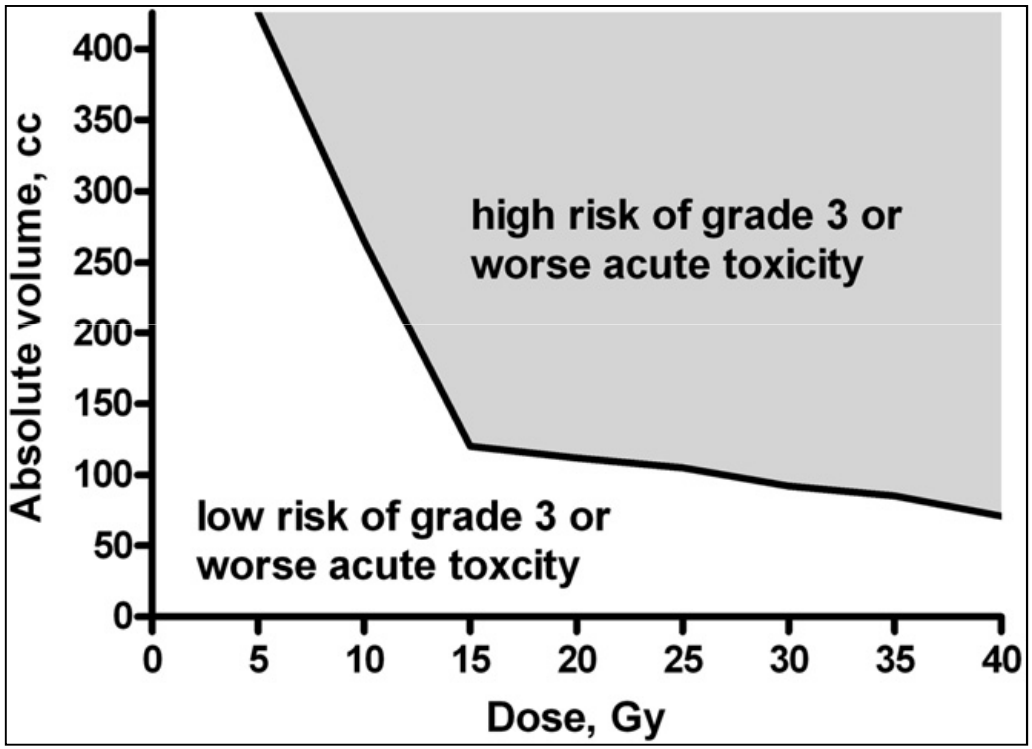
Pelvic OARs constraints: sparing the bowel

- Few evidence of quantitative dose-volume relationships (QUANTEC)



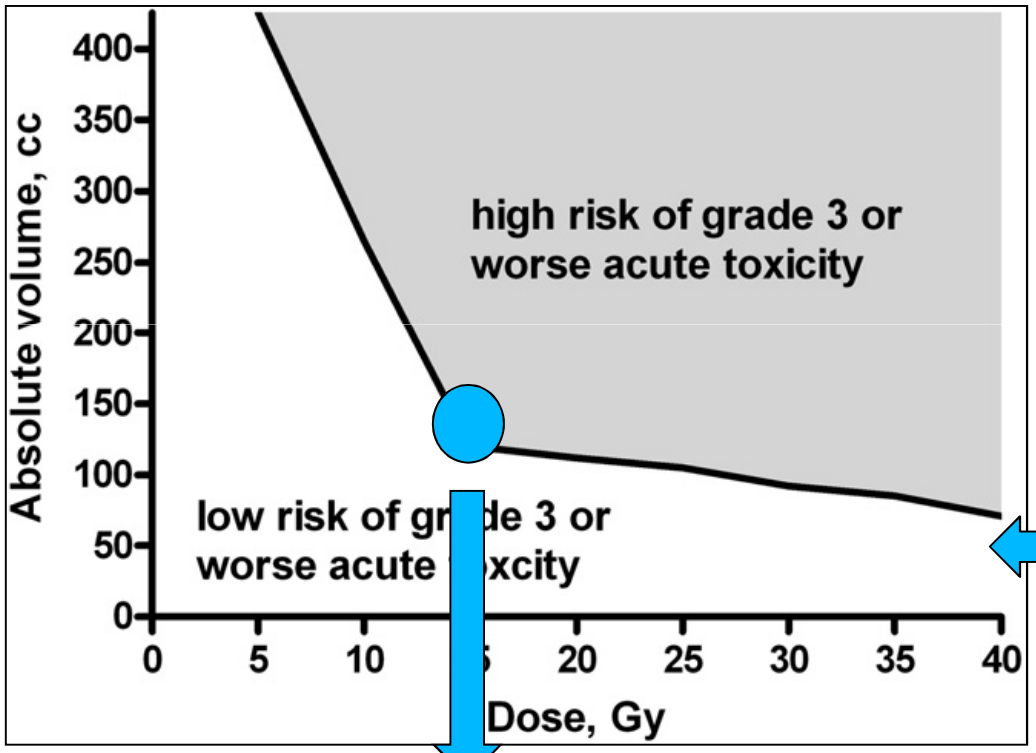
Co-factors:

- **<u>Chemotherapy</u>**
- Age
- previous surgery

Quantec: Baglan-Robertson constraints…..rectal ca (with CHT), bowel loops !

Pelvic OARs constraints: sparing the bowel

- Few evidence of quantitative dose-volume relationships (QUANTEC)



?

Co-factors:

- **<u>Chemotherapy</u>**
- Age
- previous surgery

Quantec: Baglan-Robertson constraints…..rectal ca (with CHT), bowel loops !

Is V15 really important ?

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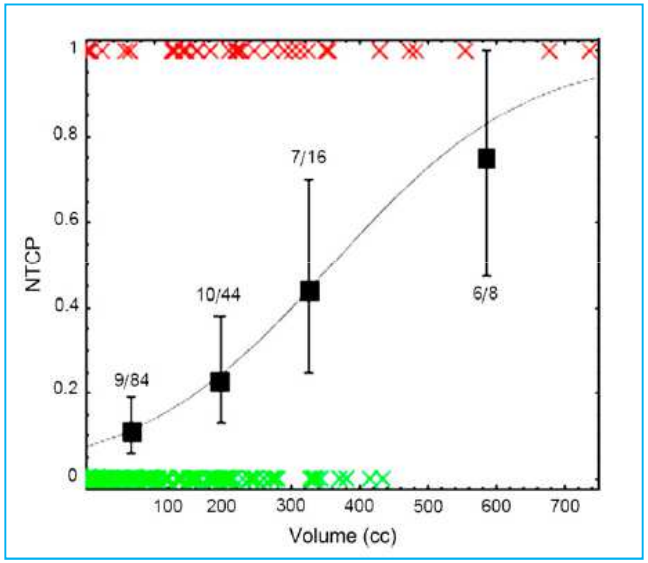
Pelvic OARs constraints: sparing the bowel

- V15 as strong predictor in a recent updated model by Robertson (2010)
- Not confirmed in the NRG0822 controlled trial (!)…WHY ?

- Robertson study: 3DCRT 3 fields (pre & post-op)
- NRG0822: IMRT (pre-op)

- Robertson study: bowel loops
- NRG0822: «peritoneal space»



- Correlation between V40-V45 and V15 for 3DCRT

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Pelvic OARs constraints: sparing the bowel

- V15 as strong predictor in a recent updated model by Robertson (2010)
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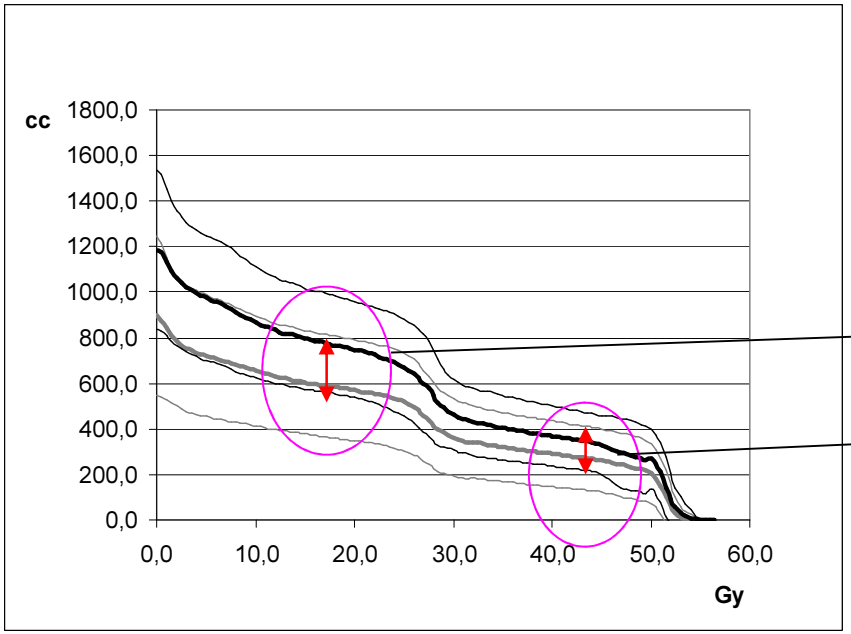
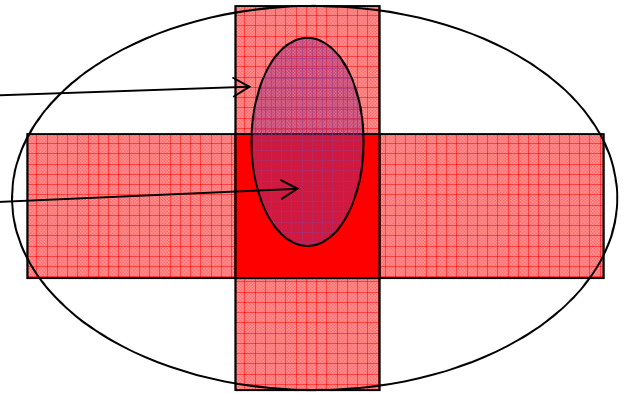


Comparing DVH of patients with/wout bowel tox (prostate ca) (Fiorino 2009)



Correlation between V40-V45 and V15 for 3DCRT

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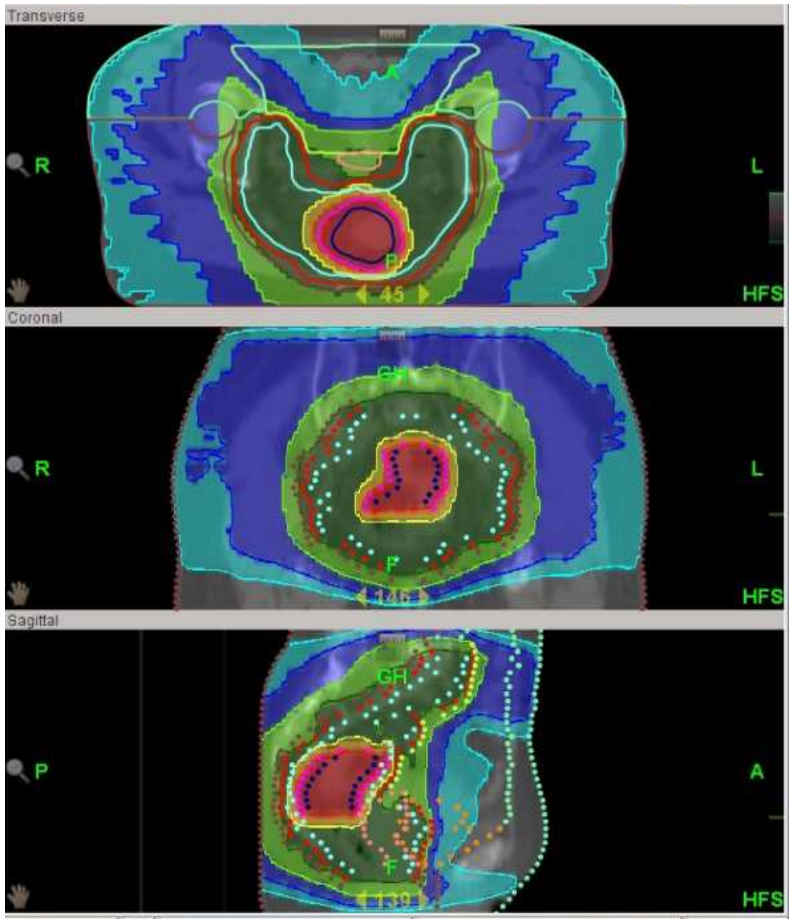
Pelvic OARs constraints: sparing the bowel

- Practical planning approach with IMRT: «as low as possible», avoidance of peritoneal space outside PTV starting to spare from «high» doses (V40-V50) and continuing to intermediate dose (V15-V20)
- Avoiding hot spots in the bowel loops overlapped with PTV
- Residual GI toxicity likely to be due mainly to the irradiation of rectum and bowel within PTV, CHT (surgery…..)
- Lack of dose-volume effect studies with prospective, patient-reported scoring of toxicity



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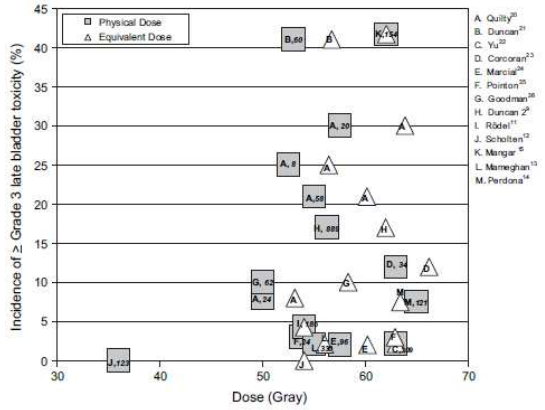
Pelvic OARs constraints: sparing the bladder

- GU toxicity, a relatively minor problem («low» dose): threshold around 50-55Gy, whole organ for RTOG G3 late tox (Quantec 2010, Fiorino 2009)
- No strong evidence of increased late GU tox compared to only surgery (Gilbert 2015)
- Recent important updates of predictors of GU tox (more relevant for prostate ca pts, Landoni 2016)
- Interplay between bladder filling and bowel sparing
- The avoidance approach of the peritoneal space should include bladder to guarantee adequate sparing of bowel during treatment (possible systematic deviations)



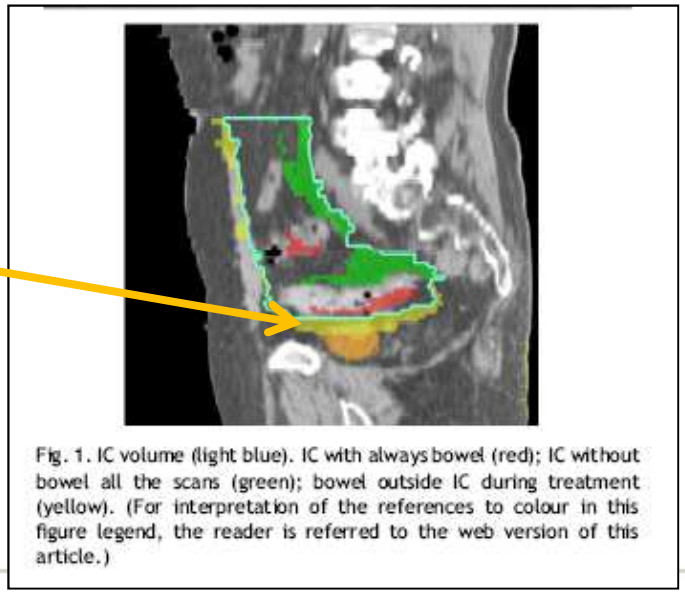


Fig. 1. IC volume (light blue). IC with always bowel (red); IC without bowel all the scans (green); bowel outside IC during treatment (yellow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Sanguineti 2008

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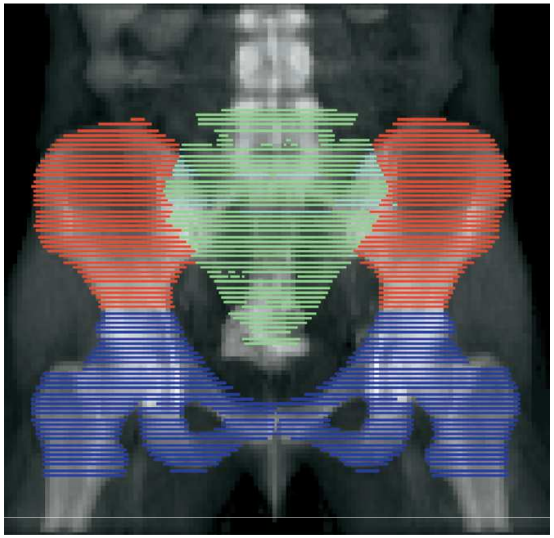
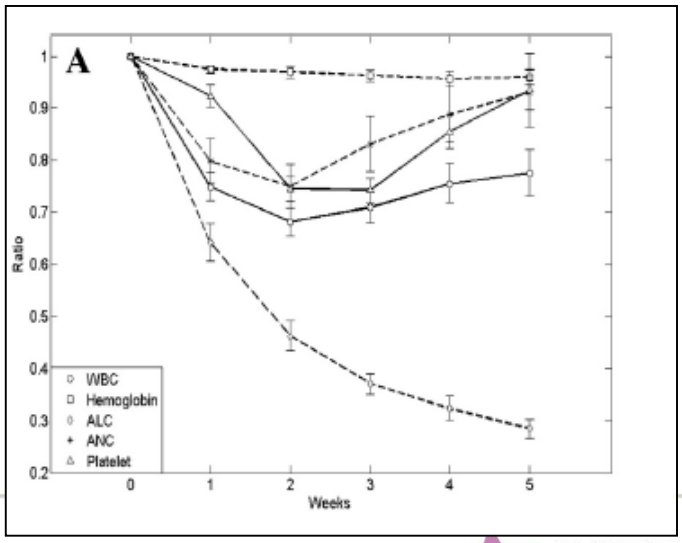
Pelvic OARs constraints: bone marrow

- Acute Hematological toxicity reported in RT+CHT for rectal ca; unclear the long-term impact
- Evidence of dose-volume effects for the pelvic bone marrow in rectal and anal canal ca. with 3DCRT +CHT (Mell 2007)
- Predictive models of hematological tox for rectal ca treated with 3DCRT/IMRT +CHT (Yang 2014, Wan 2015)
- Not yet reported BM-sparing planning strategies for rectal cancer.....potential interplay with bowel/bladder sparing





Yang 2014

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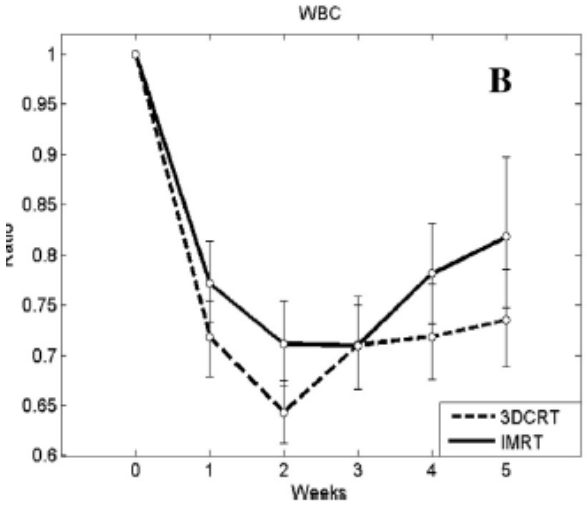
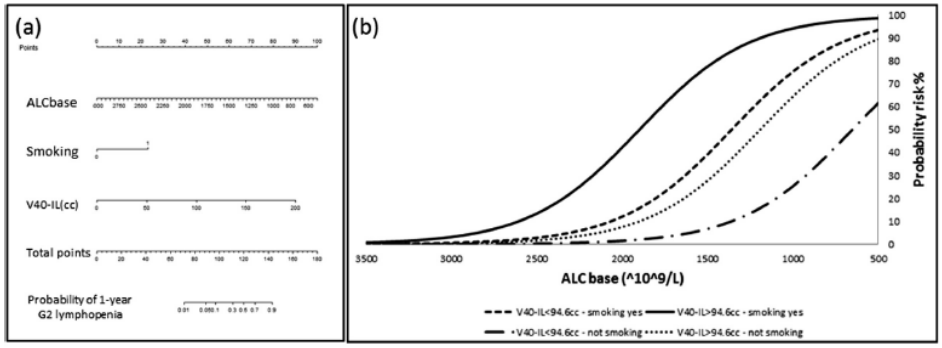
Pelvic OARs constraints: bone marrow

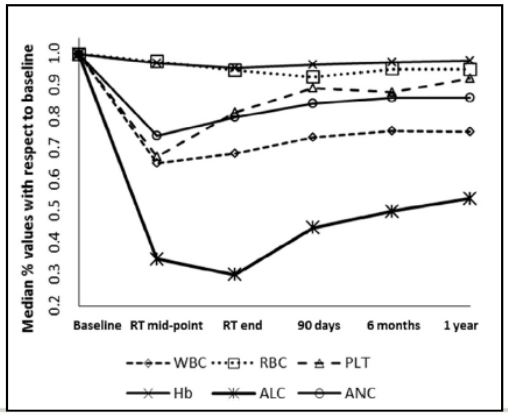
- Main dosimetry predictors (IMRT): coxal and sacral V45 mostly associated to lower nadir of WBC and neutrophils (Yang 2014)
- Worst WBC Nadir with 3DCRT



Yang 2014

- V40 of whole pelvic BM and iliac BM predicted acute and late limphopenia in a large prostate ca group (wout CHT) treated with IMRT (Sini 2016)





Sini 2016
Prostate ca pts,
no CHT

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Pelvic OARs constraints: genitals

- From recent large prospective studies & reviews, sexual problems are a major issue after rectal ca curative treatments; RT+CHT associated to an increased risk (Lange 2009, Bregendhal 2015, Kunnemann 2015, Gilbert 2015)
- Under-estimated problem in the past (?)
- Any effort should be activated to efficiently spare genitals outside PTV: beams geometry, blocking options in rotational techniques, testicle shielding when appropriate….

Table 3 Prevalence of toxicity reported by treatment type according to clinician or patient reports (PRO)

	Range of toxicity reported by treatment type (references in parentheses)				
Type of toxicity	Surgery alone	Short-course RT (25 Gy in 5)	Long-course RT (45-50.4 Gy in 25-28)	Long-course 5FU CRT (45-50.4 Gy in 25-28)	Long-course 5FU CRT with additional chemotherapy (45-50.4 Gy in 25-28)
Sexual dysfunction (males)					
Sexual function (EORTC-QLQ CR38 mean scores*)	40.8-57.4 (35, 40)	47.4-65.7 (35, 40)			
Decline in sexual life (%)		80 (42)		70 (42)	
Erectile dysfunction (%)	47.1 [(35) EORTC-QLQ CR38 mean scores]	53.9 [(35) EORTC-QLQ CR38 mean scores]	10.4 [(33) IIEF mean score†]	71 (%) (42) and 6.9 [(33) IIEF mean score†]	71 (42)
Ejaculation dysfunction (EORTC-QLQ CR38 mean scores*)	31.7 (35)	42.5 (35)			
Sexual dysfunction (females)					
Sexual function (EORTC-QLQ CR38 mean scores*)	29.9 (35)	50 (35)			
Decline in sexual life (%)		41 (42)		52 (42)	
Vaginal dryness (%)			100 (33)	86 (33)	
Dyspareunia (%)			50 (33)	86 (33)	

Gilbert 2015

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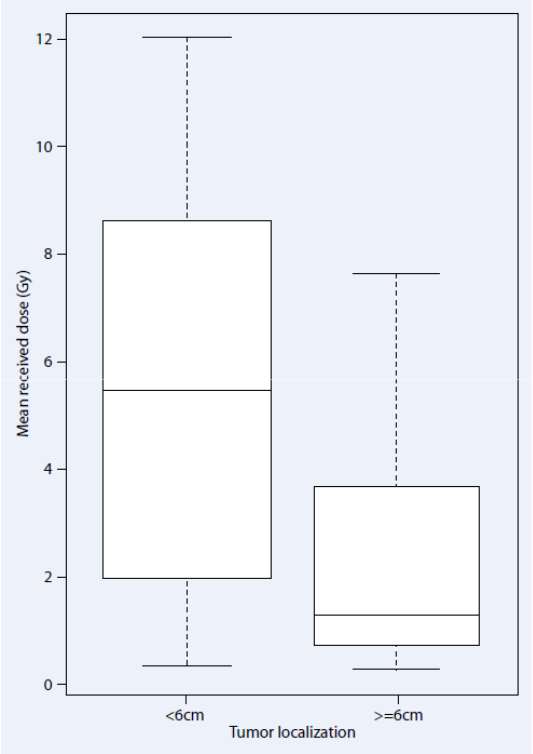
Pelvic OARs constraints: genitals

- Dose to testicles vs testosterone levels and libido: a controversial issue

- Few prospective studies including dose estimates (Piroth 2003, Dueland 2003, Hermann 2005, Yau 2009, Hennies 2012)
- Very large range of dose (<1 – 15 Gy), Evidence of transient and permament azoospermia for testicle doses above 1 and 2 Gy respectively (Yau 2009); higher rates of ipogonadism with EBRT vs HDRB (average testicles doses: 1.3 vs 0.3 Gy)
- Lack of relationship between testicle dose & testosterone/libido decrease in EBRT (Dueland 2003, Hennies 2012)
- relevant issues on accuracy in dose calculation/estimates («out-of-field» dose in TPS = high uncertainty !!!!)



Hennies 2015

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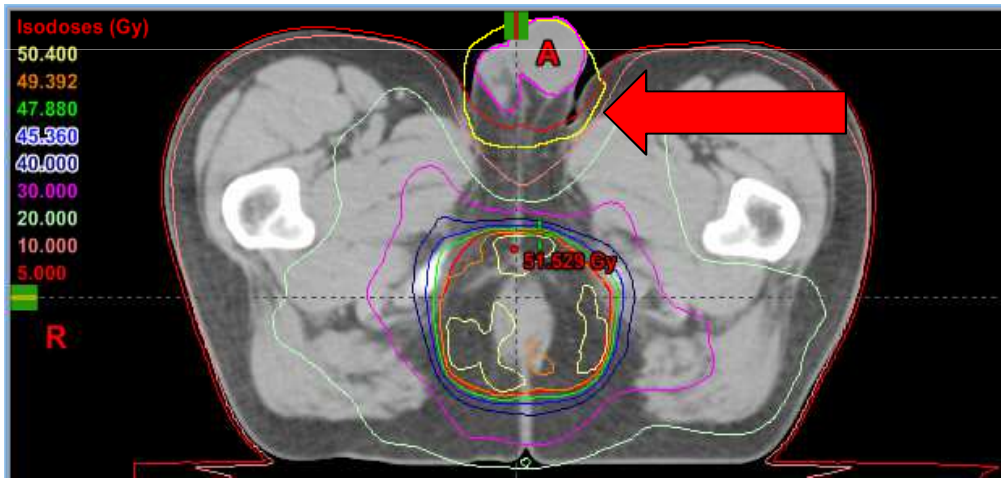
Pelvic OARs constraints: genitals

- Dose to testicles vs testosterone levels and

Pragmatically: reducing the dose to testicles as much as possible (possibly < 2 Gy)

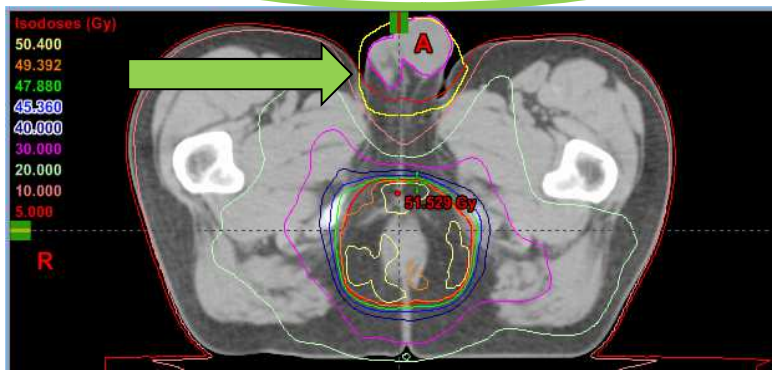
- IMRT highly efficient (blocking options in VMAT/tomo)
- Patient set-up, testicle shielding for very caudal field borders (head scatter)

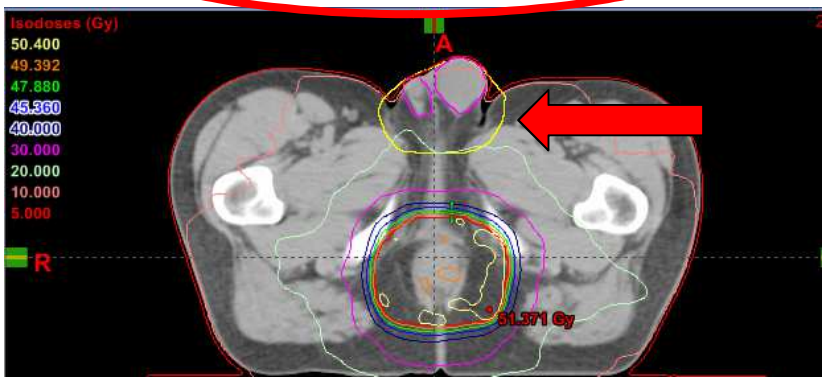


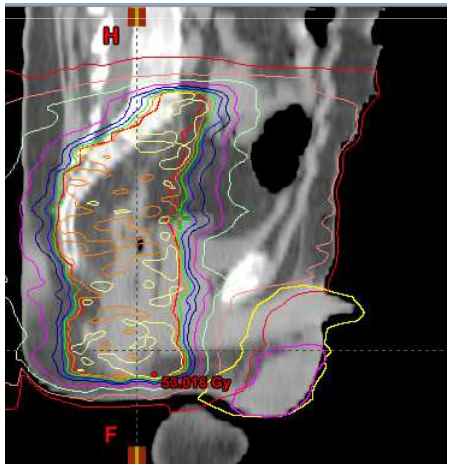
Pelvic OARs constraints: genitals

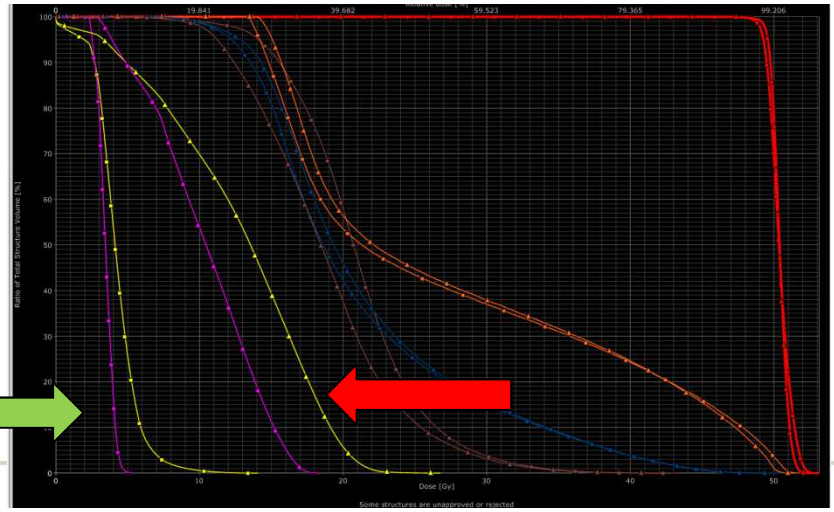
- Explicit inclusion in optimization

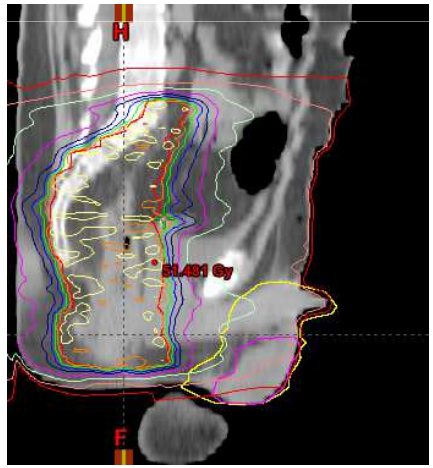
Not included











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Pelvic OARs constraints: genitals

- Dose to penile bulb (PB)/structures involved in erection
- Most experience from prostate ca RT
- Controversial results, some evidence for constraining PB<40-50Gy
- Lack of prospective trials including dose-volume data (no data to my knowledge in the rectal ca. context)
- Very relevant «confounding» factors: baseline situation, ageing, vascular problems, psychological aspects
- Prospective data suggests that avoiding overlap between PTV and PB may largely reduce erectile dysfunctions

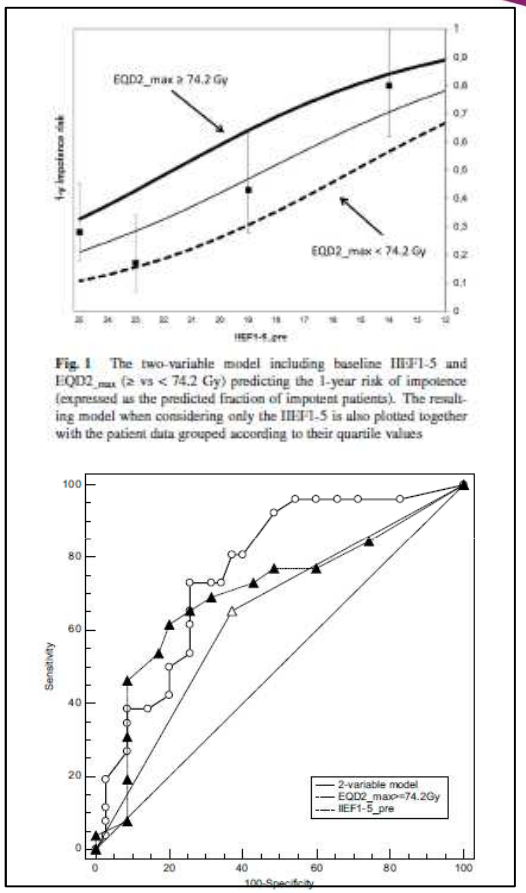

Fig. 1 The two-variable model including baseline IIEF1-5 and $EQD2_{max}$ (≥ vs < 74.2 Gy) predicting the 1-year risk of impotence (expressed as the predicted fraction of impotent patients). The resulting model when considering only the IIEF1-5 is also plotted together with the patient data grouped according to their quartile values

Cozzarini 2016

prostate ca pts, IIEF1-5 based impotence

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Pelvic OARs constraints: genitals

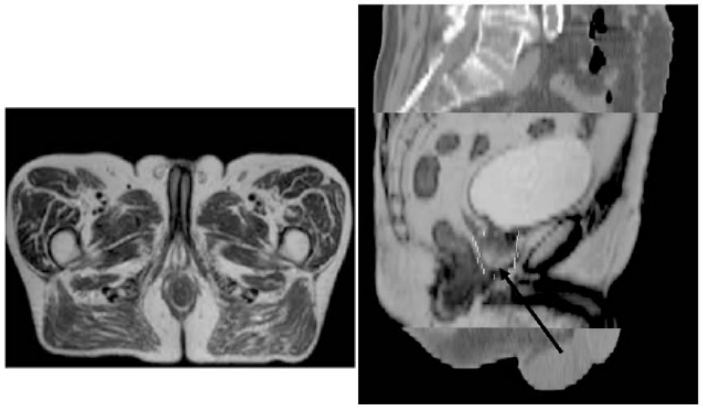
- Dose to penile bulb/structures involved in erection
- Role of IGRT to reduce caudal margins in lower tumors
- Space for PB-sparing techniques with IMRT ?

Table 4
Summary of studies on potency predictors in potent patients before radiotherapy (using a prospective questionnaire-based assessment of potency; knowledge of baseline statu well defined contouring of the penile bulb; availability of penile bulb dosimetry data; and wide range of doses).

Reference	N° pts	Score	Time	Impotence rate (%)	Prescription dose (Gy) RT technique	Dosimetry Predictors (penile bulb)	MVA[§]
Fisch 2001 [76]	21	UCSF	2 yrs	33[*]	65–72 3DCRT	D70% ≥ 70 Gy	No
Wernicke 2006 [77]	29	EDFS/ EJS	3 yrs[*]	–	66.6–79.2 3DCRT	D30%–D90%[**]	No
Mangar 2006 [78]	51	UCLA/ FACT-P	2 yrs	24[*]	64–74 Gy 3DCRT	D90% ≥ 5 0 Gy	No
Magli 2012 [79]	19	IIEF1-5	2 yrs	58[***]	72–76 3DCRT	Dmean /D90%[**]	No
Hoppe 2012 [80]	234	EPIC/ IIEF1-5	1–2 yrs	11[***]	70–72 or [illegible] Gy/fr protons		
Cozzarini 2016 [81]	62	IIEF1-5	1 yr	42[***]	74–78 or 70–74.2 (2.5 Gy/fr[**]) IMRT	EQD2max ≥ 74.2 Gy[¶]	Yes

UCSF = University of California San Francisco score
EDFS = erectile dysfunction firmness score
EJS = ejaculatory difficulty score
UCLA = University of California, Los Angeles score
FACT-P = Functional Assessment of Cancer for patients with Prostate cancer
IIEF1-5 = Short form (questions 1–5) of International Index of Erectile Function Questionnaire
EPIC = Expanded Prostate Cancer Index Composite
N° = number; pts = patients; MVA = multivariable analysis; yrs = years; fr = fraction; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity modulate radiotherapy; DX% ≥ YGy = Dose to X% of the penile bulb should not be >YGy; EQD2 = Equivalent Dose 2 Gy/fraction; Dmean = mean dose; TD = total prescribed dose
[§] Inclusion of dosimetry parameters in multivariable models with clinical variables.
[*] Severe.
[**] moderate-severe.
[***] Average follow-up (minimum follow-up: 16 months).
[**] Continuous variable.
[¶] Only mean dose to the penile bulb was considered (cobalt-grey equivalent). Mean dose to the penile bulb and total prescribed dose (TD) were poorly correlate (p = 0.10–0.12) with EPIC-based impotency score.
[¶] Only mean dose and maximum dose to the penile bulb (2 Gy-Equivalent doses) were considered.
[**] Median daily dose of the hypo-fractionated sub-group.

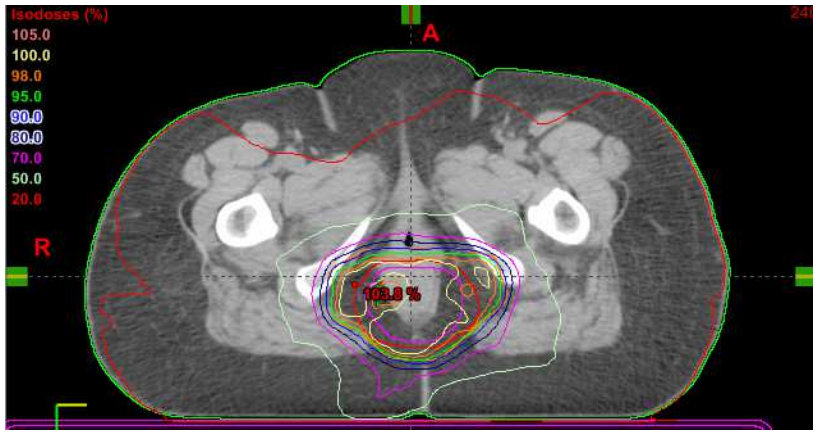
MRI Prostatic apex + IGRT with reduced margins, resulting in rare overlap between PTV and PB !

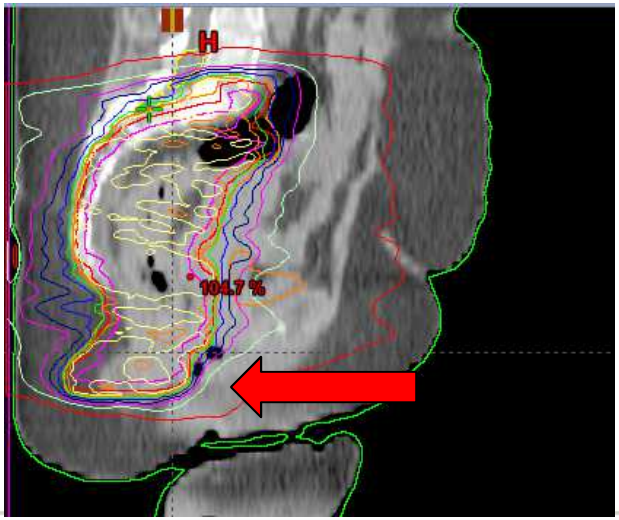


Landoni 2016
prostate ca pts, patient-reported impotence

Pelvic OARs constraints: genitals

- Dose to genitals (female)
- Under-estimated problem in the past, now quite «hot»
- Any effort should be activated to efficiently spare genitals outside PTV: beams geometry, blocking options in rotational techniques, ….
- IMRT highly effective in sparing external genitals to very low dose (even <5-10 Gy)
- Vaginal dryness/dyspareunia very commun problems importantly affecting QoL; impact of RT+CHT vs SURG only (Lange 2009, 2011, Bruheim 2010, Braendengen 2011, Incrocci 2013, Marijnen 2014, Ye 2014, Kunnemann 2015, Jensen 2015, Gilbert 2015)
- relationship with dose-volume parameters of vagina is lacking; some evidence of a dose-volume effect in cervix cancer braky (Park 2015)





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Pelvic OARs constraints: genitals

- Dose to vagina (Mirabeau-Beale 2015)
- Vaginal stenosis did not correlate with DVH/dose statistics of vagina/external genitals in a group of 52 pts treated with IMRT RT+CHT (50-54Gy) for anal canal ca. Lower age as a major risk factor
- Most part of vagina often included in PTV (median dose ≈ 55Gy)
- Need of more studies
- Potentials of image-guided IMRT to spare vagina to be still assessed (room for vagina-sparing trials ? Volumes definition issues)
- Practical suggestion: spare vagina and external genitals outside PTV «as much as possible» (no relevant interplays with other structures)

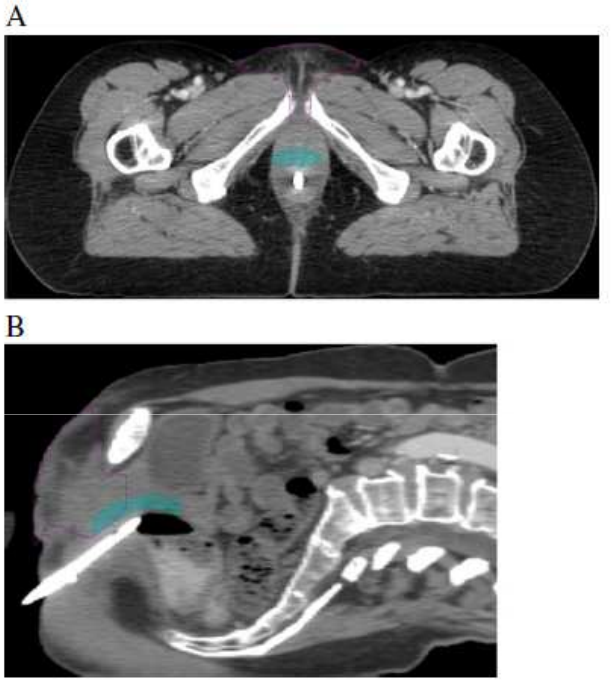

Figure 1 (A) Axial image of patient contours. (B) Sagittal image of patient contours. Cyan, vagina; pink, external genitals including mons pubis.

Mirabeau-Beale 2015

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Conclusive remarks

- 3DCRT and IMRT techniques offer good planning solutions
- IMRT should be preferred (better sparing of OARs, better conformation)
- Risk of sub-optimal planning with IMRT, be careful….
- Rotational IMRT (VMAT/IMAT/RA…., Tomo) highly effective and fast, better conformality and, sometime, better OAR sparing
- Constraints for OARs still poorly available (primarily for bowel, bone marrow, genitals)….much to be done (need of studies correlating prospective patient-reported outcomes/QoL scores vs dose-volume data)
- (Quantification of the impact of CHT poorly addressed)

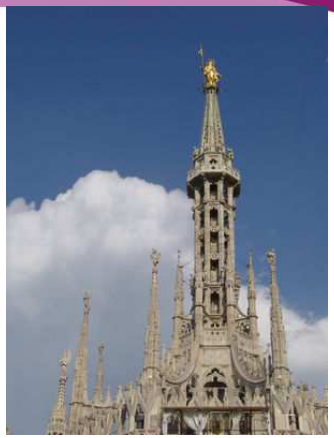
- IGRT improves accuracy; potentials to reduce margins with the aim to spare OARs in specific patients (i.e: sexual dysfunctions ?)
- Adaptive re-planning in its very early phase…

Thanks for your attention

- Thanks

P. Passoni, N. Slim (Radiotherapy)

S. Broggi, R. Raso, C. Sini (Medical Physics)



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Exercise Group 1: Adaptive experience (SIB, MRI-based tumour regression….)

C. Fiorino

Medical Physics

San Raffaele Institute, Milano, Italy

OSPEDALE SAN RAFFAELE

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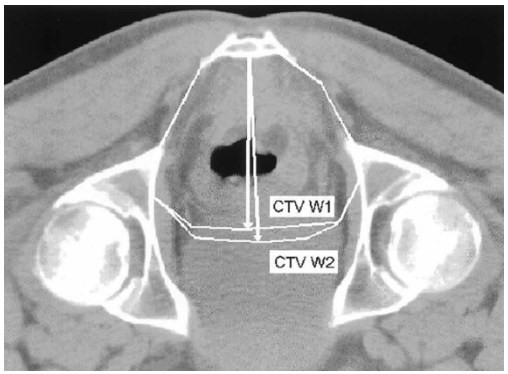
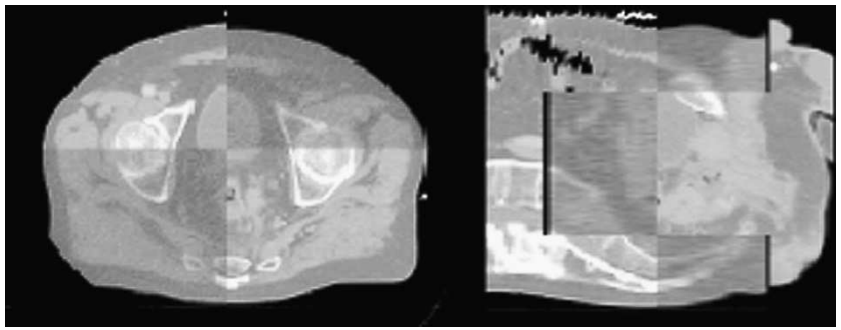
IGRT for rectal cancer

- Diagnostic kVCT to assess CTV motion
- CT in-room imaging, highly effective for image-guidance: CBCT, MVCT,...
- Image-guidance during neo-adjuv/adjuv RT
- Only rigid correction !

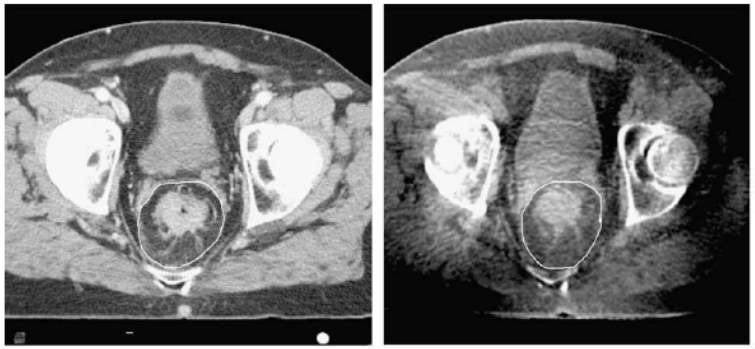


Nuyttens 2002 kVCT

Tournel 2008 MVCT Tomo



Niikamp 2009 CBCT



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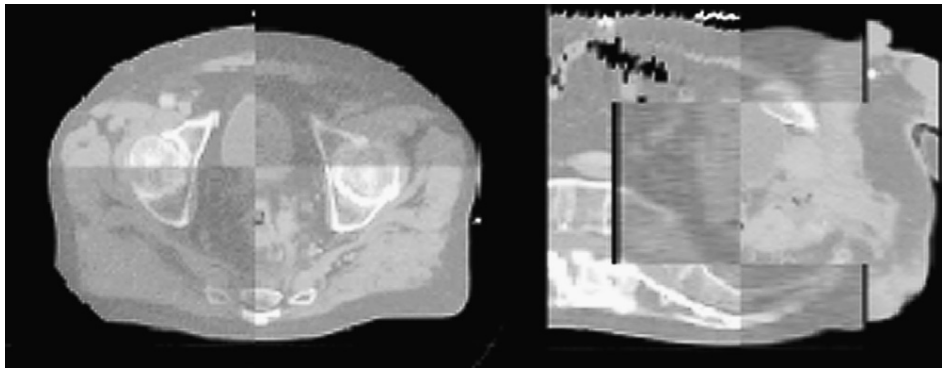
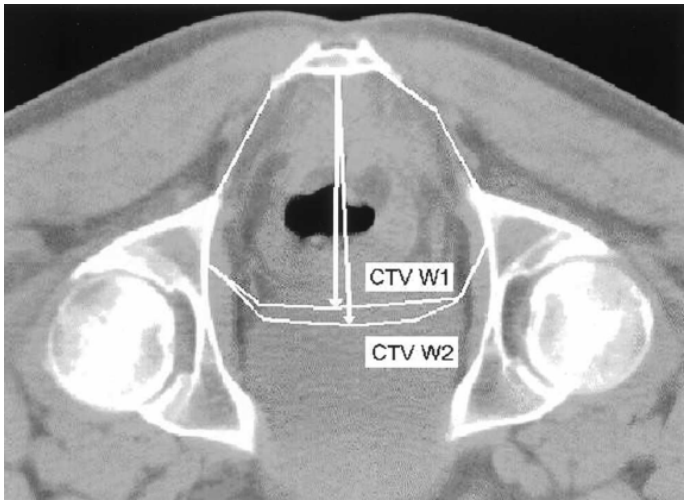
IGRT for rectal cancer

- Two step match between CT of the day and planning CT
- 1° : bony anatomy
- 2° : fine adjustment on mesorectum (generally quite well visible)
- Issues on anysotropic residual error….what margins ?
- Priority in matching the high-risk area





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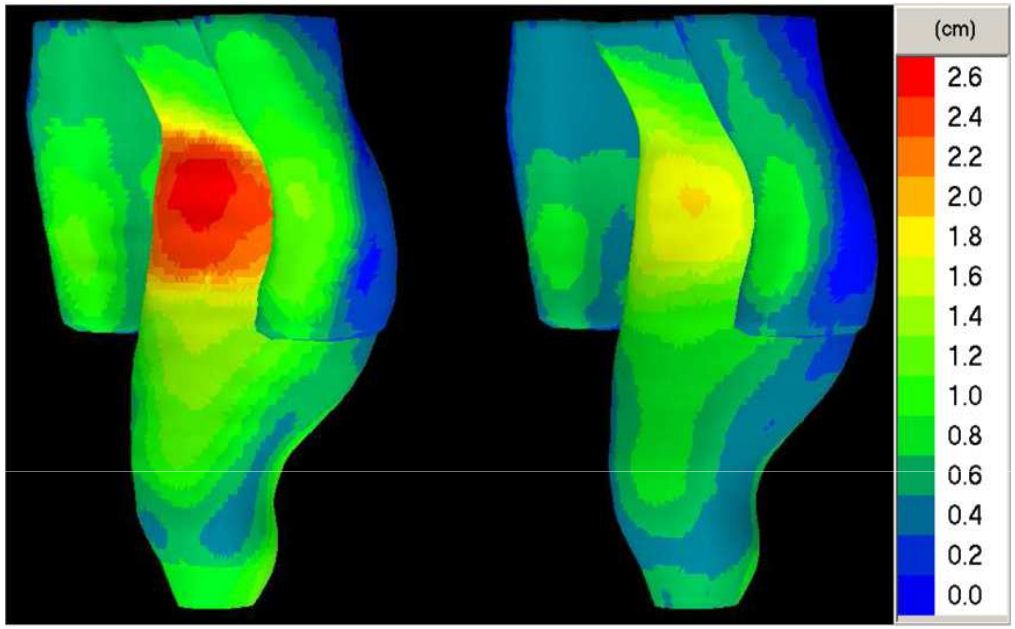
IGRT for rectal cancer

- Mesorectum reported to change in shape (mainly correlated with bladder motion)
- Main changes in ANT direction
- Larger impact for short-course, prone position and female pts
- Residual margins difficult to assess (local deformations, CTV contouring uncertainty)
- «Optimal» margins often not clinically feasible (Dmin>95%/90% pts too strict criterion? Contouring uncertainty too high..?)
- Issues concerning the real clinical impact in neo-adjuv RT(CHT)



Wout With daily correction

Njikamp 2012

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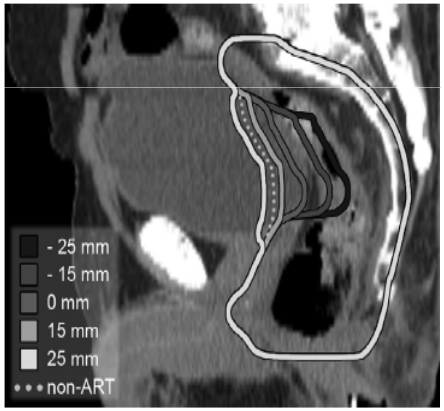
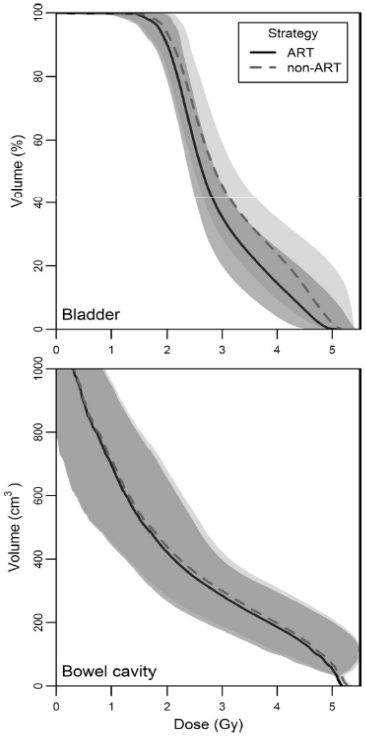
Adaptive planning

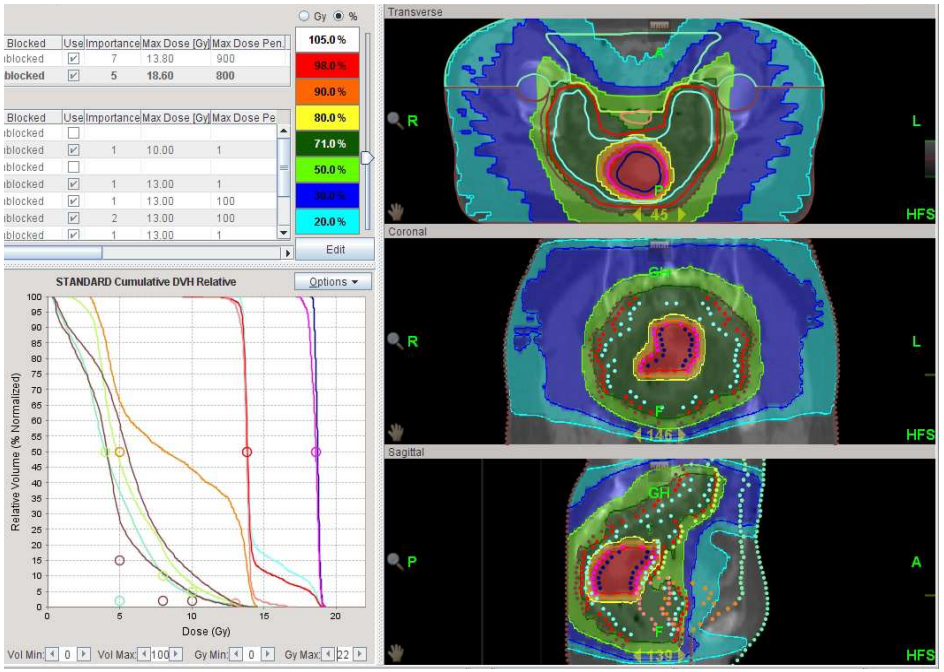
-Re-planning/plan of the day approach to take mesorectum changes into account in a 5x5 scheme,… suggested but no clinical experiences (cost-benefit ?)





Lutkenhaus 2016

- Adaptive planning to boost the residual GTV after half-RT T regression (promising approach to escalate the dose to T)….to be better discussed later (IGRT & adaptive)

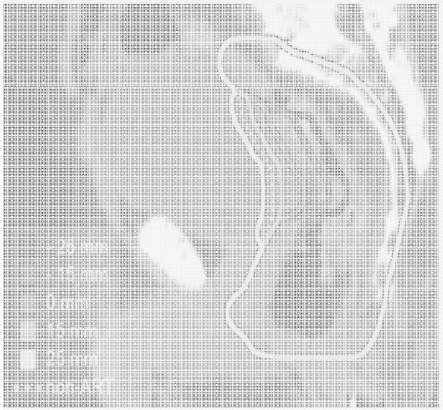


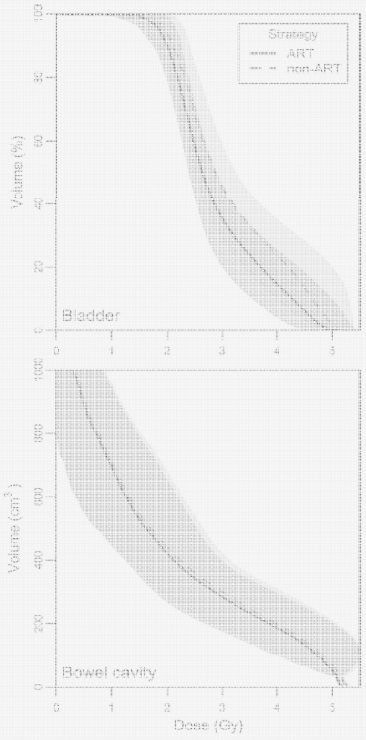
Passoni 2013

ESTRO School

Adaptive planning

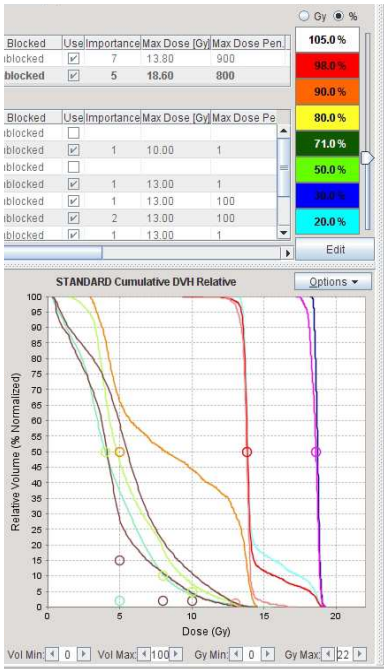
-Re-planning/plan of the day approach to take mesorectum changes into account in a 5x5 scheme,… suggested but no clinical experiences (cost-benefit ?)

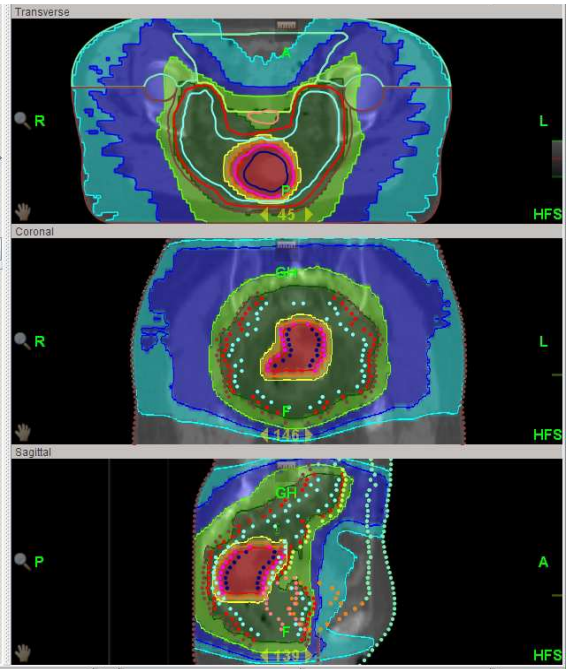




Lutkenhaus 2016

- Adaptive planning to boost the residual GTV after half-RT T regression (promising approach to escalate the dose to T)….**to be better discussed later (IGRT & adaptive)**





Passoni 2013

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Adaptive RT: background I

- Proven dose-effect response in RT+CHT regimens… boosting the tumor/mesorectum may increase pCR and major response rates

- Toxicity limits: exploring feasible protocols

- Exploiting acceleration (importance of repopulation) …reducing treatment time, Hyper/hypo in combination with IMRT (?)

- Evidence of relevant shrinkage during RT+CHT (especially in regimens including oxaliplatin), visible with MRI

- Can we exploit T shrinkage to safely boost the residual T ?

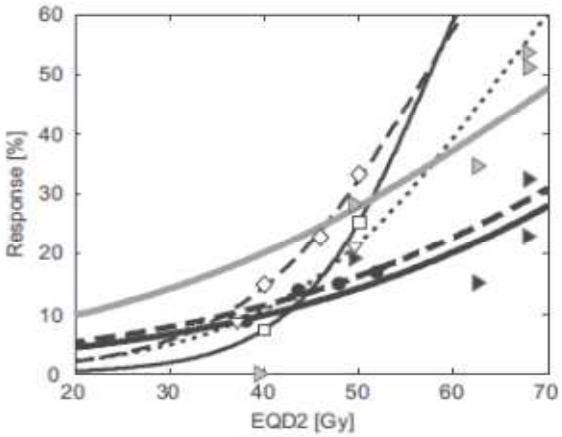


Fig. 3. Comparison of reported dose-response relationships between equivalent dose in 2 Gy fractions (EQD2) and complete response. All dose levels recalculated as EQD2, and logistic response curves fitted for each study. Each study is represented as follows: metaanalysis by Sanghera et al (6) (*bold dashed line, filled circles*), Chan et al (7) (*thin solid line, open squares*), Valentini et al (8) (*thin dotted line, open triangles*), Wiltshire et al (9) (*thin dashed line, open diamonds*), our study (*bold solid lines, filled triangles*), with response curves for complete response (*black line/triangles*) and major response (*grey line/triangles*).

Appelt 2012

ESTRO School

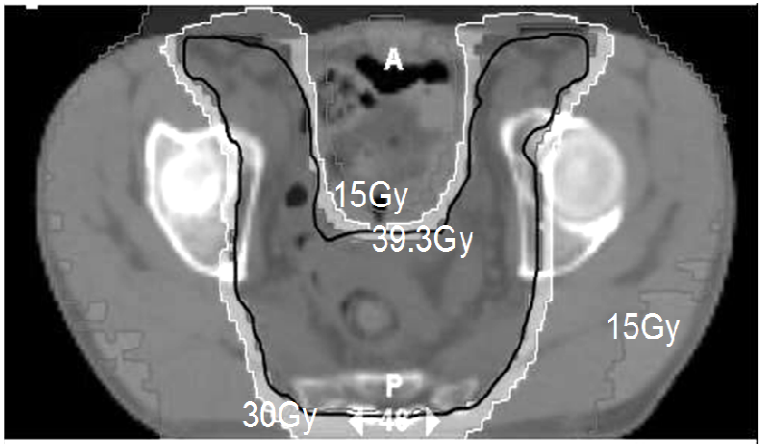
Adaptive RT: background II

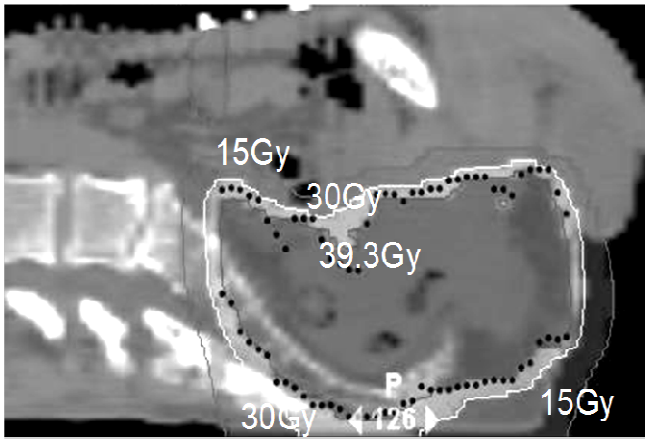
- At our Institute 2007-2009: pilot study exploring moderate hypo-fractionation, 41.4 Gy/18 fractions + Oxa/5FU*

- Daily image-guided Tomotherapy

- Feasible and efficient : G3 GI: 9%, pCR:28 % (data of first 35 pts)

- Introducing MRI for planning (+ diffusion MRI since 2013)





* Oxaliplatin 100mg/m2 on day -14, 0 (start of RT), +14; 5-FU 250mg/m2/day c.i. from day -14 to the end of RT.

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Adaptive RT: T regression as seen by MRI

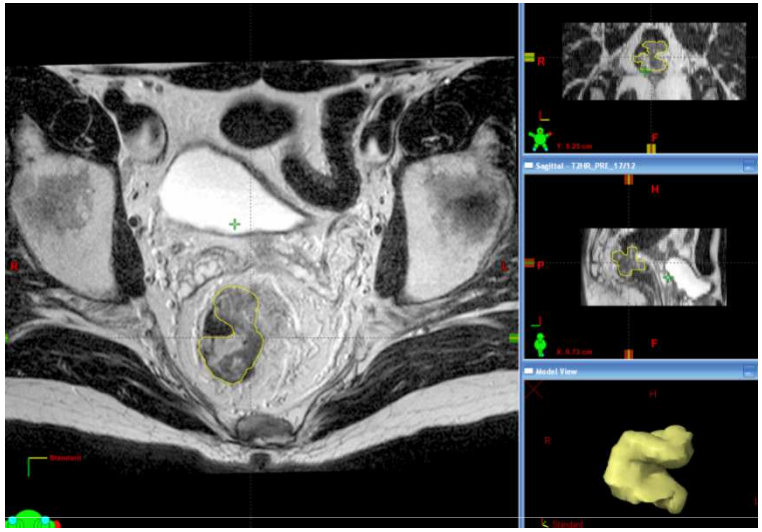
- Evidence of large T regression in most pts, already during the first half of the treatment

- T2-weighted MRI suitable for assessing tumour regression and GTV/CTV contouring

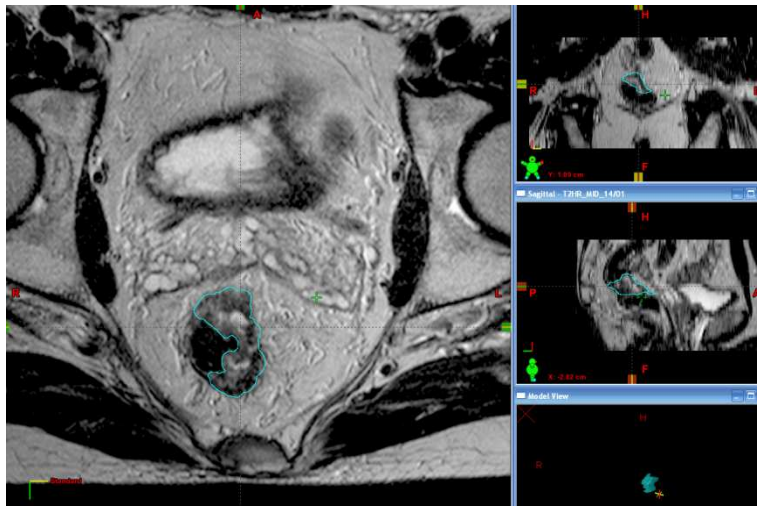
- Defining GTV_boost as the fraction of rectum corresponding to visible tumor at half-RT MRI

- Dose/fractionation ?

- Margins ?



Planning
MRI_GTV: 28cc



Mid-therapy (fr 9)
MRI_GTV: 7cc

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Adaptive RT: choosing the adaptive scheme

Applying LQ model including repopulation:

- Original scheme: **$BED = nd\,(1 + d/\alpha/\beta) - \gamma/\alpha\,(T - Tk)$**

where: d, daily dose, n n° fractions, γ/α repopulation factor (0.6Gy/day), Tk delay time (7 days), α/β=10 (Widder et al, 2005)

- Adaptive scheme:

$BED = md\,(1 + d/\alpha/\beta) + (n-m)d_{adapt}\,(1 + d_{adapt}/\alpha/\beta) - \gamma/\alpha\,(T - Tk)$

Assessing m and d_{adapt} to escalate the boost dose to EQD2=54Gy

- Practical limitations:

imaging for adaptive boosting not before half-RT

Leaving time for image matching, re-contouring, re-planning, scheduling….

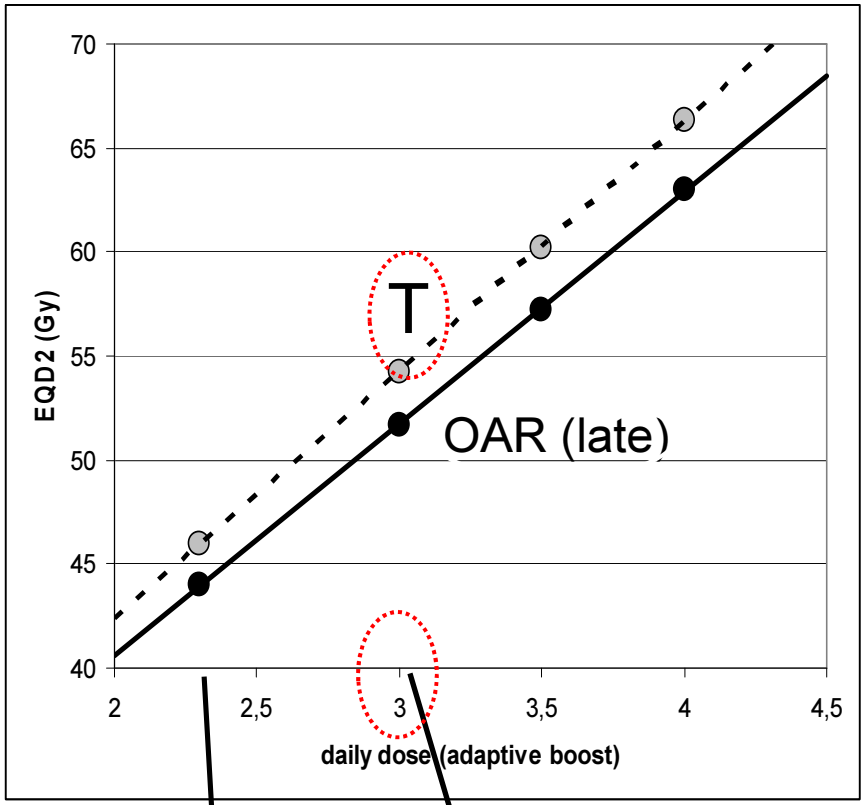
Adaptive RT: choosing the adaptive scheme

- MRI @ half therapy (fraction 9)

- Concomitant boost in the last 6 (3 days left)

- Calculating d_{adapt} to escalate to EQD2=54Gy ⇒ ≈ 3Gy/fr in the last 6 fractions (out of 18)

- Corresponding EQD2 for OAR (late tox, $\alpha/\beta=3$) slightly lower than for T



Summary of ART scheme:

Fractions 1-12: 2.3 Gy/fr (27.6 Gy) @ PTV1
Fractions 13-18: 2.3 Gy/fr (13.8 Gy) @ PTV1
concomitantly 3.0 Gy/fr (18Gy) @ PTV_{boost}

Total dose: 41.4Gy PTV1; 45.6Gy PTVboost (18 fractions)

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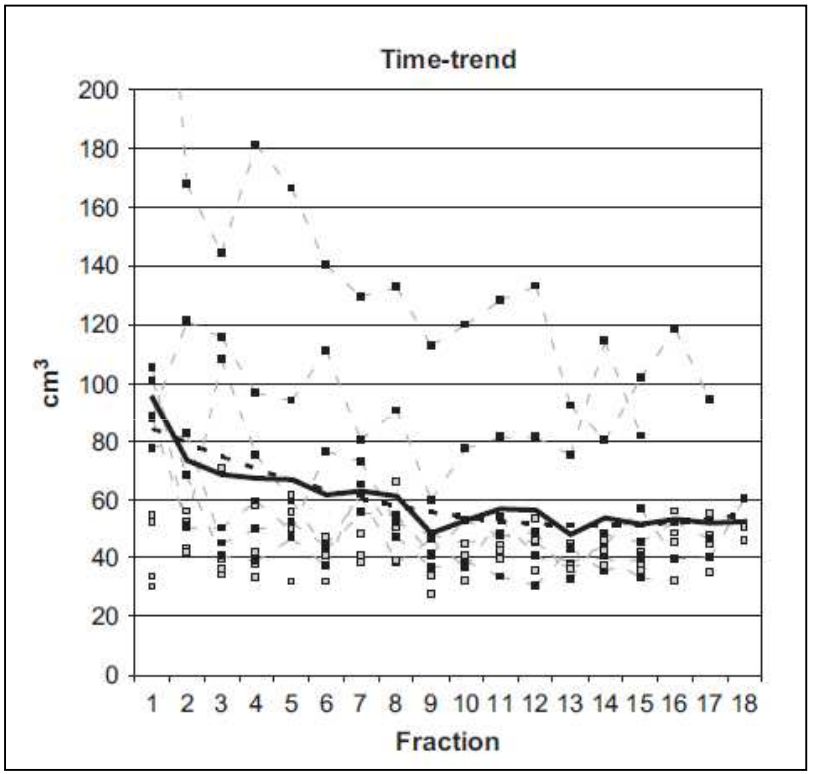
ART: margins for the boosting phase

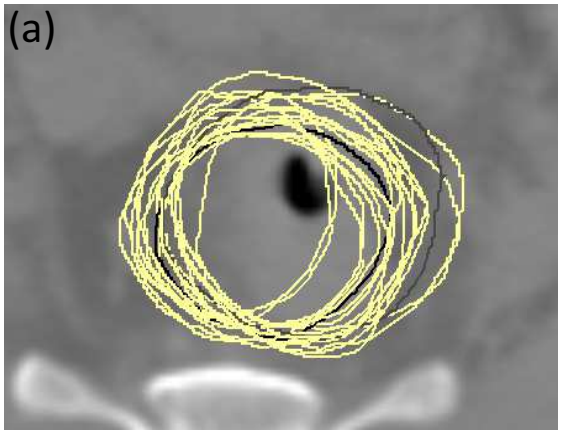
Maggiulli 2012

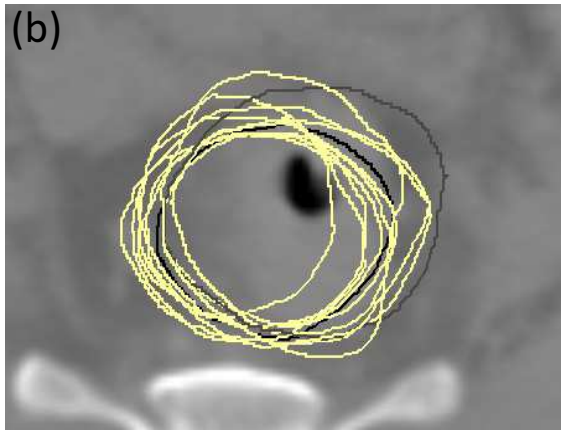
- Rectal motion as a surrogate of GTV/CTVboost
- Assessment of rectal motion based on MVCT daily images (Maggiulli 2012, Raso 2015)
- Trend for rectal volume reduction in 6/10 pts
- Residual deformation error after rigid correction (mimicking daily correction)
- Assessing a method to define «safe» margins for the boost based on local differences between contours and probability coverage



ESTRO School

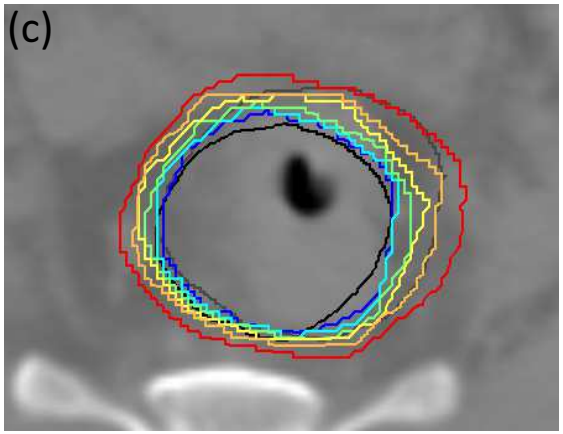
ART: margins for the boosting phase

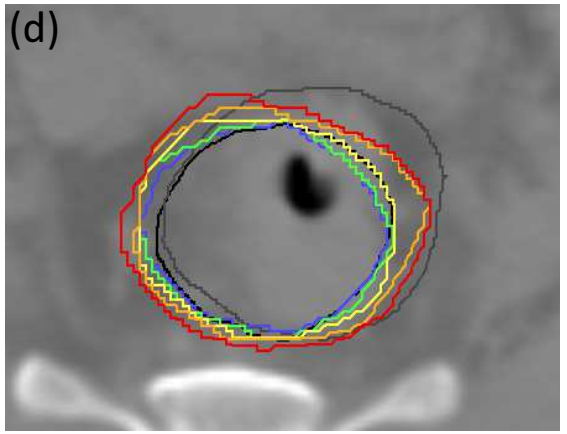


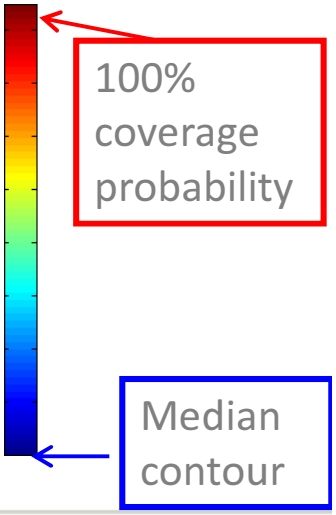


Raso 2015

Daily rectal contours for the whole treatment (a) and second part of treatment (b)







Coverage of 18, 16, 14, 12, 10, 9 over 18

Coverage of 9, 8, 7, 6, 5 over 9

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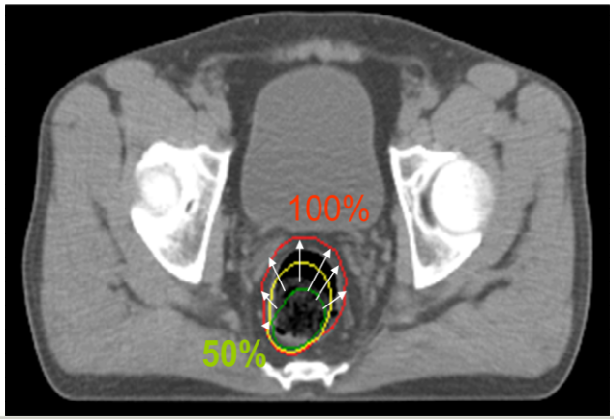
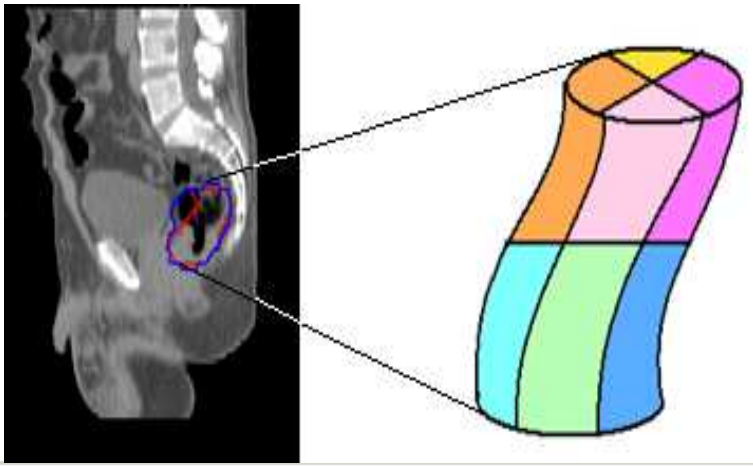
ART: margins for the boosting phase

- Margins as the local distance between ref contour and high-probability contour (for instance 90% ≈ missing 1/9 fractions)
- Splitting the rectum in 8 sectors (anysotropic motion)
- Assessing for each sector the «best» margin value based on the % of voxels (95-99%) included in the high-probability contour
- Prospectively evaluating the appropriatness on an independent population





Raso 2015

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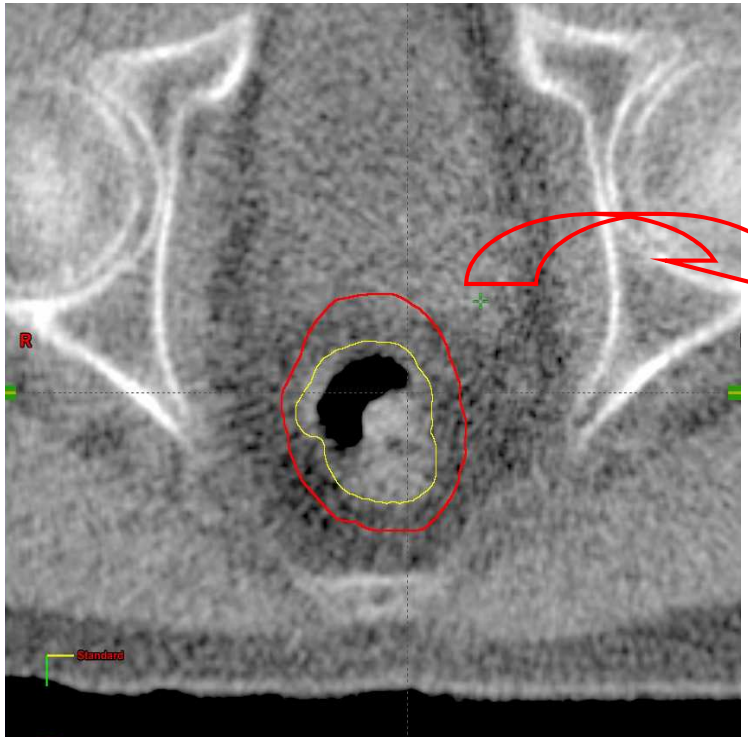
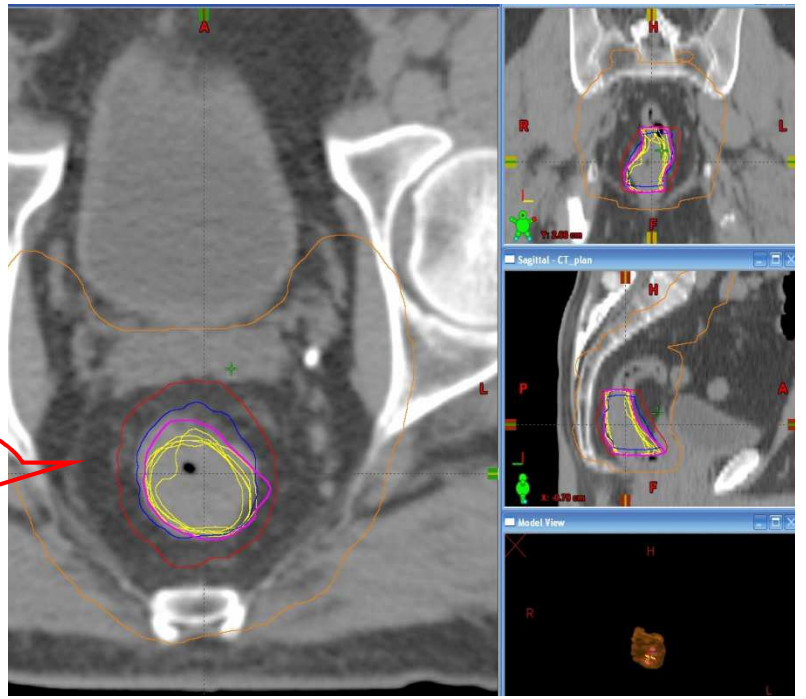
ART: margins for the boosting phase

prospective MVCT
verification of rectal motion





Red: PTV$_{adapt}$

Yellow: daily rectum

Purple: Envelope (boost phase)

Raso 2015

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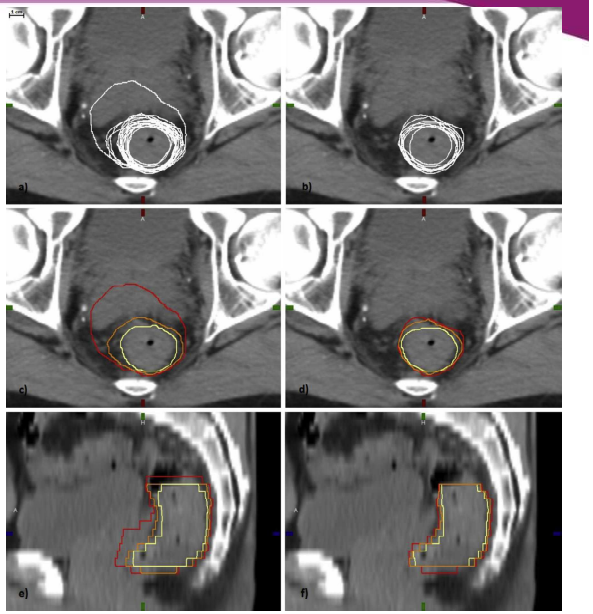
ART: margins for the boosting phase

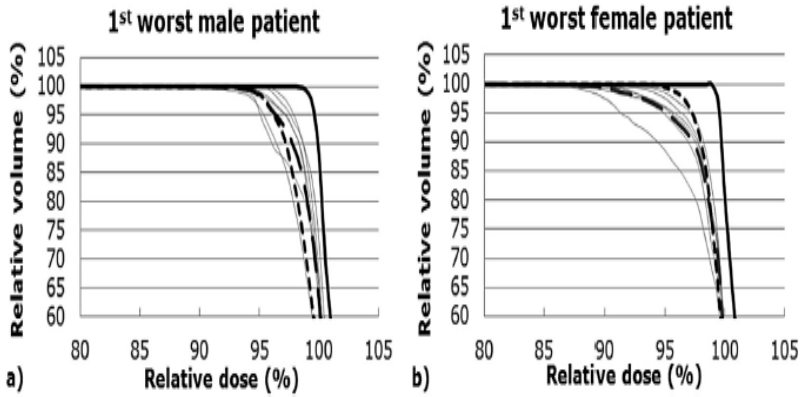
- Margins for the adaptive phase within 5mm, excepting anterior/superior for females (7-8 mm)

- (Corresponding margins for the whole treatment much larger, expecially ANT up to 15mm)

- Margin goodness prospectively confirmed on 20 pts (including dosimetric confirmation with dose-of-the day calculation on the most critical pts)



Whole 2nd (ART) part



Reference contour	UP-ANT	UP-POST	UP-R	UP-L	LOW-ANT	LOW-POST	LOW-R	LOW-L
M(90,90) (mm)								
1st fraction	9.0	3.0	3.0	4.5	4.9	1.9	4.5	3.3
9th fraction	5.8	2.3	3.4	3.5	6.5	3.3	3.4	4.7
$M(90,90)^{PTV}$ (mm)								
1st fraction	11.7	7.8	6.5	5.2	8.2	4.4	6.2	5.2
9th fraction	7.7	3.5	3.8	3.5	6.5	3.6	4.2	4.7
$M(90,90)^{PTV}$ (mm)								
1st fraction	14.7	9.8	6.5	7.1	11.1	6.8	8.2	7.3
9th fraction	7.9	4.4	4.9	3.5	6.5	4.7	5.6	5.3

Raso 2015

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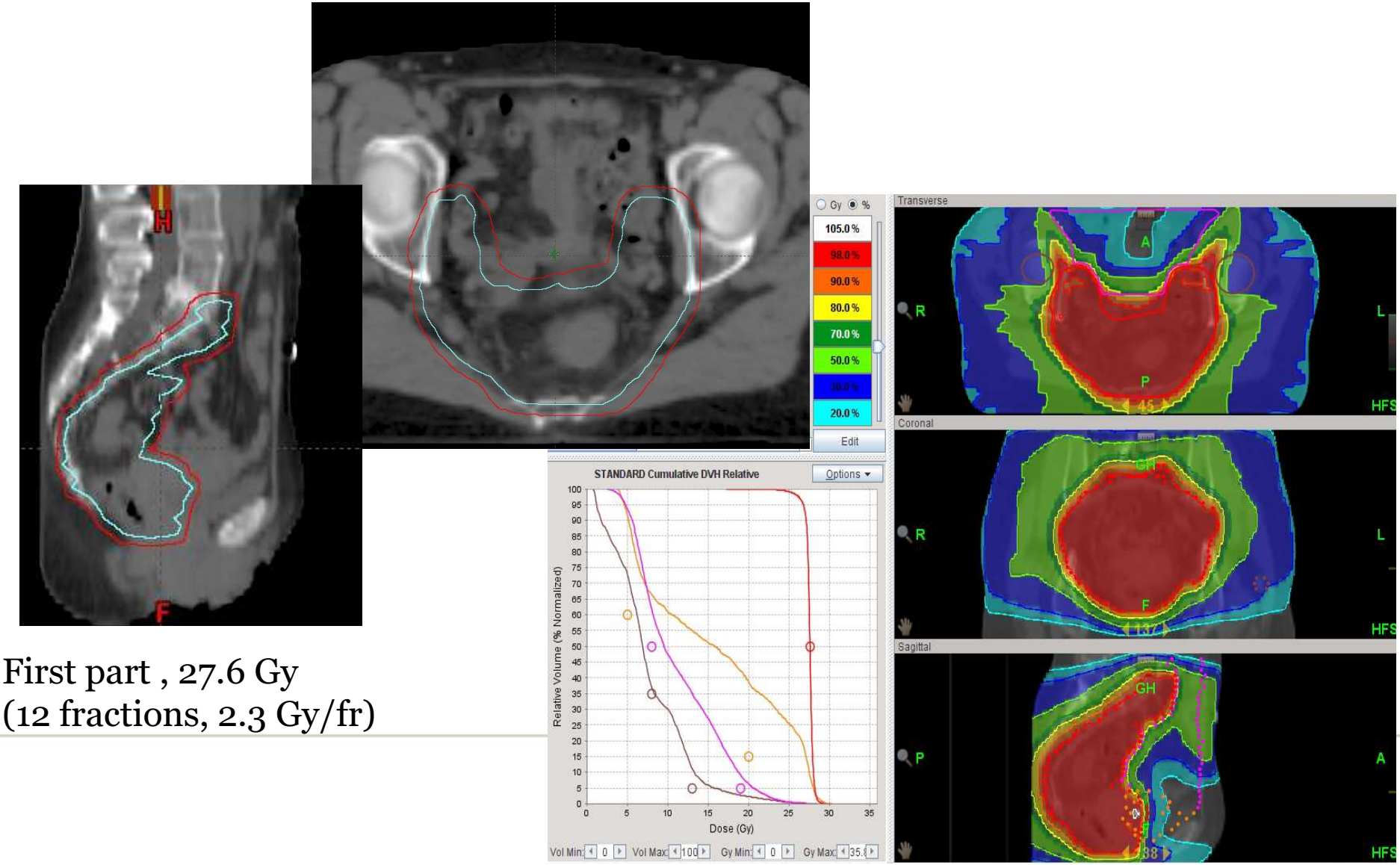
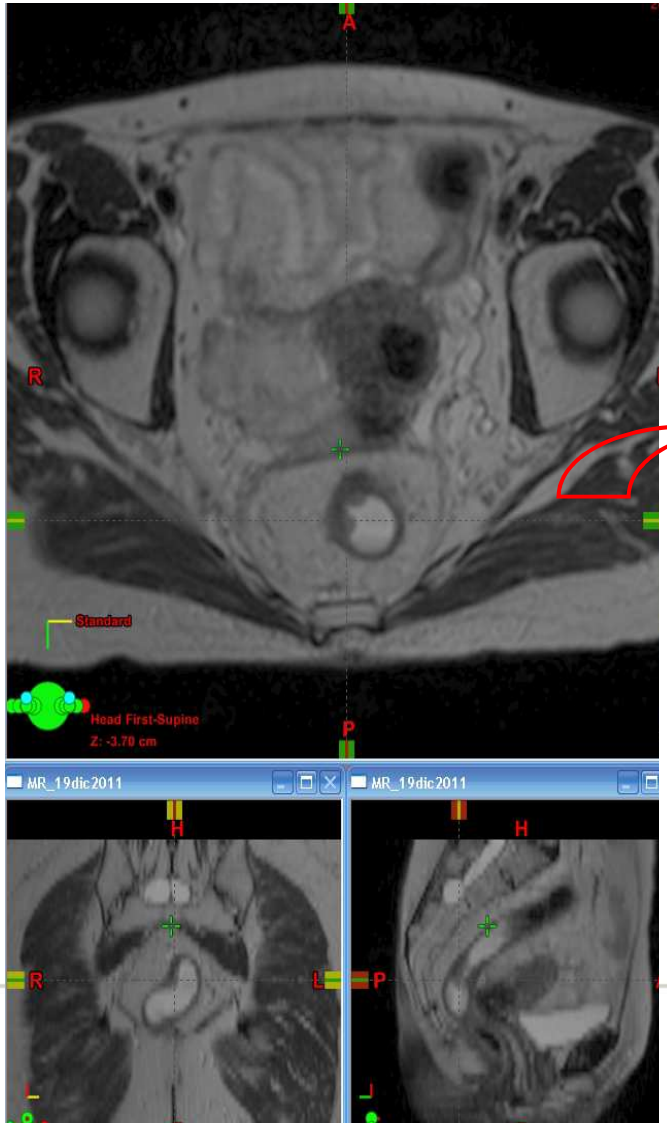
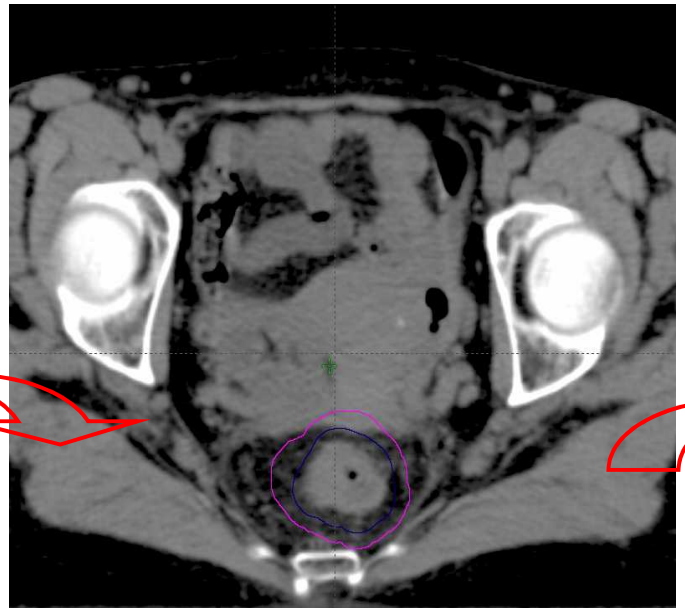
ART: planning and practical issues



First part , 27.6 Gy
(12 fractions, 2.3 Gy/fr)

ART: planning and practical issues





Half therapy imaging (CT/MRI)

Defining GTVadapt on MRI

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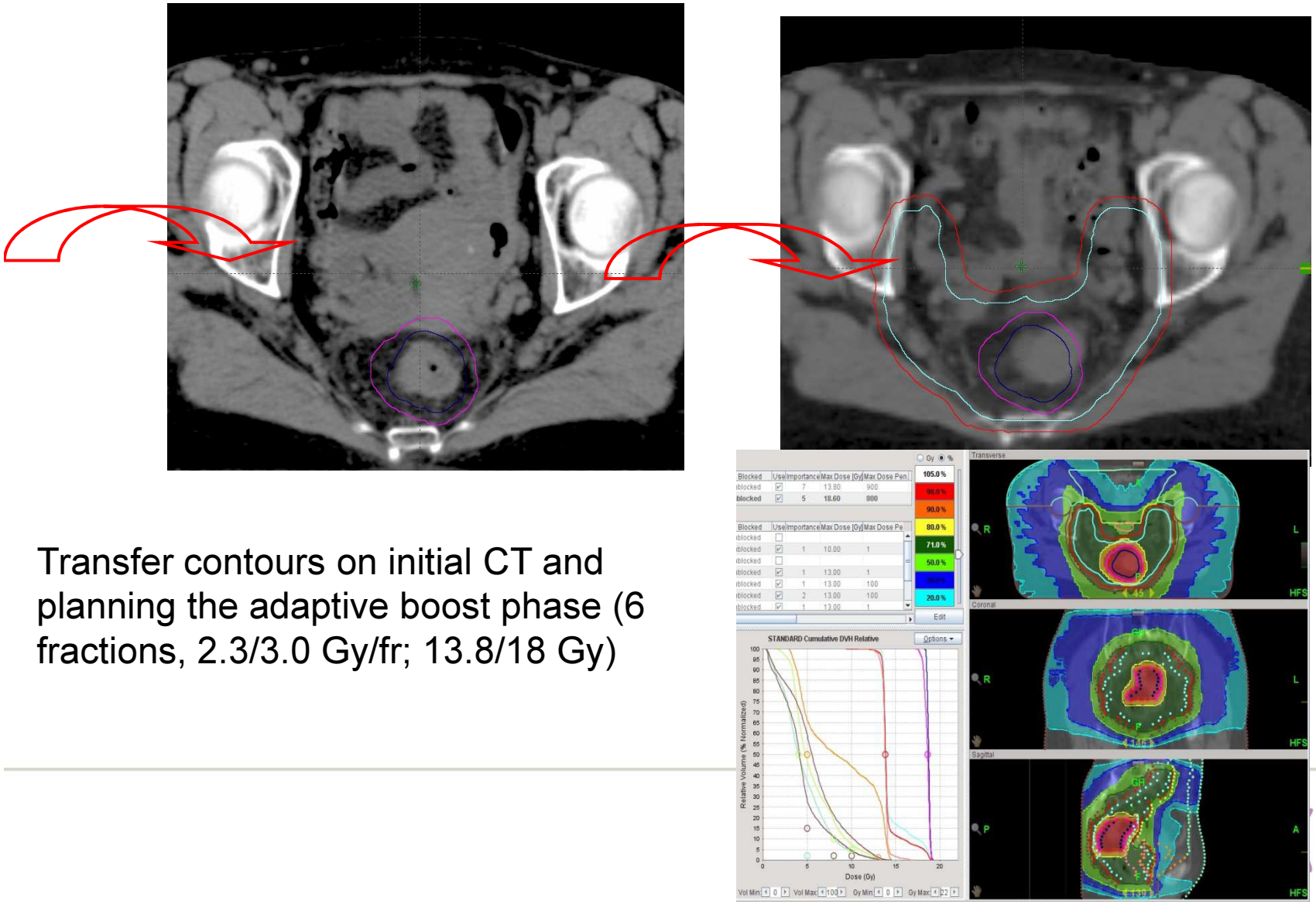
ART: planning and practical issues



Transfer contours on initial CT and planning the adaptive boost phase (6 fractions, 2.3/3.0 Gy/fr; 13.8/18 Gy)

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ART: clinical results

- Feasibility and promising results reported on the first 25 patients (Passoni Int J Rad Oncol Biol Phys 2013): 3/25 G3 GI (12%); full RT,Oxal,5FU dose in 96%, 96%, 88% of pts; no other G3 tox; 2 cCR pts refused surgery: (8%); pCR: 7/23 (30%); TRG≥3: 21/23 (91%);

- Major response rate (cCR+pCR+TRG3 with viable cells ≤10%): 21/25 (84%)

- Updated results on 62/78 pts confirmed these results (G3 GI: 13.5%; pCR+cCR: 29%, Major response rate: 79%

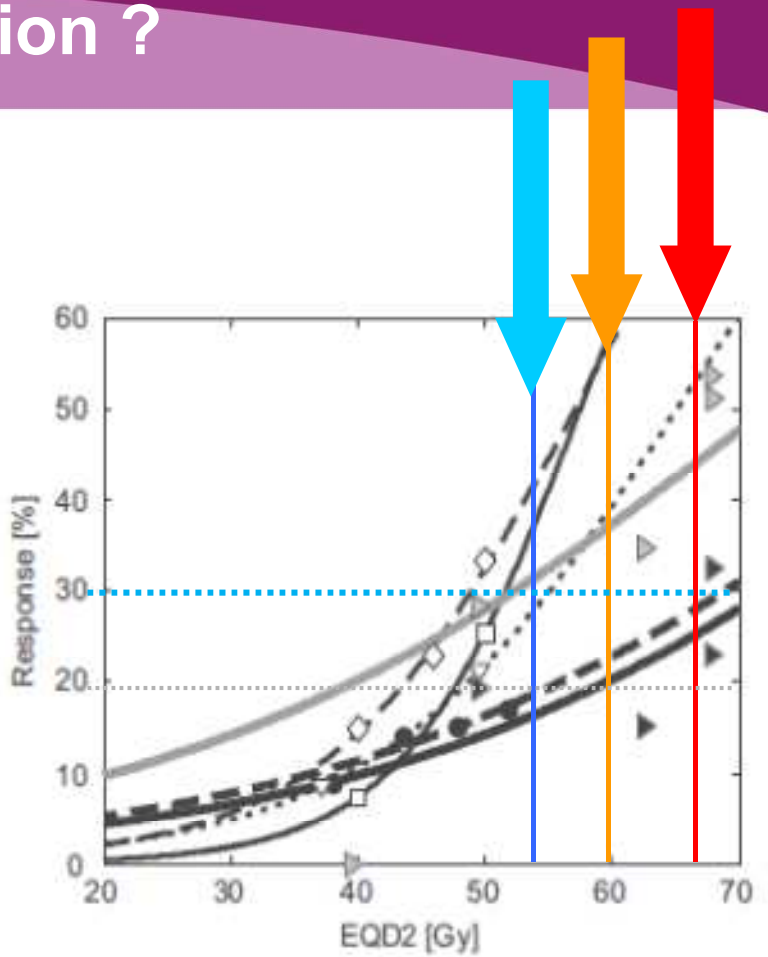
- Room for further dose escalation ?

- Individualizing the ART boost based on the early response ?

ART: room for dose escalation ?

3Gy/fr	3.5	4	dadapt
54Gy	60	66	EQD2(T)
52Gy	57	63	EQD2(OAR)
12%	?	?	G3 GI
29%*	?	?	pCR+cCR

*average rate of pCR from randomized trials with oxaliplatin: 18%



Appelt 2012

- Potentials in exploring protocols of watchful waiting ? (Appelt 2015, Renehan 2016)

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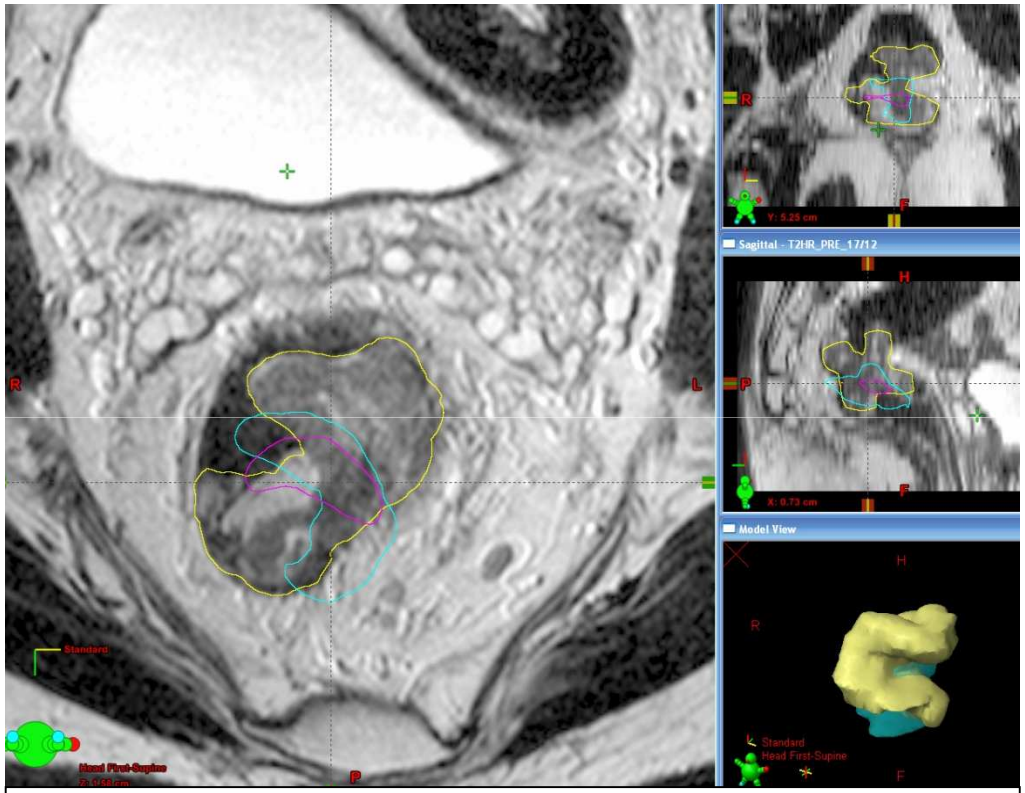
ART optimization based on early response ?

- Analyses of MRI-based T regression correlated with pCR
- May Mid-RT MRI (average volume reduction: -56%) predict the pathological response ?
- A poisson-based radiobiological model, incorporating the individual early response, well predicts pCR and residual cells (Raso, ESTRO 2016)
- Potentials for selection of pts for ART and adaptation of boost dose (work in progress…)



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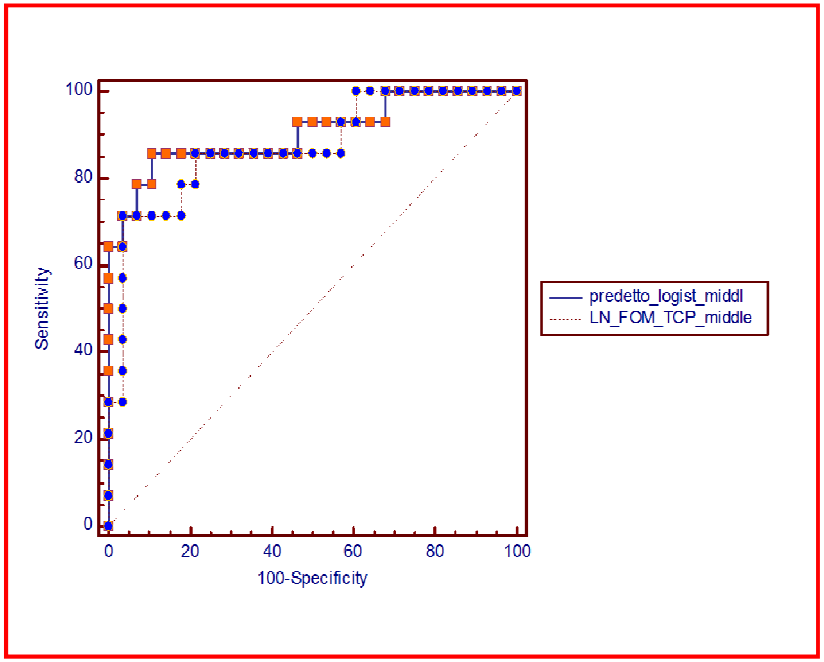
ART optimization based on early response ?

- Analyses of MRI-based T regression correlated with pCR
- May Mid-RT MRI (average volume reduction: -56%) predict the pathological response ?
- A poisson-based radiobiological model, incorporating the individual early response, well predicts pCR and residual cells (Raso, ESTRO 2016)
- Potentials for selection of pts for ART and adaptation of boost dose (work in progress...)



$TCP_D=(1-\Delta V_D)^{V\_PRE}$

AUC: 0.87 (specificity: 71.4%, sensitivity: 96.4%) (not lower discriminative power compared to post_RT MRI, AUC:0.82 n.s.); n=42 pts

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Conclusive remarks

- IGRT for rectal cancer: relevant to improve accuracy of delivery
- Mesorectum changes occurr and can be corrected only in part, is it an issue ?
- IGRT for boosting: GTV/rectal motion can be (better) modeled
- Even with daily image-guided correction, still relevant residual error due to deformation (margins need to be carefully assessed)
- Trend in rectal changes and reduction of motion during long-course RCHT («small» margins were found to be adequate for adaptive SIB in the second part of treatment)
- Shrinkage of T may be relevant and may be exploited to optimize adaptive approaches (to boost the residual T)
- ART with this approach was implemented (78 pts treated up to now)
- Promising results and room for further dose escalation on residual T
- Predicting the response based on (mid-RT) MRI response

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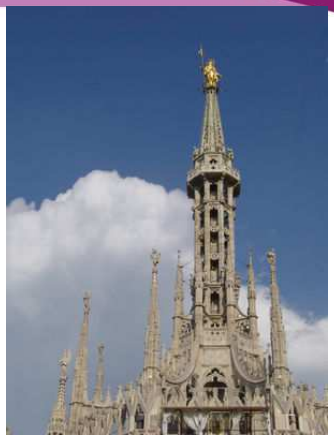
Thanks for your attention

- Thanks

P. Passoni, N. Slim (Radiotherapy)

S. Broggi, R. Raso (Medical Physics)

F. De Cobelli, A. Palmisano, A. Dichiara (Radiology)



OSPEDALE SAN RAFFAELE

ESTRO School

Rectal Cancer: Newer chemotherapy and targeted agents combined with RT

Claus Rödel
Department of Radiotherapy
University of Frankfurt
Germany

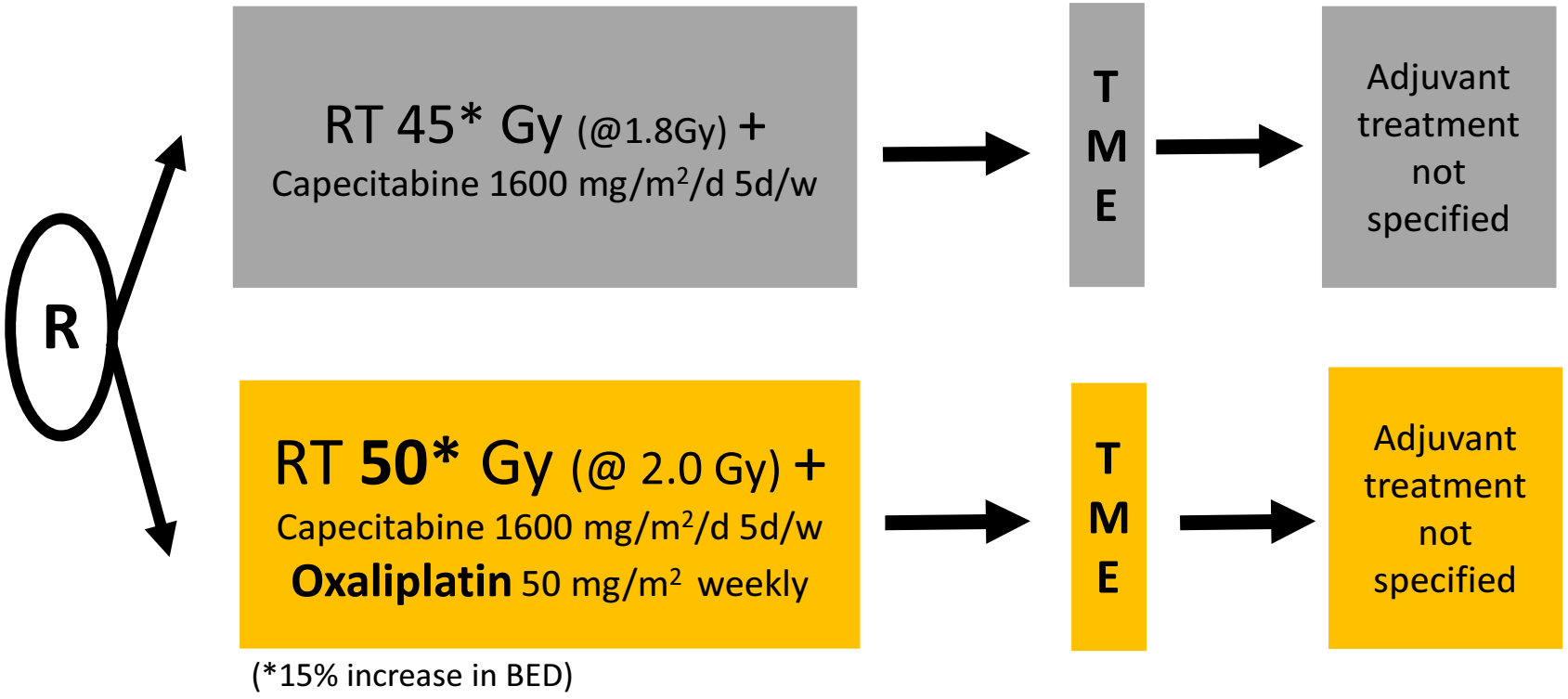
Statement – CRT and Oxaliplatin?

- The rationale to add oxaliplatin (and other concurrent systemic agents) to CRT for rectal cancer is **not** primarily for radiosensitization, pCR, or even local control (– *unless organ preservation is attempted*).

- The most important objective is to improve DFS/OS

ACCORD 12/0405-Prodige-Trial

Inclusion criteria: cT3-4 Nx, ≤ 80 years , PS 0-1



(*15% increase in BED)

Primary endpoint: pCR (11% to 20%), 590 pts required

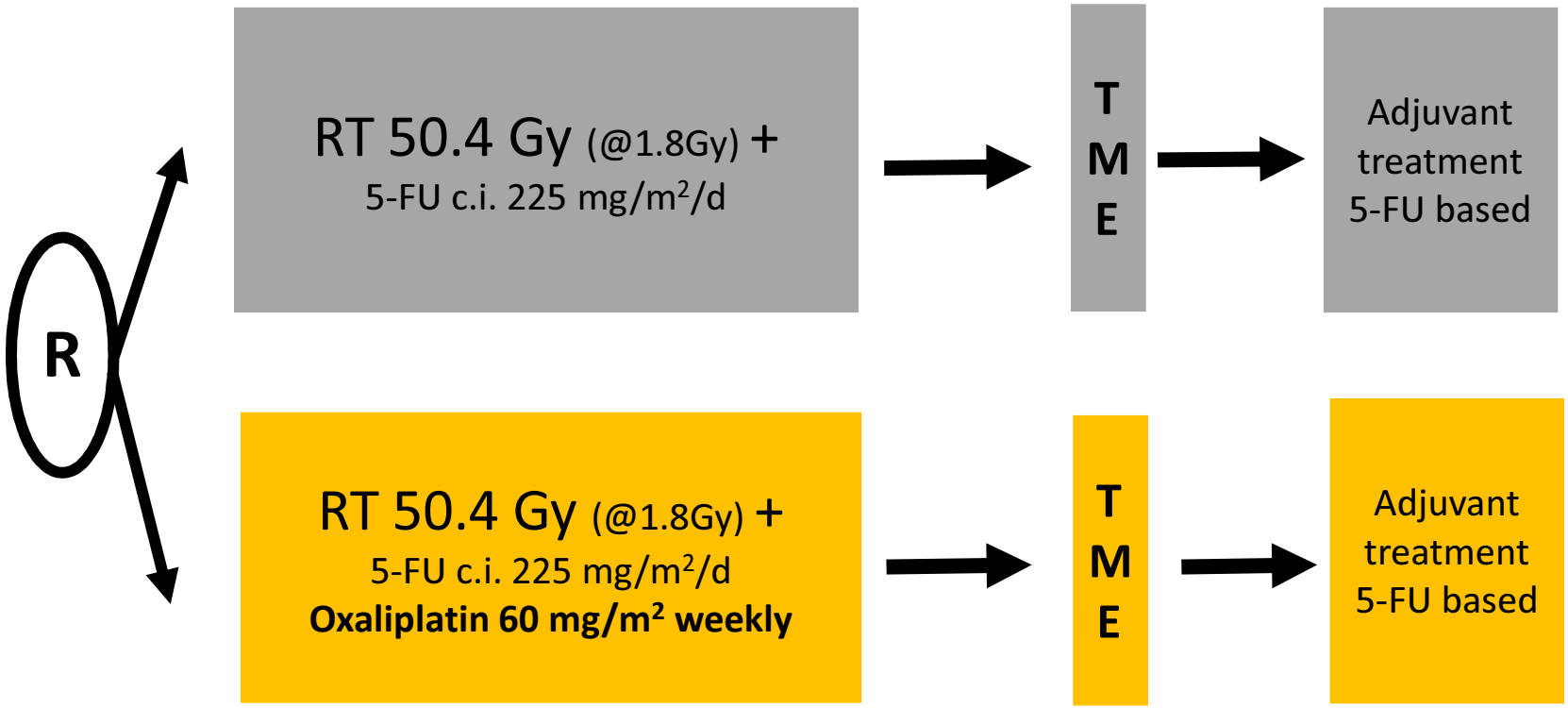
ACCORD 12/0405-Prodige-Trial

	RT 45 Gy Cape	RT 50 Gy CapeOx	P-value
Number of pts	293	291	
ypT0/TRG 4 (%)	**13.9**	**19.2**	**.09**
Grade 3/4 Tox		▲	
Compliance to CRT		▼	
			Gérard et al., J Clin Oncol 2010
Local Relapse @5y (%)	8.8	7.8	.78 HR 0.92
Disease-free Survival @ 5y (%)	**60.4**	**64.7** **Δ4.3%**	**.25** **HR 0.86**

Doyen J et al., ESTRO 2016

STAR-01

Inclusion criteria: cT3-4 or N+, ≤ 75 years



Primary endpoint: OS (30% reduction in mortality rates); 690 pts required.

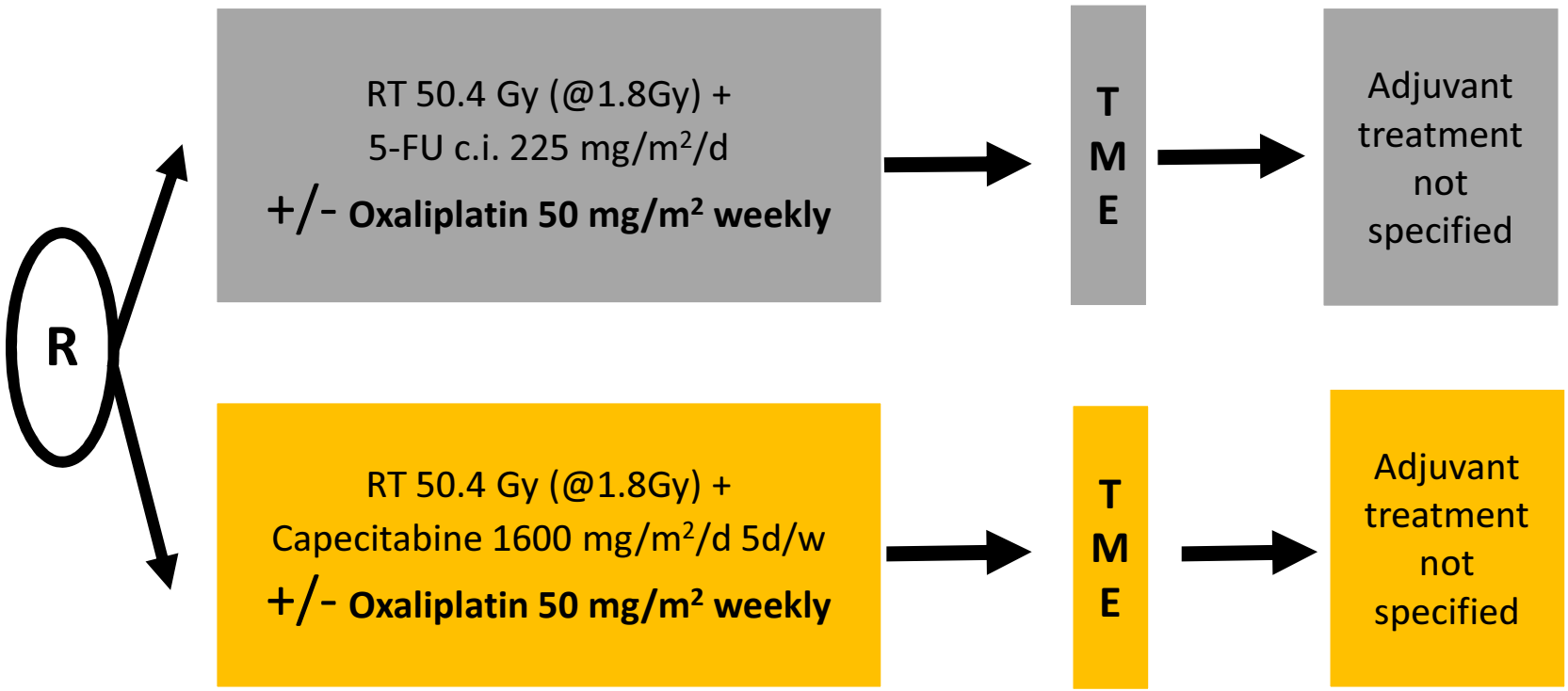
pCR as protocol-planned comparative analysis

STAR-01

	RT 50.4 Gy 5-FU	RT 50.4 Gy 5-FU/Ox	P-value
Number of pts	358	347	
pCR (%)	**16**	**16**	**.9**
Grade 3/4 Tox		▲	
Compliance to CRT		▼	
			Aschele et al., J Clin Oncol 2011
Local Relapse @5y (%)	pending	pending	
Disease-free Survival @ 5y (%)	pending	pending	

NSAPB R-04

Inclusion criteria: cT3-4 or N+ M0



Primary endpoint: Time to locoregional failure

Secondary: pCR, sphincter-sparing surgery, downstaging, tox

NSAPB R-04

	RT 50.4 Gy 5-FU or Cape	RT 50.4 Gy 5-FU/Cape+Ox	P-value
Number of pts	636	640	
pCR (%)	**17.8**	**19.5**	**.42**
Grade 3/4 Tox		▲	
Compliance to CRT		▼	

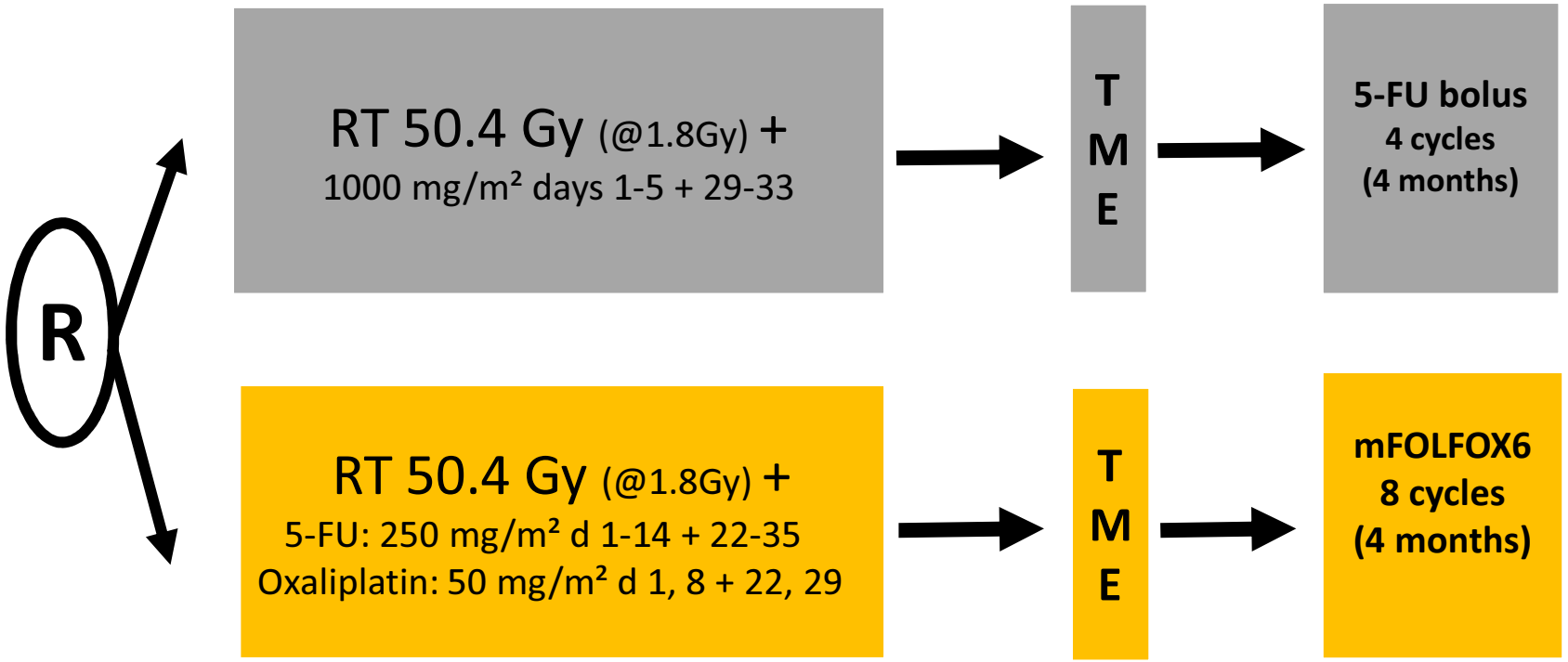
O'Connell et al., J Clin Oncol 2014

Local Relapse after R0 @3y (%)	5.1	3.1	.21 HR 0.71
Disease-free Survival @ 5y (%)	**64.2**	**69.2** **Δ 5%**	**.34** **HR 0.91**

Allegra et al., J Natl Cancer Inst 2015

CAO/ARO/AIO-04 (similar design PETACC-6)

Inclusion criteria: cT3-4 or N+



Primary endpoint: 3y-DFS (75% to 82%); 1200 pts

pCR as unplanned exploratory analysis

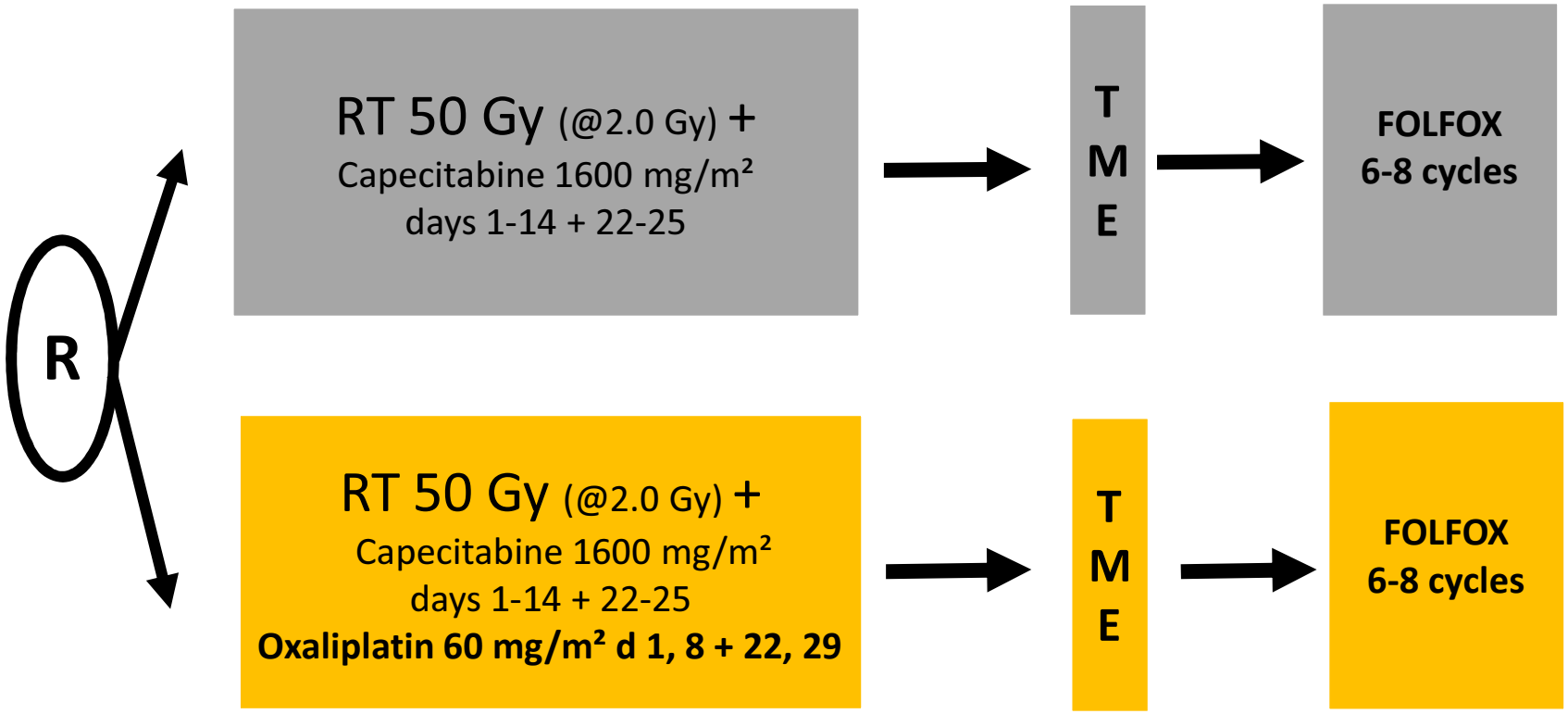
CAO/ARO/AIO-04

	RT 50.4 Gy 5-FU	RT 50.4 Gy 5-FU/+Ox	P-value
Number of pts	623	613	
pCR (%)	**13**	**17**	**.04**
Grade 3/4 Tox		=/▲	
Compliance to CRT		=	
			Rödel et al., Lancet Oncol 2012
Local Relapse after R0/1 @3y (%)	4.6	2.9	
Disease-free Survival @ 3y (%)	**71.2**	**75.9 △4.7%**	**.03 HR 0.79**
			Rödel et al., Lancet Oncol 2015

(full paper from similar PETACC-6 pending)

Chinese Study

Inclusion criteria: cT3-4 or N+



Primary endpoint: 3y-OS (84 to 96%); 206 pts

Chinese Study

	50 Gy CAPE	RT 50 Gy CAPOX	P-value
Number of pts	102	106	
pCR (%)	**19.4**	**23.3**	**.5**
Acute tox grade 3+4		▲	
Compliance		▼	
Local Failure @3y (%)	5.8	4.8	.7
Disease-free Survival @ 3y (%)	**69.9**	**80.5 Δ10.6%**	**.08**

Jiao et al., Chin J Cancer Res 2015

Disease-free Survival

Colon Cancer Stage II/III	n	Absolute Difference	HR	P-value
MOSAIC	2246	**5% (3y)**	0.77	.002
NSABP C-07	2407	**4% (3y)**	0.80	.003

Rectal Cancer Stage II/III Neoadjuvant oxaliplatin				
ACCORD 12	584	**4.3% (5y)**	0.86	0.25
NSAPB R-04	1284	**5% (5y)**	0.91	0.34
CAO/ARO/AIO-04	1236	**4.7% (3y)**	0.79	0.03
Chinese	206	**10.6% (3y)**	n.g.	0.08

STAR-01 and full paper of *PETACC-6 pending*

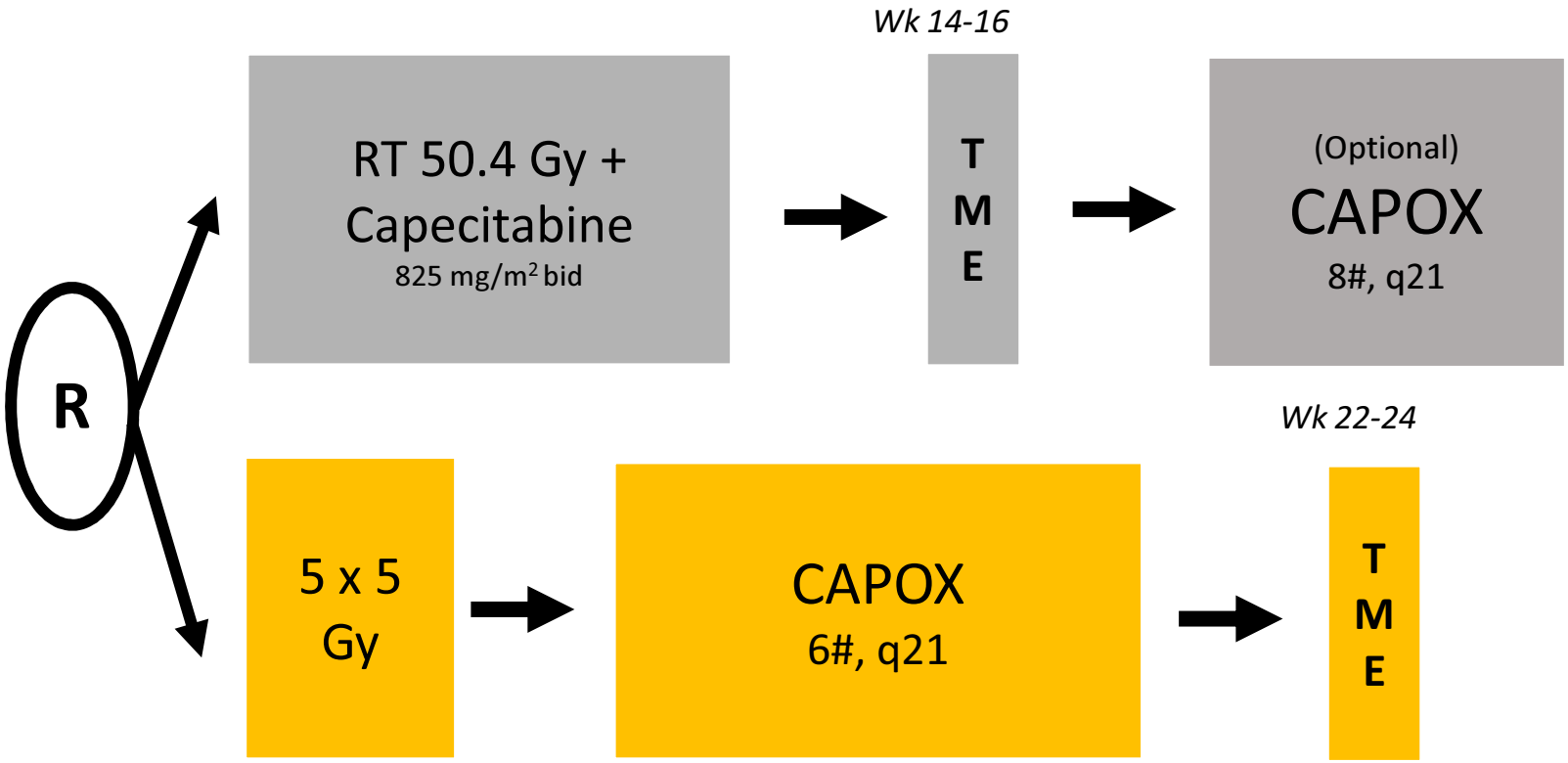
Three ways to incorporate oxaliplatin into CMT:

- Use a pre and postoperative regimen with less tox and high compliance (CAO/ARO/AIO-04)
- Use oxaliplatin after preop 5-FU/Cape CRT in adjuvant setting only (NCCN-guidelines, ADORE*)
- Find better ways ...

**Hong et al., Lancet Oncol 2014*

RAPIDO-Trial (randomized phase III)

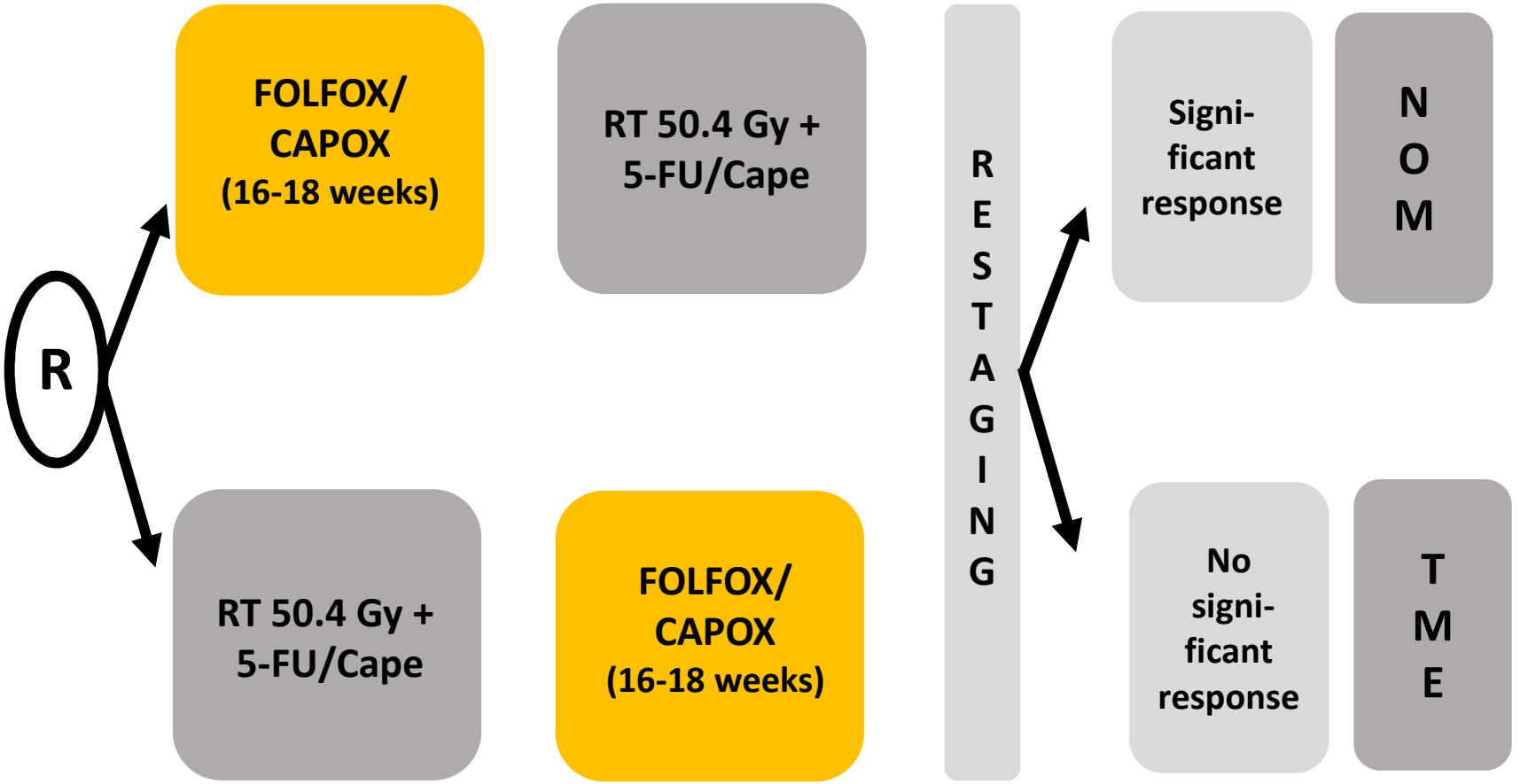
MRI-defined high-risk criteria:
cT4 or MRF+ or N2 or lateral N+ or EMVI+



Primary endpoint: 3y-DFS (50% > 60%), 885 pts. required

MSKCC-Trial (randomized phase II)

MRI-staged T2-3 N0 or T any N+



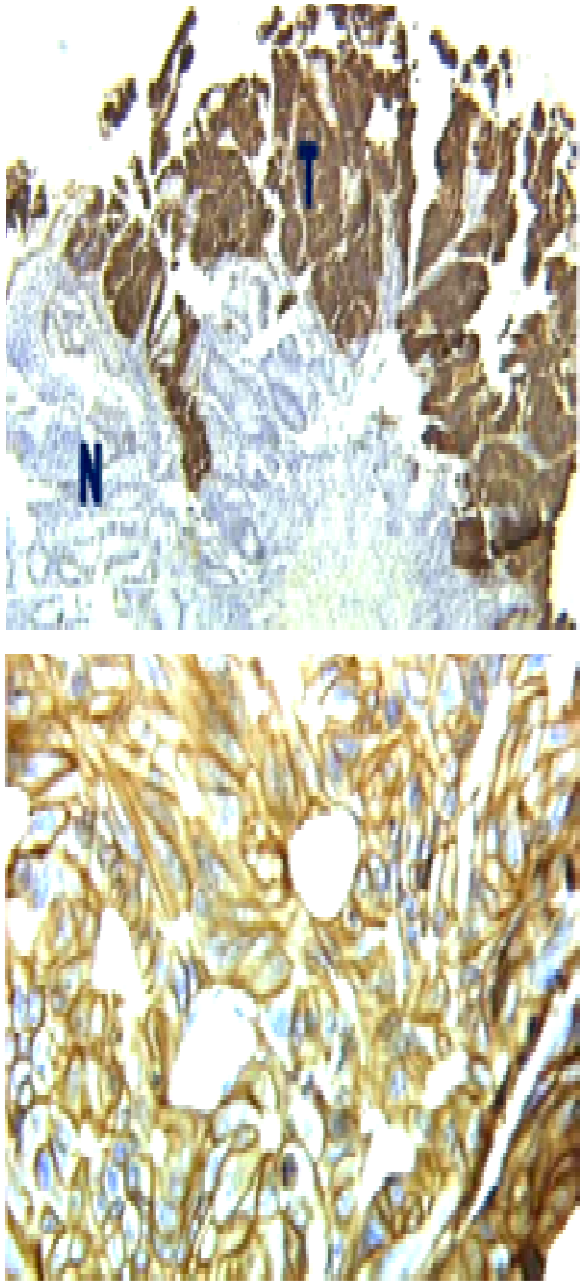
The

EGFR

and

RAS

story….



EGFR as Predictive Biomarker

EGFR - → **pCR: 8/35** **29%**

EGFR + → **pCR: 2/52** **4%**

p=0.006

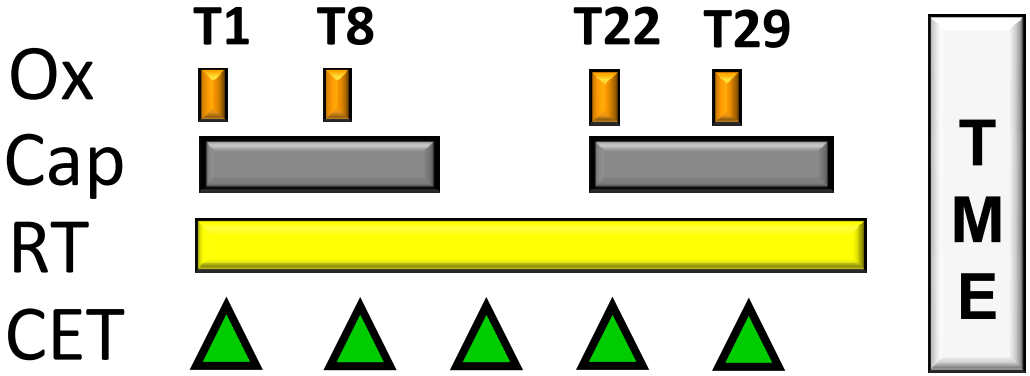
Giralt J. et al., Radiother Oncol 2005

Clinical trials with EGFR-Inhibition in RC

Series	n	Treatment	pCR
Bertolini, 2007	40	RT + 5-FU + *Cetuximab*	8%
Machiels, 2007	30	RT + Cape + *Cetuximab*	5%
Rödel, 2008	48	RT + Capox+ *Cetuximab*	9%
Hofheinz, 2008	50	RT + Capiri+ *Cetuximab*	8%

CAO/ARO/AIO-Experimental Track

Phase I/II: Inclusion of molecular-targeted therapy



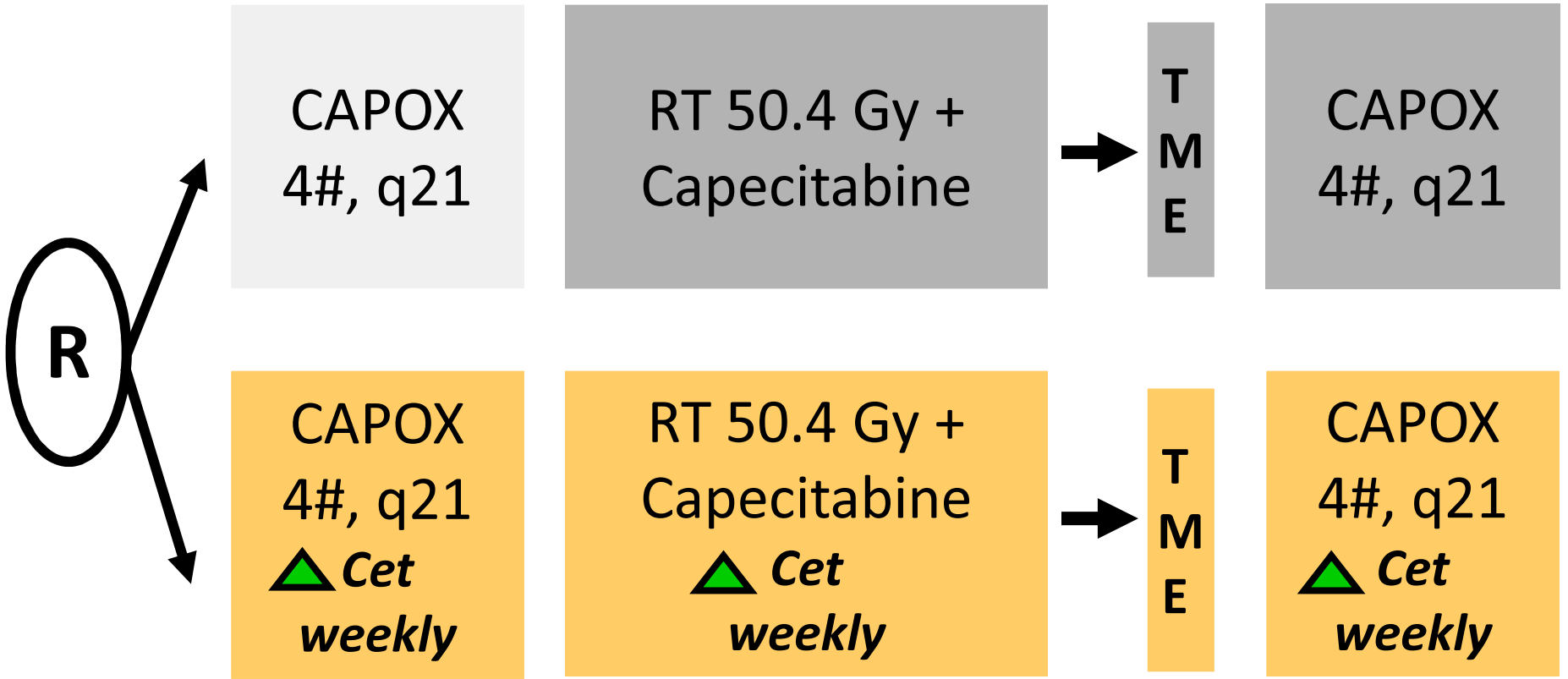
	CET-CAPOX-RT ▲ (n=45)	CAPOX-RT (n=95)
Complete TRG (%)	9	18
Intermediate TRG /%)	55	68
Poor TRG (%)	36	15

Rödel C. et al., Int J Radiat Oncol Biol Phys 2008
Weiss C. et al., Int J Radiat Oncol Biol Phys 2010
Fokas E., et al., Int J Radiat Oncol Biol Phys 2013

Biomarker Studies
Grimminger PG. et al., Clin Cancer Res 2011
Hu-Lieskovan S. et al., Clin Cancer Res 2011

EXPERT-C Trial (randomized phase II)

MRT- defined high risk:
≤ 1mm to mesorectal fascia, T3 ≥ 5mm, low-lying T3, V1, T4



Dewdney A et al. , J Clin Oncol 2012

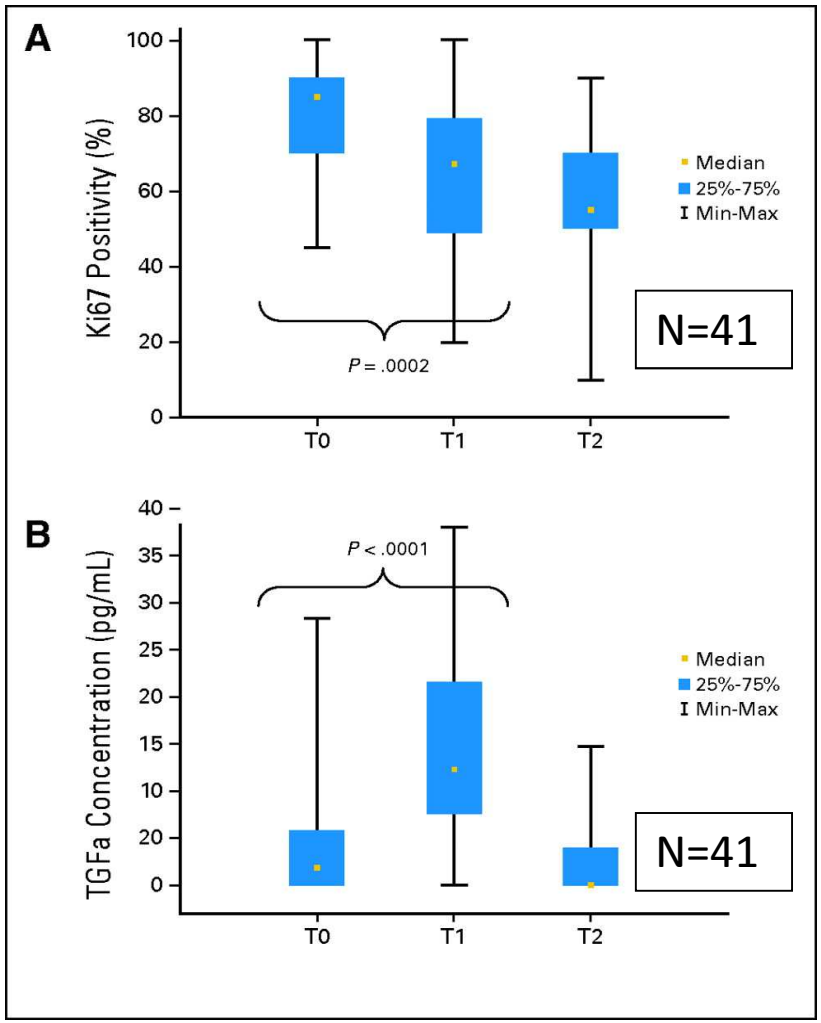
EXPERT-C Trial

	CAPOX All treated (n=81)	CAPOX+C All treated (n=83)	P
pCR (primary endpoint)	14%	18%	.45

	CAPOX KRAS/BRAF wild type: n=44	CAPOX+C KRAS/BRAF wild type: n=46	P
After neoadjuvant chemo	51%	73%	.04
After CRT	76%	89%	.12
At surgery: pCR (+ rCR)	9.1%	10.9%	1.0
PFS at 5 years	68%	75%	.23

Dewdney A et al., J Clin Oncol 2012
Sclafani E et al., Eur J Cancer 2014

Molecular Response to Cetuximab and Efficacy of Preoperative Cetuximab-Based Chemoradiation in Rectal Cancer



Mikroarray:

Downregulation of genes involved in proliferation

K-ras status:

Not related to outcome parameters (TRG, DS, DFS)

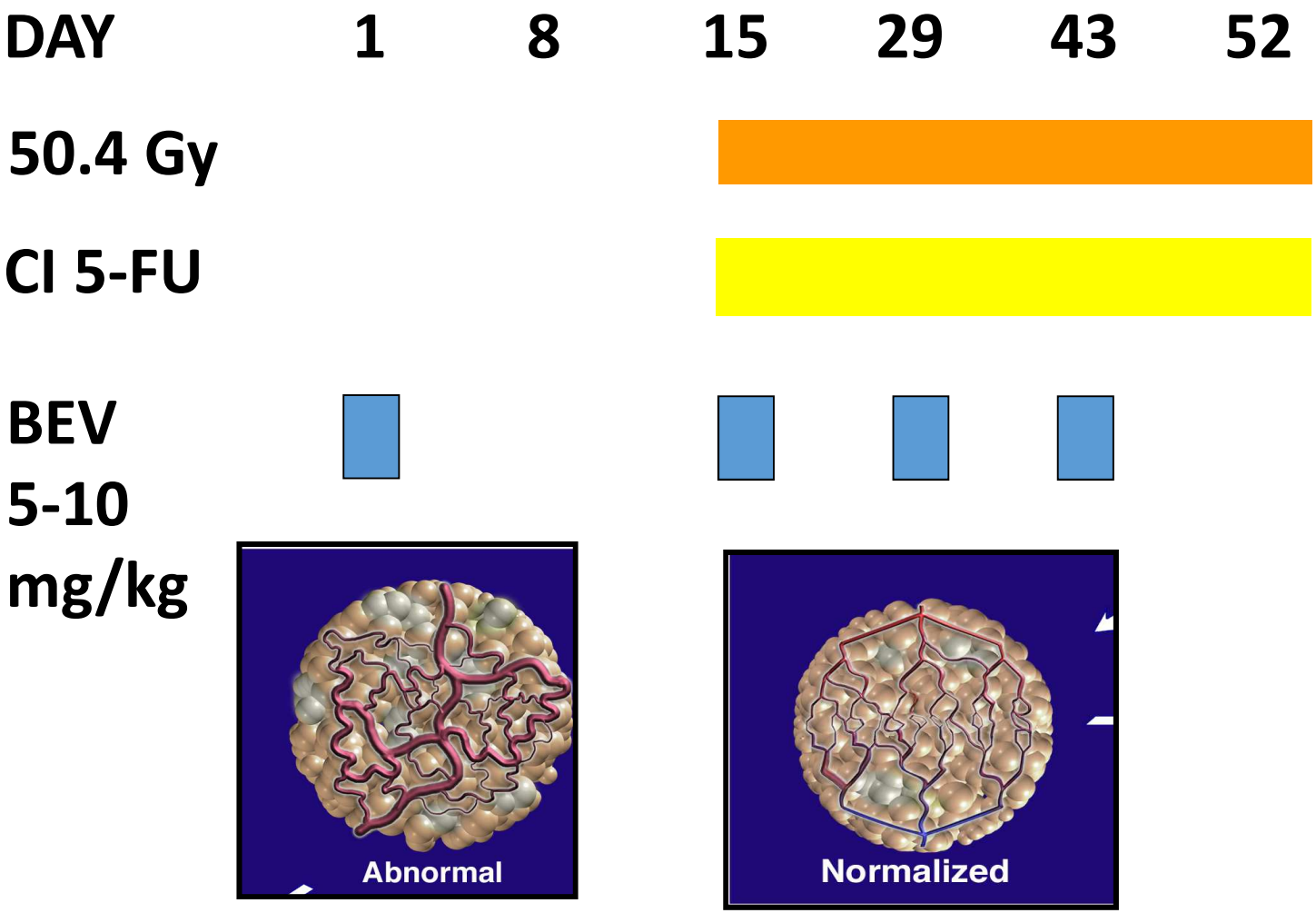
Debucquoy, A. et al. J Clin Oncol, 2009

The EGFR and KRAS story

adapted to chemoradiotherapy for rectal cancer

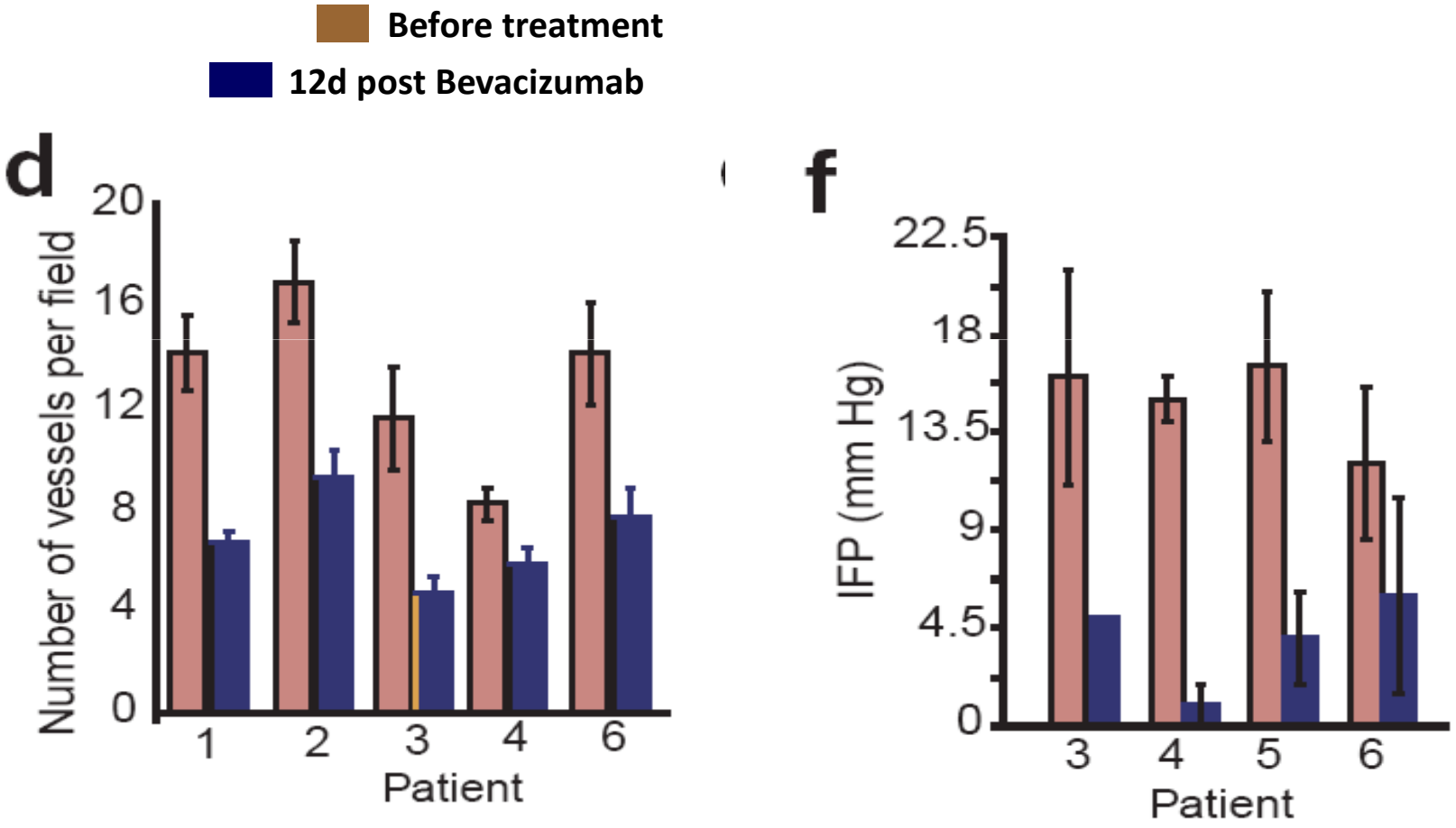
What may be true for RT and EGFR-Inhibition in head&neck cancer and for palliative chemotherapy in metastatic colorectal cancer, may not apply to combined CRT protocols...

Phase I Preop. Bevacizumab/5-FU-RT



Willett CG et al., Nat Med 2004;10:145-7

Response to anti-VEGF in RC



Willett CG et al., Nat Med 2004

Clinical trials (selection) with VEGF-Inhibition in RC

Series	n	Treatment	pCR	TOX/Postop complications
Willett, 2009	32	BV + RT + 5-FU	16%	Presacral abscess (2); Delayed healing (2); Wound infection (3); Hematoma (1); Ileus (2); neurogenic bladder (1); …
Velenic, 2011	61	BV + RT + Cape	13%	Presacral abscess (12); Delayed healing (18); Anastomotic leackage (7) …
Dellas, 2013	70	BV + RT + CAPOX	17%	Presacral abscess (1); Delayed healing (1); Anal fistula (1); …
Salazar, 2015	90	BV + RT + Cape ***vs*** RT + Cape	16% *vs* 11% (p=0.5)	Grade 3-4 tox: 16% vs 13% Surgical: 43% vs 39%
AXE BEAM Verstraete, 2015	80	BV + RT + CAP ***vs*** BV + RT + CAPOX	(n=59) 11% *vs* 36%	**Translational study:** Decrease in MVD; **Small increase in hypoxia;** PDGFA, PDGF-BB; CA-IX , **α**-SMA as potential biomarkers

…beyond EGFR- and VEGF-Inhibition

Author/ Group	Mode of Action	Drug/Schedule	Comments
O'Neil; 2010	**Proteasome Inhibition**	Bortezomib + 5-FU/RT	Phase I (n=9); (DLT: diarrhea)
Ree; 2010	**Histone Deactylase Inhibition**	Vorinostat + palliative RT 30 Gy in 10#)	Phase I (n=17) (DLT: fatique, anorexia, diarrhea)
Czito; 2015	**PARP Inhibition**	Veliparil + Cape/RT	Phase I (n=25); pCR 28% (DLT: skin, nausea)
Buijsen; 2013	**PI3-K/AKT Inhibition**	Nelfinavir + Cape/RT	Phase I (n=11) pCR 27% (DLT: cholangitis, liver-enzymes)
Moos; 2014	**RAF/MEK/ERK and VEGF-R**	Sorafenib + Cape/RT	Phase II (n=40) pCR 15% (Grade 4: 3% neutropenia; Grade 3: diarrhea

Conclusion

- Cape/5-FU based CRT remains standard
- Oxaliplatin + CRT: more tox, less compliance
- But: DFS improved even if only added to CRT (!?!)
- CAPOX/FOLFOX as induction-/consolidation Tx (?)
- EGFR-/VEGF-Inhibition: no phase III data
- Other pathways: early phase I/II

Wait and see concept after clinical complete response

Chris Cunningham

Oxford UK

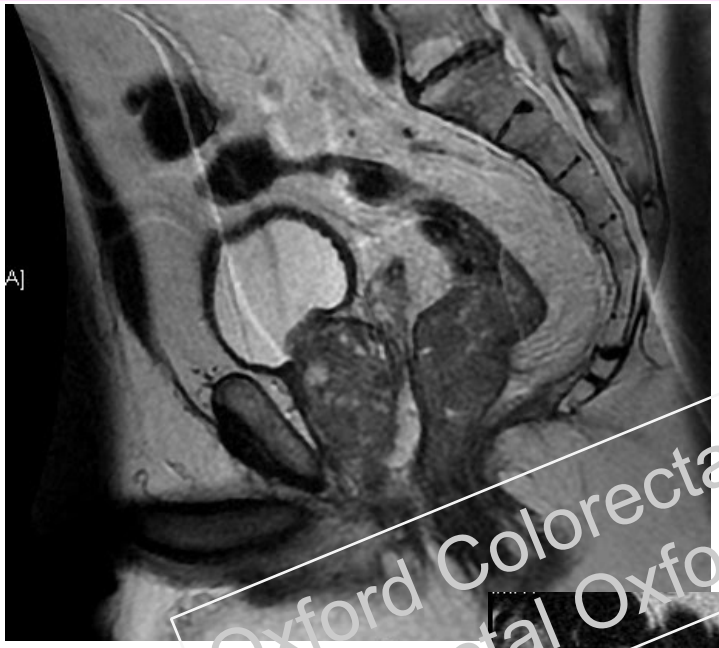
75 year old male

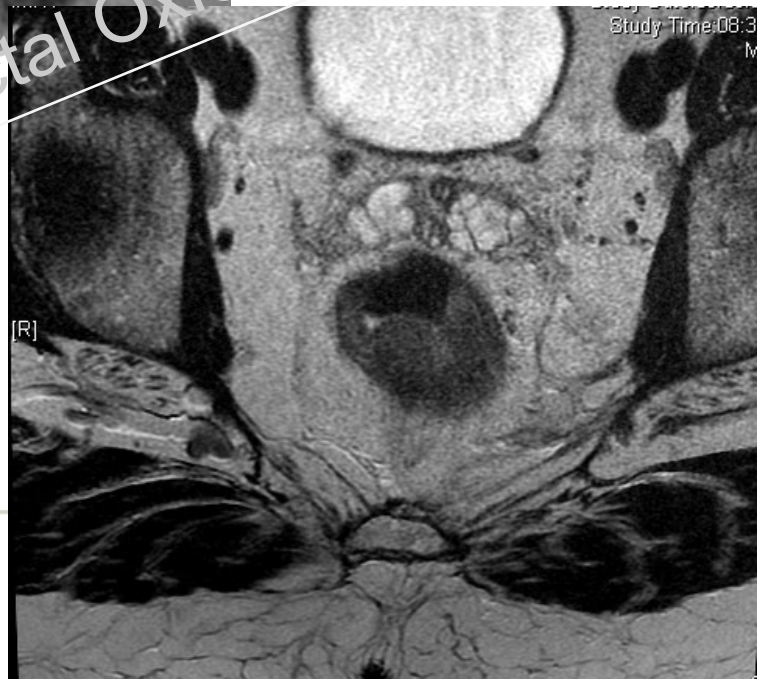
Low rectal cancer

T3N1

Threatened margin

CRT then APER

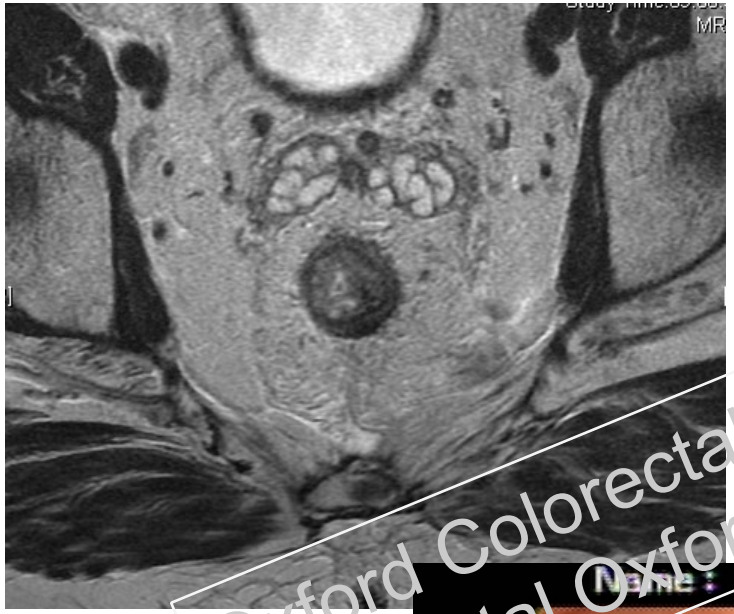


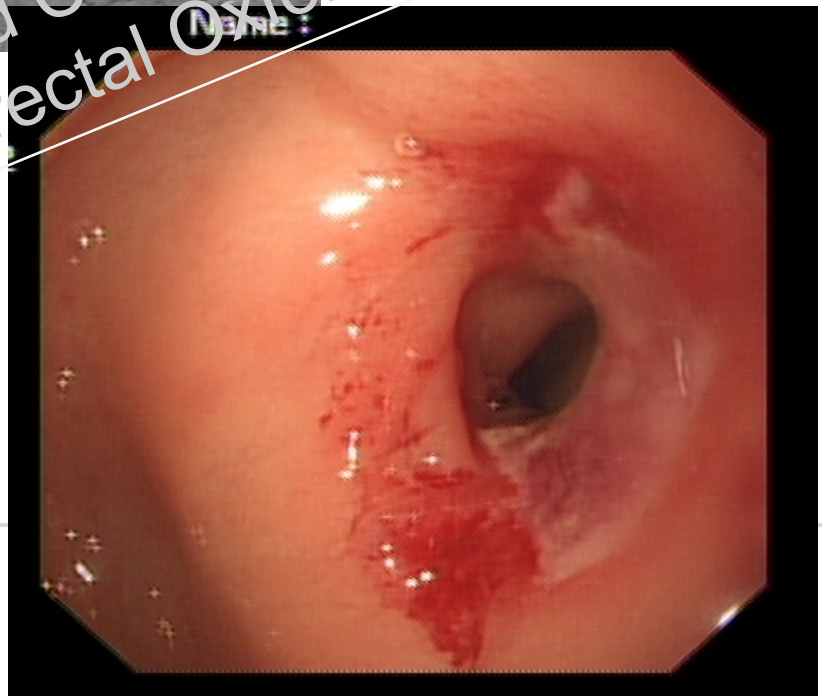


75 year old male

Post CRT

TRG1/2

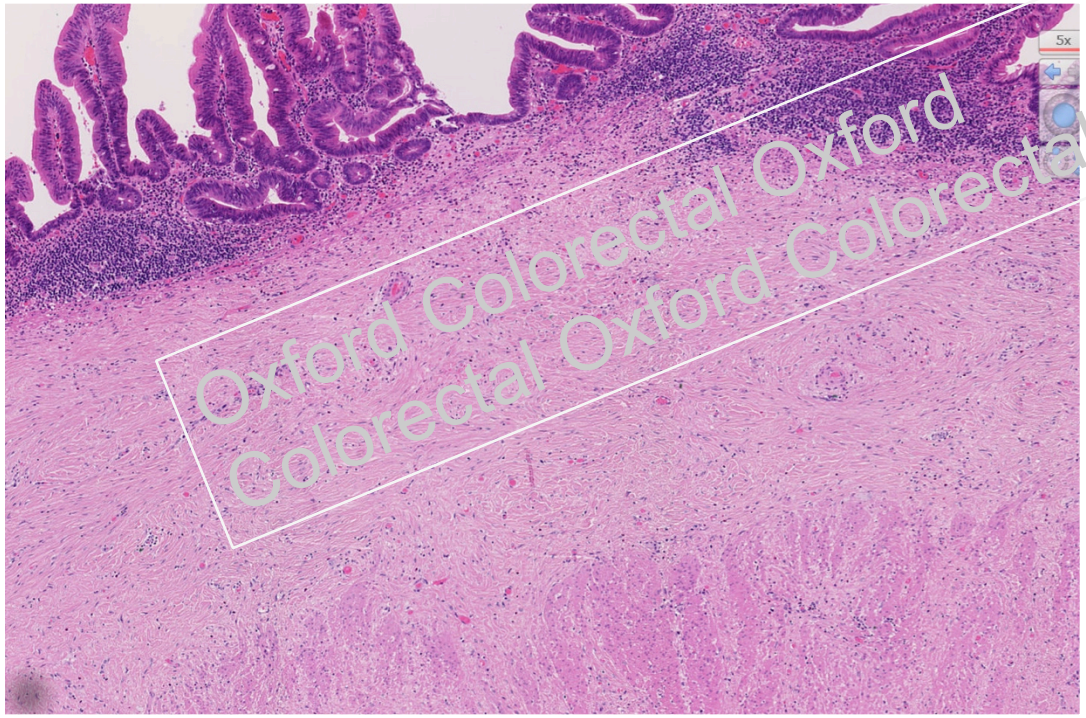




75 year old male

Post CRT

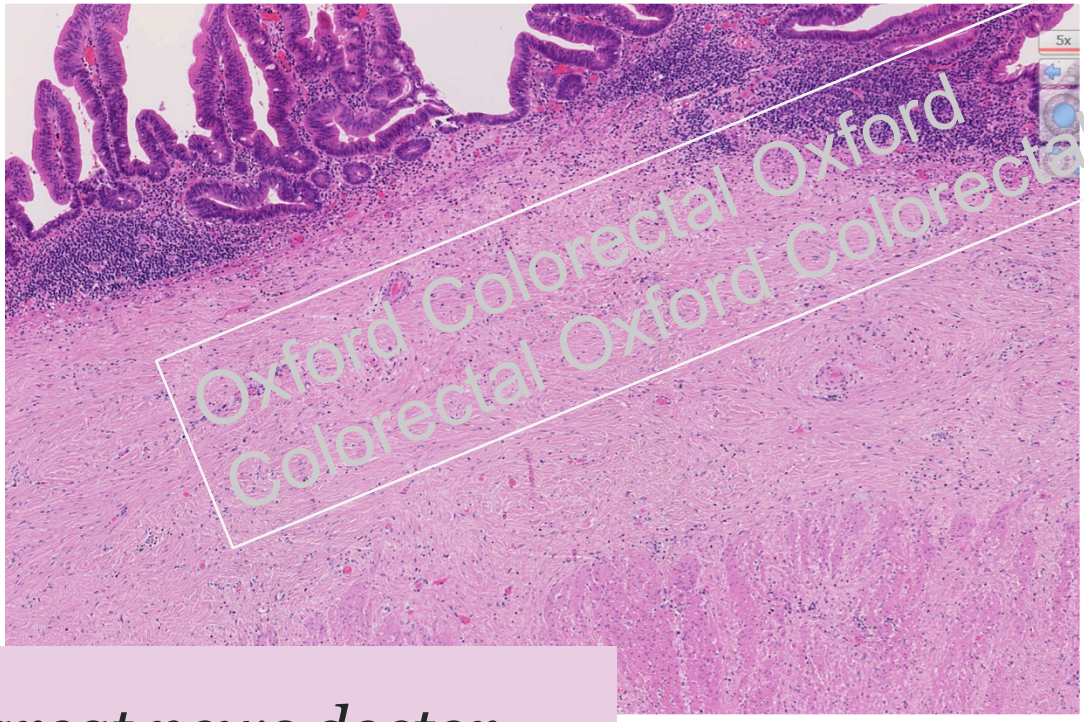
TRG1/2



75 year old male

Post CRT

TRG1/2



"That's great news doctor, when will my bottom heal up?"

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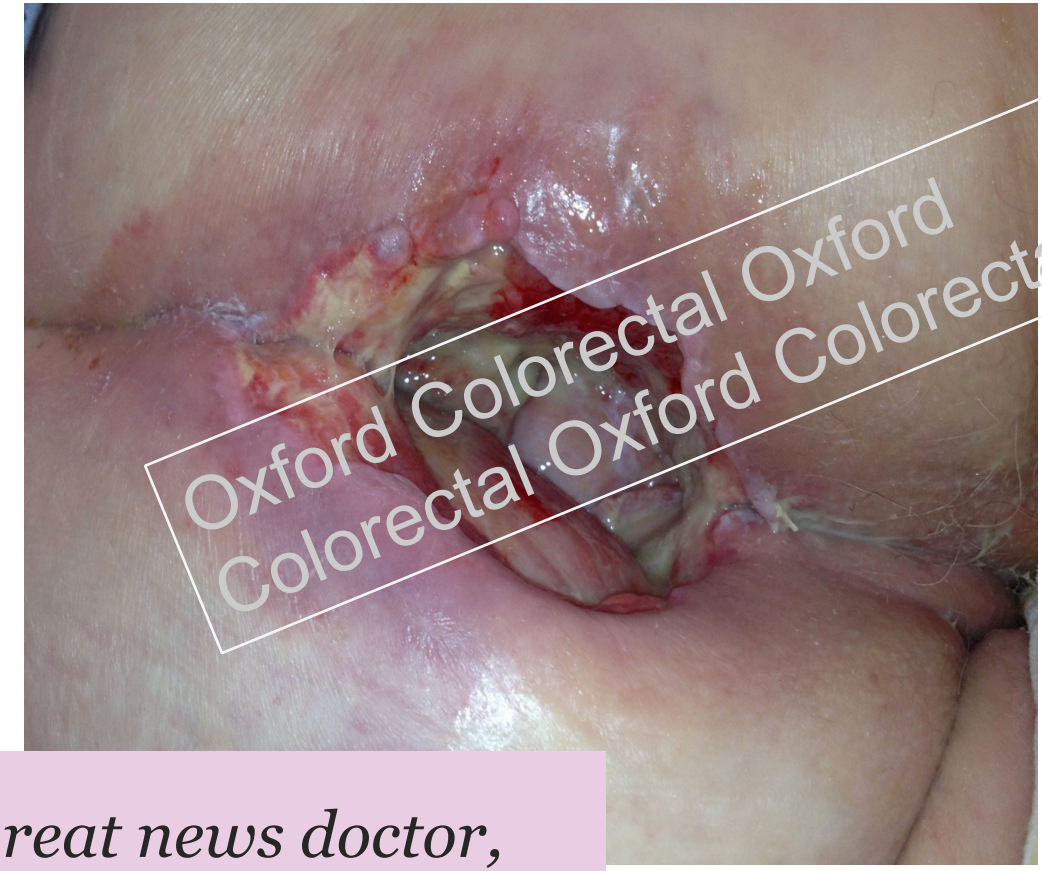
75 year old male

Post CRT

TRG1/2



"That's great news doctor, when will my bottom heal up?"

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What do you need to consider WAW after CCR?

Patient engagement

MDT “Buy-in”

Expert (confident) radiology

Expert (consistent) endoscopy and DRE

Infrastructure to support this!

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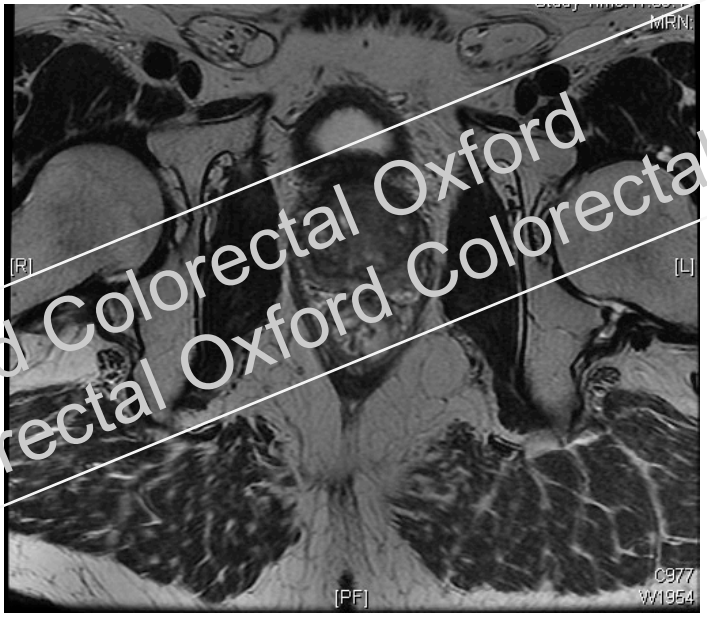

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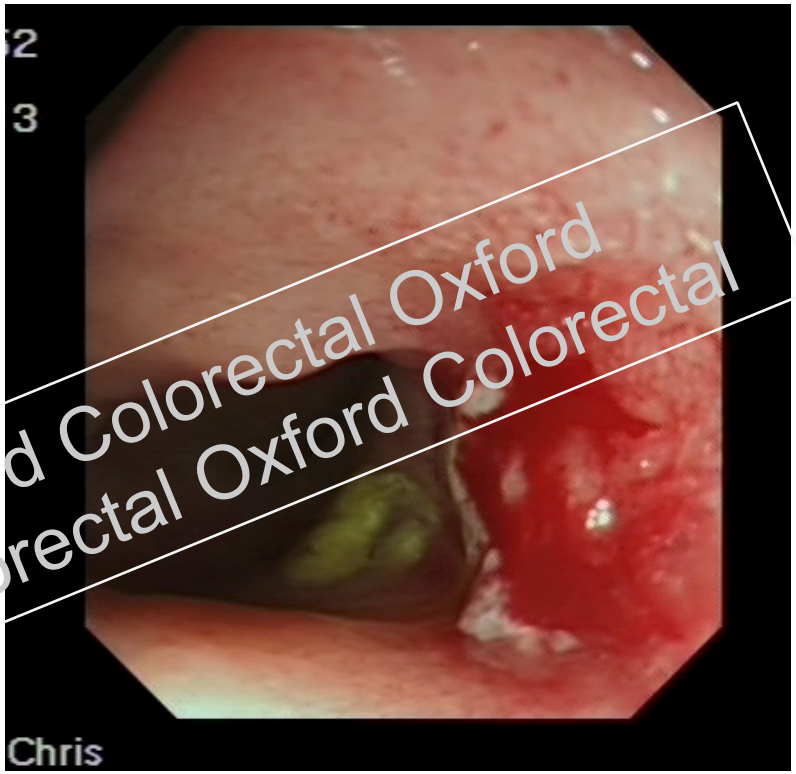

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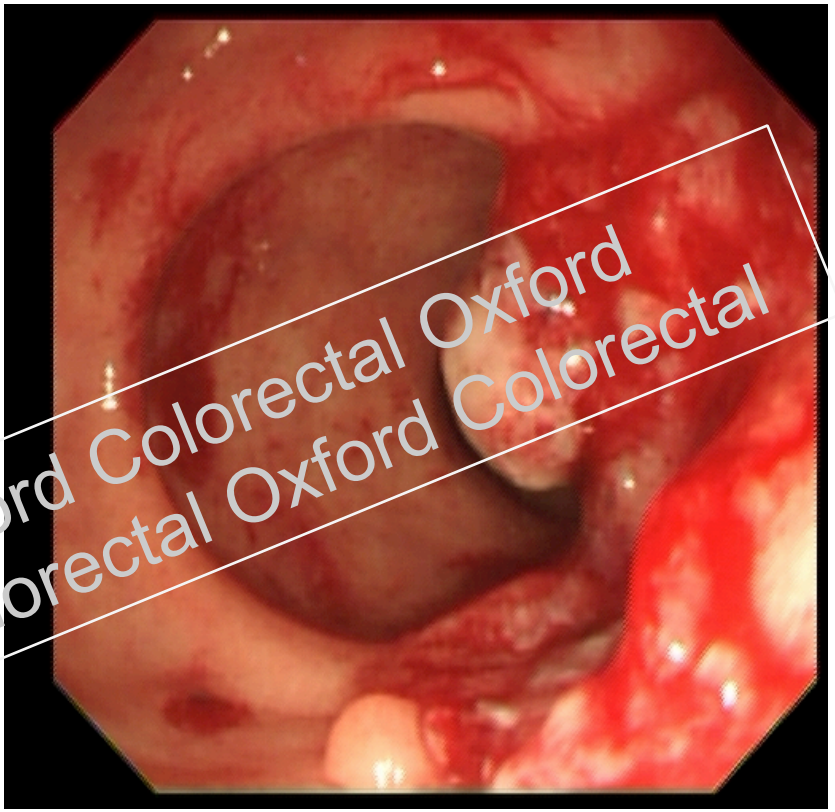

When is the concept of WAW discussed?

Pre-treatment?

6 week post CRT MRI?

12 week post treatment assessment?

When is the concept of WAW discussed?

"Doctor, my symptoms have gone.... is this operation really necessary?"

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When is the concept of WAW discussed?

"Well….we know that it is the best way of achieving cure"

When is the concept of WAW discussed?

"Well….we know that it is the best way of achieving cure"

"Let's think of it as deferring your operation"

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Deferral of surgery is a better concept

Repeat MRI and Endoscopic (DRE) assessment at 18-24 weeks

Discuss surveillance plan and consequences of missing regrowth

Deferral of surgery is a better concept

Repeat MRI and Endoscopic (DRE) assessment at 18-24 weeks

Discuss surveillance plan and consequences of missing regrowth

3 monthly CEA, MRI and endoscopy assessment for 2 years

Thereafter 6 monthly for year 3-5

Annually for 5-10 years?

Deferral of surgery is a better concept

Repeat MRI and
Endosco
assessm
weeks

Discuss su
and cons
missing regrowth

3 monthly CEA, MRI and
endoscopy assessment

nthly for

Annual for 5-10 years?

Formal review at MDT and agreement with WAW plan

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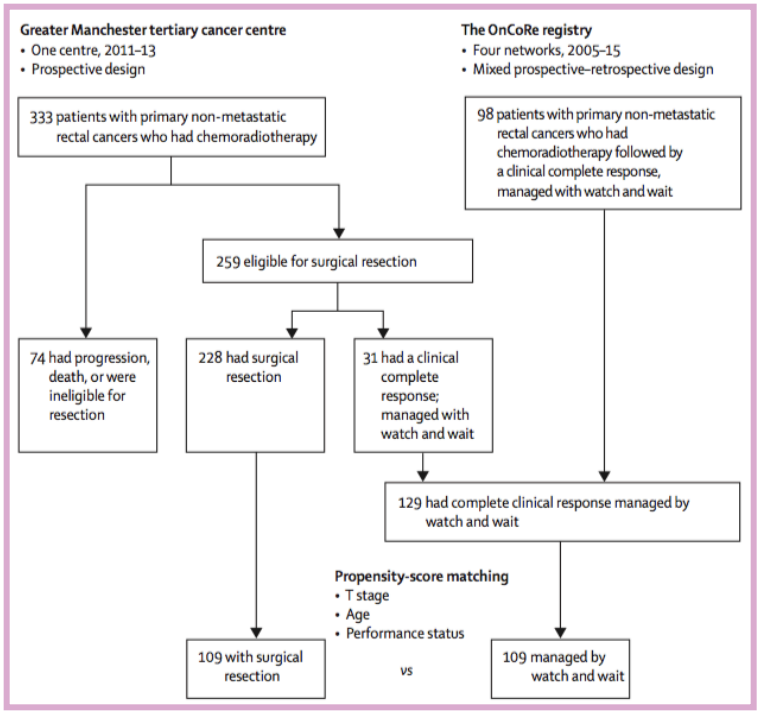
What can patients expect compared to traditional approach?

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



129 patients on WAW schedule

109 patients on traditional surgical pathway

Renehan et al The Lancet Oncology. 2015

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

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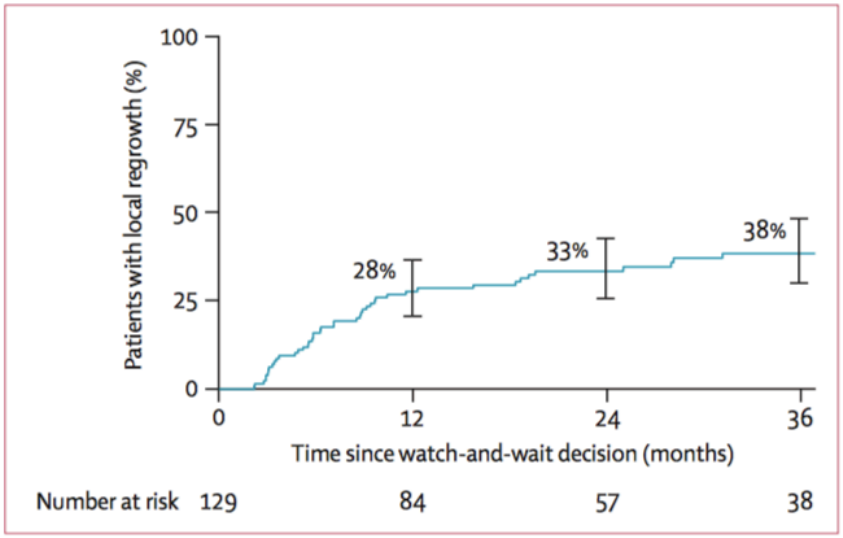

***Figure 2*: Actuarial local regrowth rates in the 129 patients with a clinical complete response managed by watch and wait**
Percentages shown on the graph are actuarial rates at 12, 24, and 36 months after multidisciplinary team decision to watch and wait was made; vertical lines show 95% CI.

129 patients on WAW schedule

109 patients on traditional surgical pathway

Renehan et al The Lancet Oncology. 2015

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

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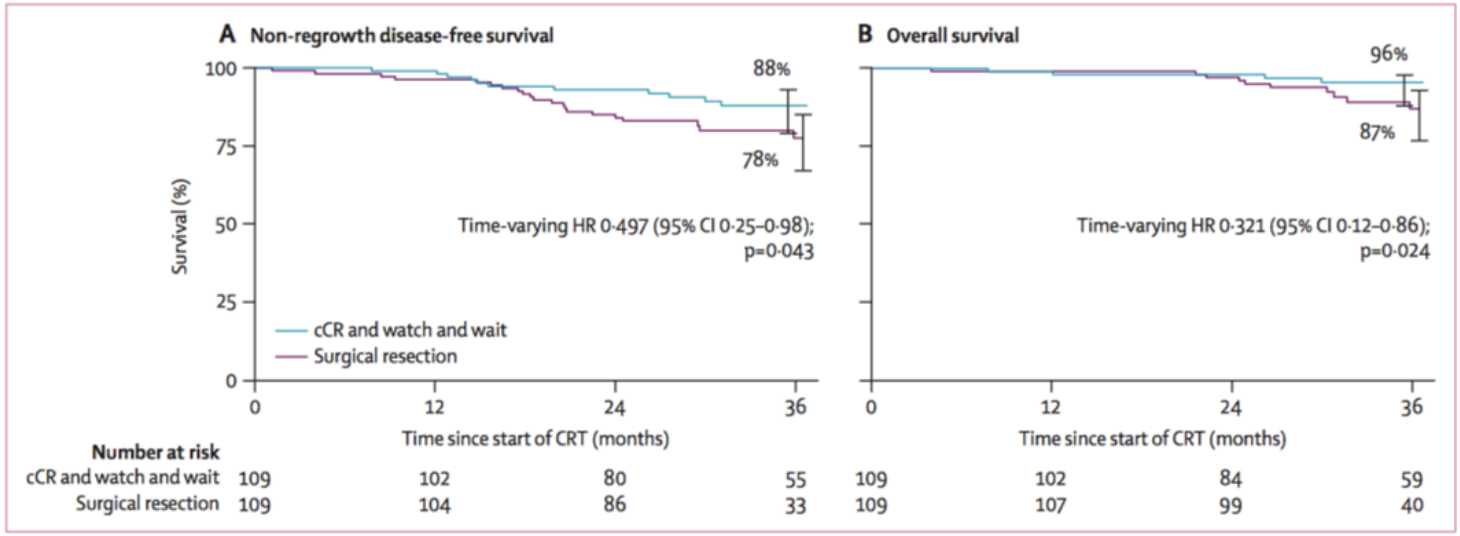

***Figure 3*: Non-regrowth disease-free survival (A) and overall survival (B) in the 218 patients in the matched analysis cohort**
Percentages shown on the graphs are 3-year non-regrowth disease-free survival (A) and 3-year overall survival (B); vertical lines show 95% CIs. We included propensity score as a covariate in the models. cCR=clinical complete response. CRT=chemoradiotherapy. HR=hazard ratio.

Renehan et al The Lancet Oncology. 2015

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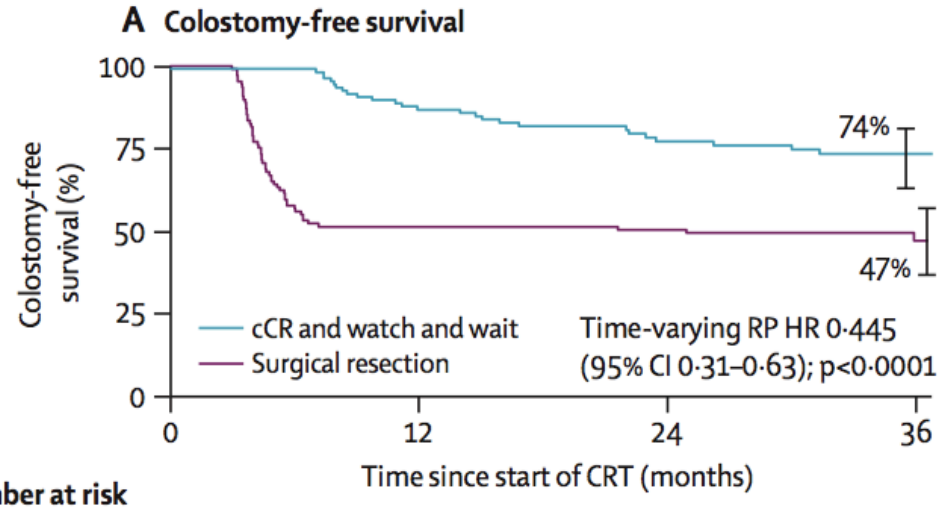

Number at risk				
cCR and watch and wait	109	90	68	46
Surgical resection	109	56	53	20

Renehan et al The Lancet Oncology. 2015

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Don’t underestimate the burden of surveillance

What do you need to consider WAW after CCR?

No booking | Booked, pending | Waiting on results | Required-by date breached

Add Investigation | Add Contact | Book MDT

Next MDT	Category	Question
	Rectal	Watch and wait - review scans

Print History

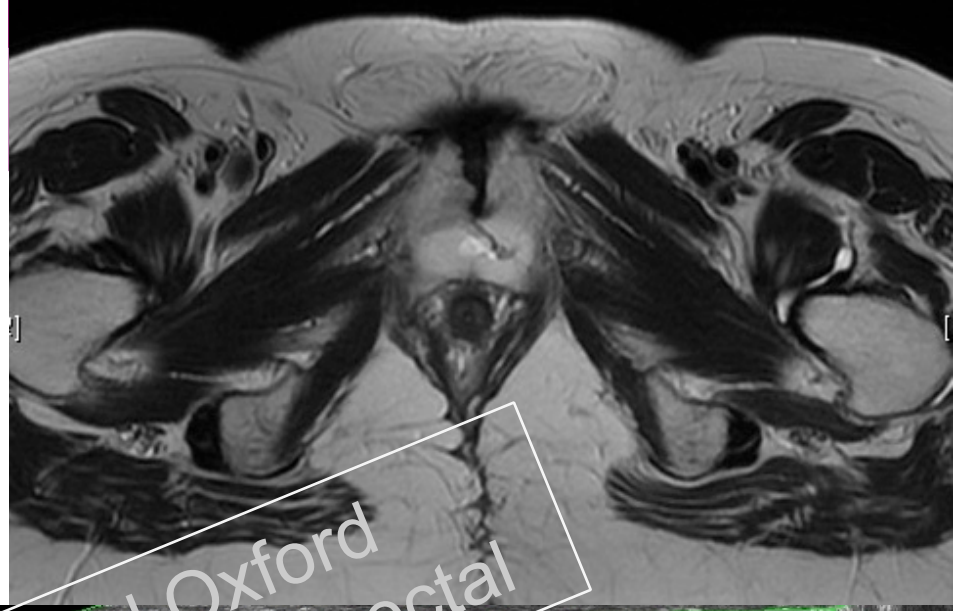
Event	Req/Booked	Seen/Done	Result/Decision/Procedure	Outcome: Comments		
Flex-sig	09/2016				Select	Delete
MRI	06/2016				Select	Delete
MDT	08/02/2016	08/02/2016	Other decision	Recent biopsies have returned normal. Continue under TEM surveillance.	Select	Delete
MRI	02/2016		Not done	Further investigation: Not booked	Select	Delete
Flex-sig	10/03/2016	10/03/2016	Normal	Further investigation: Scope, healthy post CRT scar	Select	Delete
CT scan	16/12/2015	16/12/2015	Normal	Further investigation: No metastatic disease	Select	Delete
MRI	16/12/2015	16/12/2015	Normal	Further investigation: No evidence of disease recurrence	Select	Delete
Flex-sig	26/11/2015	26/11/2015	Normal	Further investigation: Cancer site appears helahty. Bx just distal to this (rectum 1) and from the site itself (rectum 2). May consider TEM of cancer site if adenoma on bx - Bx = NO EVIDENCE OF DYSPLASIA OR MALIGNANCY	Select	Delete
MRI	25/09/2015	25/09/2015	Normal	Further investigation: no evidence of disease recurrence.	Select	Delete
Flex-sig	27/08/2015	27/08/2015	Normal	Further investigation: scar biopsy ? adenoma	Select	Delete
MRI	27/05/2015	27/05/2015	Normal	Further investigation: no evidence of disease relapse.	Select	Delete
Flex-sig	16/04/2015	16/04/2015	Normal	Further investigation: Last biopsies showed adenoma therefore early review arranged. The post CRT scar was healthy with no evidence of regrowth. Recent MRI normal and repeat arranged for next month. Further biopsies taken today	Select	Delete
CT scan	18/02/2015		Normal		Select	Delete
Colonoscopy	12/02/2015	12/02/2015	Normal	Further investigation	Select	Delete
MRI	18/02/2015		Normal	No evidence of recurrence.	Select	Delete
				Area of scarring from previous		

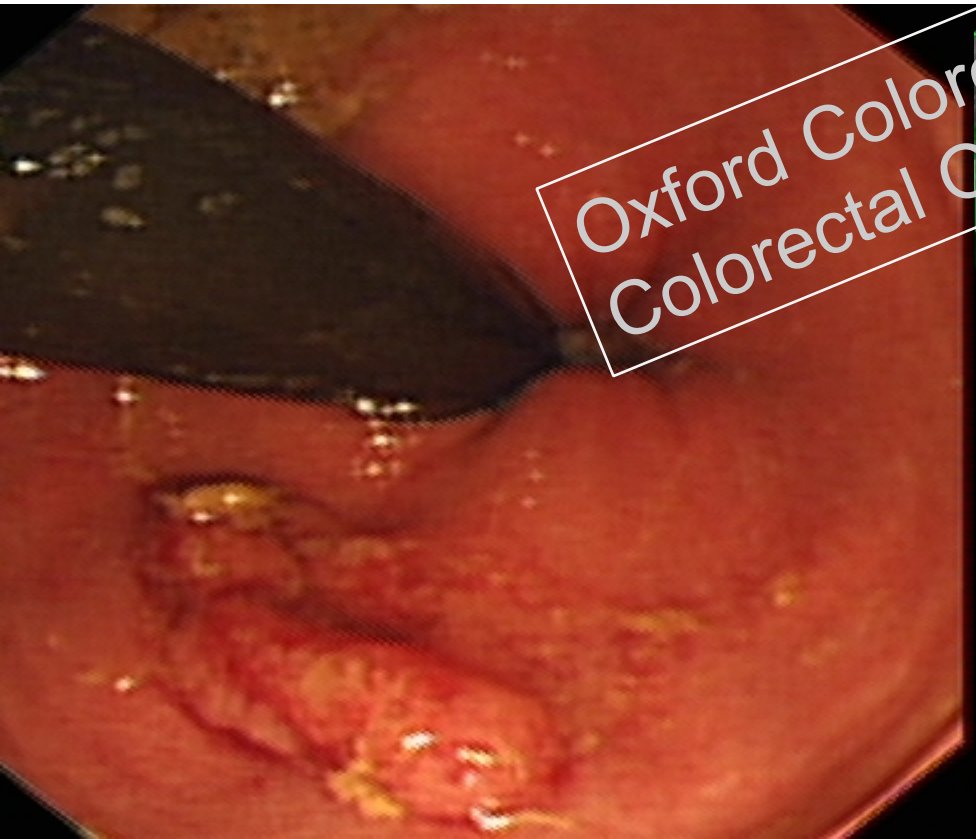
Tracking investigations

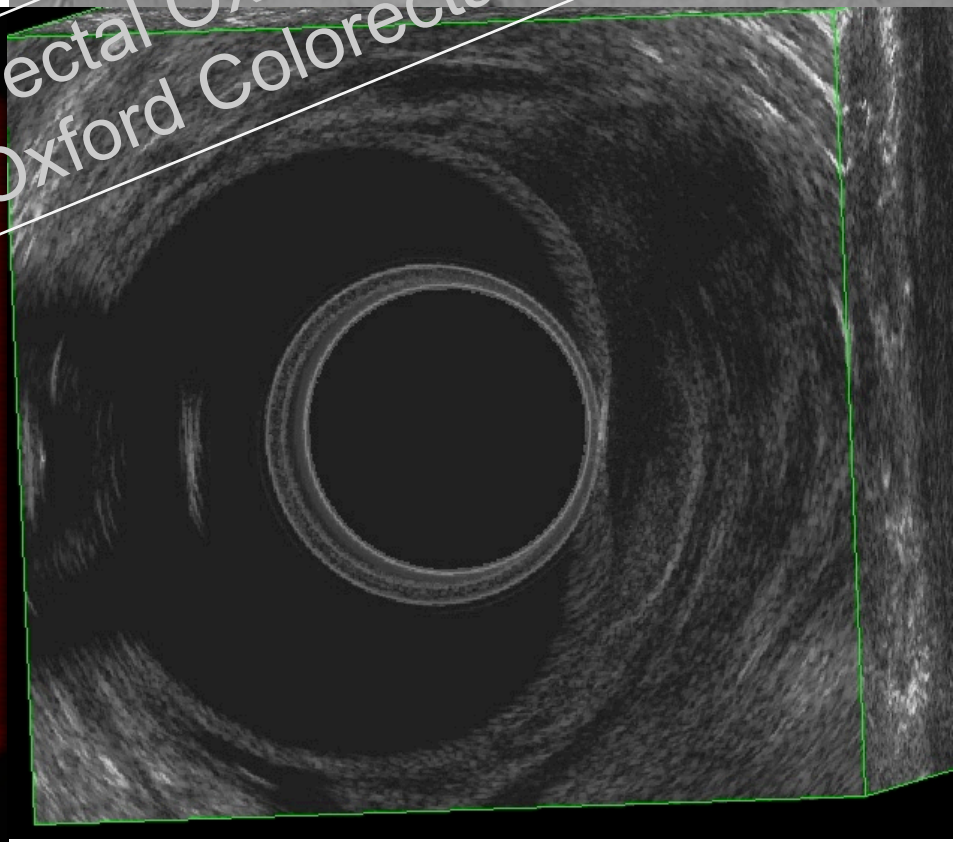
Auditing outcomes

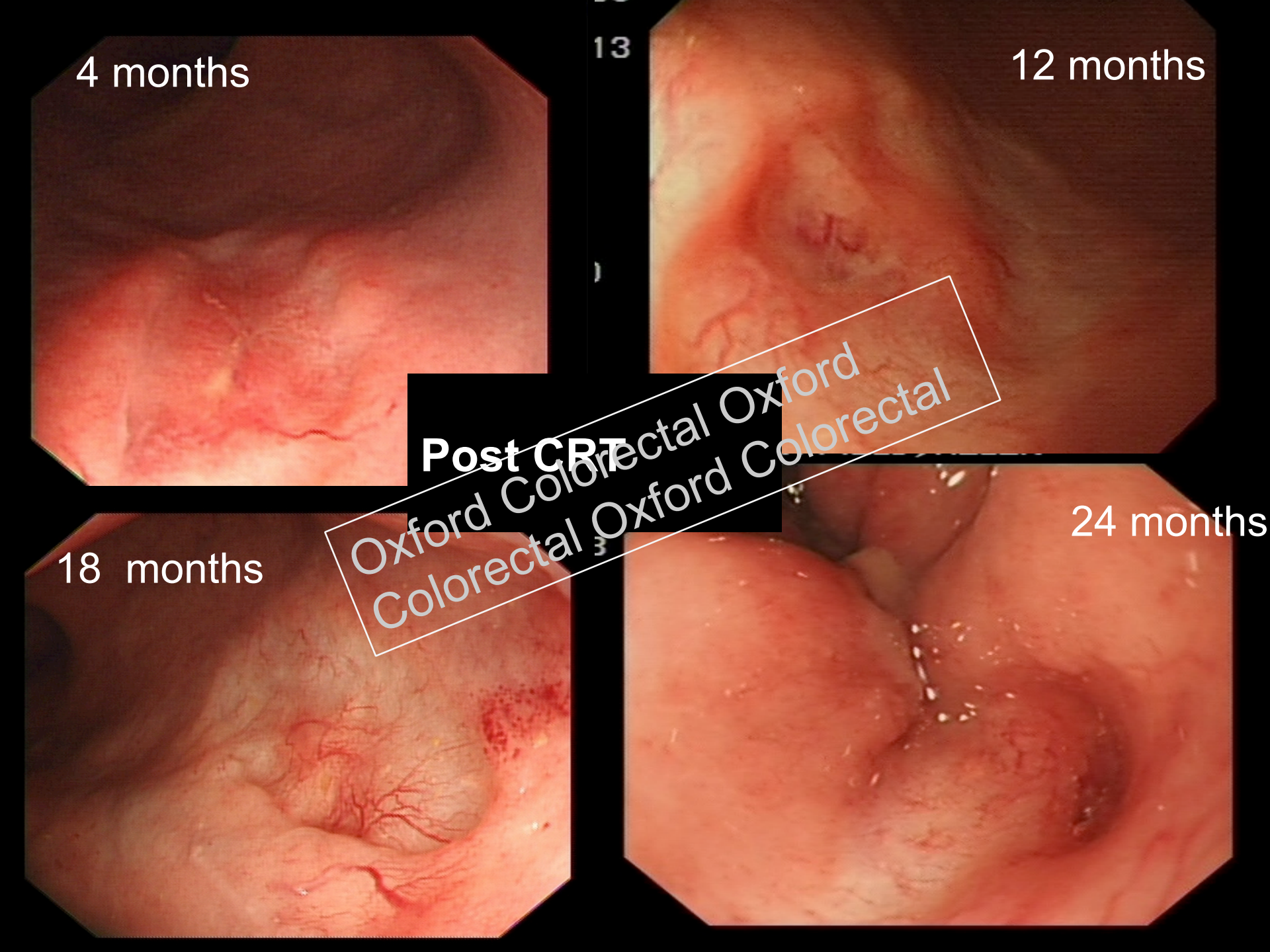
ESTRO School

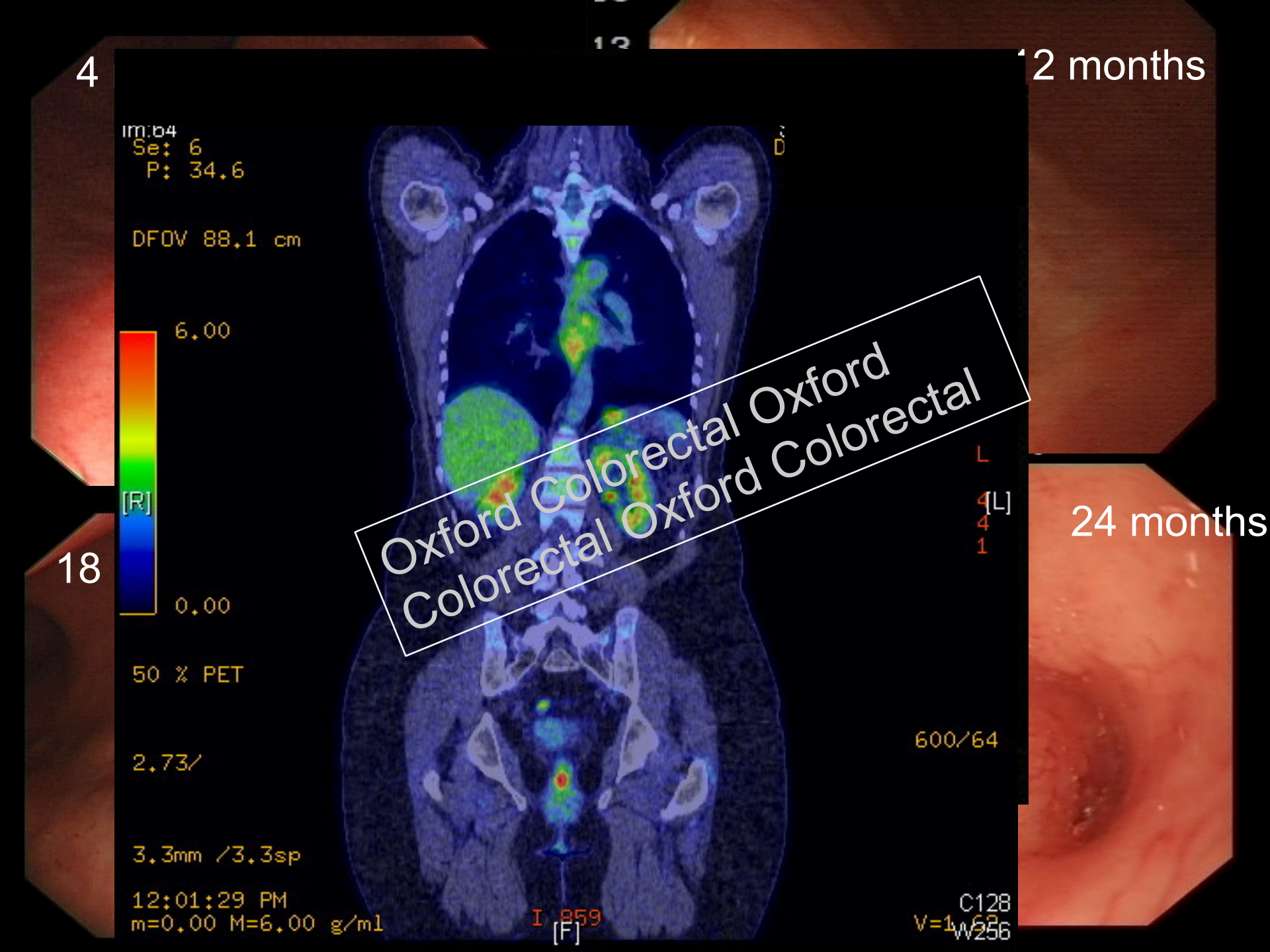
42 year old woman with
LOW RECTAL CANCER



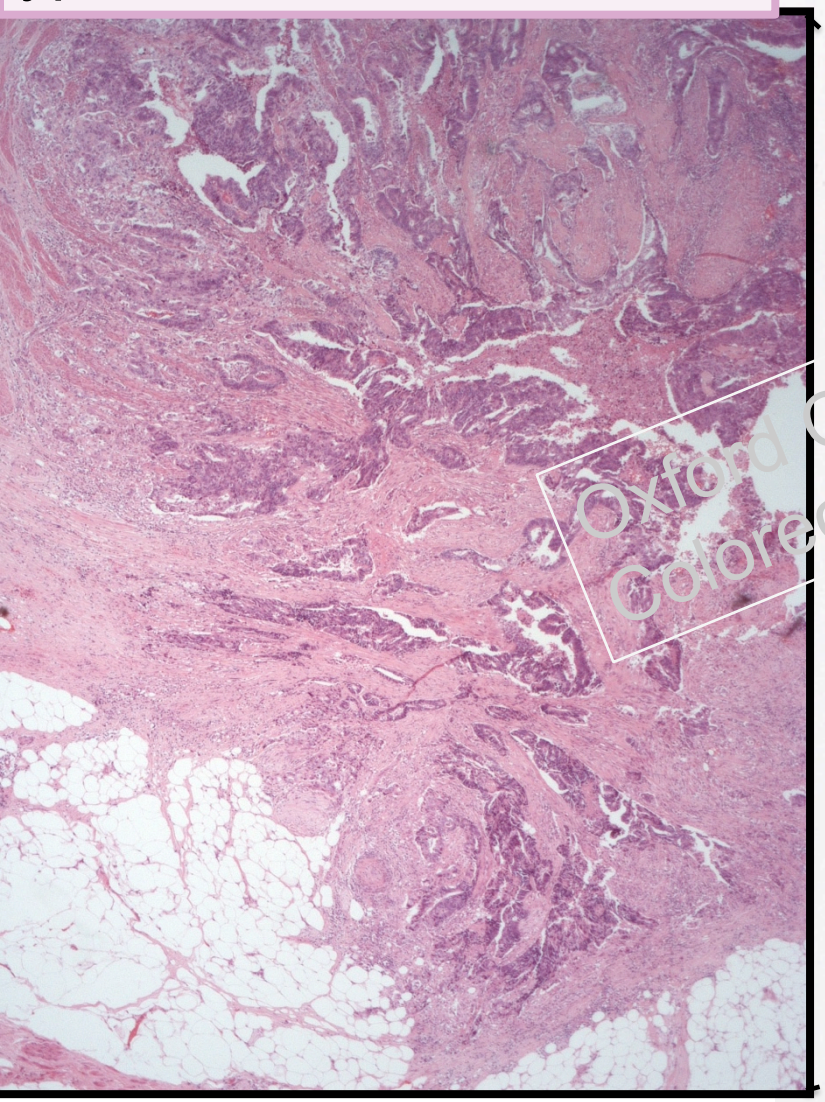


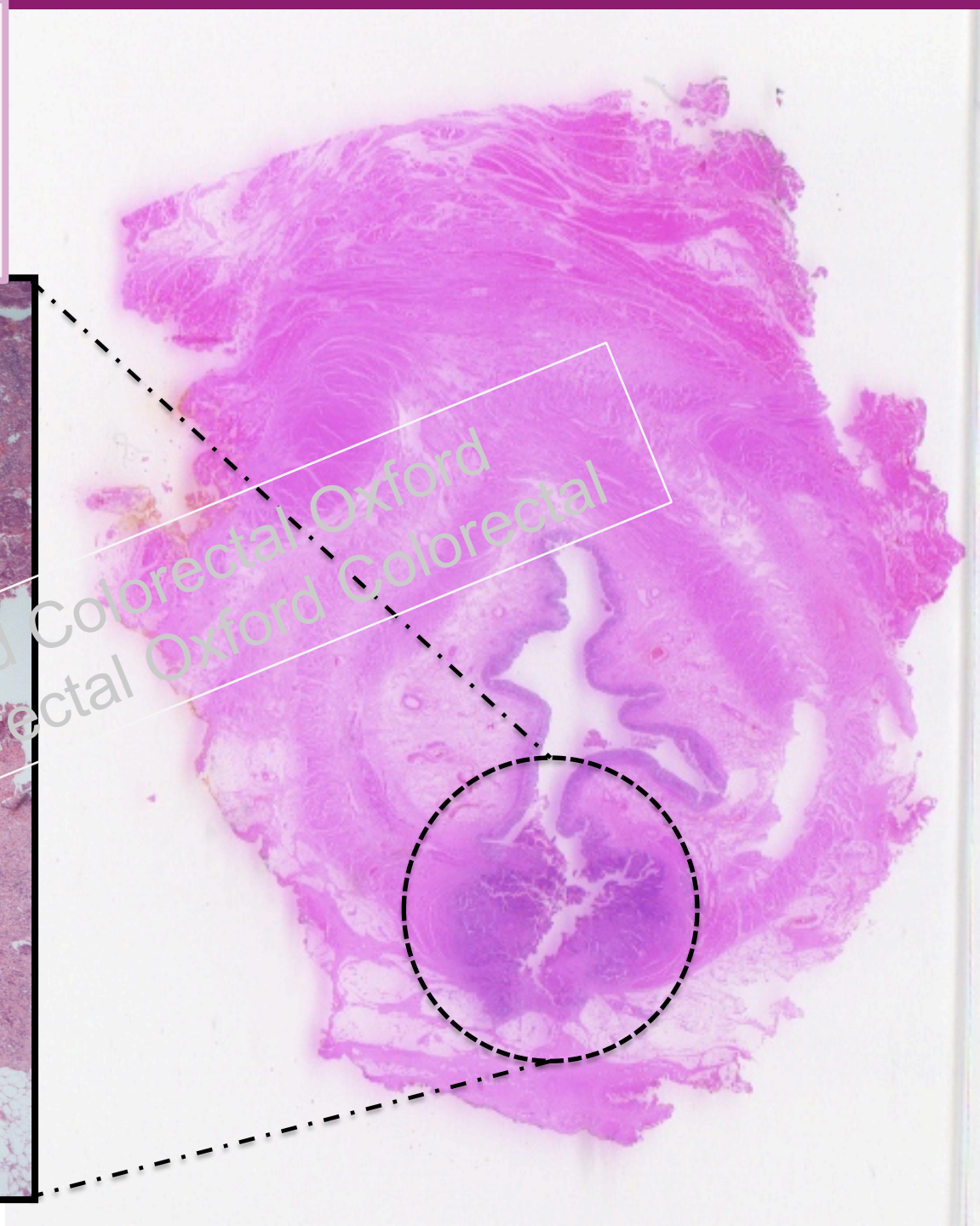



4 months
12 months
Post CRT
18 months
24 months
Oxford Colorectal Oxford
Colorectal Oxford Colorectal


4
12 months
18
24 months
Im:64
Se: 6
P: 34.6
DFOV 88.1 cm
6.00
[R]
0.00
50 % PET
2.73/
3.3mm /3.3sp
12:01:29 PM
m=0.00 M=6.00 g/ml
[F]
600/64
C128
W256
[L]
Oxford Colorectal Oxford
Colorectal Oxford Colorectal

RESIDUAL TUMOUR: EXTENSION INTO MESORECTAL FAT
ypT3

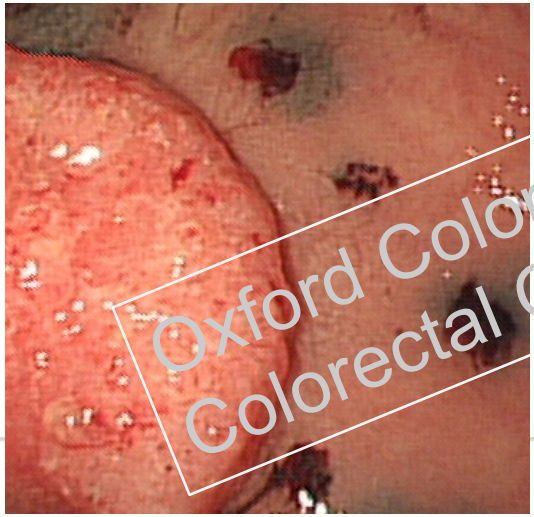


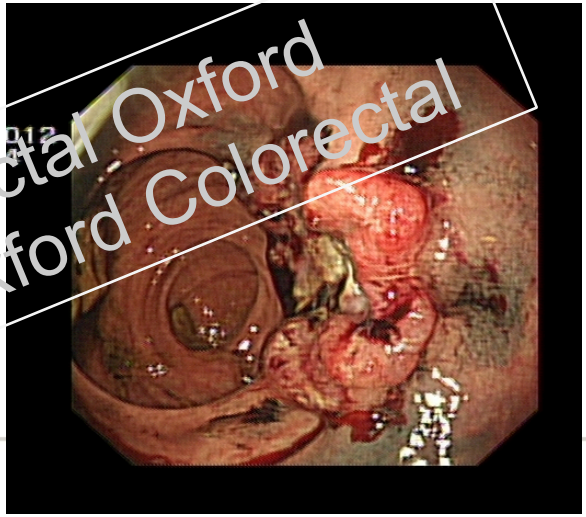


Distribution of Residual Cancer Cells in the Bowel Wall After Neoadjuvant Chemoradiation in Patients With Rectal Cancer

Marjun P. Duldulao, M.D.[1] • Wendy Lee, B.A.[1] • Leanne Streja, Dr.P.H.[2]
Peiguo Chu, M.D.[3] • Wenyan Li, B.A.[1] • Zhenbin Chen, Ph.D.[1]
Joseph Kim, M.D.[1] • Julio Garcia-Aguilar, M.D., Ph.D.[4]

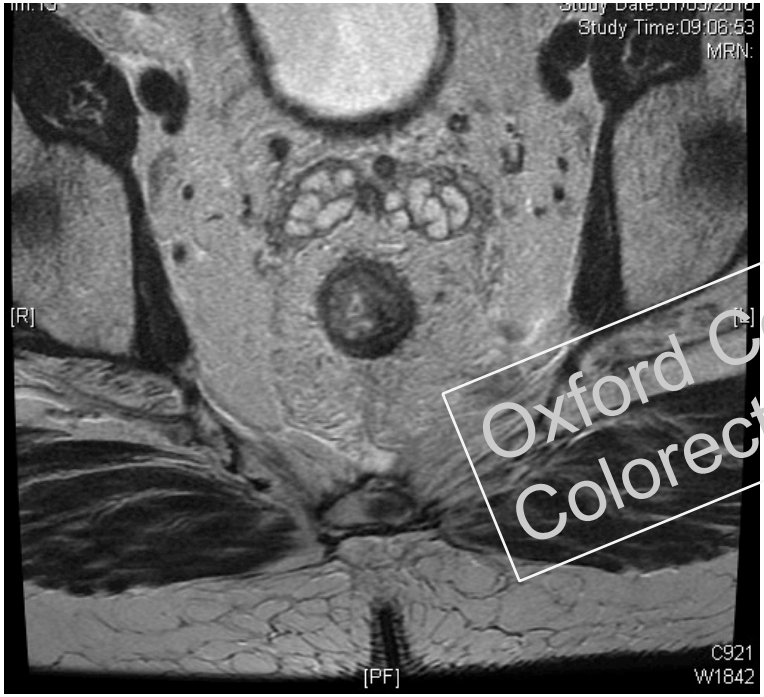
1 Department of General Oncologic Surgery, City of Hope Comprehensive Cancer Center, Duarte, California
2 Biostatistics, City of Hope Comprehensive Cancer Center, Duarte, California
3 Pathology, City of Hope Comprehensive Cancer Center, Duarte, California
4 Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York

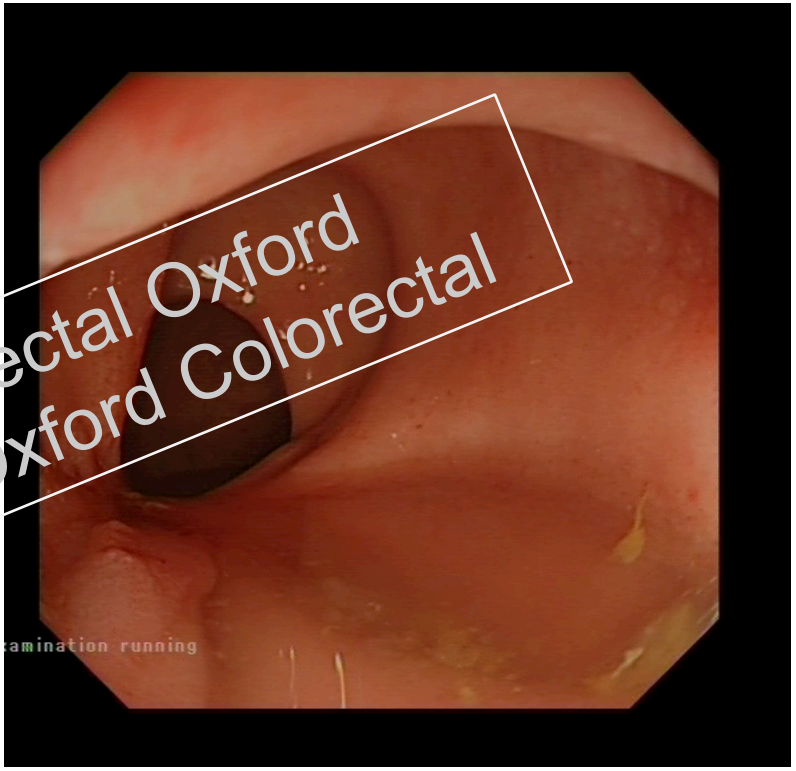




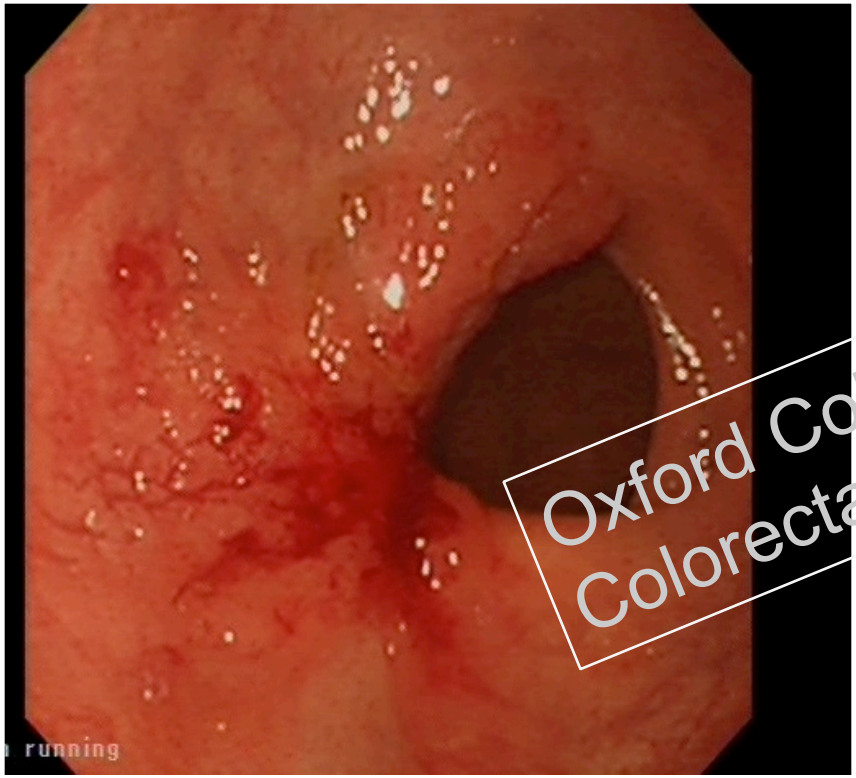
Is there a role for local excision?

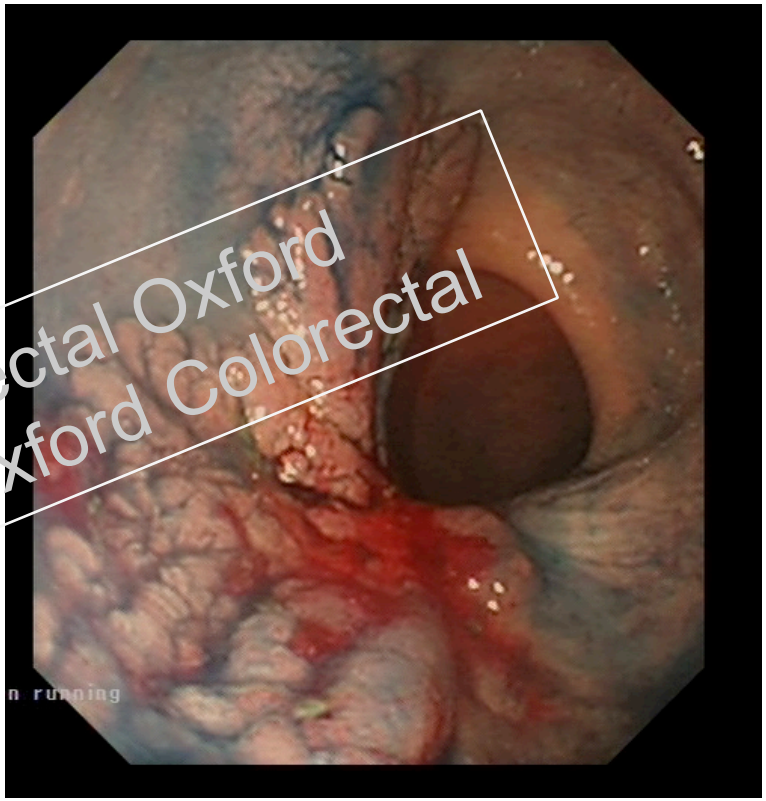
TEM after CRT for residual disease





TEM after CRT for residual disease

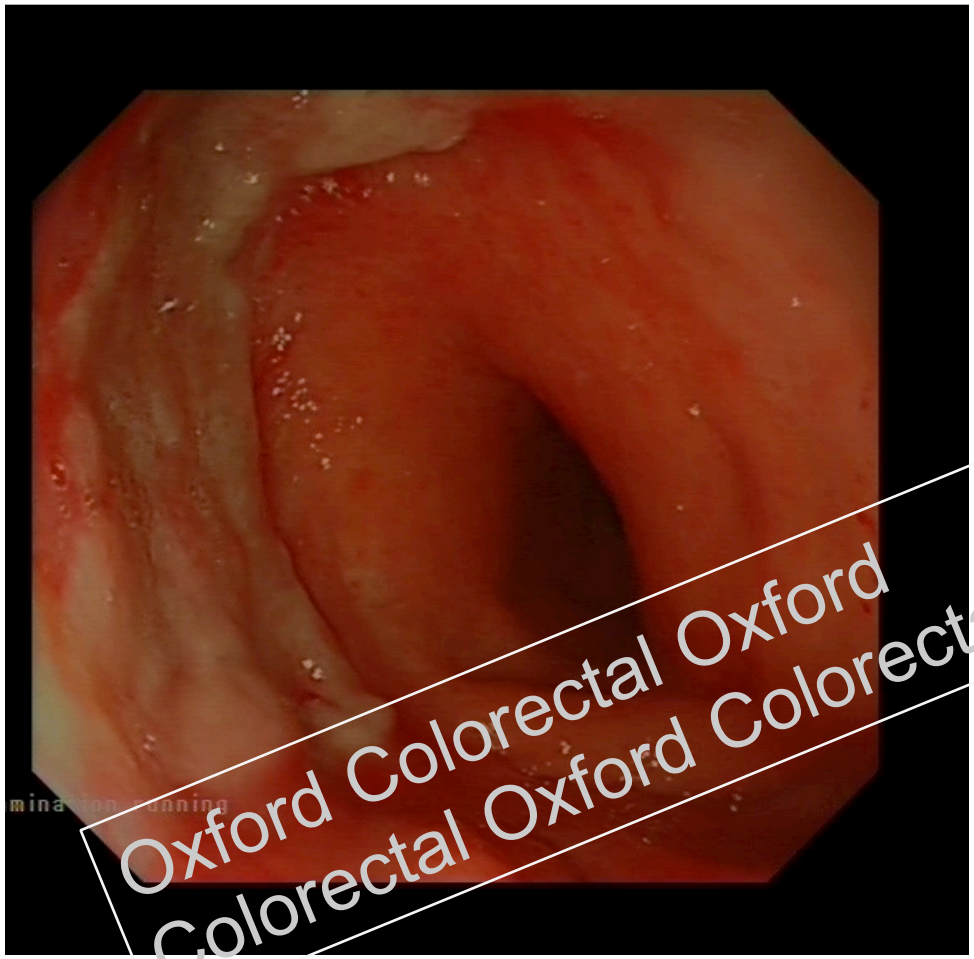




TEM after CRT

Adenoma only

TEM after CRT



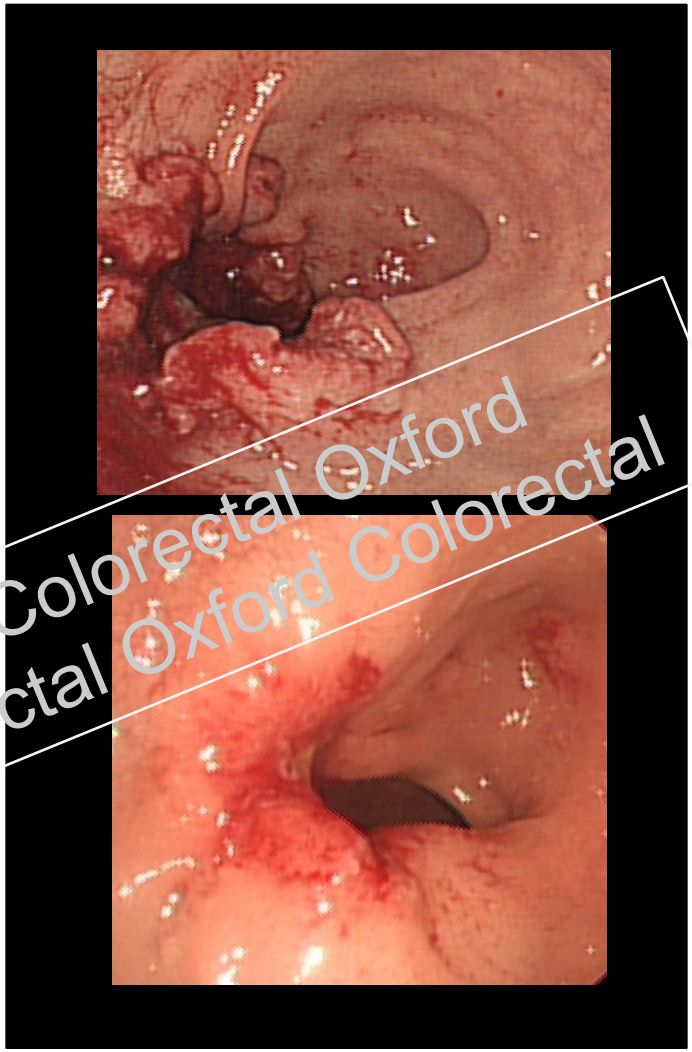
Post TEM dehiscence and poor function for 3-6 months

Summary

Deferral strategy needs
- engagement of patient and MDT

Inadequate evidence to inform
- outcomes

Recruitment to trials is advised
- but this practice is evolving



Bruxelles May 2016

On-Going Trials

of Chemo-Radio-Therapy

Rob Glynne-Jones
Mount Vernon Cancer Centre

5 Options for chemotherapy in locally advanced rectal cancer

- **Induction** - pre RT (Short-course(SCPRT) or chemoradiation (CRT)(Contre, ?CREATE)

5 Options for chemotherapy in locally advanced rectal cancer

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-

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- **NACT alone Without radiation** (Prospect, Bacchus)
- **Post-op adjuvant**

Advantage for NACT in rectal cancer

- Compliance should be increased to 90-95%
- Systemic Chemo can start immediately rather delayed many weeks post surgery
- Very few progress
- Can assess response to chemotherapy
- If 3 months sufficient from IDEA can be short and cost-effective

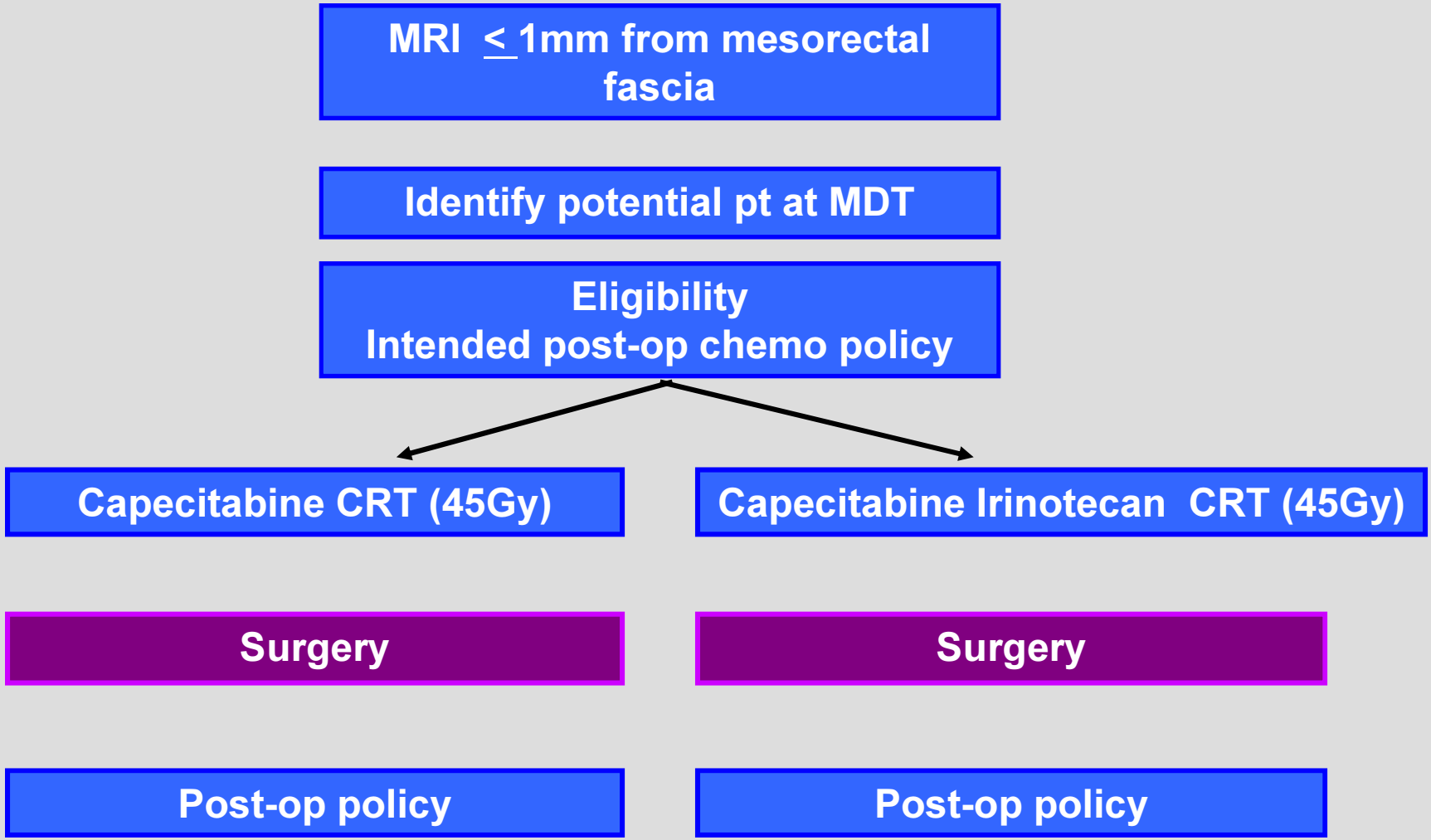
Clinical trials – several strategies

- Integrating chemotherapy into chemoradiation schedules
- Integrating induction chemo (IC) and CRT or SCPRT
- Integrating consolidation chemo (CC) after CRT or SCPRT
- Neoadjuvant chemotherapy alone instead of SCPRT/CRT

Problems with all trials

- Primary endpoint
- Imaging/staging
- Quality assurance
- Watch and wait
- Pathology stage
- Adjuvant chemotherapy
- You need to do it fast before practice changes

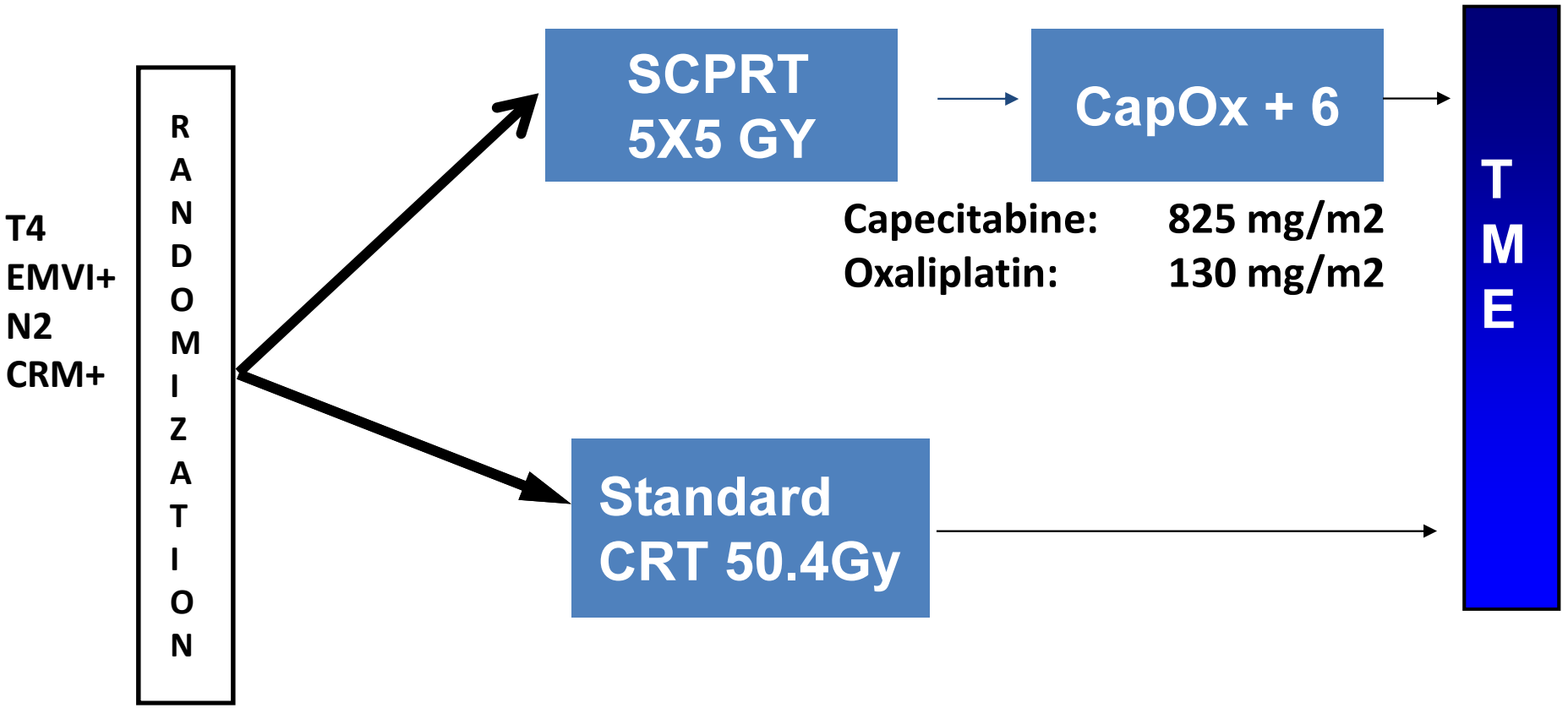
Aristotle National UK Trial schema n=920



Primary endpoint 2 year DFS

RAPIDO Trial

N = 885 patients



Primary endpoint 3 year DFS

Unicancer Prodige 23
NCT01804790

Staging :- cT3/T4 Evaluated by TRUS and/or MRI

N=460

Capecitabine 800mg/m2
50 Gy CRT

S

depending on ypTNM and the center's choice

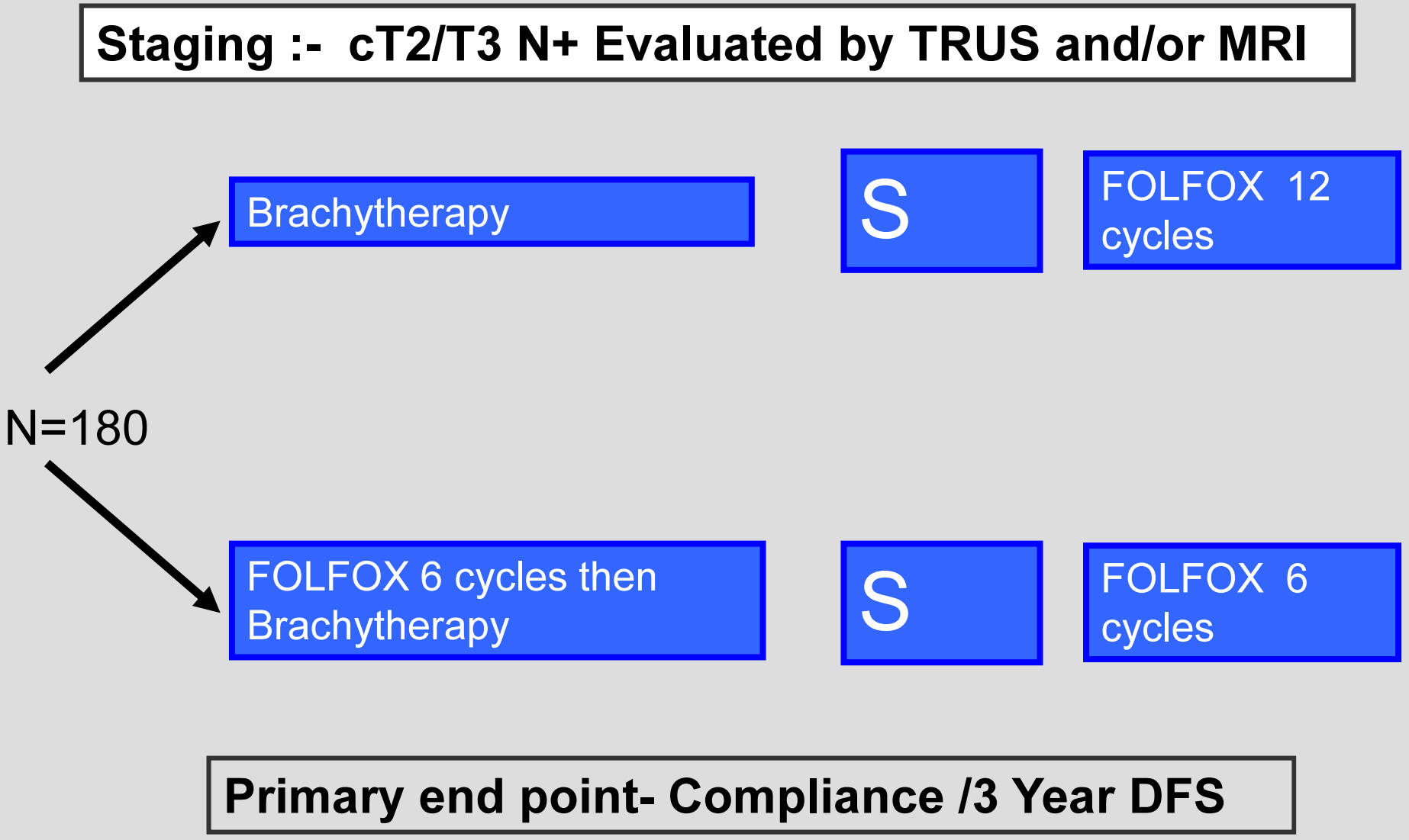
mFolfirinox, 6 cycles then
Capecitabine 800mg/m2
Then 50 Gy CRT

S

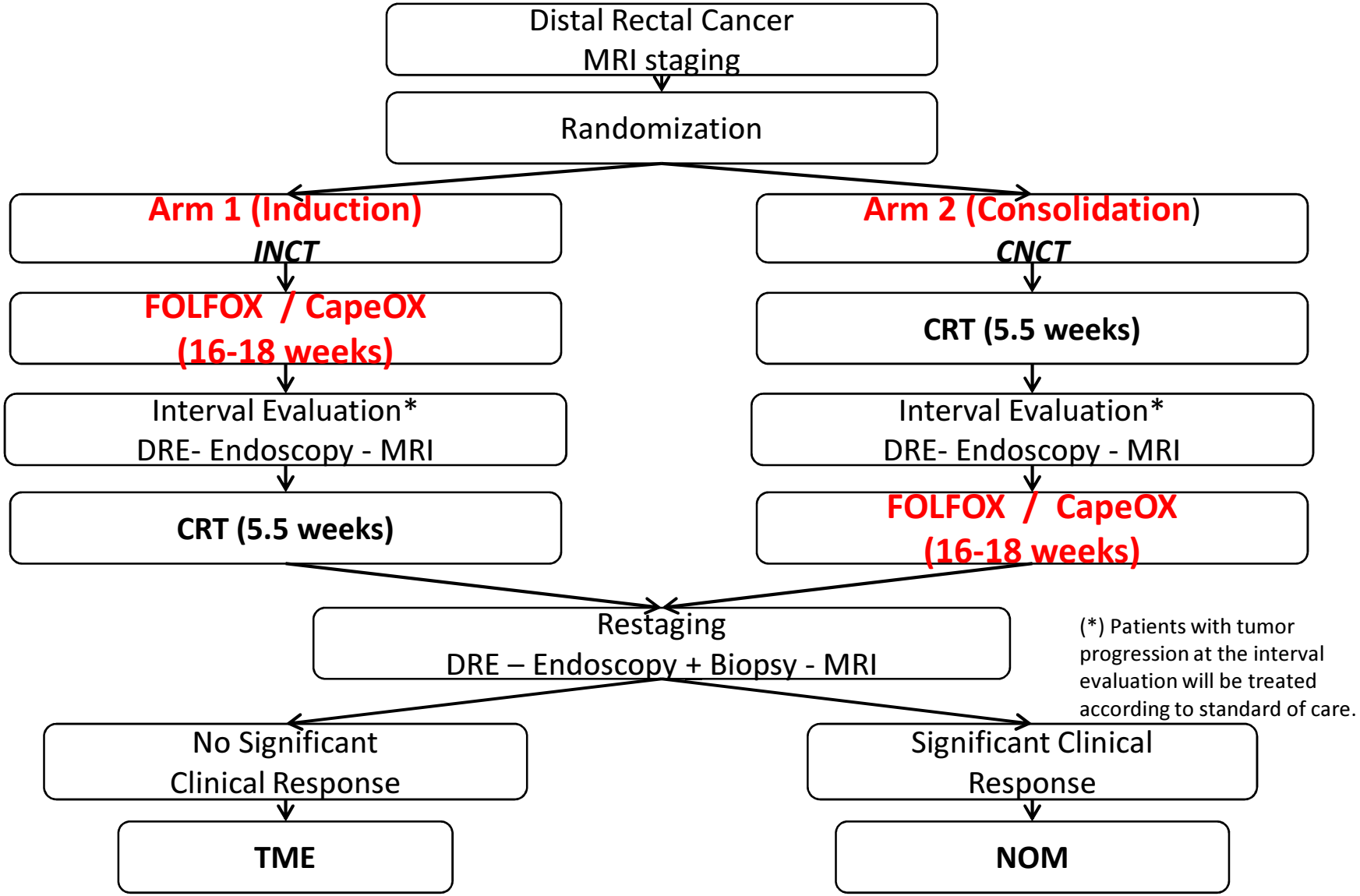
depending on ypTNM and the center's choice

Primary end point- 3 Year DFS

Dr. Te Vuong, Sir Mortimer B. Davis - Jewish General Hospital NCT01274962



MSKCC Schema: Protocol 13-213



(*) Patients with tumor progression at the interval evaluation will be treated according to standard of care.

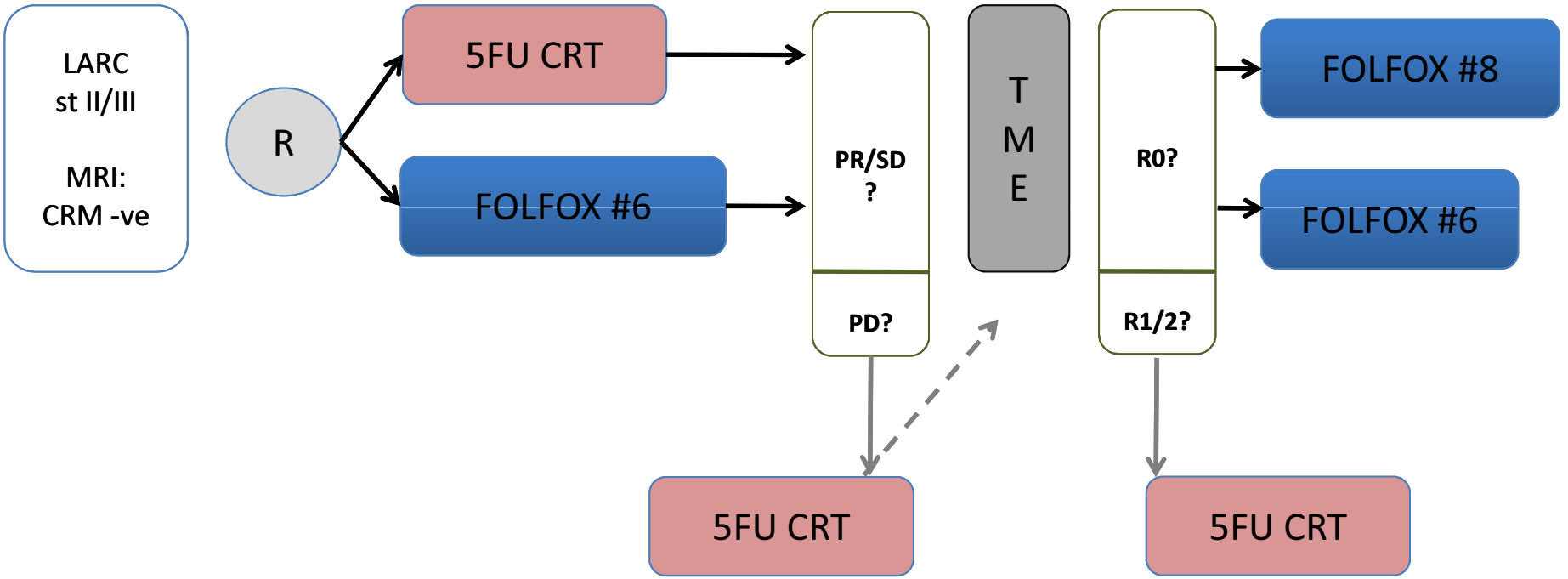
PROSPECT TRIAL

(Alliance)

Eligibility	T2N1, T3N0, T3N1 rectal ca
	5-12cm from anal verge
Accrual:	1010 pts over 5 years

US Prospect Alliance Intergroup phase III trial

ACOSOG, Z9062, CALGB, E81001



N planned: 1010

1° endpoint: 3y DFS

2° toxicity, local failures, OS,

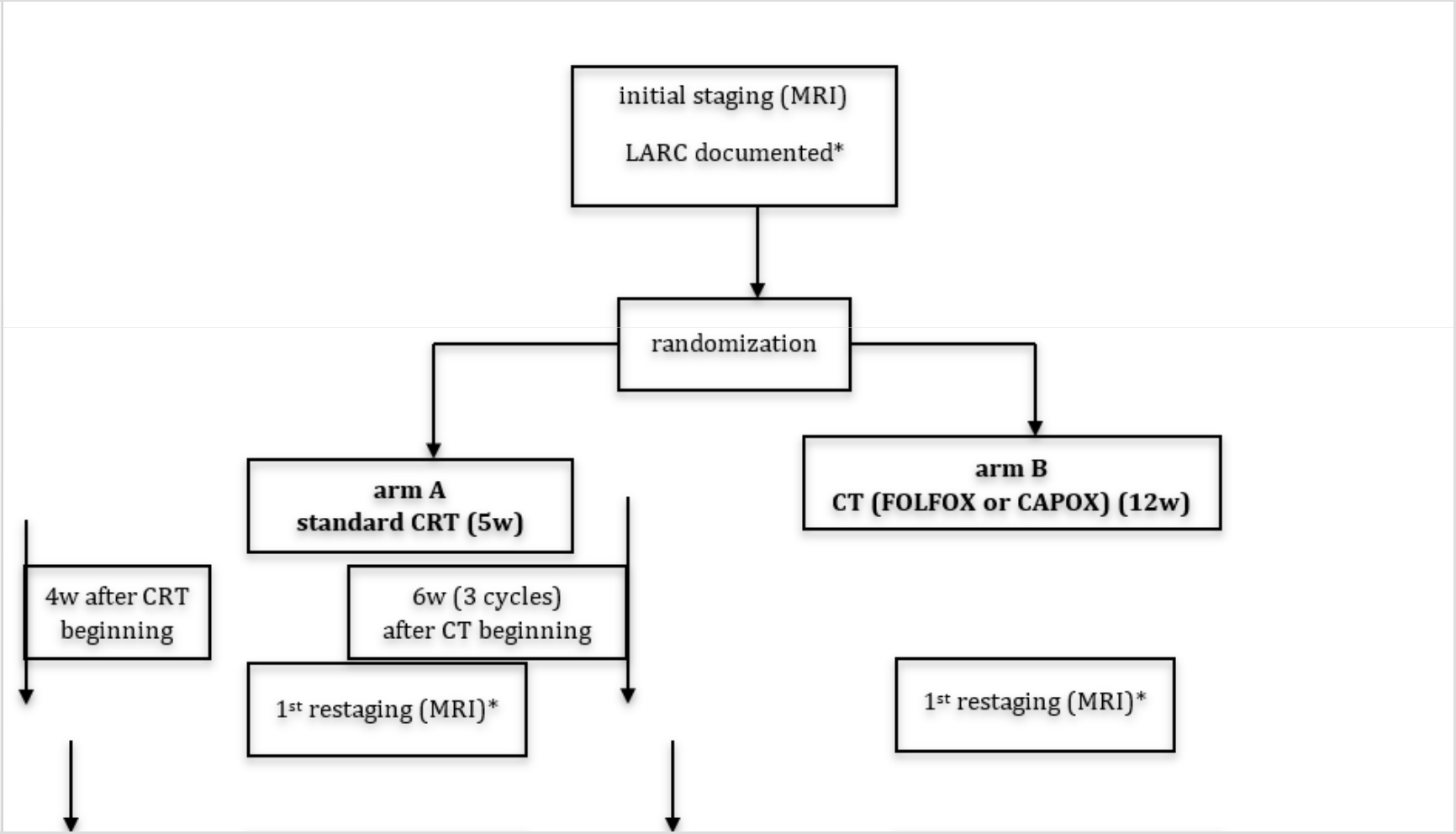
Prospect Study Endpoints

Primary Outcomes:

- Randomized Phase II Component (366 patients with early stopping rule if failure to complete R0 resections or if high rate of Local Recurrence)
  - R0 Resection Rate
  - Time to local recurrence (TLR)

- Phase III Component (644 additional patients) : Co-primary endpoints
  - Time to local recurrence (TLR)
  - Disease free survival (DFS)

NEARCHOS Greek trial



CREATE

Chemotherapy, **R**adiotherapy or **Ea**ch **T**hen **E**xcision for Operable Rectal Cancer at High Risk of Systemic Recurrence

Simon Gollins, David Sebag-Montefiore,

Advantage for NACT in rectal cancer

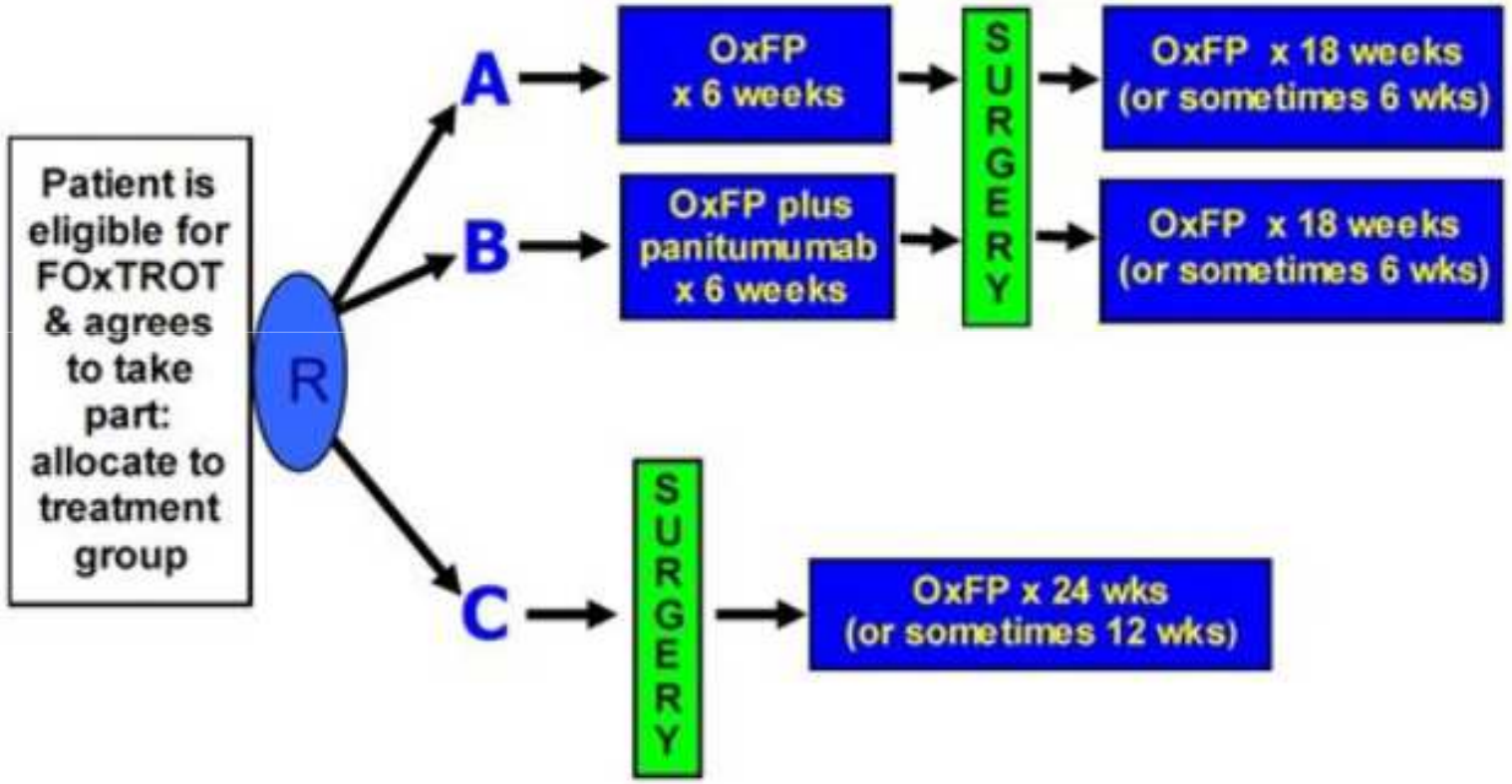
- Compliance should be increased to 90-95%
- Systemic Chemo can start immediately rather delayed many weeks post surgery
- Very few progress
- Can assess response to chemotherapy
- If 3 months sufficient from IDEA can be short and cost-effective

12 versus 24 weeks of FOLFOX or XELOX

Nov 2013 SCOT
6000 patients
randomised

FOxTROT design

recurrence free survival – 2 yrs



Early or late surgery

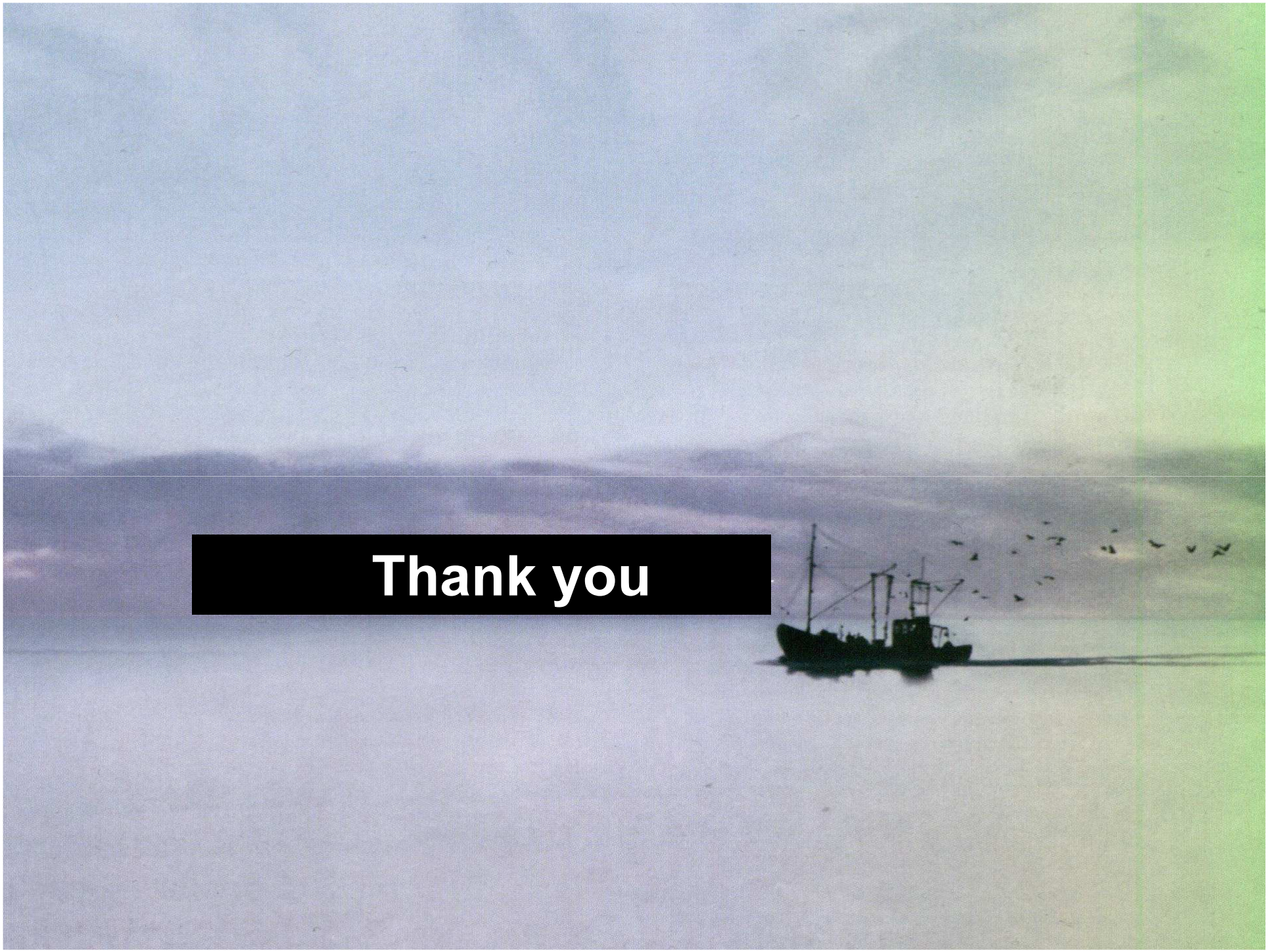
Foxtrot Compliance

- 96% (95 of 99) of patients started
- 89% (85 of 95) completed preoperative chemotherapy

- grade 3-4 gastrointestinal toxicity in 7% (seven of 94) of patients.

FOXTROT Margin status

	Preop and Postop chemo n=99	Postop chemo only n-50	P value
R0	95 (96%)	40 (80%)	)
R1/R2	5 (4%)	10 (20%)	) 0.002


Thank you

Anal SCC
Staging and re-staging

gina.brown@rmh.nhs.uk

Standards for assessment

- T staging – based on clinical assessment of maximum tumour length
- N staging – extrapolated from experience in rectal cancer
- M staging – requires CT TAP
- ERUS – not indicated
- PET-CT – changes stage in 30% - uncertain whether this improves outcomes.

Reporting standards

The tumour involves the circumference of the rectum from O'clock to the O'clock position

Tumour is [confined to] [extends through] the muscularis propria:
Extramural spread is [ ] mm at the O'clock position

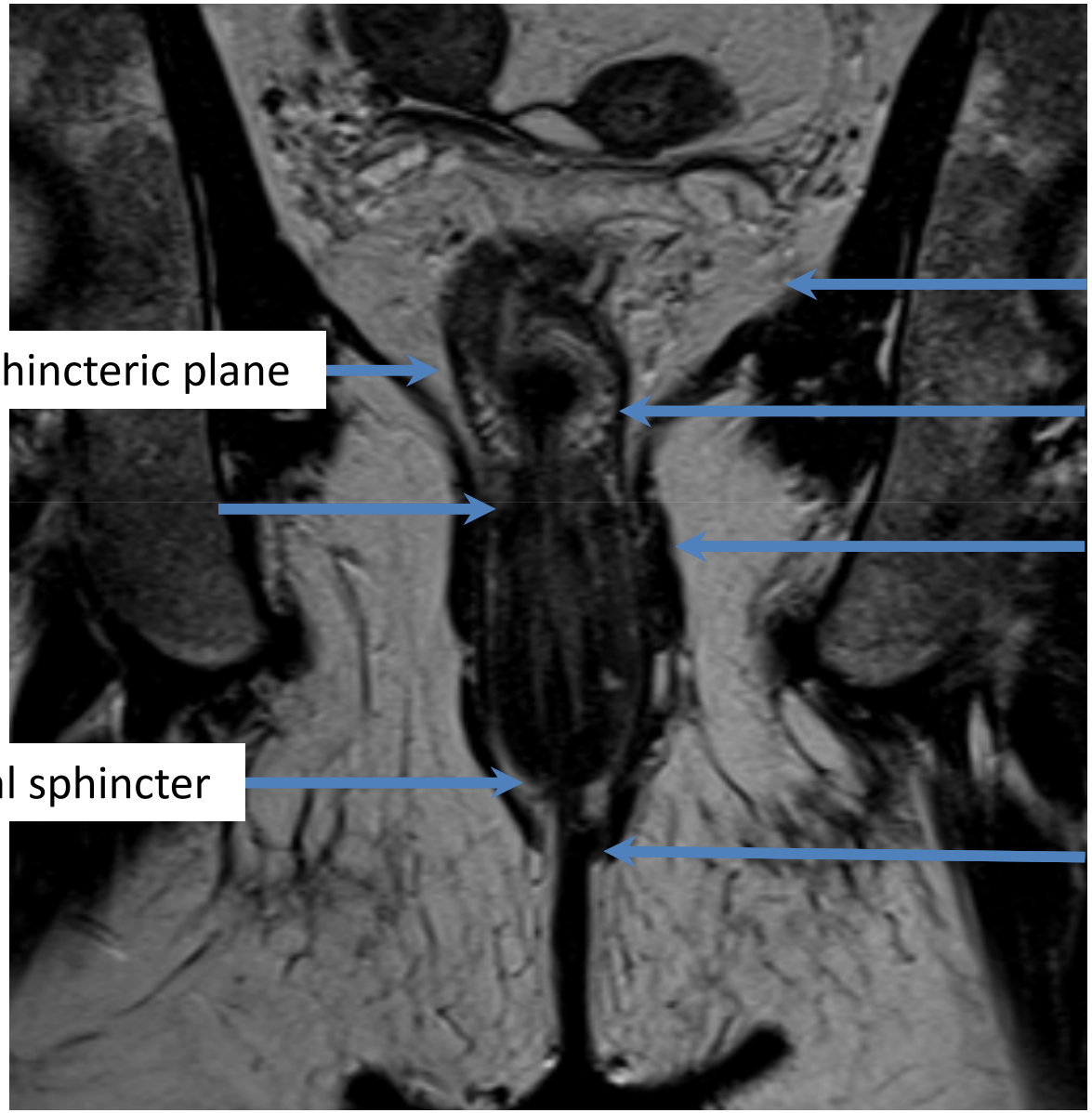
Lymph node assessment
Mesorectal nodes
Only benign reactive and no suspicious nodes shown
[ ] mixed signal/irregular border nodes in the mesorectum only

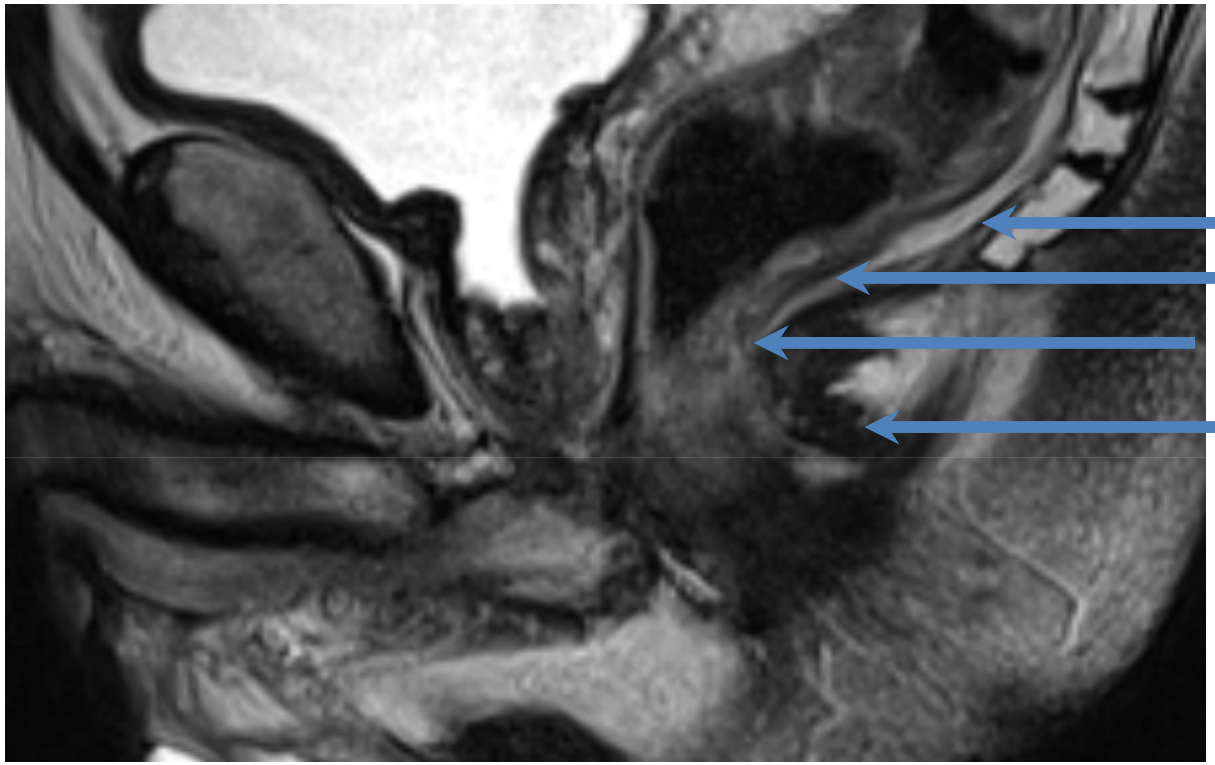
Pelvic side wall lymph nodes:
[None] [Benign] [Malignant mixed signal/irreg border]
Location: [Obturator fossa • R •L] . [External Iliac Nodes • R •L] [Internal iliac • R •L]

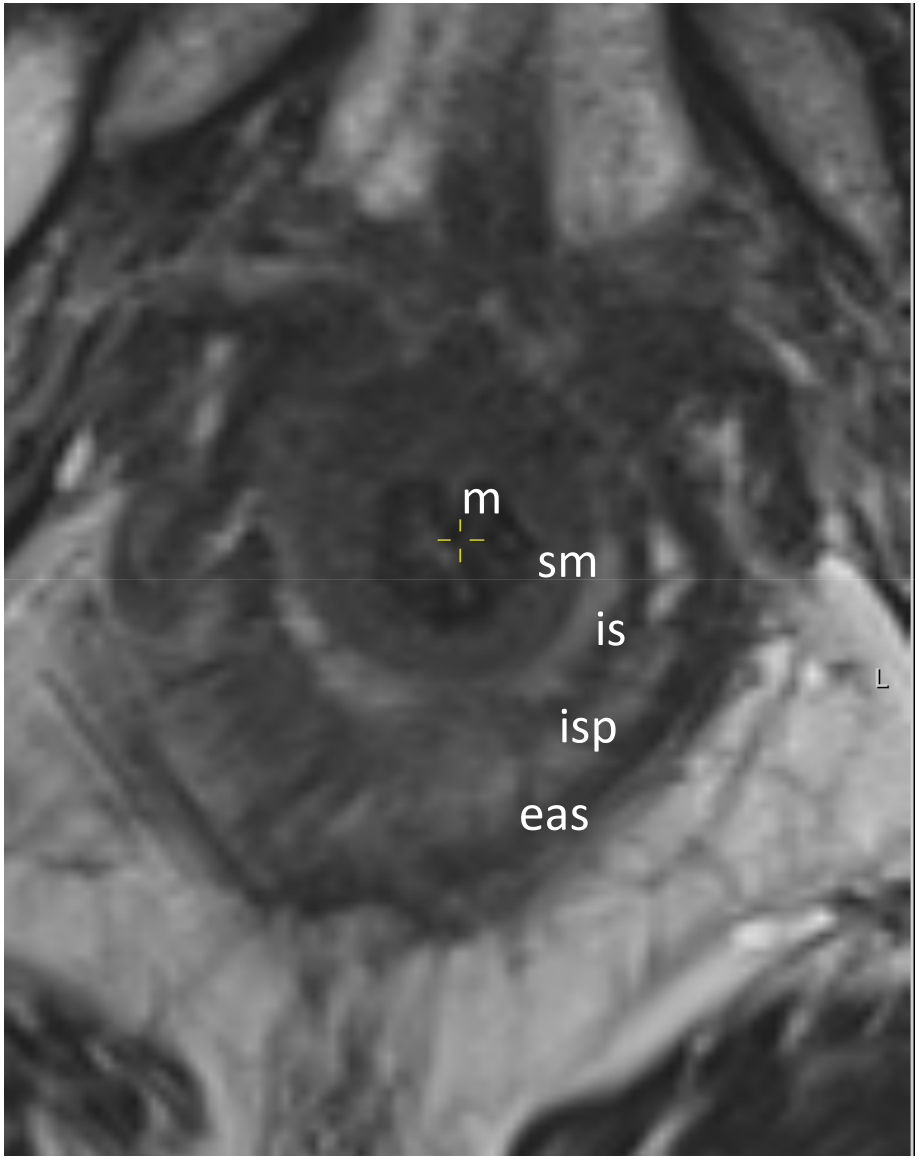
Inguinal nodal territory
Only benign reactive and no suspicious nodes shown
[ ] mixed signal/irregular border nodes in the mesorectum only [N2]

Overall Nodal Status:
No nodal disease: N0
Perirectal nodal disease only: N1
Unilateral inguinal and/or Pelvic sidewall nodes: N2
Bilateral inguinal/pelvic sidewall or Perirectal plus inguinal/pelvic sidewall N3

Summary: MRI Overall stage: T N M


levator muscles
intersphincteric plane
muscularis propria and internal sphincter
external sphincter
internal sphincter
lower fibers of the external sphincter


levator
Puborectalis sling
ISP
External
sphincter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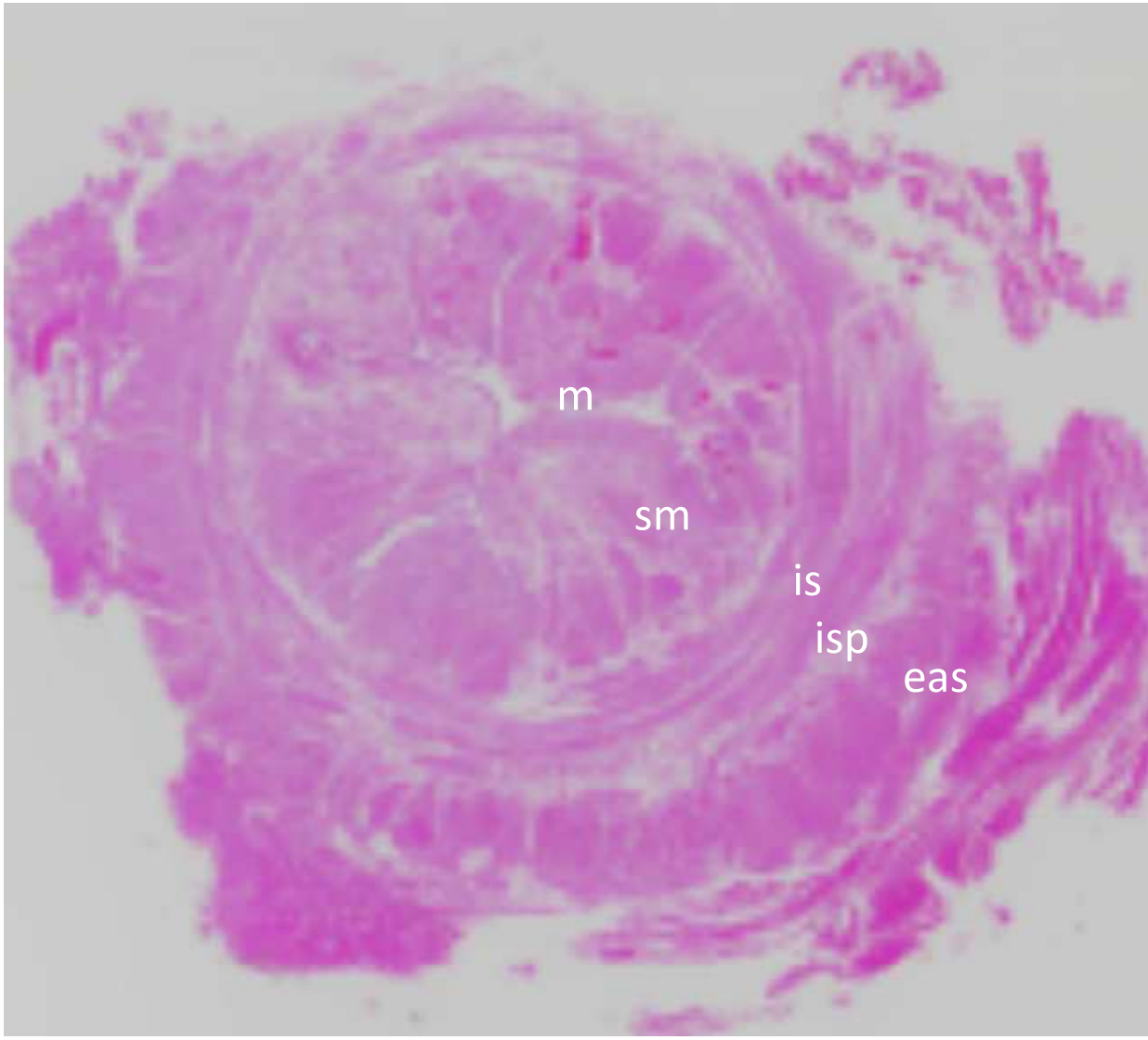
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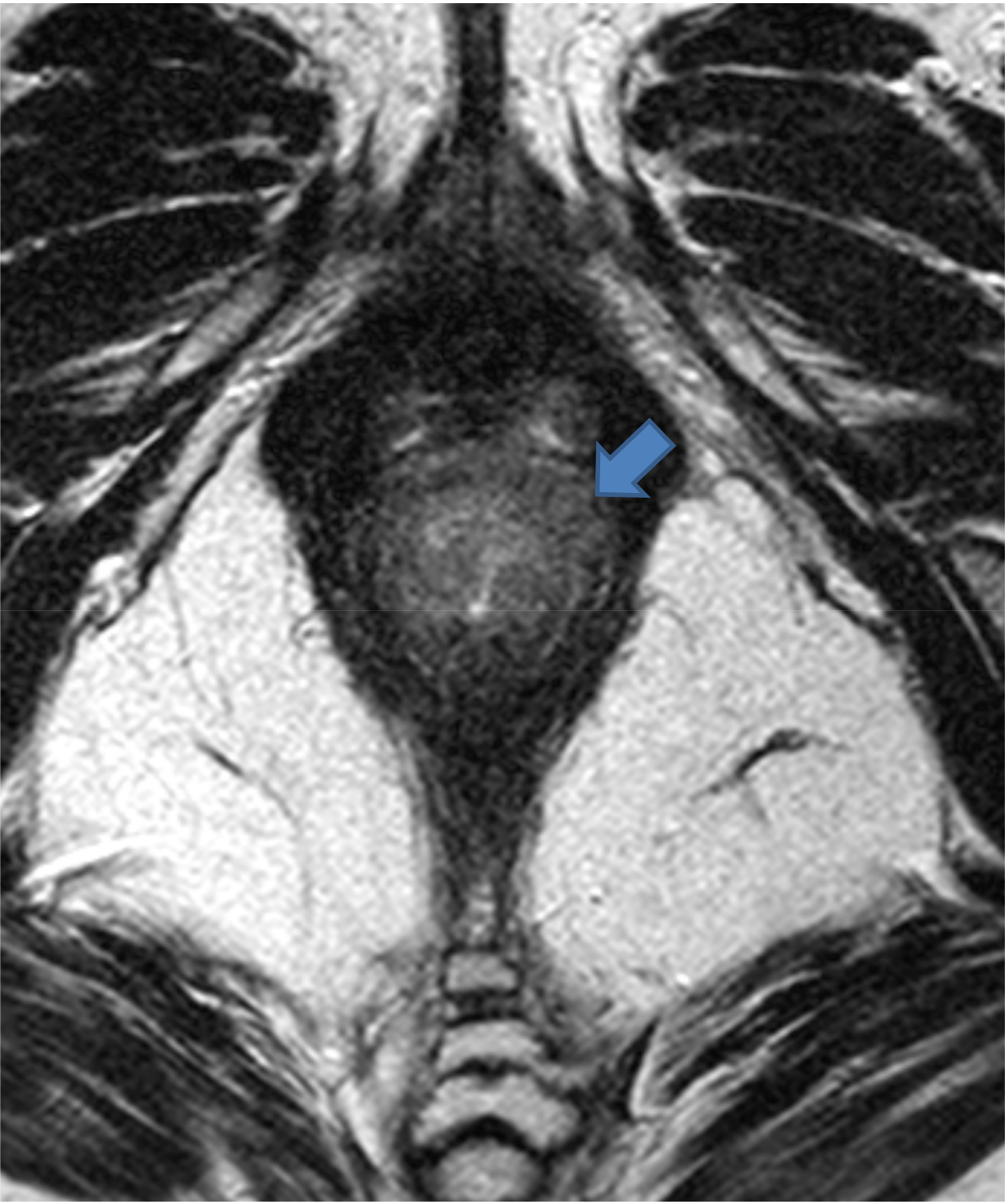
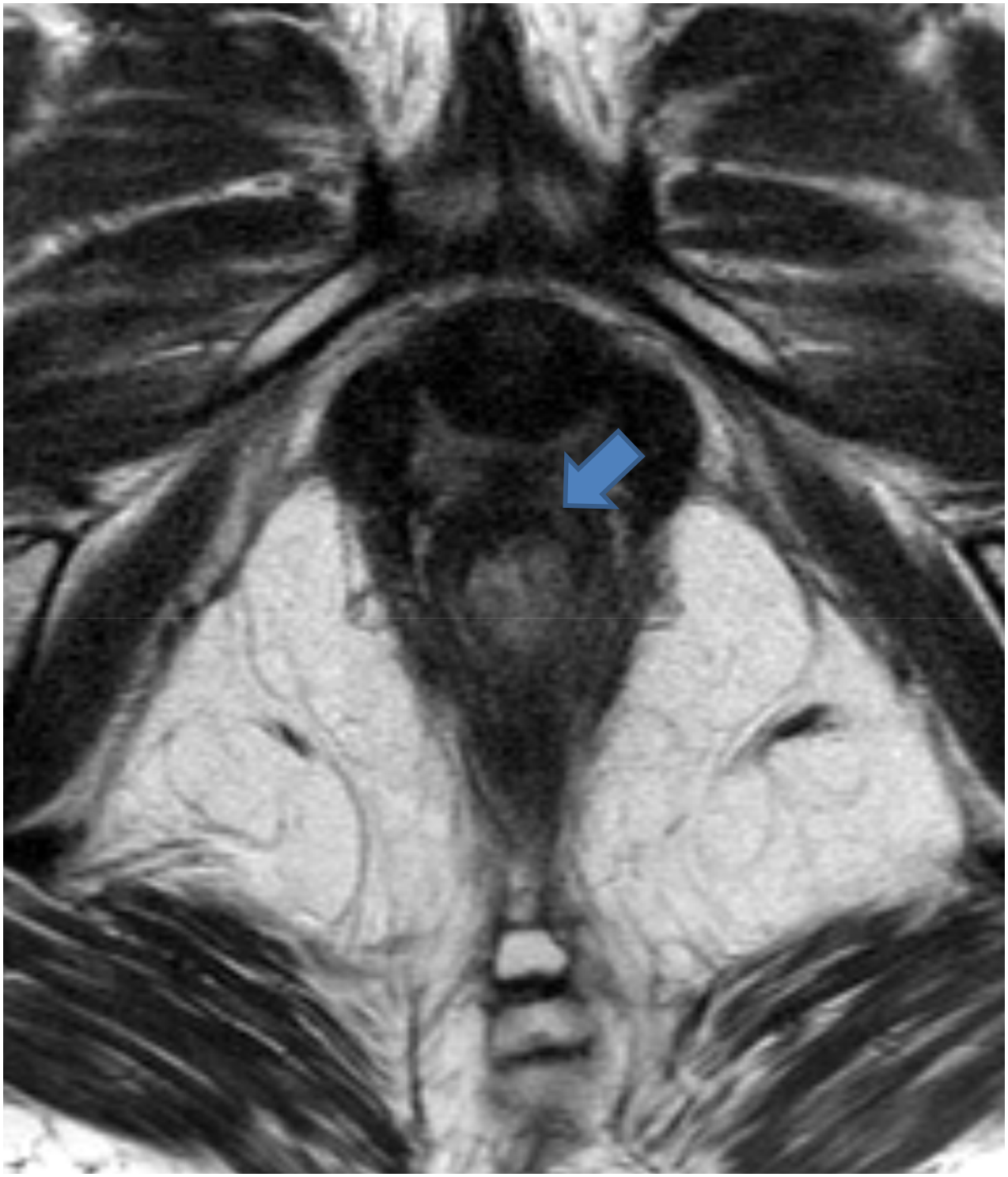
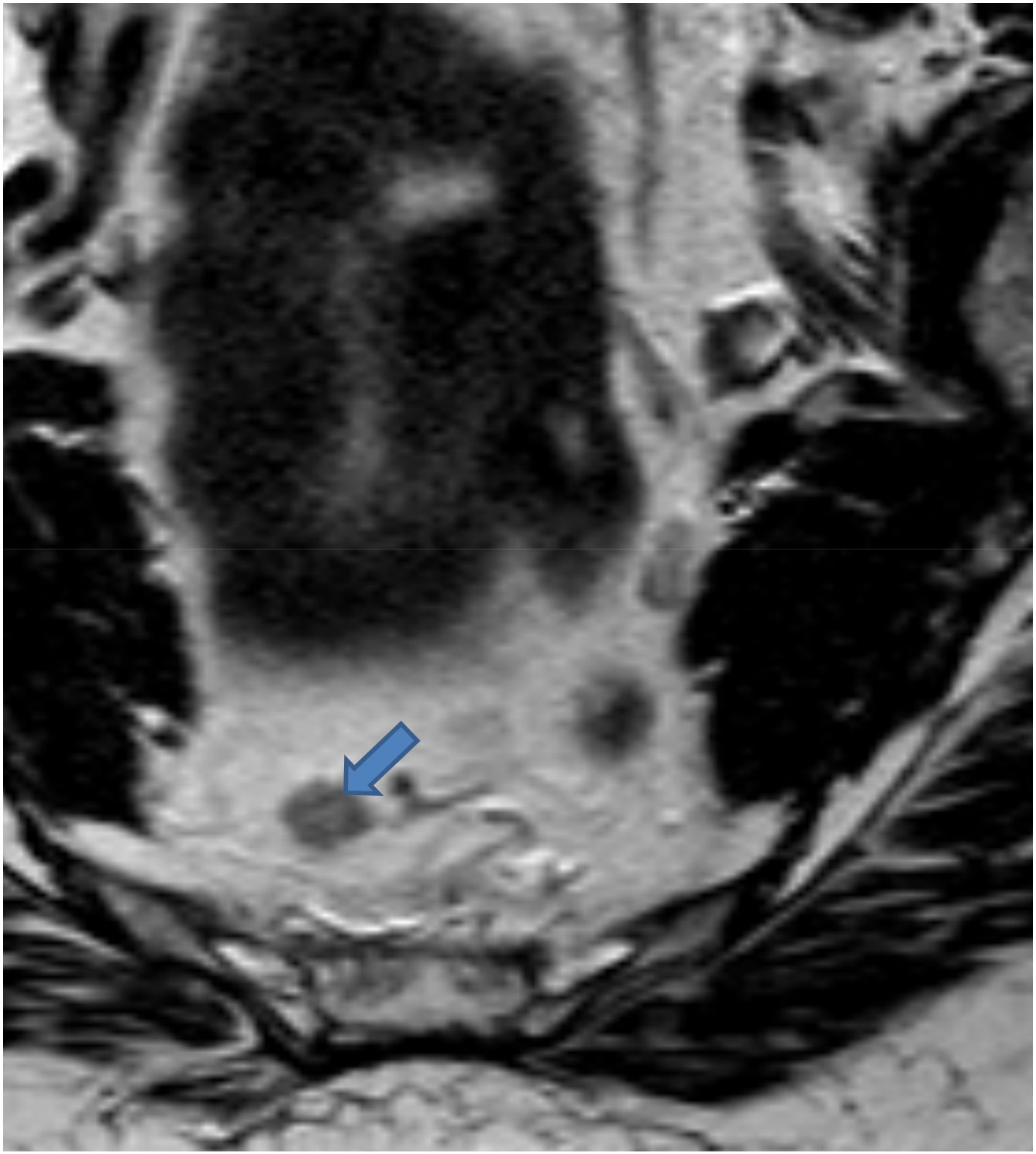
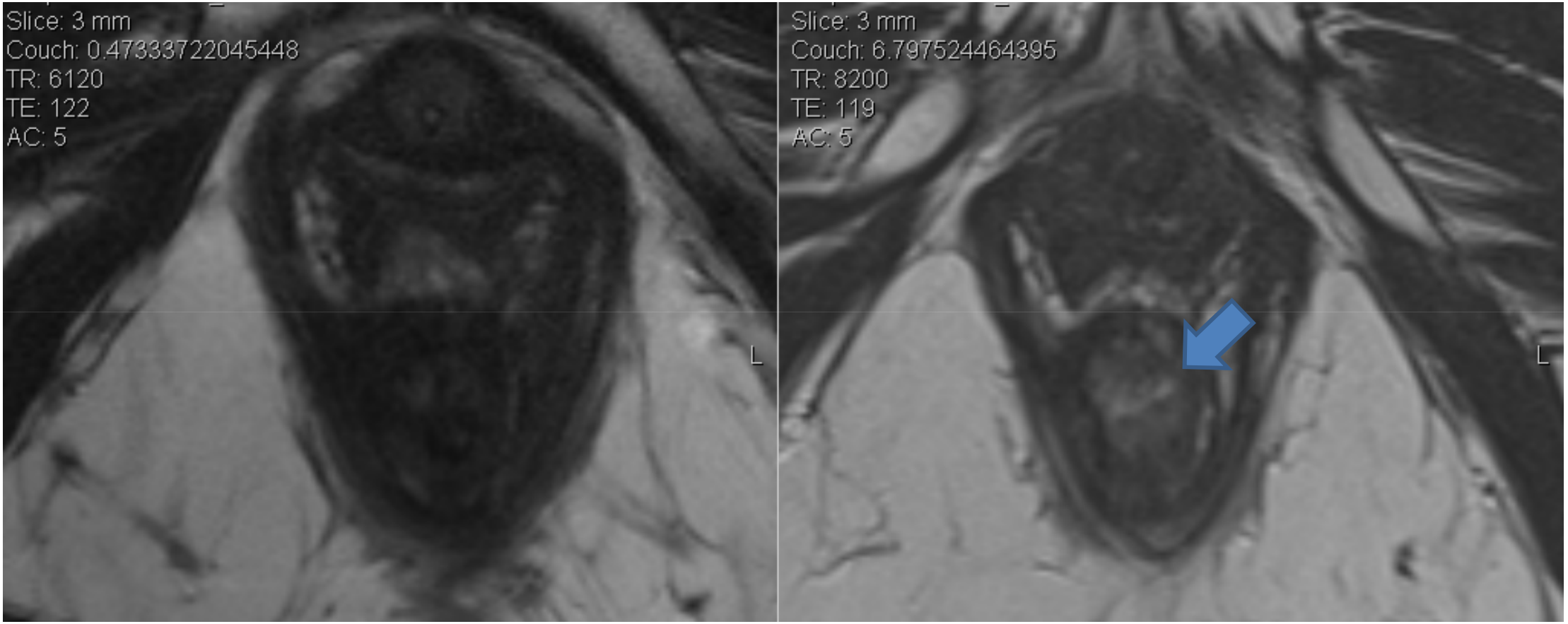
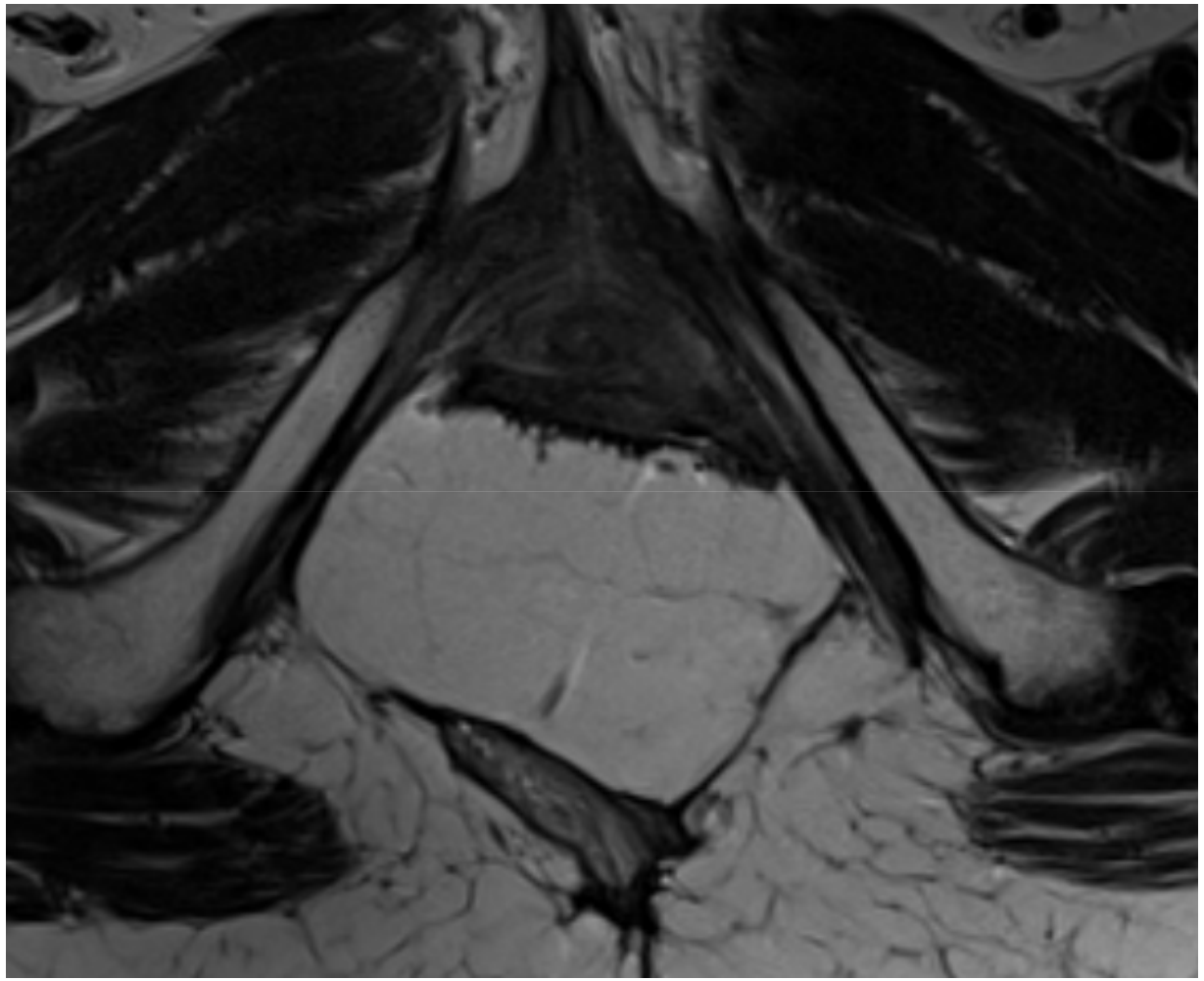
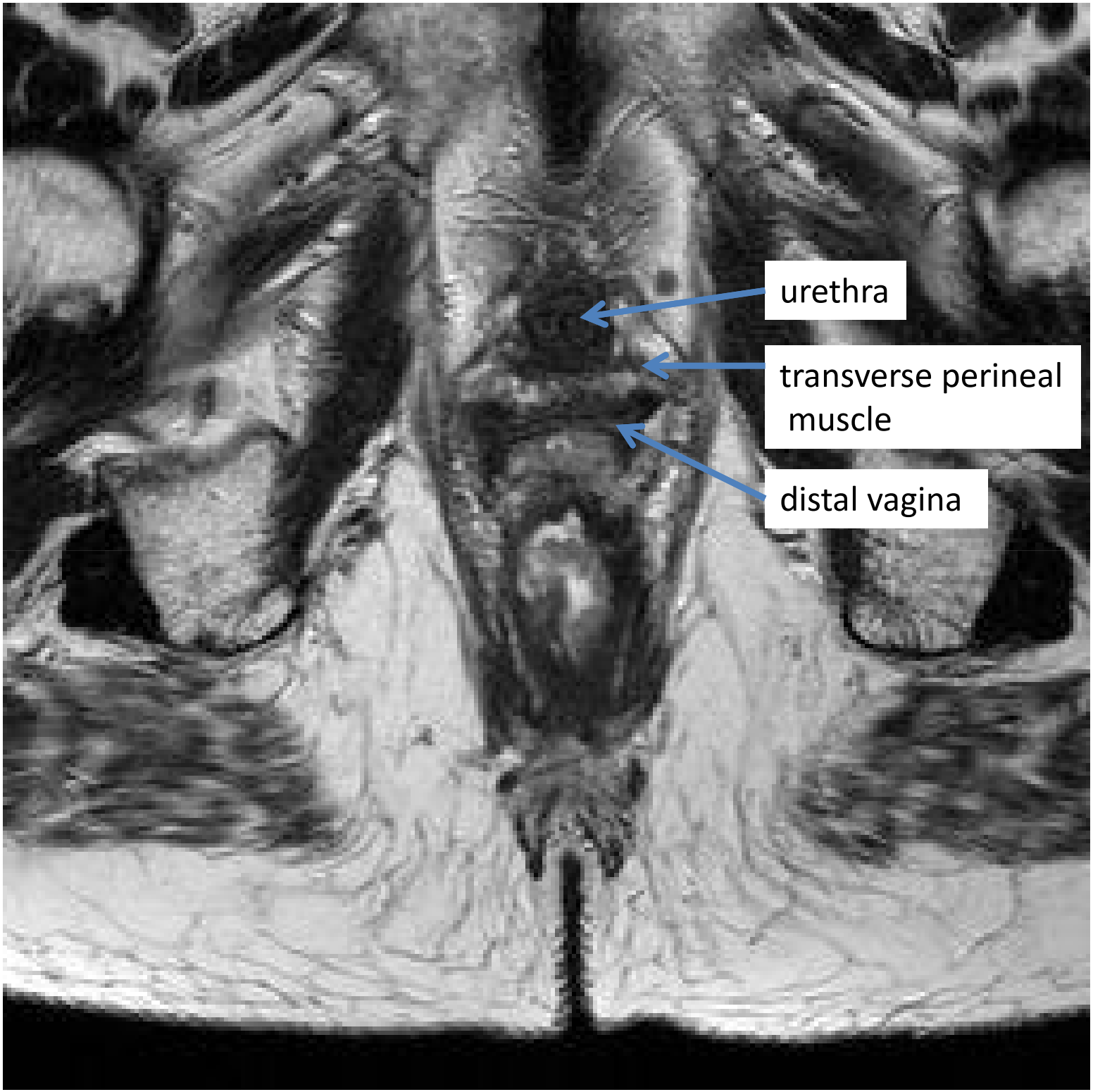


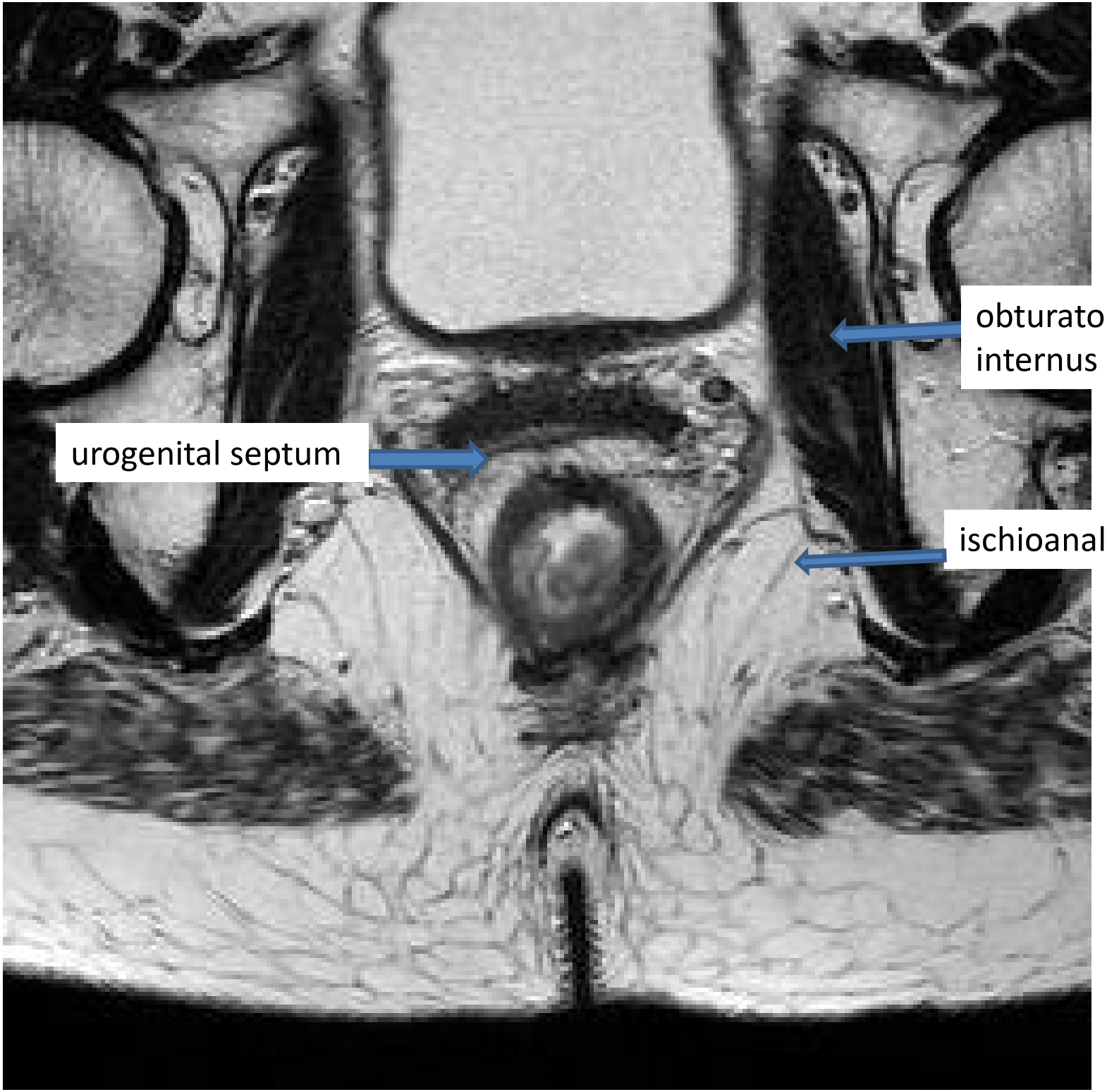


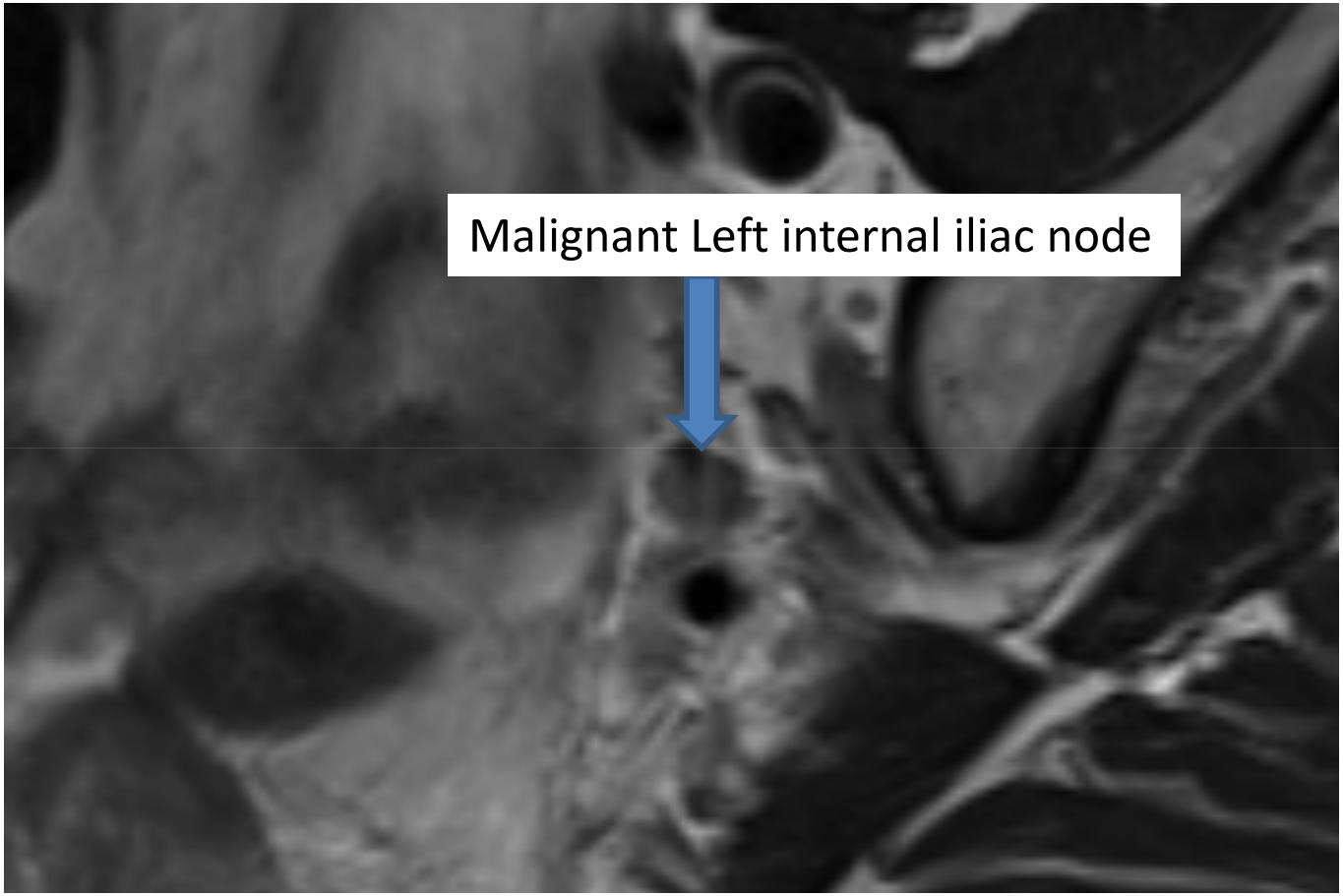


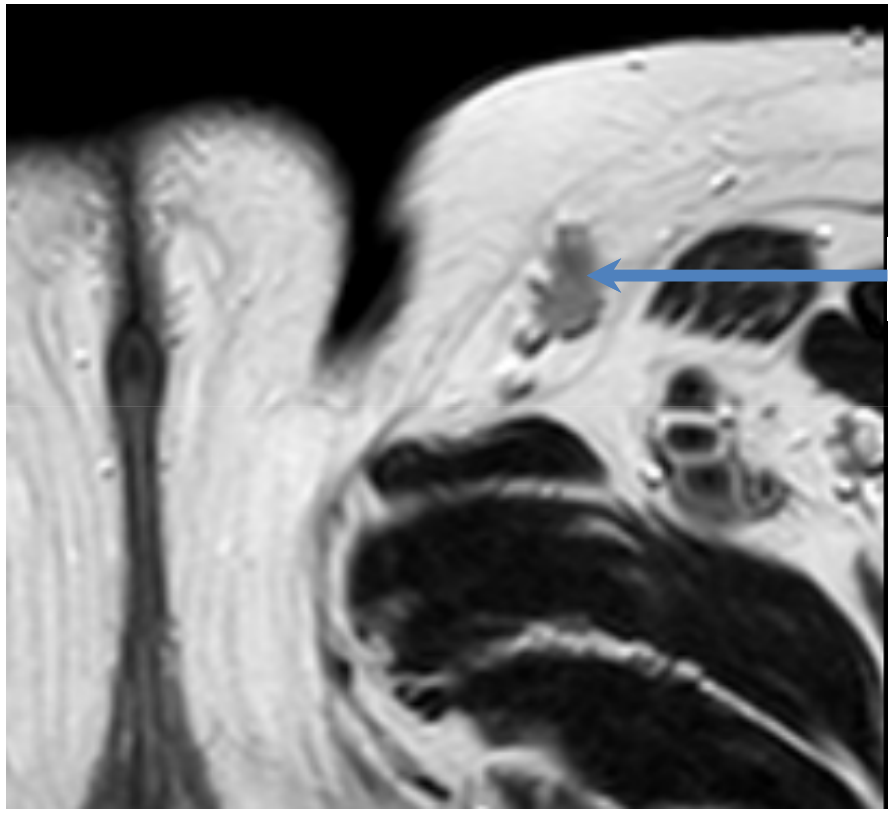

Slice: 3 mm
Couch: 0.47333722045448
TR: 6120
TE: 122
AC: 5
L
Slice: 3 mm
Couch: 6.797524464395
TR: 8200
TE: 119
AC: 5
L

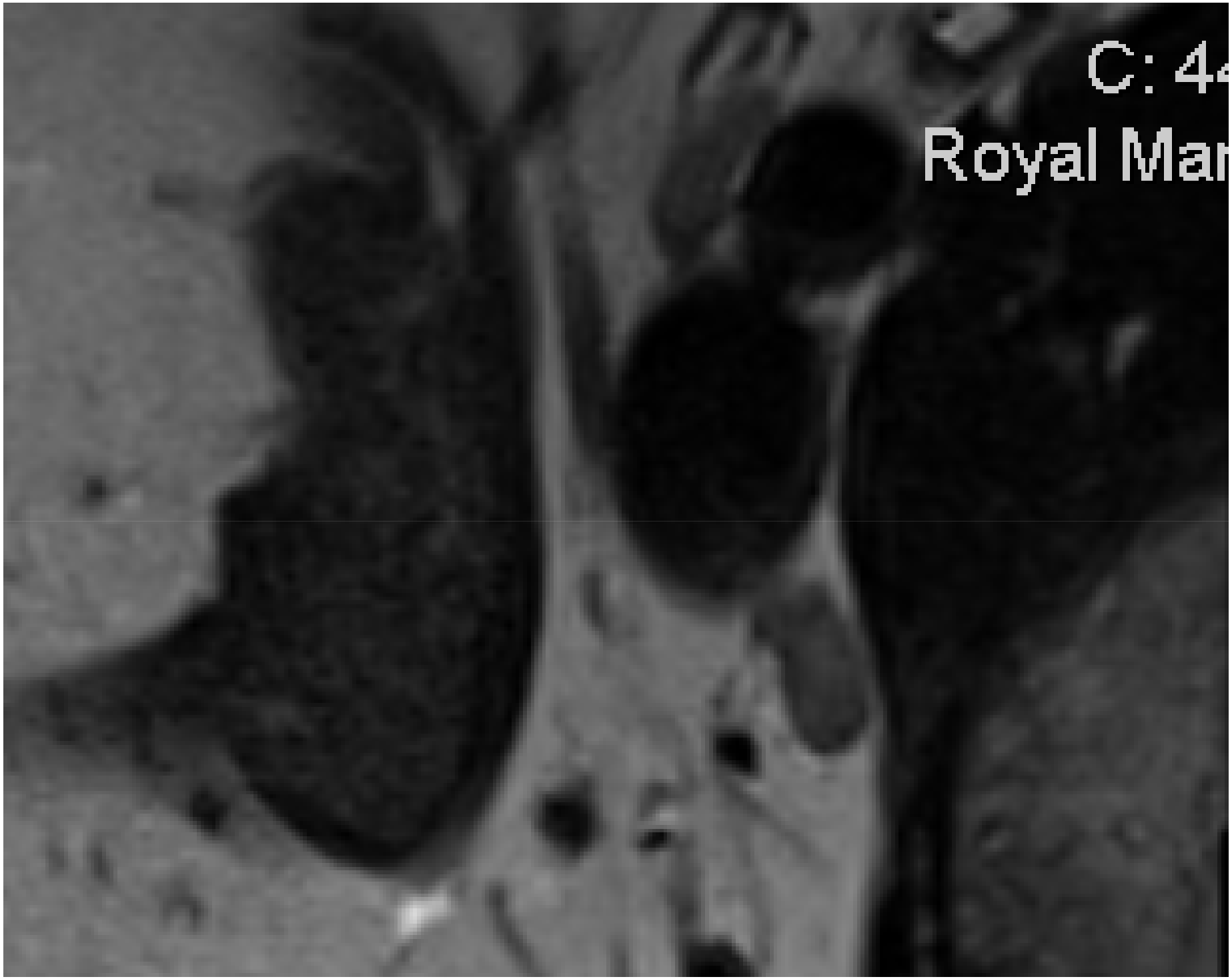



urethra
transverse perineal muscle
distal vagina


obturator
internus muscle
urogenital septum
ischioanal fossa


Malignant Left internal iliac node


Biopsy proven malignant inguinal node


C: 4
Royal Mar

Current guidelines:

What is considered standard of care for RT?

Karin Haustermans

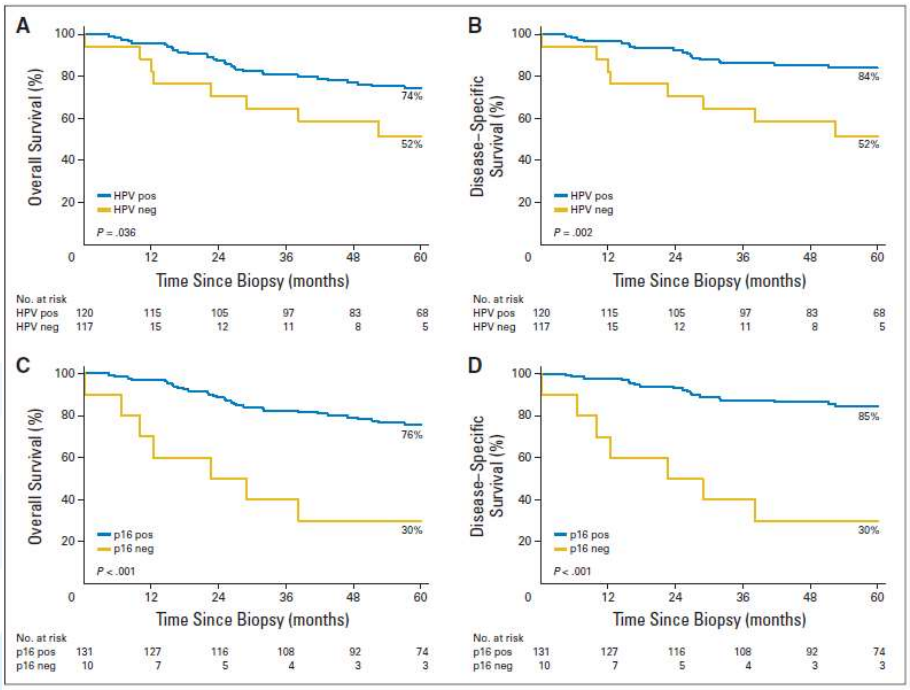
Department of Radiation Oncology

UZ Leuven

ESTRO School

Incidence and risk factors

- Rare disease
  - Annual incidence: 1/100 000 (USA)
  - Incidence is rising over the last 25 years
- 5 year survival: +/- 60%
- Risk factors:
  - HPV (in 90% of the patients)
  - HIV or HSV (secondary role in disease progression)
  - Immune suppression (transplant recipients)
  - Cigarette smoking (persistence HPV)



143 patients, PCR and p16

Serup-Hansen et al, JCO 2014

Pretreatment evaluation

- Specific history
- Symptoms (sphincter competence)
- Predisposing factors (history of HPV and HIV infections)
- Associated disease (CIS)
- Comorbidities possibly impacting on treatment

Disease staging

- To determine:
  - Tumor location
  - Tumor size
  - Nodal involvement
  - Distant Metastasis
- Primary tumor :
  - Clinical examination, preferentially under anesthesia
- Nodes
  - Clinical examination
  - Fine needle aspiration inguinal
- Radiological TN staging : MRI
  M staging : CT

Note : FDG-PET, inguinal sentinel N biopsy : investigational

Treatment of localized anal cancer

- Prior to mid-1980's: abdominoperineal resection as standard treatment

- Nigro et al: XRT 30 Gy + 5 FU Mito C (3 patients)

→ 2 AP resection tumour sterilised

→ 1 refusing surgery in complete clinical remission

⟶ No need for APR?

Mid eighties first phase III trials

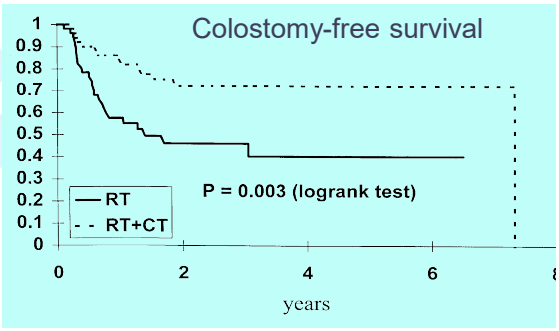
	Arm A	Arm B
US (RTOG 8704)	XRT+ 5 FU	XRT + 5 FU-Mito C
EORTC 22861	XRT	XRT + 5 FU-Mito C
UKCCCR ACT I	XRT	XRT + 5 FU-Mito C

US (RTOG-8704)

	XRT+ 5 FU	XRT + 5 FU-MMC	p value
Complete response	86%	92,2%	
Colostomy- free survival	59%	71%	0,014
Colostomy rate	22%	9%	0,002
DFS	51%	73%	
OS	71%	78,1%	0,31

EORTC 22861

	XRT	XRT + 5 FU-MMC	p value
Complete response	54%	80%	
Local Failure rate (5 years)	50%	32%	0,02
Colostomy free survival	Increase by 32% (see graph)		0,03
DFS (5 years)	Estimated improvement by 18%		
OS	54%	58%	0,17



ACT-I

- RT 45Gy/20-25 fractions
- CRT (5FU 2 x 4d. Mito 12 mg/m)

After 6 weeks boost:

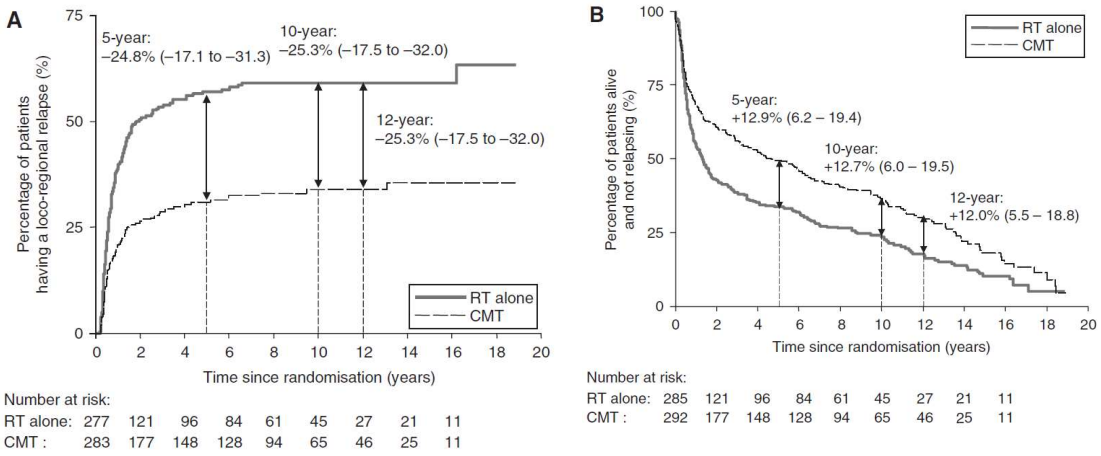
- Irdidium implant to 25Gy (10Gy/d.)

or

- External beam irradiation: 15Gy in 6 fractions

Northover, Br J Cancer 2010

ACT-I



Northover, Br J Cancer 2010

Toxicities in phase III trials

Acute	Haematological	↗	significant
	Diarrhoea	↗	significant
	Skin/mucositis	↗	significant
Late			?

Phase III Results: Summary

- ↗ Local control
- ↗ Colostomy-free survival
- ↗ DFS

Conclusions from early randomised trials

- CMT standard as first line treatment
- Level of Evidence I
- Needs expertise

Predictors of outcome

- LRF
  - T > 4 cm
  - N positive
  - RT incomplete
  - RT interruption
  - Early T response
- Survival
  - T > 4 cm
  - N positive
  - Early T response

Tournier, Rangeard, Roohipour, Das

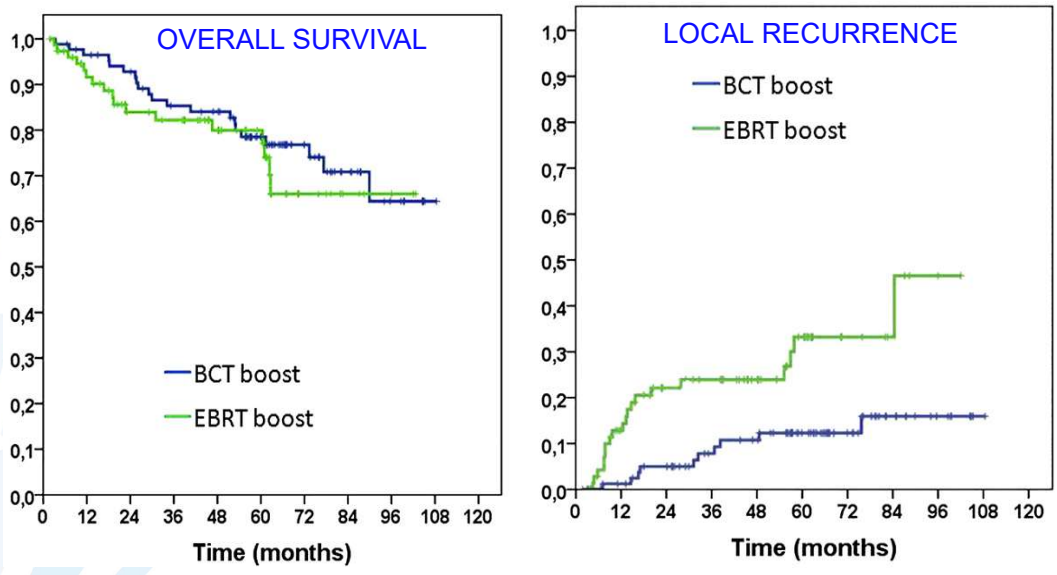
Unsolved questions

- Role of brachytherapy
- Management of inguinal region
- Type and scheme of CT
- Optimizing RT delivery

Unsolved questions

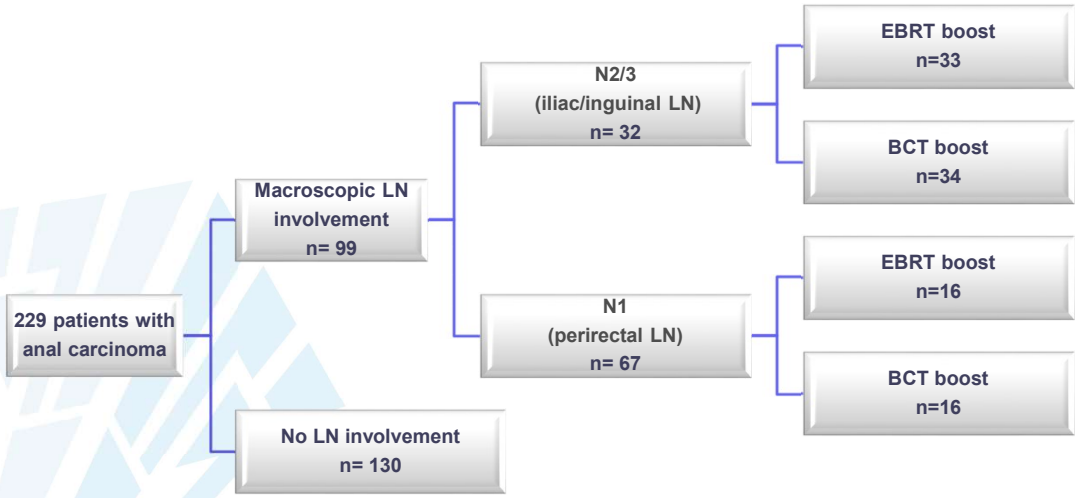
- Role of brachytherapy
- Management of inguinal region
- Type and scheme of CT
- Optimizing RT delivery

Boost with brachytherapy ?

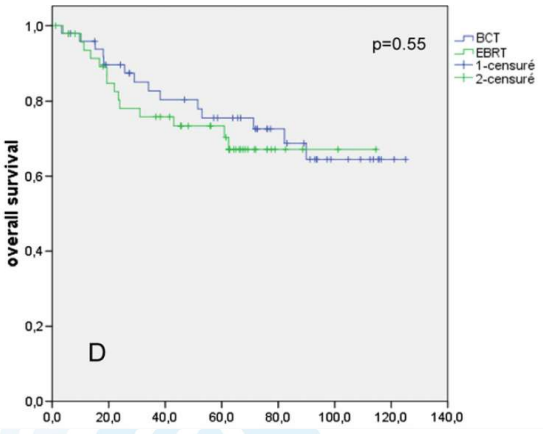


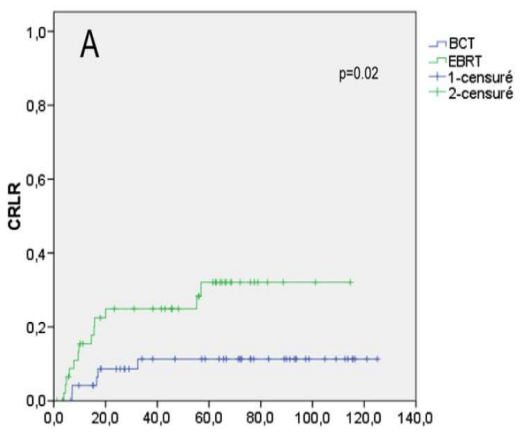
Hannoun-Levi, IJROBP 2011

CORS-03 study



CORS-3 study





BCT boost is superior to EBRT boost for local control , without an influence on OS

→ N1 status should not be a contraindication for a BCT boost technique

Laurence Moureau-Zabotto et al, IJROBP 2013

Unsolved questions

- Role of brachytherapy
- Management of inguinal region
- Type and scheme of CT
- Optimizing RT delivery

Management of the inguinal region

- Involvement %

Overall	T1-2	T3-4
25	< 10	15-30

- Risk increased
  - T below dentate line
  - Pelvic nodes
  - Anal margin involved
- Pic factor : 5-year survival ~ 50 %

Management of inguinal region (CMT)

- N negative
  - ENI 36 Gy if
    - T within 1 cm from a/m
    - Invasion of anal margin
    - Pelvic nodes involved
- N positive
  - CMT 60 Gy

Salvage surgery

Note : delayed CR possible up to ≥ 4 months

if incomplete clinical response 16 weeks after CRT

↓

True cut biopsy

↓

AP resection

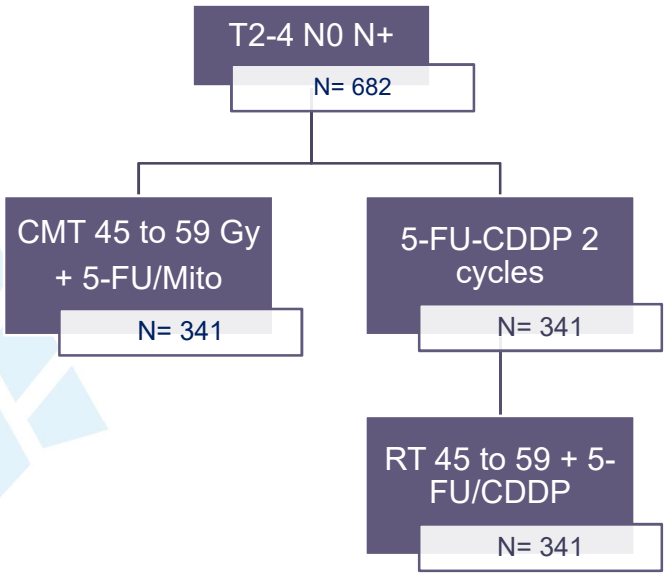
well-trained team

Akbari. Dis Colon Rect 2004

Unsolved questions

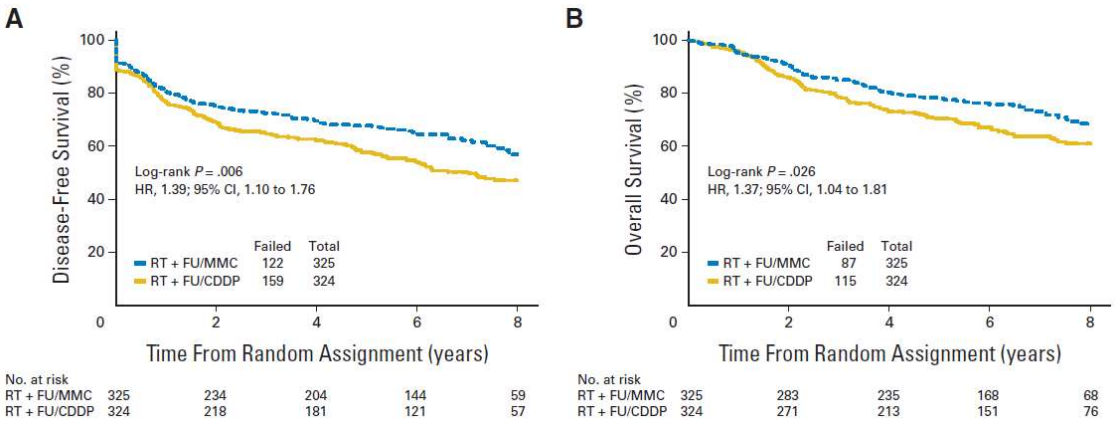
- Role of brachytherapy
- Management of inguinal region
- Type and scheme of CT
- Optimizing RT delivery

Intergroup RTOG 98-11



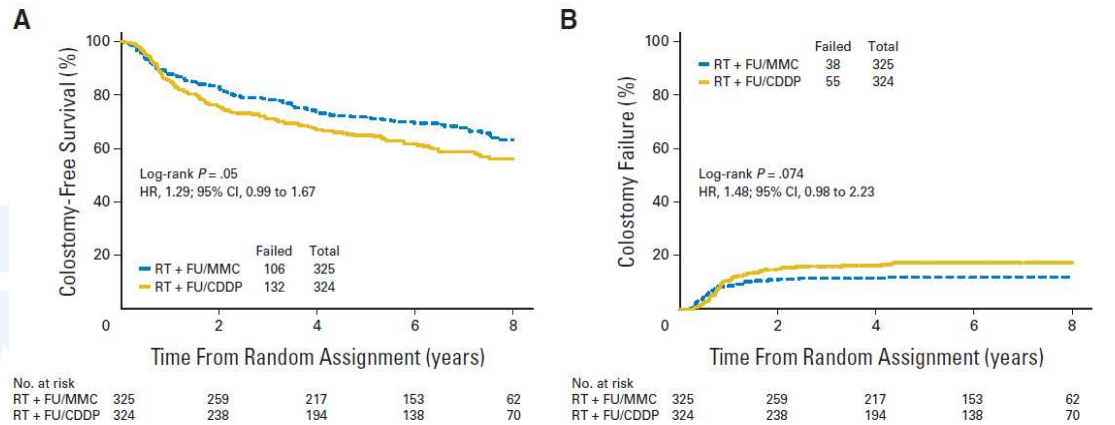
Gunderson, J Clin Oncol 2012

Intergroup RTOG 98-11: DFS & OS



Gunderson, J Clin Oncol 2012

RTOG 98-11: colostomy free survival



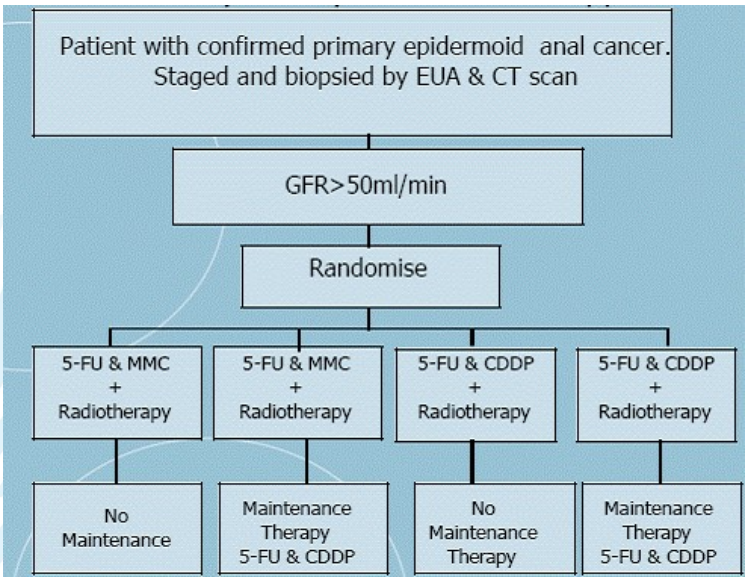
Gunderson, J Clin Oncol 2012

Intergroup RTOG 98-11: conclusions

- CCR with FU/MMC /5FU has a significant impact on DFS and OS versus induction plus concurrent FU/CDDP
- CCR with FU/MMC /5FU has borderline significance for CFS, CF and LRF

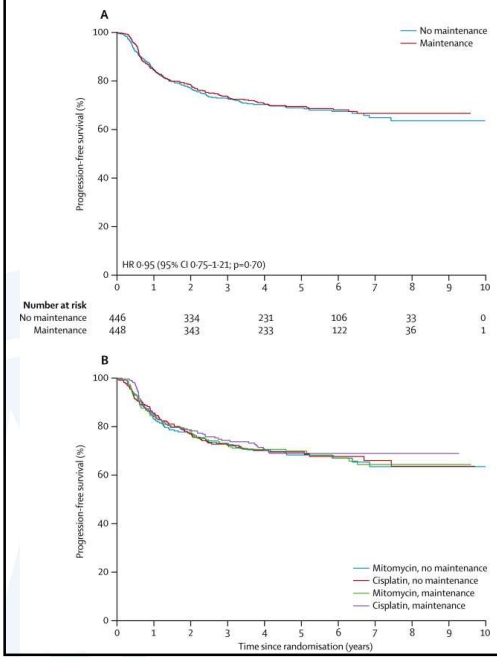
→ MMC/5FU remains the standard of care for patients with anal canal carcinoma

ACT-II



James, Lancet Oncol 2012

ACT-II



	Mitomycin group (n=432)	Cisplatin group (n=431)
Complete response	391 (90·5%)	386 (89·6%)
Partial response	14 (3·2%)	24 (5·6%)
Stable disease	5 (1·2%)	6 (1·4%)
Progressive disease	22 (5·1%)	15 (3·5%)

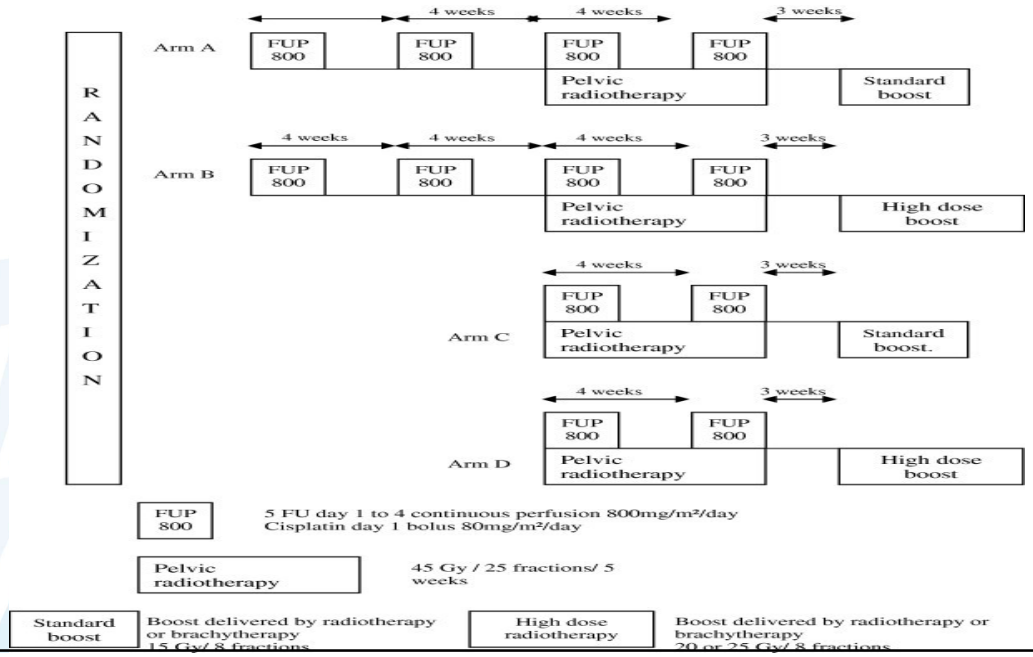
Table 2: Primary tumour response at 26 weeks

Fluorouracil and mitomycin with 50,4Gy radiotherapy in 28 daily fractions should remain standard practice

The addition of maintenance in routine clinical practice is not justified

James, Lancet Oncol 2012; Hutchinson, Nat Rev Oncol 2013

France Accord 03



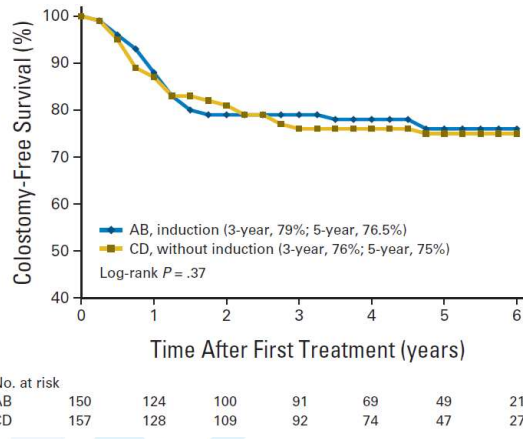
France Accord 03

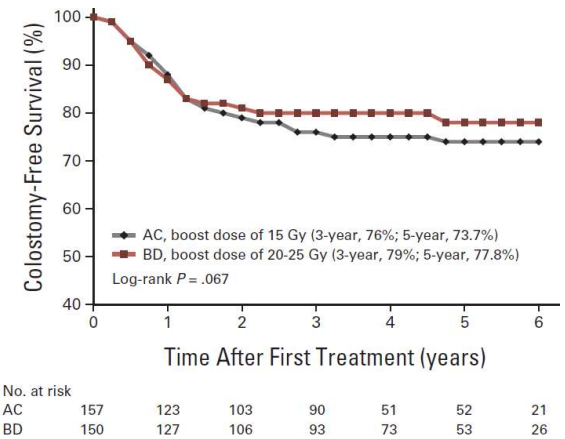
Upfront CT ⟷ not

No differences found

60 Gy ⟷ 66 Gy

France Accord 03





Unsolved questions

- Role of brachytherapy
- Management of inguinal region
- Type and scheme of CT
- Optimizing RT delivery

RTOG 0529

- Prospectively assess the utility of DP-IMRT in reducing the acute morbidity of 5FU/MMC chemoradiation
  - Primary endpoint: reduction of grade 2+ GI and GU AEs by at least 15%.
  - Secondary endpoints:
    - Potential reduction of all AEs with DP-IMRT
    - The investigator's ability to perform DP-IMRT within the radiation planning guidelines delineated

Kachnik, IJROBP 2013c

RTOG 0529

Table 5 Comparisons of acute treatment-related adverse events*

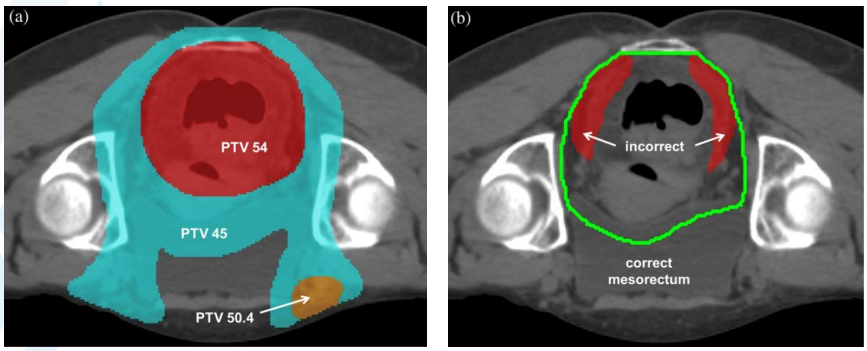
Adverse events	0529 (n=52)	98-11 (Arm 1†) (n=325)	*P* value (1-sided proportions test§)
Grade 2+			
GI/GU‡	40 (77%)	249 (77%)	.50
Derm	39 (75%)	271 (83%)	.10
GI	38 (73%)	237 (73%)	.50
GU	8 (15%)	66 (20%)	.18
Heme	38 (73%)	275 (85%)	.032
Overall	49 (94%)	318 (98%)	.12
Grade 3+			
GI/GU	11 (21%)	120 (37%)	.0052
Derm	12 (23%)	159 (49%)	<.0001
GI	11 (21%)	117 (36%)	.0082
GU	1 (2%)	11 (3%)	.32
Heme	30 (58%)	201 (62%)	.29
Overall	43 (83%)	283 (87%)	.23

Kachnik, IJROBP 2013c

RTOG 0529

Table 3 Dose-painted intensity modulated radiation therapy final pretreatment compliance scores* (n=51)†

	PTV anal	PTV nodal	PTV small bowel	PTV femoral heads
Per protocol	44 (86%)	48 (94%)	28 (55%)	39 (76%)
Minor deviation	7 (14%)	3 (6%)	20 (39%)	11 (22%)
Major deviation	0 (0%)	0 (0%)	3 (6%)‡	1 (2%)‡



Kachnik, IJROBP 2013c

RTOG 0529 conclusions

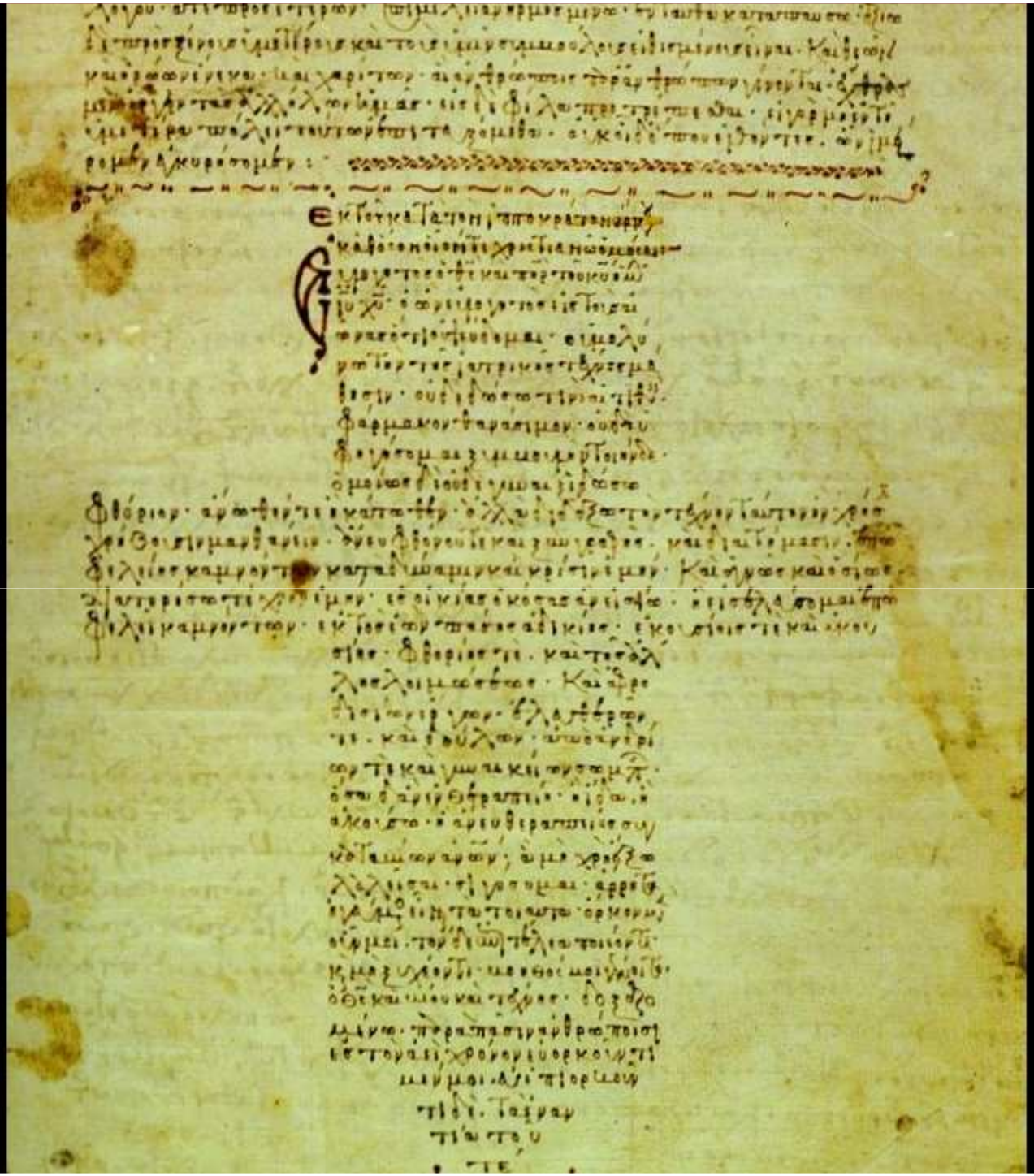
- Primary endpoint: reduction of grade 2+ GI and GU AEs by at least 15% NO
- Secondary endpoints:
  - Potential reduction of all AEs with DP-IMRT YES
  - Ability to perform DP-IMRT within the radiation planning guidelines delineated YES

Kachnik, IJROBP 2013c

Current (European) Guidelines:
What is considered standard of care for concurrent and adjuvant chemotherapy ?

Rob Glynne-Jones
Mount Vernon Cancer Centre
on behalf of NCRI anal cancer subgroup

ESTRO School



NCCN Guidelines Version 2.2016
Rectal Cancer

NCCN Guidelines Index
Rectal Cancer Table of Contents
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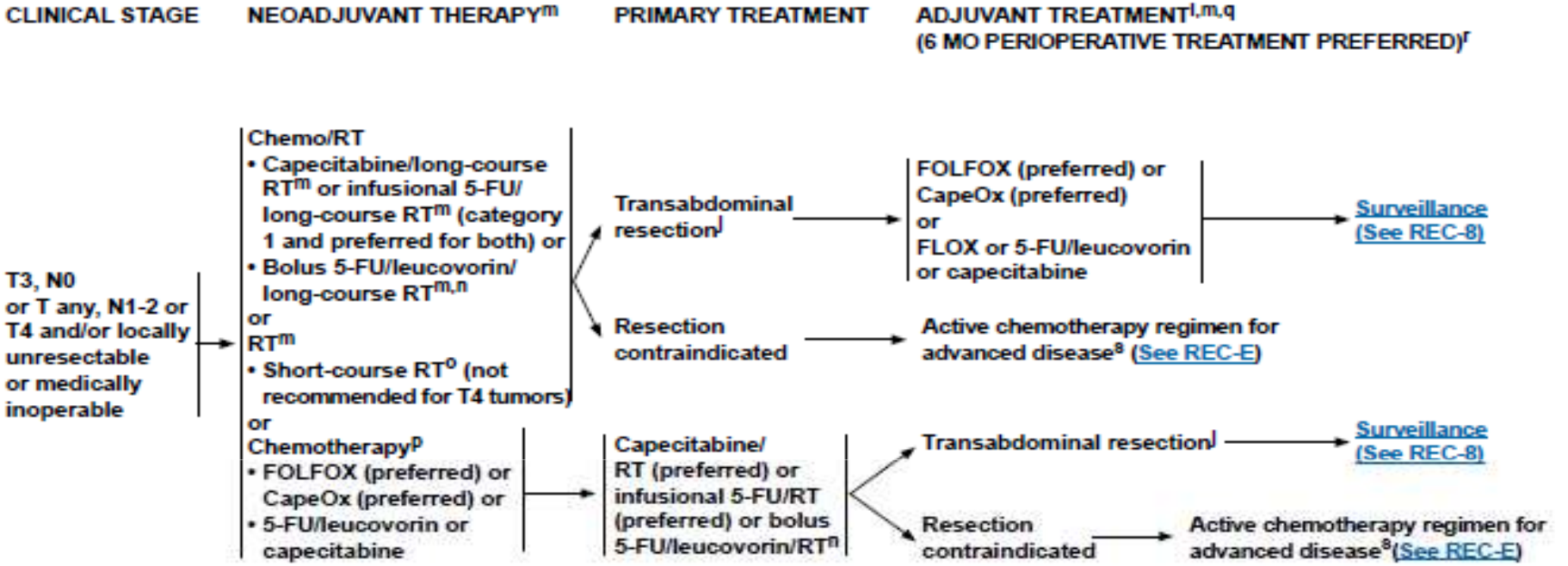

[j]See Principles of Surgery (REC-B).
[l]See Principles of Adjuvant Therapy (REC-C).
[m]See Principles of Radiation Therapy (REC-D).
[n]Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[o]Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for down-staging and the possibility of long-term toxicity.
[p]Fernandez-Martos C, Pericay C, Aparicio J, et al: Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010;28:859-865.

Cercek A, Goodman KA, Hajj C, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Canc Netw 2014;12:513-519.
[q]Postoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results.
[r]Total duration of perioperative chemotherapy, inclusive of chemotherapy and radiation therapy, should not exceed 6 months.
[s]FOLFOXIRI is not recommended in this setting.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Rectal Cancer

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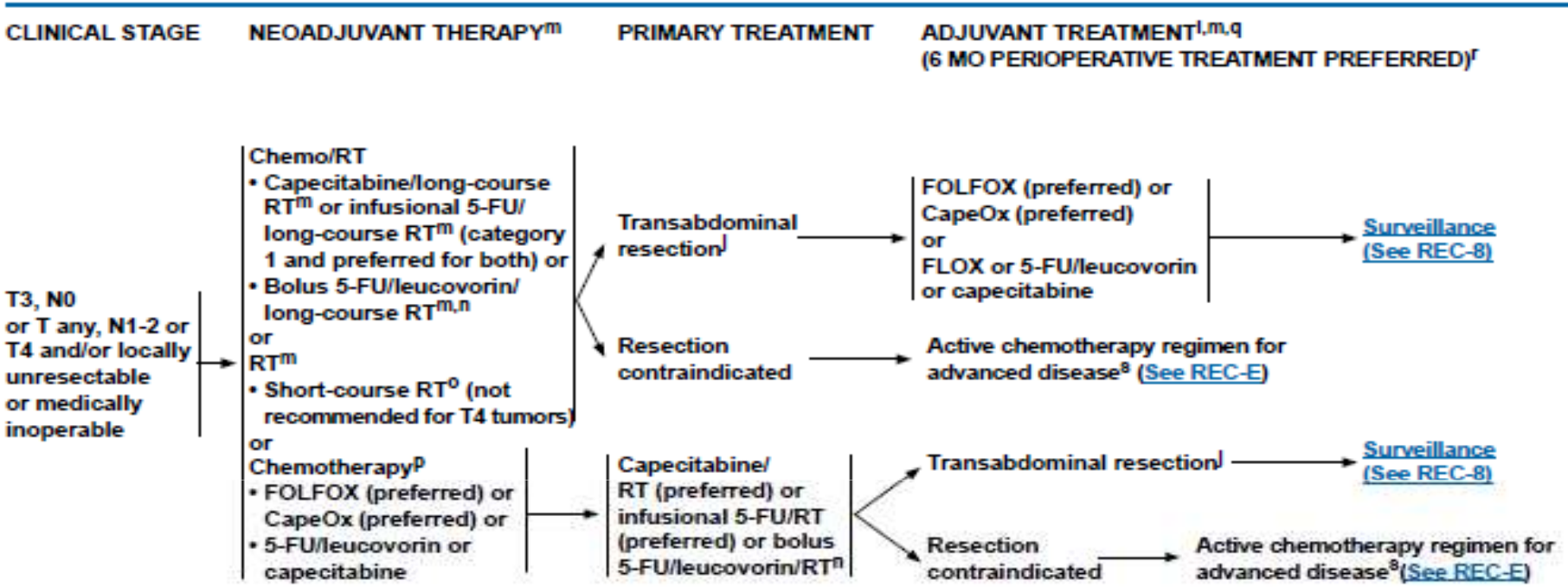

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School

Current ESMO Guidelines

- **Glimelius** B, Tiret E, Cervantes A, Arnold D; ESMO Guidelines Working Group.
- Ann Oncol. 2013 Oct;24 Suppl 6:vi81-8

Risk group	TN substage	Therapeutic options
Very early	*c*T1 sm1 (-2?) N0	Local excision (TEM). If poor prognostic signs (sm ≥ 2, high grade, V1), resection (TME) (or possibly CRT)
Early (good)	*c*T1-2; *c*T3a (b) if middle or high, N0 (or cN1 if high), mrf-, no EMVI	Surgery (TME) alone. If poor prognostic signs (crm+, N2) add postop CRT or CT[a]. (CRT with evaluation, if cCR, wait-and-see, organ preservation)
Intermediate (bad)	*c*T2 very low, *c*T3mrf- (unless cT3a(b) and mid- or high rectum, N1-2, EMVI+, limited *c*T4aN0	Preop RT (5 × 5 Gy) or CRT followed by TME. (if CRT and cCR, wait-and-see in high risk patients for surgery)
Advanced (ugly)	*c*T3mrf+, *c*T4a,b, lateral node+	Preop CRT followed by surgery (TME + more extended surgery if needed due to tumour overgrowth). 5 × 5 Gy with a delay to surgery in elderly or in patients with severe comorbidity who cannot tolerate CRT

- To my mind muddied by watch and wait

Guidelines for Postoperative adjuvant chemotherapy

Poulsen et al Acta Oncol 2015

Table I. International and national guidelines on postoperative adjuvant chemotherapy for rectal cancer.

	ESMO	NCCN	Norway	Sweden	Finland	Denmark	Spain	Dutch	NICE
Year	2013 [22,23]	2012 [2]	2013 [24]	2014 [25]	2009 [26]	2013 [27]	2013 [28]	2014 [29]	2011 [30]
RC High-risk stage II	FU/5FU	5FU/Ox#	No	5FU	5FU-Ox§	5FU(+ Ox)	Yes*	No	Yes
RC stage III	FU/5FU	5FU/Ox	No	5FU(+ Ox)	5FU-Ox	5FU(+ Ox)	Yes*	No	Yes
After preop. CRT**	n.s.	Yes	No	No	n.s.	Yes	No	No	n.s.

ONLY ESMO GUIDELINES state level of evidence supporting the recommendations

ESTRO School

The European Society for Medical Oncology rectal cancer guidelines 2013 state

"Standard preoperative chemoradiotherapy means a dose of 45-50.4 Gy, 1.8 Gy/fraction, or alternatively 50 Gy, 2 Gy/fraction together with a fluoropyrimidine"

Evidence base for the 2 Options for radiotherapy in locally advanced rectal cancer

- **Preoperative long course chemoradiotherapy CRT (25-28 X 1.8Gy Gy)**

- **(Post-op CRT as adjuvant)**

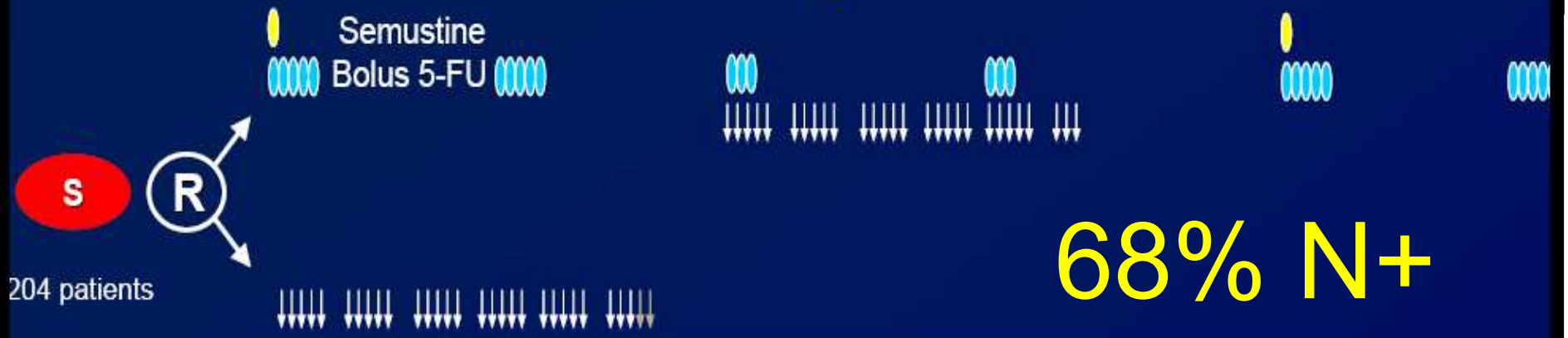
Postoperative Trials : Rectal Cancer

Randomised Trials of post-op CRT

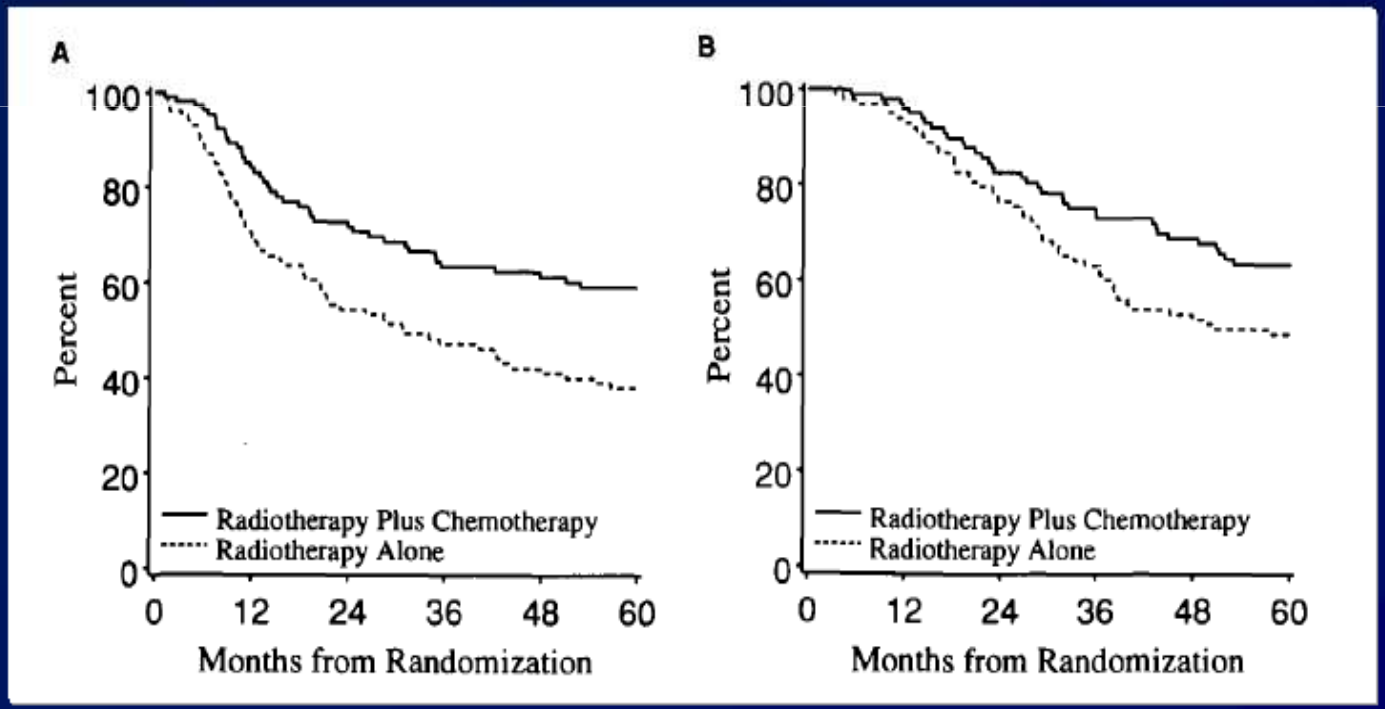
- GITSG
- NCCTG (Krook et al 1991)
- NSABP R02
- Intergroup (Infusional 5FU)

Further Intergroup studies

NCCTG/Mayo 794751



68% N+

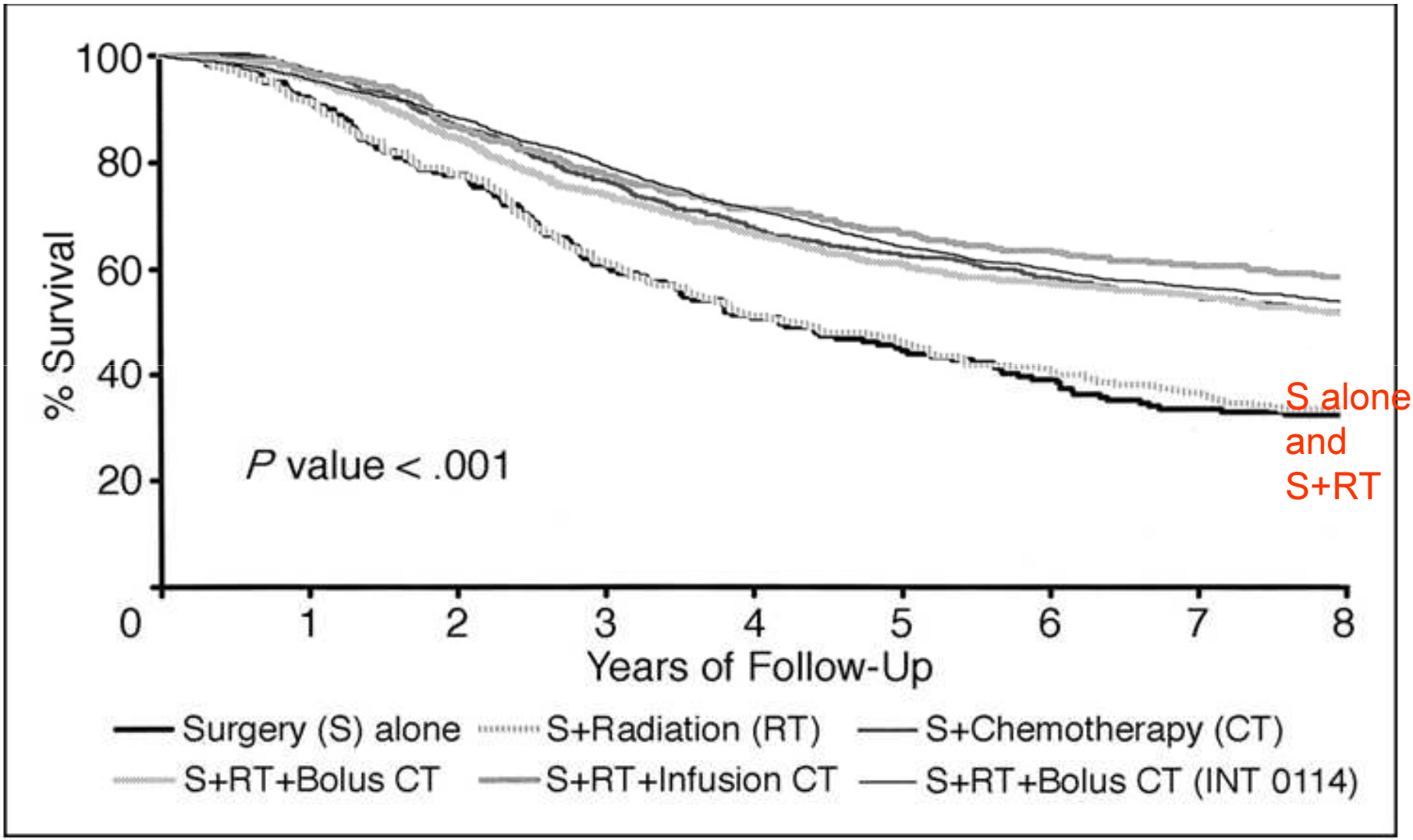


Disease-free survival

Overall survival

Krook et al. N Eng J Me 1991

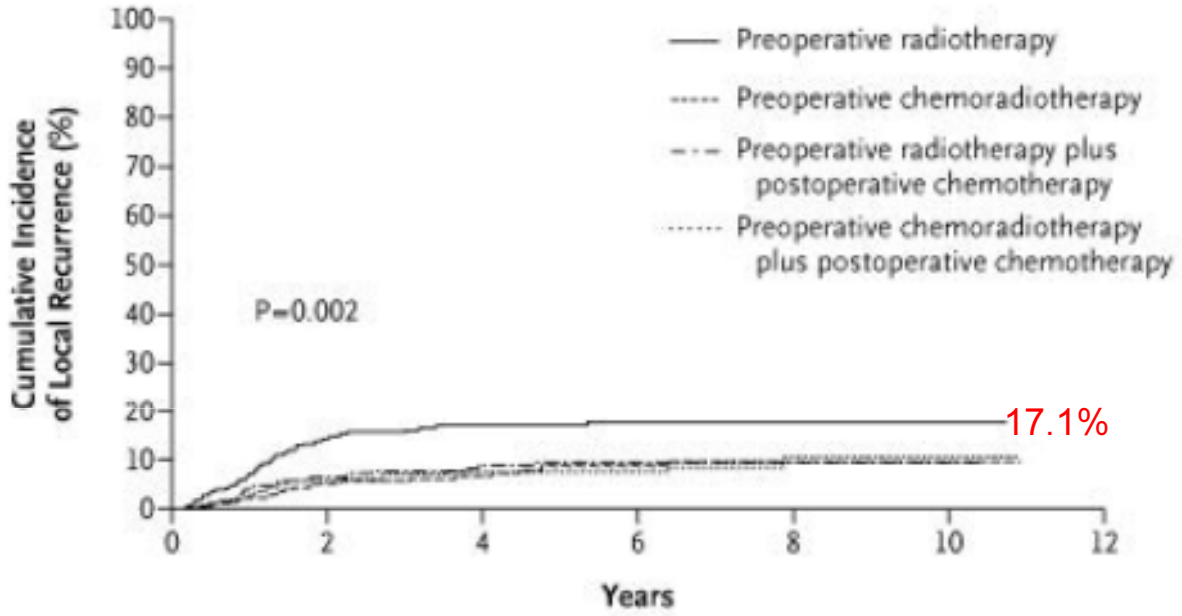
Impact on overall survival of 6 methods of treatment in rectal cancer pooled analysis



Gunderson, L. L. et al. J Clin Oncol; 22:1785-1796 2004

EORTC 22921 Trial

Local recurrence as a first event at 5 years was **17.1%** in the preoperative-radiotherapy group vs 8.7%, 9.6% and 7.6% in the group receiving preoperative chemoradiotherapy and postoperative chemotherapy.



No. at Risk						
Preoperative radiotherapy	252	147	87	60	24	6
Preoperative chemoradiotherapy	253	165	99	52	22	5
Preoperative radiotherapy plus postoperative chemotherapy	253	156	103	65	29	6
Preoperative chemoradiotherapy plus postoperative chemotherapy	253	159	113	59	20	3

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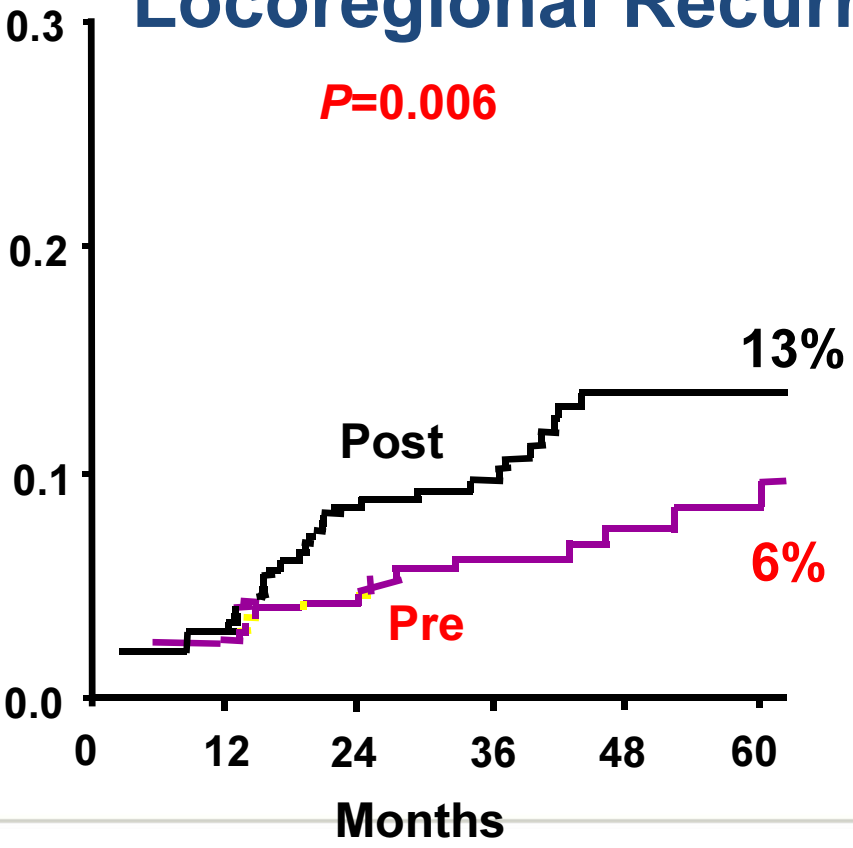
So you need chemotherapy in there somewhere!

(but I will come back to this)

Pre- vs post-operative chemoradiation CAO/ARO/AIO-94

Locoregional Recurrences

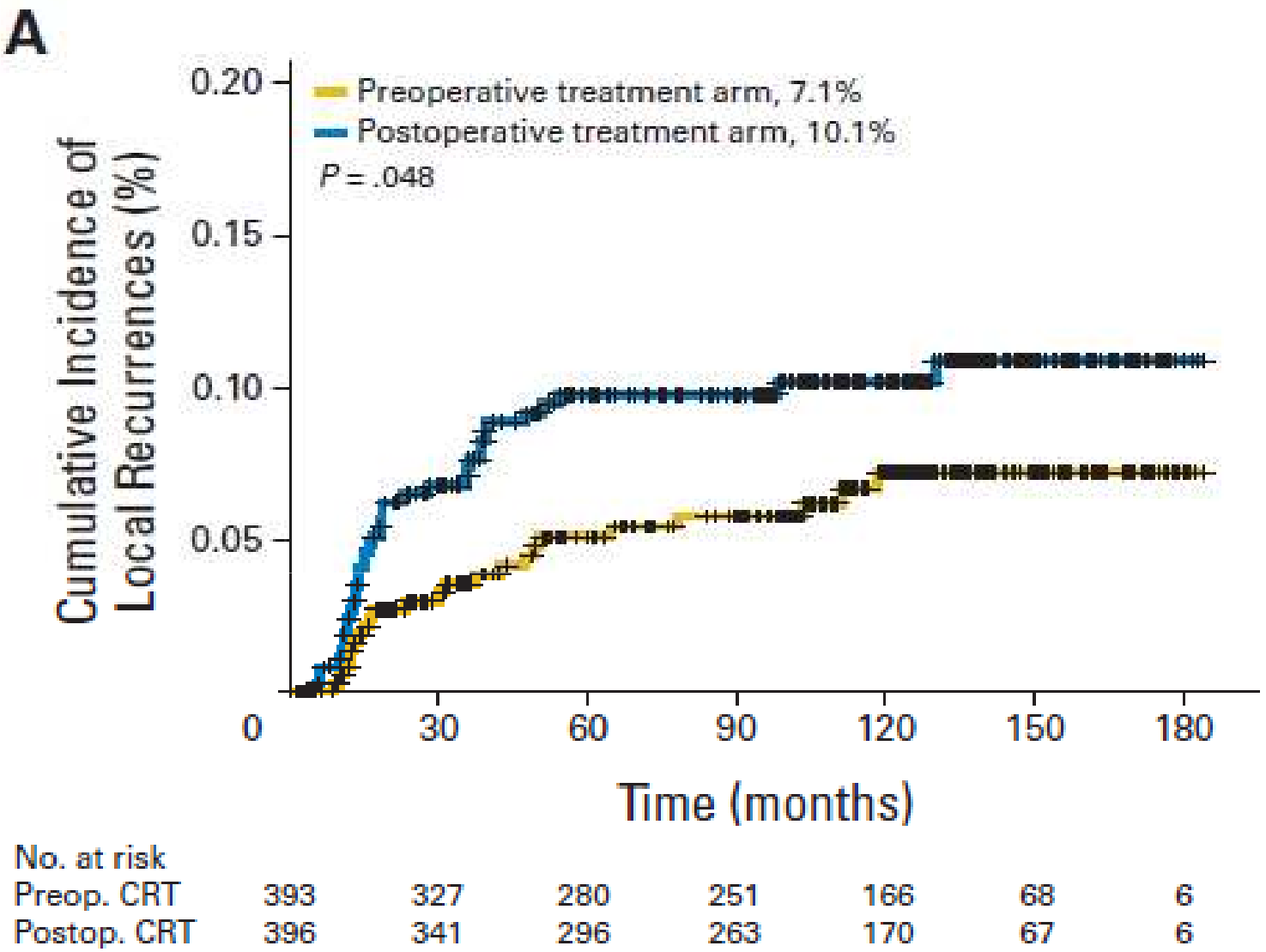


Acute G3/4 adverse events
27% vs 40% (p=0.001)

Long-term G3/4 adverse events
14% vs 24% (p=0.01)

There is a standard for chemoradiation

Sauer R. et al., N Engl J Med 2004;351: 1731-39



Long-term data on LOC REC from German study – 5/22 local recurrences ie 23% after 5 years (not like CR07)

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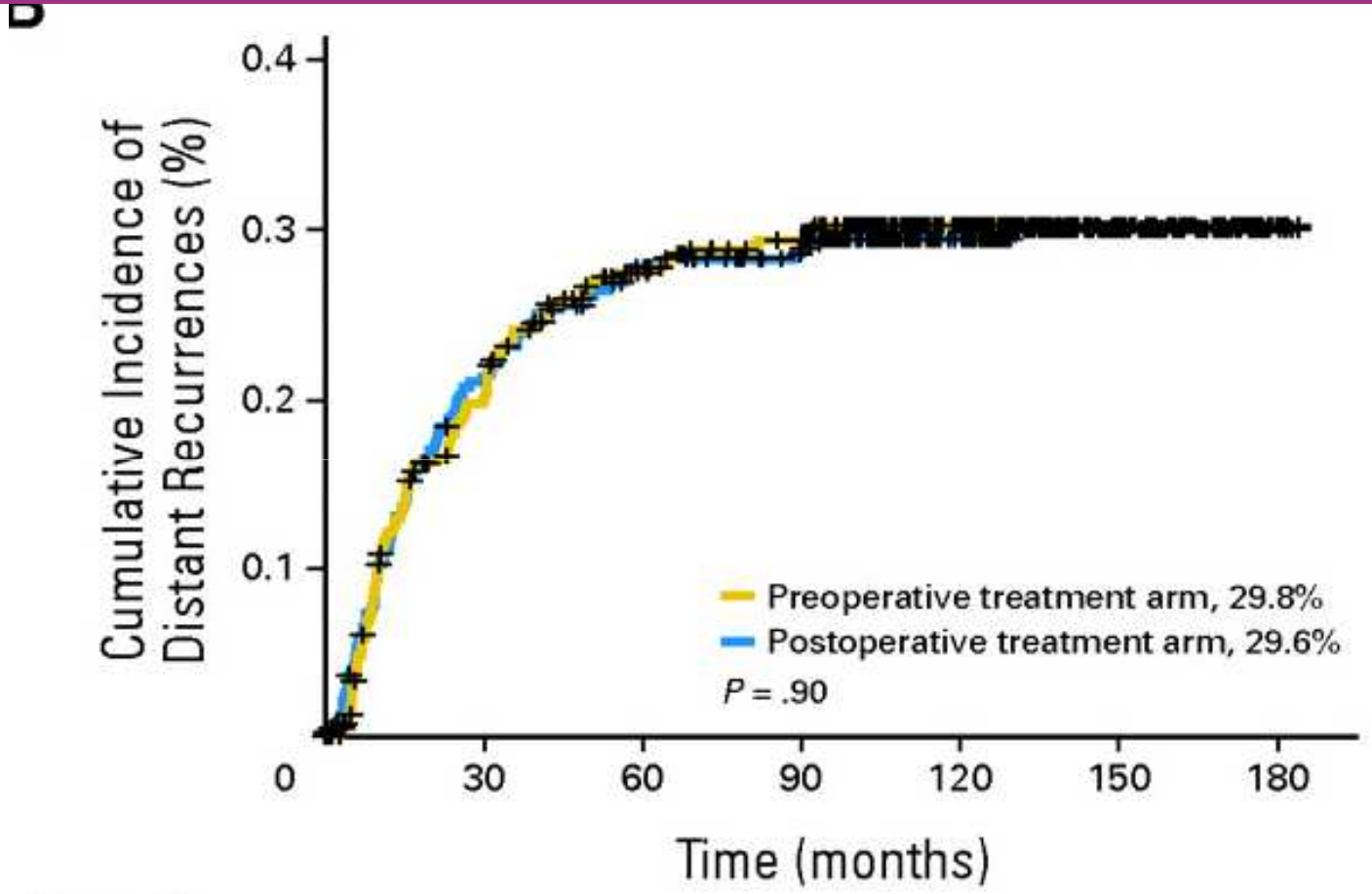
Pre- vs post-operative chemoradiation CAO/ARO/AIO-94



No. at risk							
Preop. CRT	393	295	262	241	158	60	5
Postop. CRT	396	310	267	246	162	63	6

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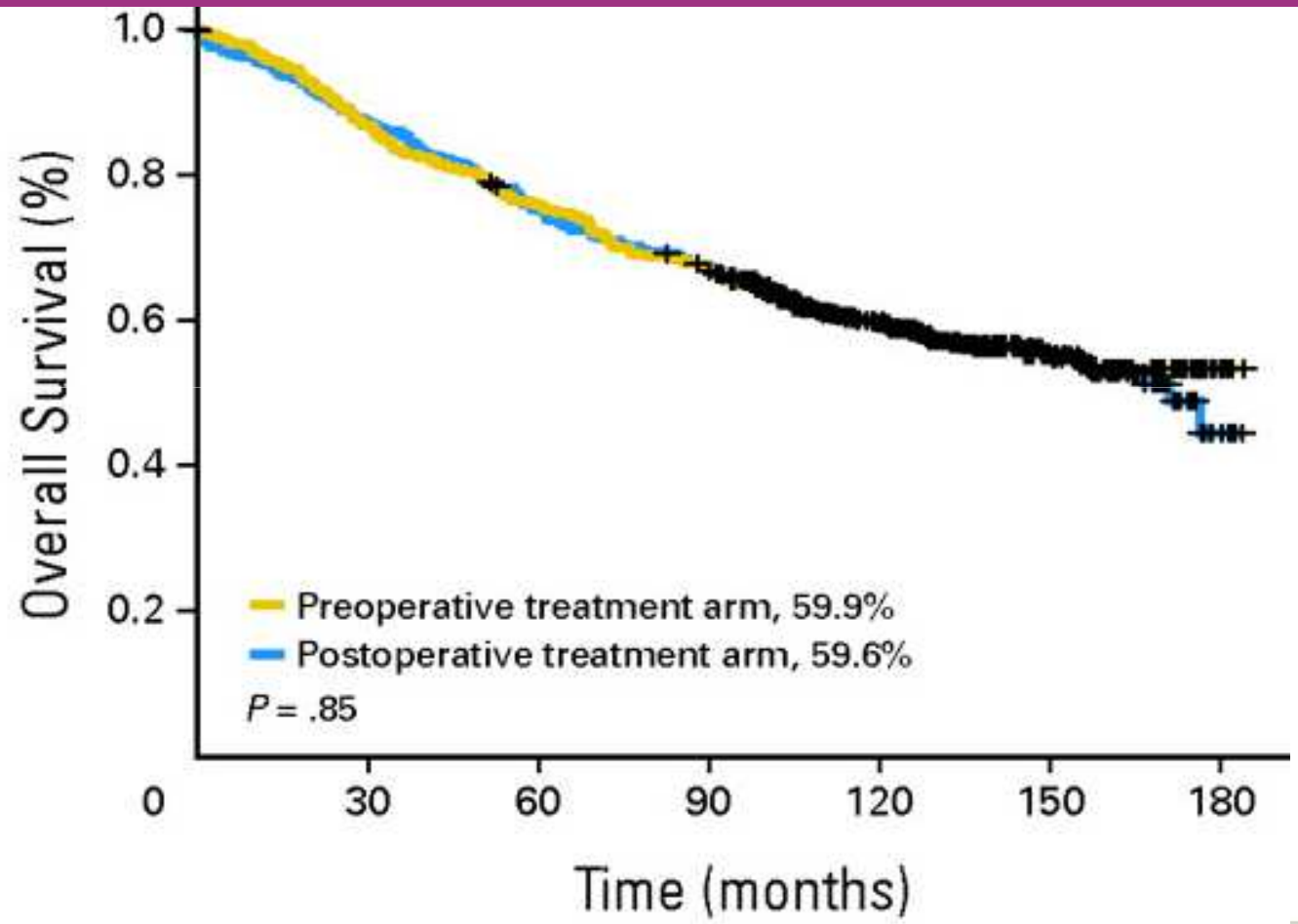
Pre- vs post-operative chemoradiation CAO/ARO/AIO-94



No. at risk							
Preop. CRT	404	351	305	268	174	67	6
Postop. CRT	395	342	295	262	172	70	6

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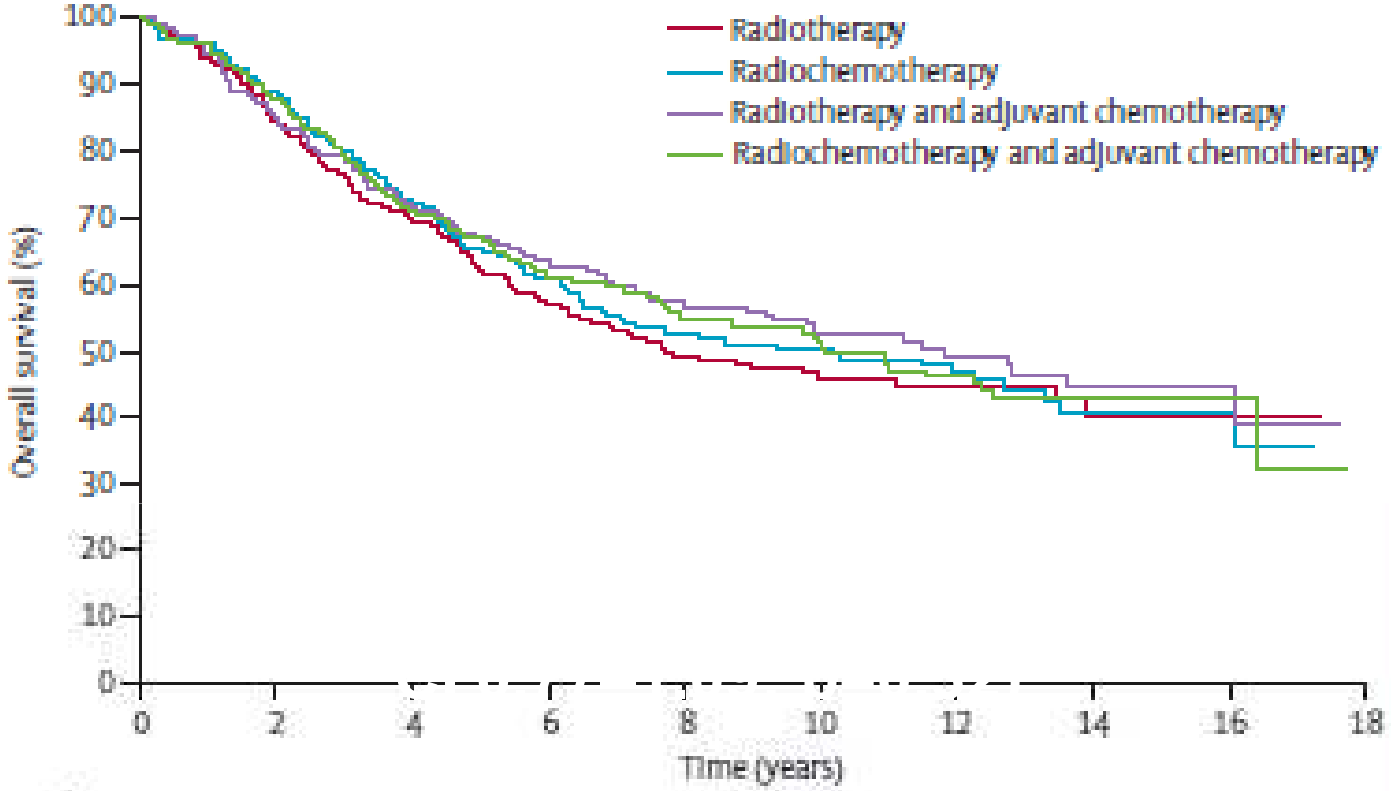
EORTC 22921 – Overall Survival



Number at risk									
Radiotherapy	252	208	165	129	98	62	32	15	5
Radiochemotherapy	253	223	173	135	96	66	41	19	9
Radiotherapy and adjuvant chemotherapy	253	212	171	140	102	69	42	18	8
Radiochemotherapy and adjuvant chemotherapy	253	221	174	143	108	77	44	18	4

So why have post-op CRT studies shown an improvement in survival

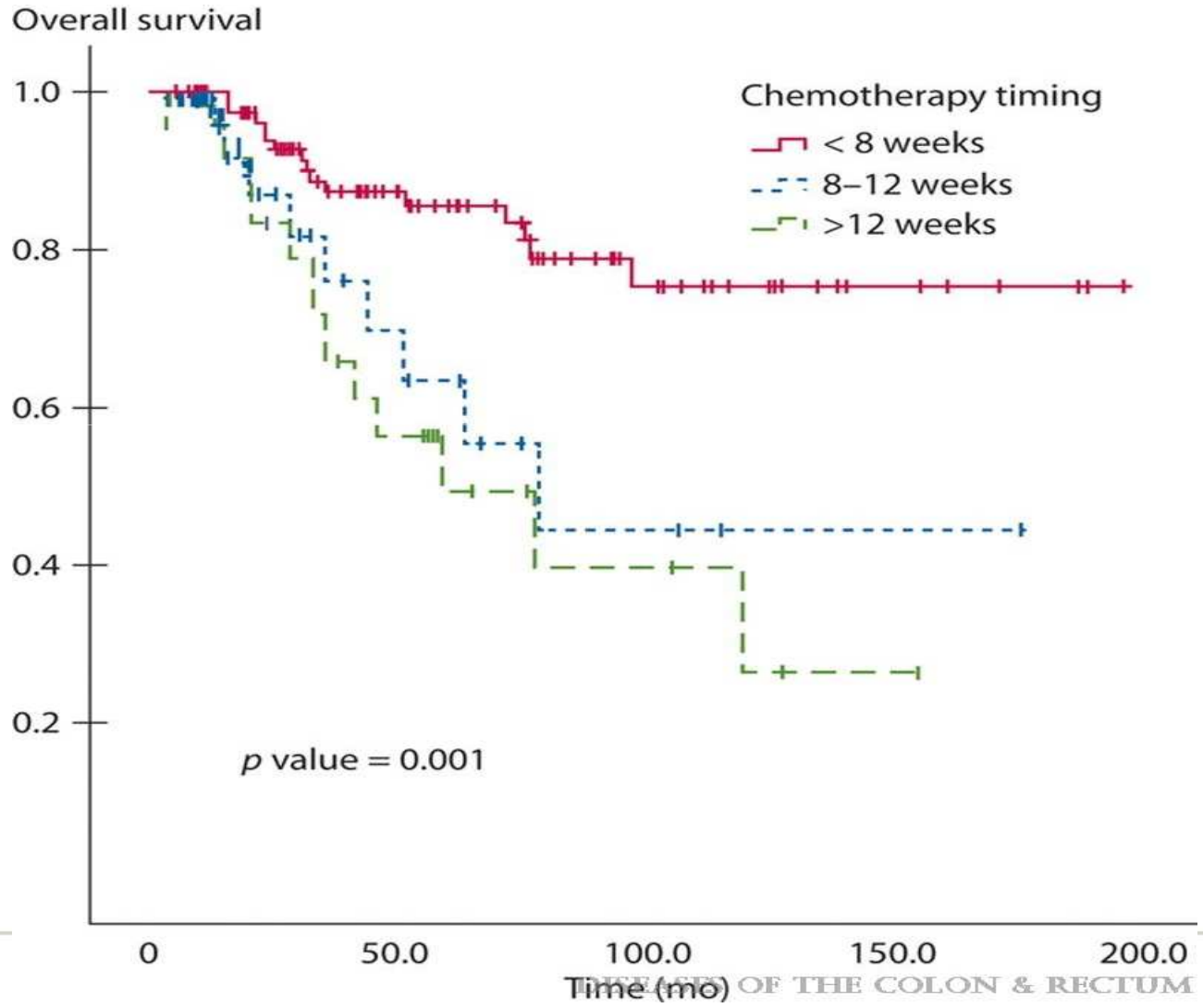
whereas preop CRT has not?

Suggests that in the trials

50-60% cN0

Compliance to postoperative adjuvant chemotherapy approx 50%

Timing of start of Adjuvant Postoperative Chemotherapy:

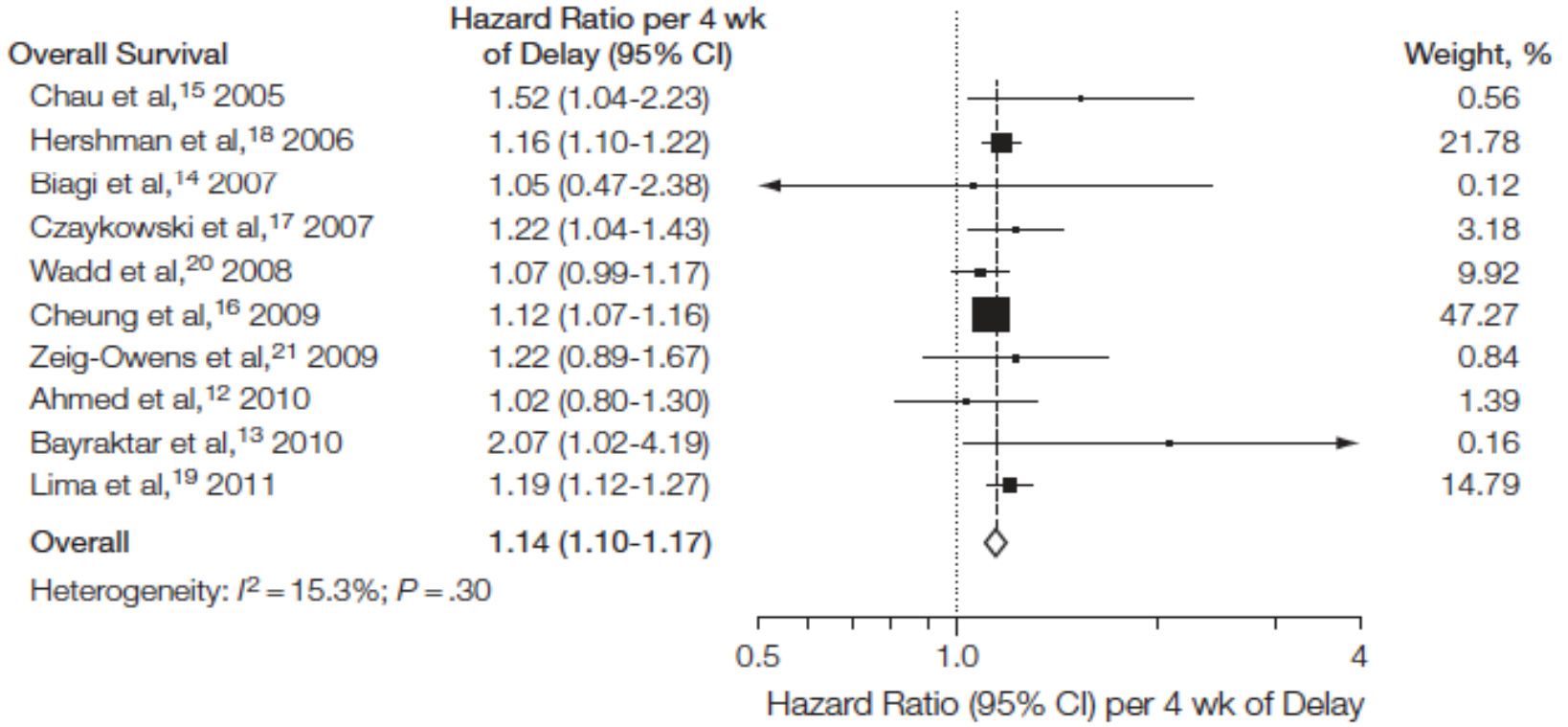


Tevis et al, DCR 2013

Association Between Time to Initiation of Adjuvant Chemotherapy and Survival in Colorectal Cancer

A Systematic Review and Meta-analysis

Increase in interval to start Adjuvant Chemotherapy
was associated with a **decrease in overall survival**



Biagi JJ et al., JAMA 2011 Jun 8;305(22):2335-42

Champalimaud Foundation

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So - What about?

- Oxaliplatin
- Irinotecan
- Biologicals

So what have the trials shown us?

All 5 Oxaliplatain trials used low dose oxaliplatin as a radiosensitizer with CRT

2 trials mandated oxaliplatin also as postoperative adjuvant (so if benefit which component?)

Some of the 5 trials did not mandate TME (NB the German trial did)

Phase III trials – Investigating

Trial	Eligibility	Fluoropyrimidine Platform
CAO/ARO/AIO-04	<12cm from anal verge T3/T4 cN0/N+ TRUS, CT and/or MRI	5FU 1000mg/2 X 5 days 1-5 + 29-33
NSABP R04 N=1606	<12cm; resectable stage II, III TRUS or MRI – CT if T4/ N1-2	PVI 5FU vs Capecitabine
FFCD N=598	Palpable; resectable; T3/4 N0-2; T2 distal anterior	Capecitabine in both arms
STAR – 01 N=747	Resectable stage II, III (c stage) <12cm from anal verge	PVI 5FU in both arms
PETTAC 6 N=1090	Stage II or III resectable or expected to become resectable <12cm from anal verge	Capecitabine in both arms

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Phase III: CAO/ARO/AIO-04

Best arm of CAO/ARO/AIO-94:

RT 50.4 Gy + 5-FU
1000 mg/m² days 1-5 + 29-33
623 patients

From Phase I/II Studies:

RT 50.4 Gy + 5-FU/OX
Ox: 50 mg/m² d 1, 8, 22, 29
5-FU: 250 mg/m² d 1-14 + 22-35

Note: Chemo gap 3rd week of RT !

613 patients

T

M

E

5-FU
500 mg/m² d 1-5, q29
4 cycles (4 months)

mFOLFOX6
Oxaliplatin: 100 mg/m² d1,q15
Folinic Acid: 400 mg/m² d1
5-FU: 2400 mg/m² d1-2
8 cycles (4 months)

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Endpoint	STAR-01	ACCORD 12/0405	CAO/ARO/ AIO-04	NSABP R-04	PETACC-6
PCR	16% both arms	14% vs 19%	12.8% vs 16.5% (p=0.038)	19% vs 21%	11.5% vs 13%
CRM	4% vs 7%	8% vs 13%	5% vs 6%	No data	2% vs 2%

Oxaliplatin Phase III trials: Control arm in red

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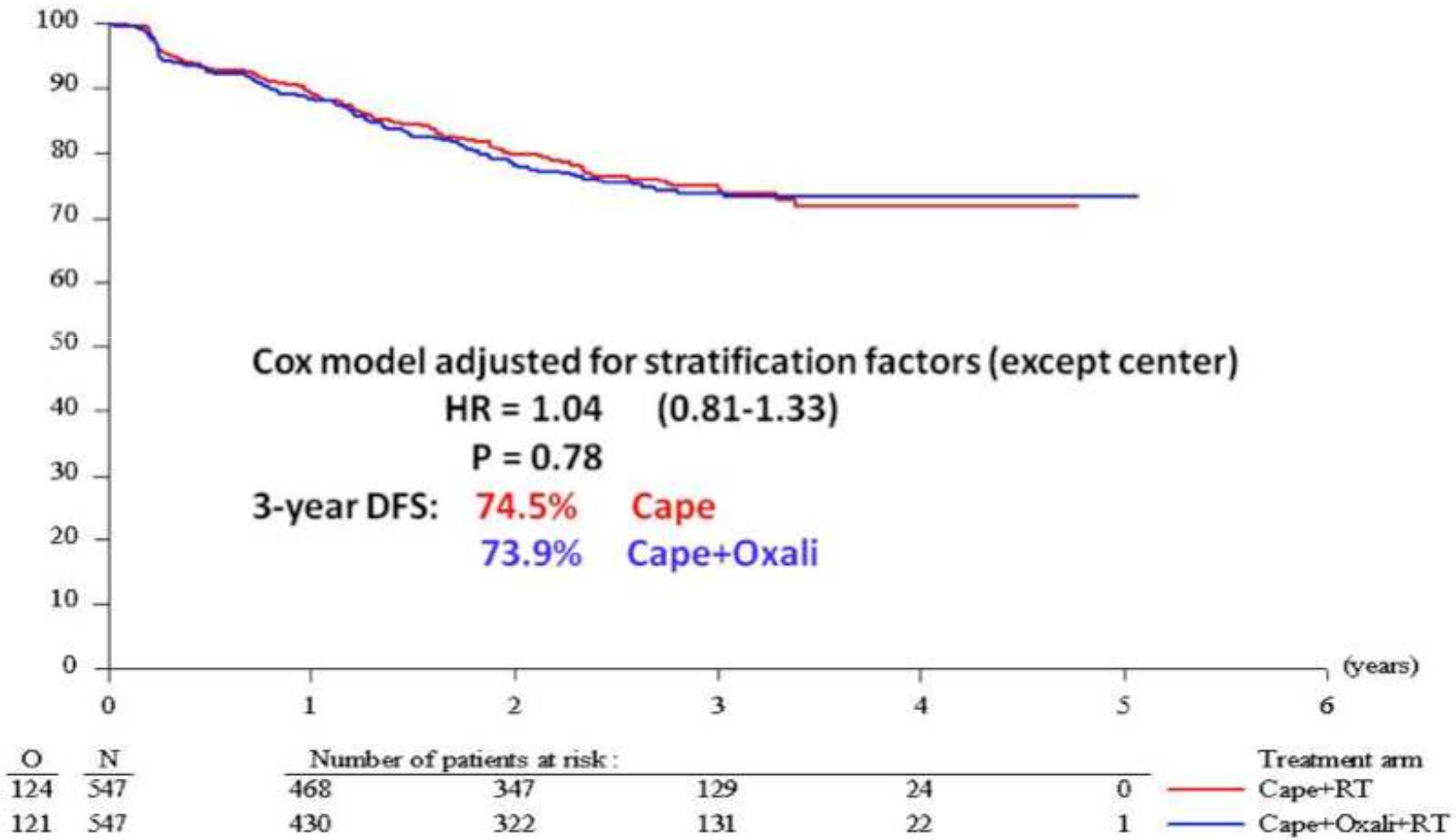
PETACC-6



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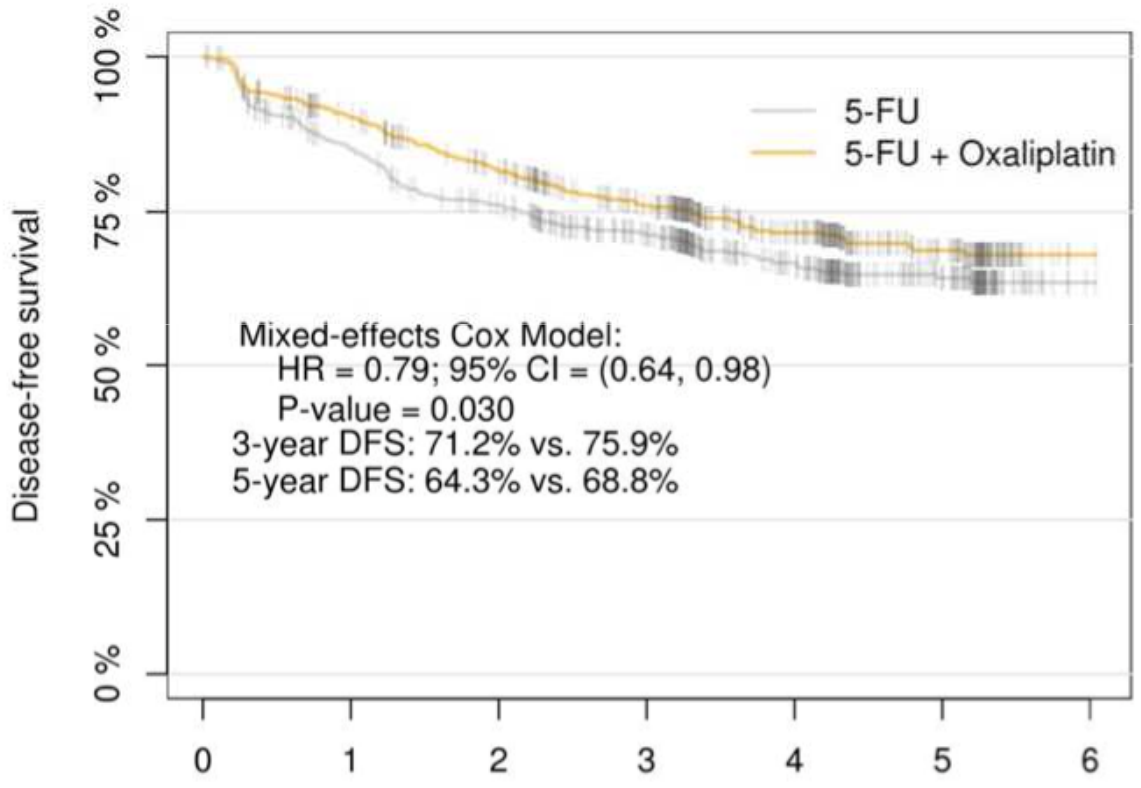
CAO/ARO/AIO-04 Trial



N at risk							
5-FU	623	509	441	363	233	114	1
5-FU/OX	613	522	447	364	230	110	1

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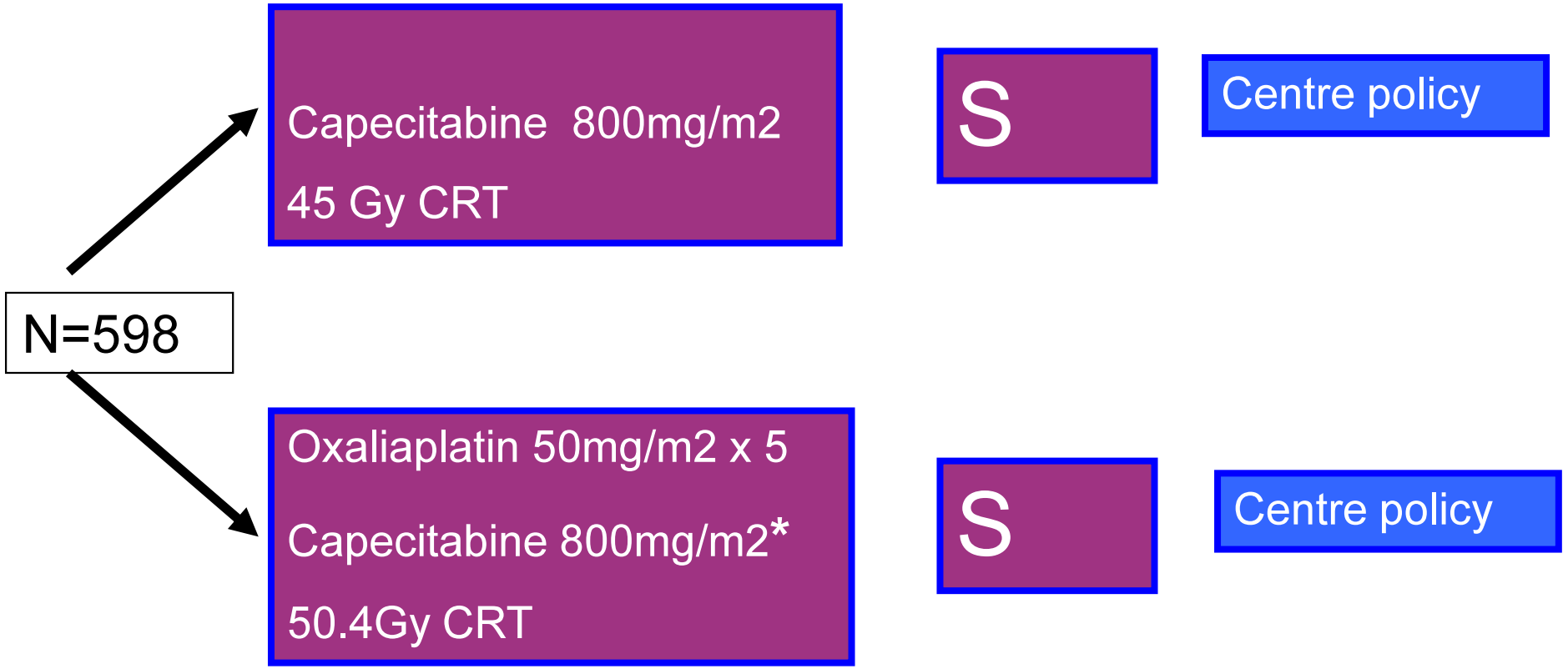
Prodige/ACCORD 12/0450 trial

Staging :- Evaluated by TRUS and/or MRI



Primary end point- pCR 11% - 20% 85% power

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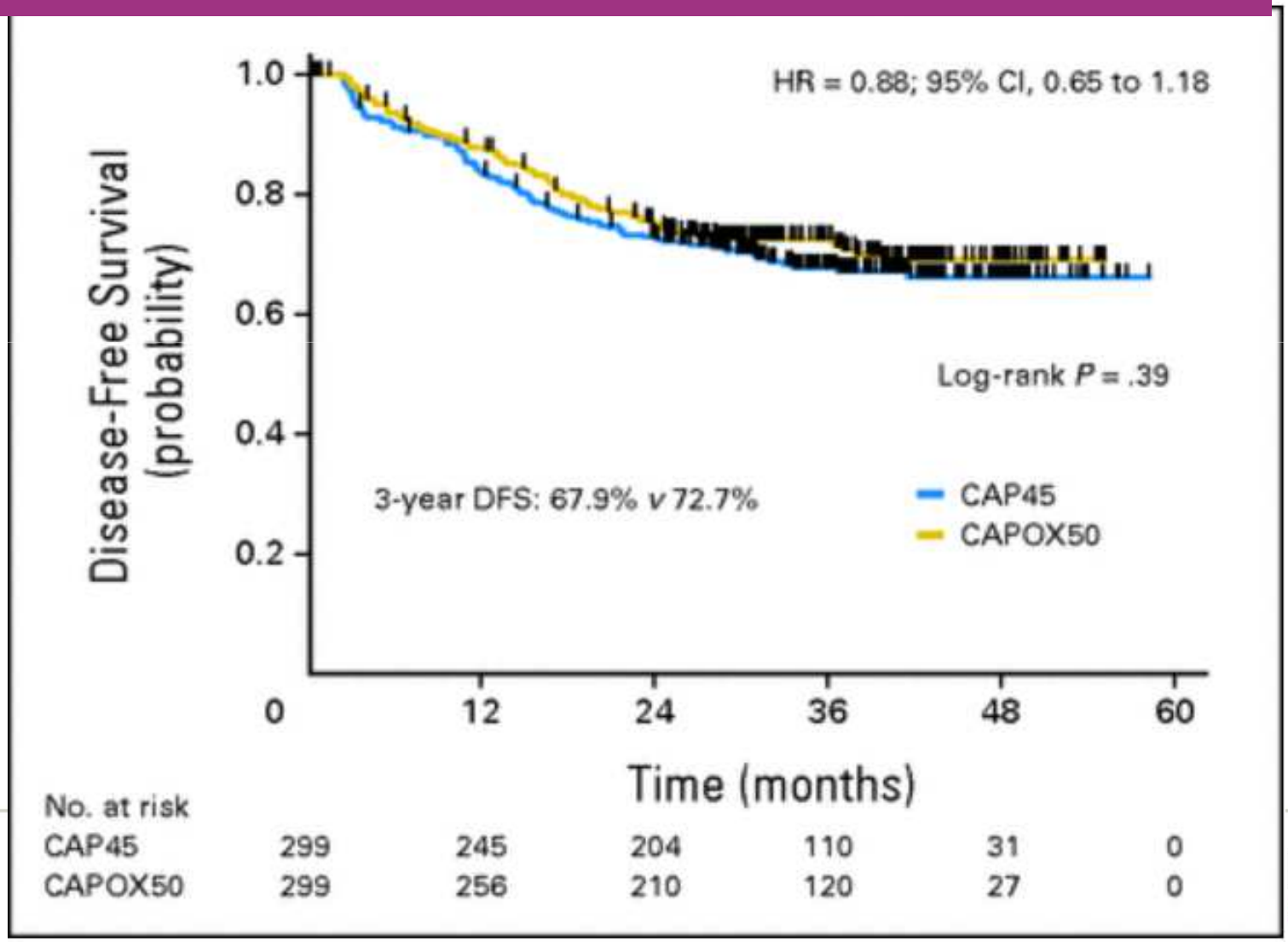
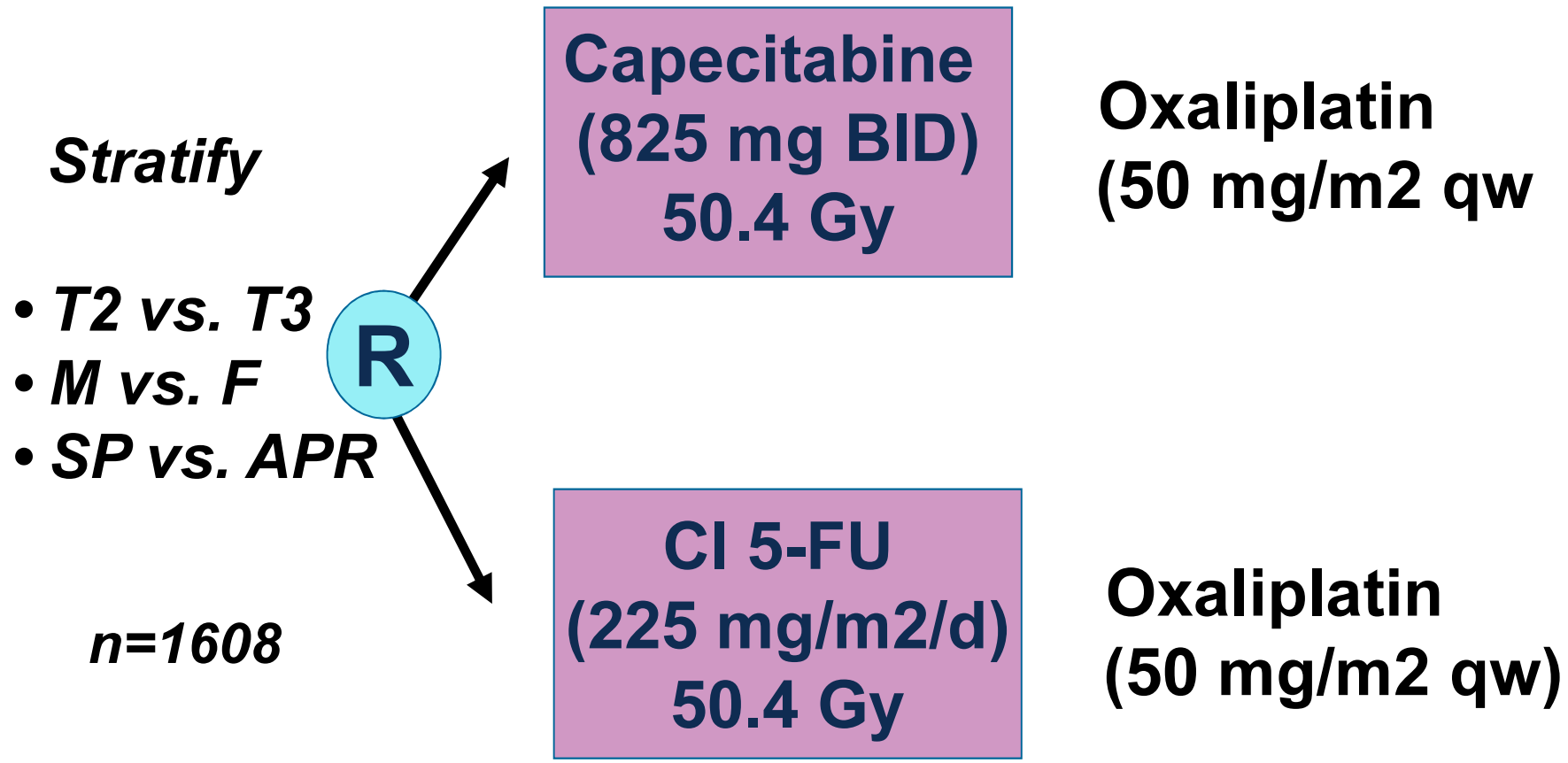
DFS: ACCORD 12/0405 PRODIGE 2



"50Gy and capecitabine is a new standard"

5-FU = Cape in Pre-op Rectal Cancer: NSABP R-04



NSABP R-04, Allegra et al; ASCO GI

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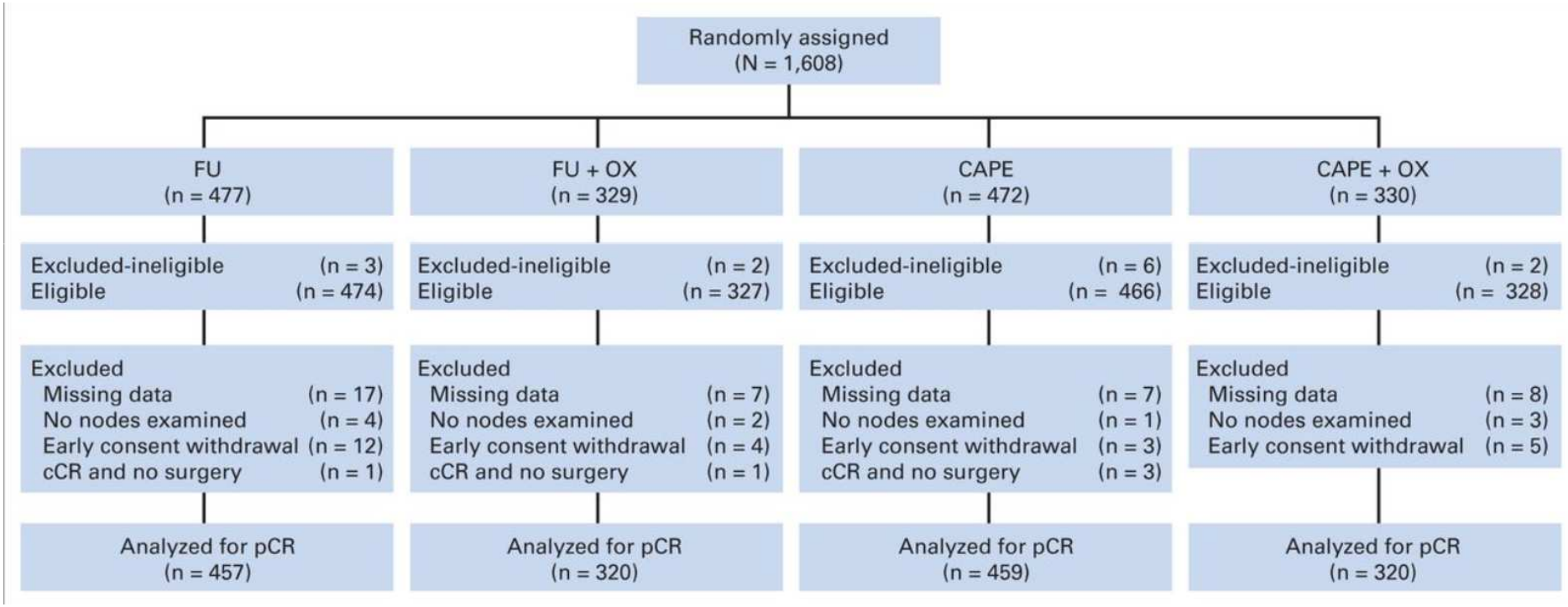
NSABP R-04



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NSABP R-04 establishes capecitabine as standard of care

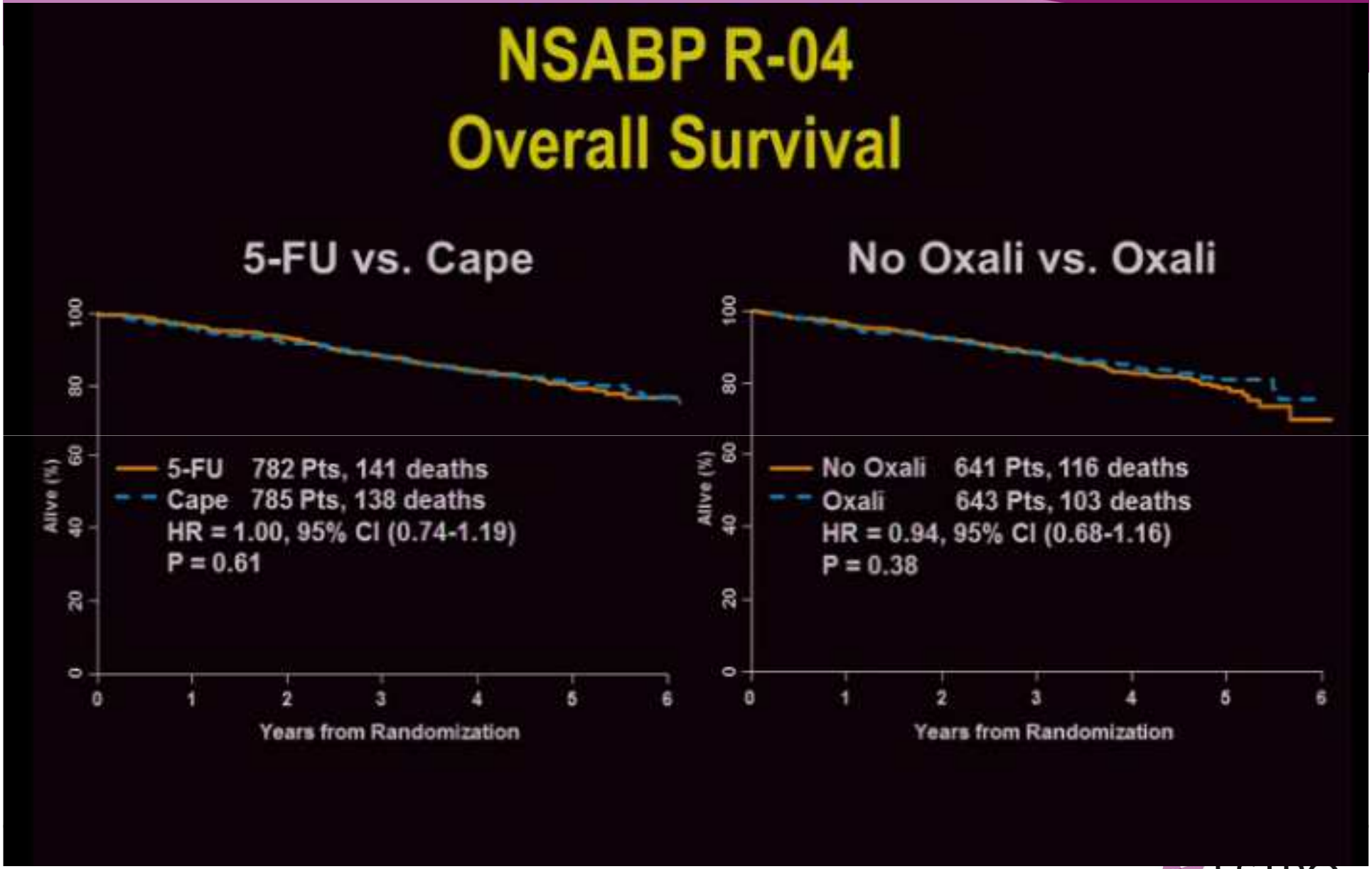
5-FU vs capecitabine

3-year local-regional tumour event rates (11.2% vs 11.8%),

5-year DFS (66.4% vs 67.7%)

5-year OS (79.9% vs 80.8%);

NSABP R-04
Overall Survival



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So what about postoperative adjuvant chemotherapy after Chemoradiation?

clinical practice guidelines

Annals of Oncology 24 (Supplement 6): vi81–vi88, 2013
doi:10.1093/annonc/mdt240

Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

B. Glimelius[1], E. Tiret[2], A. Cervantes[3] & D. Arnold[4], on behalf of the ESMO Guidelines Working Group*

[1]Dept of Radiology, Oncology and Radiation Science, Akademiska sjukhuset, Uppsala University, SE-751 85 Uppsala, Sweden; [2]2AP-HP, Hôpital Saint-Antoine, Pierre et Marie Curie University, Paris 6, France; [3]Department of Hematology and Medical Oncology, INCLIVA, University of Valencia, Valencia, Spain; [4]Klinik fuer Tumorbiologie, Freiburg, Freiburg, Germany

These Clinical Practice Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO)

" As in colon cancer stage III (and 'high-risk' stage II), adjuvant chemotherapy can be given, even if the level of scientific evidence for sufficient benefit is much lower than in colon cancer [33, 34, 35] [II, B]."

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Adjuvant chemotherapy in Colon Cancer

Good evidence for fluoropurimidines

Definite Benefit in Stage III (stage II QUASAR)

Good evidence for **Oxaliplatin** stage III

?Small benefit for 5FU in stage II

? Benefit Stage II for oxaliplatin

? Benefit over 70 years

Meta-analysis - reduction in risk of disease recurrence (25%) with adjuvant chemotherapy compared to observation (**HR=0.75,** CI: 0.68-0.83).

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Postoperative adjuvant chemotherapy in rectal cancer operated for cure.

Sune Høirup Petersen[1,*], Henrik Harling[2], Lene Tschemerinsky Kirkeby[3], Peer Wille-Jørgensen[4], Simone Mocellin[5]

Database Title

The Cochrane Library

Editorial Group: Cochrane Colorectal Cancer Group

Published Online: 14 MAR 2012

Assessed as up-to-date: 31 JAN 2012

DOI: 10.1002/14651858.CD004078.pub2

Only 1/21 trials received preoperative CRT

Only 2/21 received SCPRT

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Evidence in order of strength

Specific randomised trials (Quasar, EORTC 22921, Sainato, SCRIPT, Chronicle, ADORE)

Composite trials (PETACC-6 and German trial)

Individual patient Meta-analyses (often selected – some used retrospective data)

Pooled analyses

Systematic reviews

Nomograms based on randomised trials -Valentini

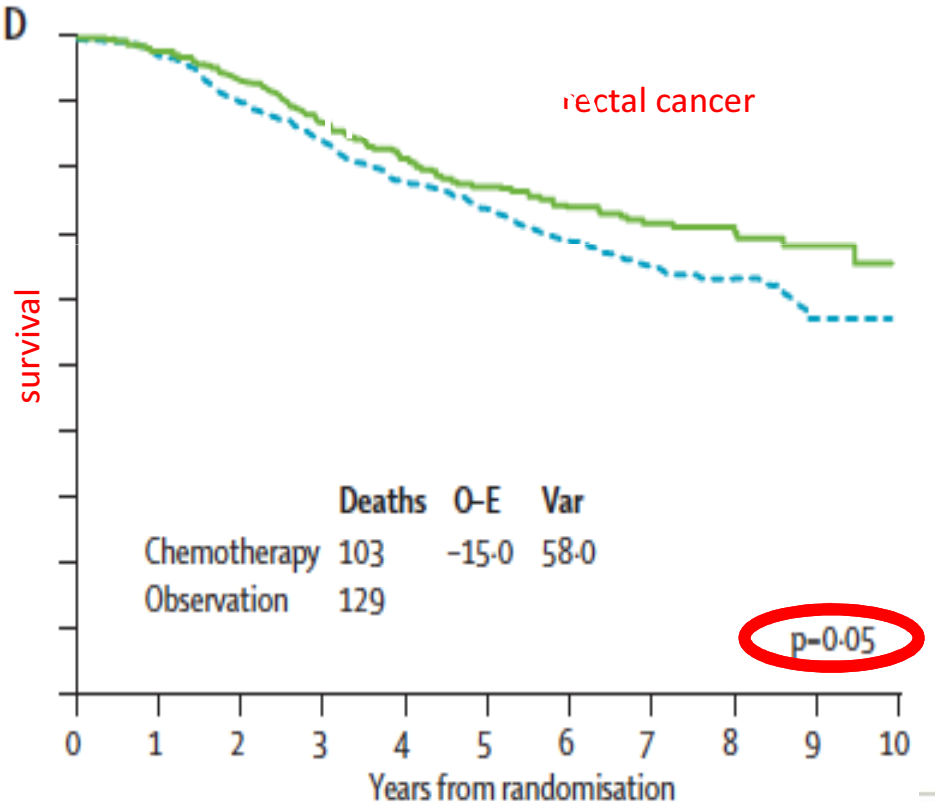
SCPRT 5x5Gy in Red

Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study

QUASAR Collaborative Group*

Colon 71% / **Rectal 29%**
Stage II 91% / Stage III 8%

	Chemotherapy (n=1622)	Observation (n=1617)
Stage		
I	8 (0·5%)	8 (0·5%)
II	1483 (91%)	1480 (92%)
III	131 (8%)	129 (8%)
Site		
Colon	1148 (71%)	1143 (71%)
Rectum (or both)	474 (29%)	474 (29%)



Lancet 2007; 370: 2020–29

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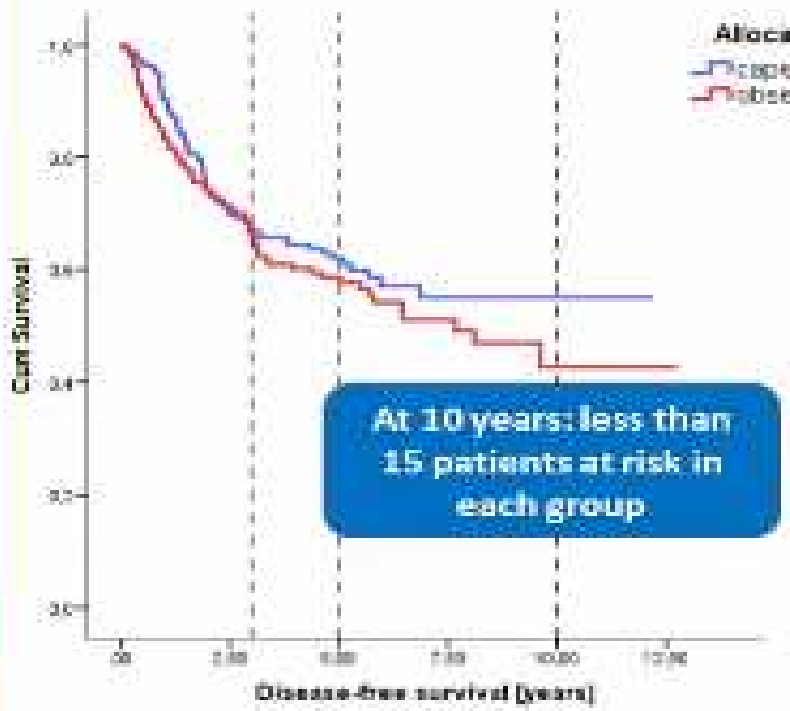
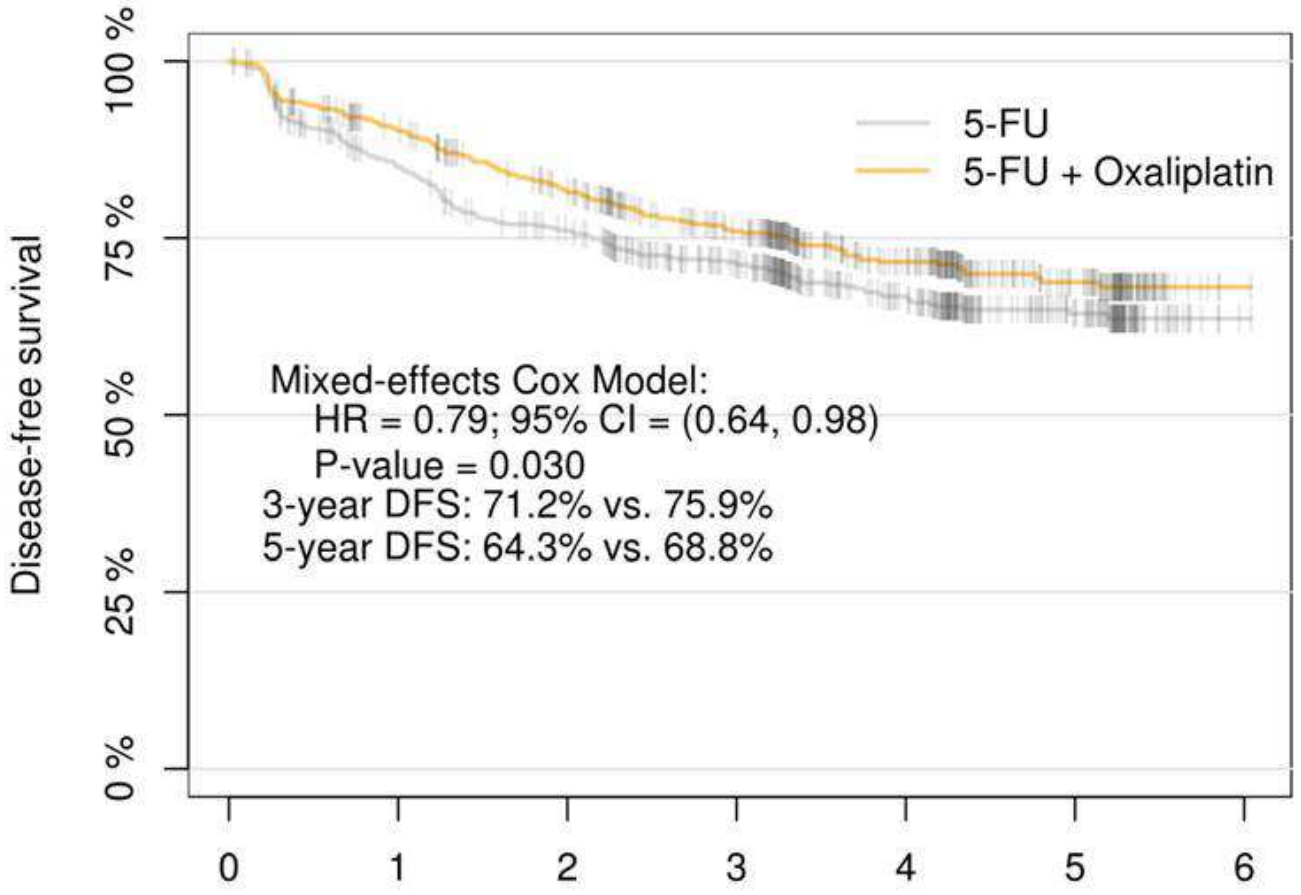
SCRIPT study

Results - Disease-free Survival



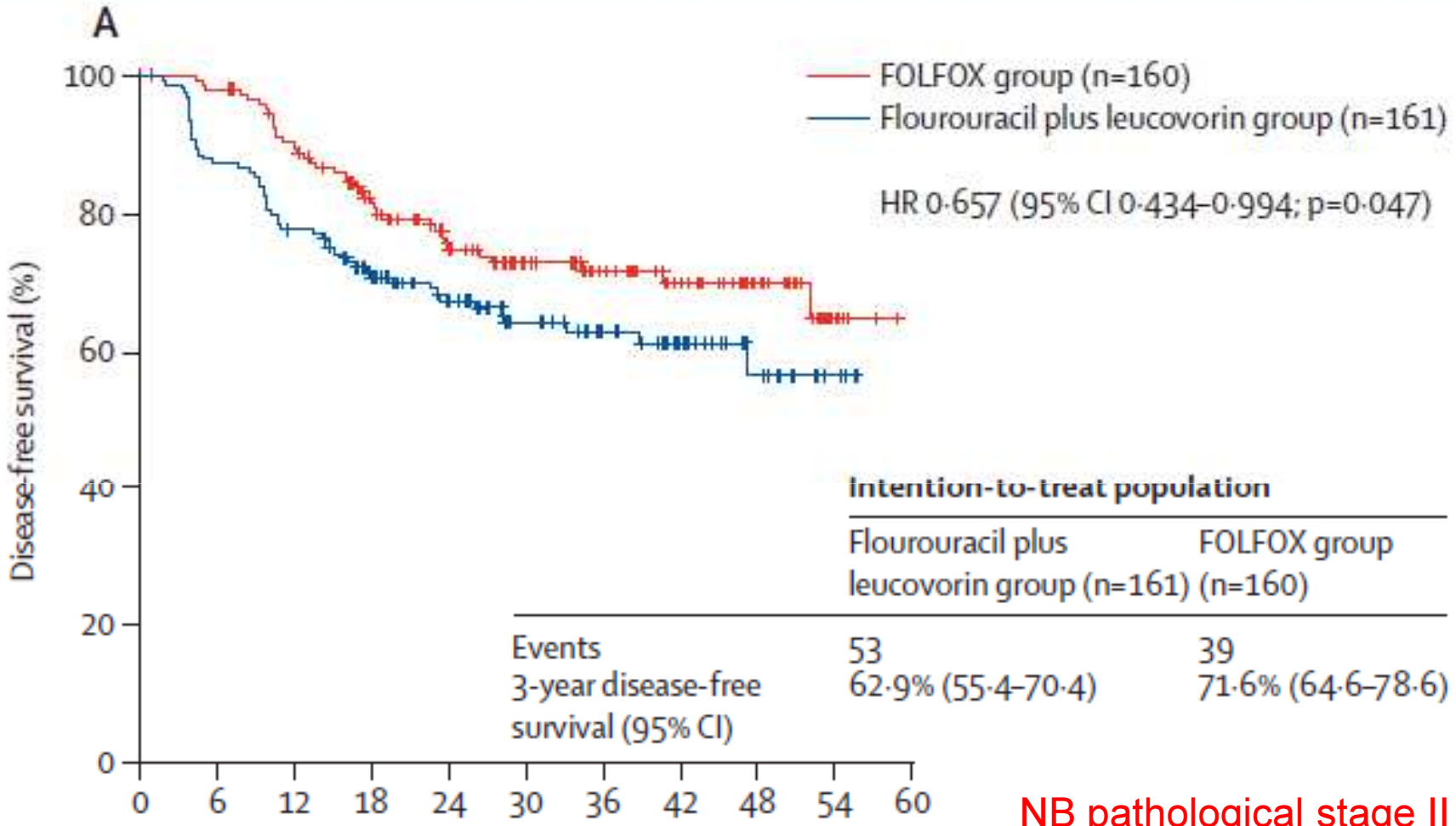
- p = 0.246
- 3-year DFS
  - Chemotherapy 67.4%
  - Observation 66.1%
- 5-year DFS
  - Chemotherapy 62.0%
  - Observation 58.4%
- 10-year DFS
  - Chemotherapy 55.6%
  - Observation 43.5%

Disease-free Survival: Intention-to-treat analysis



N at risk							
5-FU	623	509	441	363	233	114	1
5-FU/OX	613	522	447	364	230	110	1

THE ADORE PHASE II TRIAL : Disease Free Survival



Intention-to-treat population	Flourouracil plus leucovorin group (n=161)	FOLFOX group (n=160)
Events	53	39
3-year disease-free survival (95% CI)	62·9% (55·4–70·4)	71·6% (64·6–78·6)

Number at risk											
Flourouracil plus leucovorin group	161	129	114	95	76	53	41	27	12	3	0
FOLFOX group	160	143	128	105	83	64	50	38	23	5	0

NB pathological stage II
no significant difference

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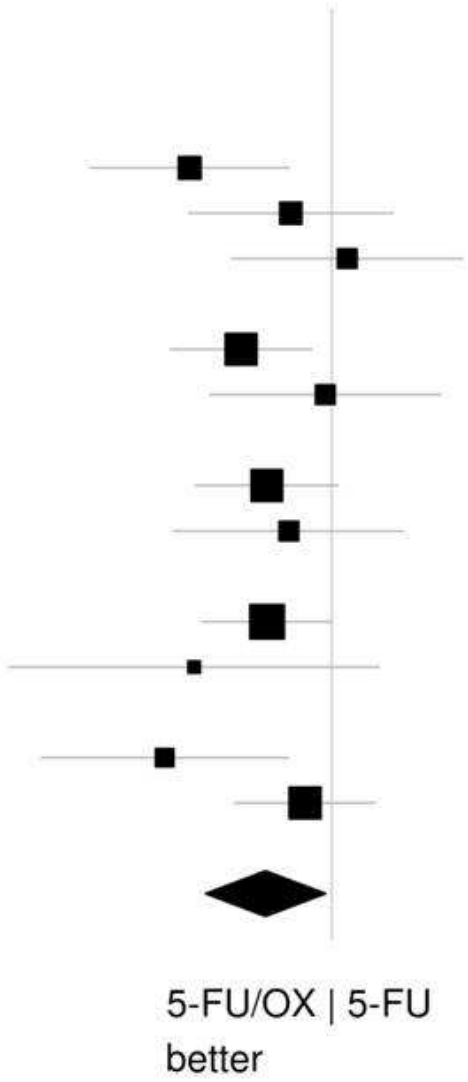
Subgroup Analysis of DFS: Pretreatment factors

Intention-to-treat

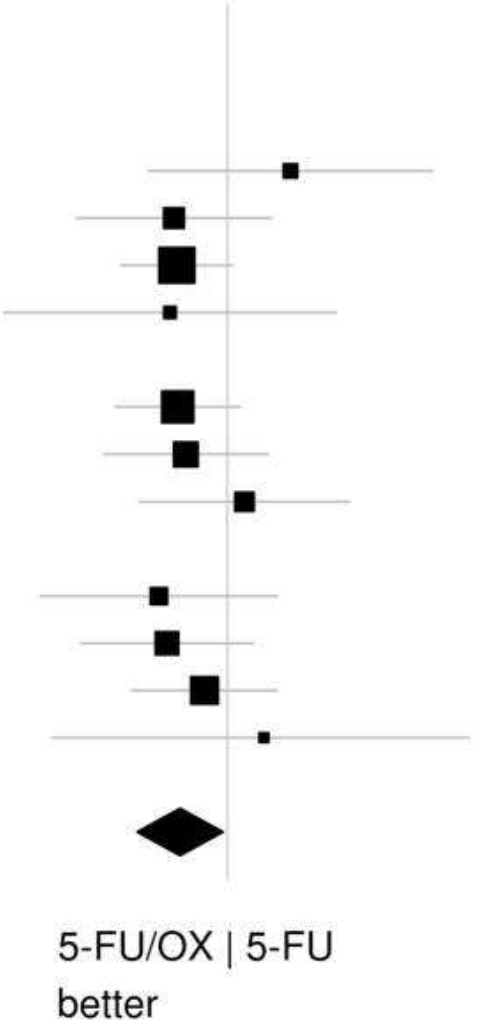
Variable	5-FU Events/n	5-FU/OX Events/n	HR 95% CI
Age, years			
< 61	84/241	52/230	0.61 (0.43, 0.86)
61-70	64/233	58/238	0.87 (0.61, 1.24)
> 70	50/149	49/145	1.06 (0.71, 1.58)
Gender			
Male	149/440	112/434	0.73 (0.57, 0.93)
Female	49/183	47/179	0.98 (0.65, 1.46)
ECOG, PS			
0	136/475	115/483	0.80 (0.62, 1.02)
1-2	58/141	43/123	0.86 (0.58, 1.28)
cT-category			
cT3	164/537	139/549	0.80 (0.64, 1.00)
cT4	27/50	14/41	0.62 (0.32, 1.18)
cN-category			
cN0	58/159	33/146	0.56 (0.36, 0.86)
cN+	134/451	123/452	0.91 (0.71, 1.16)
Total			
all	**198/623**	**159/613**	**0.79 (0.64, 0.98)**



Subgroup Analysis of DFS: Pathological factors

Intention-to-treat

Variable	5-FU Events/n	5-FU/OX Events/n	HR 95% CI
ypT-category			
ypT0-1	13/122	21/153	1.36 (0.68, 2.72)
ypT2	41/183	29/160	0.77 (0.48, 1.24)
ypT3	120/278	92/260	0.78 (0.60, 1.03)
ypT4	17/26	9/17	0.76 (0.34, 1.70)
ypN-category			
ypN0	94/423	75/416	0.78 (0.58, 1.06)
ypN1	53/131	45/133	0.82 (0.55, 1.22)
ypN2	44/60	30/42	1.09 (0.65, 1.81)
TNM stage			
Stage I	30/176	19/148	0.72 (0.40, 1.28)
Stage II	48/148	40/154	0.74 (0.49, 1.13)
Stage III	71/169	57/154	0.89 (0.63, 1.28)
ypT0ypN0	6/81	9/104	1.19 (0.43, 3.36)
Total			
all	**198/623**	**159/613**	**0.79 (0.64, 0.98)**



Trials randomising up front before CRT

The majority of patients are over-staged and probably Stage II

Compliance is poor in timing to start and doses received

Other trials randomising after CRT

TRIAL	Patient number	Primary endpoint	OS	DFS	HR for DFS
QUASAR (92% stage II)	3239 overall 968 rectal 203 preop RT	all-cause mortality.	80% versus 83.4%	Not stated	0.78 CI [0.44-1.22] (p=0·004)
PROCTOR SCRIPT	437	OS	5-year-OS 79·2% vs 80·4% (HR 0·93)	5-year-DFS 55·4%vs62·7 %(HR0·80)	0.80 CI [0.60-1.07] (p=0·13).
GERCOR	357 69% preop RT	DFS	OS HR =0.87	5-year DFS 58% vs 63%	0.80, (p=0.154)
Chronicle	113	DFS	3-year-OS 89% vs 88% (HR 1·18)	5-year DFS 71% vs 78%	0.80 (p=0.50)
ADORE	321	DFS	3-year-OS 86%vs95% (HR 0·46)	3-year DFS 63% vs 72%	0.63 (p=0.03)

So consider postop histology

Factors to consider 2

The type and quality of surgery are major (non-randomized) prognostic factors

Poor compliance may compromise the activity of adjuvant chemotherapy

After preoperative chemoradiation and surgery, time to start adjuvant chemotherapy is probably too long

Any benefit from 5FU may be achieved by the preop 5FU ie pCR

Conclusions

1. 5FU-based CRT (45-50Gy) more effective (downsizing) than RT but no improvement in SpS, DFS or OS
2. Capecitabine is an equivalent option
3. Watch and wait remains experimental
4. Radio-sensitizing 5FU-based CRT not improved by additional oxaliplatin ?
5. Biologicals have not yet delivered
6. Postop adjuvant chemotherapy after SCPRT or CRT remains of unproven benefit


Thank you for listening

Role of salvage surgery for non-responders, surgery for locoregional recurrent disease

Chris Cunningham

Oxford UK

Predicting failure after CRT for anal cancer

ORIGINAL CONTRIBUTION

Nomogram for Predicting Overall Survival and Salvage Abdominoperineal Resection for Patients with Anal Cancer

Vassiliki L. Tsikitis, M.D.[1] • Kim C. Lu, M.D.[1] • Jong S. Kim, Ph.D.[2]
Kevin G. Billingsley, M.D.[3] • Charles R. Thomas, Jr., M.D.[4] • Daniel O. Herzig, M.D.[1]

1 Department of Surgery, Oregon Health & Science University, Portland, Oregon
2 Fariborz Maseeh Department of Math & Statistics, Portland State University, Portland, Oregon
3 Department of Surgical Oncology, Oregon Health & Science University, Portland, Oregon
4 Department of Radiation Oncology, Oregon Health & Science University, Portland, Oregon

National Cancer Database 1998 through 2010; 1778 patients

Predictors of APR after completion of CRT were size of tumor and nodal disease ($p < 0.001$)

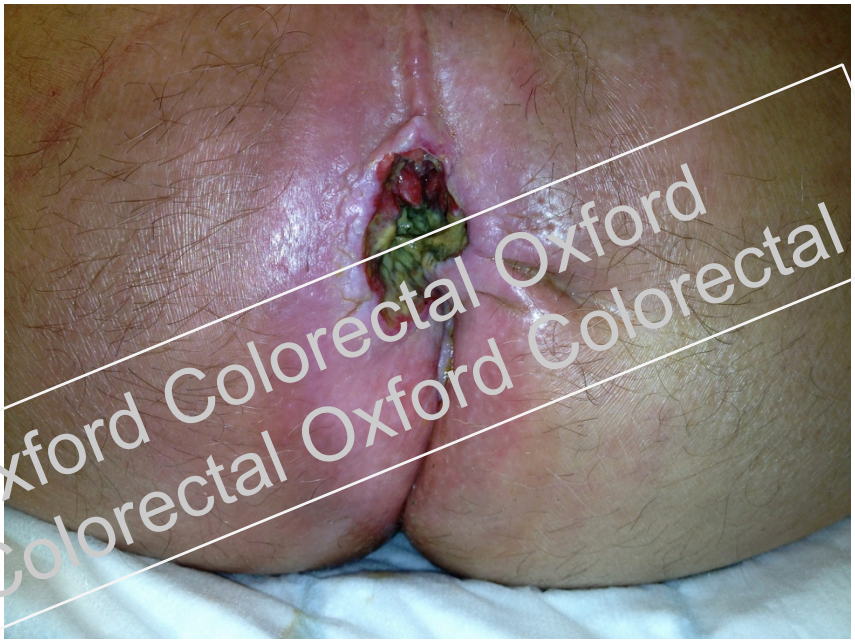
Tsikitis et al. DCR 2016;59:1-7

What does the RO need from the surgeon?

Help to obtain early diagnosis of residual or recurrent disease

Joint/shared clinics

Open access to EUA



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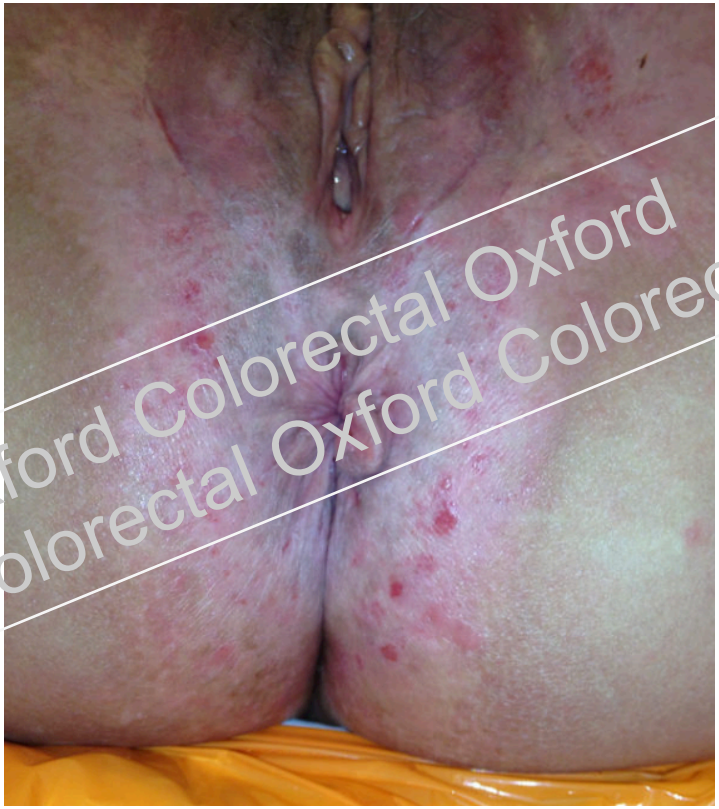
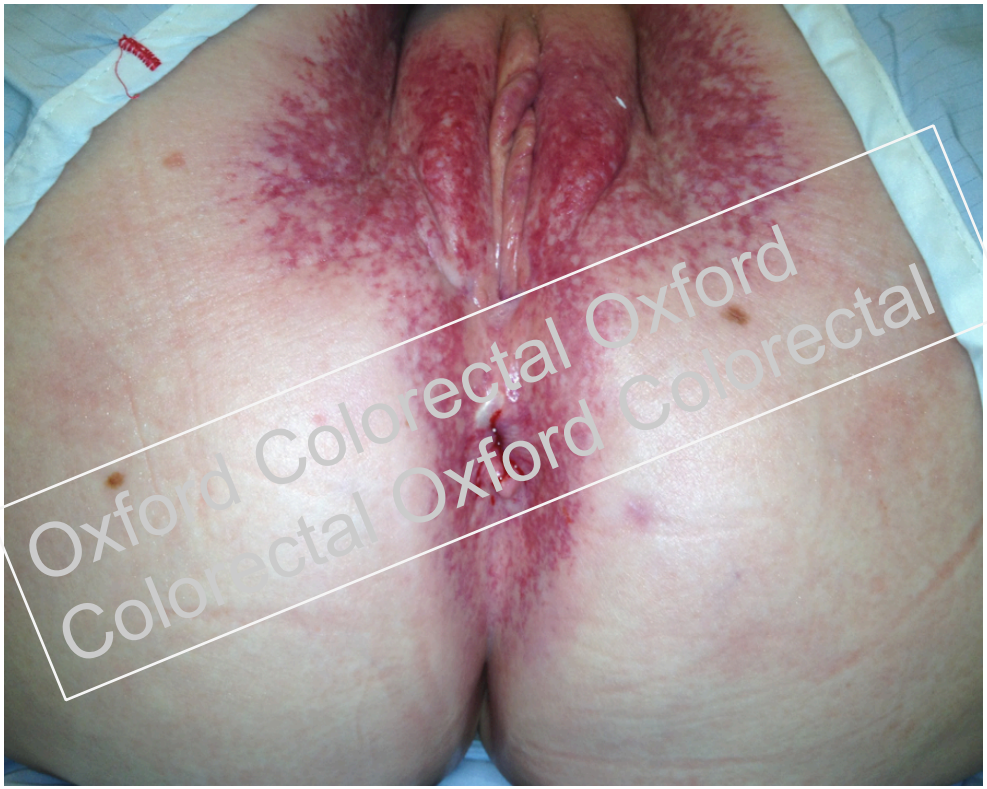


What does the RO need from the surgeon?

Surgery must achieve Ro resection



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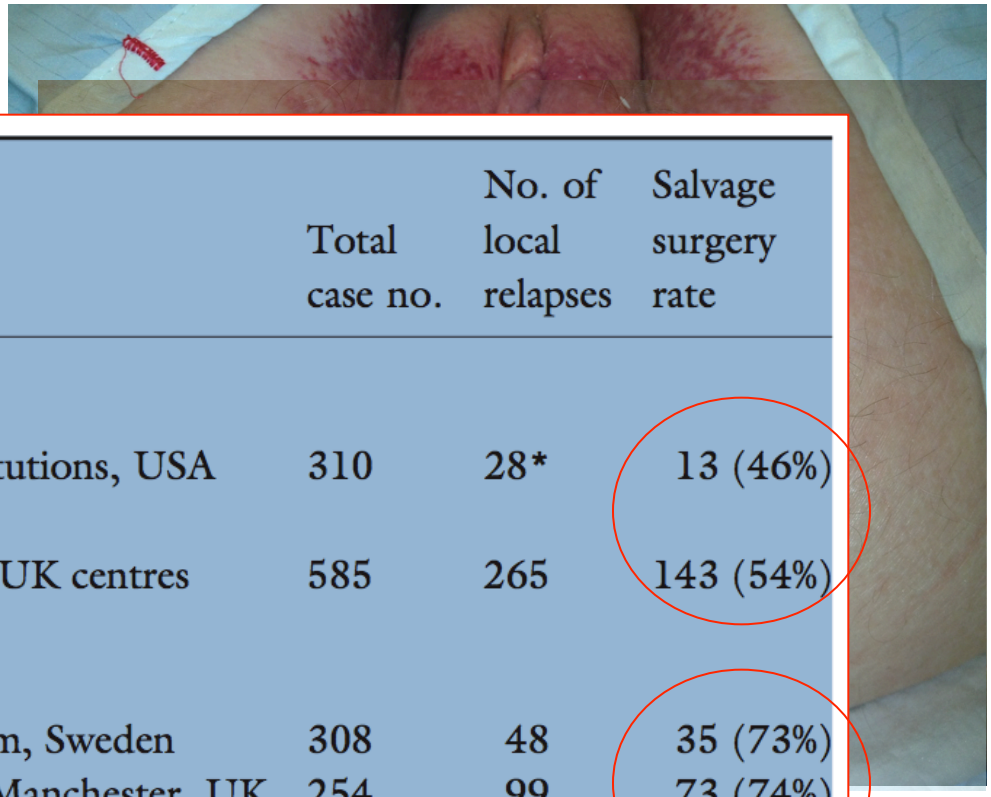

Authors & year	Centre/ Country	Total case no.	No. of local relapses	Salvage surgery rate
Multi-centred setting				
Intergroup trial 1996 [19]	104 institutions, USA	310	28*	13 (46%)
UKCCCR ACT I Trial 1996 [14]	Multiple UK centres	585	265	143 (54%)
Centralised setting				
Nilsson *et al.* 2002 [8]	Stockholm, Sweden	308	48	35 (73%)
Renehan *et al.* 2005 [2]	Christie Manchester, UK	254	99	73 (74%)

Renehan & O'Dwyer Colorectal Disease. 2011;13:44-52.

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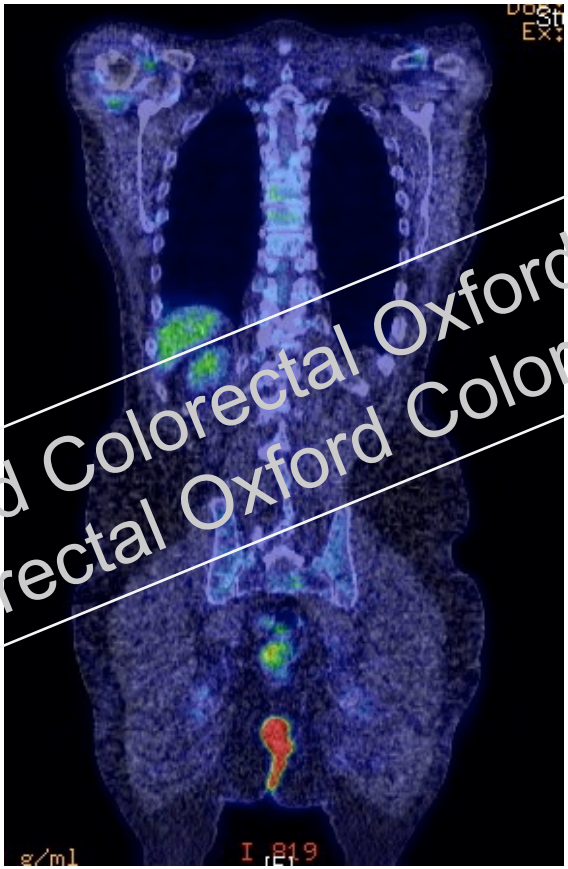
What does the surgeon need to know?

Patient is fit for surgery

Absence of metastatic disease



Volume of radical surgery in anal cancer?

100 cancers diagnosed at MDT

Radical (curative) CRT in 70%

Failure over 3 years in 25%

Half of these failures are amenable to surgery

Approximately 10-12 cases for radical surgery per 100 cases of anal cancer diagnosed

1200 cases of anal cancer in UK pa, approximately 150 radical operations

How do patients do after salvage surgery?

Table 2 Summary of oncological outcomes after salvage surgery for relapsed anal cancer.

Authors & year	Centre/Country	No. of cases	Median FU (months)	Further loco-regional disease	Survival
Ellenhorn *et al.* 1994 [6]	Memorial Sloan-Kettering Cancer Center, New York, US	38	43	23 (61%)	5-year actuarial survival: 44%
Pocard *et al.* 1998 [7]	Saint Antoine, Paris, France	21	40	Not stated	Overall 3-year survival: 58%
Allal *et al.* 1999 [21]	Geneva, Switzerland	26	22	15 (58%)	Crude 5-year survival: 45%
Smith *et al.* 2001 [22]	Toronto-Sunnybrook Regional Cancer Centre, Ontario, Canada	22	30	18 (82%)	Crude 5-year survival: 23%
van der Wal *et al.* 2001 [23]	Johns Hopkins, Baltimore, US	17	53	Not stated	5-year actuarial survival: 47%
Nilsson *et al.* 2002 [8]	Stockholm, Sweden	39	33	15 (38%)	Crude 5-year survival: 52%
Hill *et al.* 2003 [24]	Multi-centred, UKCCCR	133	30	58 (44%)	'67 (50%) died of anal cancer'
Akbari *et al.* 2004 [9]	Memorial Sloan-Kettering Cancer Center, New York, US	57*	24	79%	5-year actuarial survival: 33%
Ghouti *et al.* 2005 [10]	Marseille, France	36	67	23 (66%)	Crude 5-year survival: 69%
Renehan *et al.* 2005 [2]	Christie Manchester, UK	73	45	Not stated	5-year cancer-specific survival: 40%
Mullen *et al.* 2007 [12]	MD Anderson Cancer Center, Texas	31	29	12 (39%)	5-year actuarial survival: 64%
Lefevre *et al.* 2009 [13]	Saint Antoine, Paris, France	95	Not stated	Not stated	Overall 5-year survival: 58%
Sunesen *et al.* 2009 [20]	Aarhus, Denmark	49	Not stated	Not stated	Overall 5-year survival: 61%

Renehan & O'Dwyer Colorectal Disease. 2011;13:44-52.

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Local pelvic disease control after salvage surgery > 50%

5-year post-salvage surgery survival rate > 40%

Renehan & O'Dwyer Colorectal Disease. 2011;13:44-52.

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How do patients do after salvage surgery?

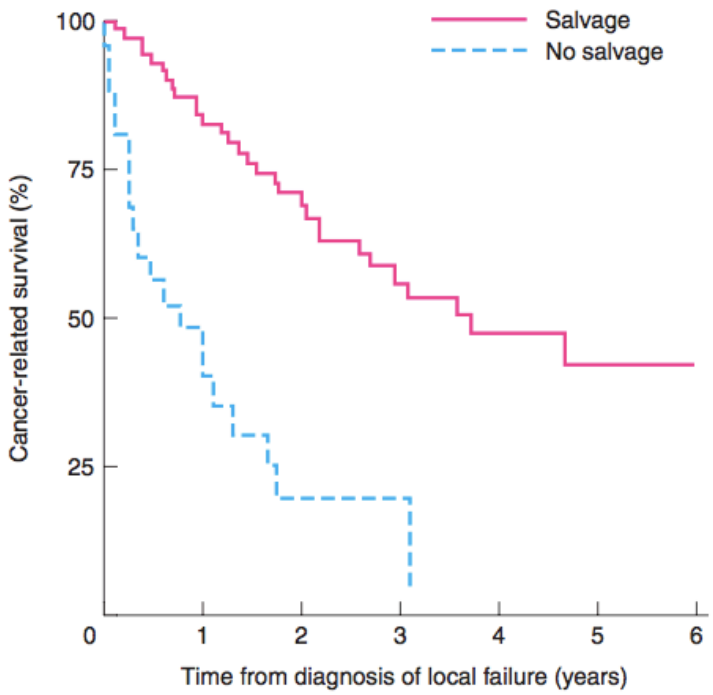

Fig. 2 Cancer-related survival after local disease failure

Survival after loco-regional disease failure

Salvage vs no salvage

Renehan et al British journal of surgery. 2005;92:605-14

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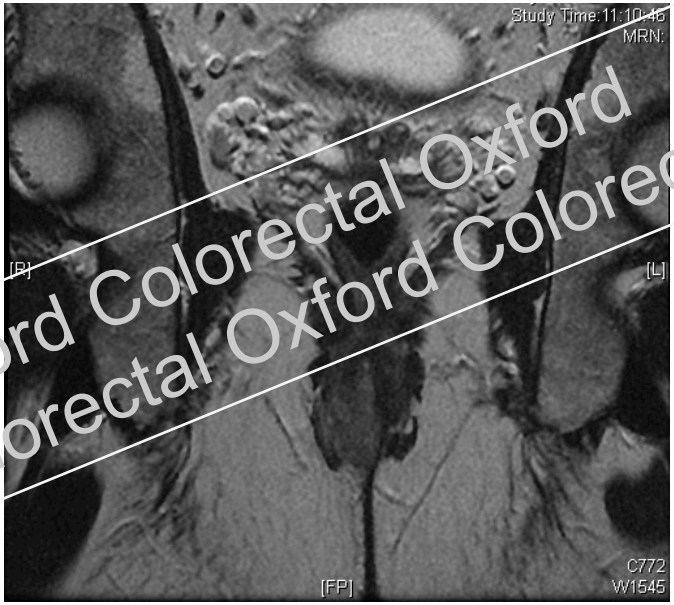
Loco-regional failure in anal cancer

Patients who fail to respond or suffer early recurrence have a poorer prognosis



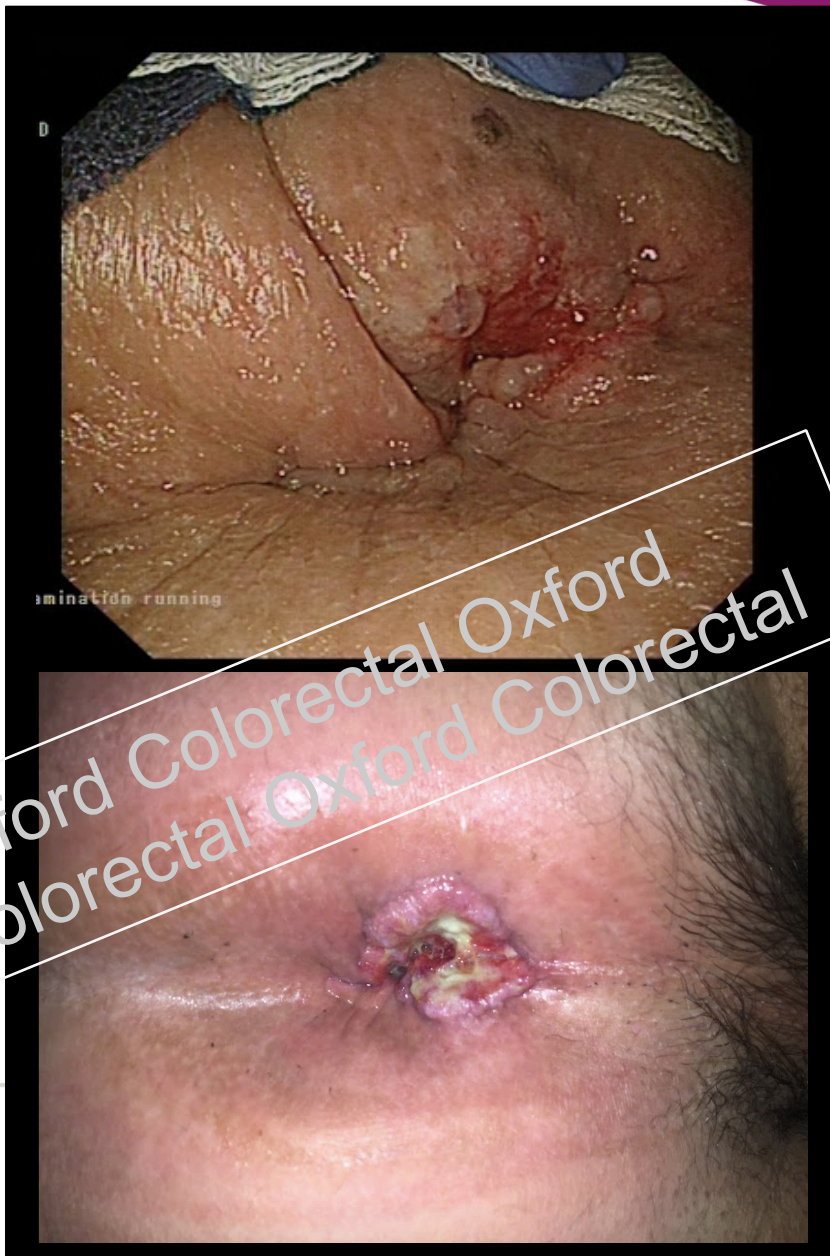
Rob Glynne-Jones, 2016 in press

Loco-regional failure in anal cancer

Low threshold for examination under anaesthetic and biopsy

Prompt diagnosis and surgery is required

Driven by RO



Operative planning and resection for anal cancer

There is no equivalent of "TME" in anal cancer

Operative planning needs to be individualized

Based on MRI and EUA

Operative planning and resection for anal cancer

Aim to achieve R0 resection

If you cannot do this another specialist should get involved

Operative planning and resection for anal cancer

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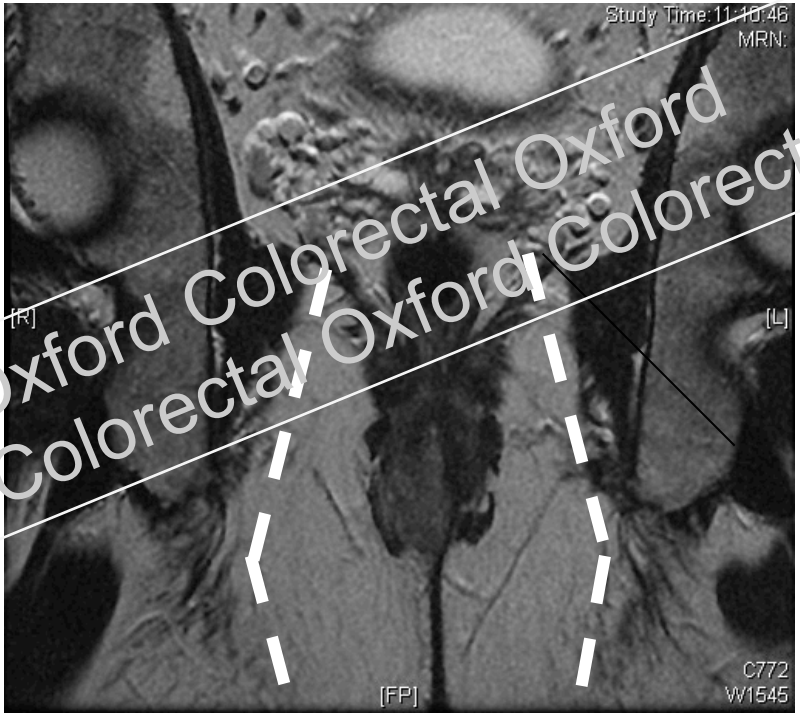

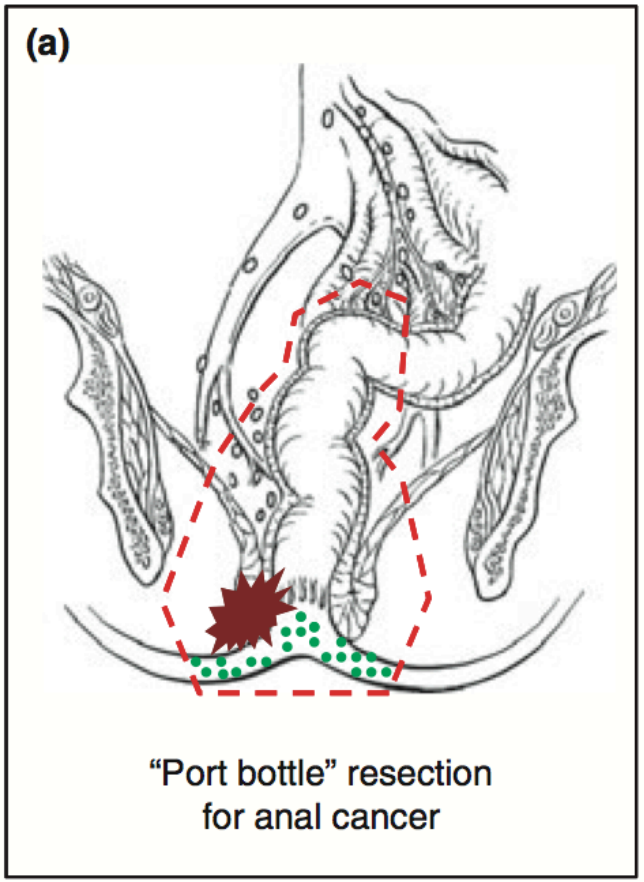

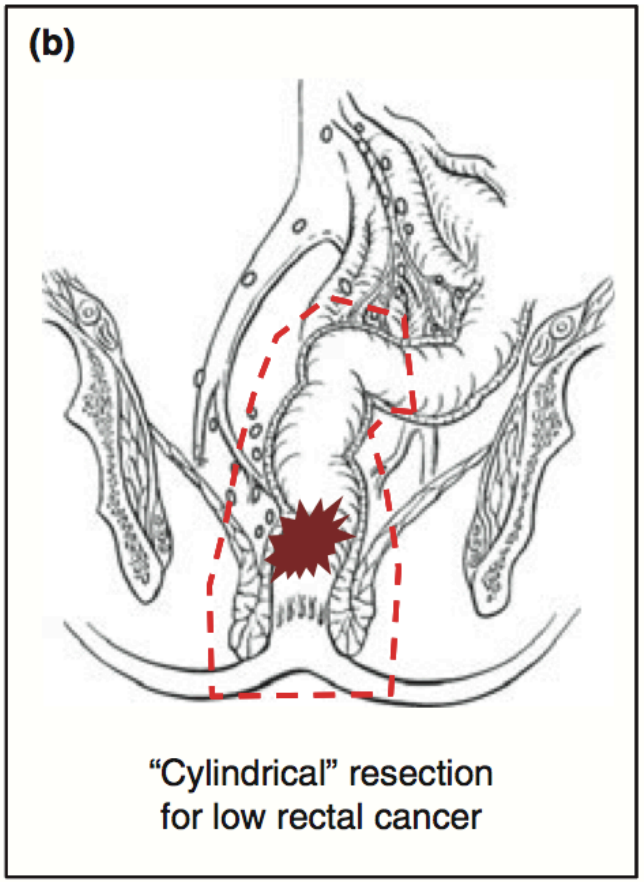

Renehan & O'Dwyer Colorectal Disease. 2011;13:44-52.

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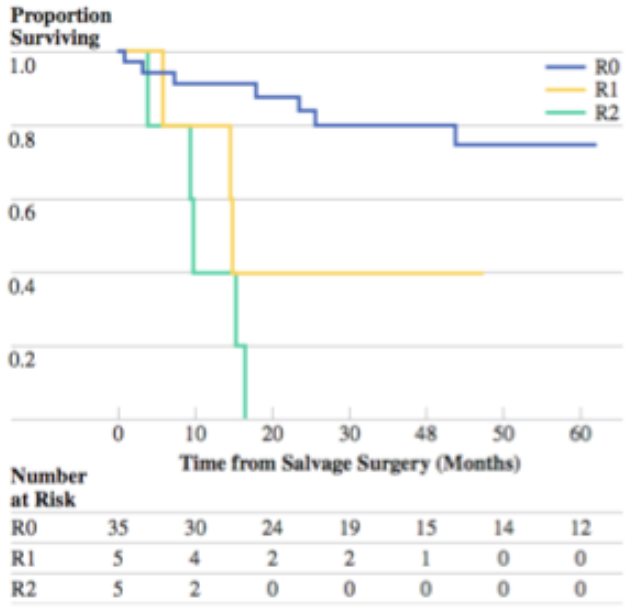

Number at Risk							
R0	35	30	24	19	15	14	12
R1	5	4	2	2	1	0	0
R2	5	2	0	0	0	0	0

FIG. 2 Overall survival after anal cancer salvage surgery according to margin status of resection. R0, free resection margin. R1, microscopically involved margin only. R2, macroscopically and microscopically involved margin

Sunesen Ket al. Ann Surg Oncol. 2009;16:68-77

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Operative planning and resection for anal cancer

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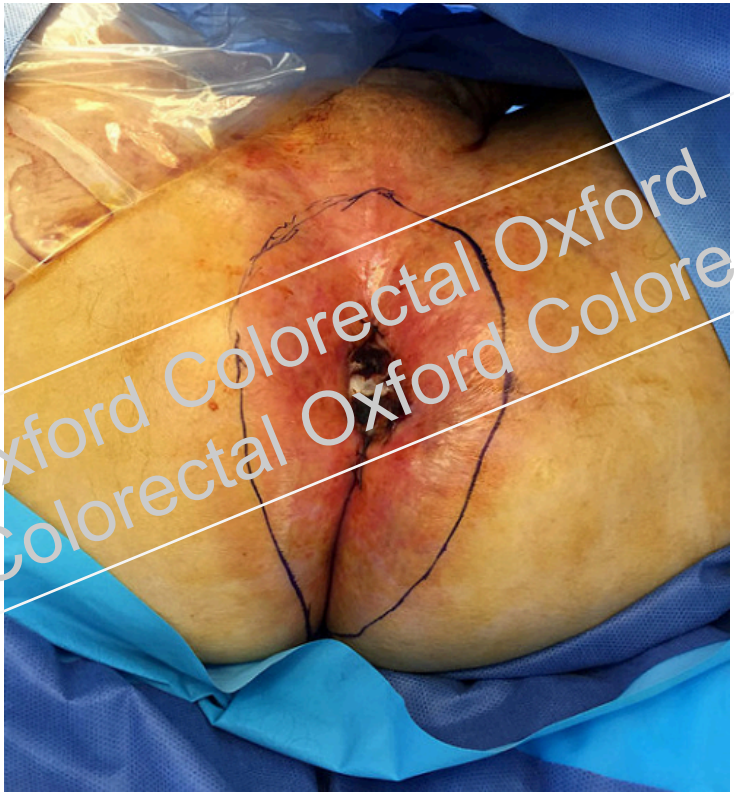

Operative planning and resection for anal cancer

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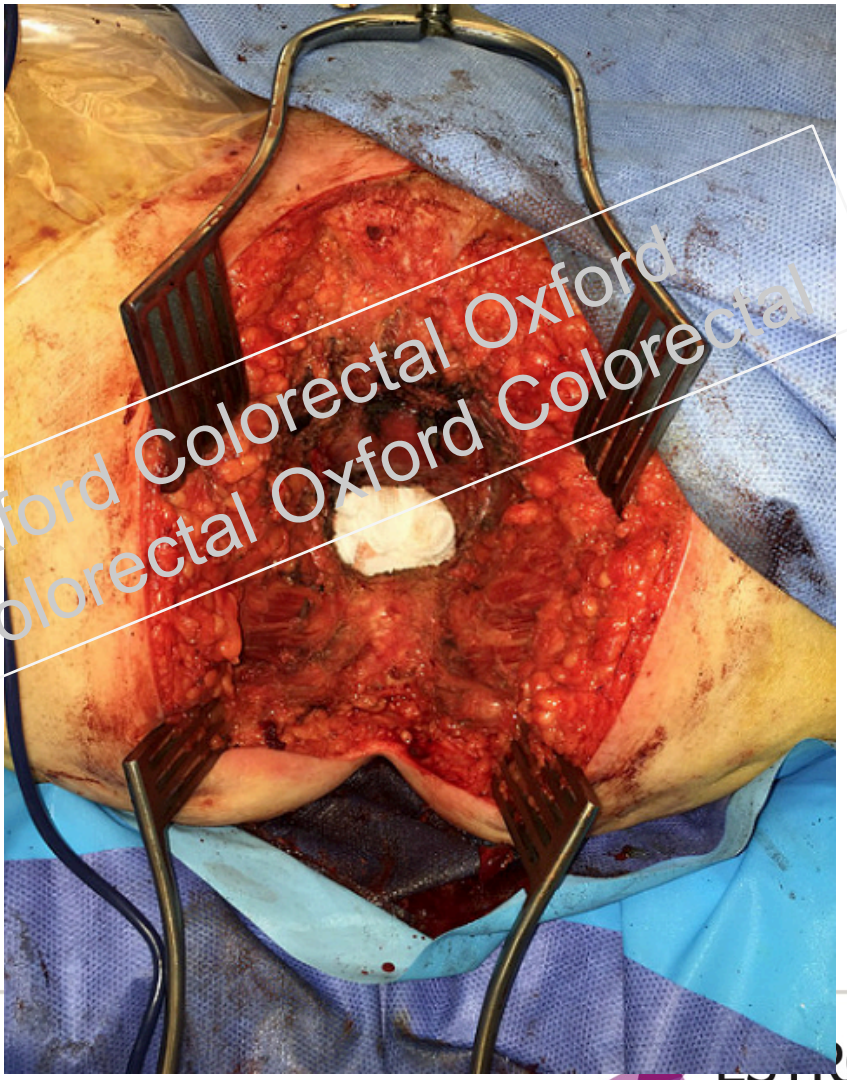
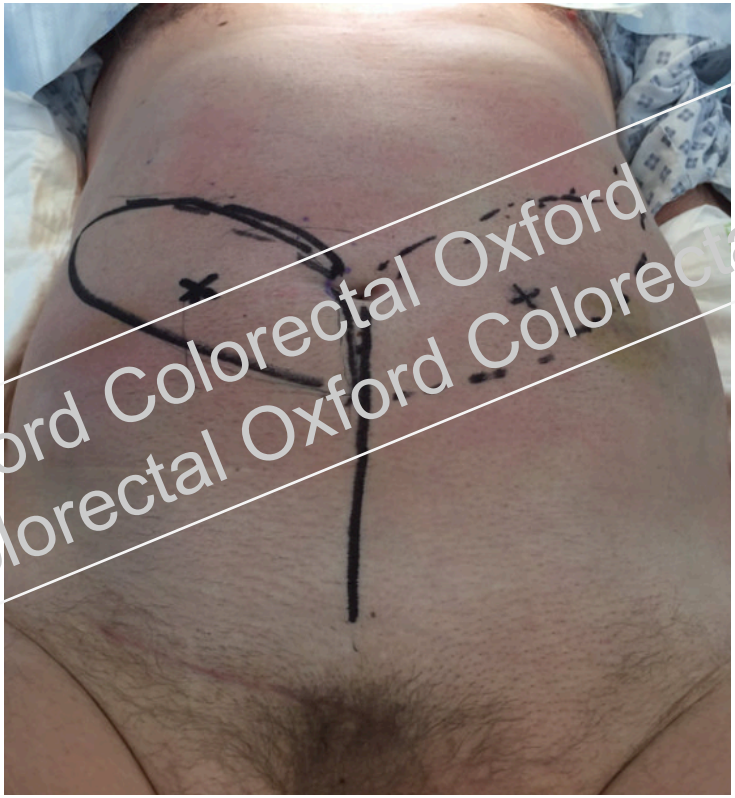


Flap reconstruction

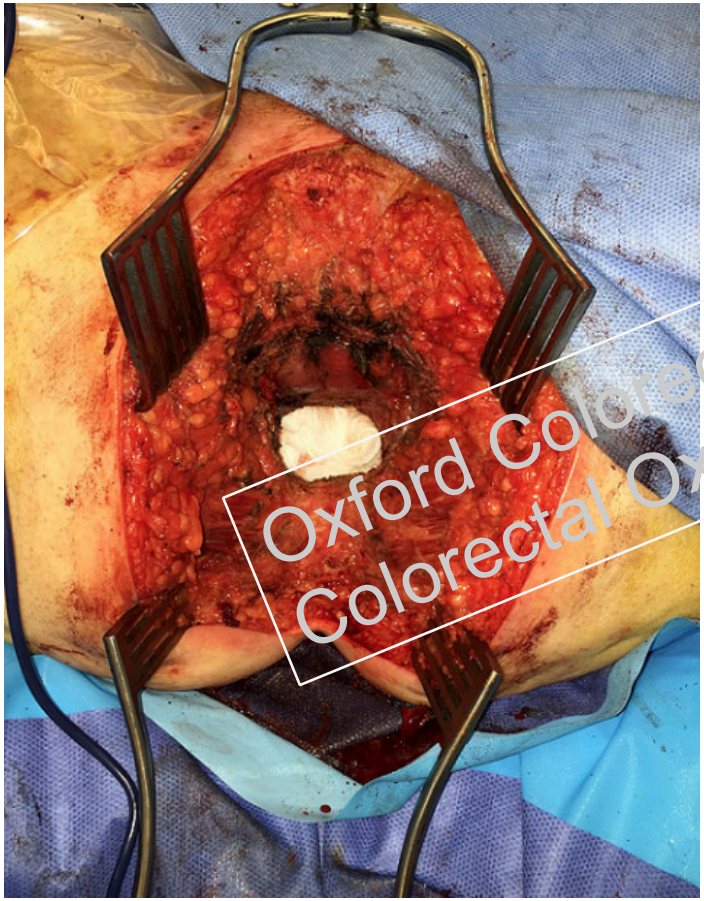
Vertical rectus abdominus myocutaneous flap

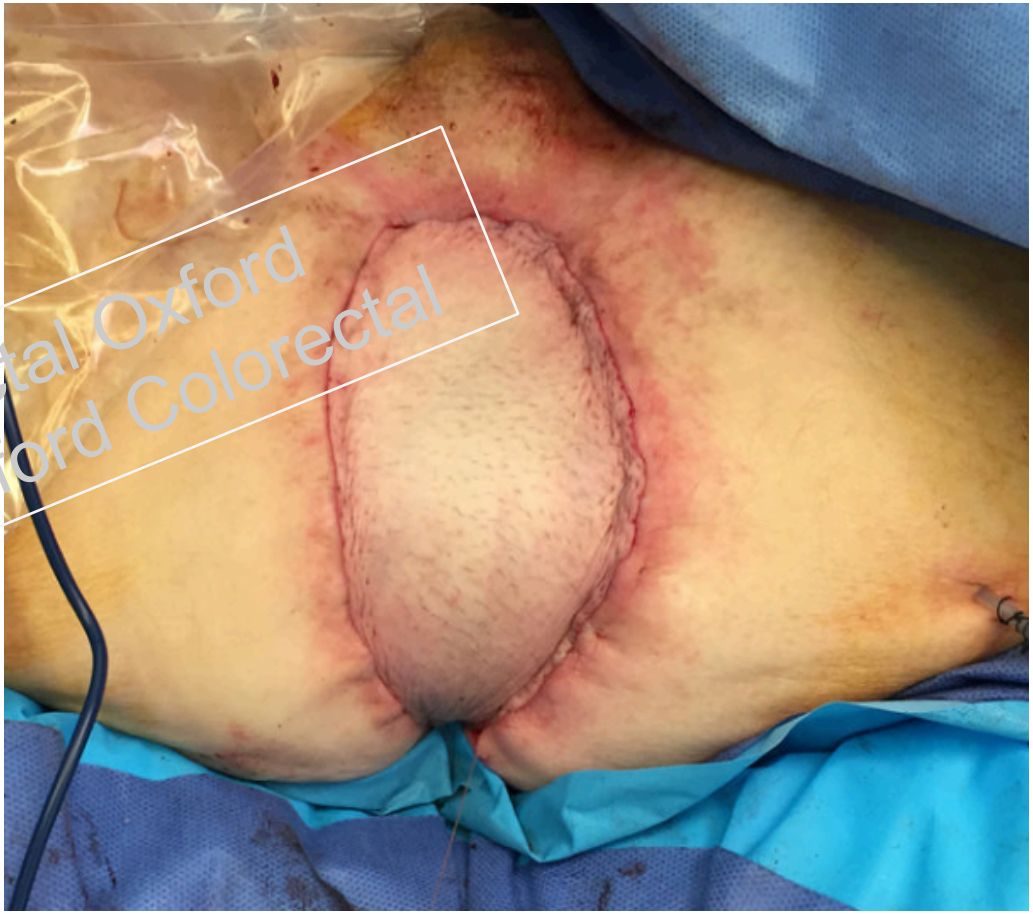
Local fascial or myocutaneous

70% women require posterior vaginectomy

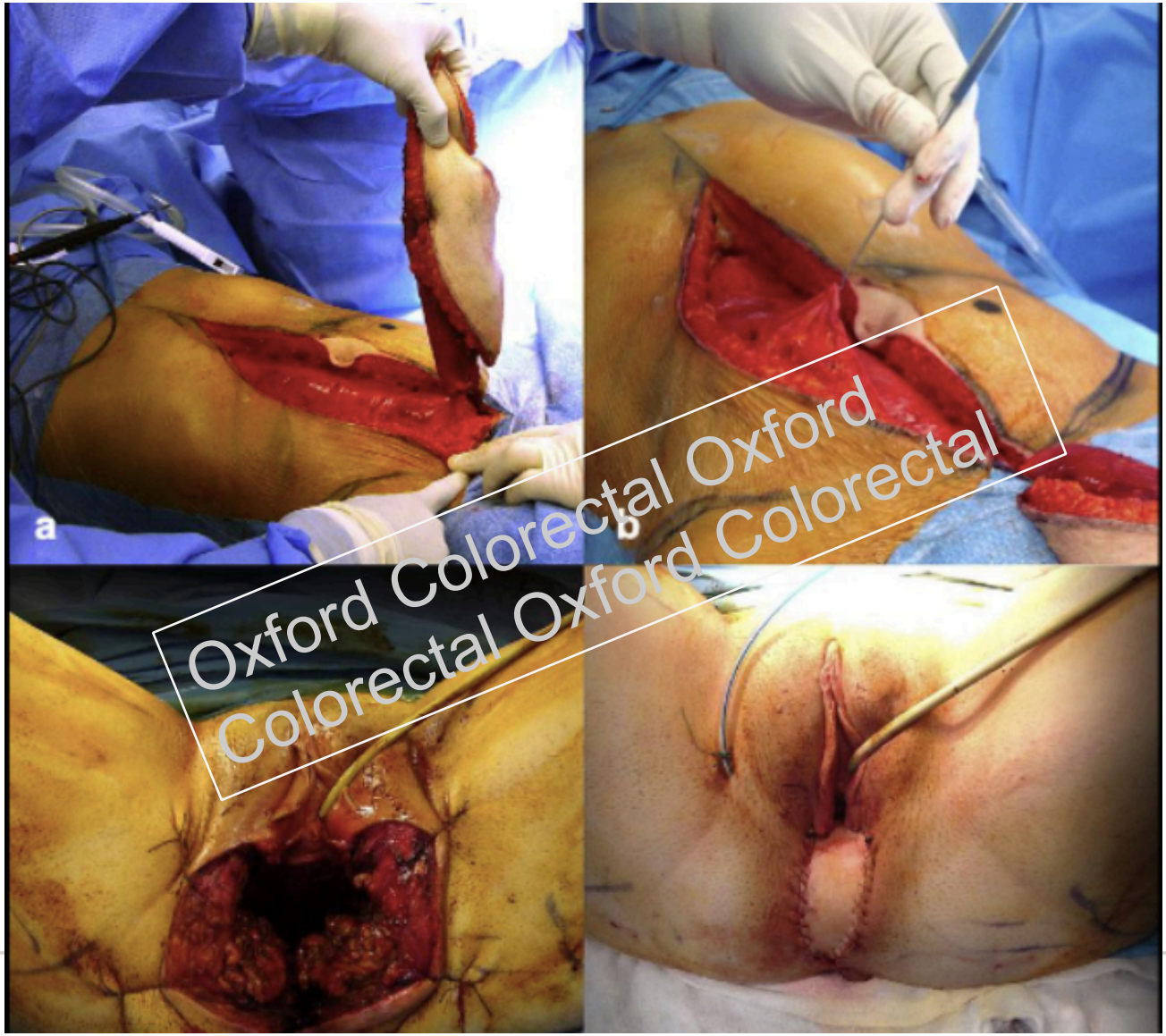


Flap reconstruction





Flap reconstruction



Courtesy of Alex Ramsden

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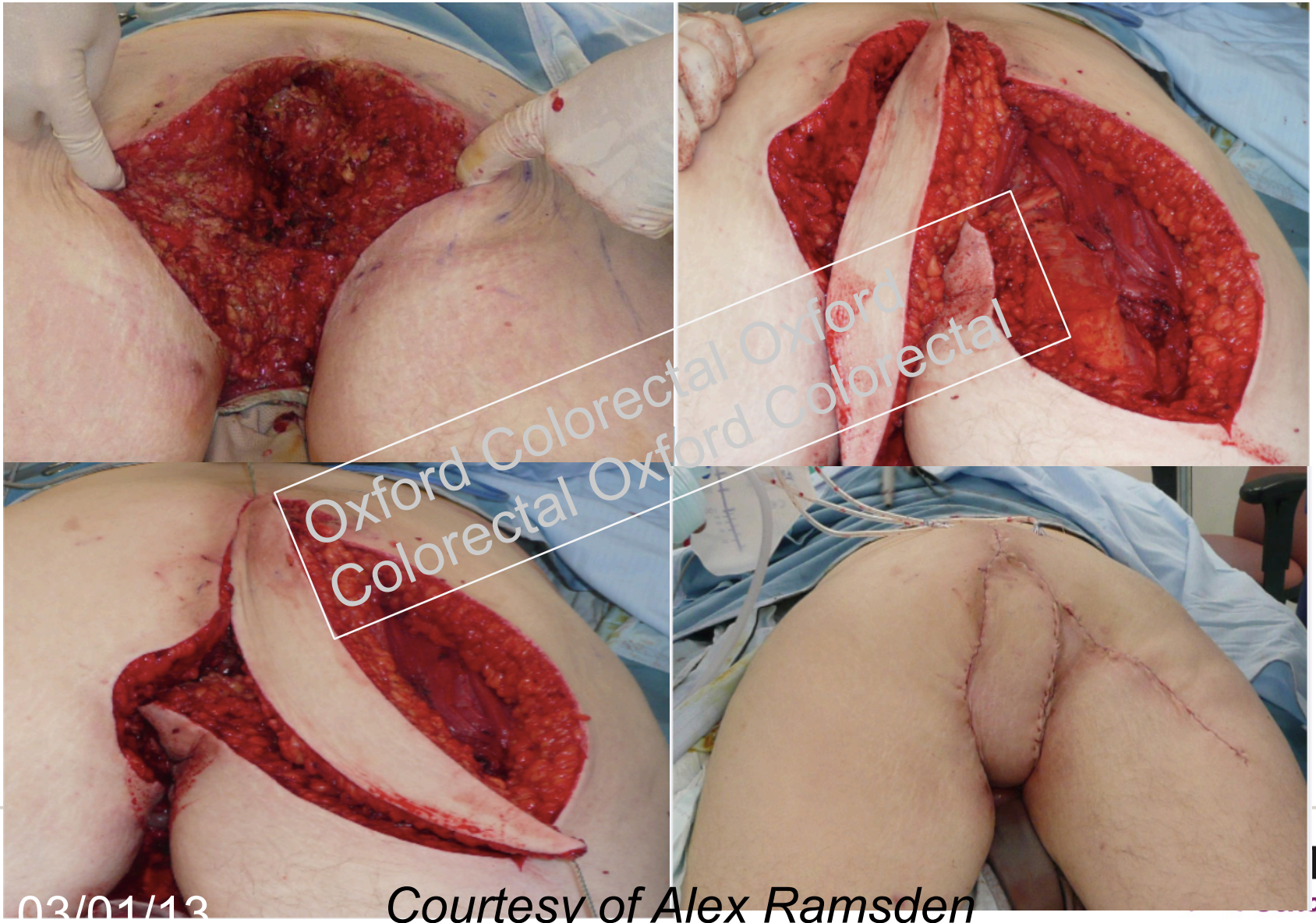
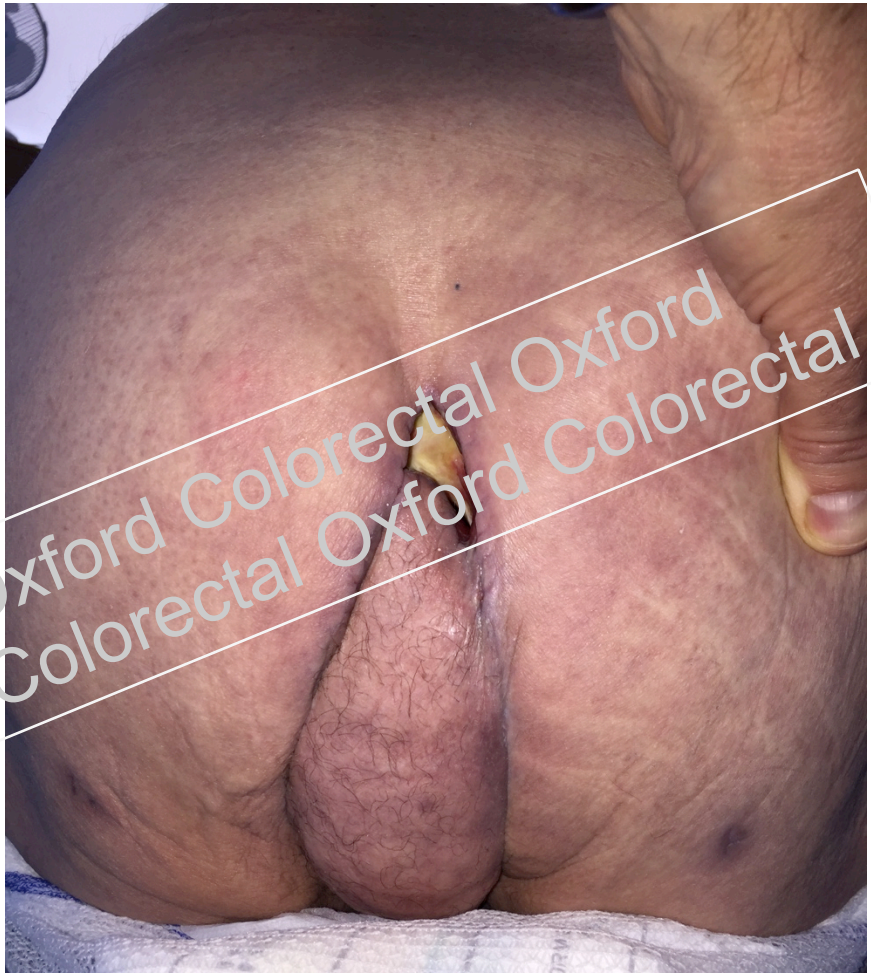
Flap reconstruction



Courtesy of Alex Ramsden

Operative planning and resection for anal cancer

Wound healing problems in 25-40%

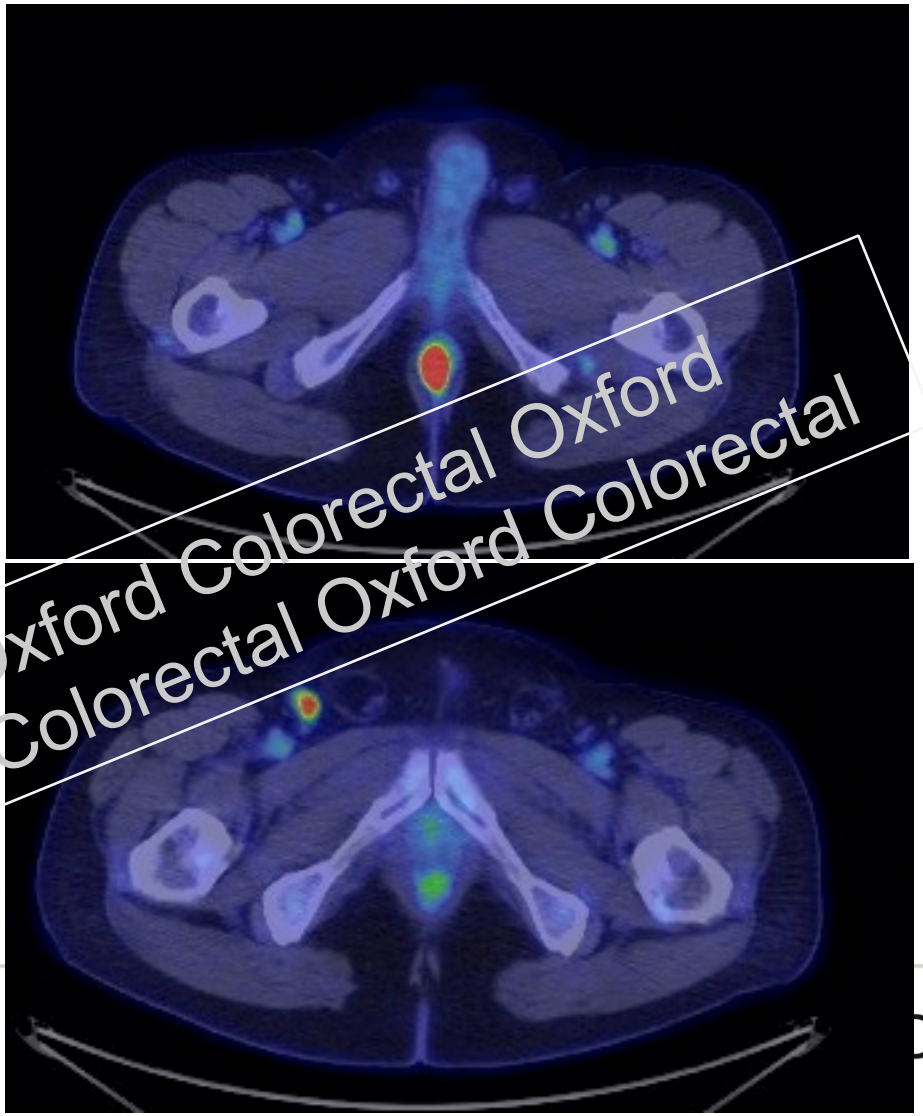


Operative planning and resection for anal cancer

Managing nodal disease

Groin dissection if disease failure

High morbidity



Summary

Operative management of anal cancer is challenging

Multi-disciplinary surgical and post operative teams needed

High morbidity

Early action once evidence of failure

Aim for R0 resection

Atlas and contouring guidelines for anal cancer radiotherapy

Karin Haustermans

Department of Radiation Oncology

UZ Leuven

ESTRO School

International Journal of
Radiation Oncology
biology • physics

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Clinical Investigation: Gastrointestinal Cancer

Australasian Gastrointestinal Trials Group (AGITG) Contouring Atlas and Planning Guidelines for Intensity-Modulated Radiotherapy in Anal Cancer

Michael Ng, M.B.B.S.(Hons), F.R.A.N.Z.C.R.,[*]
Trevor Leong, M.B.B.S., M.D., F.R.A.N.Z.C.R.,[†,‖]
Sarat Chander, M.B.B.S., F.R.A.N.Z.C.R.,[†] Julie Chu, M.B.B.S., F.R.A.N.Z.C.R.,[†]
Andrew Kneebone, M.B.B.S., F.R.A.N.Z.C.R.,[‡,**]
Susan Carroll, M.B.B.S., F.R.A.N.Z.C.R.,[§,**] Kirsty Wiltshire, M.B.B.S., F.R.A.N.Z.C.R.,[†]
Samuel Ngan, M.B.B.S., F.R.C.S.Ed., F.R.A.N.Z.C.R.,[†,‖] and Lisa Kachnic, M.D.[¶]

*Radiation Oncology Victoria, Victoria, Australia; [†]Department of Radiation Oncology, Peter MacCallum Cancer Centre, Victoria, Australia; [‡]Department of Radiation Oncology, Northern Sydney Cancer Centre, Royal North Shore Hospital, NSW, Australia; [§]Department of Radiation Oncology, Sydney Cancer Centre, Royal Prince Alfred Hospital, NSW, Australia; [¶]Department of Radiation Oncology, Boston Medical Center, Boston University School of Medicine, Boston, MA; [‖]University of Melbourne, Australia; and **University of Sydney, Australia

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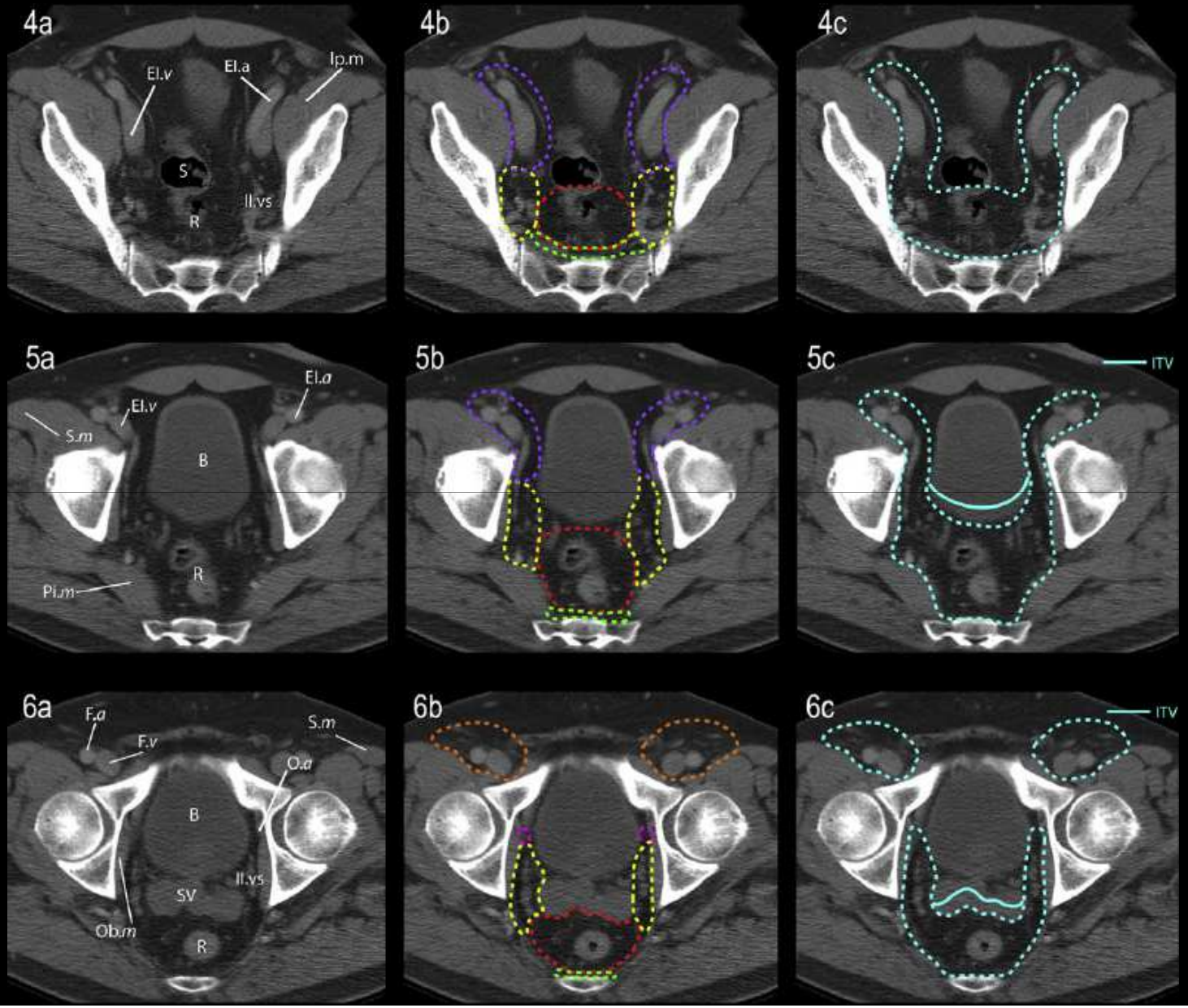
Htpp://www.analimrtguidance.co.uk

Delineation of elective nodal volumes

- Mesorectum
- Presacral space
- Internal iliac lymph nodes
- Ischiorectal fossa
- Obturator nodes
- External iliac lymph nodes
- Inguinal lymph nodes

Mesorectum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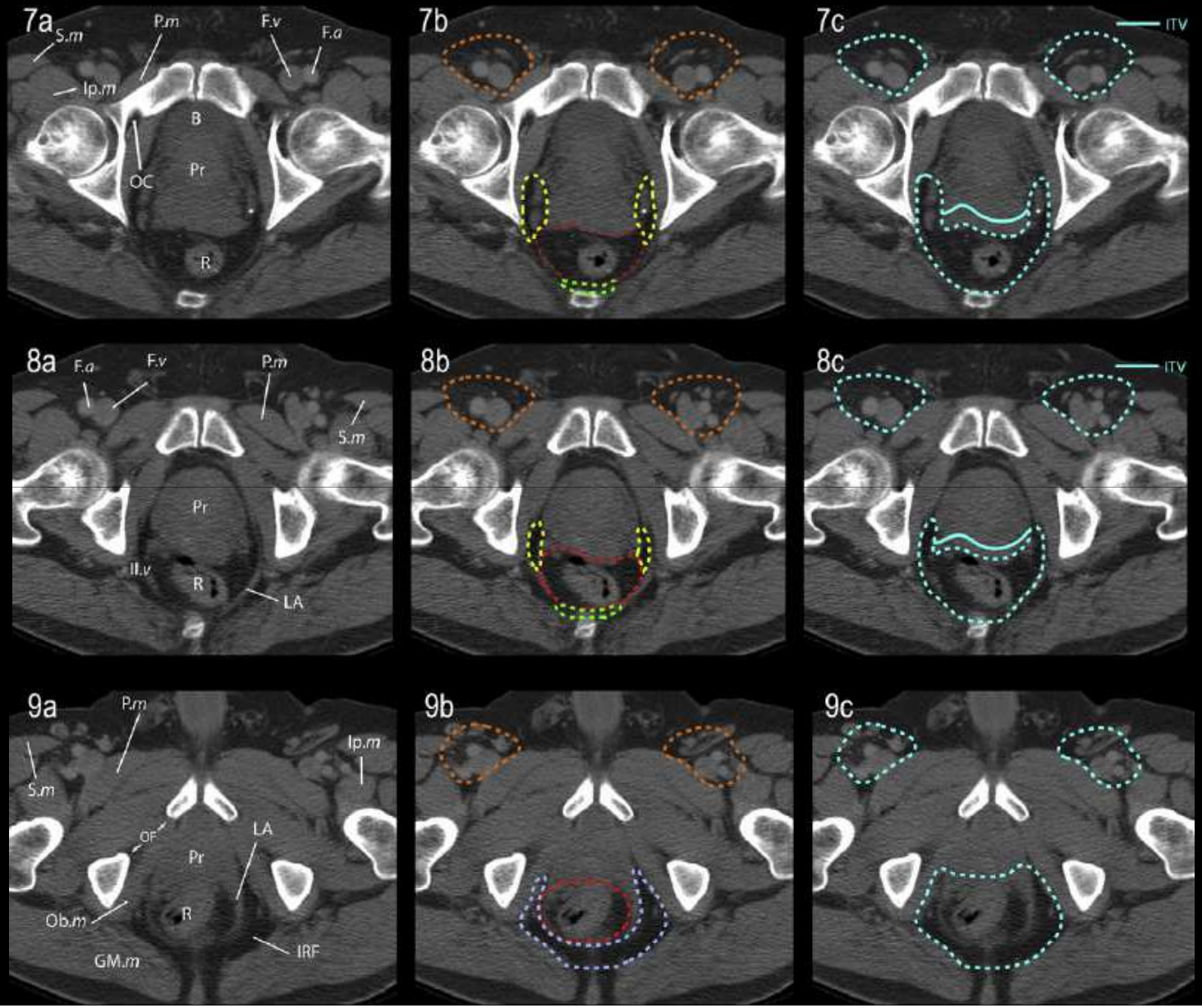
Mesorectum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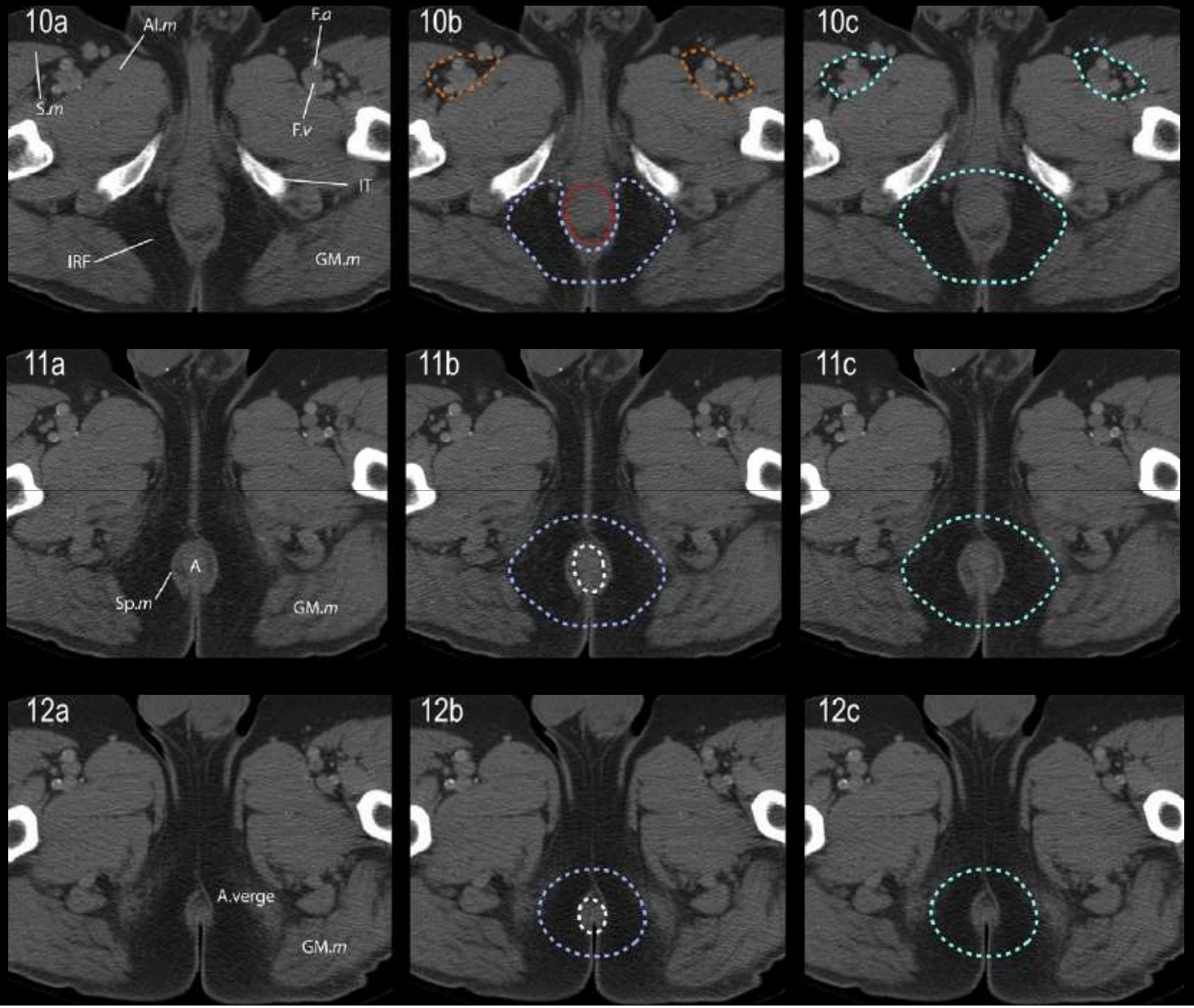
Mesorectum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Sp.m
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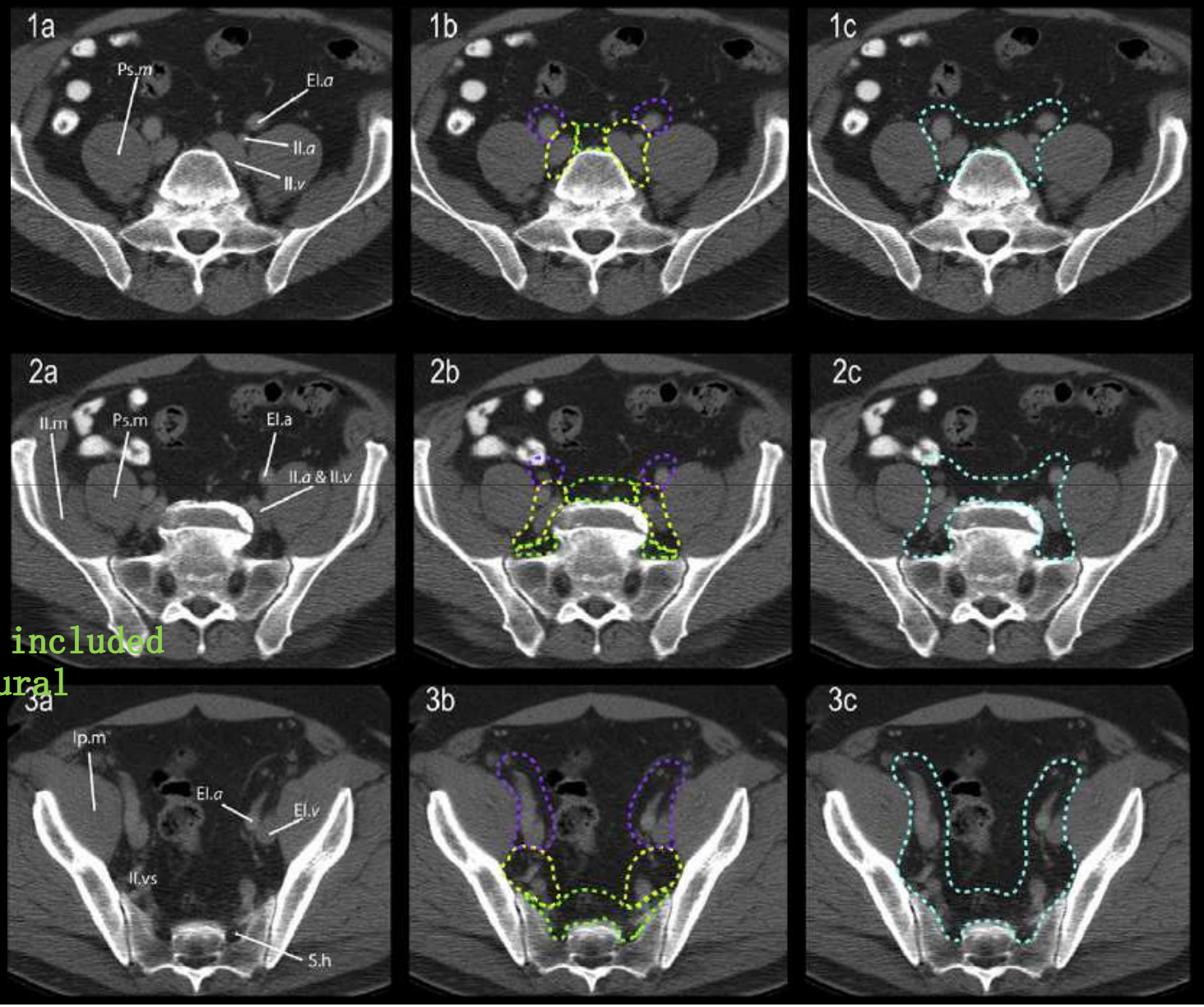
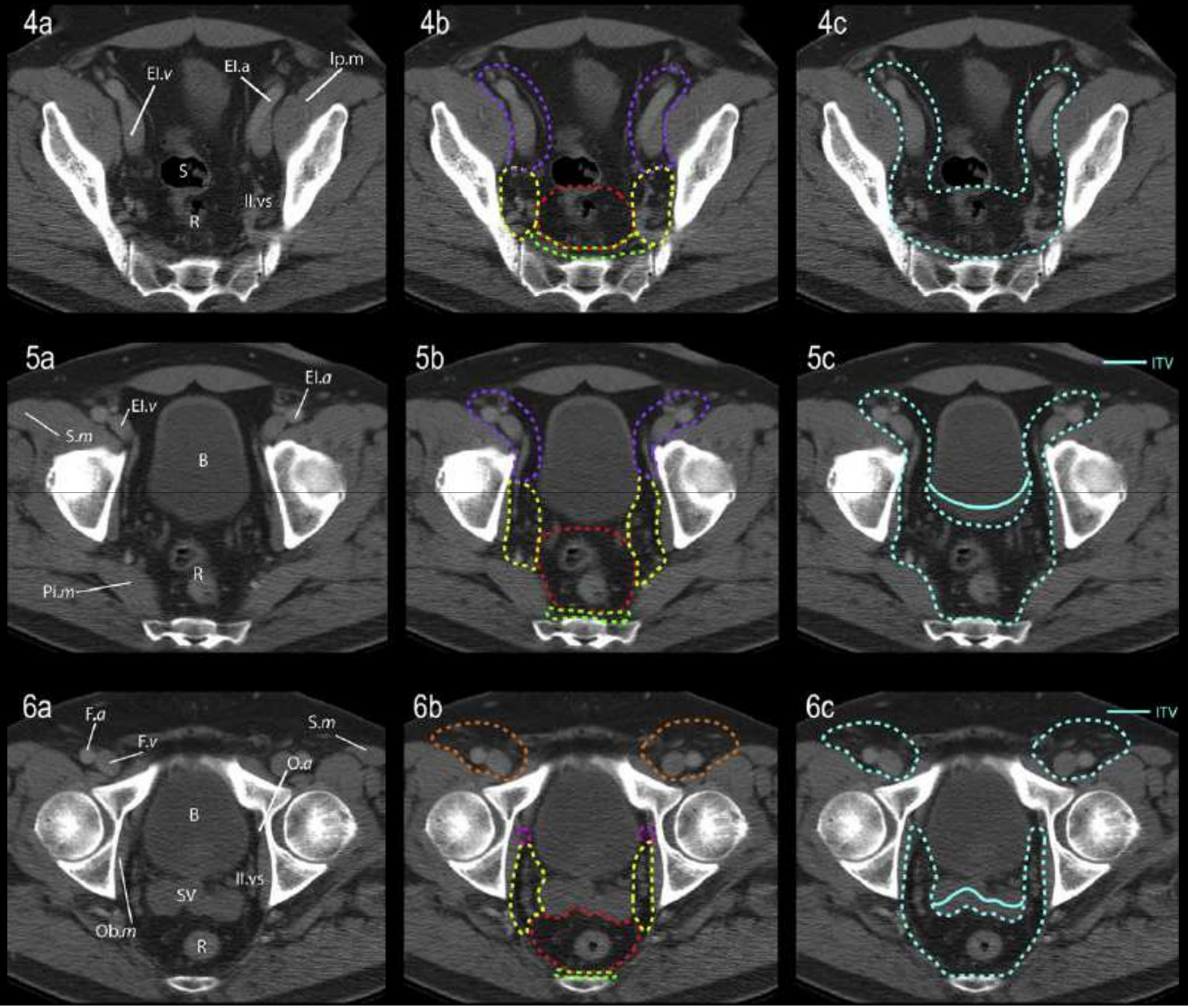
A.verge
GM.m
12b
12c

Presacral space

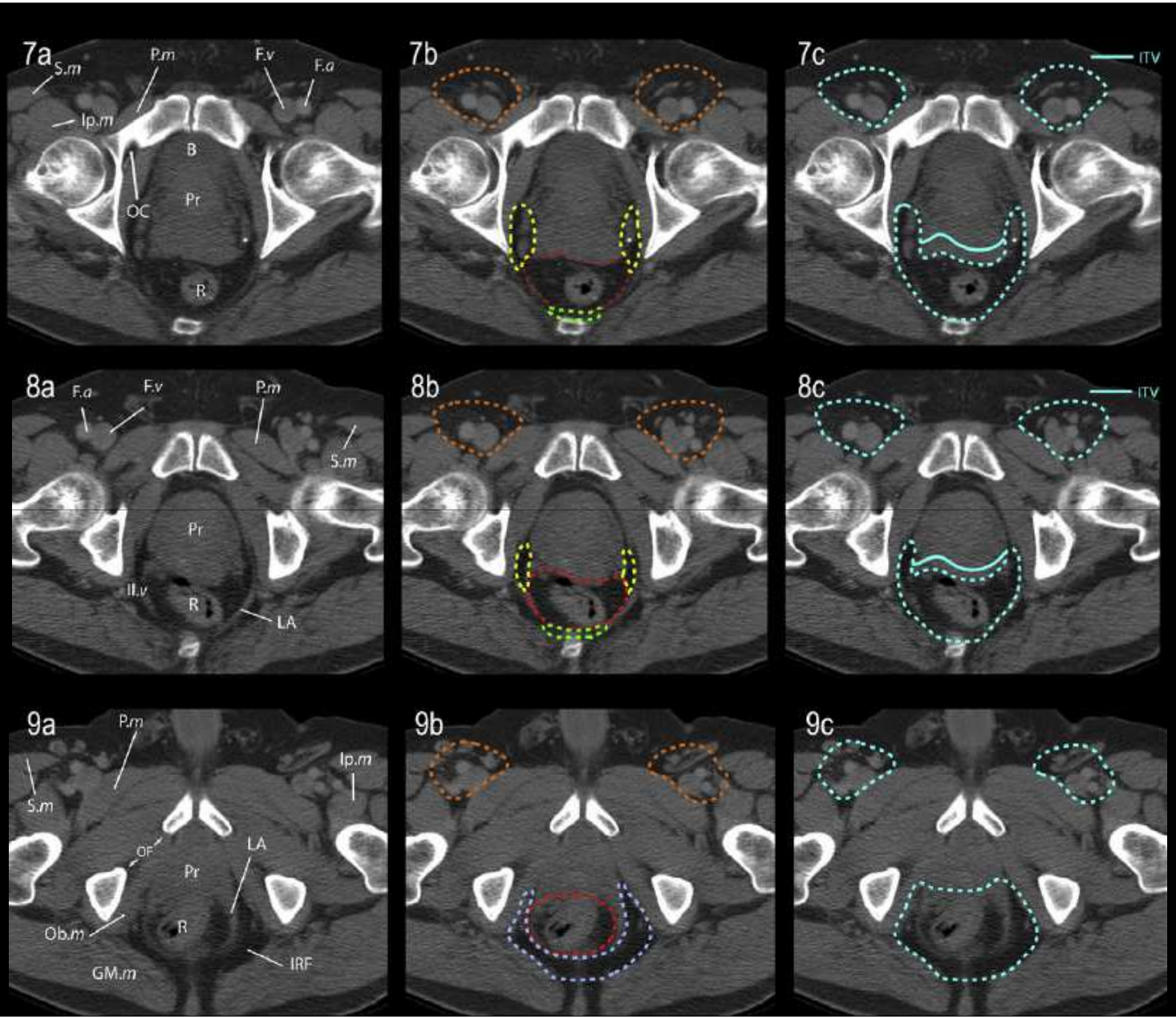


Sacral neuroforamina not included
Waldeyer's fascia is natural barrier

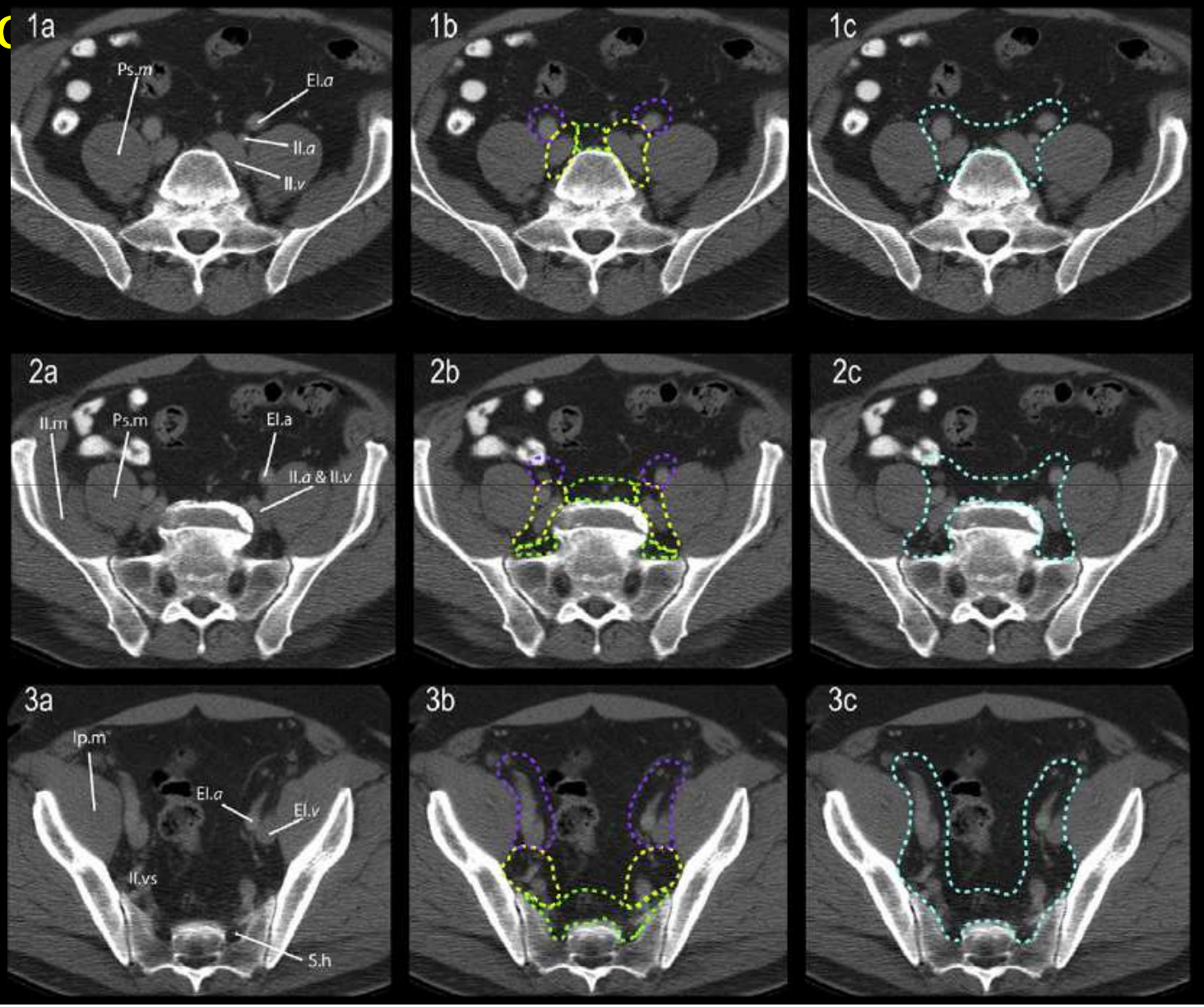
Presacral space



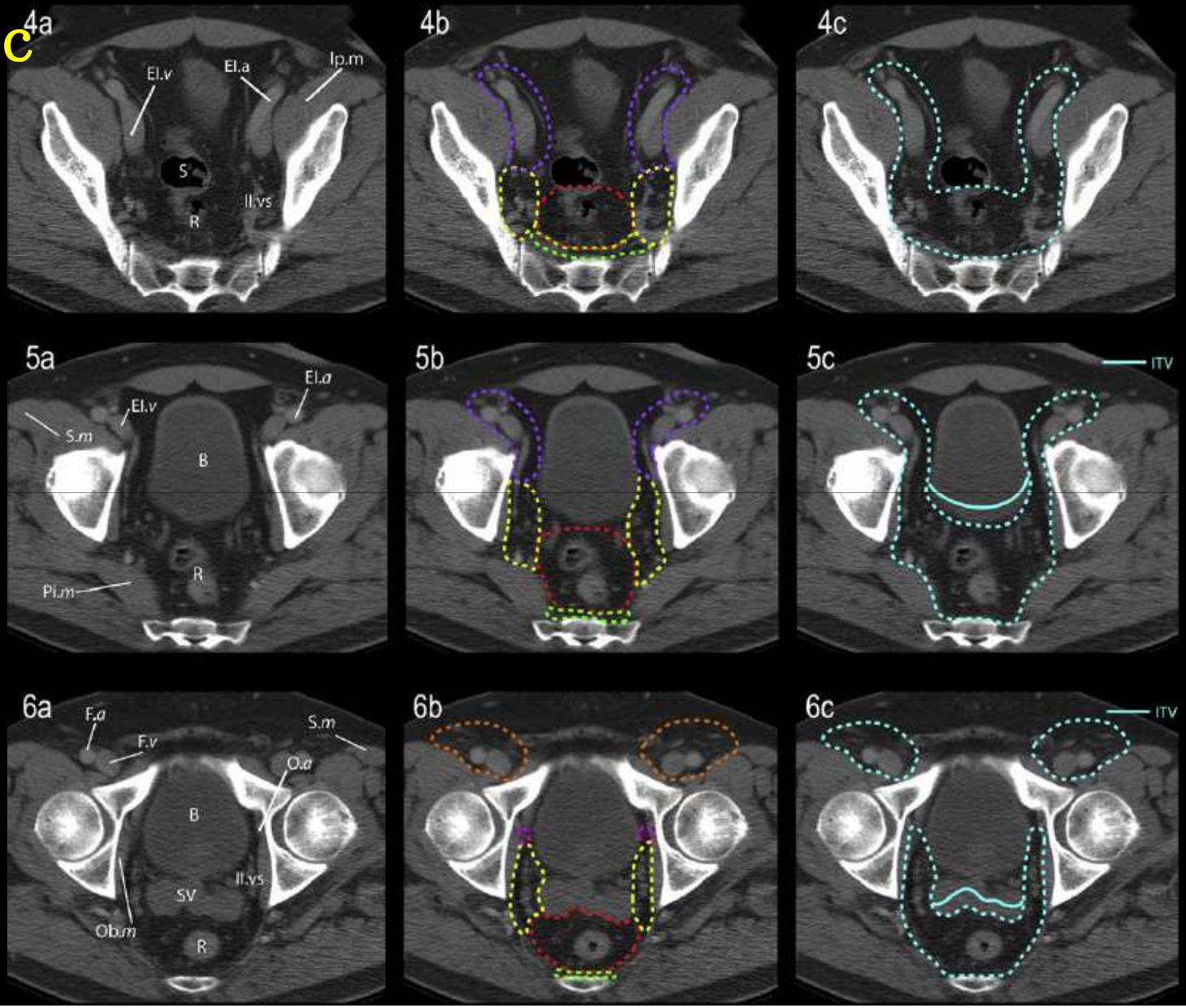
Presacral space



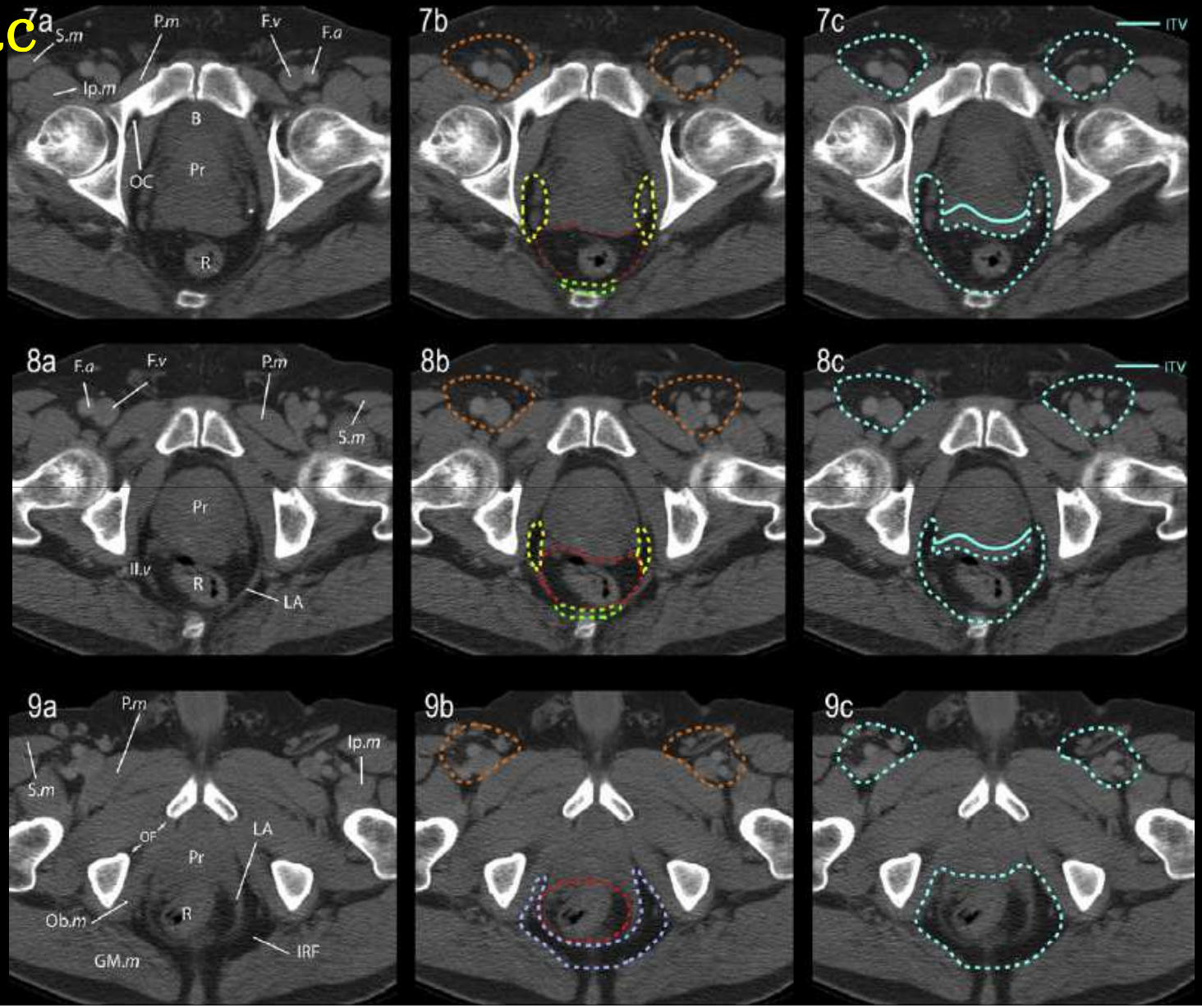
Internal iliac lymph nodes



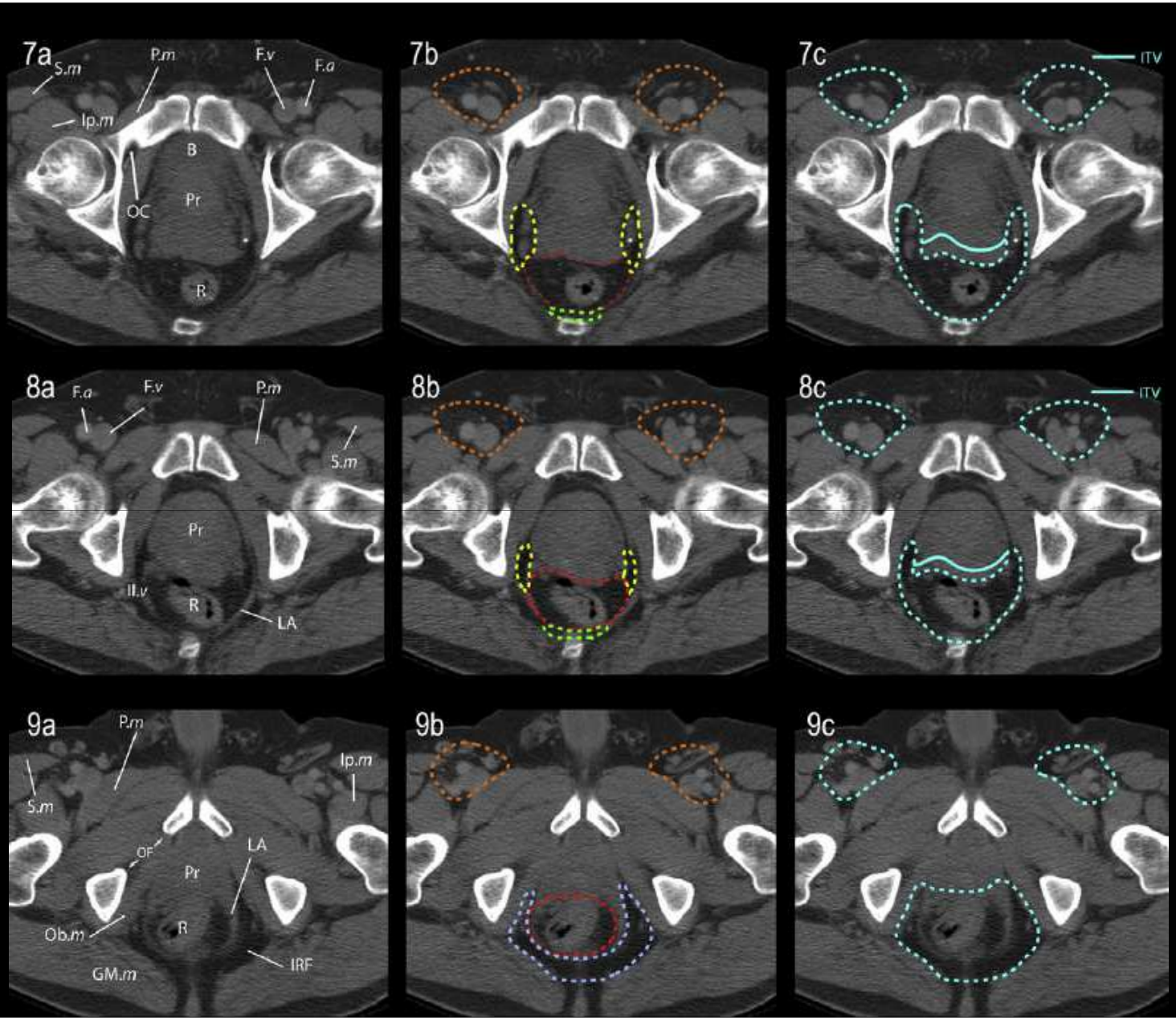
Internal iliac lymph nodes



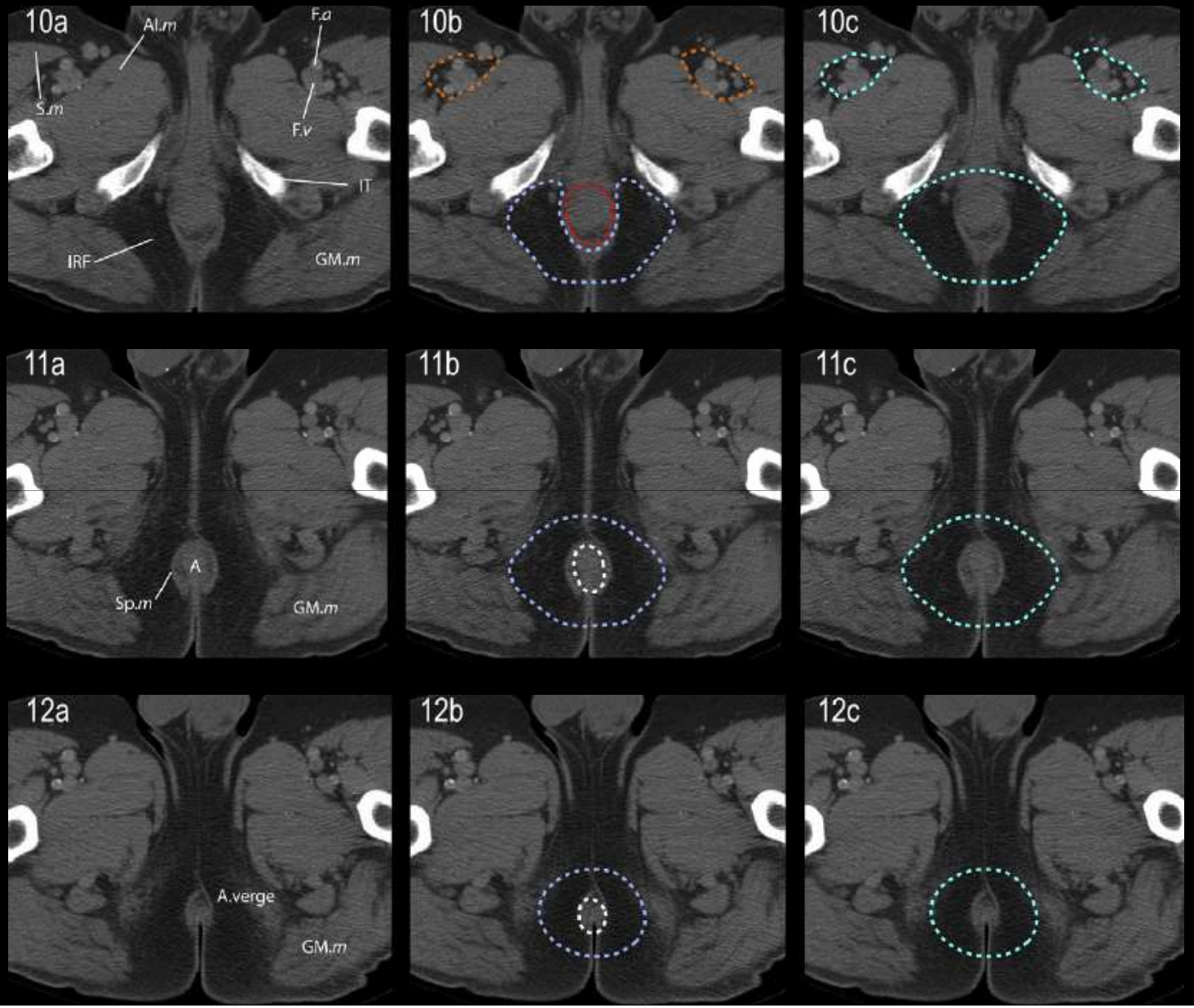
Internal iliac lymph nodes



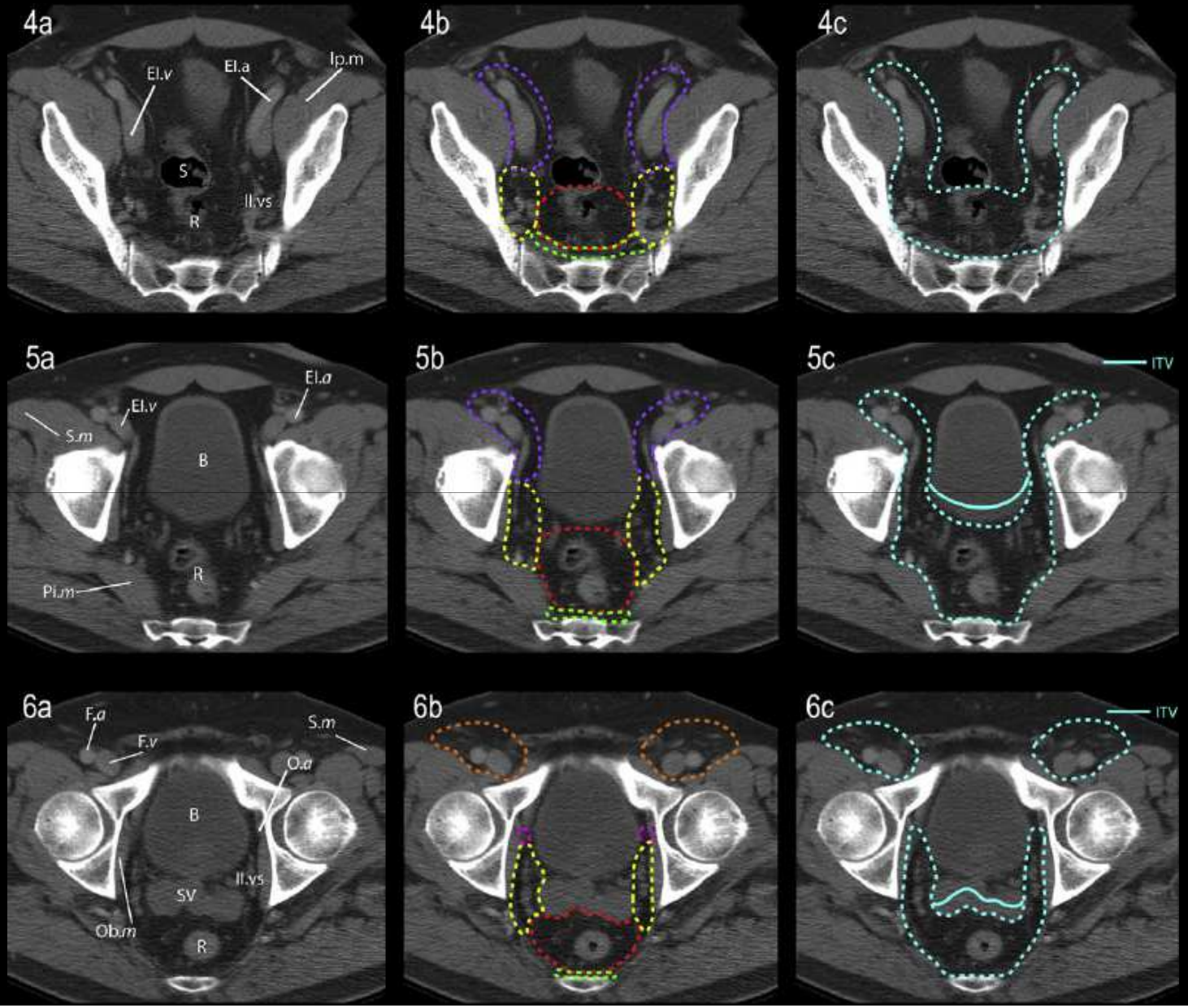
Ischiorectal fossa



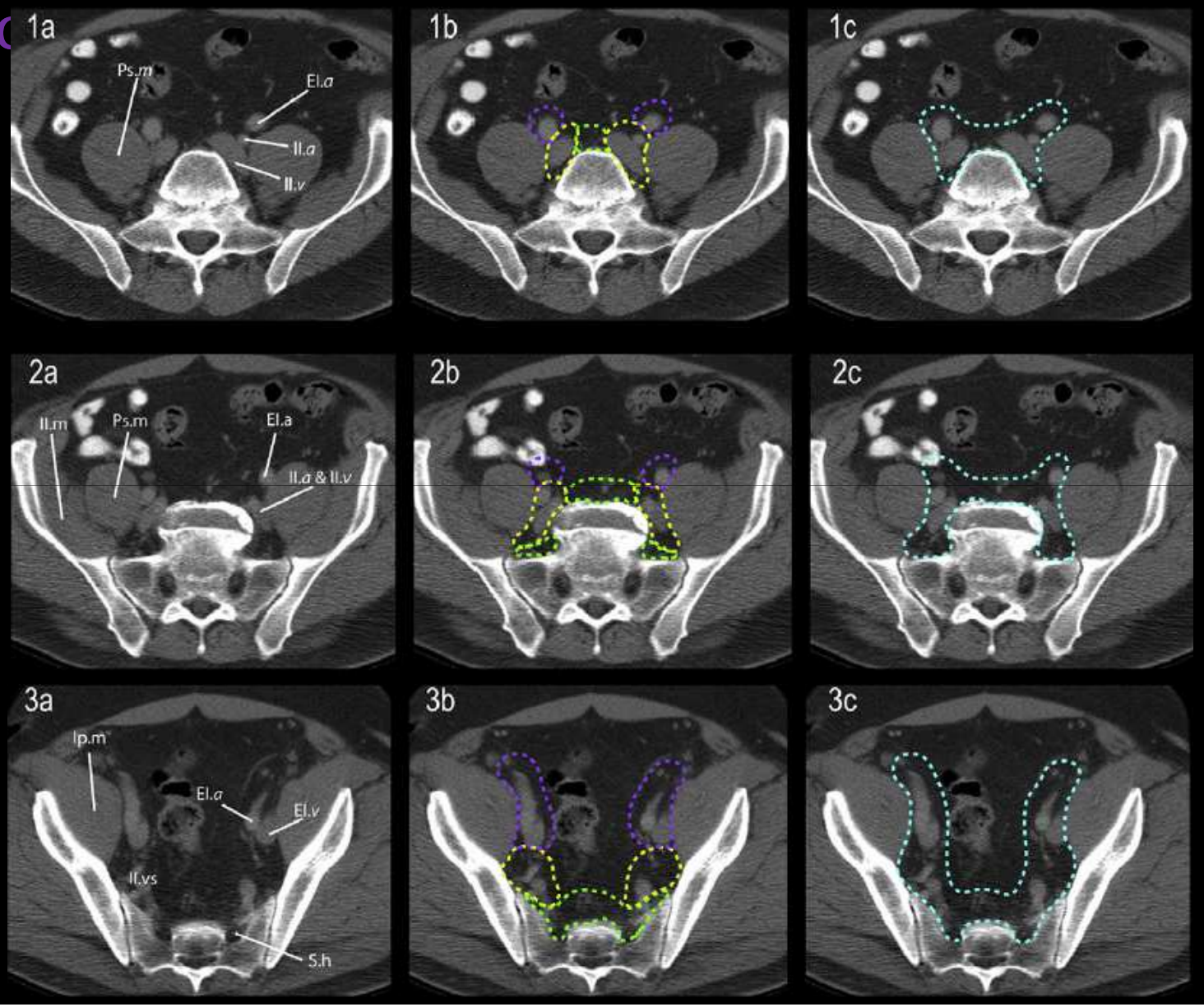
Ischiorectal fossa



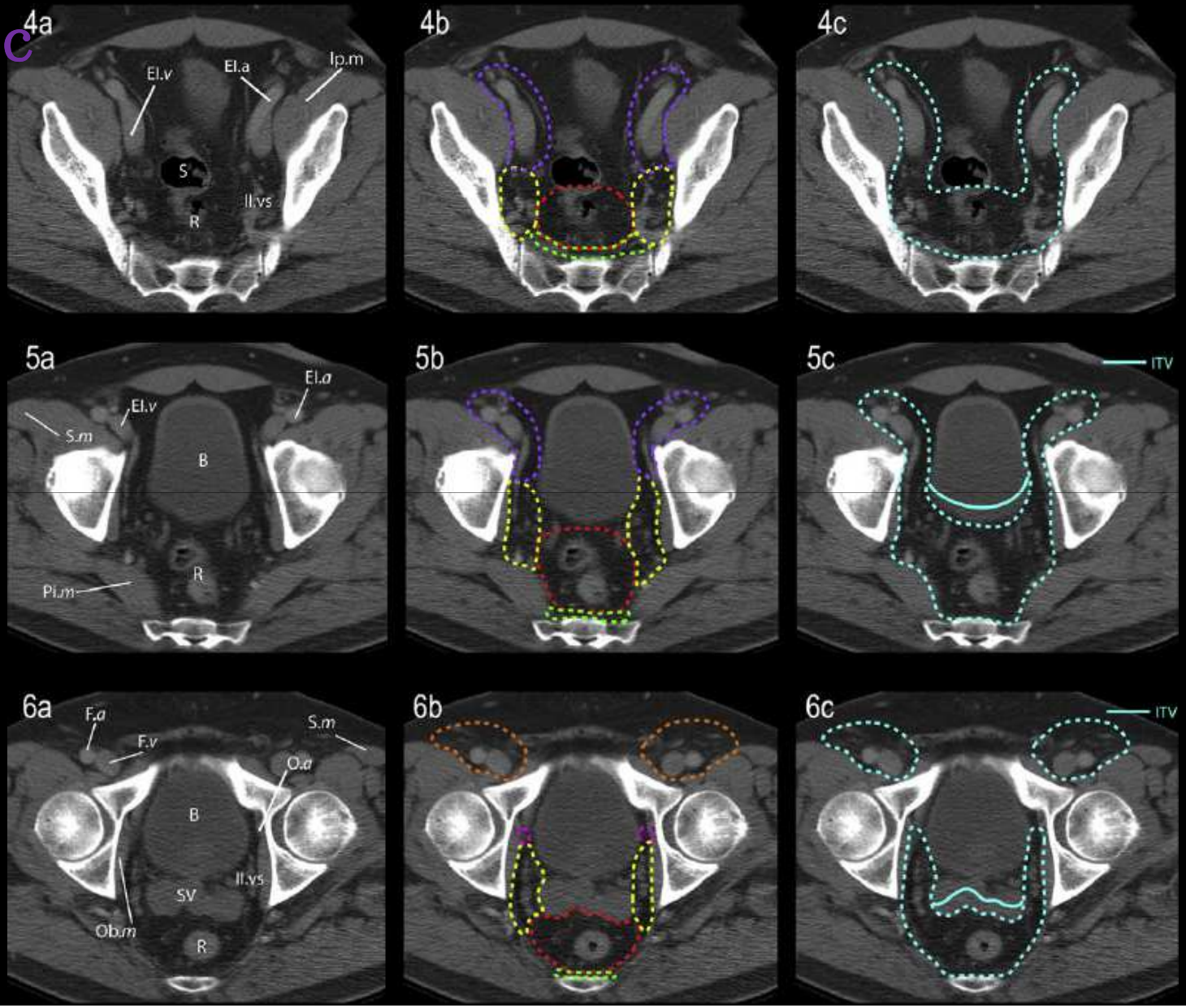
Obturator nodes



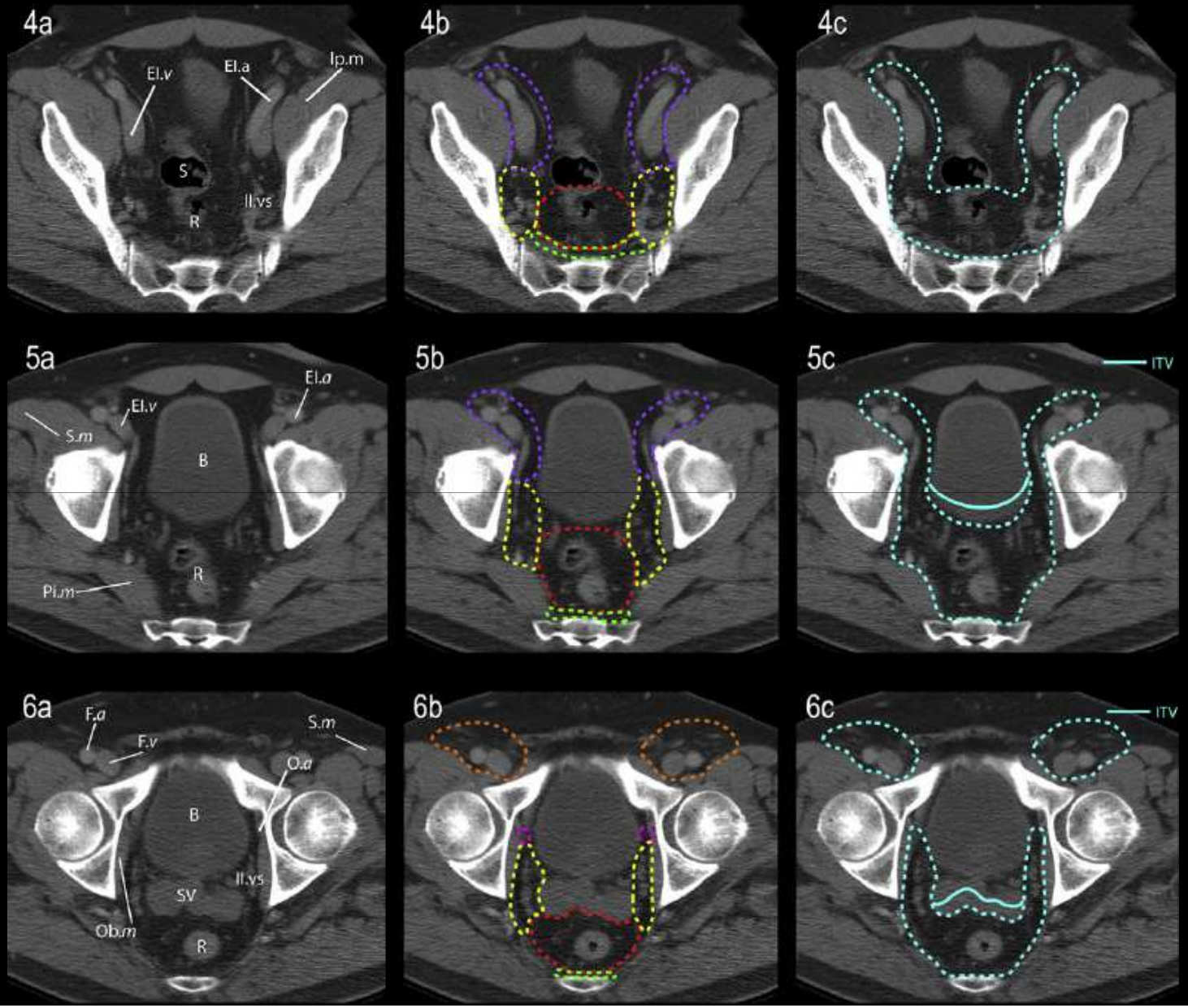
External iliac lymph nodes



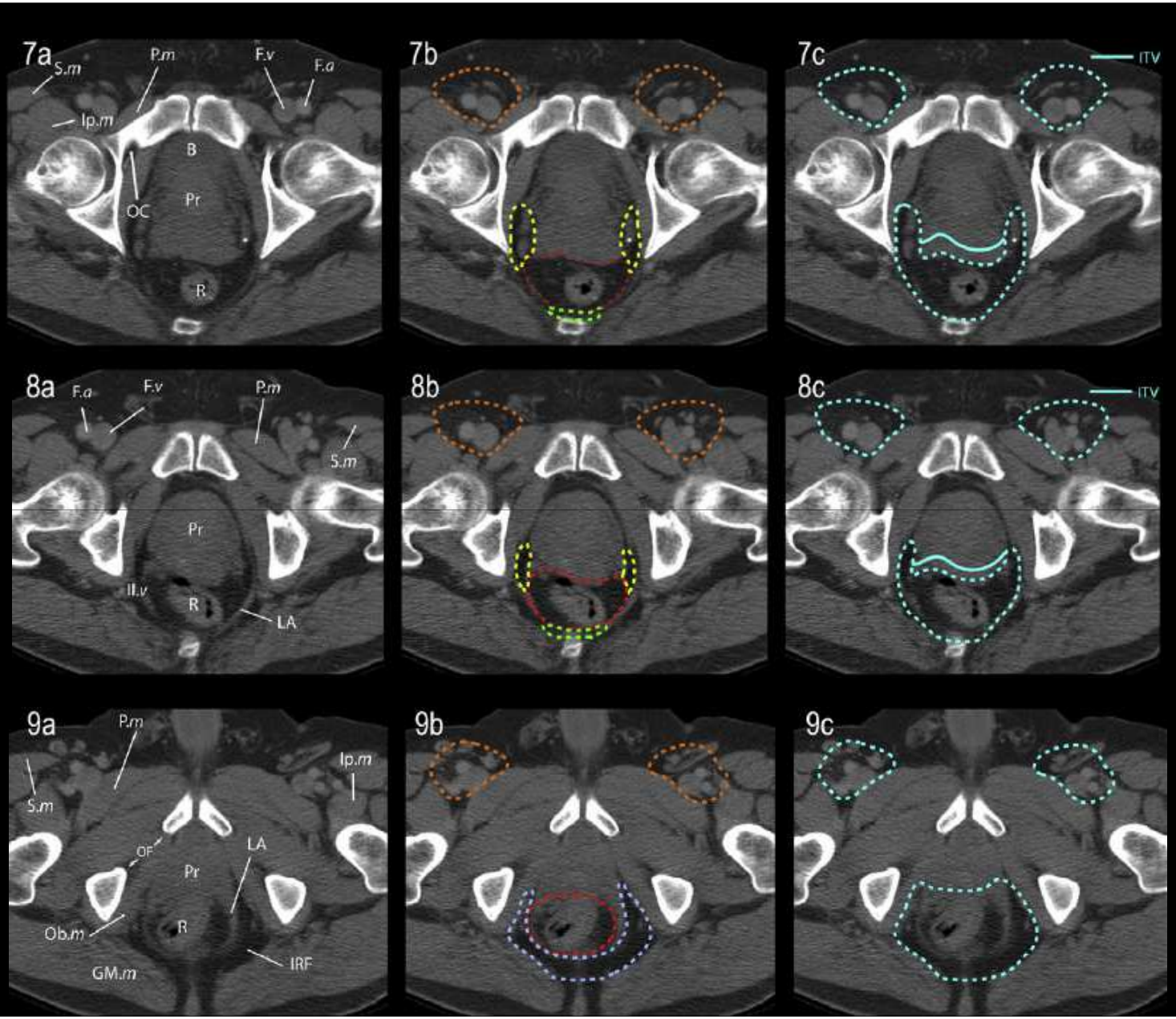
External iliac lymph nodes



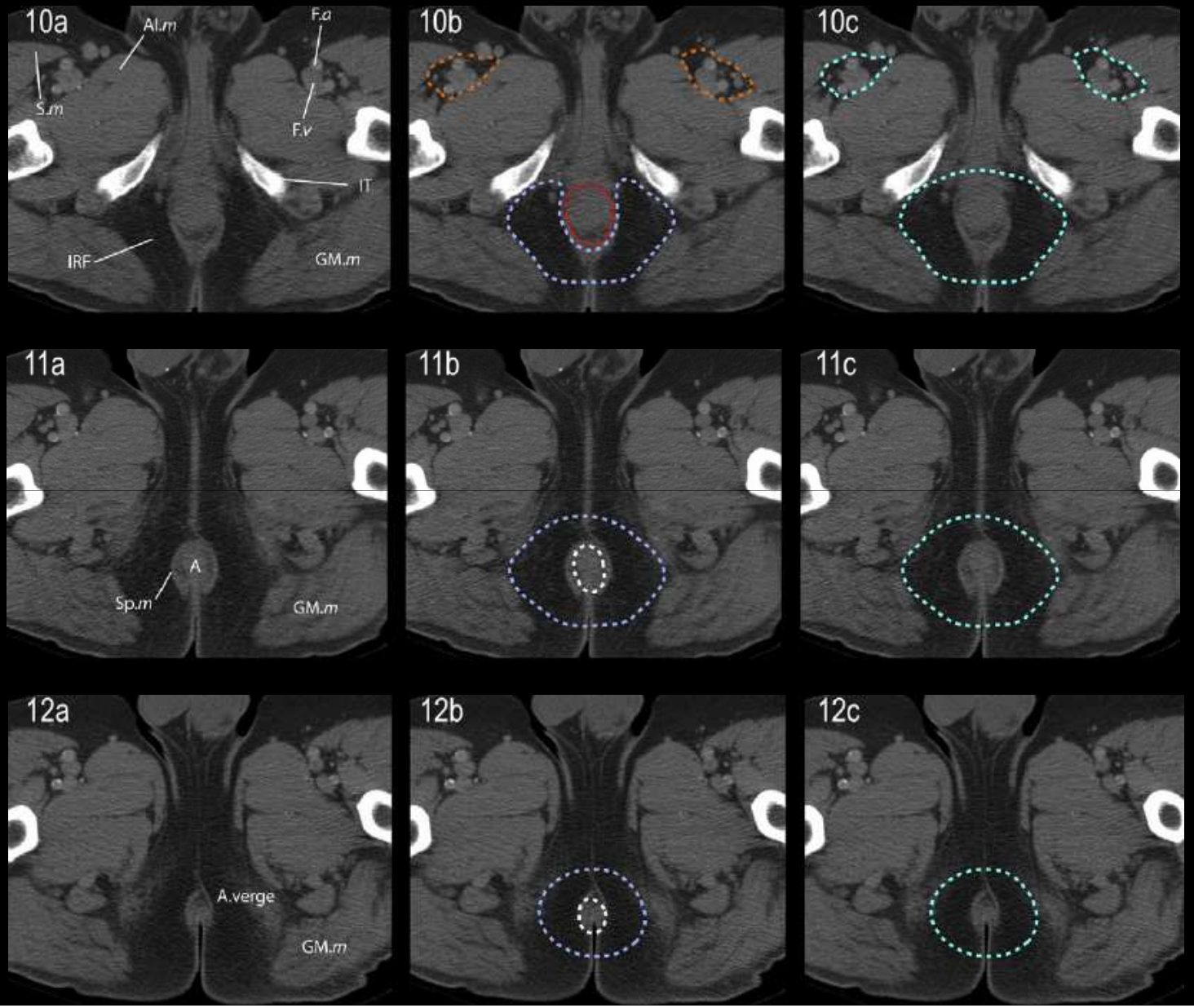
Inguinal nodes



Inguinal nodes

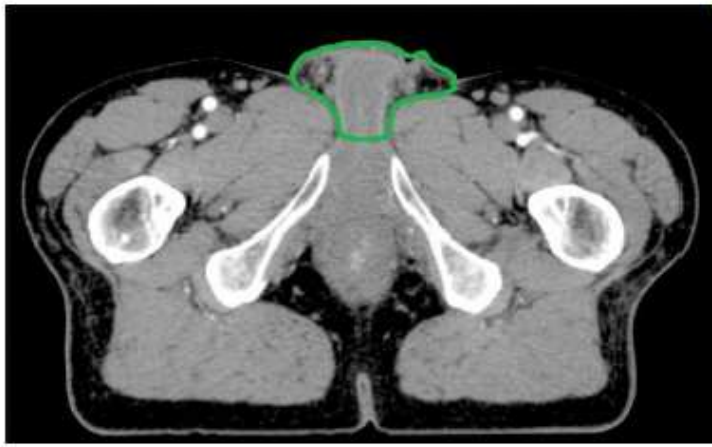


Inguinal nodes

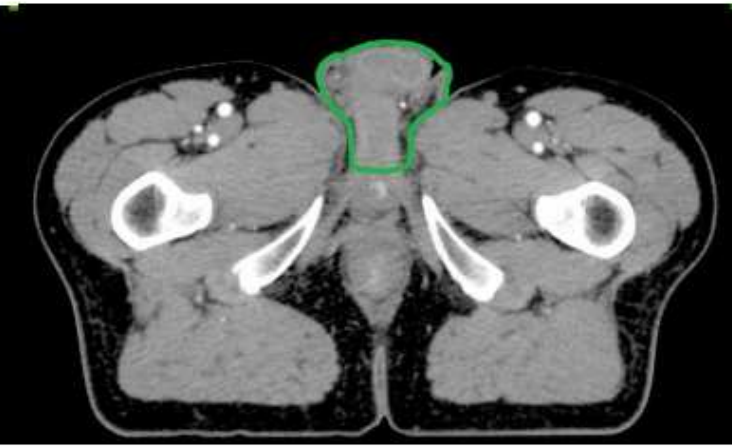


Male:

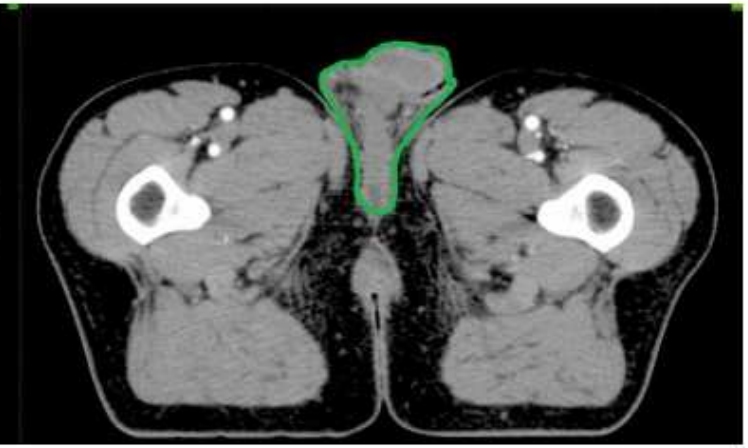
A



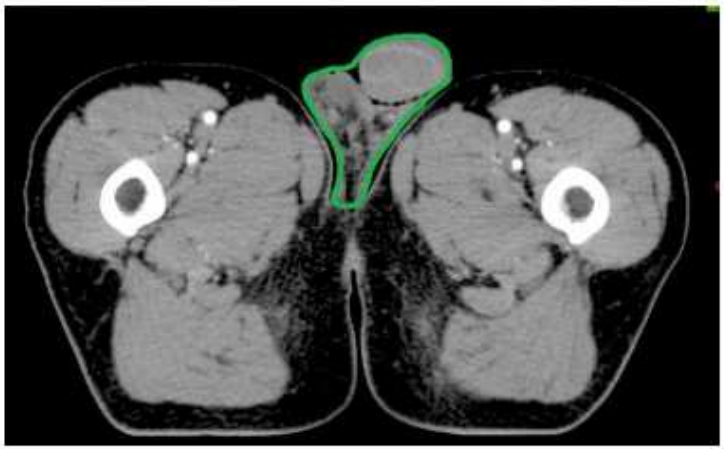
B



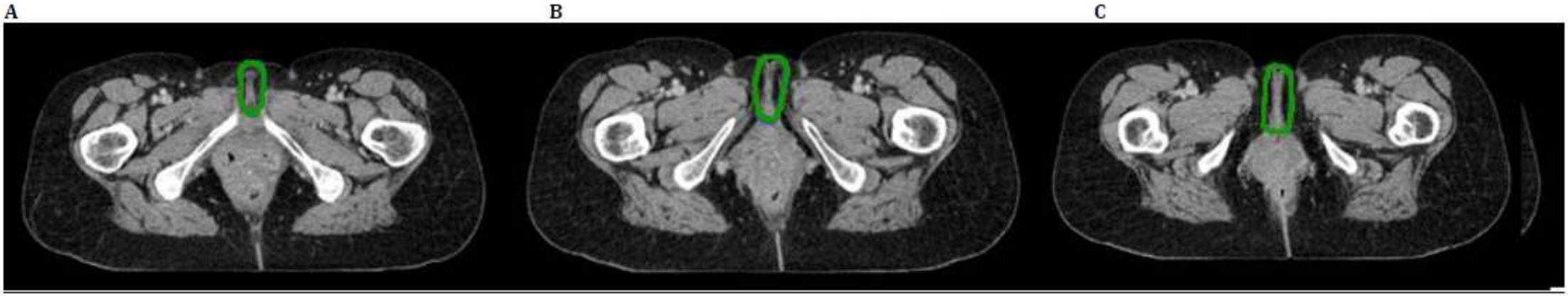
C



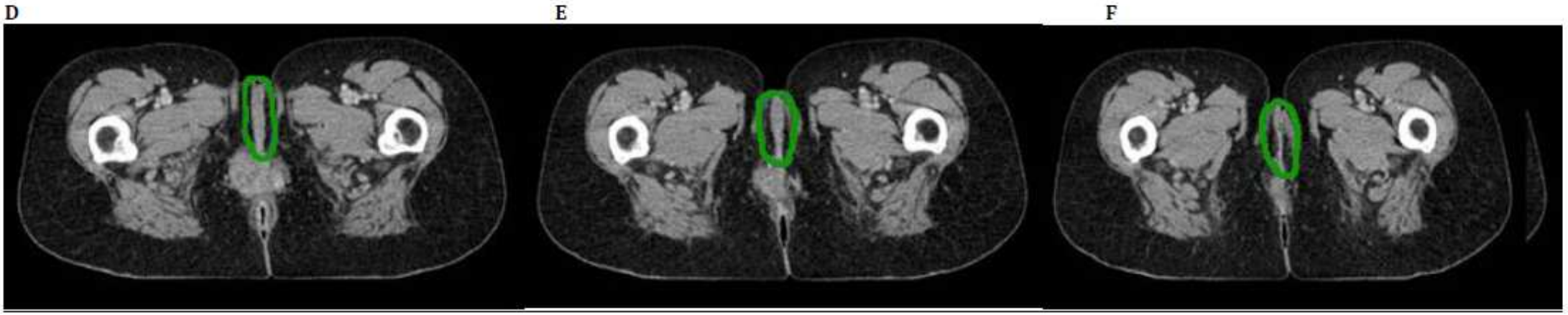
D



Female:



Superior slice: First image demonstrating the vulva mucosa (usually around the inferior border of the symphysis)



Inferior slice: Last slice where the vulva are visible.

Elective nodal volumes covered per stage of disease

- All nodal volumes should be covered for all stages
- **Exception:**

  cT1N0: the elective irradiation can be omitted of

  - inguinal nodes
  - high pelvic lymph nodes (caudal border of SI joint)

Delineation of primary tumor

STRUCTURE	MARGIN
GTV	Primary tumor, based on all available imaging
CTV	GTV + anal canal (anorectal junction – anal verge) + internal and external sphincters + 20 mm isotropic margin
PTV	5-10 mm (5-7 mm with daily IGRT)

Delineation of involved nodes

STRUCTURE	MARGIN
GTV	Involved node (MR registration)
CTV	Involved nodes or nodal region with 10-20 mm margin, respecting the anatomical boundaries
PTV	5-10 mm (5-7 mm with daily IGRT)

Therapeutic Schema

Dose prescription T1 /T2 N0 (and T2N1 at clinician's discretion)

- Elective (PTV_Elec) = 40 Gy in 28# (1.43 Gy per #) in 5.5 weeks
- Gross nodal disease (PTV_Nodes) = 50.4Gy in 28# (1.8Gy per #) in 5.5 weeks
- Gross anal disease (PTV_Anal) = 50.4 Gy in 28# (1.8 Gy per #) in 5.5 weeks

Dose prescription T3/4N0 or Tany N2/3 (and T2N1 at clinician's discretion)

- Elective (PTV_Elec) = 40 Gy in 28# (1.43 Gy per #) in 5.5 weeks
- Gross nodal disease (PTV_Nodes) = 50.4Gy in 28# (1.8Gy per #) in 5.5 weeks.
- Gross anal
- Disease (PTV_Anal) = 53.2 Gy in 28# (1.9Gy per #) in 5.5 weeks

Concurrent Chemotherapy

Concurrent chemotherapy should be prescribed in all patients that are considered fit for standard treatment.

Acceptable regimens are:

- Mitomycin 12mg/m2 Day 1 with 5FU 1000mg/m2 days 1-4 and day 29-32
- Mitomycin 12mg/m2 day 1 with Capecitabine 825mg/m2 BD on days of XRT.

Pre-Treatment

Patient Simulation and Immobilisation:

- Standard position: supine with immobilisation for popliteal fossa and feet
- Prior to pre-treatment scan, the clinician will assess the diagnostic imaging and ascertain whether the tumour is adequately bolused by the surrounding buttocks ie. 5mm of tissue surrounding GTV
- If there is not 5mm of tissue around whole GTV, tailored wax or sheet bolus should be considered in patients in whom additional bolus is required, this is more likely in ACT5 for nodal disease or larger primary tumours
- The distal point of macroscopic disease or anal verge will be wired prior to imaging, whichever is more inferior
- For tumours that have been excised, mark excision scar with radio-opaque marker where possible
- All patients must be scanned with a comfortably full bladder (>250mls)
- Strongly recommend the use of IV contrast to aid delineation of pelvic vessels
- The use of oral contrast is at the discretion of the site but may aid in delineation of small bowel
- Once patient is scanned, tattoo and document as per local protocol

Delineation

- If possible the diagnostic or planning MRI and PET/CT can be fused with planning CT: The treating consultant should review and approve the registration
- The GTV should be determined by the treating clinician using the planning CT, clinical data, MRI and PET/CT
- The borders of the GTV should not be defined using the PET/CT
- Principles of microscopic disease extent, in the vicinity of gross disease - There is no surgical data regarding the microscopic extent of anal cancer tumours. One study investigating a small number of SCC skin recommends CTV 11 mm for SCC <2 cm, and 14 mm for SCC > 2 cm [1]. We have therefore elected to have a smaller margin for early cancers (10mm) while using 15mm for locally advanced cancers

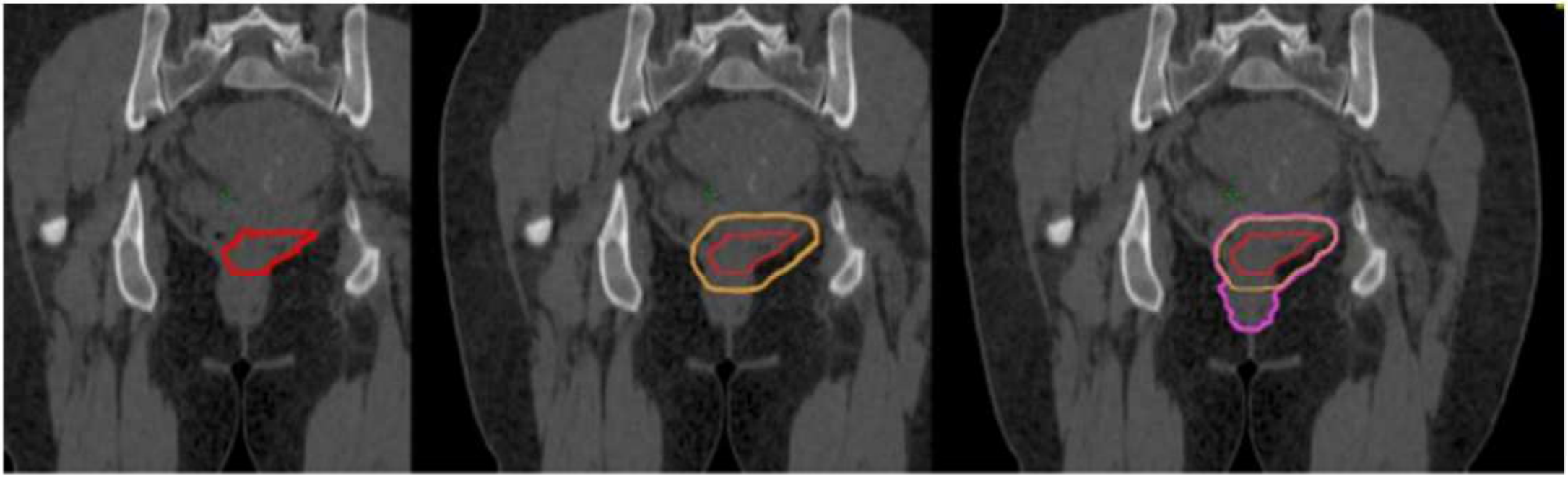
Volume Definitions

Good prognosis T1N0 Tumours

In small, good prognosis tumours it may be appropriate to offer CRT to the primary tumour plus a margin rather than deliver elective nodal irradiation. In these cases:

- **GTV_A** = Includes the gross primary anal tumour volume
- **CTV_A =** GTV_A + 10mm. Following this, manually enlarge to ensure coverage of entire anal canal including outer border, from the ano-rectal junction (approximately 4cm superiorly from anal verge identified by the radio-opaque marker) to the anal verge including the internal and external anal sphincters. Edit to exclude bone and muscle. (See Figure 1) Edit to exclude muscle and bone.
- **PTV_Anus** = CTV_A + 10mm

Example of a case with tumour extending into lower rectum aiming to demonstrate the steps to produce CTV_A.



3. ***To create GTV_A:*** ■
Draw the GTV_A using clinical findings, planning CT, diagnostic MRI.

2. ***To create GTV + margin:*** ■
Enlarge the GTV_A by the suggested margin (10mm for early tumours, 15mm for locally advanced).

1. ***To create CTV_A:*** ■
Enlarge the GTV + margin to incorporate the entire outer border of anal or rectal lumen around GTV, anal canal and anal verge including internal and external sphincters.

Early Tumours

GTV_A = Primary Tumour	**GTV_N** = Involved Nodes	
CTV_A = GTV_A + 5mm	**CTV_N** = GTV_N + 5mm	**CTV_ALL** = CTV_A + CTV_N + CTV_E
PTV_Anal = GTV_A + 10mm*	**PTV_Nodes** = GTV_N + 5mm*	**PTV_ELEC** = CTV_ALL + 5 mm

* These margins are appropriate for patients treated with daily online imaging. We recommend centres audit their local set up regularly.

Locally Advanced Tumours

GTV_A = Primary Tumour	**GTV_N** = Involved Nodes	
CTV_A = GTV + 15mm	**CTV_N** = GTV_N + 5mm	**CTV_ALL** = CTV_A + CTV_N + CTV_E
PTV_Anal = GTV_A + 10mm*	**PTV_Nodes** = GTV_N + 5mm*	**PTV_ELEC** = CTV_ALL + 5 mm

* These margins are appropriate for patients treated with daily online imaging. We recommend centres audit their local set up regularly.

Planning Parameters

Prescription Point - 100% to the median dose in PTV (ICRU 83)

Target coverage and OAR requirements, both objectives and mandatory constraints are documented on Anal IMRT planning sheet (Appendix 4).

Preferred priority of structures in planning

1) PTV's – these will always take priority over any OAR constraint.
2) Small bowel
3) Femoral Heads
4) Genitalia
5) Bladder

CASE

Female (°03/12/1951)

Problem: anal blood loss, general good condition

Clinical examination:
DRE: tumor palpable laterally at 5-6 o'clock, normal sphincter tone
No inguinal nodes palpable

CASE

Colonoscopy:

Tumor at anorectal junction

Pathology: squamous cell carcinoma, invasion cannot be assessd

ERUS:

Tumor 2,4 x 1,1 cm, invasion of internal anal sphincter

No invasion of the external anal sphincter

CASE

DW-MRI

Lesion at the anorectal verge, posteriorly and laterally located (left side)
Close proximity of the internal anal sphincter without invasion of the external sphincter
Necrotic, partly confluent nodes with extracapsular extension around the right internal iliac vessels

^{18}F-FDG PET/CT

Hypermetabolic lesion in the anal canal
Hypermetabolic nodes at the right internal iliac vessels
No hematogenous metastases

CASE

Treatment plan

cT2N2 SCC at anorectal junction

Chemoradiotherapy:

45 Gy/ 1,8 Gy on tumor and elective nodes

boost of 14,4 Gy/ 1,8 Gy on the macroscopic tumor and involved nodes

CI of 5-FU (225mg/m²/d) + mitomycine (10mg/m²) d1 and $d1_{boost}$

CASE

Female (°03/03/1968)

Problem: SCC of the anal canal, asymptomatic

Clinical examination:
DRE: small exofytic lesion of 7-8 mm at 12 o'clock, 5 mm from the internal anal sphincter, normal sphincter tone
No inguinal nodes palpable

CASE

Colonoscopy:

polipoid lesion of 1cm at the level of the linea dentata
Pathology: squamous cell carcinoma, invasion cannot be assessed

DW-MRI:

Diffusion restrictive lesion 37mm cranial from the anal verge, anteriorly and laterally located (right side). Not clearly visible on T1/T2-weighted images

^{18}F-FDG PET/CT:

Moderate to strong hypermetabolism at the level of the anal canal
No lymph nodes or hematogenous metastases

CASE

Treatment plan:

cT1N0M0 SCC at the level of the linea dentata

Chemoradiotherapy:

45 Gy/ 1,8 Gy on pelvis posterior

CI of 5-FU (225mg/m²/d) + mitomycine (10mg/m²) d1

Treatment planning: state of the art II (Anal cancer)

C. Fiorino

Medical Physics

San Raffaele Institute, Milano, Italy

OSPEDALE SAN RAFFAELE

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Summary

Techniques for external beams optimization:

- 3DCRT
- IMRT (vs 3DCRT)
- Rotational techniques (IMAT/VMAT, Tomotherapy)
- Sequential and simultaneous boosting
- IGRT and potentials for plan adaptation

- Sparing bowel and bladder
- Sparing bone marrow (haematological tox)
- Sparing genitalia

- Conclusive remarks

Summary (addition peculiar to anal cancer…)

Techniques for external beams optimization:

- 3DCRT
- IMRT (vs 3DCRT)
- Rotational techniques (IMAT/VMAT, Tomotherapy
- Sequential and simultaneous boosting
- IGRT and potentials for plan adaptation

Peculiar issues with respect to rectal ca

- Sparing bowel and bladder
- Sparing bone marrow (haematological tox)
- Sparing genitalia
- Skin toxicity

- Conclusive remarks

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Pelvic OARs constraints: Main References

Systematic review

Dose–volume effects for normal tissues in external radiotherapy: Pelvis

Claudio Fiorino [a,*], Riccardo Valdagni [b], Tiziana Rancati [b], Giuseppe Sanguineti [c]

[a] Medical Physics Department, San Raffaele Scientific Institute, Milan, Italy
[b] Prostate program, Scientific Directorate Fondazione IRCCS – Istituto Nazionale dei Tumori, Milan, Italy
[c] Radiotherapy Department, The John Hopkins University, Baltimore, MD, USA

Radiother. Oncol. 2009

QUANTEC, IJROBP 2010

QUANTEC: ORGAN-SPECIFIC PAPER **Pelvis: Rectum**

RADIATION DOSE–VOLUME EFFECTS IN RADIATION-INDUCED RECTAL INJURY

Jeff M. Michalski, M.D.,* Hiram Gay, M.D.,* Andrew Jackson, M.D.,† Susan L. Tucker, Ph.D.,† and Joseph O. Deasy, Ph.D.*

QUANTEC: ORGAN-SPECIFIC PAPER **Pelvis: Bladder**

RADIATION DOSE–VOLUME EFFECTS OF THE URINARY BLADDER

Akila N. Viswanathan, M.D., M.P.H.,* Ellen D. Yorke, Ph.D.,† Lawrence B. Marks, M.D.,† Patricia J. Eifel, M.D.,‡ and William U. Shipley, M.D.¶

QUANTEC: ORGAN-SPECIFIC PAPER **Pelvis: Penile Bulb**

RADIATION DOSE–VOLUME EFFECTS AND THE PENILE BULB

Mack Roach, III, M.D., FACR,* Jiho Nam, M.D.,† Giovanna Gagliardi, Ph.D.,‡ Issam El Naqa, Ph.D.,§ Joseph O. Deasy, Ph.D.,§ and Lawrence B. Marks, M.D.†

Predicting toxicity in radiotherapy for prostate cancer

Valeria Landoni [a], Claudio Fiorino [b], Cesare Cozzarini [c], Giuseppe Sanguineti [d], Riccardo Valdagni [e,f,g], Tiziana Rancati [e,*]

[a] Medical Physics, Istituto Nazionale Tumori Regina Elena, Rome, Italy
[b] Medical Physics, Raffaele Scientific Institute IRCCS, Milan, Italy
[c] Radiotherapy, Raffaele Scientific Institute, Milan, Italy
[d] Radiotherapy, Istituto Nazionale Tumori Regina Elena, Rome, Italy
[e] Prostate Cancer Program, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[f] Radiation Oncology 1, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[g] Clinical Sciences and Community Health, University of Milan, Milan, Italy

Physica Medica (EJMP), Landoni et al. 32: 521-532, 2016 (update of the period 2009-2016)

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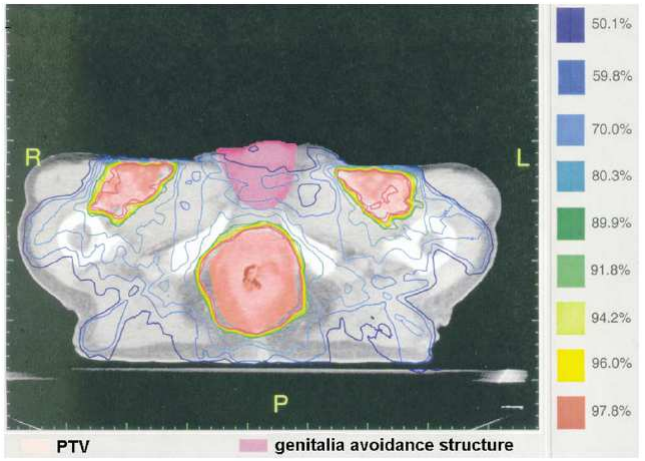
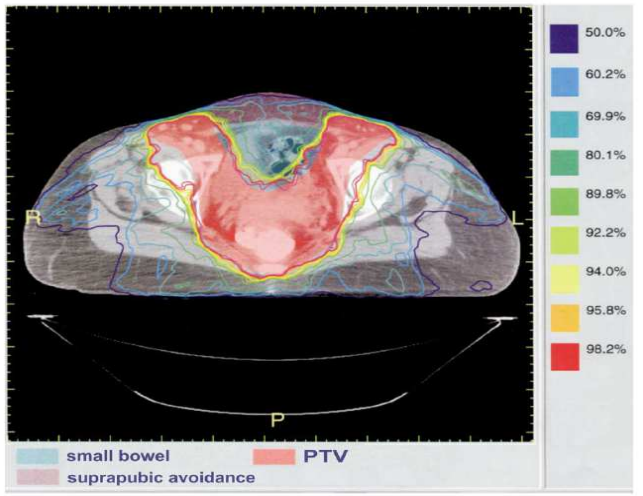
IMRT (vs 3DCRT)

- Differently from rectal ca.: larger volumes, more caudal border, (generally) higher doses, (always) concomitant to CHT, more complex shape, more concavity of PTV
- 3DCRT: very large incidence of severe acute tox (mainly skin, GI, hematological) and treatment breaks
- In the early 2000, several planning studies demonstrated a large gain of (sub-optimal*) IMRT vs 3DCRT (Moran 2004, Chen 2005, Milano 2005, Menkarios 2007)
- Largest sparing for genitals and bowel





Milano 2005

* Few segments, manual optimization, few fields, not stressing modulation….

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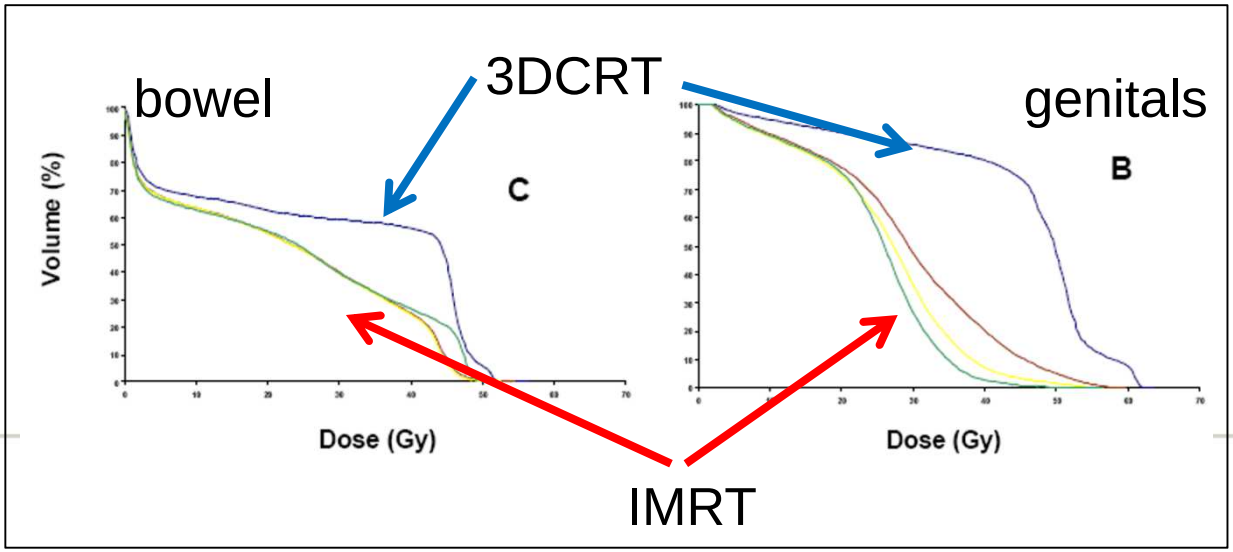
IMRT (vs 3DCRT)

Table 3. Volume of critical structures receiving greater than the threshold dose for 45 Gy treatment

Organ	Threshold dose (Gy)	Volume above threshold (%)			*p* values*		
		AP/PA†	AP/PA§	IMRT	AP/PA† vs. AP/PA‡	AP/PA† vs. IMRT	AP/PA‡ vs. IMRT
Small bowel	30	91.4 ± 7.9	87.4 ± 10.1	54.1 ± 7.2	NS	<0.00002	0.0001
	40	87.7 ± 11.1	40.4 ± 25.0	24.3 ± 9.7	0.003	0.0001	NS
Bladder	30	100 ± 0	100 ± 0	92.1 ± 12.3	NS	NS	NS
	40	100 ± 0	99.3 ± 1.5	44.3 ± 17.8	NS	0.0002	0.0002
Genitalia/perineum	30	95.4 ± 4.3	95.6 ± 4.0	52.4 ± 31.5	NS	0.008	0.009
	40	85.7 ± 9.8	85.7 ± 9.5	5.0 ± 5.2	NS	<0.00001	<0.00001
Iliac bone marrow	10	59.4 ± 11.8	58.3 ± 11.9	72.7 ± 16.0	NS	0.004	0.004
	20	52.9 ± 11.7	48.9 ± 14.5	58.9 ± 12.1	0.0002	NS	0.04

Abbreviations as in Table 2.
Mean ± standard deviation.
* Two-tailed paired *t*-test.
† No field reduction.
‡ Field reduction to sacroiliac joint after 30.6 Gy as described in the text.

Milano 2005



Menkarios 2007

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IMRT (vs 3DCRT)

- Evidence that IMRT reduces toxicity compared to 3DCRT
- Reduction of treatment breaks
- Institutional series & Phase II studies (Salama 2007, Tsai 2006, Meyer 2008, Pepek 2010, Bazan 2011, Kachnic 2013, Janssen 2014)

Table 5 Comparisons of acute treatment-related adverse events*

Adverse events	0529 (n=52)	98-11 (Arm 1†) (n=325)	*P* value (1-sided proportions test§)
Grade 2+			
GI/GU‡	40 (77%)	249 (77%)	.50
Derm	39 (75%)	271 (83%)	.10
GI	38 (73%)	237 (73%)	.50
GU	8 (15%)	66 (20%)	.18
Heme	38 (73%)	275 (85%)	.032
Overall	49 (94%)	318 (98%)	.12
Grade 3+			
GI/GU	11 (21%)	120 (37%)	.0052
Derm	12 (23%)	159 (49%)	<.0001
GI	11 (21%)	117 (36%)	.0082
GU	1 (2%)	11 (3%)	.32
Heme	30 (58%)	201 (62%)	.29
Overall	43 (83%)	283 (87%)	.23

Abbreviations: GI = gastrointestinal; GU = genitourinary; Derm = dermatologic; Heme = hematologic.

EDITORIAL

RTOG 0529: Intensity Modulated Radiation Therapy and Anal Cancer, a Step in the Right Direction?

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Table 2. Comparison of Treatment Breaks, Toxicity, and Outcome in Patients With Squamous Cell Carcinoma of the Anus Treated With IMRT

	Bazan (N=46)	Salama (N=53)	Pepek (N=29)[a]
Median follow-up, mo	32 (IMRT) 26 (CRT)	14.5	19
Treatment breaks, %	34.5 (IMRT) 88.0 (CRT)	41.5	NR[b]
Acute GI toxicity, grade 3-4, %	7 (IMRT) 29 (CRT)	15.1	10
Acute skin toxicity, grade 3-4, %	21 (IMRT) 41 (CRT)	37.7	0
Acute hematologic toxicity, grade 3-4, %	21 (IMRT) 29 (CRT)	58.5	24
Overall survival, %	88 (3 y) IMRT	93.4 (1.5 y)	100 (2 y)
LRC, %	92 (3 y) IMRT	83.9 (1.5 y)	95 (2 y)
CFS, %	91 (3 y) IMRT	83.8 (1.5 y)	91 (2 y)

IMRT indicates intensity-modulated radiotherapy; CRT, conventional radiotherapy; NR indicates not reported; GI, gastrointestinal; LRC, locoregional control; CFS, colostomy-free survival.
[a] Includes only patients with squamous histology.
[b] Reports a value of 18% for all patients but not separately for patients with squamous histology.

Kachnic 2013 (RTOG0529: 45Gy elective nodes; 50.4-54 GTV + 5FU/MMC)

Bazan 2011

ESTRO School

IMRT (vs 3DCRT)

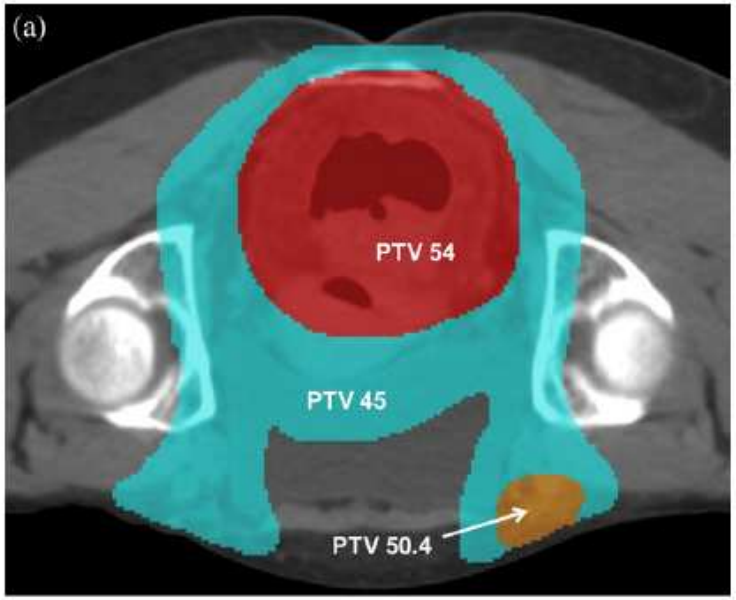


Table 1 Dose-painted intensity modulated radiation therapy dose constraints for normal tissues

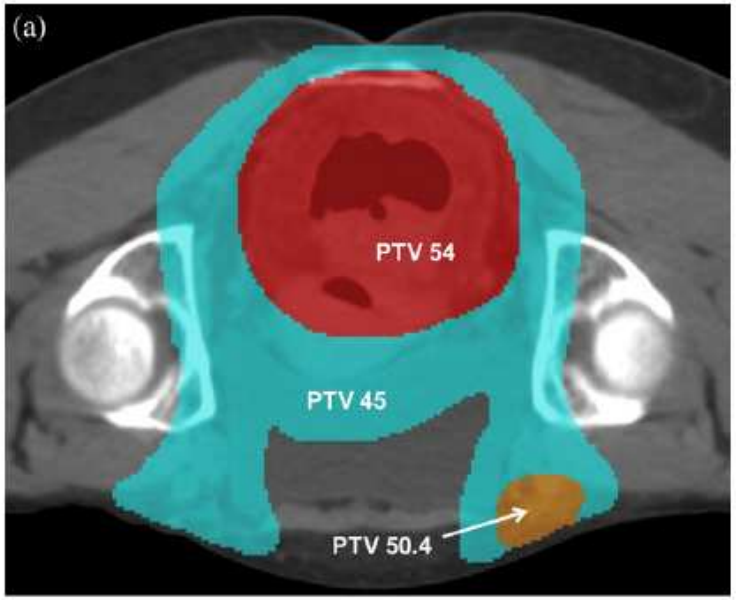
Organ	Dose (Gy) at <5% volume	Dose (Gy) at <35% volume	Dose (Gy) at <50% volume
Small bowel*,†	45 (<20 cc)	35 (<150 cc)	30 (<200 cc)
Femoral heads*	44	40	30
Iliac crest	50	40	30
External genitalia	40	30	20
Bladder	50	40	35
Large bowel†	45 (<20 cc)	35 (<150 cc)	30 (<200 cc)

Organs are listed in order of decreasing priority.
* Assigned criteria for major and minor violations; major violations were considered as part of the feasibility secondary endpoint.
† Dose constraints based on absolute volume instead of % volume.

Kachnic 2013

- IMRT «must» be the standard (!)
- Are we next to «the limit» ?

IMRT (vs 3DCRT)



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† Dose constraints based on absolute volume instead of % volume.

Kachnic 2013

- IMRT «must» be the standard (!)
- Are we next to «the limit» ?

Skin «constraints» ?

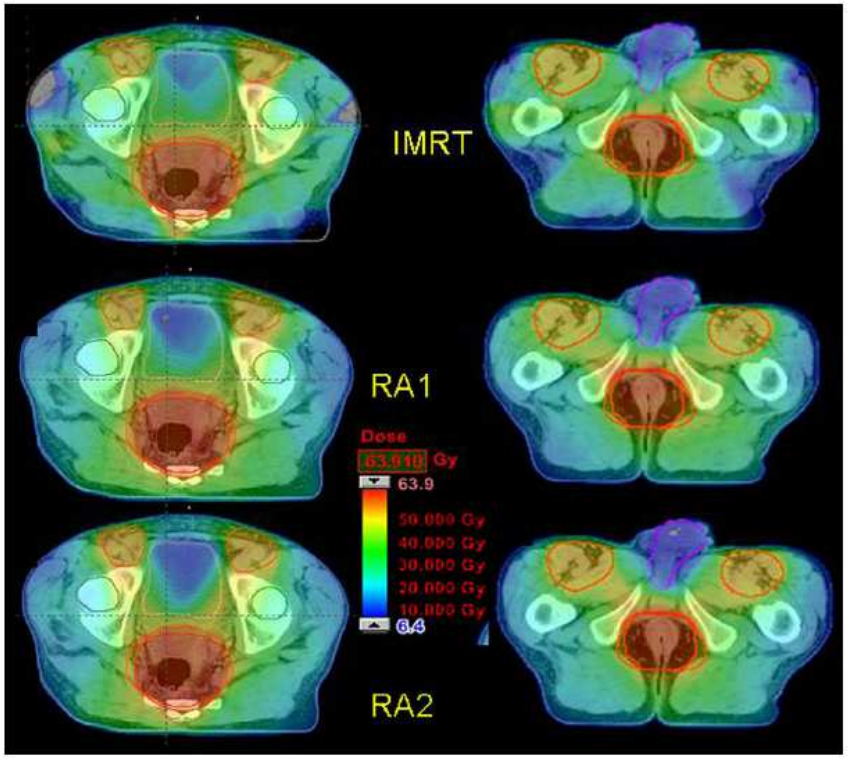
Rotational IMRT

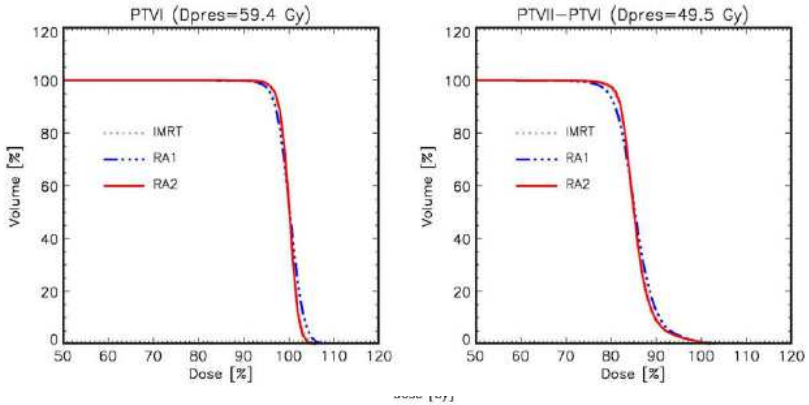
- ...PROBABLY NOT YET !

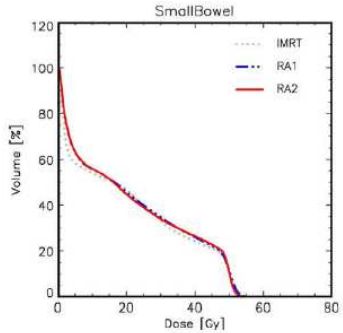
ESTRO School

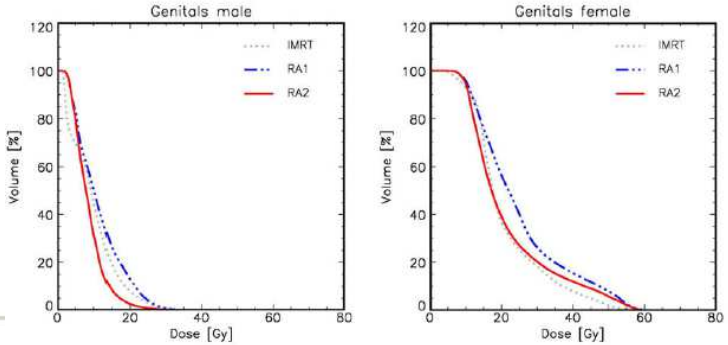
Improving IMRT in anal cancer: Rotational

- RA vs 7-9 fields IMRT (Clivio 2009, Vieillet 2010)
- One single arc detrimental ☹
- Two arcs similar or better than IMRT







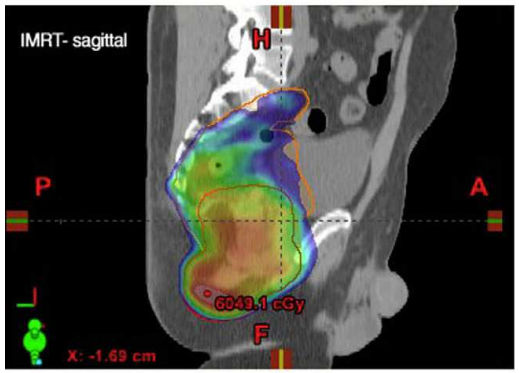


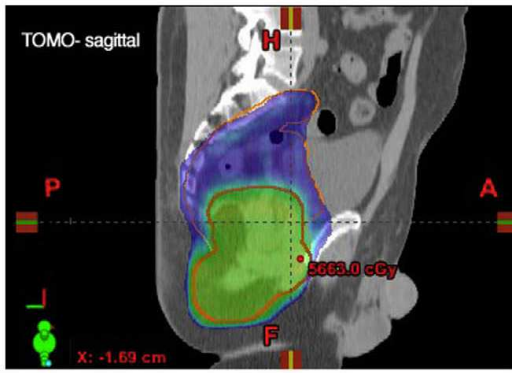
Clivio 2009

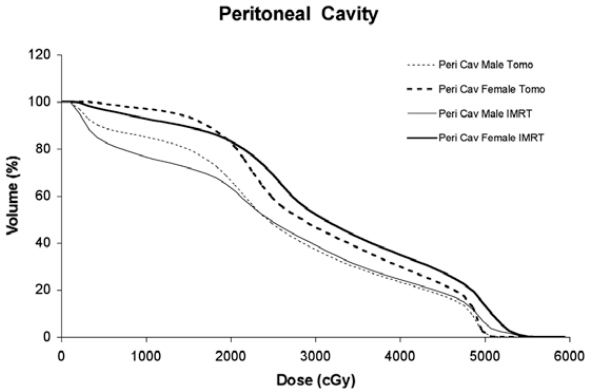
ESTRO School

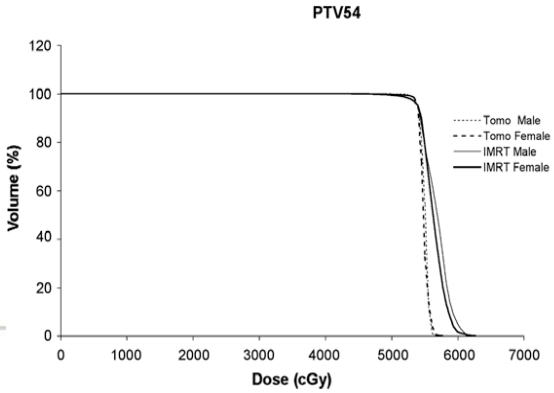
Improving IMRT in anal cancer: Rotational

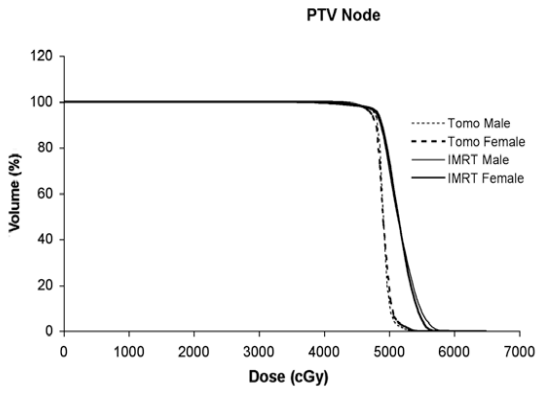
- Better sparing of bowel, genitals, bladder with Tomotherapy vs 9-fields IMRT
- More homogenous dose distribution (and improved conformality)
- More efficient e fast delivery (valid for all rotational techniques, still more for IMAT/VMAT/RA)

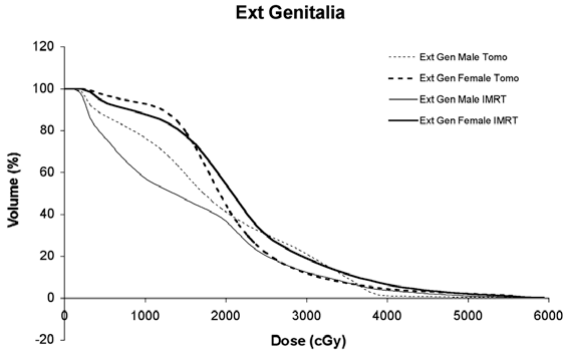












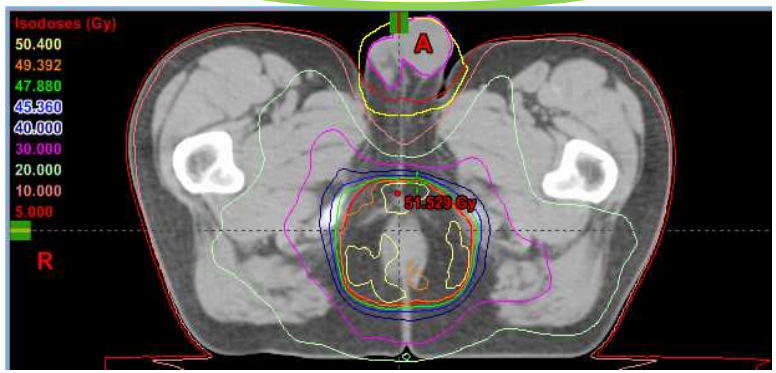
Joseph 2010

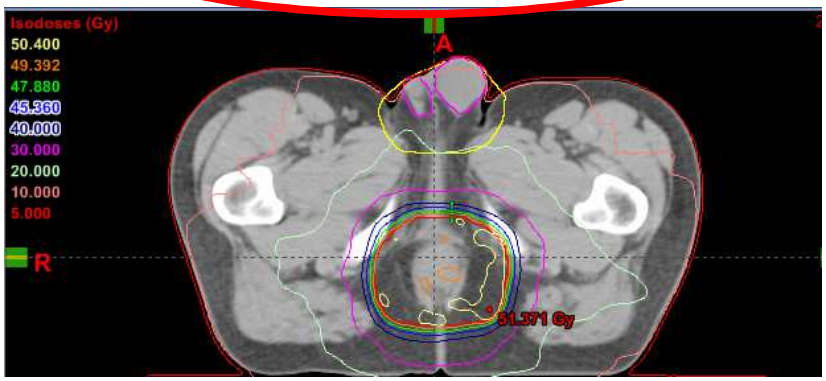
ESTRO School

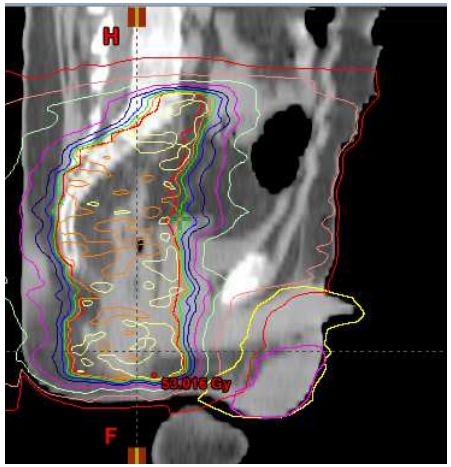
Improving IMRT in anal cancer: sparing genitals

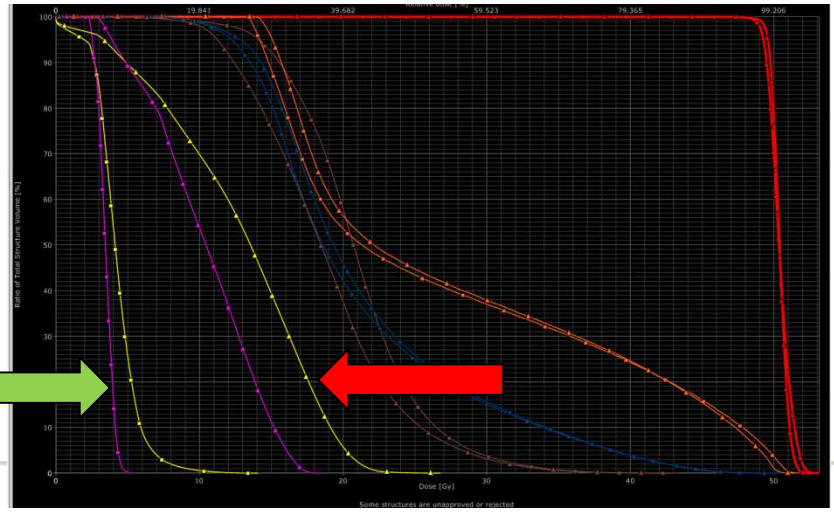
- Explicit inclusion in optimization

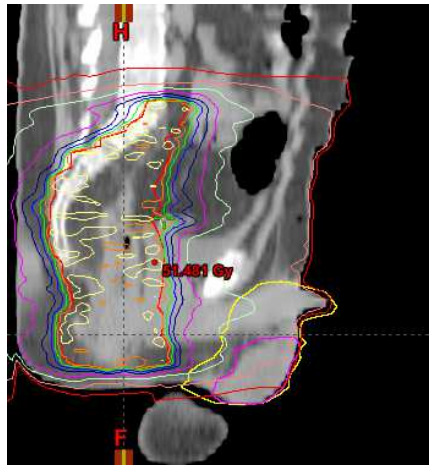
Not included







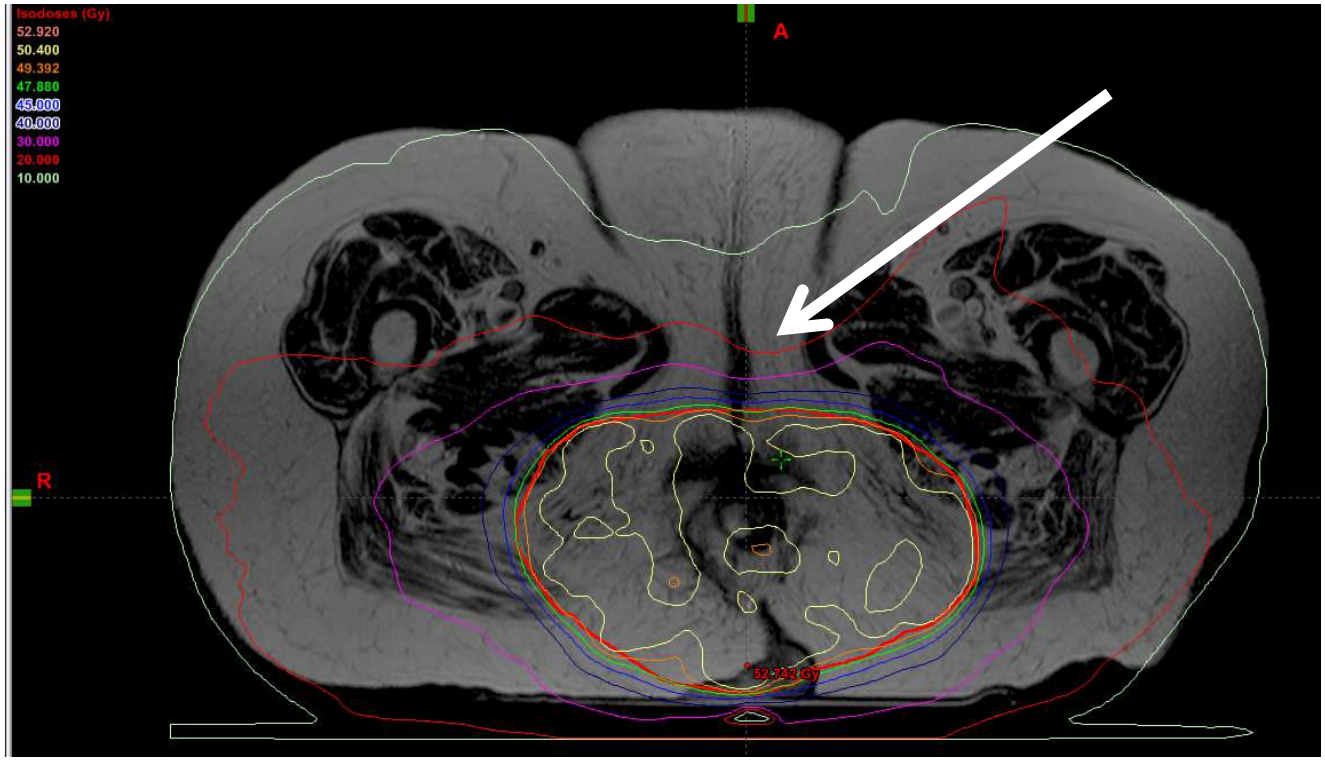




ESTRO School

Improving IMRT in anal cancer: sparing genitals

- «Stressing» the dose to genitals (sexual dysfunctions among the most relevant late effects): limitations when inguinal nodes need to be irradiated (?)
- Limits not yet fully explored (i.e.: rotational techniques with blocking, protons ?)



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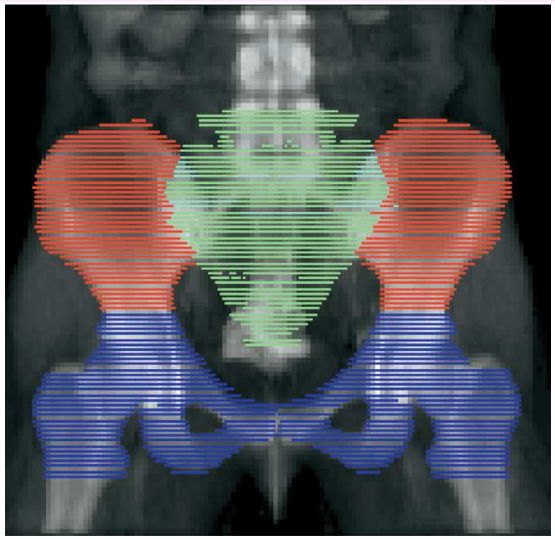
IMRT to spare bone marrow ?

- Acute Hematological is relevant for anal ca RT
- Evidence of dose-volume effects for the pelvic bone marrow in rectal and anal canal ca. with 3DCRT (Mell 2007)
- V40 more predictive (Mell 2008), very few recent updates (Franco 2016, Julie 2016)
- BM-sparing planning for anal cancer rarely reported .....potential interplay with bowel/bladder sparing (?)



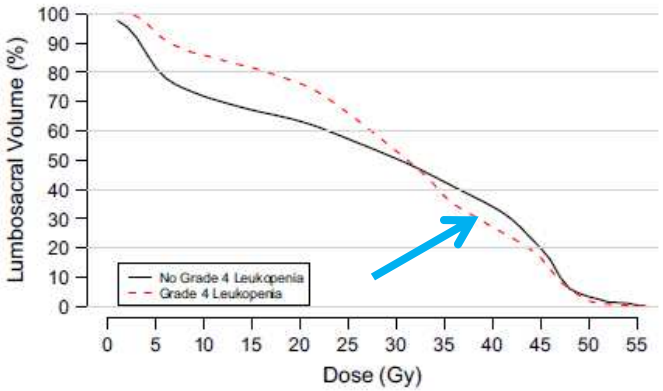


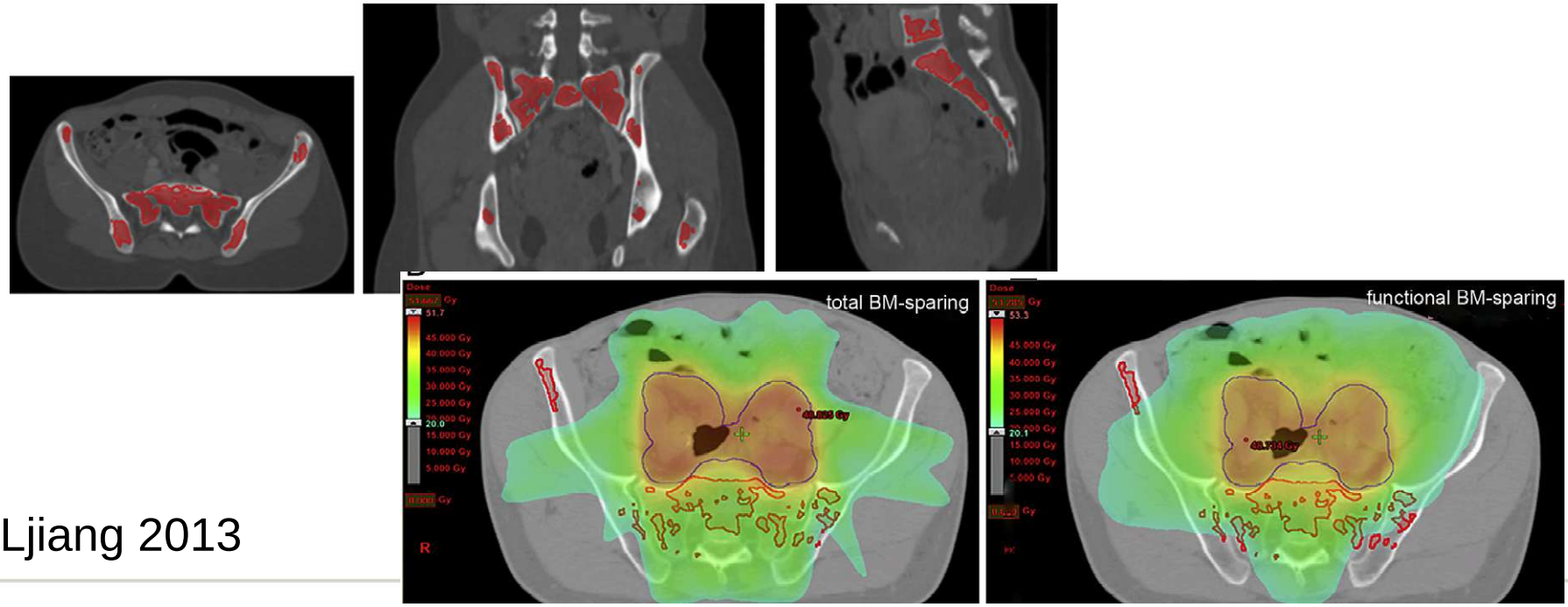
Fig. 2. Lumbosacral bone marrow dose-volume histograms for patients with (n = 14) and without (n = 34) Grade 4 leukopenia. p = 0.62 for comparison of area under the curve, $p < 0.05$ for comparison of area under the curve from 0 to 20 Gy (Mann-Whitney U test).

Mell 2008

ESTRO School

IMRT to spare bone marrow ?

- Pilot trial sparing active bone marrow (19 gyno, 12 anal ca pts)
- PET FDG +/- quantitative MRI (fat fraction map)
- Not large differences if sparing functional vs total BM
- Promising early results (3/10 grade 3 vs 9/19); phase II trial in progress



Ljiang 2013

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Protons to spare bone marrow ?

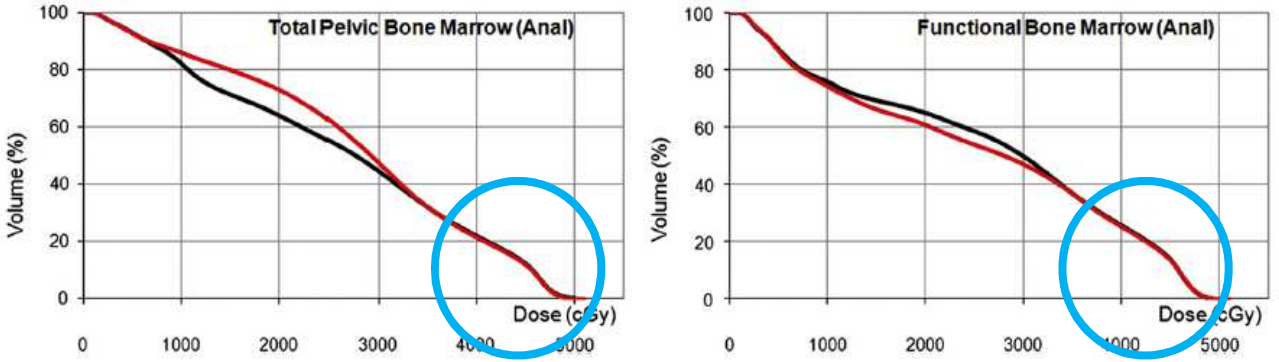
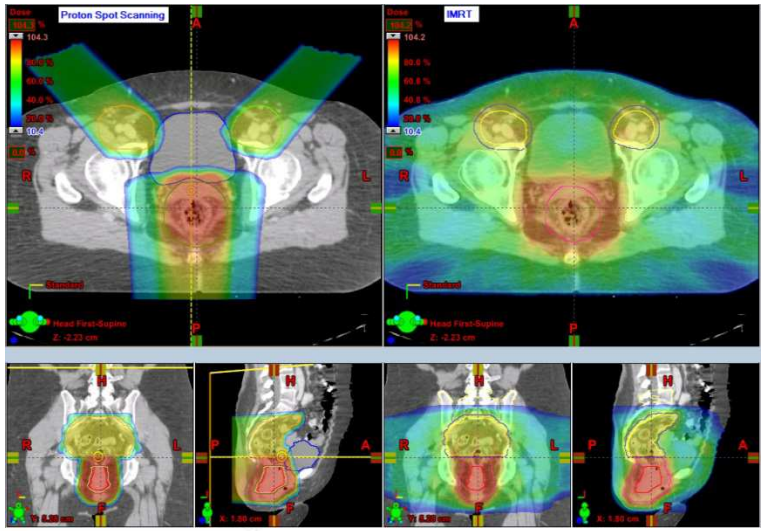


Fig. 2. Mean bone marrow (BM) dose-volume histograms for functional BM-sparing intensity modulated radiation therapy (IMRT) plans (red lines) vs total BM-sparing IMRT plans (black lines), by disease site.

Ljiang 2013
X-Rays IMRT

- Scanning protons vs IMRT
- Major gains for intermediate-low dose levels
- Benefit to be proven



Dose volumes[a]	IMRT[b]	Proton therapy[b]	*P* value
Bone Marrow			
V10	84 (79–90)	37 (31–43)	.008
V20	75 (66–81)	31 (26–38)	.008
V30	52 (42–63)	27 (22–33)	.008
V40	21 (11–33)	17 (9–21)	.055

Anand 2016

ESTRO School

Improving IMRT in anal cancer: skin tox

- Reducing skin toxicity ? (Joseph 2015)

Study	Ajani et al. [2] - RTOG 9811	Milano et al. [12]	Salama et al. [13]	Kachnic et al. [9] -RTOG 0529	Han et al. [8]	Current study
No. of patients	324	13	53	52	58	57
RT technique	3D-CRT	IMRT	IMRT	DP-IMRT	IMRT	HT
Target	Phase1: pelvis, perineum, inguinal nodes, anus sup border at L5/S1& inf border 2.5cm below anus Phase2: sup border reduced to bottom of SI joint Phase3 Boost: Tumor/Node +2-2.5cm	Phase1: pelvic field: GTV + all regional nodes, sup border 1cm below L5-S1 Phase2 boost: GTV +1cm	CTV: GTV and areas at risk (nodal region) +1cm PTV: CTV +1cm	CTV_T: GTV +2.5cm CTV_N: GTV +1cm PTV: CTV +1cm	CTV_T: GTV +1.5cm sup/inf & 1cm radially PTV_T: CTV +7mm CTV_{N0}: Vessel +1.5-2cm; CTV_{N+}: Node +1cm PTV: CTV +7mm	CTV_T/N+ve: GTV +1-1.5cm PTV_T: CTV_T/N+ve +1cm CTV_{N0}: Vessel +7mm PTV_N: CTV_{N0} +1cm
Dose	Phase1: 30.6Gy/17fr Phase2: 14.4Gy/8fr Phase3 boost: 10-14Gy/5-7fr	Phase1: 45Gy/25fr Phase2: 9Gy/5fr	Phase1: 45Gy/25fr Phase2: 9Gy/5fr	T2N0: 42Gy to PTV_{N0} & 50.4Gy to PTV_T /28fractions T3-4N0-3: 45Gy to PTV_{N0}; 50.4Gy to PTV_N <3cm & 54Gy to PTV_N >3cm; 54Gy to PTV_T	T1: 45Gy/25fr T2 (2.1-4cm): 54Gy/30fr T2-4(>4cm): 63Gy/35fr N0: 27Gy/15fr N+ve: 58.5-63Gy/35fr	PTV_T: 54Gy/30fr PTV_{N0}: 45Gy/30fr
Percent of patients with acute toxicity scores (%)						
Gastrointestinal Grade 2 Grade ≥3	 38% 35%	 69% 0%	 57% 15%	 52% 21%	 59% 9%	 53% 18%
Dermatologic Grade 2 Grade ≥3	 35% 48%	 100% 0%	 55% 38%	 52% 23%	 45% 47%	 60 % 11 %
Hematologic Grade 2 Grade ≥3	 23% 61%	 15% 69%	 21% 59%	 15% 58%	 26% 40%	 26 % 46 %
Genitourinary Grade 2 Grade ≥3	 19% 3%	 0% 0%	 11% 0%	 13% 2%	 19% 0%	 14 % 4 %

?

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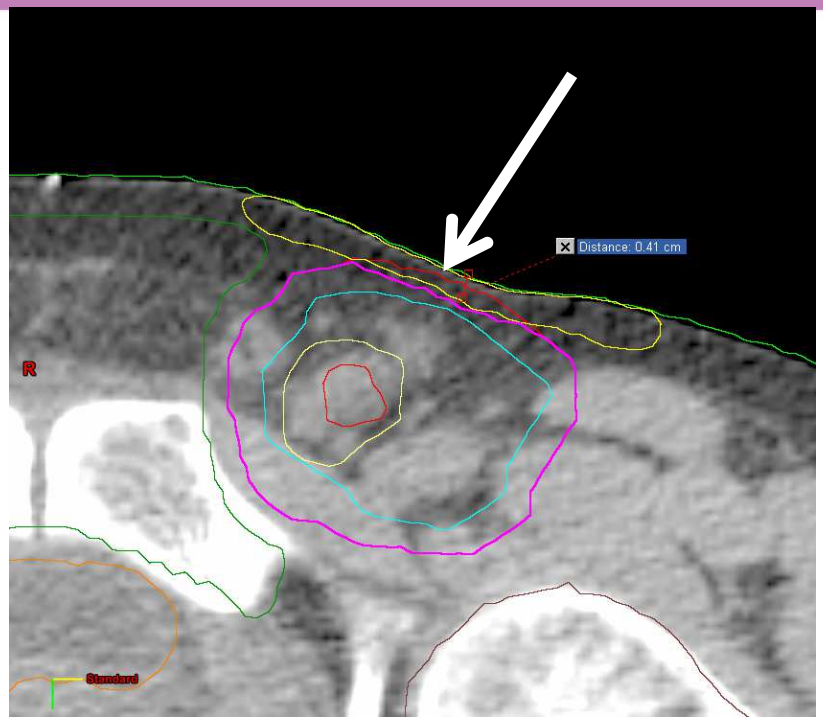
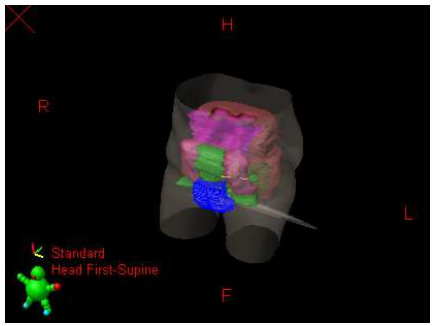
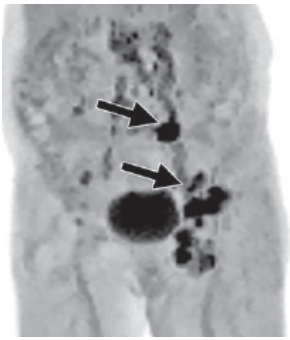
Improving IMRT in anal cancer: skin tox

- Rotational technique may help (better conformality)
- Explicit inclusion of constrained «skin region» & PTV corrections near the skin….(be careful…)
- Role of IGRT
- Impact of bolus
- Inguinal nodes vs no inguinal node (role of sentinel lymphonode, PET imaging…)







Joseph 2015 «…. PTV45 volumes were limited to 3–5 mm from the skin surface. Bolus was used for 4 patients with perianal extension.»

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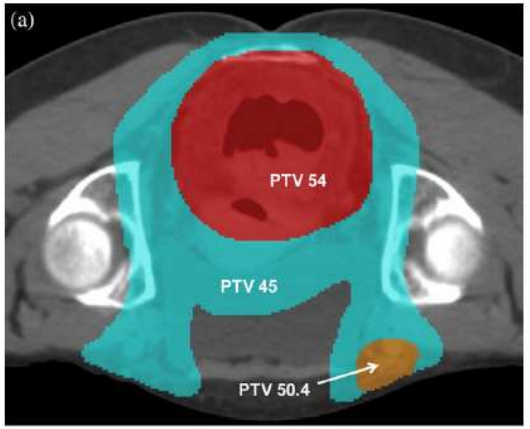
Conclusive remarks

- IMRT should be «mandatory»
  (better sparing of OARs, better conformation)
- Quite strong evidence of clinical benefit using IMRT
- Rotational IMRT (VMAT/IMAT/RA…., Tomo) highly effective and fast, better conformality and, sometime, better OAR sparing
- Potential of IMRT not yet fully assessed, in particular for improving the sparing of genitals and bone marrow (a Phase II trial in progress)
- Skin toxicity could be reduced (very sensitive to CTV/PTV definition, planning strategies)
- IGRT /ART (?)

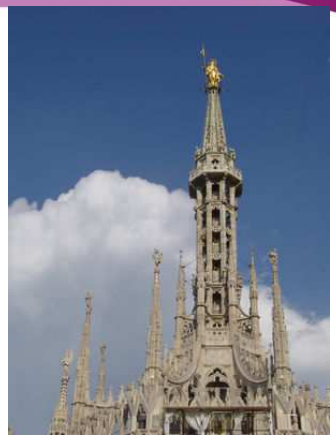


Thanks for your attention

- Thanks

P. Passoni, N. Slim (Radiotherapy)

S. Broggi, R. Raso, C. Sini (Medical Physics)



OSPEDALE SAN RAFFAELE

ESTRO School

Dose constrains for organs at risk, acute/late toxicity, supportive treatment during RT

Maria Antonietta Gambacorta

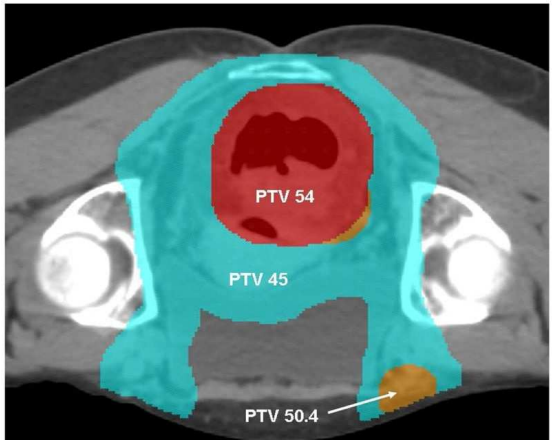
Radiotherapy Department

Fondazione Universitaria Policlinico A. Gemelli

Anal cancer treatment

Exclusive chemoradiation

- Large volumes
- Myelotoxic conc CT (mytomicin or cisplatin +5FU)
- High doses
- OAR surrounded by PTV (horse-shoe shape)
- Brachitherapy



Toxicity

- GI and GU
- Bone marrow
- Skin and external genitalia
- BT→Anal stenosis/necrosis

Bone marrow

- RT-CT ≈ **60% Haematological Toxicity (HT)**

- **Dose constraints:**
  - Iliac crests: V50< 5%, V40 <35%, V30 < 50%
    (RTOG 0529 G3+ HT 57%)

- **Bone marrow in the flat bones**
  - ≈ 50% in the pelvis
  - Red BM (active); Yellow BM (inactive)

Kachnich LA et al Int J Radiat Oncol Biol Phys 2012

Bone marrow

What happens during radiotherapy?

RT effect on BM

Fat composition **changes** during RT

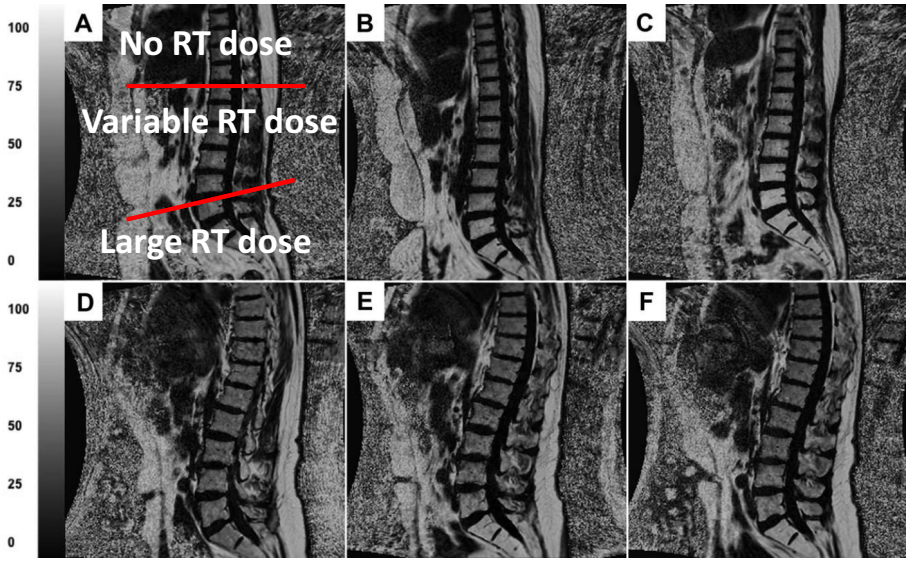
MR

PRE **DURING** **AFTER**

C3-T9

T10-L3

L4-S2



High myelotoxic (anal, cervix)

Low myelotoxic (prostate, rectum)

↑Proton Density Fat Frantion (PDFF)→ Yellow BM

Carmona R et al Int J Radiat Oncol Biol Phys 2014

RT effect on BM

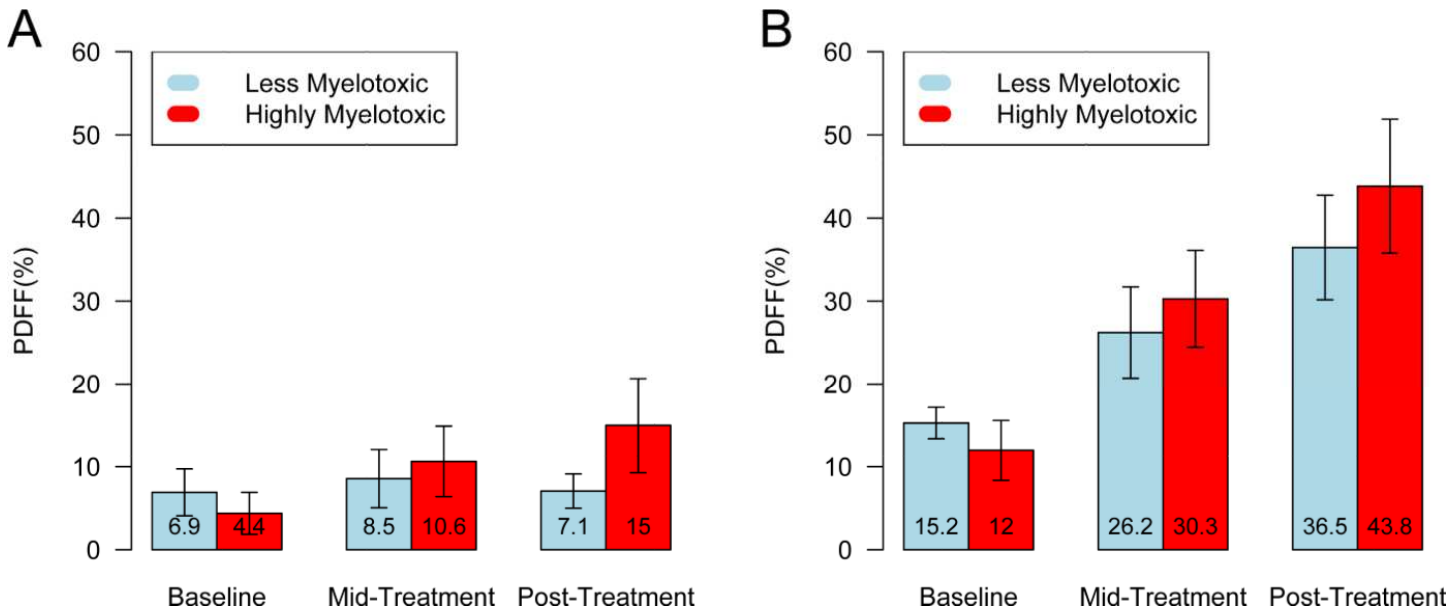


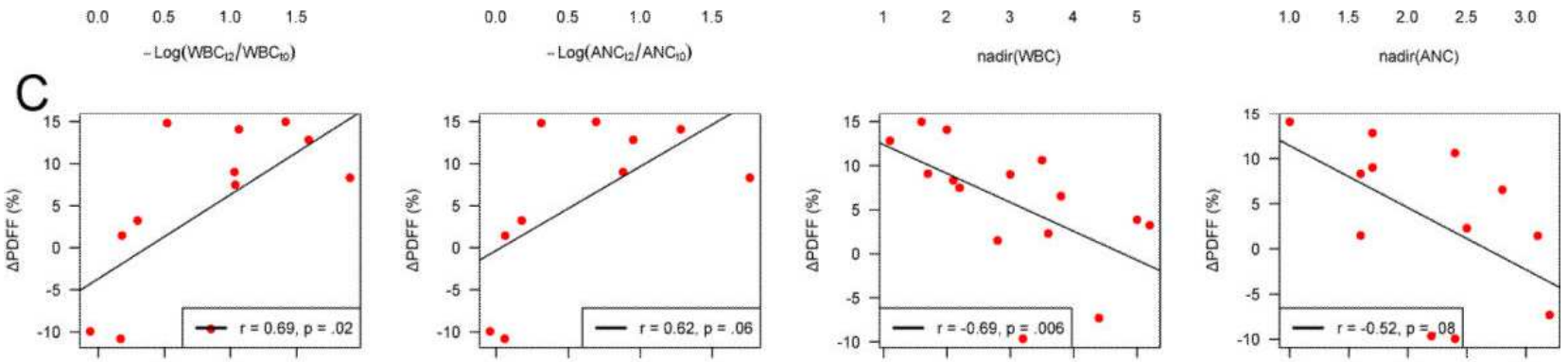
Fig. 2.
Bar plots of the mean difference (95% confidence intervals) in proton density fat fraction (PDFF(%)) for (A) T10-L3 and (B) L4-S2 relative to C3-T9, by treatment group and visit. PDFF(%) values are labeled within bars.

PDFF → 0.43% per Gy

Carmona R et al. Int J Radiat Oncol Biol Phys 2014

RT effect on BM

Bone Marrow composition → peripheral blood count cell count



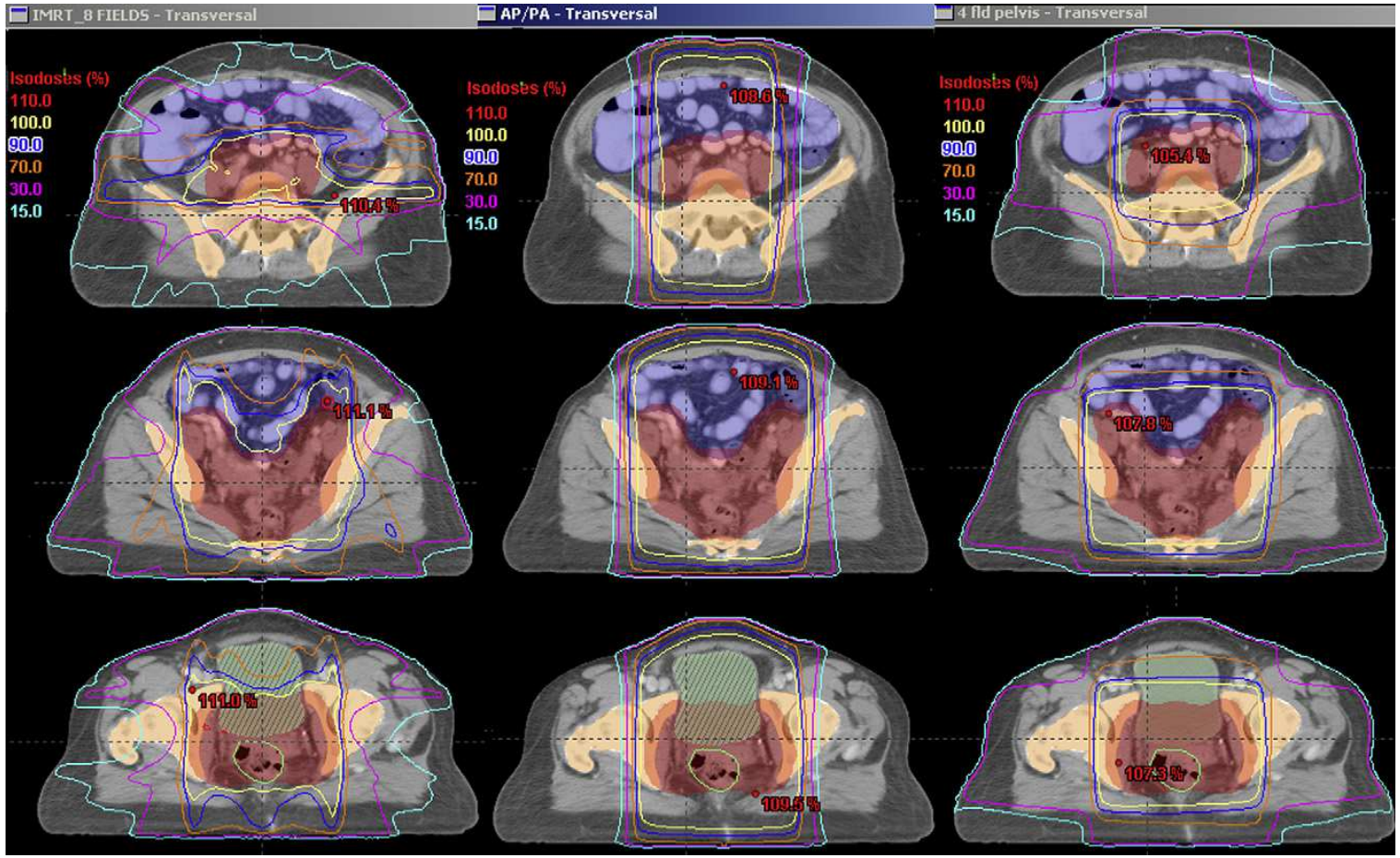
Increasing PDFF %→ decreasing WBC and ANC

Carmona R et al. Int J Radiat Oncol Biol Phys 2014

Bone Marrow

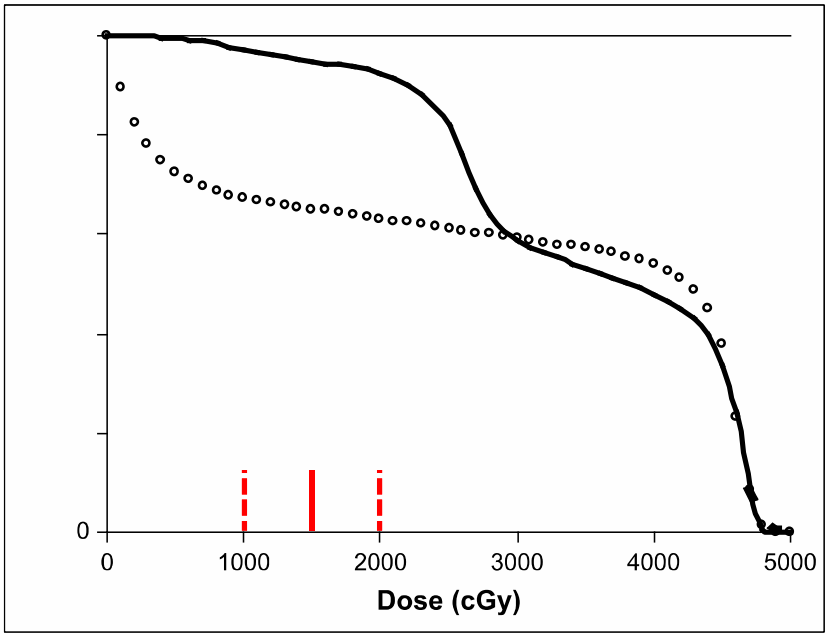
How to reduce dose?

BM and RT Technique

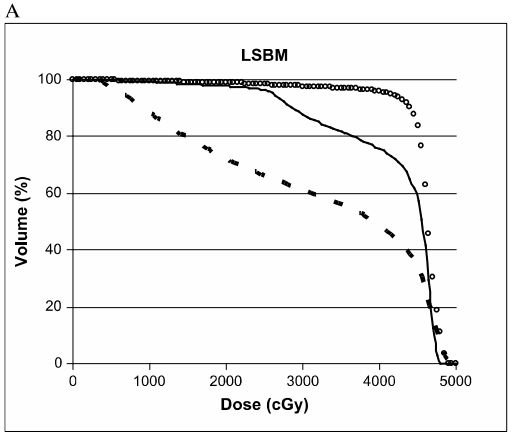


Loren K et al. Int J Radiat Oncol Biol Phys 2008

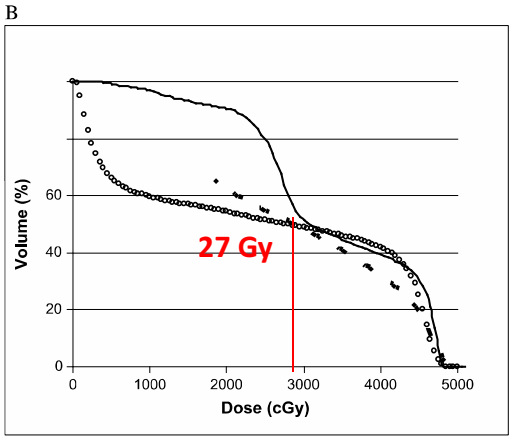
BM and RT Technique



LumboSacral BM

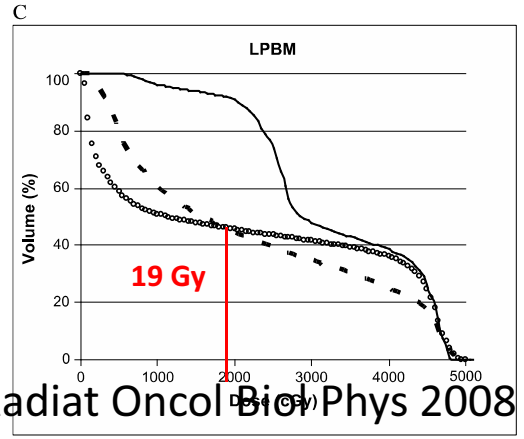


Iliac BM



APPA: advantage at doses < 10Gy
IMRT: advantage in doses > 20Gy

Lower Pelvis BM



Different dose distribution in different BM sites

Loren K et al. Int J Radiat Oncol Biol Phys 2008

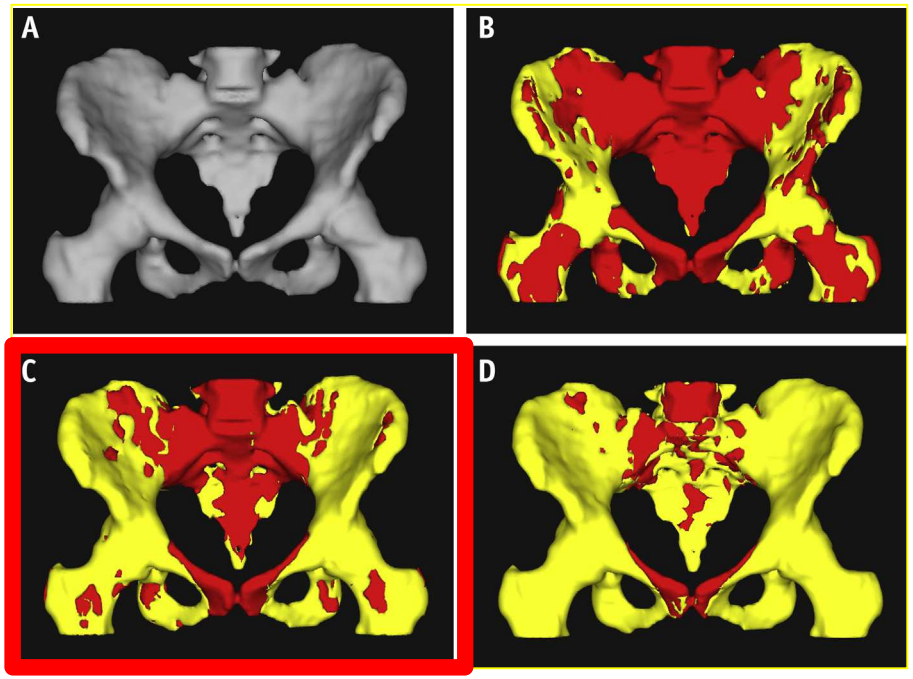
Loren K et al. Int J Radiat Oncol Biol Phys 2008

Bone Marrow

What to delineate?

BM delineation: sub-regions definition

PET used for sub-regions definition



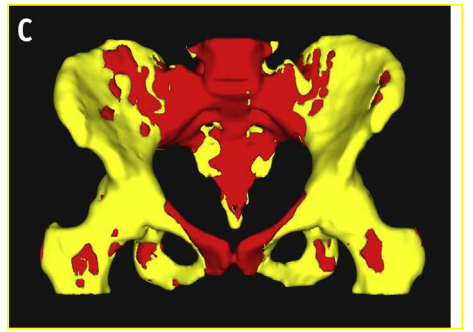
Total BM vs

Active BM$_{(\geq 50\% \text{ SUV max})}$

Inactive BM$_{(\leq 50\% \text{ SUV max})}$

Rose BR et al. Int J Radiat Oncol Biol Phys 2016

BM delineation



V_{10}	−0.038	−0.068 to −0.008	.016	0.197
V_{20}	−0.032	−0.056 to −0.008	.012	0.206
V_{30}	−0.018	−0.034 to −0.002	.040	0.166
V_{40}	−0.016	−0.033 to 0.001	.067	0.149
ABM_{50}				
EUD	−0.026	−0.050 to −0.001	.046	0.162
Mean dose	−0.030	−0.059 to −0.001	.049	0.159
V_{10}	−0.012	−0.025 to 0.001	.081	0.143
V_{20}	−0.012	−0.024 to 0.000	.069	0.148
V_{30}	−0.012	−0.022 to −0.002	.030	0.177
V_{40}	−0.007	−0.016 to 0.002	.147	0.123
IBM_{50}				
EUD	−0.073	−0.121 to −0.025	.005	0.239
Mean dose	−0.079	−0.135 to −0.024	.008	0.223
V_{10}	−0.042	−0.076 to −0.008	.019	0.192
V_{20}	−0.033	−0.058 to −0.008	.015	0.200
V_{30}	−0.018	−0.034 to −0.002	.032	0.173
V_{40}	−0.016	−0.034 to 0.002	.076	0.144

1. **Association** between pelvic **BM** irradiation and **HT**
2. ABM delineation **did NOT** improved prediction of HT
3. Use of **PET** for BM subregions delineation **NOT SUPPORTED**
4. Entire BM delineation:

   top L5 → ischial tuberosities

Rose BR et al. Int J Radiat Oncol Biol Phys 2016

Skin and external genitalia

Skin and external genitalia

- Common toxicity in anal RT → superficial target:
  - All patients experience a skin tox
  - **moist desquamation up to 45% (3D-RT)**

- Influencing factors: obesity, cigarettes, chronic sun exposure

- **Onset at the 2° wk of RT→ peak in the last 2 wks → disappear 4-5 wks after RT**

Treatment breaks → increased OTT → decreased RT effect

Toxicity scales

Table 1 Frequently used grading of acute radiation dermatitis

	RTOG	LENT/SOMA	CTCAE 4.0
0	No change from baseline/no symptoms	No change from baseline/no symptoms	Non change over baseline/no symptoms
1	Follicular, faint or dull erythema, epilation, dry desquamation, decreased sweating	Minor symptoms present that require no treatment	Faint erythema or dry desquamation
2	Tender or bright erythema, patchy moist desquamation, moderate edema	Moderate symptoms present that require conservative treatment	Moderate to brisk erythema, patchy moist desquamation, mostly confined to skin folds and creases, moderate edema
3	Confluent moist desquamation other than skin folds, pitting edema	severe symptoms, which have a significant negative impact on daily activities, and which require more aggressive treatment	Moist desquamation other than skin folds and creases, bleeding induced by minor trauma or abrasion
4	Ulceration, hemorrhage necrosis	Irreversible functional damage, necessitating major therapeutic intervention	Life-threatening consequences, skin necrosis or ulceration of full thickness dermis, spontaneous bleeding from involved site, skin graft indicated
5	Death related to treatment effects	Death or loss of organ	Death

Support Care Cancer
DOI 10.1007/s00520-013-1896-2

REVIEW ARTICLE

Clinical practice guidelines for the prevention and treatment of acute and late radiation reactions from the MASCC Skin Toxicity Study Group

Rebecca K. S. Wong &René-Jean Bensadoun &
Christine B. Boers-Doets &Jane Bryce &Alexandre Chan &
Joel B. Epstein &Beth Eaby-Sandy &Mario E. Lacouture

EBM

Practice

Prophylaxis and management of acute radiation-induced skin toxicity: a survey of practice across Europe and the USA

A. O'DONOVAN, BSC, ASSISTANT PROFESSOR, *Applied Radiation Therapy Trinity (ARTT), Trinity College Dublin, Dublin,* M. COLEMAN, BSC, RADIATION THERAPIST, *Applied Radiation Therapy Trinity (ARTT), Trinity College Dublin, Dublin, Ireland,* R. HARRIS, D CLIN RES, MSC, PGD, PGCCE, DCR (T), TECH IOSH, PROFESSIONAL OFFICER FOR RESEARCH, *The Society and College of Radiographers, London, UK,* & P. HERST, PHD, MPHIL MSC, SENIOR LECTURER, *Department of Radiation Therapy, University of Otago, Wellington, New Zealand*

O'DONOVAN A., COLEMAN M., HARRIS R. & HERST P. (2015) *European Journal of Cancer Care* **24**, 425–435

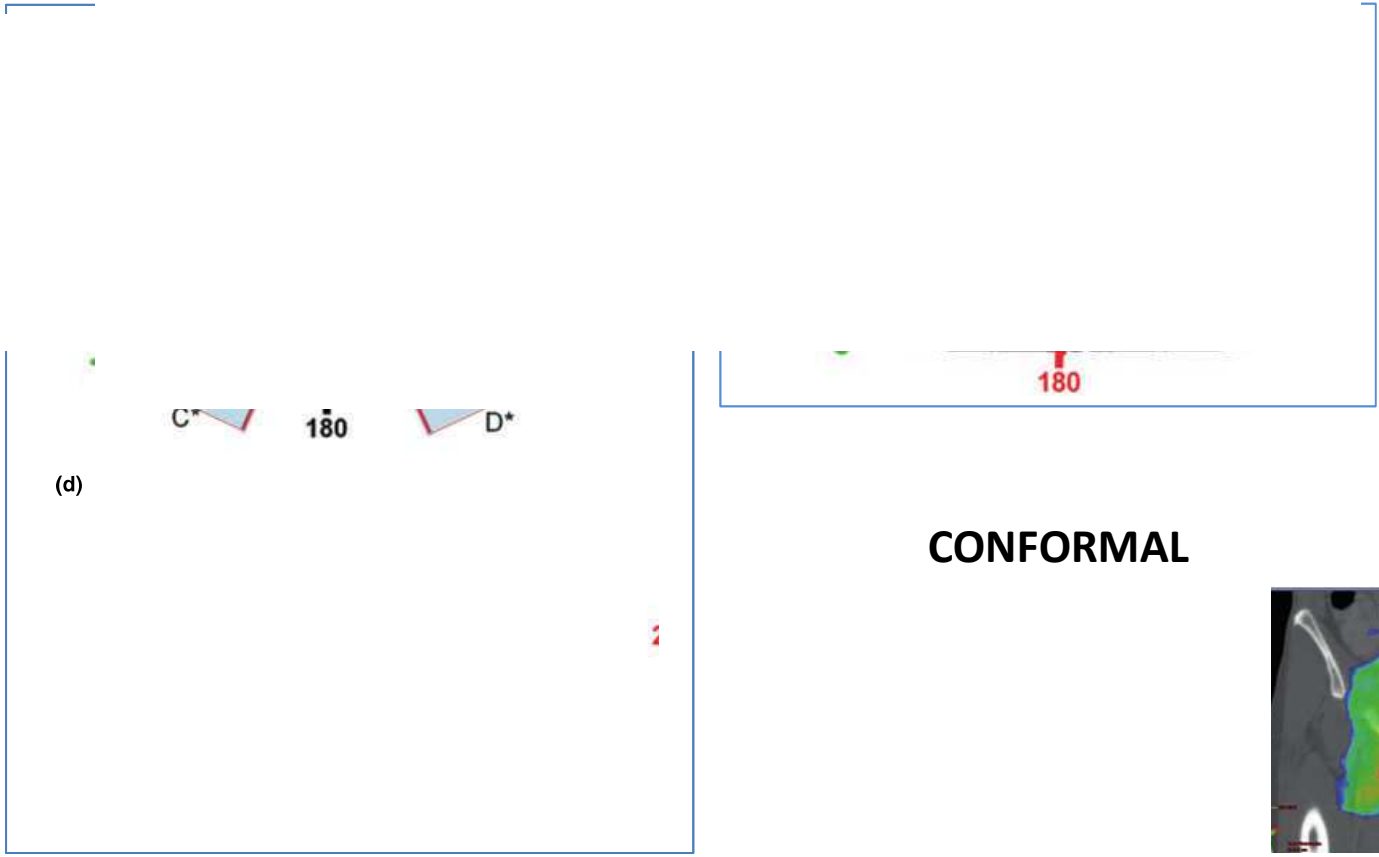
Prophylaxis and management of acute radiation-induced skin toxicity: a survey of practice across Europe and the USA

Skin toxicity management

Management: Lack of evidence-based practice

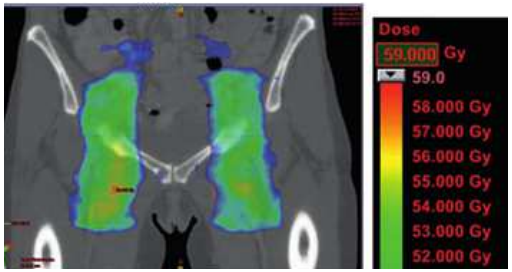
Reaction	Management
Prophylaxis	• Gentle skin washing with mild soap (neutral pH, non parfumed ingredients) • Aqueous cream (NOT definitive evidences)
Erythema	• Aqueous cream (NOT definitive evidences) • **Calendula cream** • Jaluronic acid (NOT definitive evidences) • Aloe vera (contraindicated)
Dry desquamation	• Aqueous cream (NOT definitive evidences) • **Hydrocortisone 1%** (NOT prolonged use → thinning of the skin)
Moist desquamation	• Polyuretane (exudate with crosts) • Hydrogel (exudate with crosts, debridement) • Hydrocolloids (G3-G4) • Antibiotics

talia



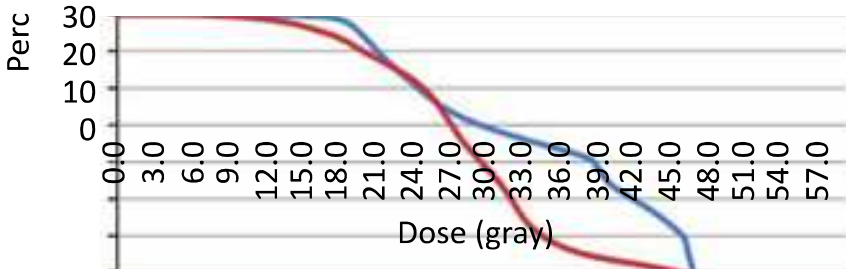
CONFORMAL

IMRT



Sale C et al. J Med Radiat Science 2013

IMRT for external genitalia



	Conformal technique	IMRT
Variable	Mean (SD)	Mean (SD)
Genitalia		
Maximum	55.38 (1.48)	45.00 (5.24)
Mean	43.37 (0.76)	23.53 (3.66)
Median	42.74 (0.92)	22.91 (4.31)
40 Gy	80.37 (13.53)	0.29 (0.27)

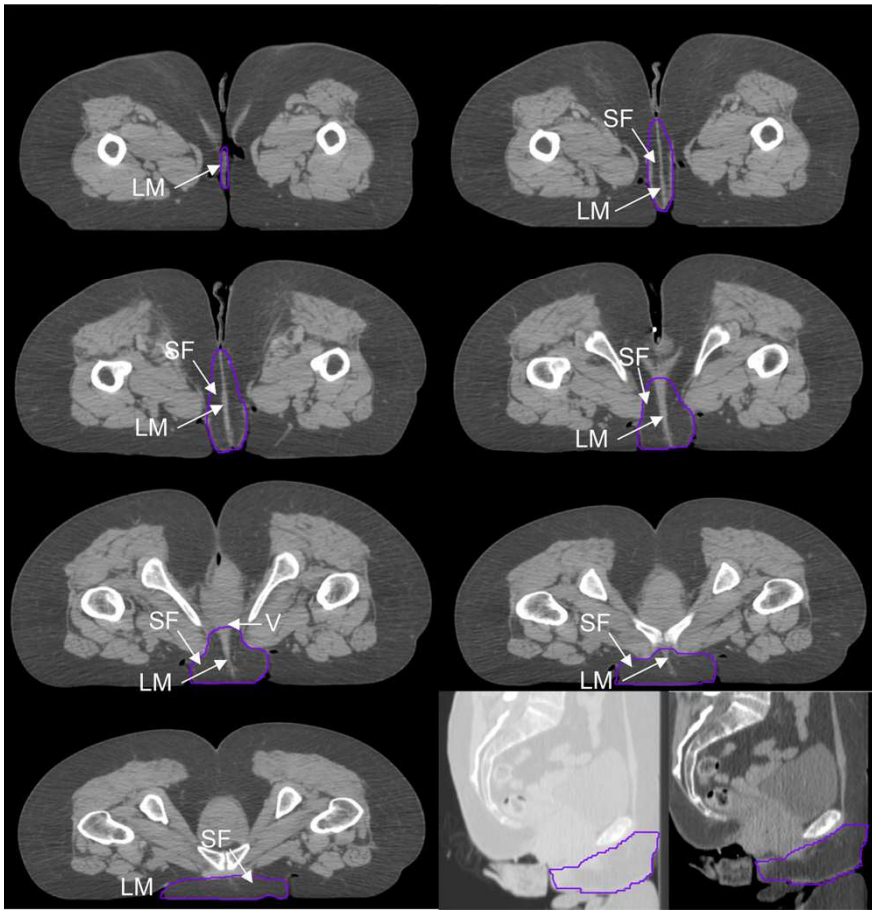
	RTOG 0529 IMRT	RTOG 9811 CONV RT
SKIN TOX G3+	23%	49%

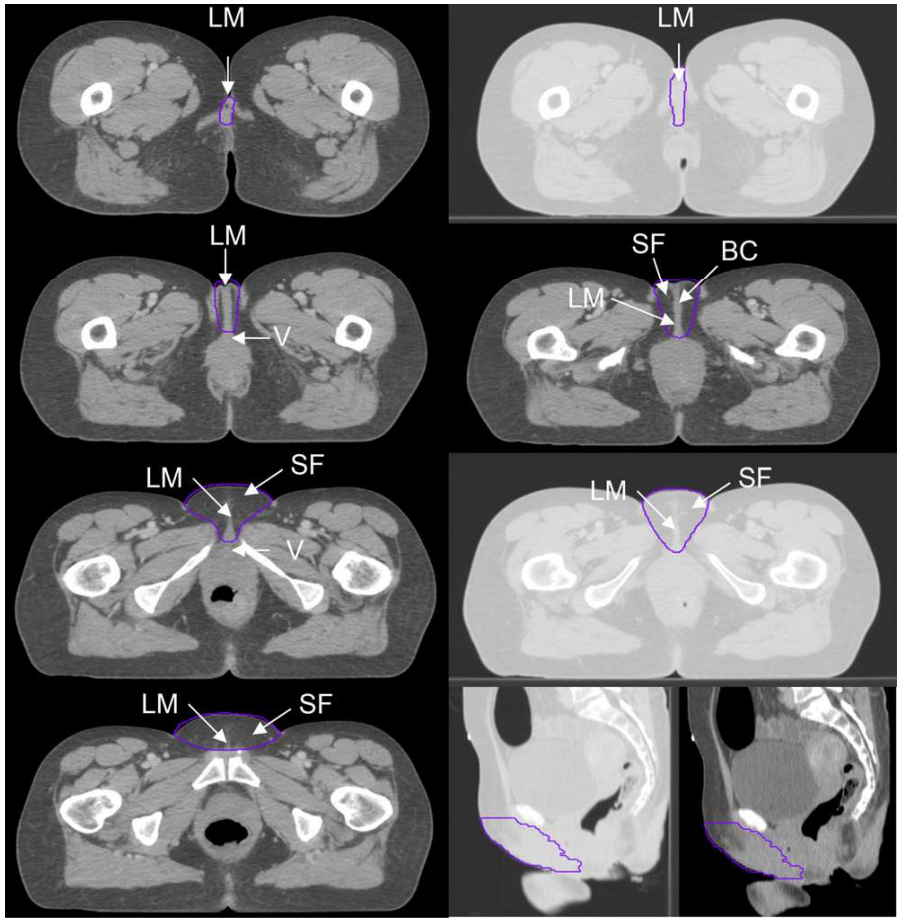
Sale C et al. J Med Radiat Science 2013
Kachnich LA et al Int J Radiat Oncol Biol Phys 2012
Ajani JA et al. Jama 2008

External genitalia delineation GL

MALE: scrotum , perineal body, corpus cavernosus penis + surrounding fat

FEMALE: clitoris, labia majora and minora + surrounding fat

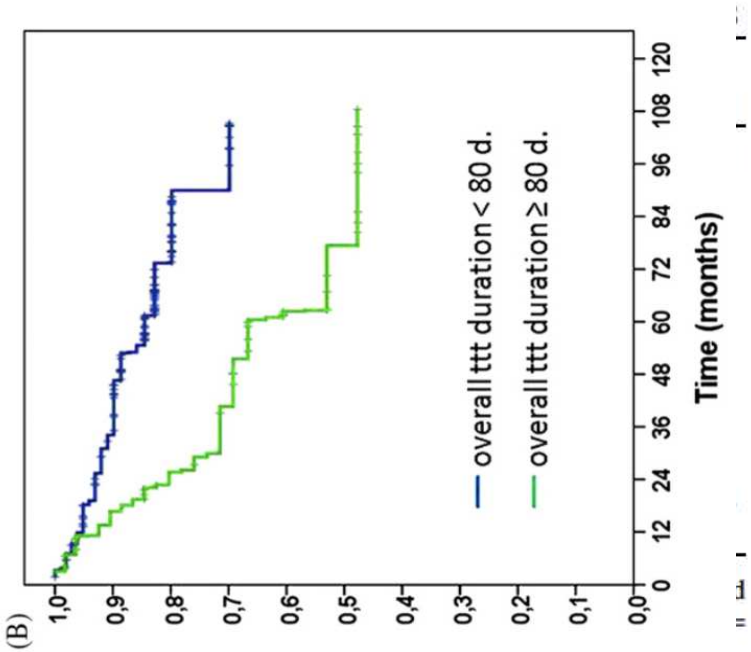


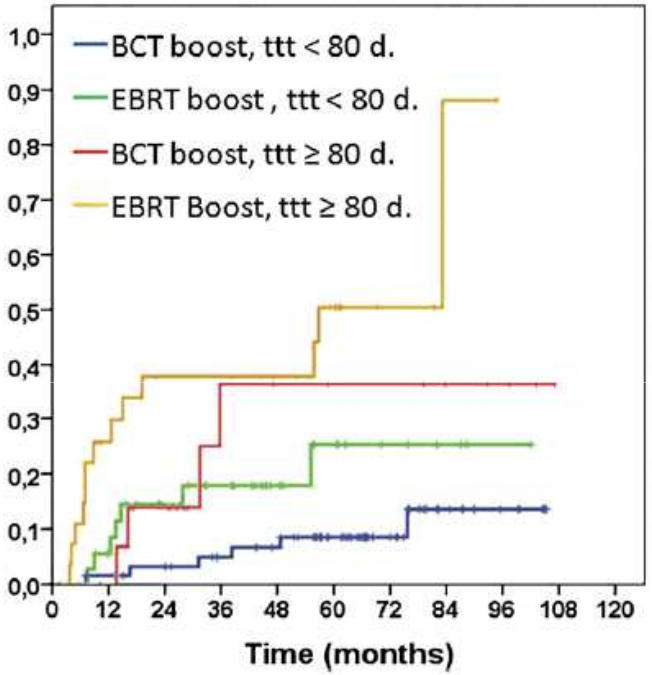


Brooks C et al. Br J Cancer 2015

Brachitherapy boost

Boost and OTT

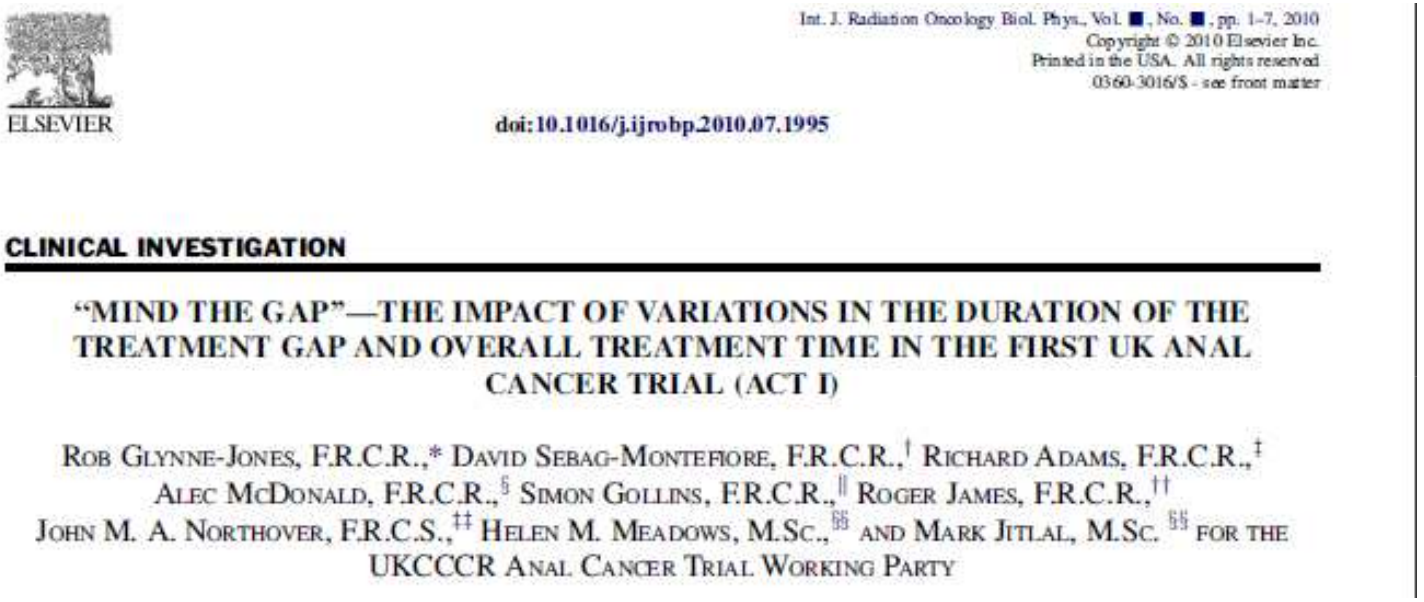




Conclusion: In anal cancer, when OTT is <80 days, BCT boost is superior to EBRT boost for CRLR. These results suggest investigating the benefit of BCT boost in prospective trials.

Hannoun-Levi JM, Ortholan C, Resbeut M, Teissier E, Ronchin P, Cowen D, Zaccariotto A, Bénézery K, François E, Salem N, Ellis S, Azria D, Gerard JP. High-dose split-course radiation therapy for anal cancer: outcome analysis regarding the boost strategy (CORS-03 study). **Int J Radiat Oncol Biol Phys. 2011**

To boost or not to boost



ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. ■, No. ■, pp. 1–7, 2010

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.07.1995

CLINICAL INVESTIGATION

"MIND THE GAP"—THE IMPACT OF VARIATIONS IN THE DURATION OF THE TREATMENT GAP AND OVERALL TREATMENT TIME IN THE FIRST UK ANAL CANCER TRIAL (ACT I)

ROB GLYNNE-JONES, F.R.C.R.,* DAVID SEBAG-MONTEFIORE, F.R.C.R.,† RICHARD ADAMS, F.R.C.R.,‡ ALEC MCDONALD, F.R.C.R.,§ SIMON GOLLINS, F.R.C.R.,‖ ROGER JAMES, F.R.C.R.,†† JOHN M. A. NORTHOVER, F.R.C.S.,‡‡ HELEN M. MEADOWS, M.SC.,§§ AND MARK JITLAL, M.SC.§§ FOR THE UKCCCR ANAL CANCER TRIAL WORKING PARTY

Gemelli ART
ADVANCED RADIATION THERAPY

- Glynne-Jones R, Sebag-Montefiore D, Adams R, McDonald A, Gollins S, James R, Northover JM, Meadows HM, Jitlal M; "Mind the gap"--the impact of variations in the duration of the treatment gap and overall treatment time in the first UK Anal Cancer Trial (ACT I). **Int J Radiat Oncol Biol Phys. 2011**

To boost or not to boost

Toxicity

577 patients - boost after 6 weeks: EBRT (15 Gy) or iridium-192 implant (25 Gy)

ULCER/RADIONECROSIS

BOOST	NO BOOST	
8%	0%	p=0.03

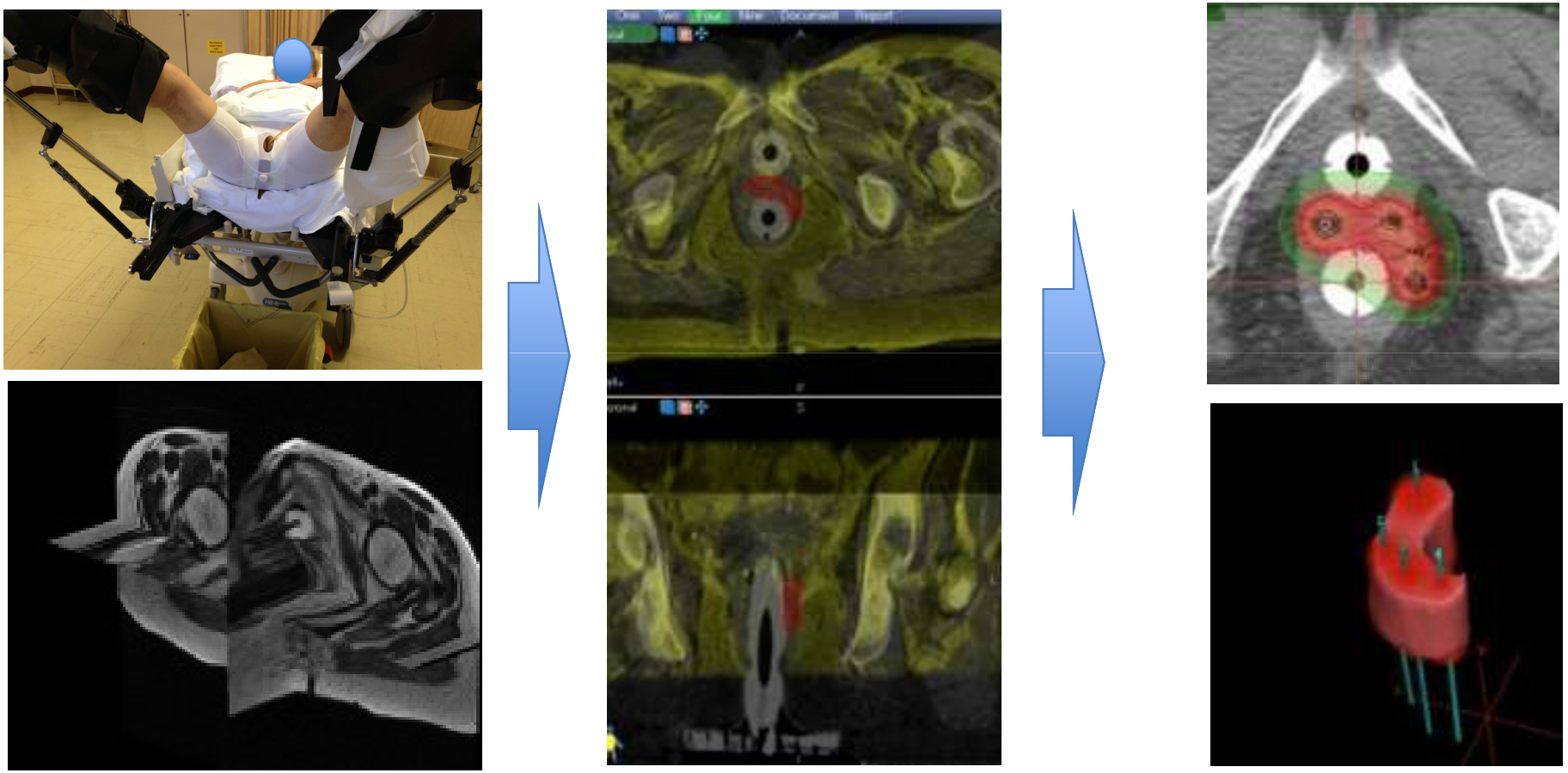
ULCER/RADIONECROSIS

BT BOOST	ERT BOOST	
14%	6%	p=0.003

Conclusions: These results question the benefit of a radiotherapy boost after a 6-week gap. The higher doses of a boost may contribute more to an increased risk of late morbidity, rather than local control.

- Glynne-Jones R, Sebag-Montefiore D, Adams R, McDonald A, Gollins S, James R, Northover JM, Meadows HM, Jitlal M; "Mind the gap"--the impact of variations in the duration of the treatment gap and overall treatment time in the first UK Anal Cancer Trial (ACT I). **Int J Radiat Oncol Biol Phys. 2011**

MR-guided BT



Tagliaferri L et al. Journal of Contemporary Brachytherapy (2015

Contra-indications

- *Tumor more than half of the circunference*
- *Tumor thickness more than 10 mm*
- *Tumor lenght more than 5 cm*
- *OTT*

- Radiotherapy in Practice - Brachytherapy Peter Hoskin, Catherine Coyle
- The GEC ESTRO Handbook of Brachytherapy
- Niehoff P, Kovács G. HDR brachytherapy for anal cancer. **J Gastrointest Oncol. 2014**

Conclusions

- Anal cancer RT-CT → highly toxic
  - Dose, volume
  - Numerous OAR (GI, GU, BM, skin-genitalia)
- IMRT → standard to decrease toxicity
- Not defined constraints for BM, skin, genitalia
- Delineation of OAR → fundamental

- BT boost → questionable when increased OTT

What's the next

Hindawi Publishing Corporation
BioMed Research International
Volume 2014, Article ID 482968, 8 pages
http://dx.doi.org/10.1155/2014/482968

Review Article

The Impact of Uterine Radiation on Subsequent Fertility and Pregnancy Outcomes

Wan Tinn Teh,[1,2] Catharyn Stern,[2,3] Sarat Chander,[4] and Martha Hickey[1]

[1] *Department of Obstetrics & Gynaecology, University of Melbourne and the Royal Women's Hospital, Parkville, VIC 3052, Australia*
[2] *Reproductive Services, Royal Women's Hospital, Parkville, VIC 3052, Australia*
[3] *Melbourne IVF, East Melbourne, VIC 3002, Australia*
[4] *Division of Radiation Oncology and Cancer Imaging, Peter MacCallum Cancer Centre, East Melbourne, VIC 3002, Australia*

Correspondence should be addressed to Wan Tinn Teh; wantinn.teh@mivf.com.au

Received 28 April 2014; Accepted 19 July 2014; Published 6 August 2014

Academic Editor: Shyh-An Yeh

Fertility and pregnancy

- Dose > 25 Gy → myometrium, endometrium, vascular damage
- Case-report: women 25 years old who was pregnant after 30Gy RT for anal cancer

Teh T W et al. Biomed Res Int 2014

Review Article

The Impact of Uterine Radiation on Subsequent Fertility and Pregnancy Outcomes

(ii) With improvements in radiotherapy delivery technology methods such as intensity modulated radiation therapy, cyberknife, tomotherapy, and stereotactic radiotherapy, there may be the potential to limit radiotherapy exposure to the uterus or to restrict exposure to part of the uterine corpus or cervix, depending on the tumour location and characteristics. Th
irradia

(iii) With the growing numbers of adult women surviving cancers managed with pelvic radiation, there is an urgent need to ensure that fertility issues are discussed prior to treatment and that further data are collected on the reproductive impact of total or partial uterine radiation in order to inform future clinical management (Figure 1).

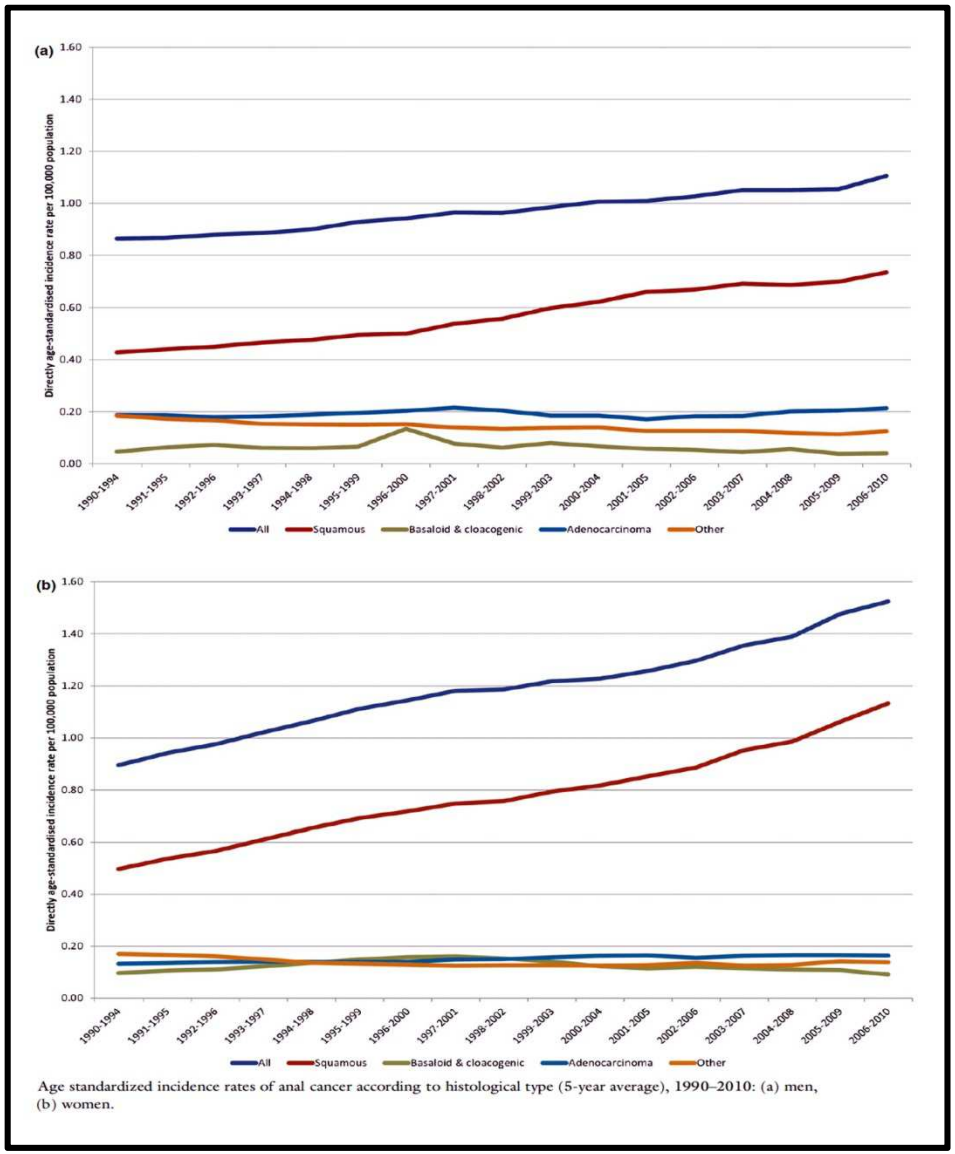
Teh T W et al. Biomed Res Int 2014

Prognostic Factors in Anal Cancer

ESTRO LOWER GI COURSE :

Technical & Clinical Challenges for Radiation Oncologists

Anal cancer – Increasingly Common

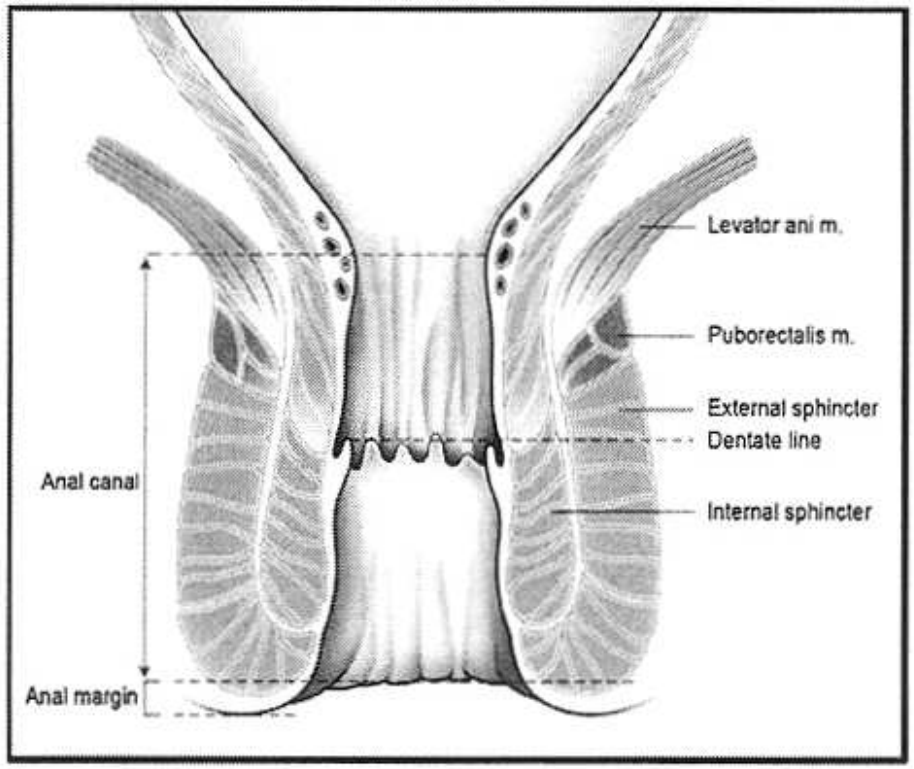


Age standardized incidence rates of anal cancer according to histological type (5-year average), 1990–2010: (a) men, (b) women.

- **English National Cancer Data Repository 1990 – 2010 (all anal cancers diagnosed in England)**
- **69 % increase in age standardised incidence for SCC in men from 0.43 per 100,000 to 0.73 per 100,000**
- **126 % increase for women from 0.5 per 100,000 to 1.13 per 100,000**
- **No change in incidence of anal adenocarcinoma**
- **Similar changes reported in Scotland, Denmark, Sweden, Australia and the USA**

(Wilkinson et al 2014)

Anal cancer – Anal Canal & Anal Margin



Most Anal tumours arise in the Anal Canal

- The anal margin is defined as the area of pigmented skin around the anal orifice - extending laterally to a radius of 5cm
- Anal margin tumours are staged as cutaneous SCCs

ANAL CANCER : UICC TNM STAGE

T STAGE

- **TX** - tumor cannot be assessed
- **T0** - no primary tumor
- **Tis** - AIN 2 & 3 ; high grade SIL
- **T1** - tumor < 2cm maximum diameter
- **T2** - tumor > 2cm & < 5cm
- **T3** - tumor > 5cm
- **T4** - tumor of any size invading adjacent organs eg. vagina, urethra,bladder (excludes rectum, peri-anal skin & sphincter muscle)

N STAGE

- **NX** - nodes cannot be assessed
- **N0** – no node metastasis
- **N1** – metastasis in peri-rectal nodes
- **N2** – metastasis in unilateral internal iliac and/or inguinal nodes
- **N3** – metastasis in peri-rectal & inguinal nodes or bilateral internal iliac node involvement or bilateral inguinal node involvement

- **any tumor between rectum and peri-anal skin**
- **anal margin tumors classified as skin cancers**

Anal Cancer : TNM stage & Outcome

- **US GI Intergroup RTOG 98-11 phase 3 anal cancer trial**
- **RCT of RT + 5FU/MMC versus RT + 5FU/CDDP & indictin chemotherapy with 5FU/CDDP**
- **T2 – T4 +/- LN metastases (excludes T1 N0-3 and M1 disease)**
- **N = 620 patients**

	No.	5yr Local Failure	5yr DM	3yr Colostomy failure	5yr DFS	5yr OS
T2 N0	323	17 %	10 %	11 %	72 %	82 %
T3 N0	96	18 %	14 %	13 %	61 %	74 %
T4 N0	31	37 %	21 %	26 %	50 %	57 %
T2 N1-3	99	26 %	27 %	11 %	57 %	70 %
T3 N1-3	46	44 %	24 %	27 %	38 %	57 %
T4 N1-3	25	60 %	24 %	24 %	31 %	42 %
T2 or 3 N0	419	17 %	11 %	11 %	70 %	80 %
T4N0 or T2-4 N1-3	201	36 %	25 %	19 %	49 %	62 %

(Gunderson et al 2013)

Anal Cancer : the importance of tumour size

- **Das et al (2007) : 167 patients treated with CRT**
- **3 yr locoregional control :**
- **T1/Tx 90 % (76 – 100)**
- **T2 86 % (76 – 96)**
- **T3 77 % (61 – 93)**
- **T4 63 % (41 – 86)**

T stage a significant independent predictor of loco-regional failure on multivariate analysis (HR 1.71)

- **Ajani et al (2009 & 2010) : RTOG 98-11 trial of RT + 5FU/MMC versus RT + 5FU/cisplatin**
- **Tumour diameter > 5cm associated with a greater risk of colostomy, worse 5 yr DFS & 5 yr OS (p = 0.0003) compared with smaller tumours**

Anal Cancer : the importance of nodal metastasis

- Das et al (2007) : 167 patients treated with CRT

	3 yr locoregional control	3 yr distant control
N0	85 %	94 %
N1	88 %	79 %
N2	84 %	75 %
N3	39 %	76 %

- N stage an independent predictor of loco-regional failure, distant metastasis and OS on multivariate analysis !

- Ajani et al (2010) : RTOG 98-11 trial
- Clinically positive nodes associated with worse 5 yr DFS and 5 yr OS ($p < 0.0001$)

Other Prognostic Factors

- **Male gender**

- **EORTC 22861 :**
- **local control p= 0.0028**
- **overall survival p=0.0034**

- **RTOG 98-11 :**
- **disease free survival p = 0.02**
- **overall survival p=0.016**

- **ACT 1 Trial :**
- **Loco-regional failure HR 1.6 (1.03-2.49) p=0.036**
- **Anal cancer death HR 1.8 (1.03-3.16) p=0.039**
- **Overall survival HR 1.56 (1.12 – 2.17) p=0.008**

Other Prognostic Factors

- **ACT 1 trial :**

➢ **low Hb associated with increased anal cancer death (p=0.008)**

- **EORTC 22861 :**

➢ **skin ulceration associated with loco-regional failure (p=0.003) and overall survival(p=0.005)**

ANAL CARCINOMA : HISTOLOGICAL CLASSIFICATION

- **SQUAMOUS CELL CARCINOMA NOS (80 - 90%)**
  - size of neoplastic cell
  - basaloid morphology
  - keratinization
  - presence of mucinous microcysts
  - degree of differentiation
  - presence of adjacent AIN

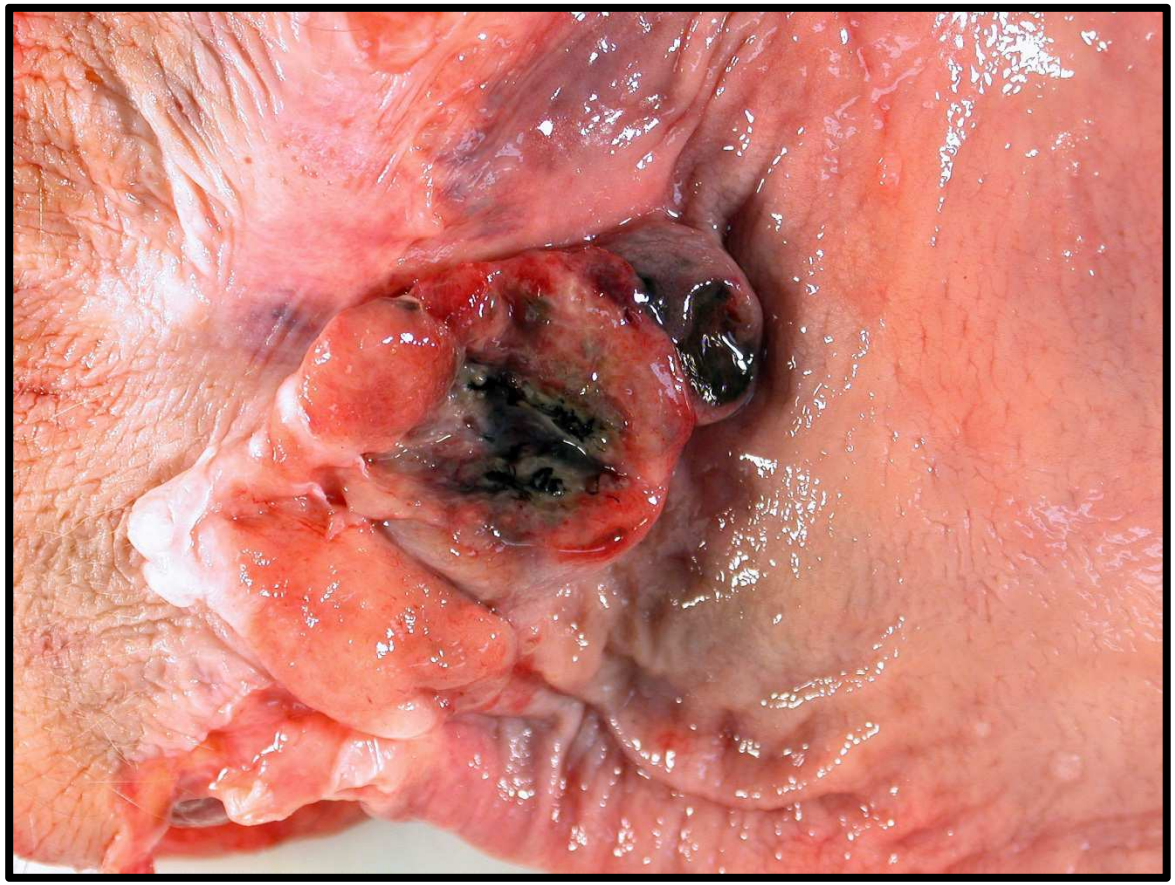
WHO 2nd Edition.
large cell keratinizing
large cell non-keratinizing
Basaloid (cloacogenic)

- **VERRUCOUS CARCINOMA (GIANT CONDYLOMA OF BUSCHKE-LOWENSTEIN) (< 1 %)**

- **ADENOCARCINOMA (anal gland, mucinous – fistula related, rectal type) (10 – 15 %)**
- **NEUROENDOCRINE CARCINOMA (large cell & small cell type) (< 2 %)**

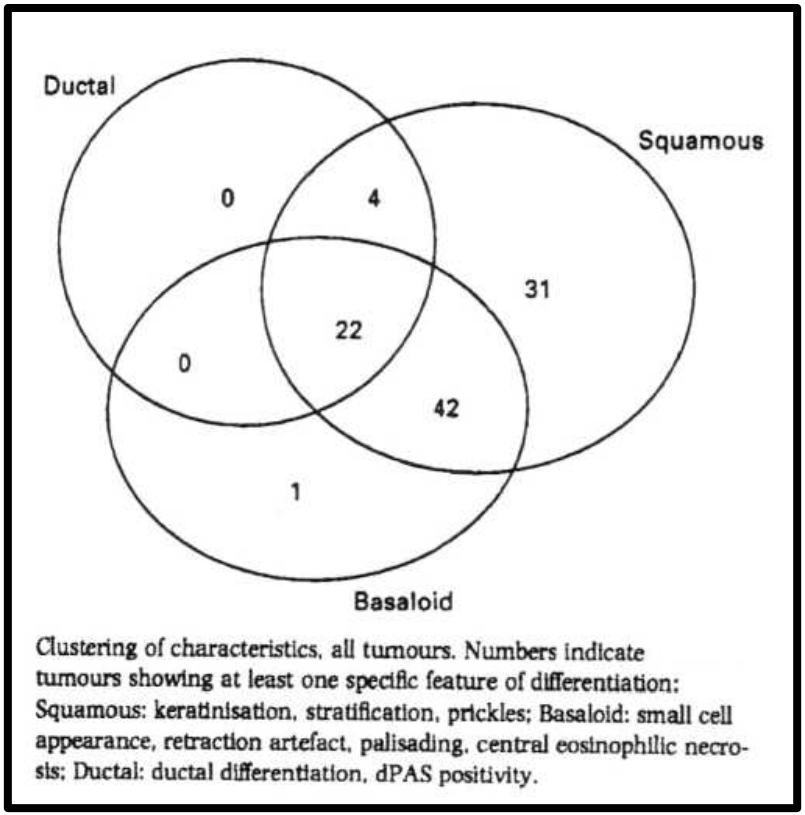
Other Cancers

- **Malignant Melanoma (< 2 %)**



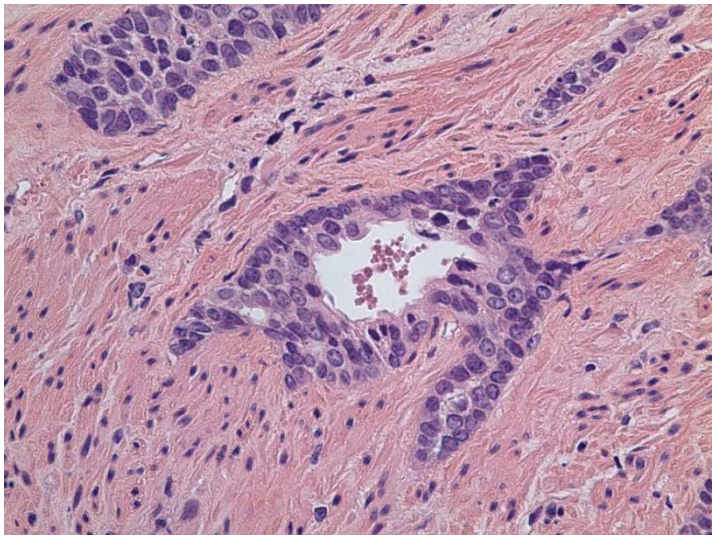
- **Lymphoma**
- **Sarcoma**

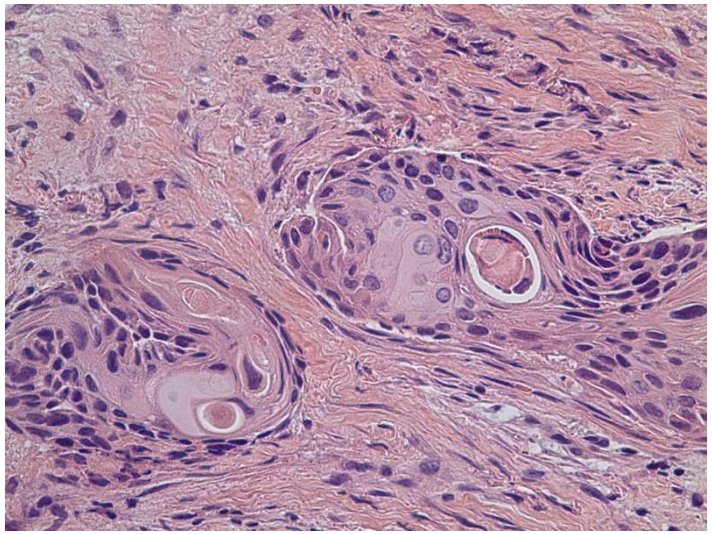
SCC of the Anal Canal : Overlap of Histological Types

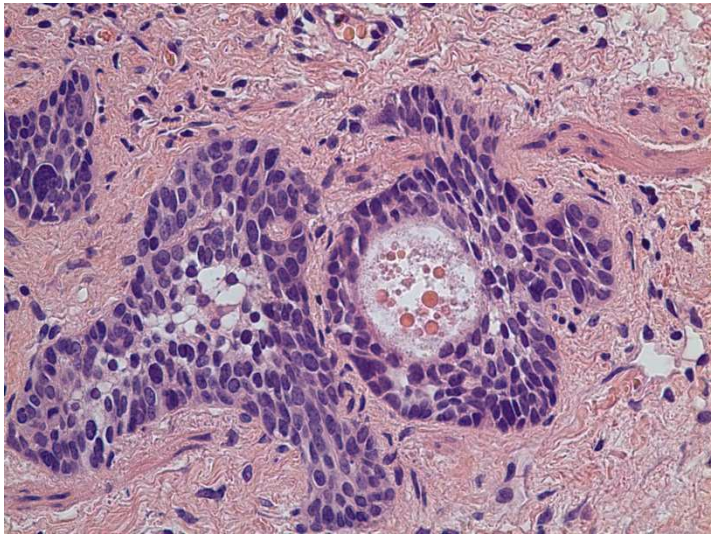


Clustering of characteristics, all tumours. Numbers indicate tumours showing at least one specific feature of differentiation: Squamous: keratinisation, stratification, prickles; Basaloid: small cell appearance, retraction artefact, palisading, central eosinophilic necrosis; Ductal: ductal differentiation, dPAS positivity.

(Williams & Talbot 1994)

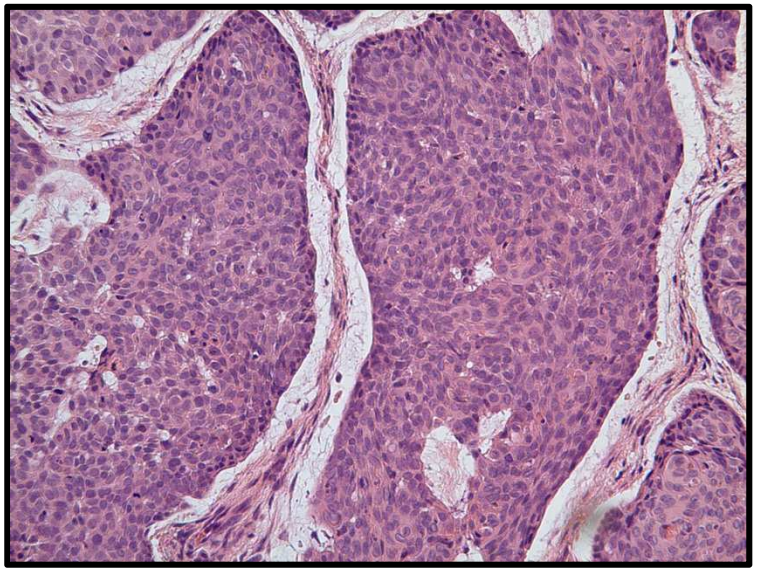


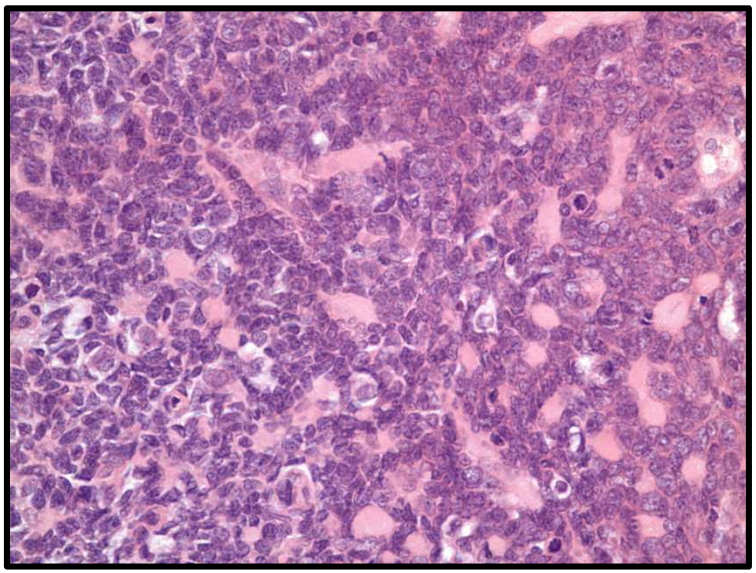


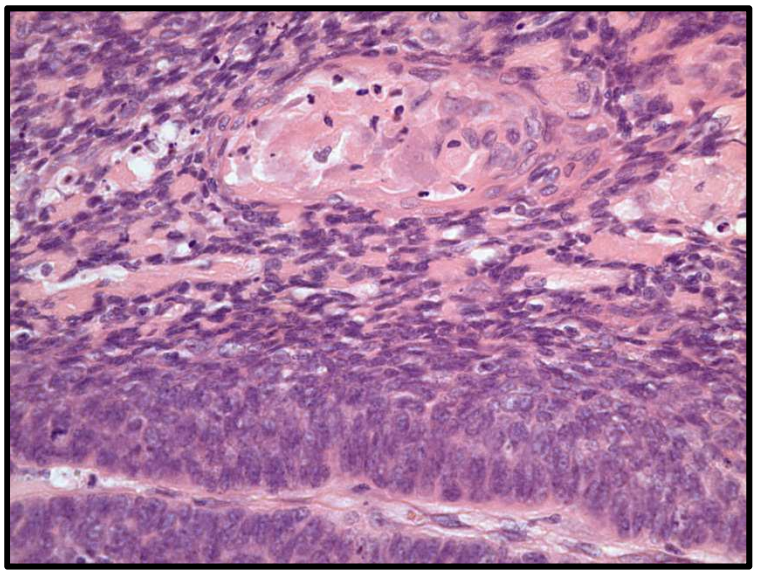


Basaloid Variant SCC

Bonnen et al (1984)	61/160	(38 %)
Dougherty et al (1984)	11/79	(13.9 %)
Shepherd et al (1989)	60/166	(36 %)

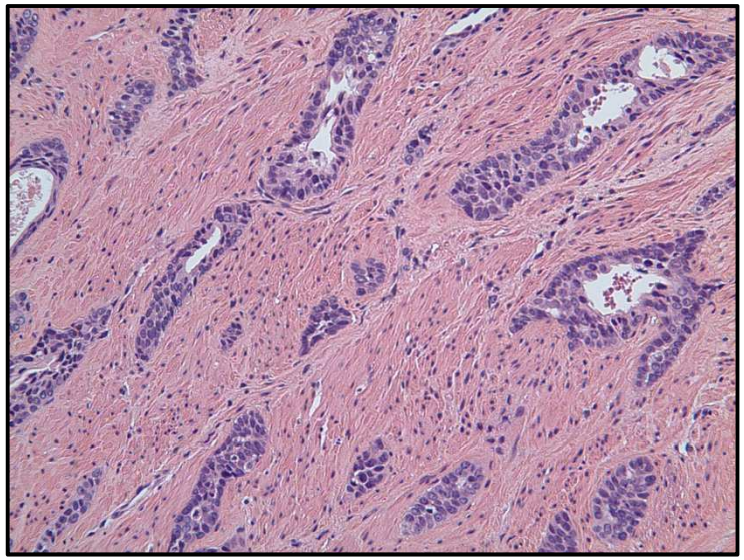


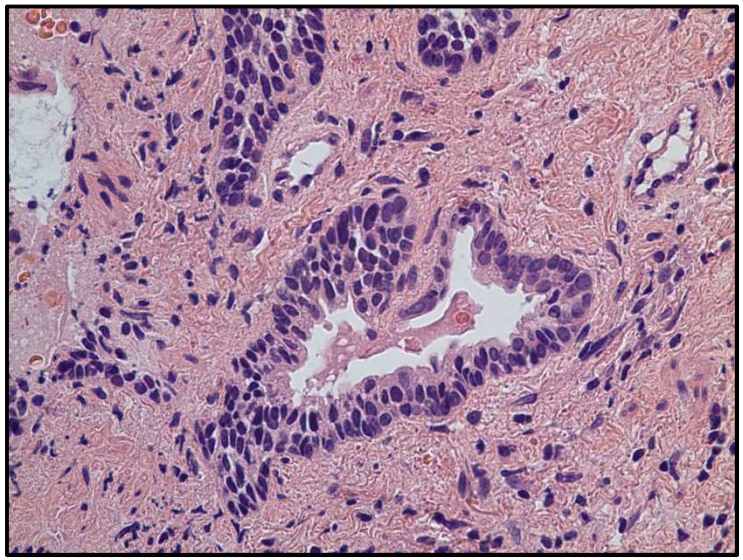


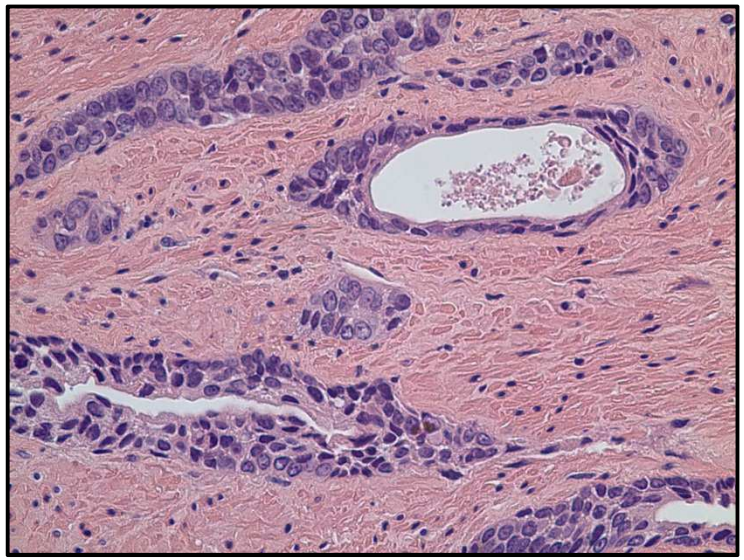


Squamous Cell Carcinoma with Mucus Microcysts (“Mucoepidermoid carcinoma of the anus”)

Morson et al (1963)	21/178	(11.8 %)
Dougherty et al (1984)	6/79	(7.6 %)
Shepherd et al (1989)	10/235	(4.3 %)







study	No.	Time period	treatment	outcome
Boman et al (1984) SCC – grades 1 to 4 Basaloid type SCC	188	1950-1976	Surgery	Grade & type correlated with stage. No significant correlation with survival after adjusting for stage.
Dougherty et al (1984) Keratinizing SCC Non-keratinizing SCC Basaloid SCC SCC with microcysts	79	Pre 1978	Surgery	No correlation of histologic type with depth of invasion or node metastasis. No correlation with survival.
Shepherd et al (1989) SCC Basaloid type Mixed type	235	1948-1985	Surgery	Histologic type not predictive of survival in multivariate analysis.
Bartelink et al (1997) SCC versus other types Histologic grade	110	1987-1994	RT & CRT	Neither type nor grade predicted local control or survival.
Myerson et al (2001) SCC – low & high grade Basaloid type	106	1975-1997	Mainly CRT	Borderline significant improved 5yr DFS for basaloid type. No effect of tumour grade.
Das et al (2007) SCC grades 1 to 3 Basaloid type	167	1992-2004	CRT	Basaloid type associated increased risk of Distant Metastasis (HR 4.23). No correlation type or grade with loco-regional failure or survival.

Biomarkers in Anal Carcinoma – Much Ado About Nothing

- **p53 : 8 studies 1996 – 2009 (n = 14 – 214)**

- immunohistochemistry used in all studies
- 34% – 100 % cancers positive (34-60% in 6/8 studies)
- All cancers treated with CRT
- **No prognostic significance in 6/8 series** ; reduced DFS in 2/8

- **p21 : 3 studies 2001 – 2006 (n = 94 – 215)**

- immunohistochemistry used in all studies
- 65 % – 71 % cancers showed positive staining
- **absent expression associated with reduced OS in one study and a trend towards reduced DFS in the other two** ; significant association with loco-regional failure in one out of three.

- **EGFR : 3 studies 2005 – 2009 (n = 21 – 38)**

- immunohistochemistry used in all 3 series
- EGFR expression seen in 55 % – 100 % of cancers
- **NO prognostic significance found**

(Lampejo et al 2010)

Biomarkers in anal Carcinoma – Much Ado About Nothing

- **BCL – 2 : 3 studies 2003 – 2009 (n = 21 – 98)**

- immunohistochemistry in all 3 studies
- BCL 2 expressed in 24 – 58 % of cancers
- associated with reduced local control and DFS in one study ; no prognostic significance in the other two

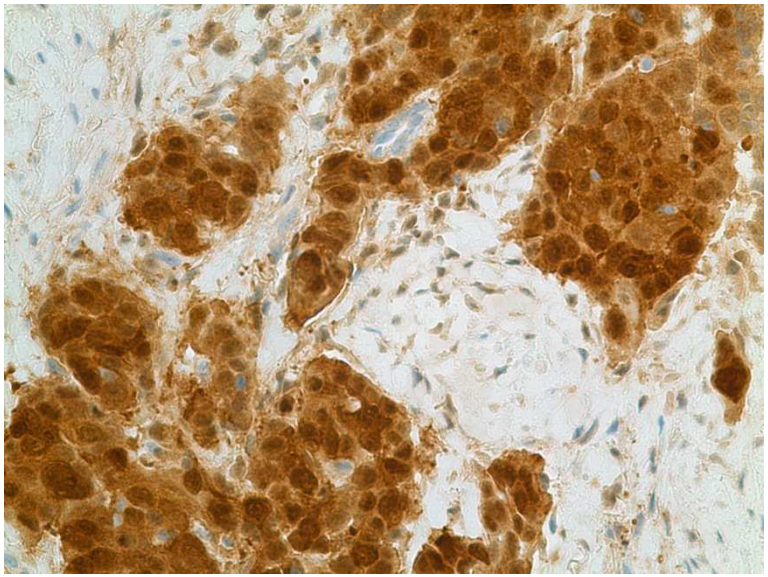
- **Ki67 : 4 studies 1998 – 2009 (n = 31 – 62)**

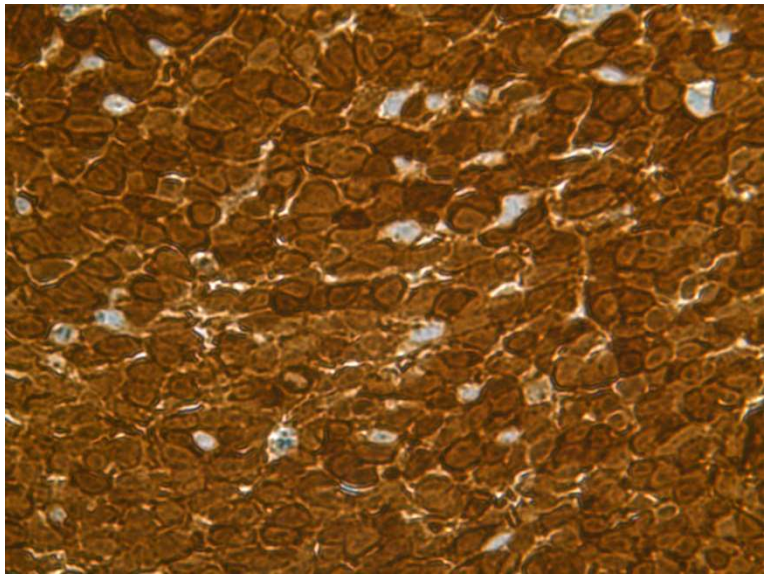
- Immunohistochemistry (MIB1) used in all studies
- No prognostic significance in 2 out of 4 studies ; elevated Ki67 associated with longer DFS in one study and improved colectomy free survival in a second study.

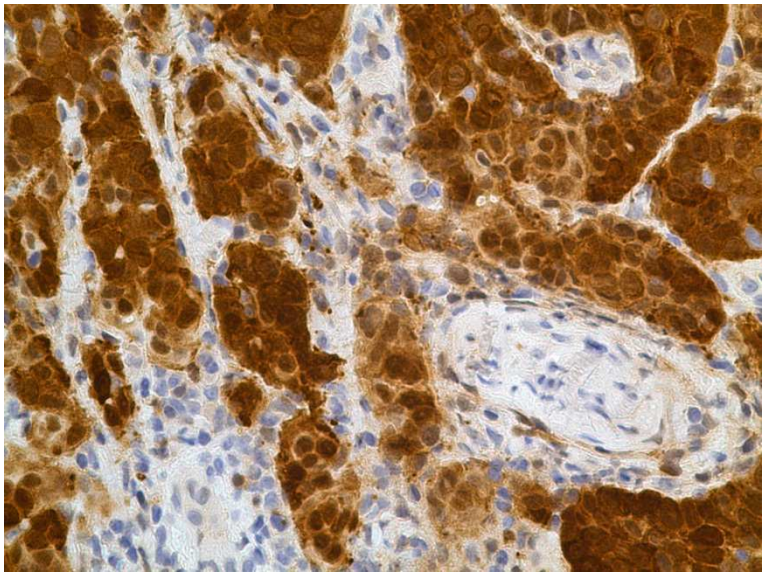
- **Others : VEGF - no prognostic significance**
  MVD - no prognostic significance
  PCNA - no prognostic significance
  Cyclins - no prognostic significance in 3 out of 4 studies

(Lampejo et al 2010)

p16 – a promising biomarker in Anal Cancer







p16 – ink4a
Chromosome 9p21
Inhibits entry into S phase of the cell cycle
Binds CDK4/6 inhibiting formation of the cyclin-CDK4/6 complex
HPV E7 protein binds Rb releasing E2F transcription factor leading to increased p16 expression

p16 overexpression in anal cancer is a useful surrogate marker of high risk HPV infection !!!

Human Papilloma Virus & Anal Carcinoma

- Vuyst et al (2009) – meta-analysis of 29 international studies between 1986 – 2008

➢ Overall prevalence of HPV in AIN = **92.7 %** (1280 cases)

➢ Overall prevalence of HPV in anal carcinoma = **84.3 %** (955 cases)

	All types	HPV 16	HPV18	Multiple types
AIN 1	91.5 %	37.2 %	21.3 %	54.4 %
AIN 2 & 3	93.9 %	59.8 %	17.4 %	
SCC	84.3 %	73.4 %	5.2 %	6.8 %

- ? HPV more common in basaloid variant SCC (> 95 %)
- ? HPV associated lower T stage & N stage at diagnosis

HPV & ANAL CANCER

- **143 stage I – III anal SCCs (2000 – 2010)**
- **Single centre in Denmark**
- **52 % treated with RT ; 48 % treated with CRT**
- **Median F.U 51.2 months**
- **Recurrent disease in 23 %**
- **87.6 % HPV + (79.6% HPV16)**
- **92.9 % p16 +**

	Overall Survival	Disease Specific Survival
HPV +	74 %	84 %
HPV -	52 %	52 %
p16 +	76 %	85 %
p16 -	30 %	30 %

(Serup-Hansen et al 2014)

HPV associated Anal Cancer is genetically distinct

- Meulendijks et al (2015)
- 138 anal SCC

	No.	% p53 I/C +	% p53 disruptive mutations	3 yr loco-regional control	3yr OS
HPV+ p16+	93	10% (9/93)	6 % (1/18)	82 %	87 %
HPV- p16+	4		33 % (1/3)	75 %	75 %
HPV- p16-	10	50% (5/10)	80 % (8/10)	15 %	35 %

No difference in T or N stage between HPV+ and HPV - cancers

HIV & ANAL CANCER

Historically (pre-HAART) anal carcinoma treatment in HIV positive patients associated with lower response rate and reduced survival

Radiotherapy and chemotherapy poorly tolerated with more toxicity and breaks in treatment

More recent studies (post HAART) suggest outcomes equivalent to non-HIV+ patients

Is the prognosis of Anal cancer worse in HIV infected patients ?

- **Oehler – Janne et al (2008)**
- **40 consecutive HIV(+) patients from 4 centres in Switzerland, France & Canada treated with CRT between 1997-2006**
- **Compared with 81 HIV(-) patients**
- **98 % SCC**

	HIV (+)	HIV (-)
cCR	92%	96%
5 yr local control	38%	87%*
5 yr sphincter preservation	38%	74%**
5 yr DM free survival	91%	84%
5 yr DSS	68%	85%***
5 yr OS	61%	65%
Acute G3/4 toxicity	48%	31%
Severe skin toxicity	35%	17%
Severe haematologic toxicity	33%	12%

- **poorer local control experienced by HIV(+) group with significantly higher colostomy rate**
- **Higher treatment related toxicity**
- **Less use of MMC in HIV(+) group**
- **Longer duration of RT in HIV(+) group (? more treatment breaks)**

(* P = 0.008 ; **p = 0.035 ; *** p = 0.09)

HIV & ANAL CANCER

- **Wexler et al (2007)**
- 32 HIV+ patients treated with CRT (5FU+MMC) between 1997 and 2005
- Median tumour size 2.8 % ; **44% cT1 cN0**
- 5 yr actuarial risk of local failure = 16 %
- 3 / 32 developed distant metastases
- 5 yr overall survival = 65 %
- 5 yr cancer specific survival = 75 %
- **Fraunholz et al (2011)**
- 25 HIV + patients and 45 HIV – patients
- No difference in T or N stage at diagnosis (all M0)
- More young males in the HIV+ group
- No difference in RT dose delivered
- 72 % HIV+ received full dose of chemotherapy cf. 91 % HIV- group

	CR at 8 wks	5 yr local control	5 yr metastasis free survival	5 yr overall survival
HIV +	**84 %**	**65 %**	**86 %**	**71 %**
HIV -	**93 %** pNS	**78 %** pNS	**91 %** pNS	**77 %** pNS

SCC of the Anal Margin

- 5 – 10x less common than anal canal tumours
- more often well differentiated & keratinizing
- less often hrHPV positive (80% in women & 28% in men – Frisch et al 1999)
- Small well differentiated tumours < 2cm can be treated by local excision +/- adjuvant radiotherapy
- Larger tumours that are poorly differentiated or metastatic to inguinal lymph nodes (15 – 20 % of patients) are treated with radiotherapy or CRT

SCC of the Anal Margin

- Risk of lymph node metastasis is related to tumour size:

Tumour size	% Node Metastasis Papillon & Chassard (1992)	% Node Metastasis Cummings et al (1986)
< 2cm	0 %	0 %
2 – 5 cm	24 %	
> 5cm	67 %	25 %

SCC of the Anal Margin : Results of Radiotherapy

	number	5 yr LRC	5 yr OS	Sphincter preservation
Chapel et al 2006	26	61 %	71 %	65 %
Cummings et al 1986	29	72 %	NS	NS
Papillon et al 1992	57	88 %	59 %	90 % (in cured patients)
Touboul et al 1995	17	86 %	82 %	82 %
Bieri et al 2001	24	70 %	56 %	67 %
Peiffert et al 1997	31	77 %	67 %	84 %
Khanfir et al 2008	45	78 %	55 %	80 %

SCC of the Anal Margin : Prognostic Factors

- Anal margin tumours have been reported to have both a better and worse prognosis than anal canal lesions – ACT 1 trial found no effect for LRF or OS.
- Studies of prognostic factors specific to anal margin tumours are lacking and reported series are small

➢ Chapet et al (2007) - 26 patients treated with primary EBRT or adjuvant RT after local excision : cancer specific survival related to age, tumour differentiation, T stage & N stage

Tumour diffn	5 yr CSS
Well diffn	85 %
Mod diffn	67 %
Poor diffn	50 %

T stage	5 yr CSS
T1	100 %
T2	92 %
T3	37 %
T4	0 %

N stage	5 yr CSS
N0	93 %
N1	67 %
N2	33 %

➢ Khanfir et al (2008) – 45 patients with primary EBRT or adjuvant RT after local excision : no factors (T stage, N stage, histological grade or age) were predictive of loco-regional control

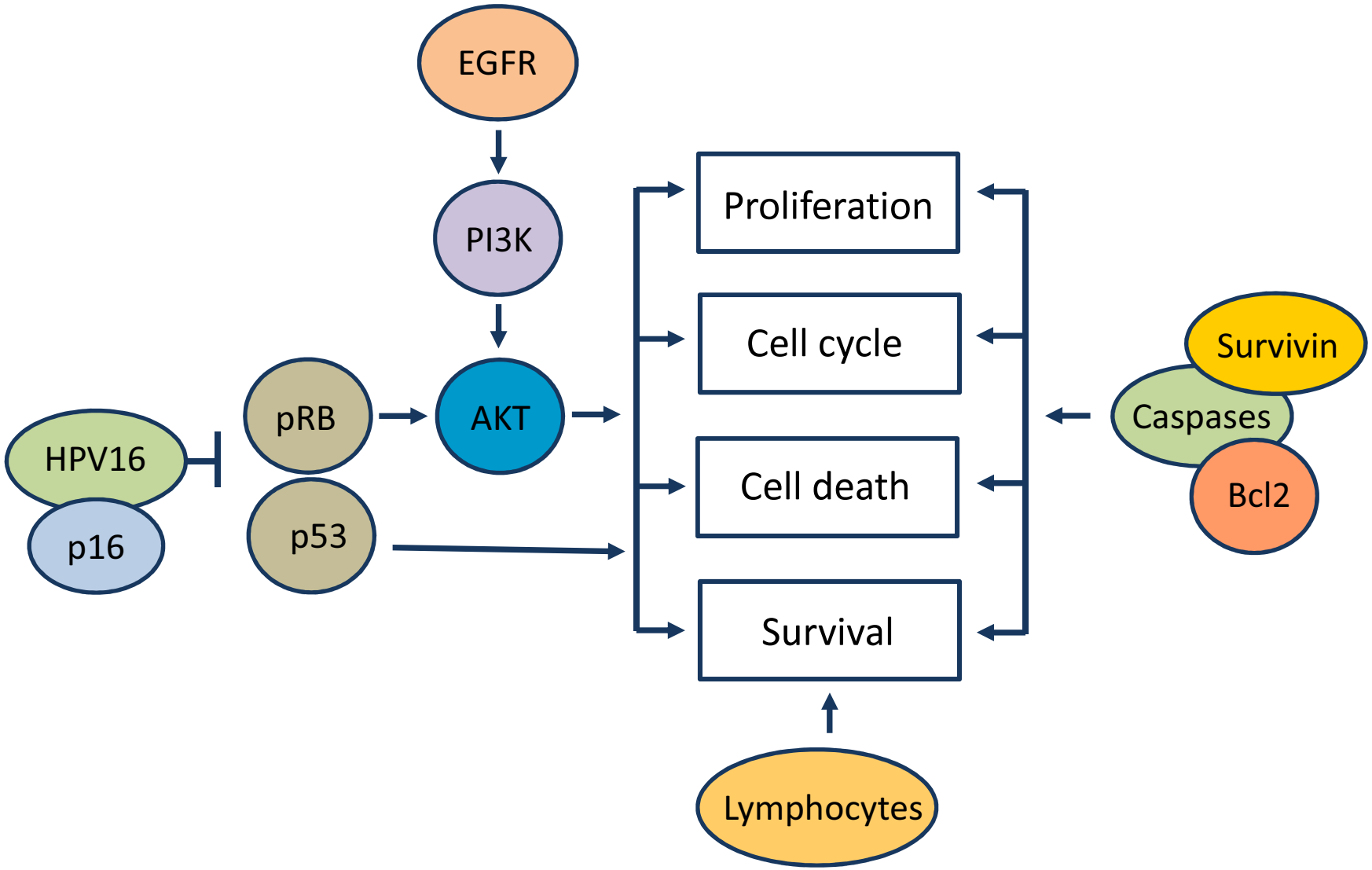
Prognostic Factors in Anal Cancer

- Tumour size
- T stage
- N stage
- Distant Metastasis
- ? Histological type (probably not !)
- ? Histological grade (probably not !)
- Presence of skin ulceration (EORTC 22861)
- Male sex (ACT 1, EORTC 22861 & RTOG 98-11)
- Low Haemoglobin (ACT 1)
- HIV status (not so important post HAART)
- HPV status & p16 immunohistochemistry

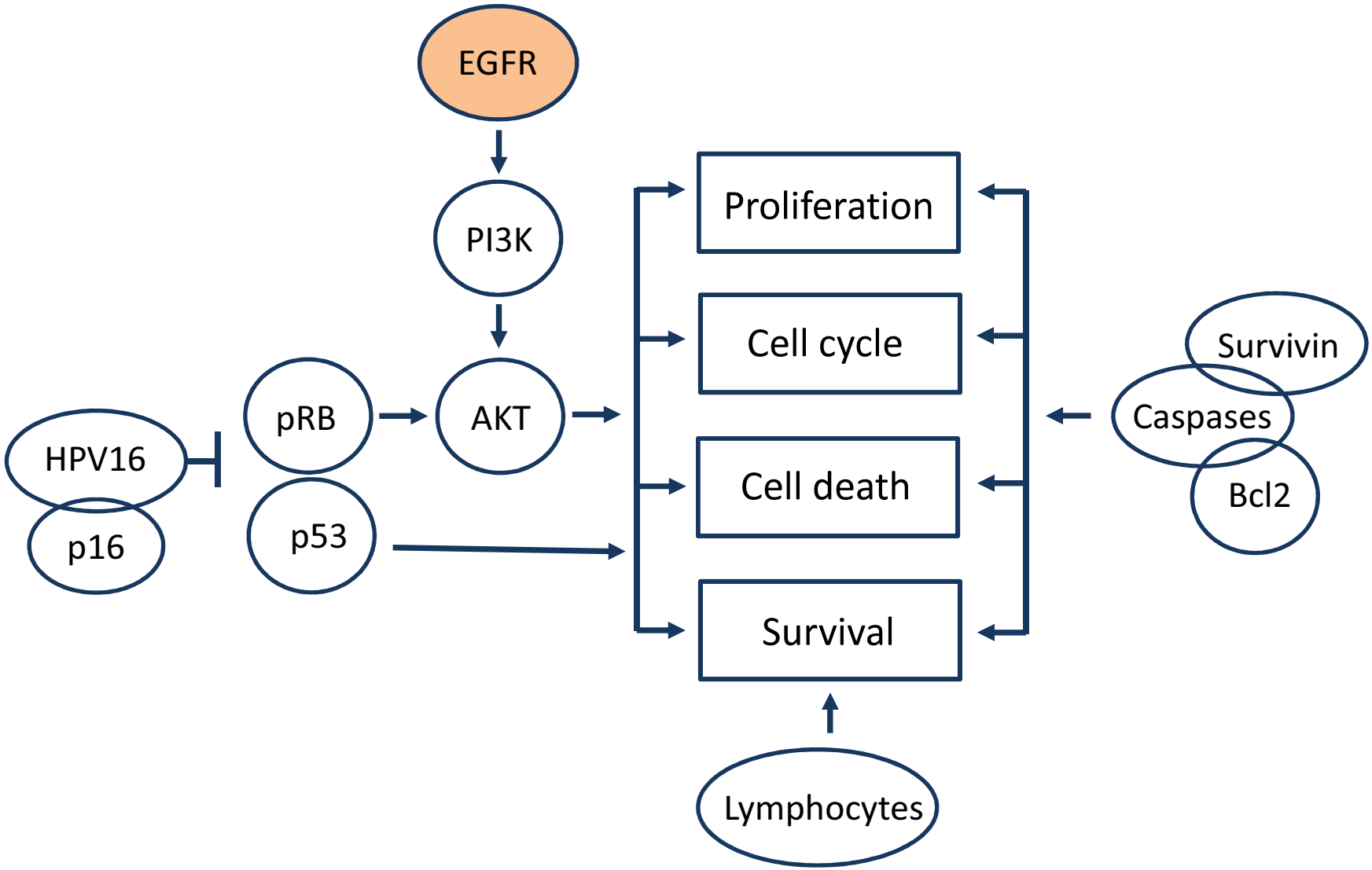
Anal Cancer: Role of molecular markers and targeted agents

Claus Rödel
Department of Radiotherapy
University of Frankfurt
Germany

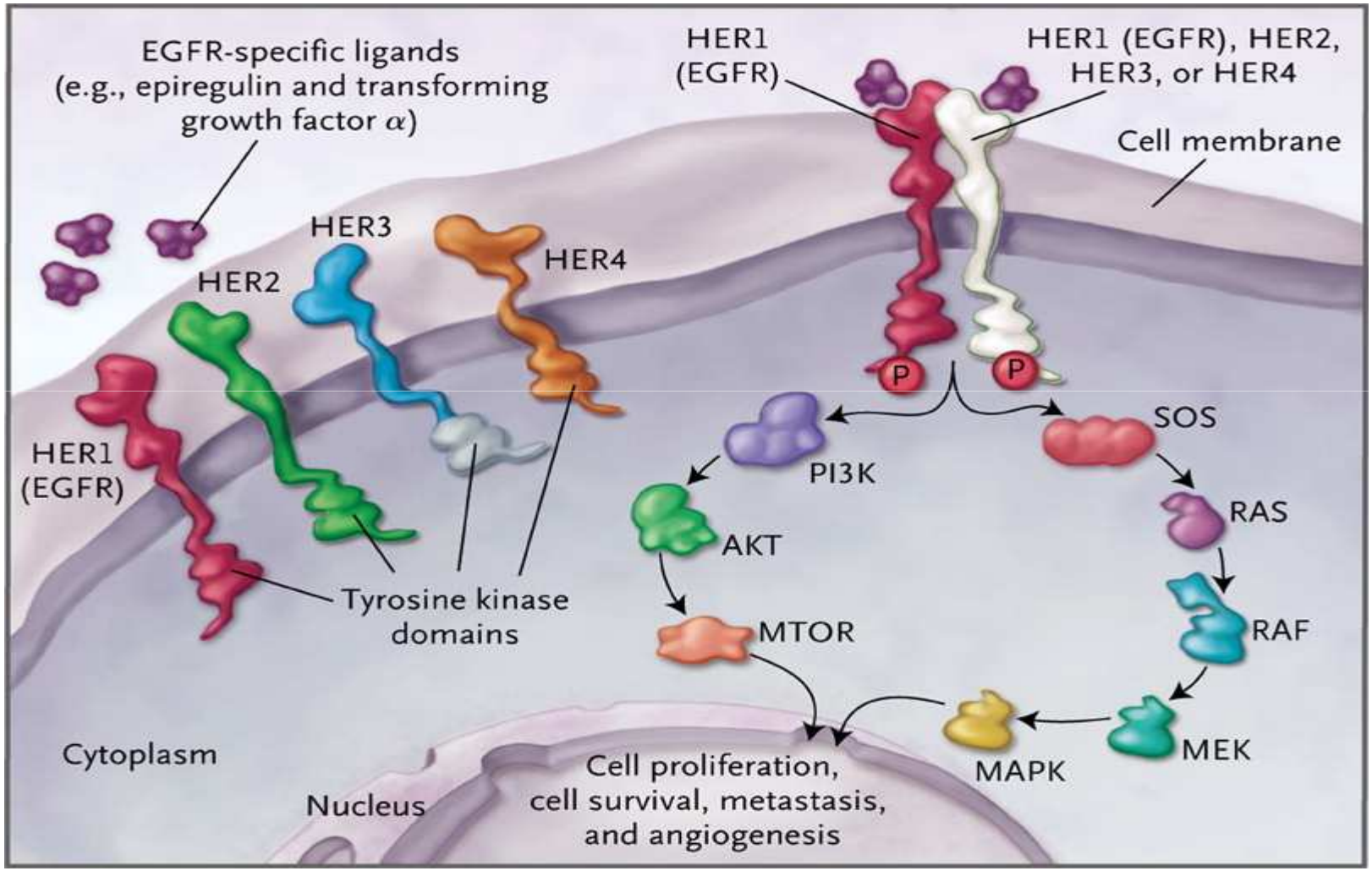
Factors mediating radiation response



Factors mediating radiation response

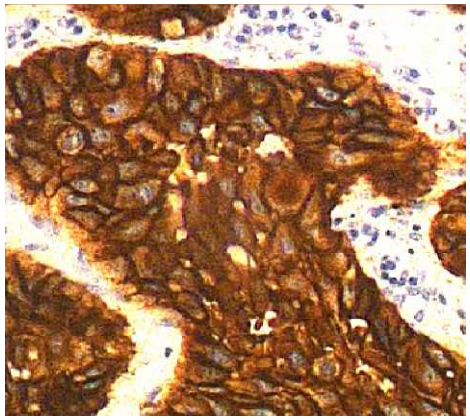
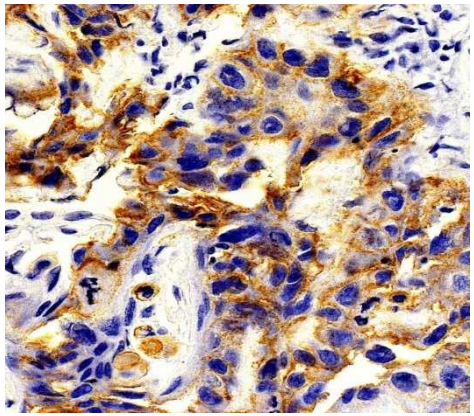
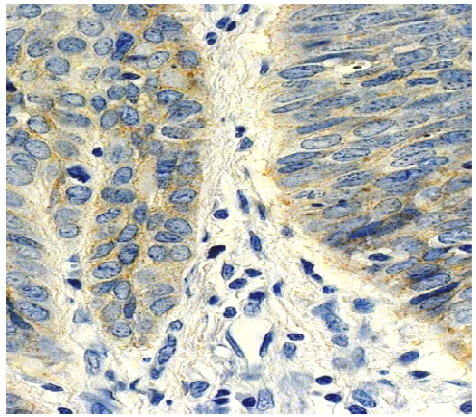


Central Role of EGFR in Proliferation



https://www.blogs.shu.edu/cancer/

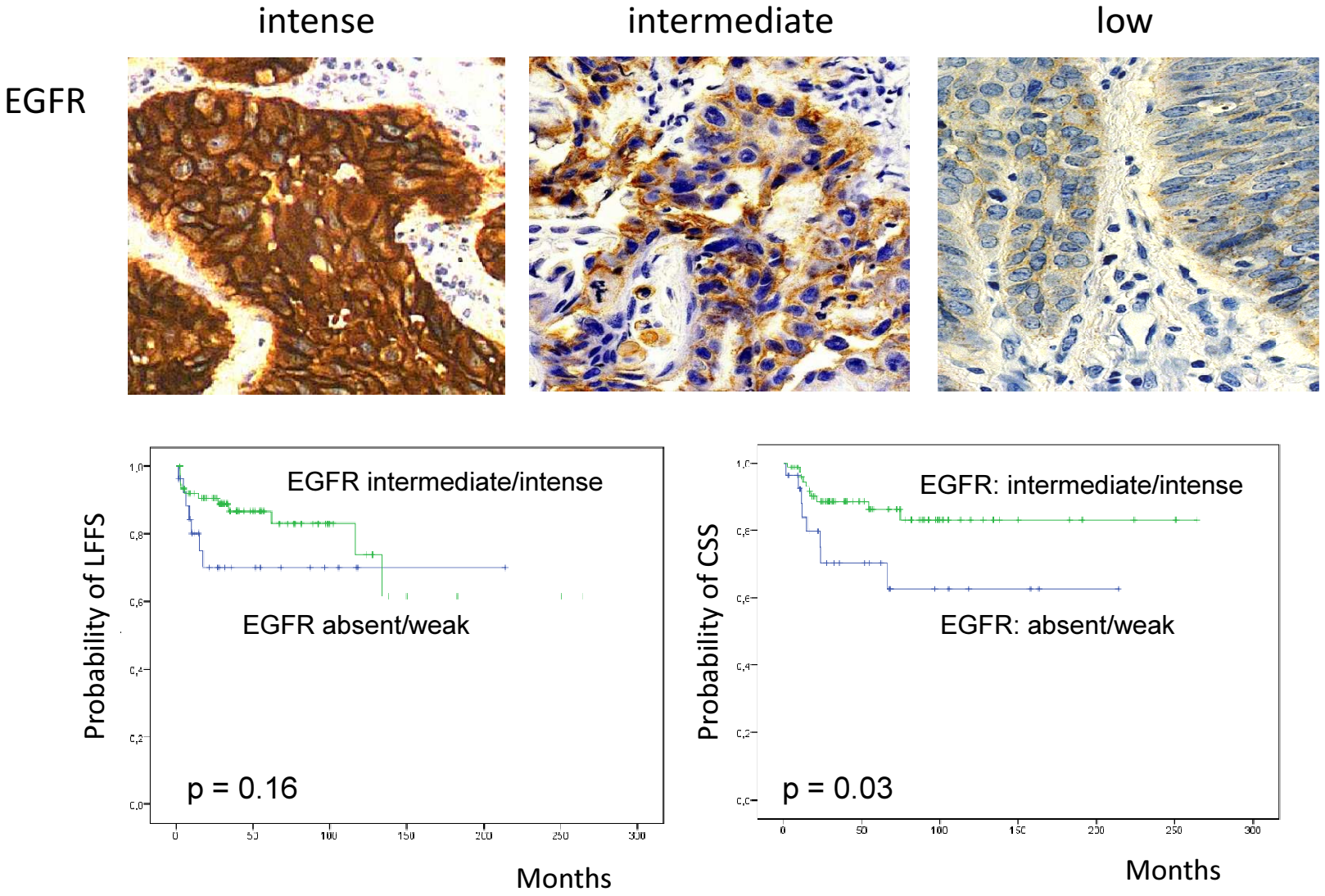
EGFR: Expression in Anal Cancer (n=103)

	intense	intermediate	low
EGFR			
	38%	**36%**	**26%**

Note: most anal cancer are RAS-wt!!

Fraunholz I, Int J Radiat Oncol Biol Phys 2013

EGFR: Prognostic Impact ?



Fraunholz I, Int J Radiat Oncol Biol Phys 2013

Prognostic Relevance of EGFR

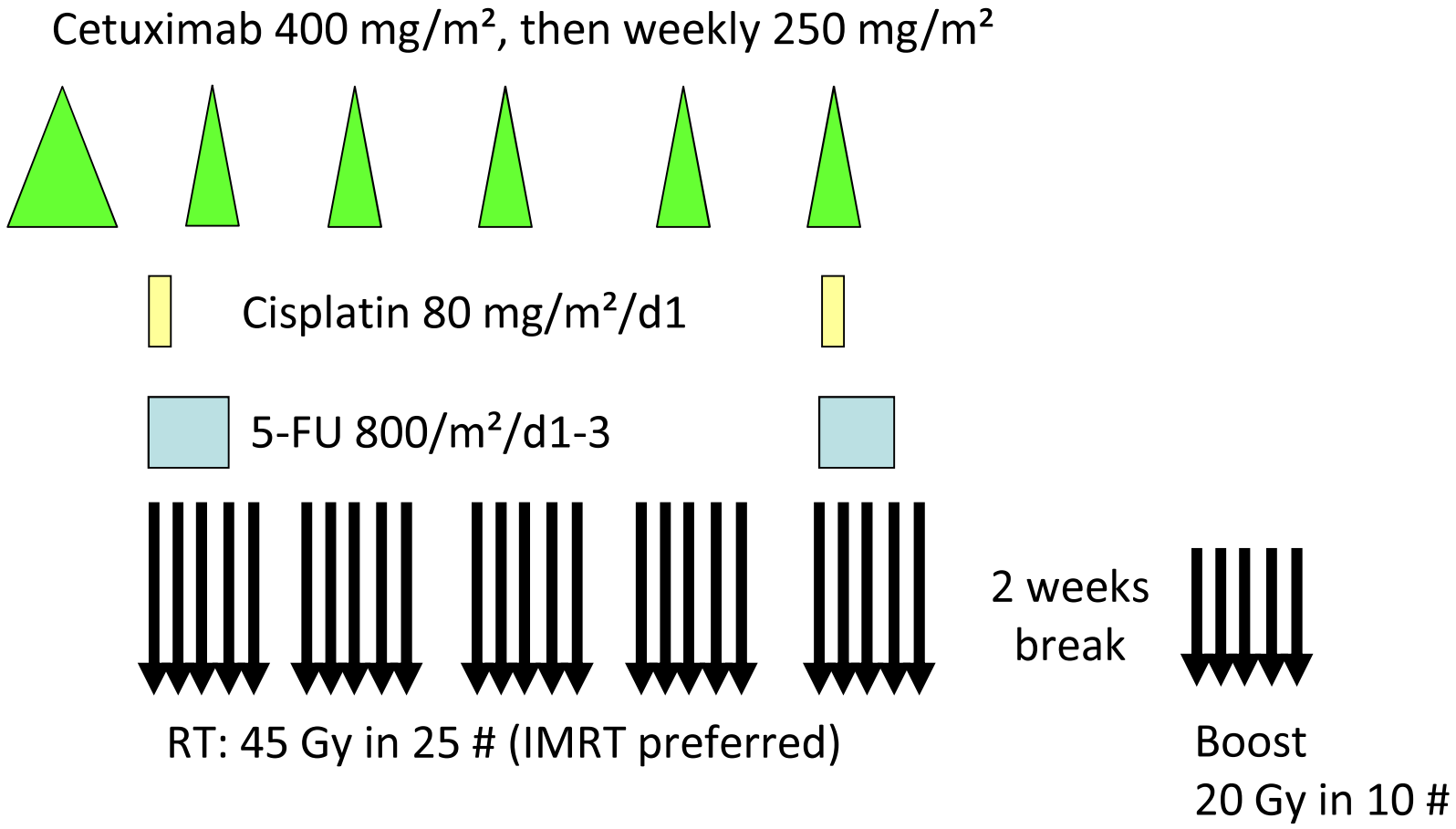
Author	Patients (n)	Results
Richter	17	significant shorter PFS and OS
Fraunholz	103	improved CSS, trend for improved DMFS
Gilbert	148	no correlation to histopathological features and clinical outcome
Mistrangelo	50	no correlation to clinical outcome
Ajani	30	no correlation to DFS

Prognostic relevance of EGFR expression still not resolved

Richter I, Neoplasma 2016, Fraunholz I, Int J Radiat Oncol Biol Phys 2013, Mistrangelo M, Colorectal Dis 2013; Gilbert DC, Radiother Oncol 2013, Ajani J, Dig Dis Sci 2010.

UNICANCER ACCORD 16 phase II trial

Inclusion: $T2_{>3cm}$-T4 or N+ M0, HIV neg;



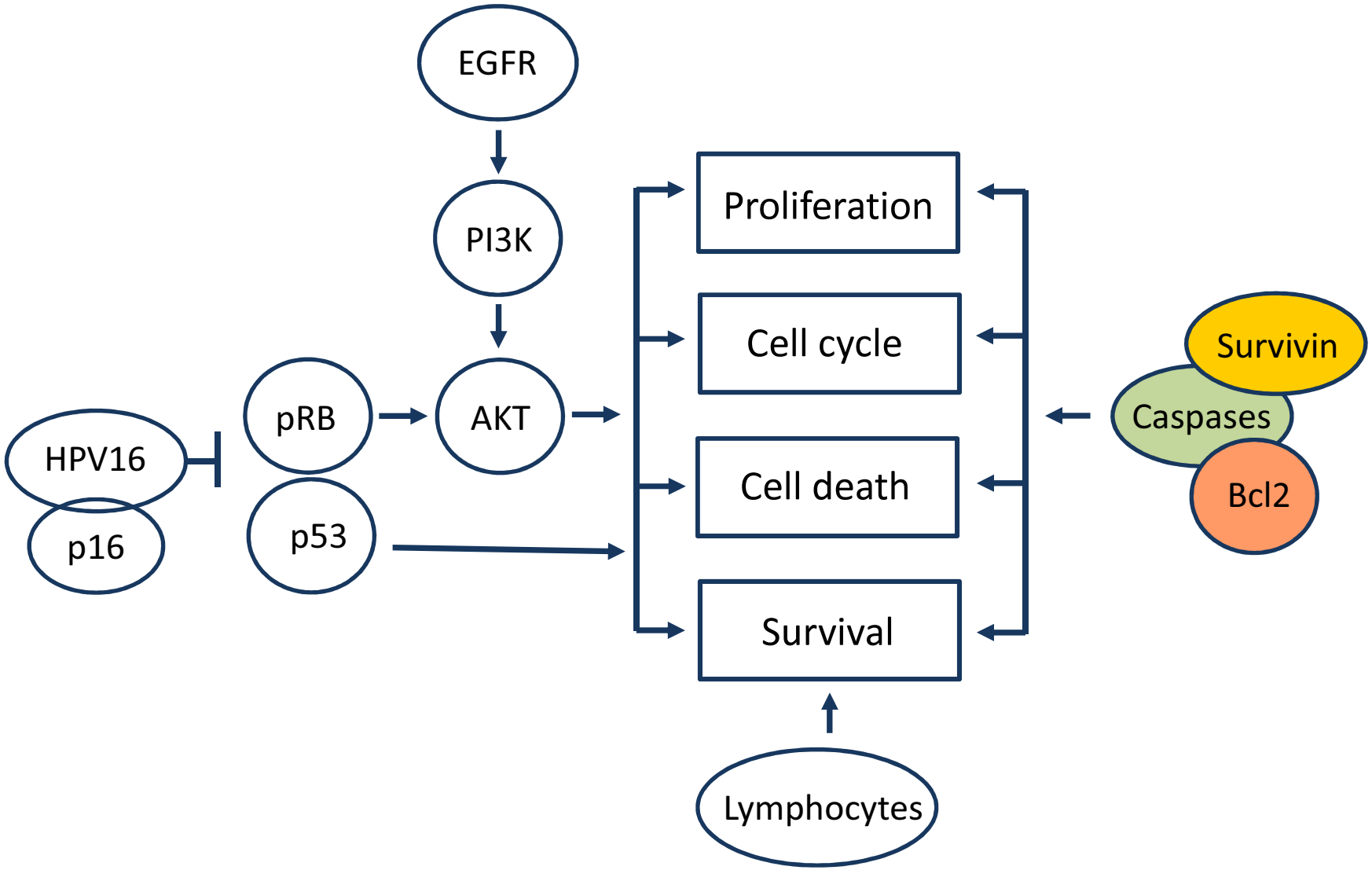
UNICANCER ACCORD 16 phase II trial

Primary endpoint: CR+PR 6 weeks after Tx; 15% increase, 81 pts required

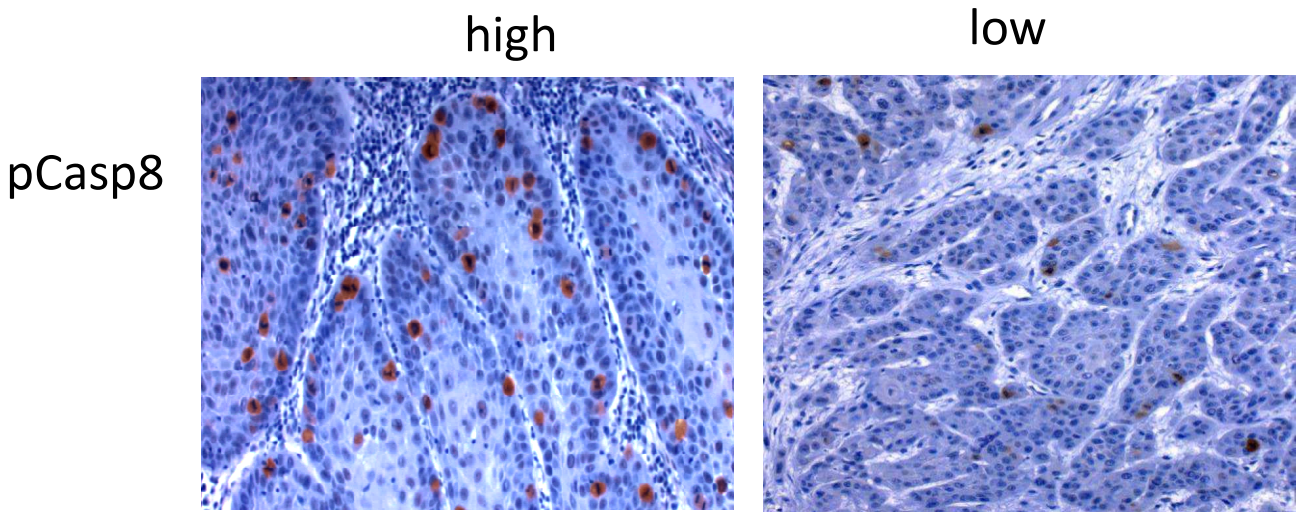
Number	10 pts, + 6 pts after amendments (IMRT mandatory, 5-FU reduced to 600 mg/m^2/d1-3
Compliance	5/16 (31%) received the entire planned tx
Acute grade 3/4 tox	14 (88%), mainly general, digestive, skin
Late grade 3/4 tox	3 pts (%), perineal necrosis, fistula, pain, ...
Response 6 weeks after Tx	11 assessable: CR 6, PR 5
Long-term outcome (med. F/U: 4.6 years)	PFS (4 years): 53%, incl. 6 Local Failures

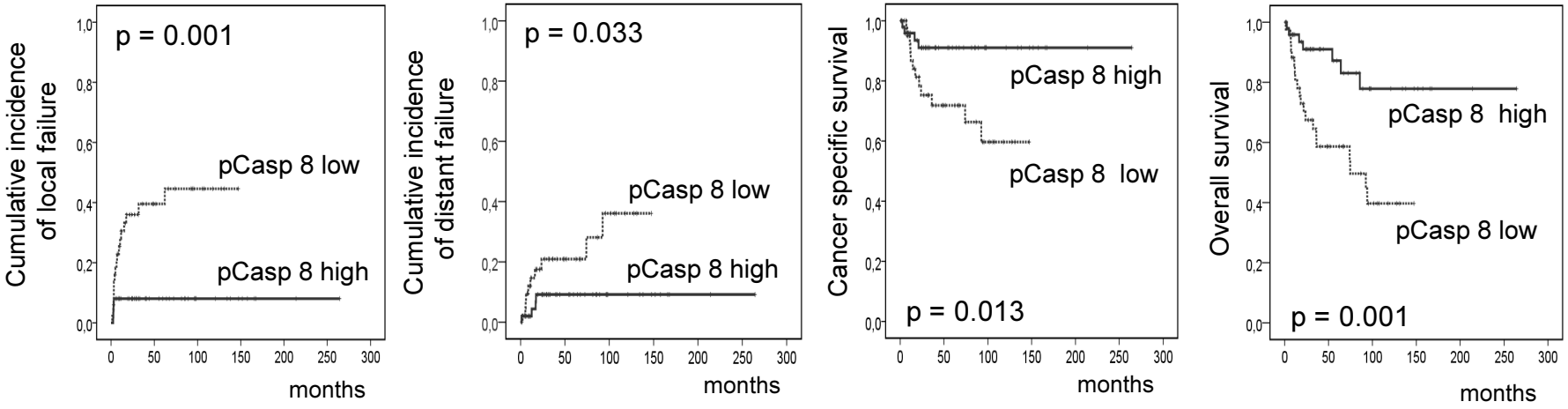
Deutsch E., et al. Ann Oncol 2013
Update: Levy A, et al. Radiother Oncol 2015

Factors mediating radiation response



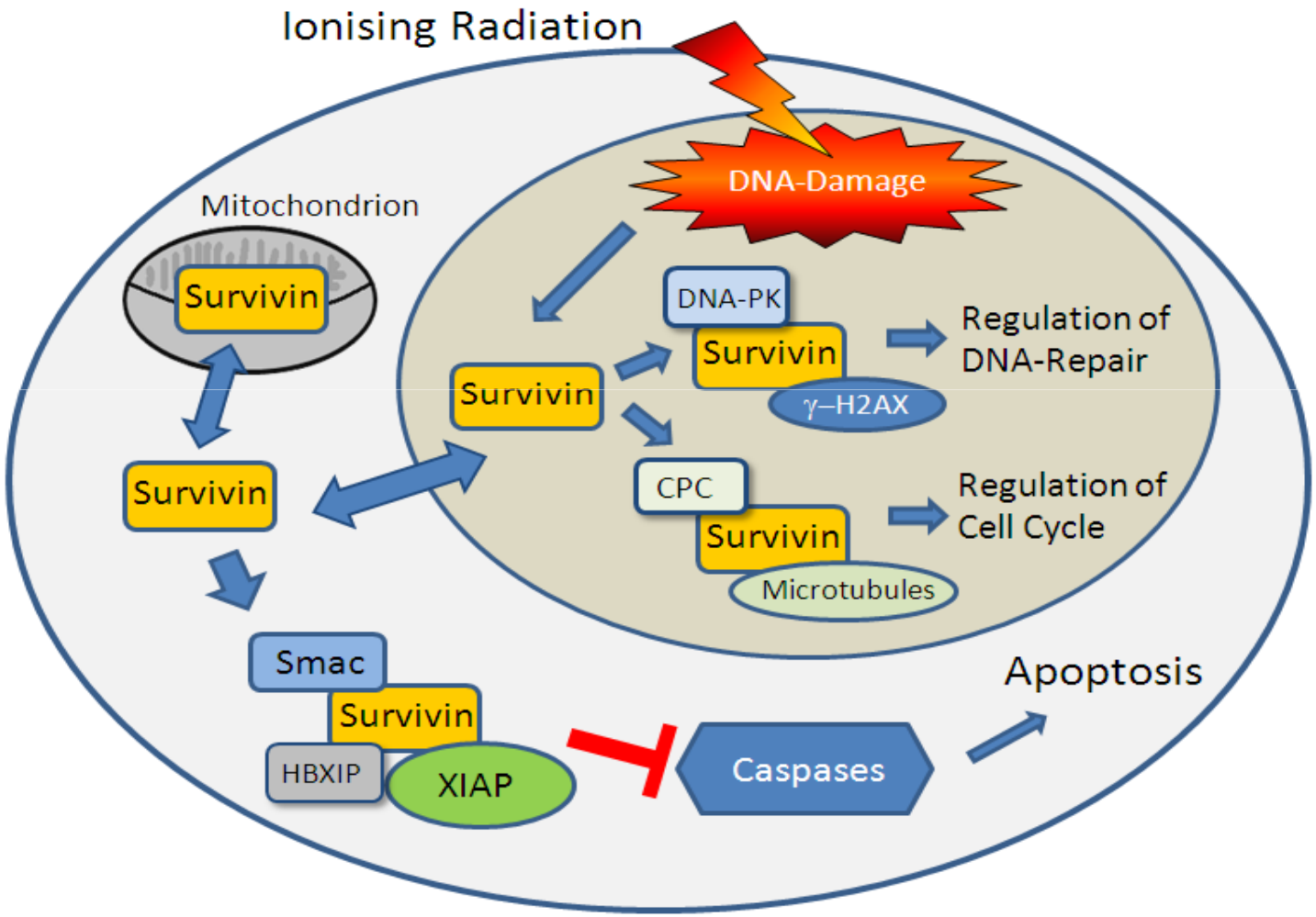
phosphoCaspase 8: Response Prediction





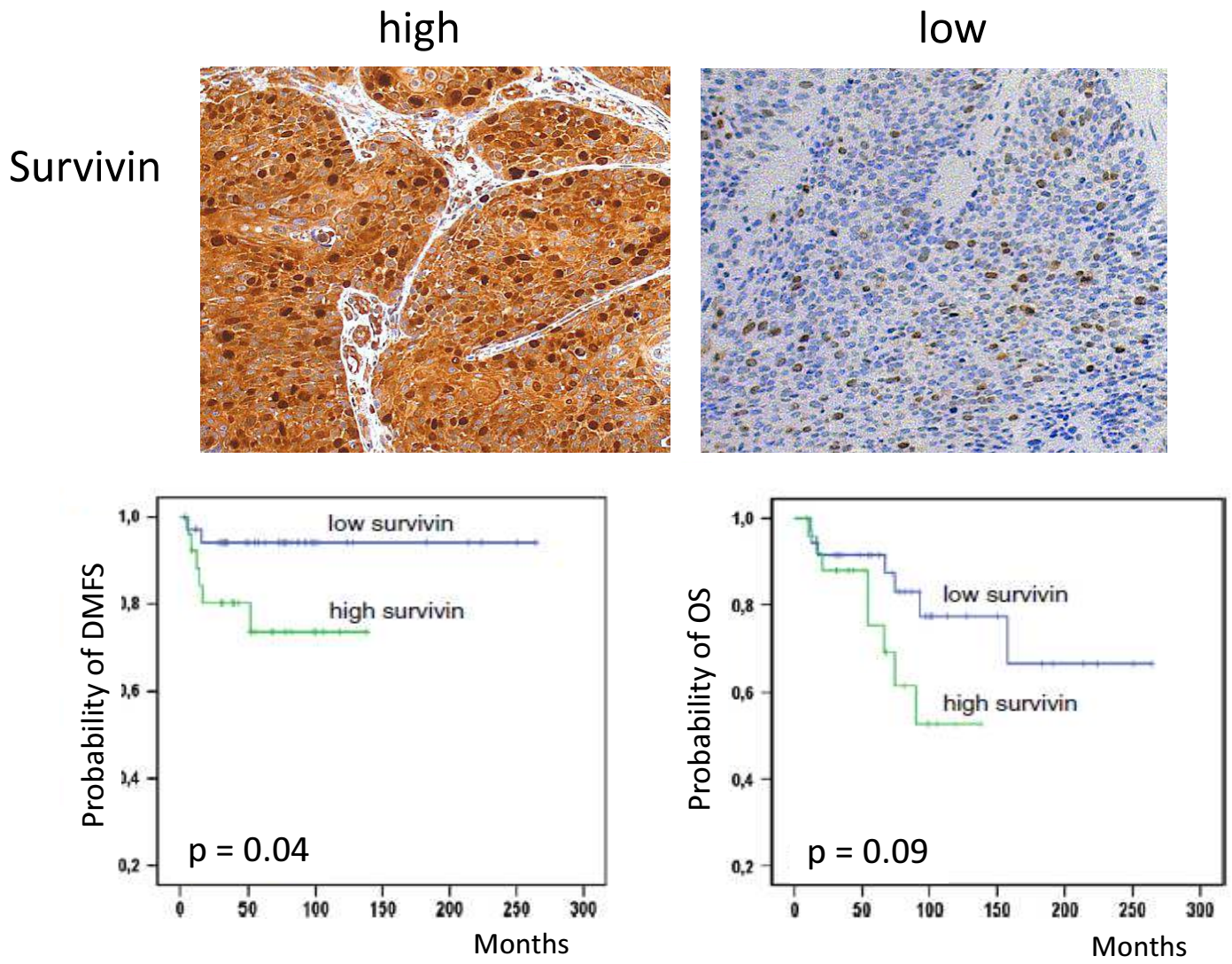
Rödel F, submitted 2016

Survivin: A Nodal Protein



Rödel F, Curr Med Chem 2012

Survivin: Response Prediction



Fraunholz I, Radiat Oncol 2012

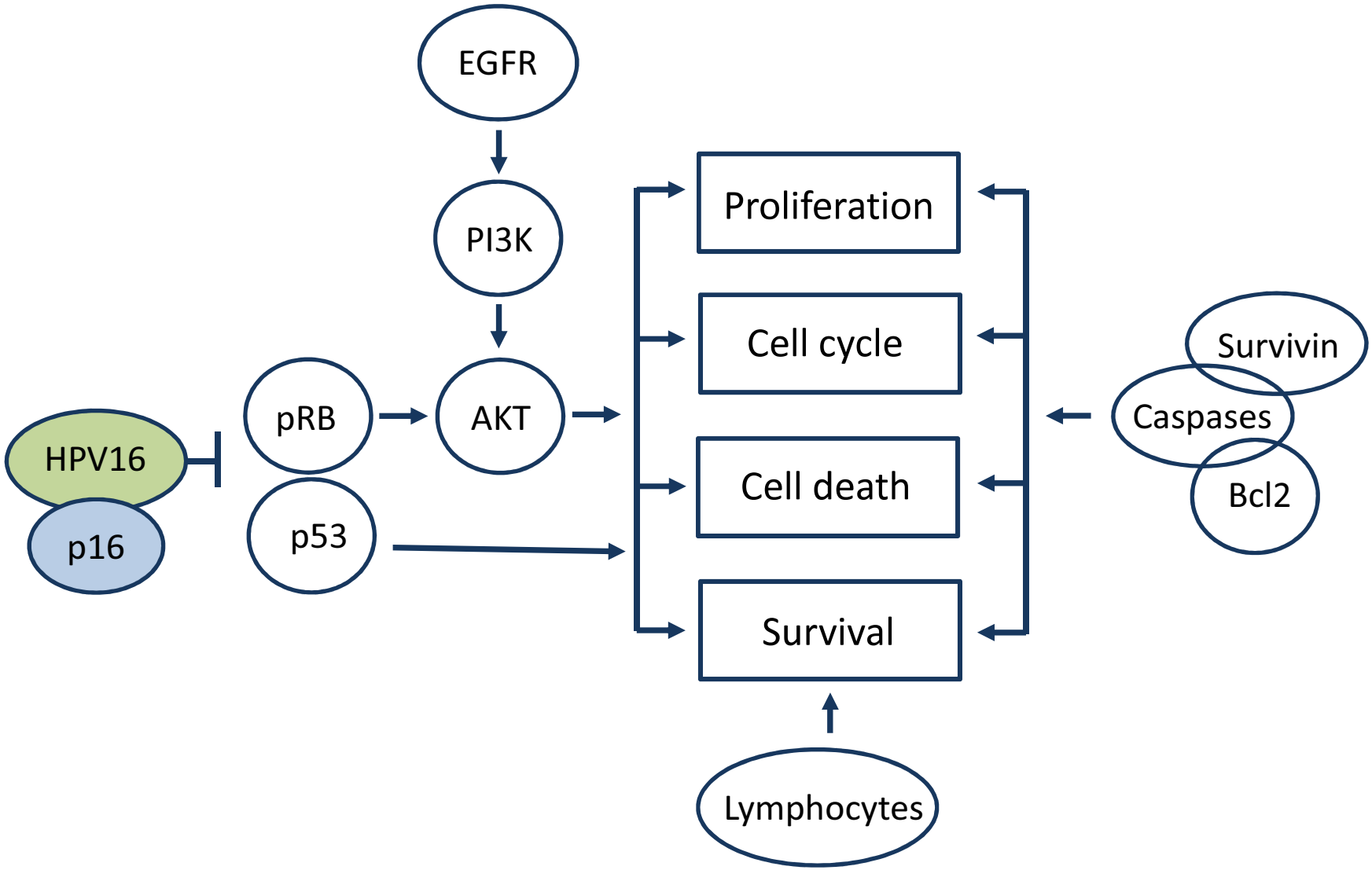
Prognostic Relevance of Apoptosis-related Markers

Author	Patients (n)	Marker	Results
Wong	58	p53	reduced local control and DFS
Allal	98	Bcl2, M30	Bcl2: improved local control and DFS M30: reduced local control and DFS
Ajani	30	NF-κB	reduced DFS
Fraunholz	62	Survivin	reduced DMFS and OS
Rödel	95	pCaspase 8	improved local and distant control, CSS and OS

Prognostic relevance of apoptosis-related markers still controversial

Rödel 2016 submitted; Fraunholz I, Radiat Oncol 2012, Allal AS, Clin Cancer Res 2003; Ajani JA, Dig Dis Sci 2010; Wong CS, Int J Radiat Oncol Biol Phys 1999

Factors mediating radiation response

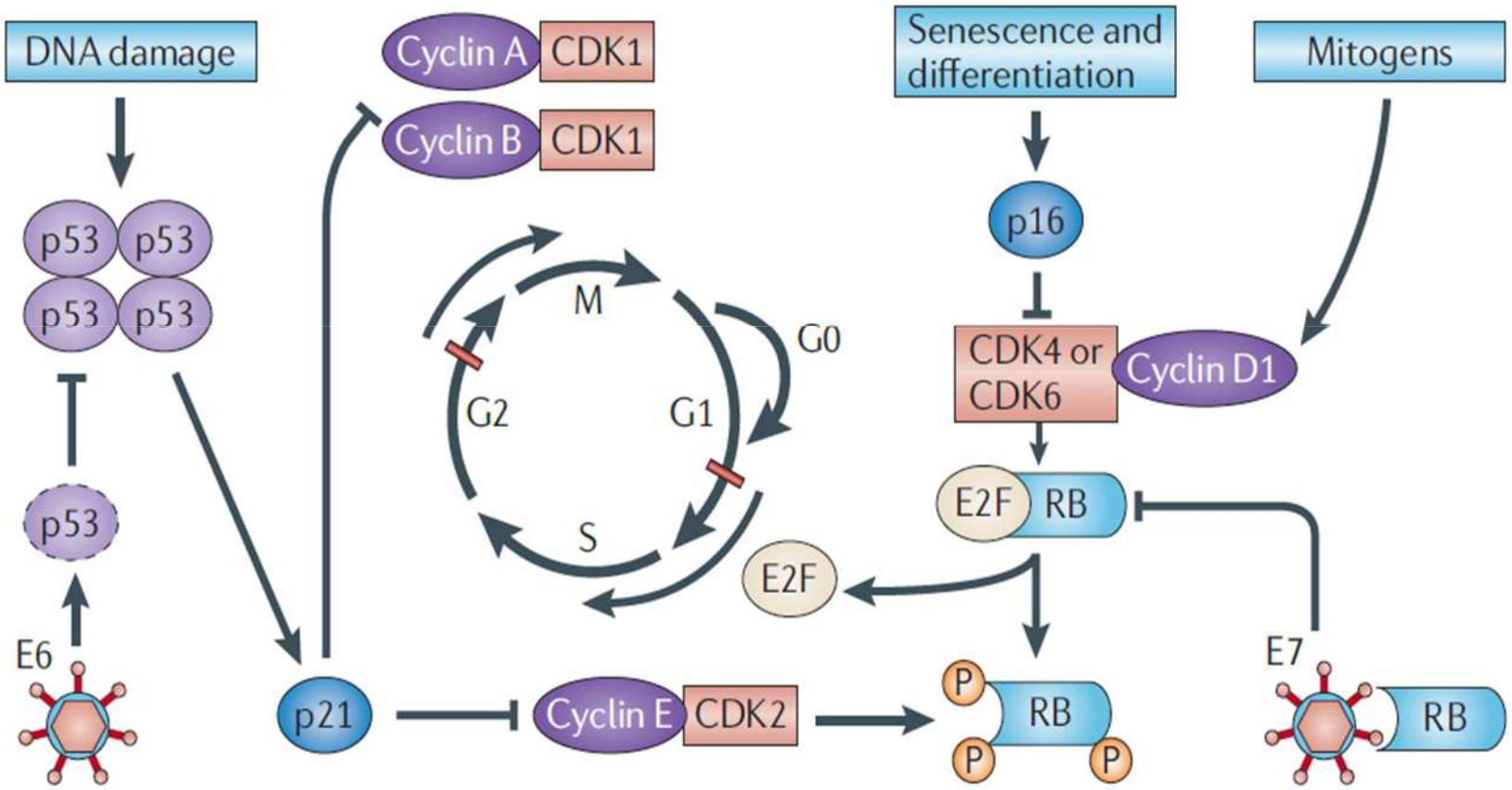


HPV-Prevalence in Anal SCC

Author	HPV total (%)	HPV16 (%)
Koerber	83.3	76.6
Mai	67.9	
Rödel	95.8	78.9
Serup-Hansen	87.5	79.8
Baricevic	95	89

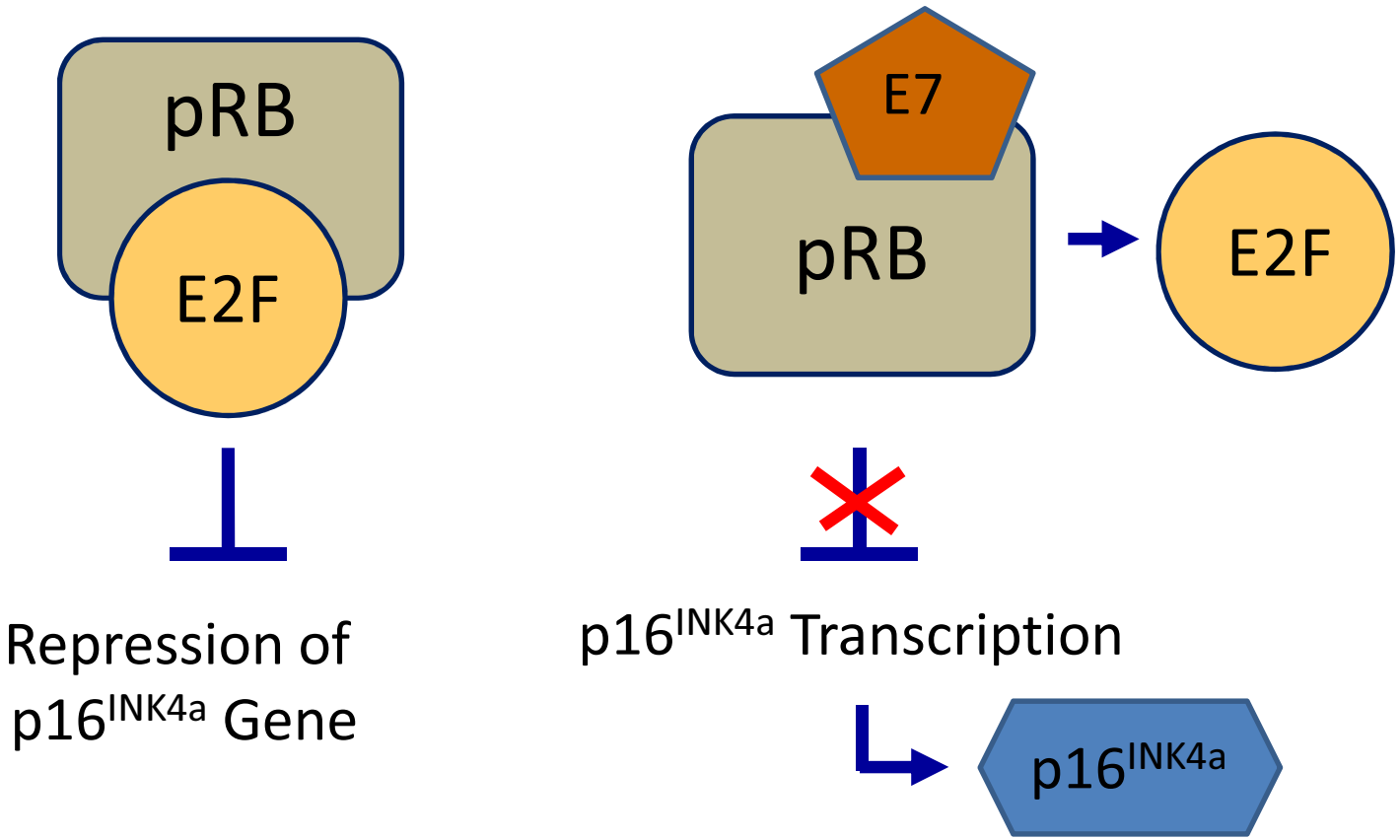
Koerber S, Radiother Oncol 2014; Mai S, Int J Radiat Oncol Biol Phys 2015; Rödel F, Int J Cancer 2015; Baricevic I, Eur J Canc 2015; Serup-Hansen E, J Clin Oncol 2014

Molecular Pathology of HPV

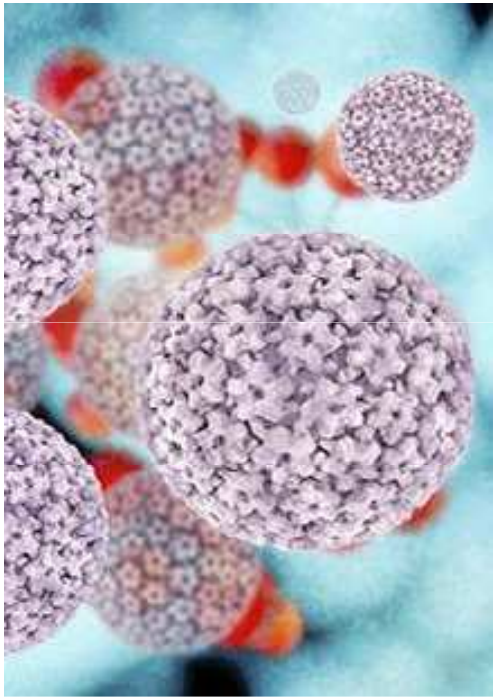


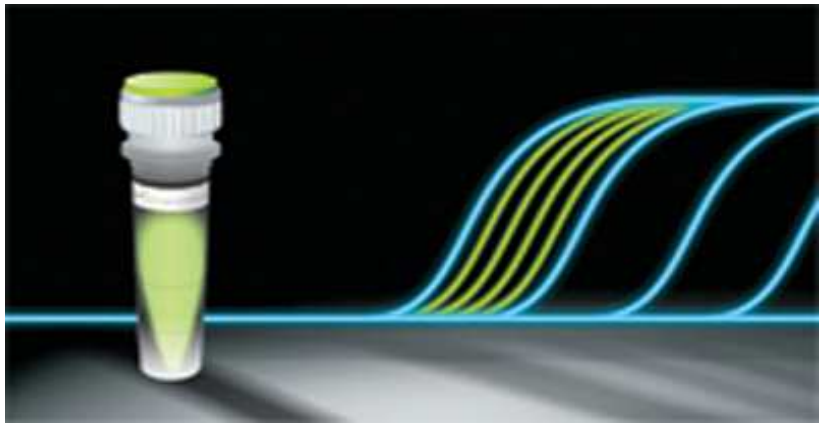
Leemans C, Nat Rev Cancer 2011

HPV E7 increases Expression of $p16^{INK4a}$

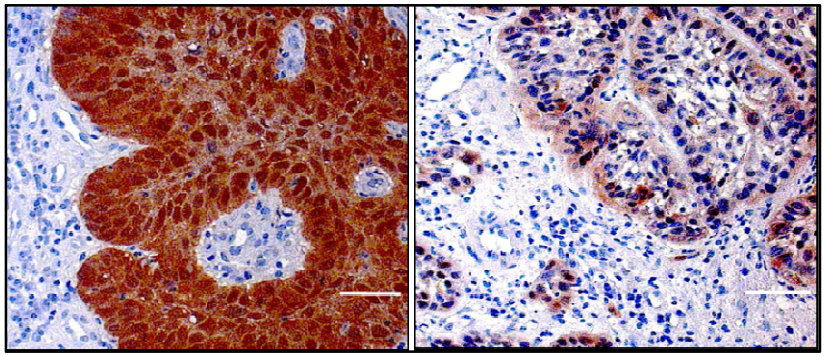


HPV-Detection



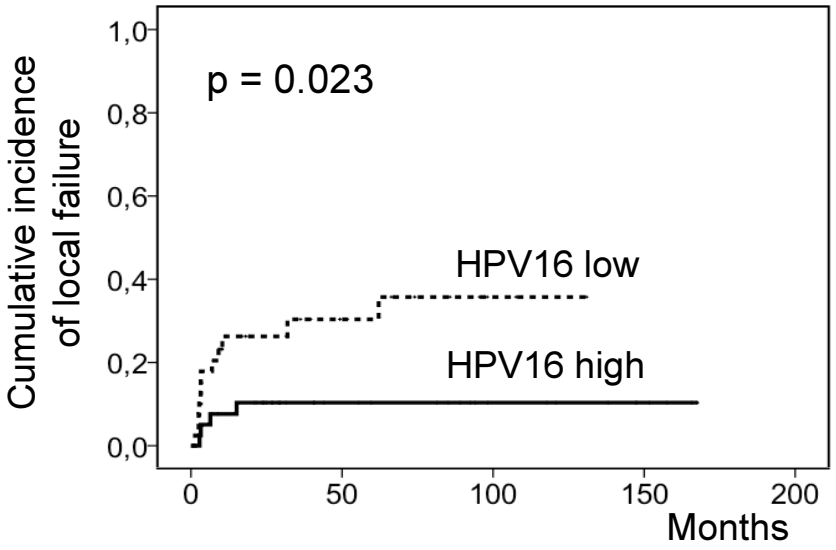


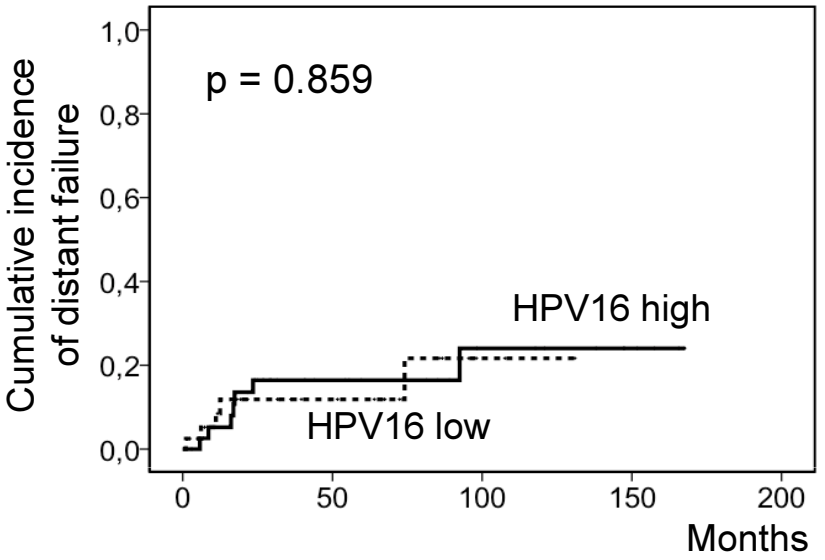
Genotype-specific quantitative PCR

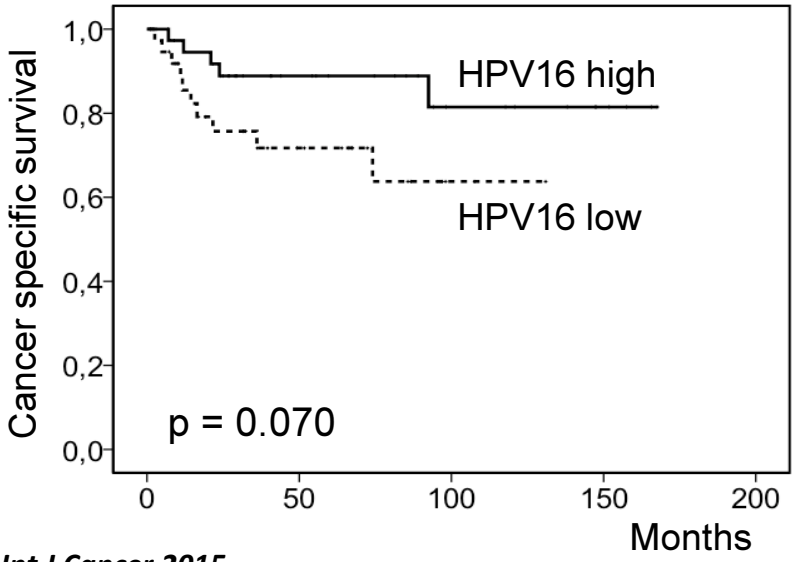


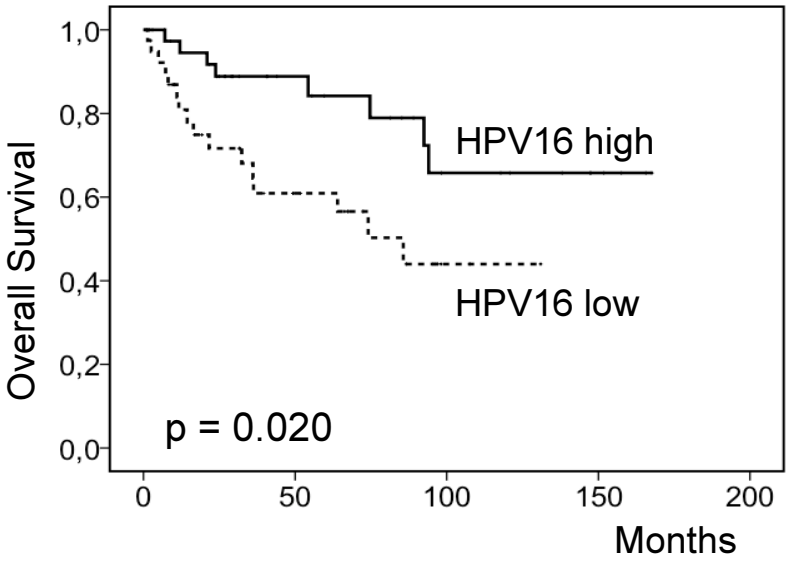
Immunohistochemistry $p16^{INK4a}$

HPV16 DNA Load: Response Prediction



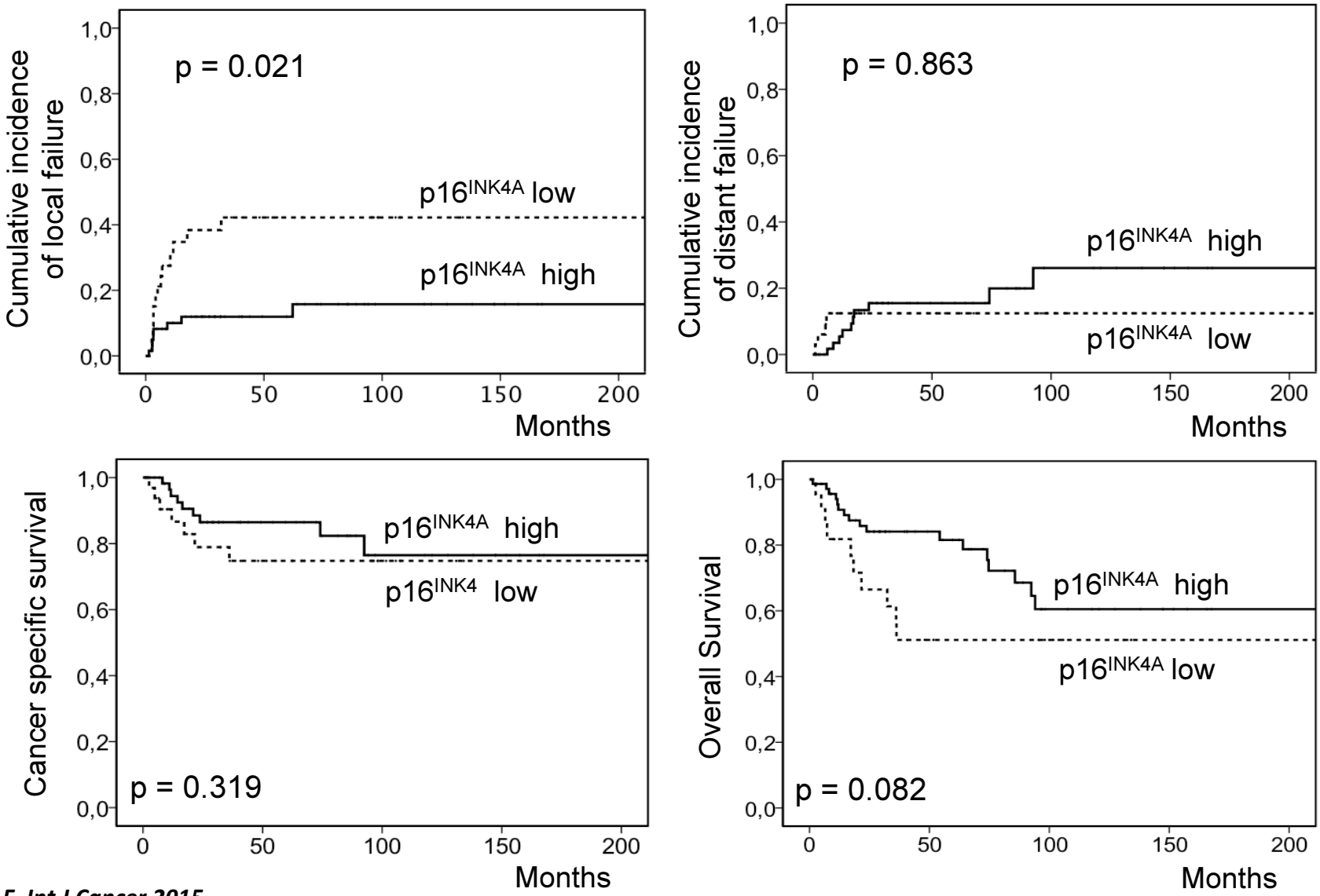






Rödel F, Int J Cancer 2015

p16^{INK4a} Detection: Response Prediction



Rödel F, Int J Cancer 2015

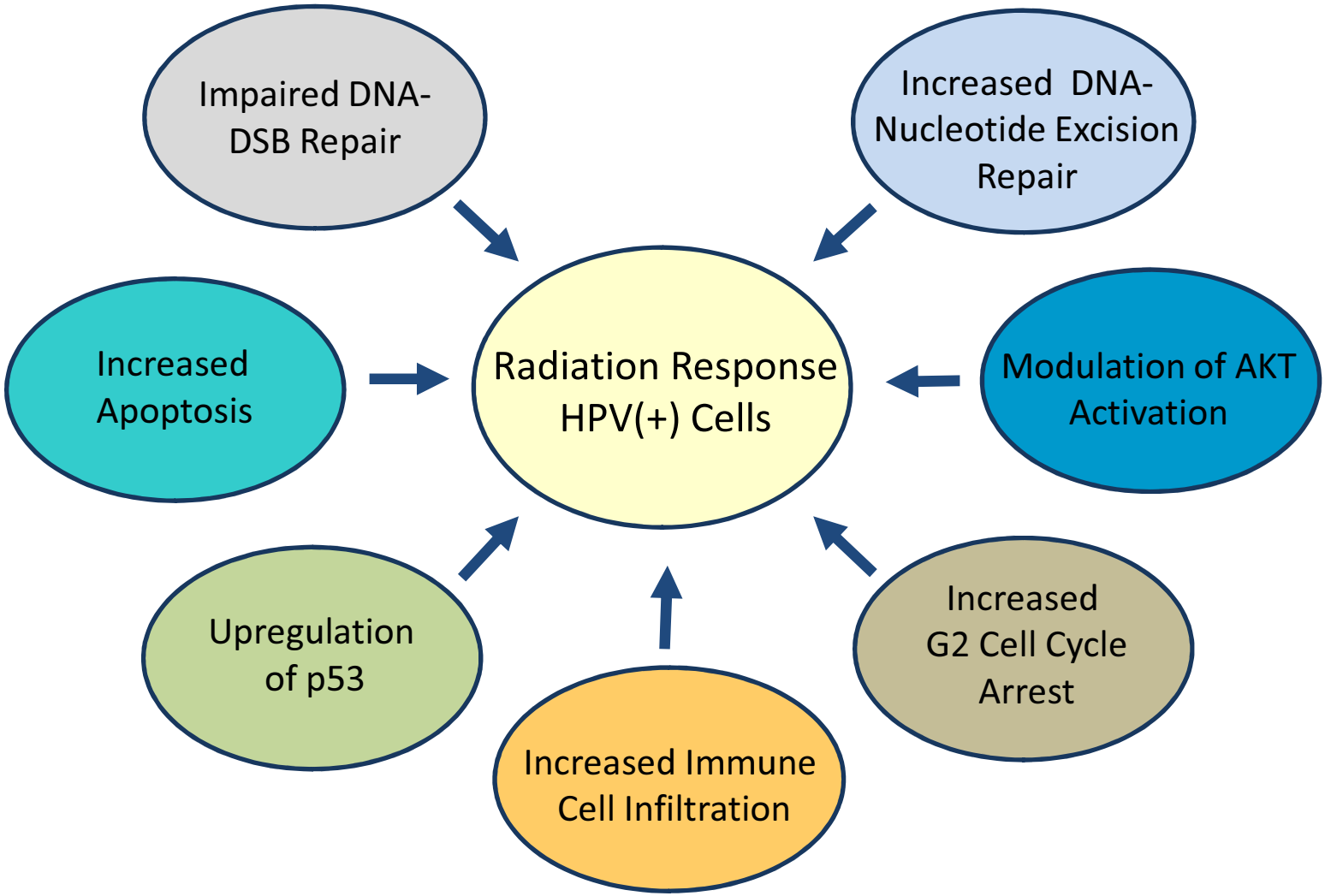
Prognostic Relevance of HPV and p16

Author	Patients (n)	Results
Körber	105	increased local control, PFS, OS
Mai	106	increased 5 years local control and trend to increased OS
Rödel	95	improved local control, CSS and OS
Serup-Hansen	143	improved DSS and OS
Baricevic	110	improved relapse-free survival and OS

HPV and p16 positivity associated with a favourable clinical response and increased survival

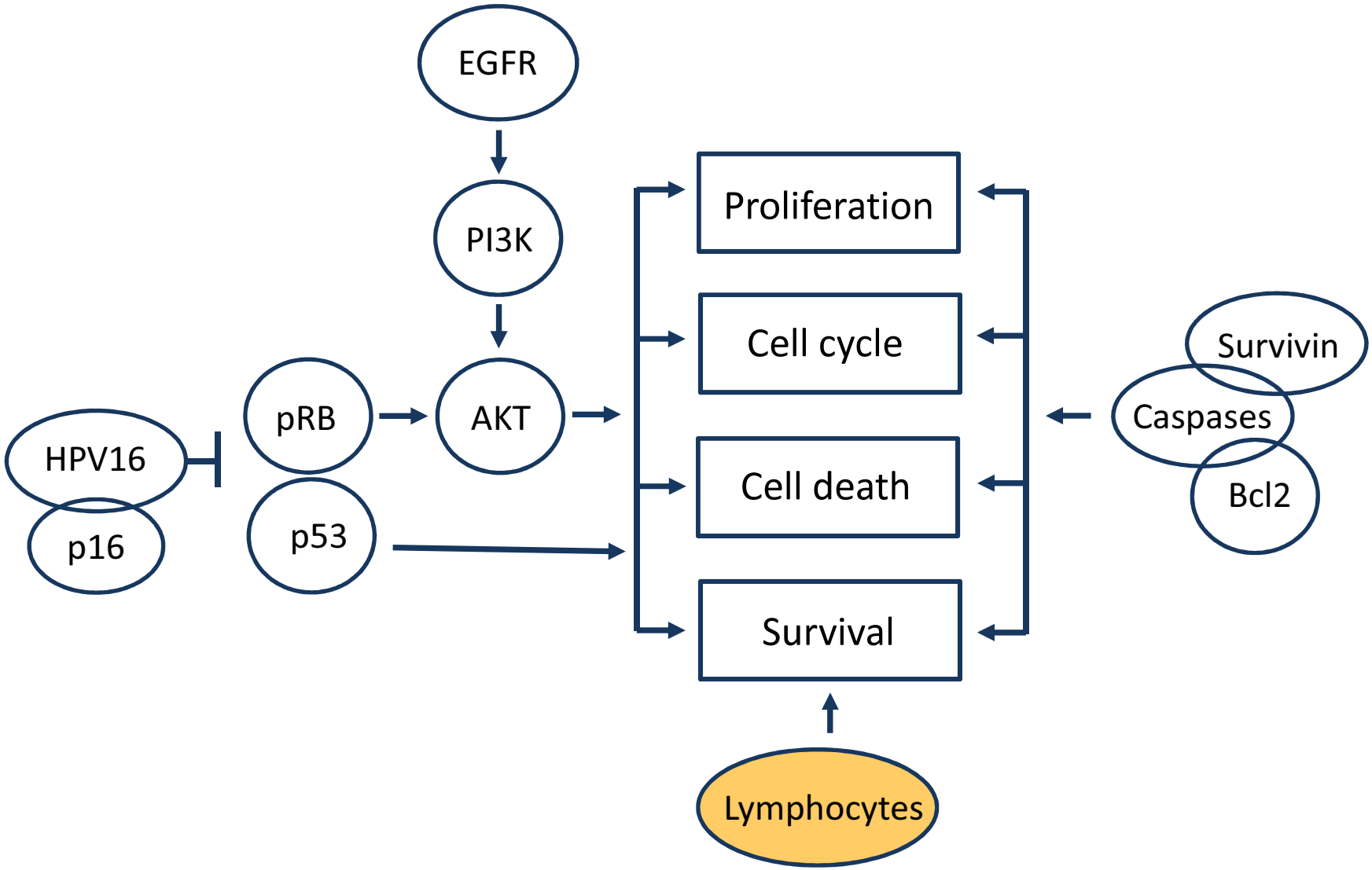
Körber S, Radiother Oncol 2014; Mai S, Int J Radiat Oncol Biol Phys 2015; Rödel F, Int J Cancer 2015; Baricevic I, Eur J Cancer 2015; Serup-Hansen E, J Clin Oncol 2014.

Modulation of Therapeutic Sensitivity by HPV

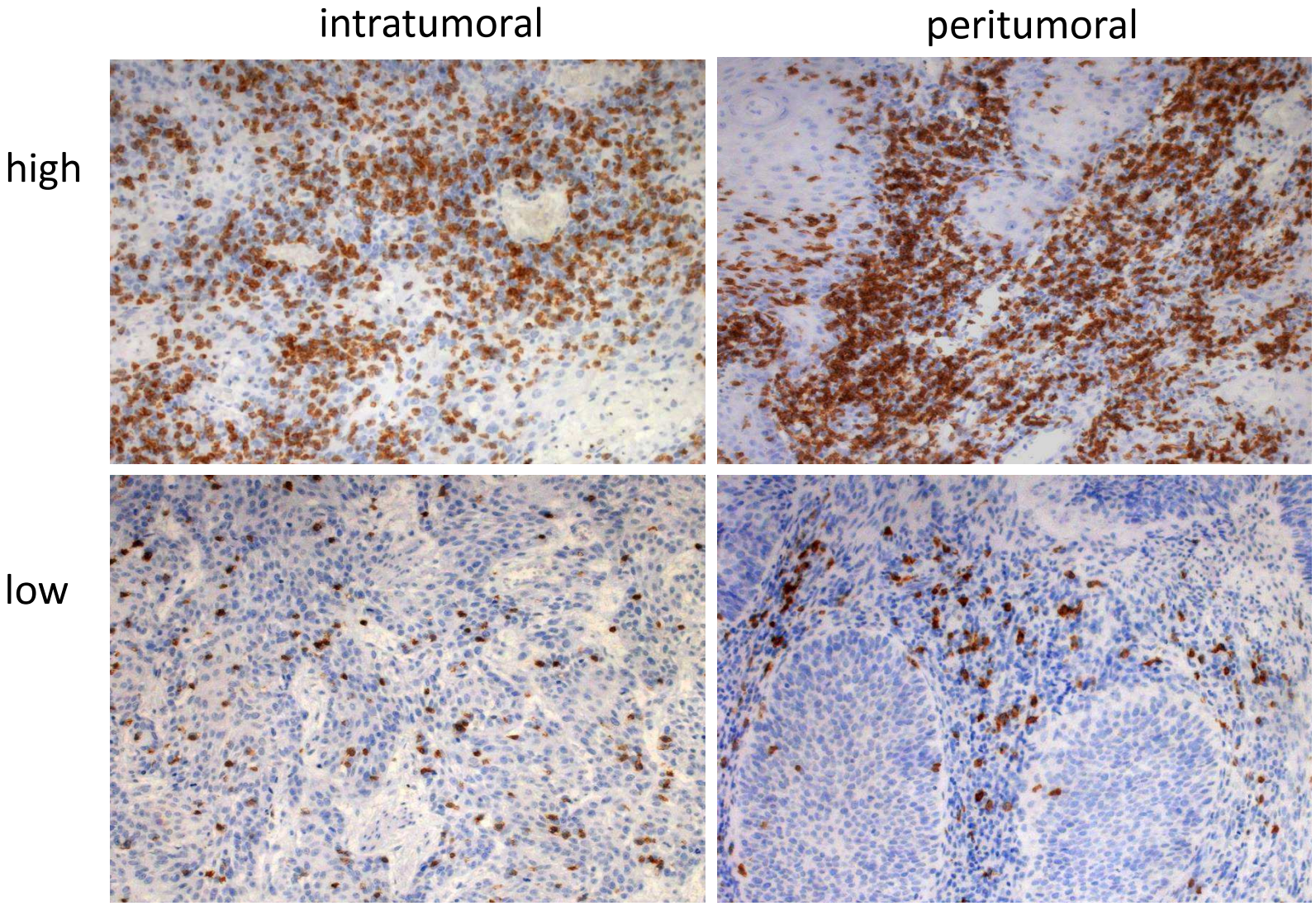


Gilbert DC, Br J Cancer 2016; Dok R, Cancer Res 2014; Arenz A, Strahlenther Onkol 2014: Rieckmann T, Radiother Oncol 2013; Kimple RJ, Cancer Res 2013; Gupta AK, Int J Radiat Oncol Biol Phys 2009.

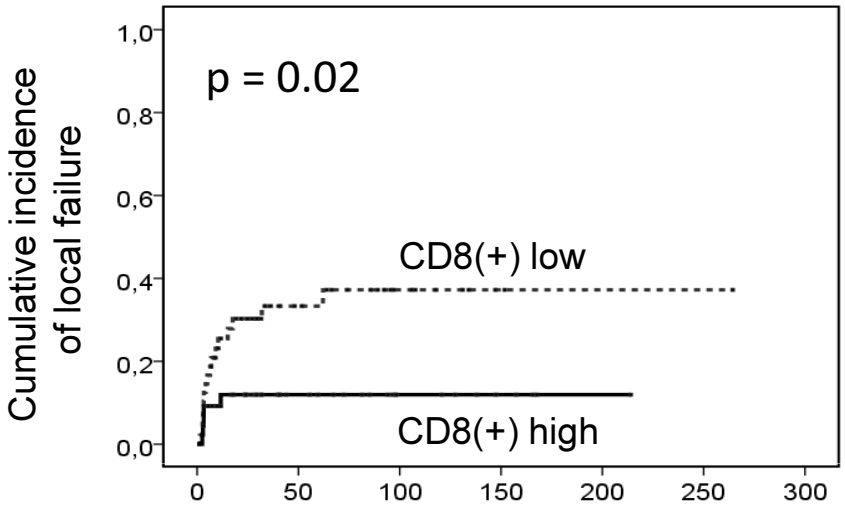
Factors mediating radiation response

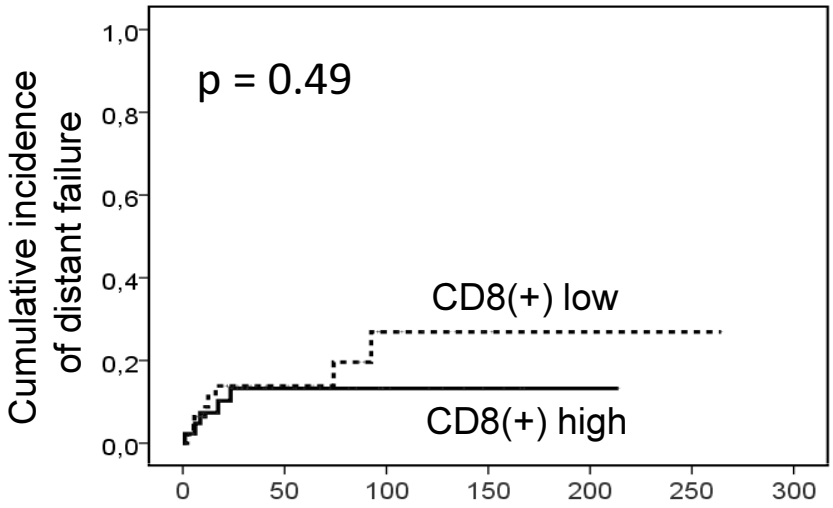


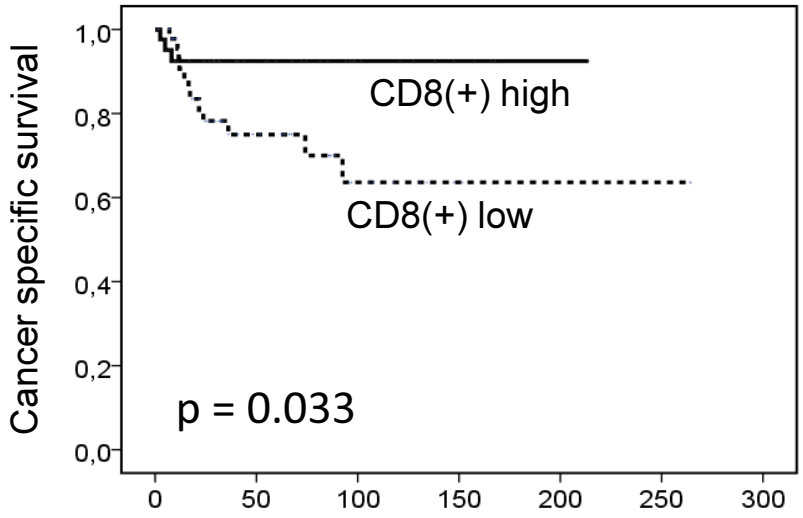
CD8(+) TILs Detection in Anal Carcinoma

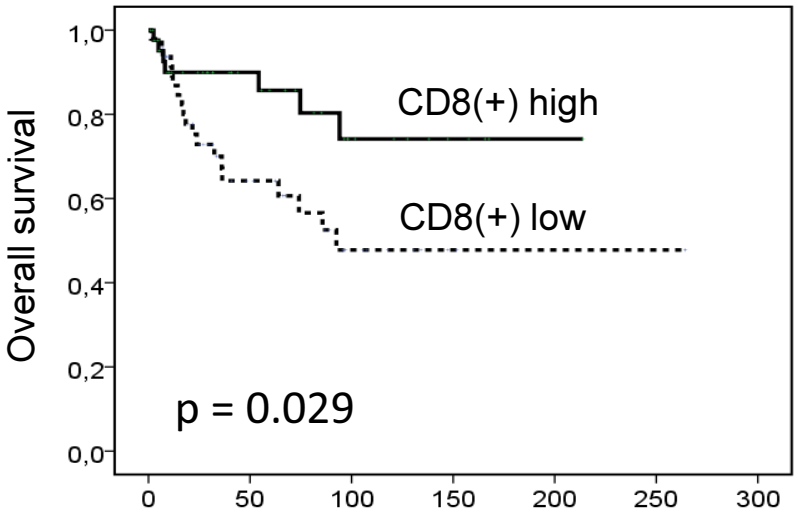


TILs: Response Prediction









Rödel F, submitted 2016

Prognostic relevance of TILs

Author	Patients (n)	Results
Grabenbauer	38	CD3/CD4: decreased 3 years NED
Rubio	277	CD3/CD8: increased 15 years survival
Hu	40	intratumoral CD8: increased DFS peritumoral CD8: increased OS
Gilbert	153	increased relapse-free survival

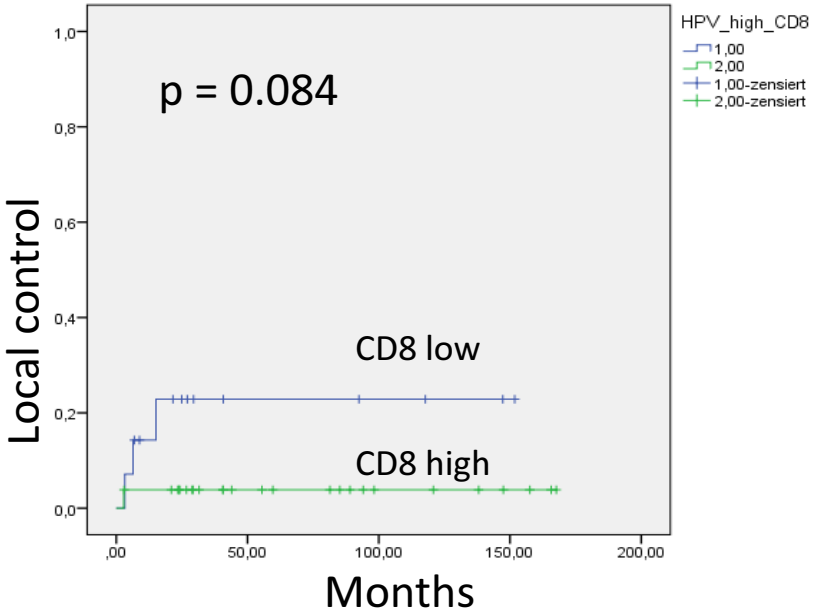
High levels of TILs, especially CD8(+) cells, are associated with a favourable clinical response and survival

Grabenbauer G, Clin Cancer Res 2006; Rubio C, Int J Clin Exp Pathol 2008; Hu W, J Surg Oncol. 2015; Gilbert DC, Br J Cancer 2016

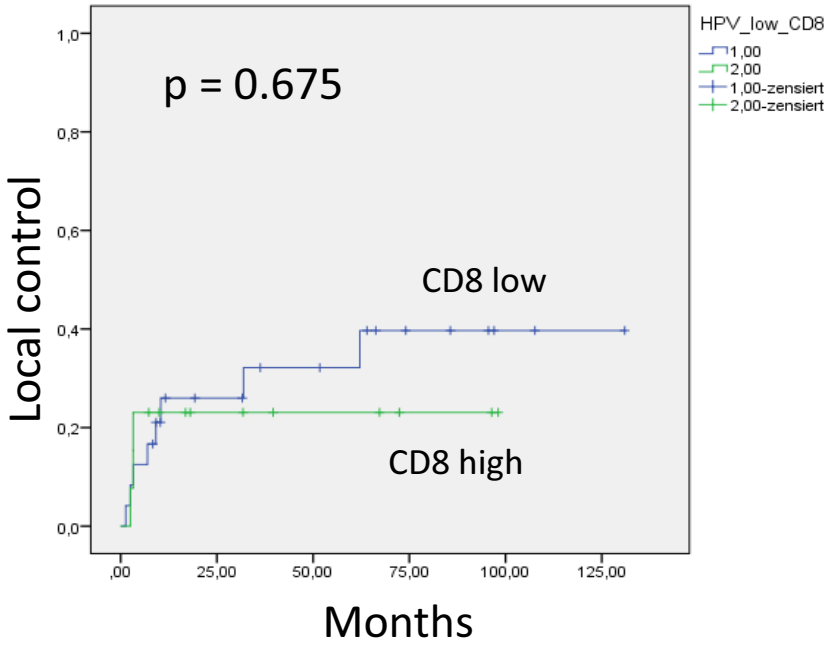
Correlation CD8(+) TILs and HPV16/p16^{INK4a}

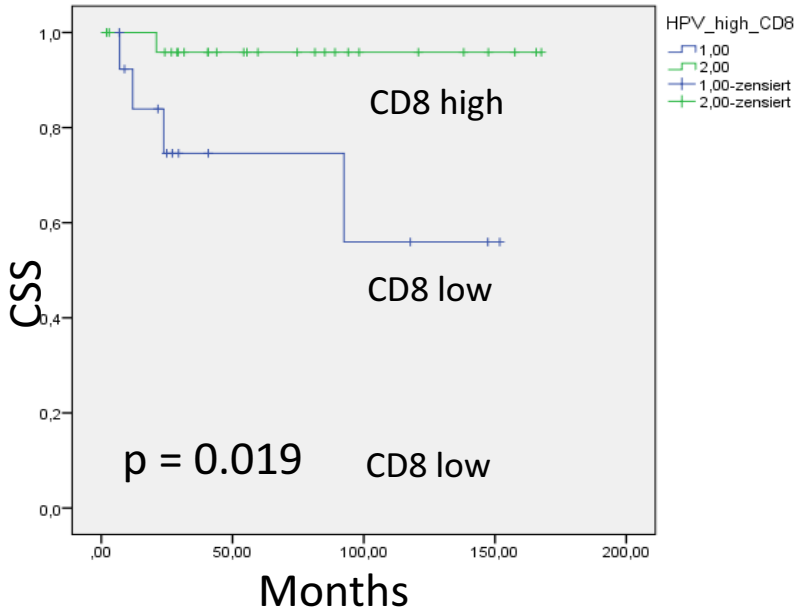
Marker	No. of patients	CD8(+) low	CD8(+) high	p-value
HPV-16 load				
HPV-16 ≤ Med	39	24 (61.6%)	15 (37.5%)	**0.033**
HPV-16 > Med	40	15 (38.4)	25 (62.5)	
p16^{INK4a}				
p16 WS ≤ 6	23	16 (33.3%)	32 (45.0%)	**0.042**
p16 WS > 6	71	32 (66.7%)	39 (55.0%)	

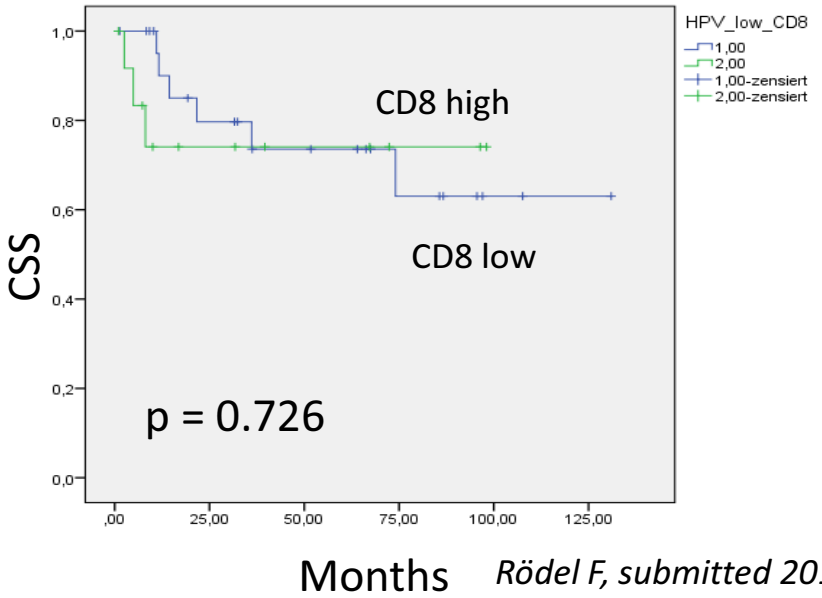
HPV 16 viral load high



HPV 16 viral load Low



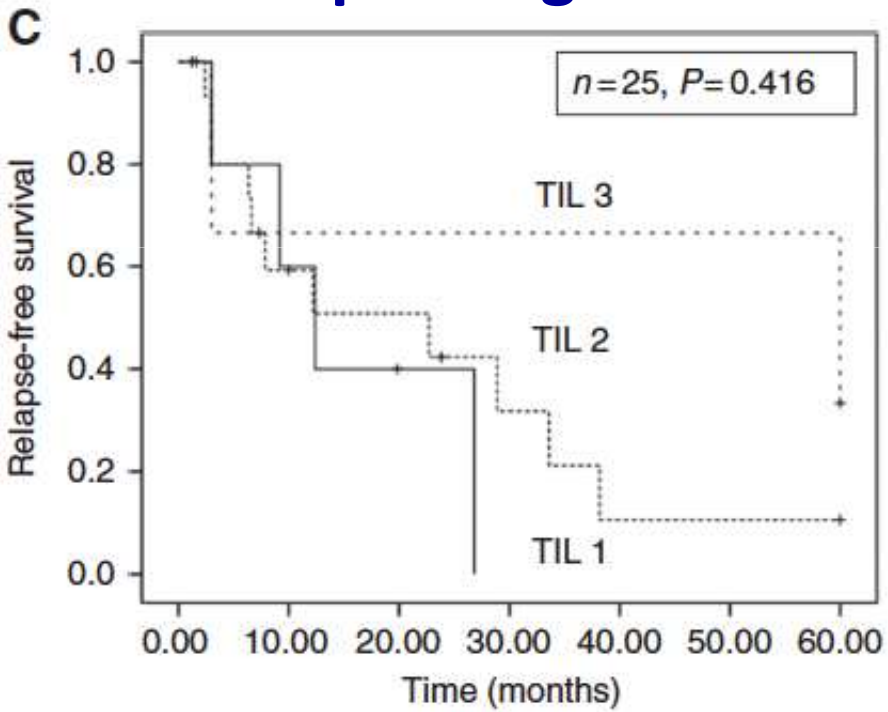




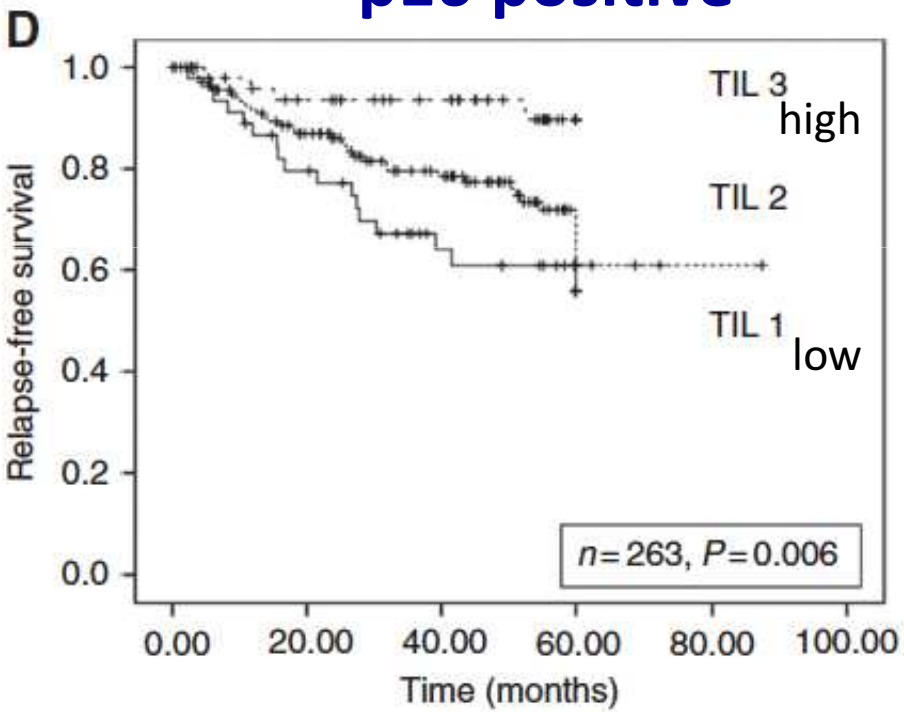
Rödel F, submitted 2016

Prognostic relevance of TILs and p16

p16 negative



p16 positive

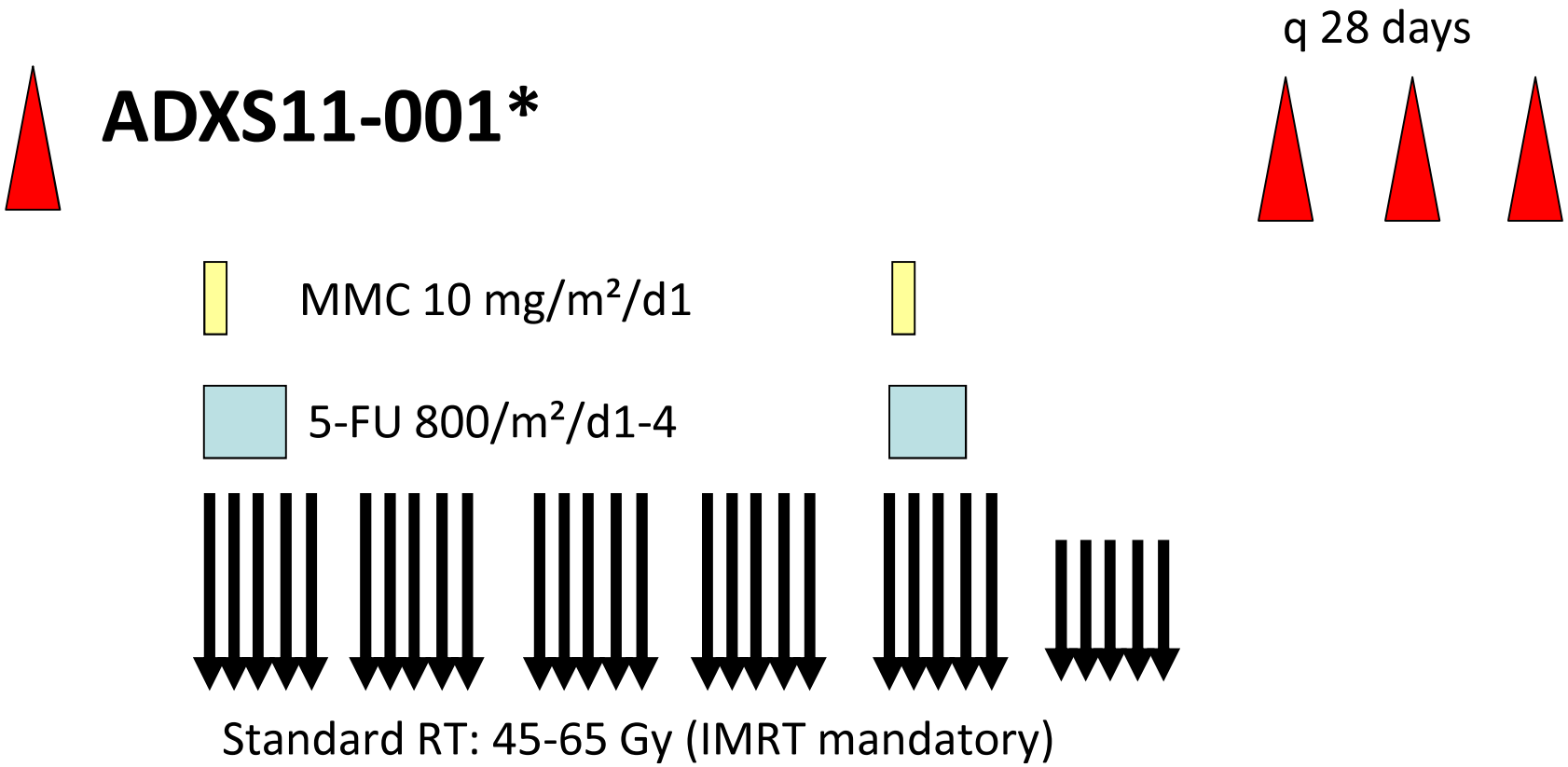


Gilbert DC et al., BJC 2016

NCT01671488 phase I/II trial

Inclusion: $T2_{>4cm}$-T4 or N+ M0, HIV neg

Primary Endpoints: SAE, CR at 6 months



*attenuated Listeria monocytogenes: secretes a protein fused to HPV E7 leading to stimulation of cell-mediated immune response

Bruxelles 2016

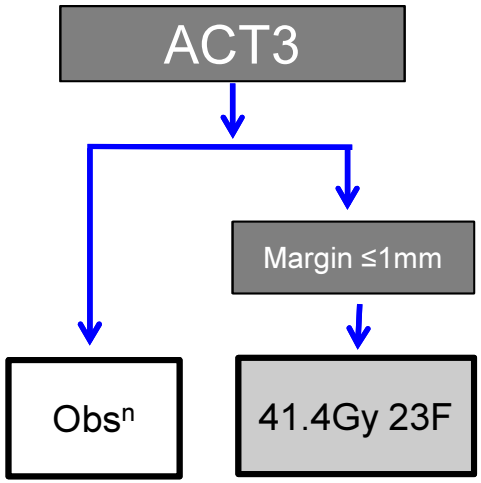
Anal cancer: Ongoing and planned clinical trials on combined modality treatment for anal cancer.

Rob Glynne-Jones
Mount Vernon Cancer Centre

PLATO - PersonaLising Anal cancer RadioTherapy dOse

T1 N0 Anal margin

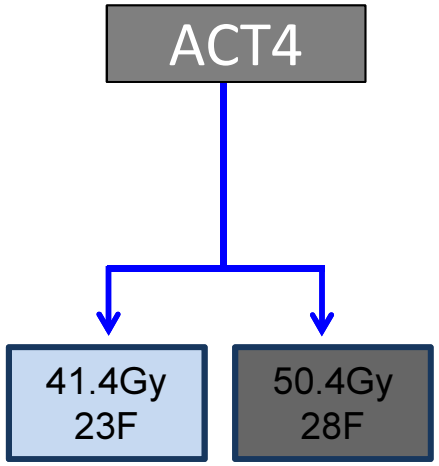
Local excision



Phase II trial

N=90

T1,T2<4cm N0

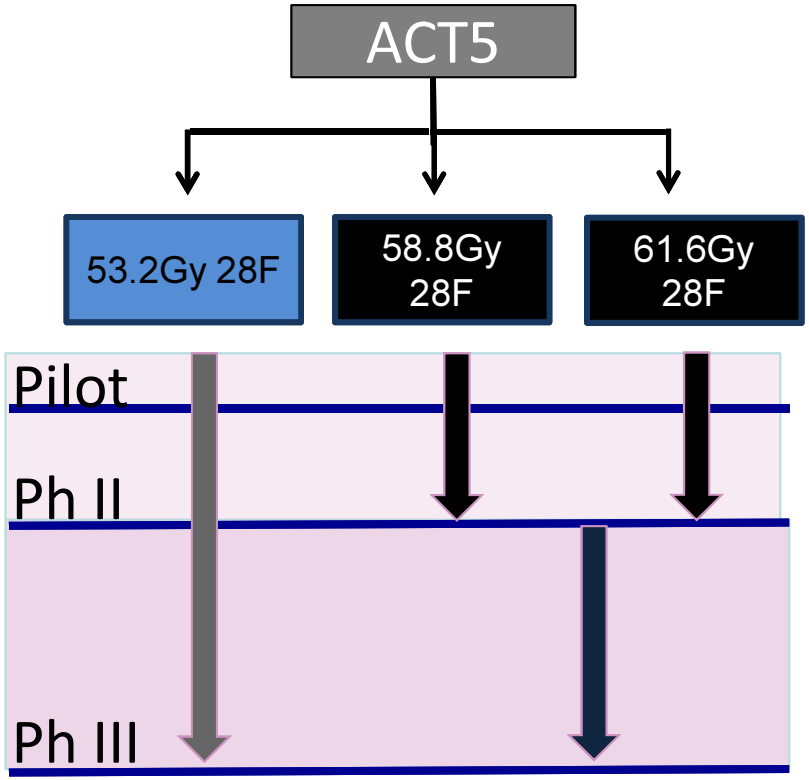


Randomised 2:1

Phase II trial

N=162

T3/4 Nany,T2N2-3



Pilot/Ph II/PhIII

N=677

Primary end point :- 3yr locoregional failure

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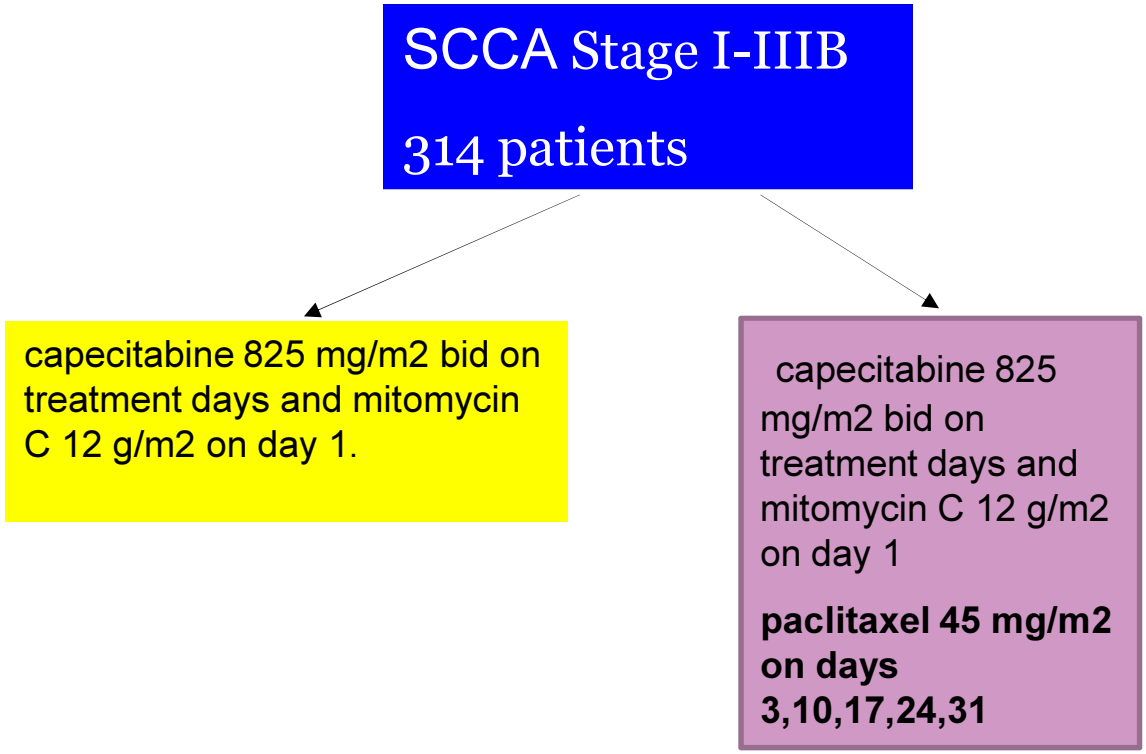
NCT02526953 Russian trial (S Gordeev) Efficacy Study of Chemoradiotherapy With or Without Paclitaxel in Squamous-cell Anal Carcinoma Patients



Primary Endpoint 3 year DFS

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p16INK4A (p16):

- Also known as cyclin-dependent kinase inhibitor 2A (CDKN2A)
- Cell cycle progression is unchecked via the activation of p16, a cyclin-dependent kinase inhibitor that functions as a checkpoint inhibitor.
- Immunohistochemistry for p16 has been used as a surrogate for HPV involvement.
- In addition to p16 - the prognosis is affected by tumour infiltrating lymphocytes TILs

Gilbert DC, et al, Tumour-infiltrating lymphocyte scores effectively stratify outcomes over and above p16 post chemo-radiotherapy in anal cancer. Br J Cancer. 2016

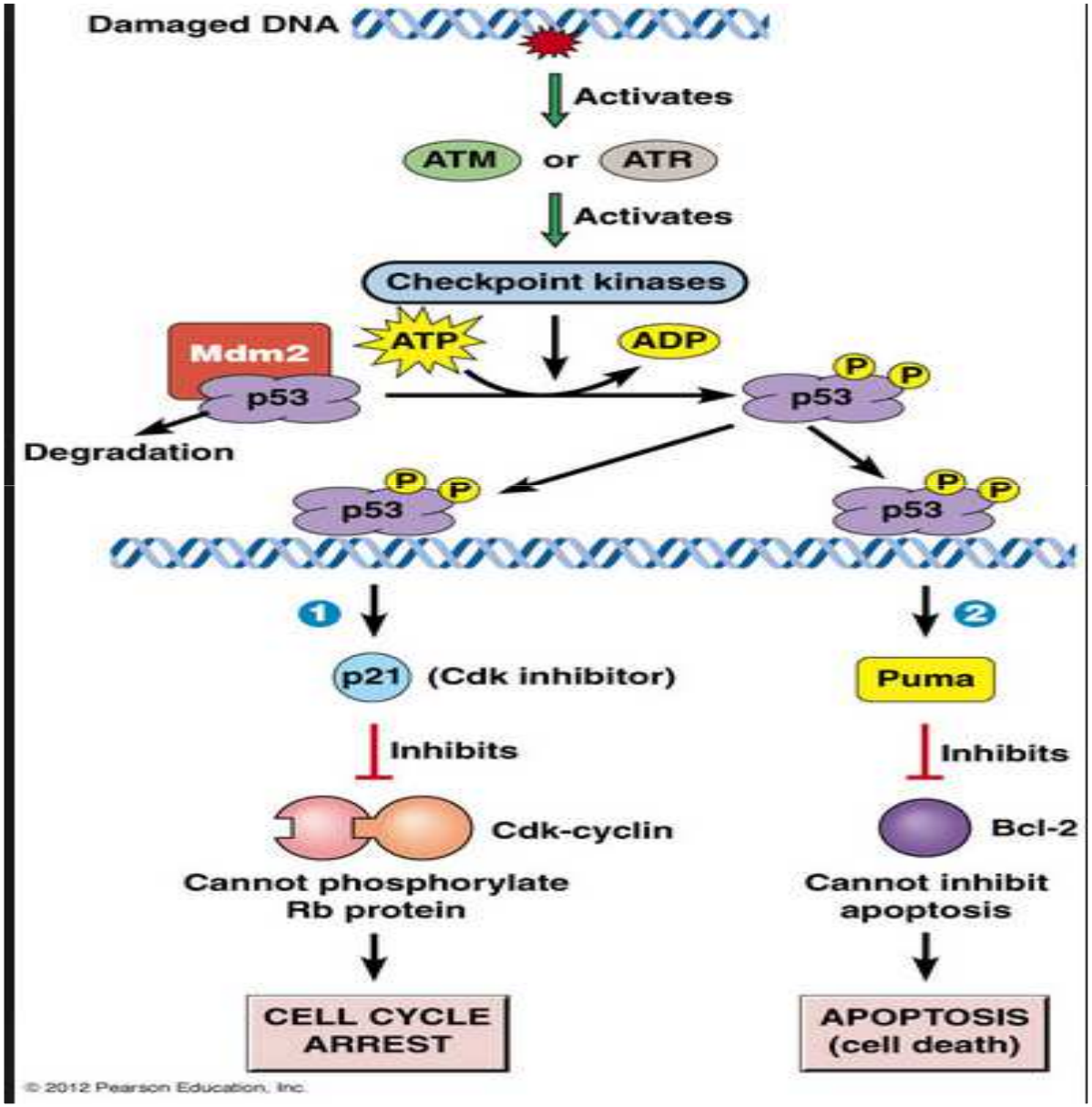
- Tissue samples of primary oral squamous cell carcinoma (OSCC) display
- hypermethylation in the promoter regions of p16.
- Cancer cells show a significant increase in the accumulation of methylation in CpG islands in the promoter region of p16
- This epigenetic change leads to the loss of tumor suppressor gene function

LY2606368

- CHK1 is a multifunctional kinase crucial for checkpoint control, DNA repair, cell cycle replication, and proliferation.
- Tumor cells with increased levels of CHK1 acquire survival advantages due to the ability to tolerate a higher level of DNA damage.
- By inhibiting CHK1, tumour DNA is damaged and unable to pass through mitosis.

- The CHK 1/2 inhibitor (LY2606368) is being investigated as a single agent in patients with metastatic SCCA and plans to integrate with CRT

Although neutropenia is side effect



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Immune checkpoints

supports trials of immunotherapy (targeting immune checkpoints

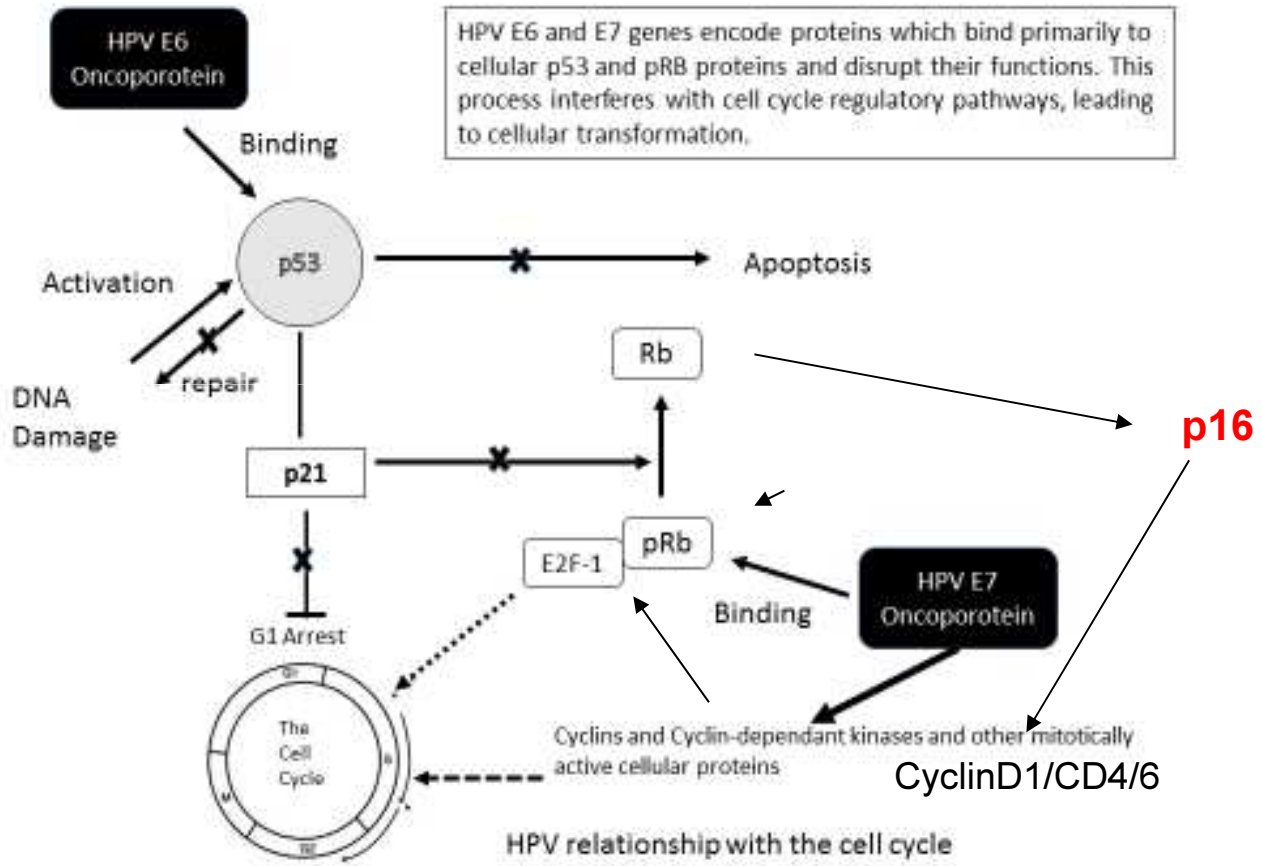
via anti CTLA4/PD1/PDL1 agents)

either in the metastatic setting

or potentially combined with chemo-radiotherapy either in the concurrent or (neo) adjuvant setting **(Illidge 2015)**

Illidge, T. Turning radiotherapy into an effective systemic anti-cancer treatment in combination with immunotherapy. Clin Oncol (R Coll Radiol). 2015 Dec;27(12):696-9

Immune checkpoint inhibitors



Hypothesis

- that combining radiation with checkpoint blockade immunotherapy will increase radiosensitisation
- improve local tumour control
- prevent the development of overt metastatic disease by reactivating anti-tumour T cells, which have become tolerant.

- Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4)/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2

Pembrolizumab a humanized monoclonal antibody against PD-1

25 heavily pretreated patients with PD-L1-positive advanced SCCA

Overall response rate of 5/25 (20%)

Stable disease in a further 10/25 patients (40%)

(Ott P et al. Preliminary safety and efficacy results from KEYNOTE-028 ESMO 2015).

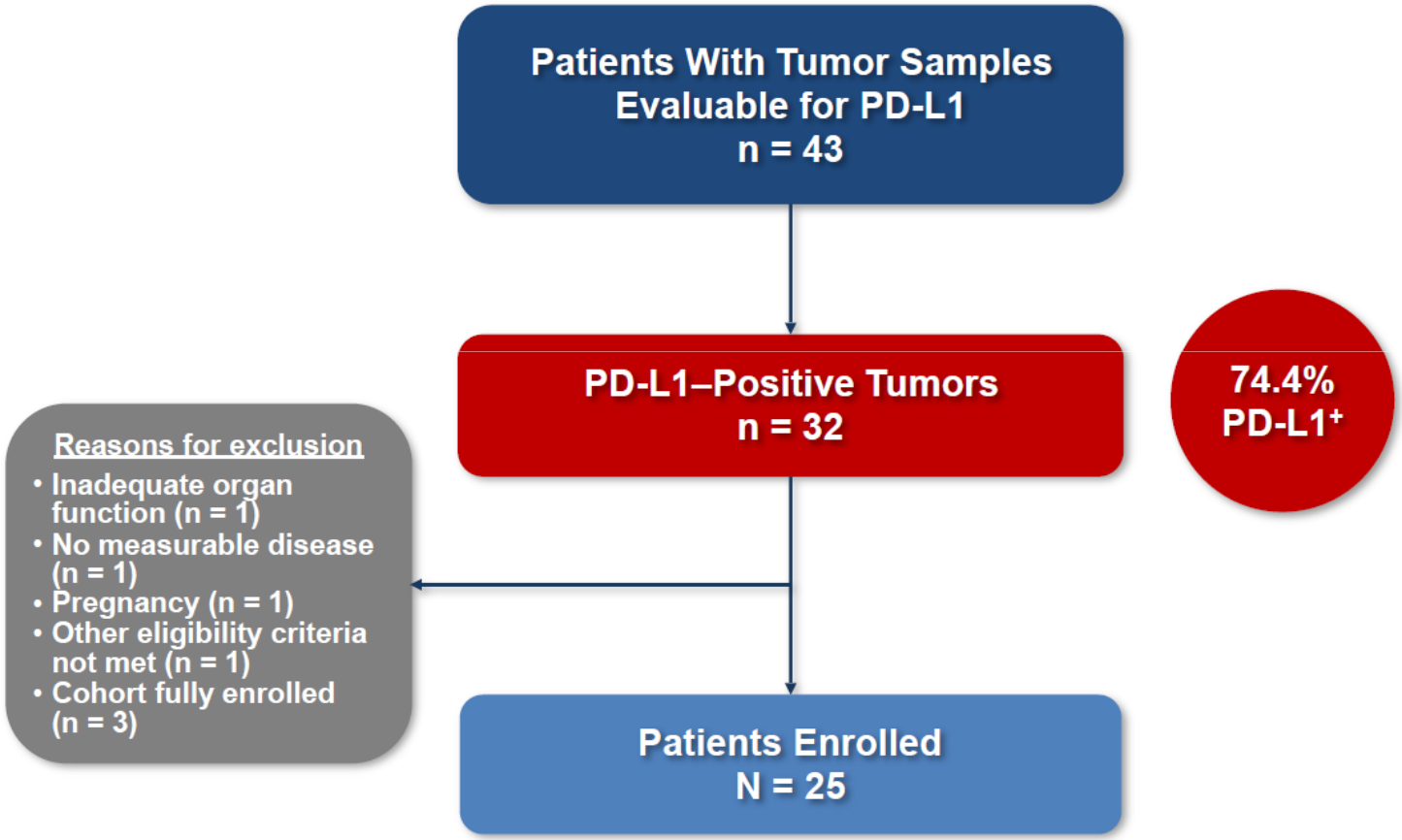
Pembrolizumab (MK-3475) For PD-L1–Positive Squamous Cell Carcinoma of the Anal Canal: Preliminary Safety and Efficacy Results From KEYNOTE-028

Patrick A. Ott,[1] Sarina A. Piha-Paul,[2] Pamela Munster,[3] Michael J. Pishvaian,[4] Emilie van Brummelen,[5] Roger B. Cohen,[6] Carlos Gomez-Roca,[7] Samuel Ejadi,[8] Mark Stein,[9] Emily Chan,[10] Matteo Simonelli,[11] Anne Morosky,[12] Sanatan Saraf,[12] Minori Koshiji,[12] Jaafar Bennouna[13]

[1]Dana-Farber Cancer Institute, Boston, USA; [2]University of Texas MD Anderson Cancer Center, Houston, USA; [3]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, USA; [4]Georgetown University, Washington DC, USA; [5]Netherlands Cancer Institute, Amsterdam, Netherlands; [6]University of Pennsylvania, Philadelphia, PA, USA; [7]Institut Claudius Regaud, Toulouse, France; [8]Virginia G. Piper Cancer Center, Scottsdale, AZ, USA; [9]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [10]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [11]Humanitas Cancer Center, Rozzano, Italy; [12]Merck & Co., Inc., Kenilworth, NJ, USA; [13]Institut de Cancérologie de l'Ouest, Nantes, France

WWW.ECCO-ORG.EU

PD-L1 Screening: Anal Cancer Cohort



Anal Canal Cancer:Baseline Characteristics

Characteristic, n (%)	N = 25
Median age, years (range)	63 (46–82)
Female	23 (92)
Race	
White	19 (76)
Black or African American	1 (4)
Not specified	5 (20)
ECOG performance status	
0	5 (20)
1	20 (80)
Histology at baseline, n (%)	
Squamous cell carcinoma	22 (88)
Carcinoid[a]	1 (4)
Endometrioid[a]	1 (4)
Mucoepidermoid[a]	1 (4)

Characteristic, n (%)	N = 25
Adjuvant or neoadjuvant systemic therapy, n (%)	6 (24)
Prior lines of therapy for advanced disease, n (%)	
0	3 (12)
1	7 (28)
2	7 (28)
≥3	6 (24)
Unknown	2 (8)
Prior therapies for advanced disease[b]	
5-FU + mitomycin	15 (60)
5-FU ± platinum ± other	14 (56)
Gemcitabine + platinum ± other	4 (16)
Chk-1 inhibitor	2 (8)
Etirinotecan pegol	2 (8)
Other	5 (20)

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Anal Canal Cancer: Antitumor Activity

(RECIST v1.1, Investigator Review)

Best Response	n	%	95% CI
Complete response	0	0	0.0–13.7
Partial response[a]	5	20	6.8–40.7
Stable disease	11	44	24.4–65.1
Progressive disease	8	32	14.9–53.5
Not assessed[b]	1	4	0.1–20.4

- ORR: 20.0% (95% CI, 6.8–40.7)
- DCR: 64.0% (95% CI, 42.5–82.0)

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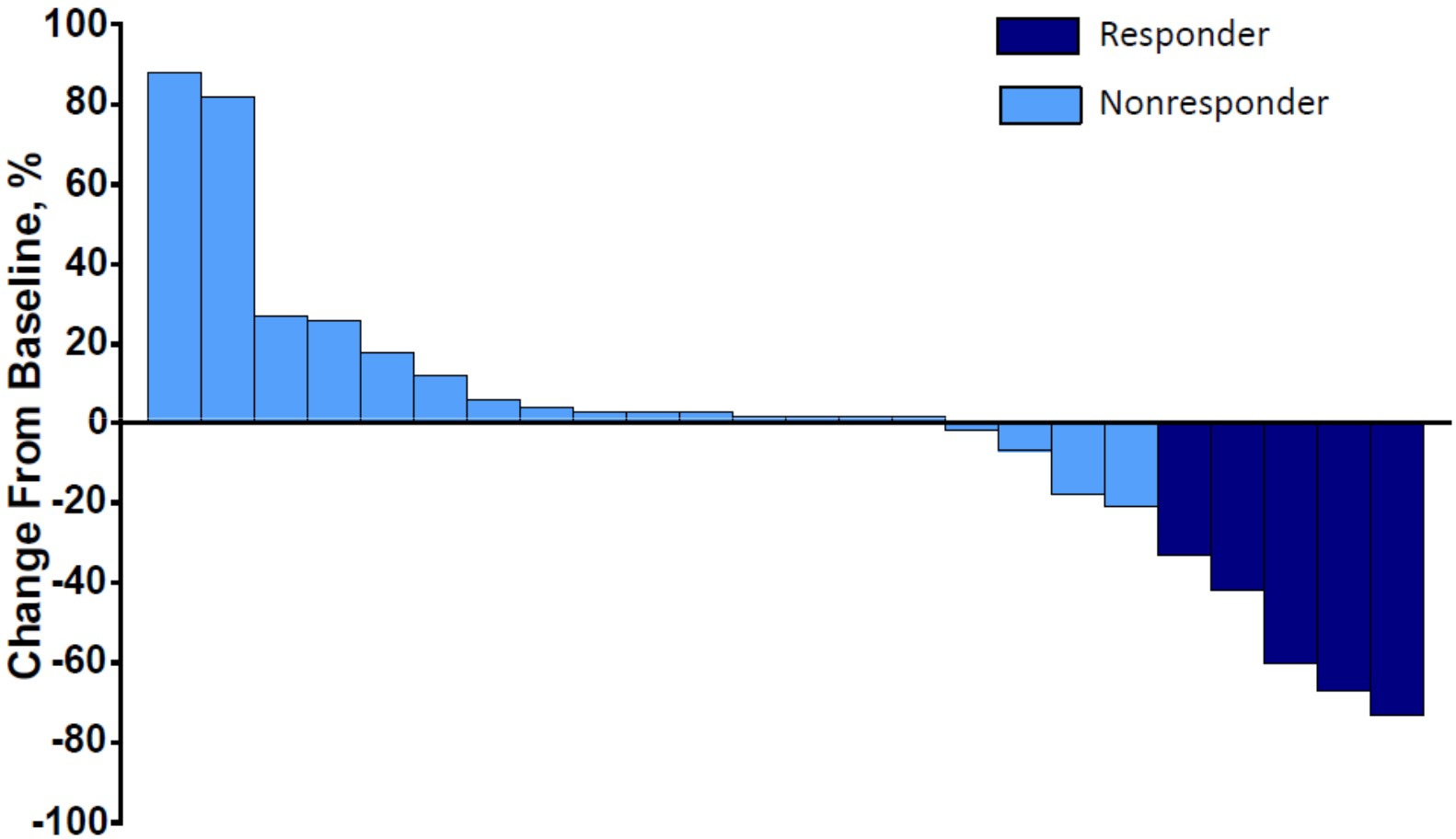
Anal Canal Cancer: Maximum Change From Baseline in Tumor Size



Includes patients with ≥1 postbaseline tumor assessment (n = 24).
Data cutoff date: July 1, 2015.

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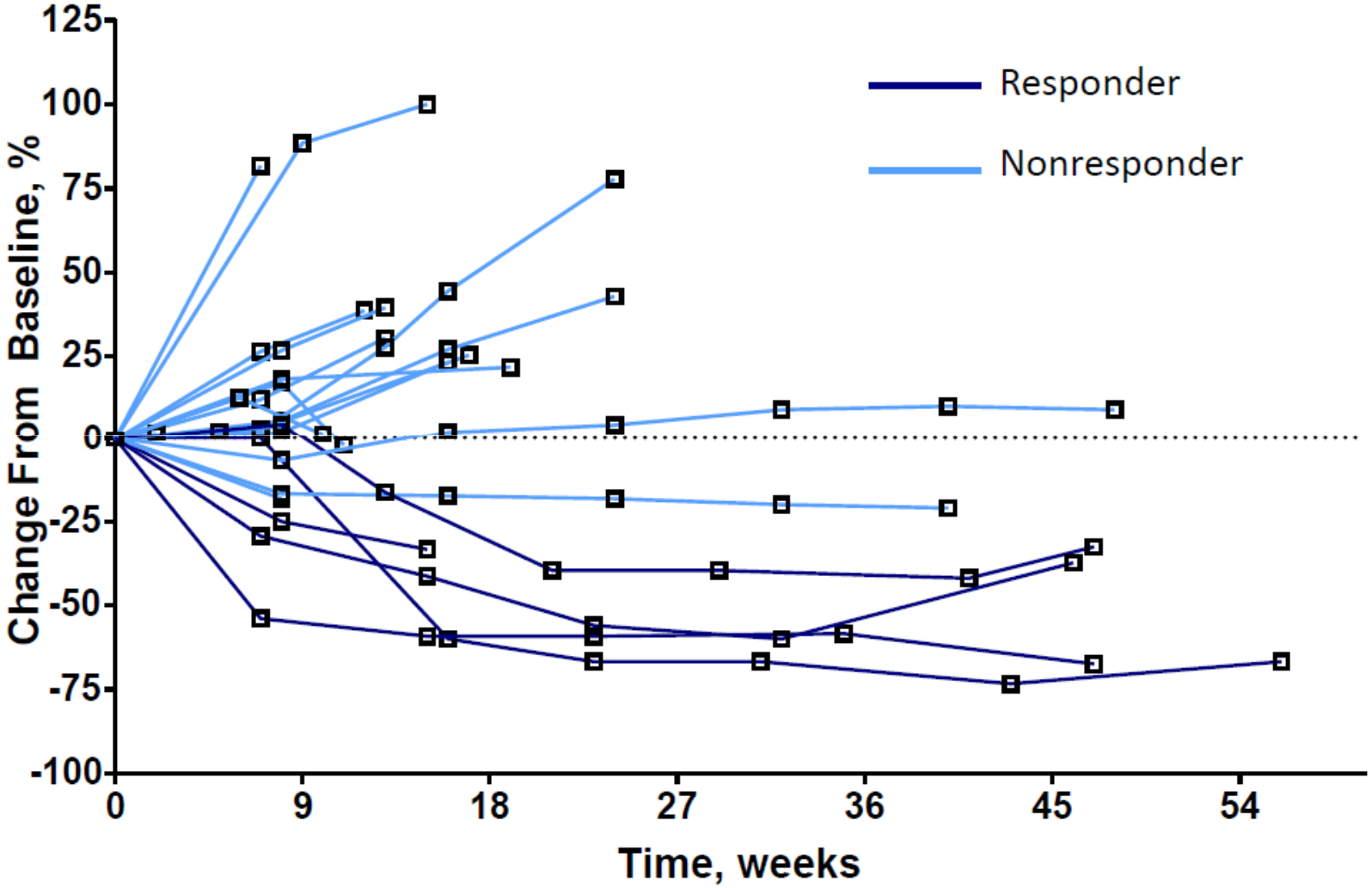
Anal Canal Cancer Longitudinal Change From Baseline in Tumor Size



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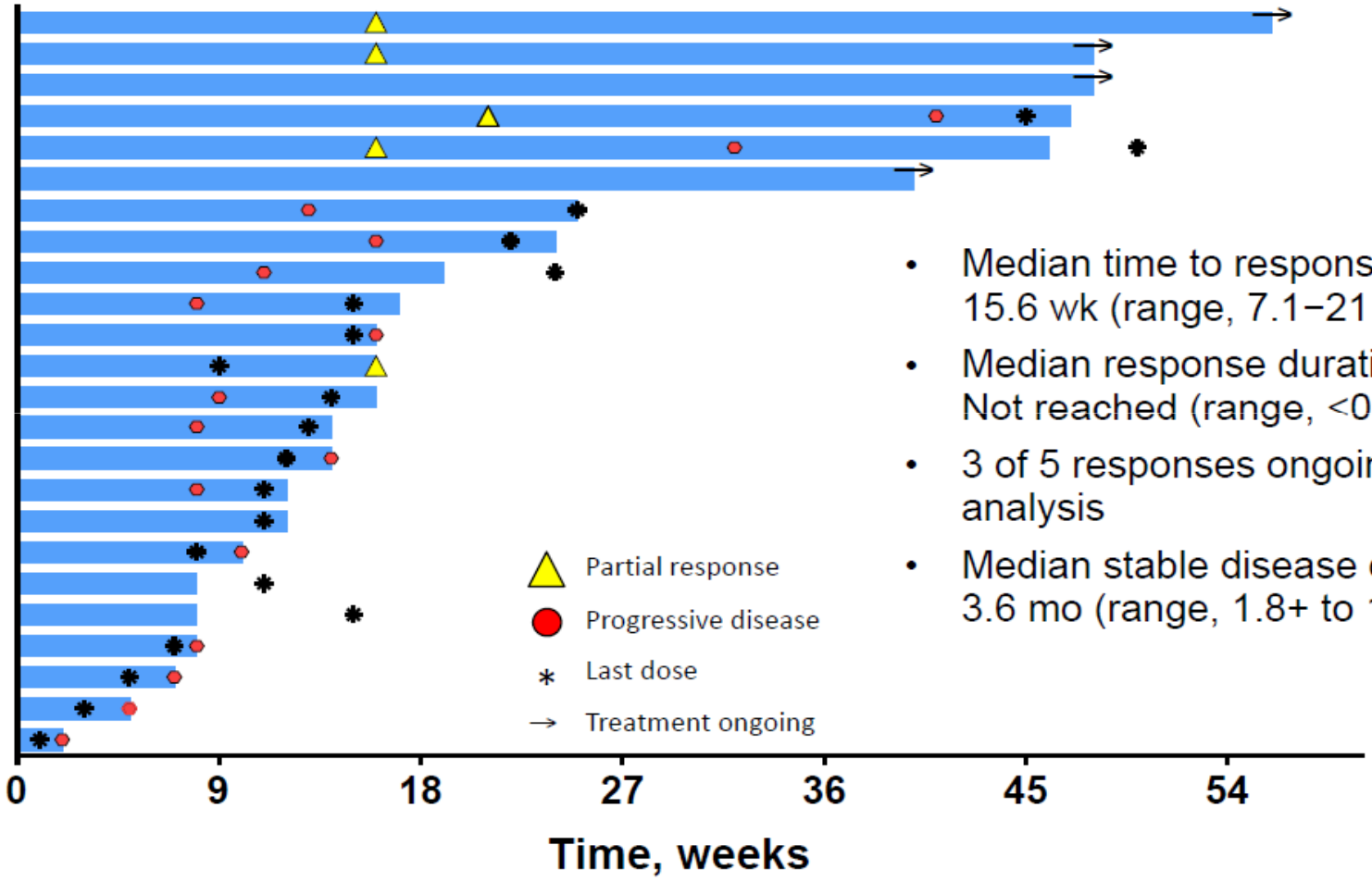
Anal Canal Cancer: Treatment Exposure and Response Duration



- Median time to response: 15.6 wk (range, 7.1–21.0)
- Median response duration: Not reached (range, <0.1+ to 9.2+ mo)
- 3 of 5 responses ongoing at time of analysis
- Median stable disease duration: 3.6 mo (range, 1.8+ to 11.0+)

PD-L1 Squamous cell carcinoma of the anus - Durable responses /stable disease in a population which was heavily pretreated

Manageable safety profile

Suggest evaluation of advanced anal cancer

PD-L1 expression was seen in

62% of advanced /unknown stage

33% of early stage (?T1/T2) disease

PD-L1-positive vs. negative patients respectively had RFS medians of 1.5 vs. 4.9 years (p = 0.068)

(Gujja ASCO abstract 2015)

Gujja S, Batra A et al. Programmed cell death-Ligand 1 (PD-L1) expression and outcome in patients with squamous cell cancer of anal canal (SCCAC). J Clin Oncol 33, 2015 (suppl); abstr 3523).

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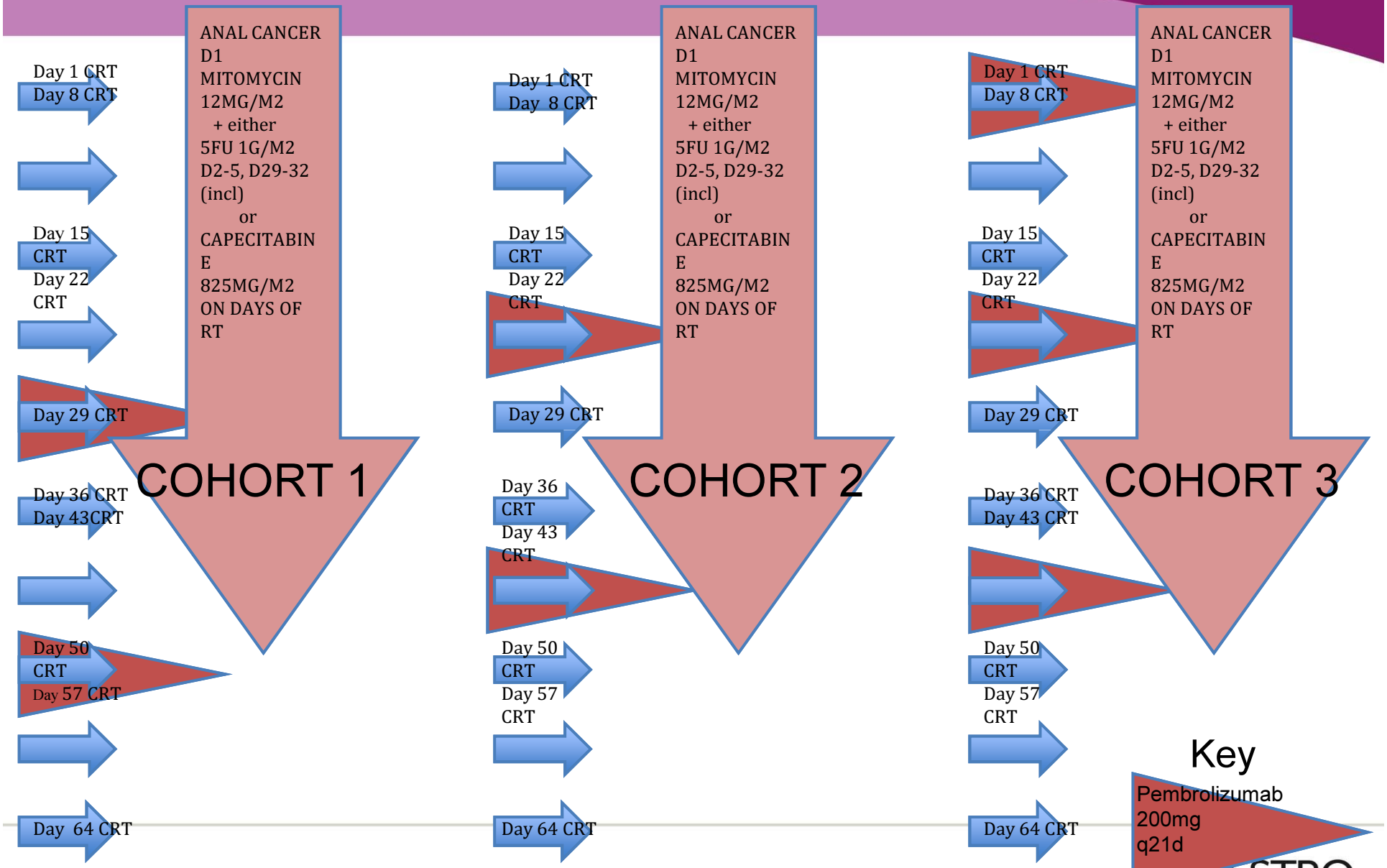
PEMBROLIZUMAB TRIAL SCHEMA



Follow up – 3 months toxicity check + MRI at 6 and 12 months

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IRCI anal cancer metastatic trial

InterAACT

An Open Label Phase II **Inter**national Multicentre Randomized **A**dvanced **A**nal **C**ancer **T**rial Comparing Cisplatin plus 5-fluorouracil (5-FU) versus Carboplatin plus Weekly Paclitaxel in Patients with Relapsed or Metastatic Disease

Clinical Protocol Version 1.0 Dated 01.02.2013

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Other planned trials

1. Chemoradiation followed by **Nivolumab**

2. Neoadjuvant **Avelumab**/Carbo taxol

ADXS11-001 immunotherapy

- live attenuated Listeria monocytogenes (Lm)
- bioengineered to secrete a HPV-16-E7 fusion protein targeting HPV transformed cells.

- Anal cancer cells infected with HPV have the tumour associated antigen HPV E7.

- So ADXS11-001 causes antigen presenting cells to be stimulated to facilitate immune cells to attach to cancer cells expressing HPV E7

- neutralizes Tregs and myeloid-derived suppressor cells (MDSCs), which protect the tumour microenvironment from immunologic recognition and contribute to tumour growth.

Thank you