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# How to intensify preoperative radiation in rectal cancer?

Karin Haustermans

UZ  
Leuven

Herestraat 49  
B - 3000 Leuven

[www.uzleuven.be](http://www.uzleuven.be)  
tel. +32 16 33 22 11

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# Preoperative radiation

- CRT + TME as standard treatment for LARC
- Response to CRT = heterogeneous

pCR  
15-27%

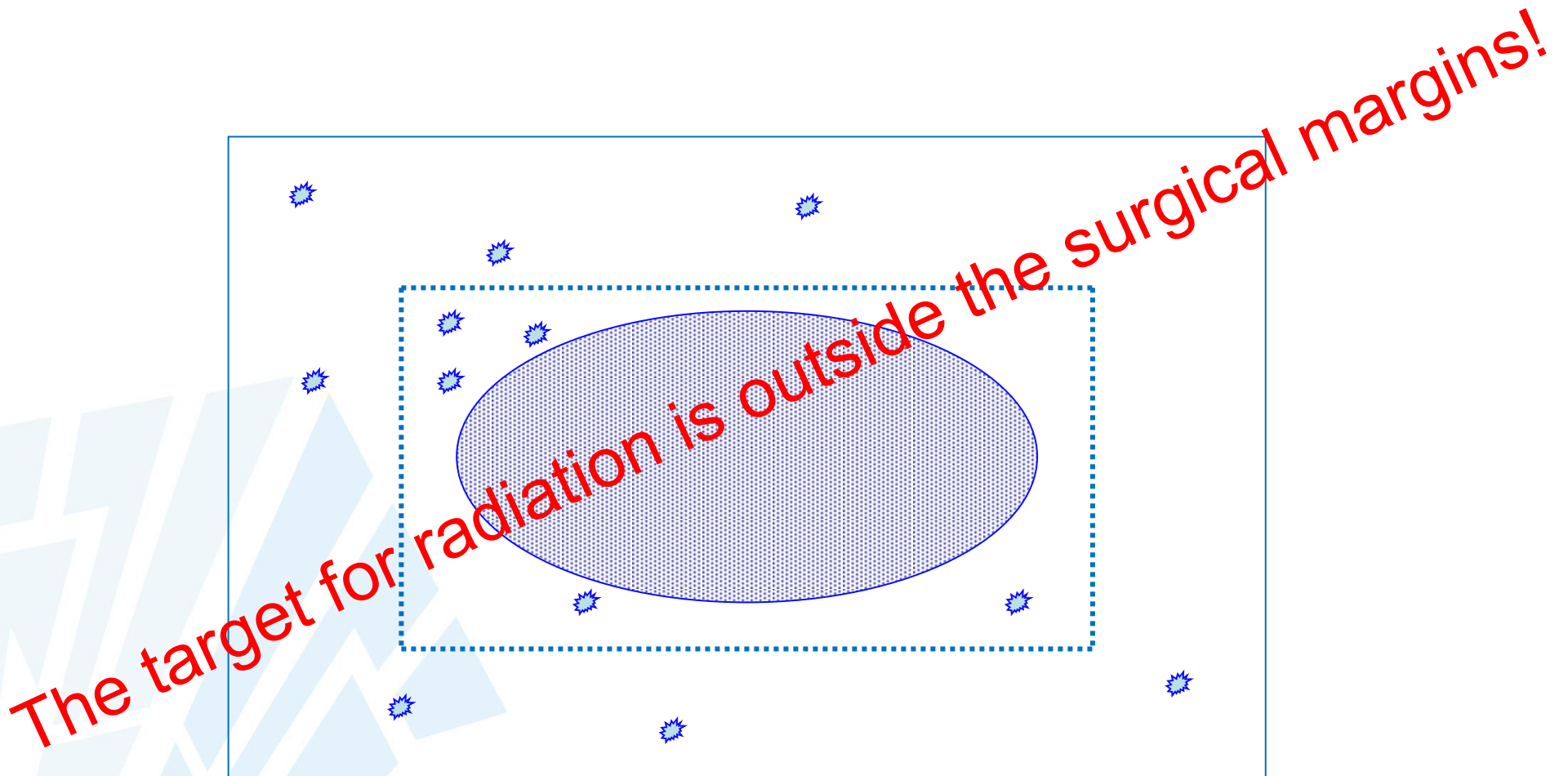
➔ Organ preservation

Borderline  
resectable

“Ugly”  
tumours

➔ Treatment intensification

# Preoperative radiation



..... Plane of excision

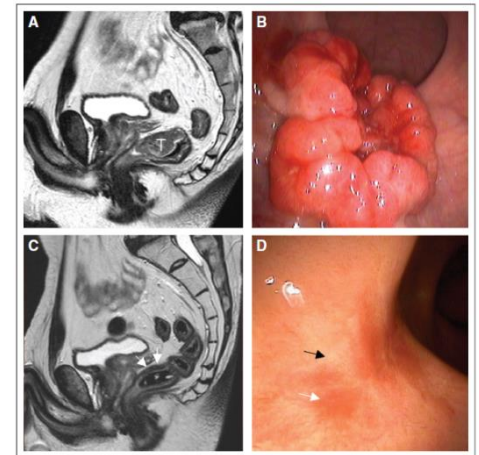
———— Irradiated volume wide around the macroscopic tumour

# Organ preservation

## Organ preservation is appealing...

- Avoidance of
  - significant postoperative mortality and morbidity
  - long-term urinary, sexual, and fecal dysfunction
  - temporary or definitive stoma
- Increasing quality of life

**... and oncological outcome seems good...**

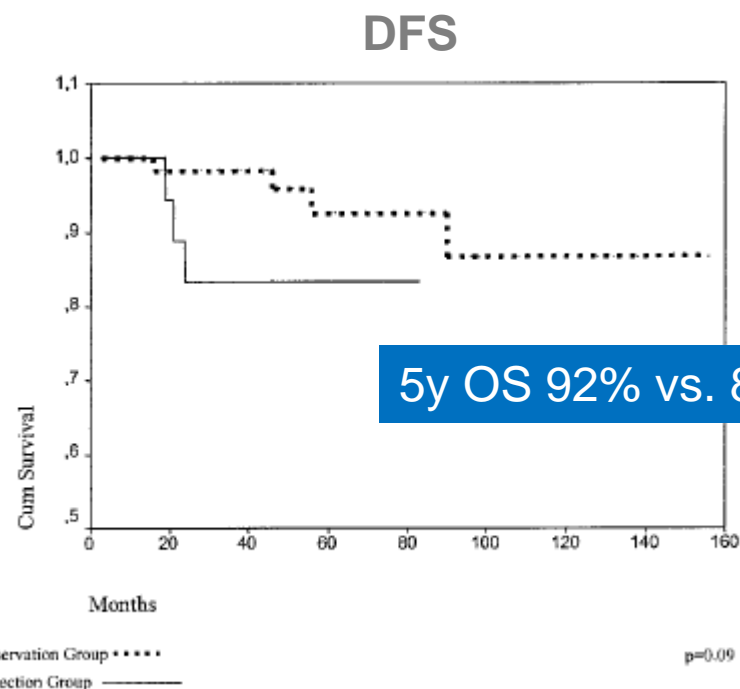
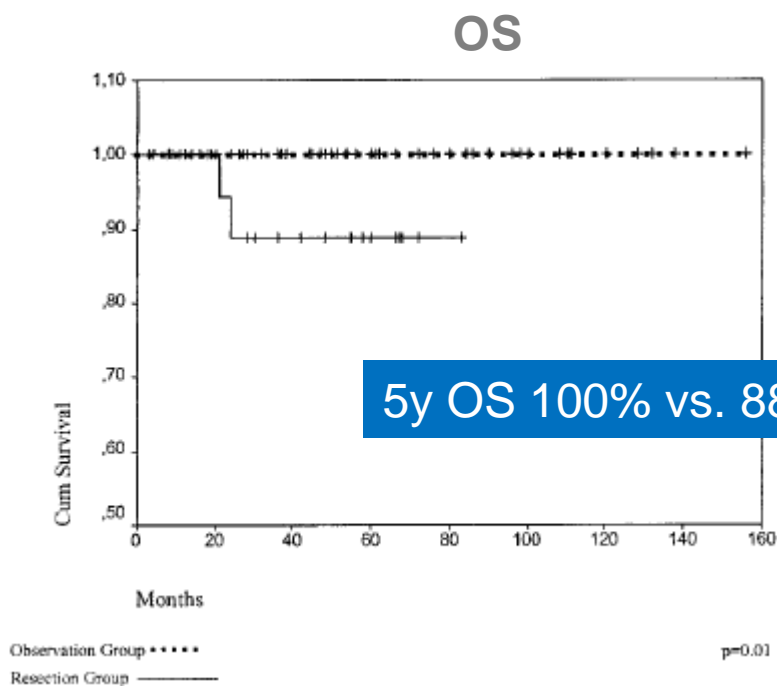


*Maas et al, JCO 2011*

# Watch-and-wait outcome

## Habr-Gama series

Resectable cancer, <7cm from anal verge  
cCR + observation (n=71) vs. pCR (n=22)



*Habr-Gama et al, Ann Surg 2004*

**Stage 0 has excellent prognosis, irrespective of treatment strategy**

# Local excision outcome

## LEADER trial

cT3, low cT2 rectal cancer

Restaging 5 weeks after CRT

- cyN0 at MRI,
- no abnormalities, scar or superficial ulcer  $\leq 2$  cm at endoscopy

→ Full thickness local excision

ypT0-1



Observation  
n= 43

> ypT0-1



TME → 9/20 refused

Mean follow-up 4 years

5y OS 88,2%

5y DFS 91,8%

5y local DFS 91,2%

**LE seems promising for patients  
with major response after CRT**

# RT dose escalation

- Organ preservation is appealing...
- ... and oncological outcome in responders seems to be good ...

## How to increase the response rate?

- increasing the dose of radiation?
- longer interval to surgery?
- addition of chemotherapy?
- addition of molecular agents?

# RT dose escalation

- Organ preservation is appealing...
- ... and oncological outcome in responders seems to be good ...

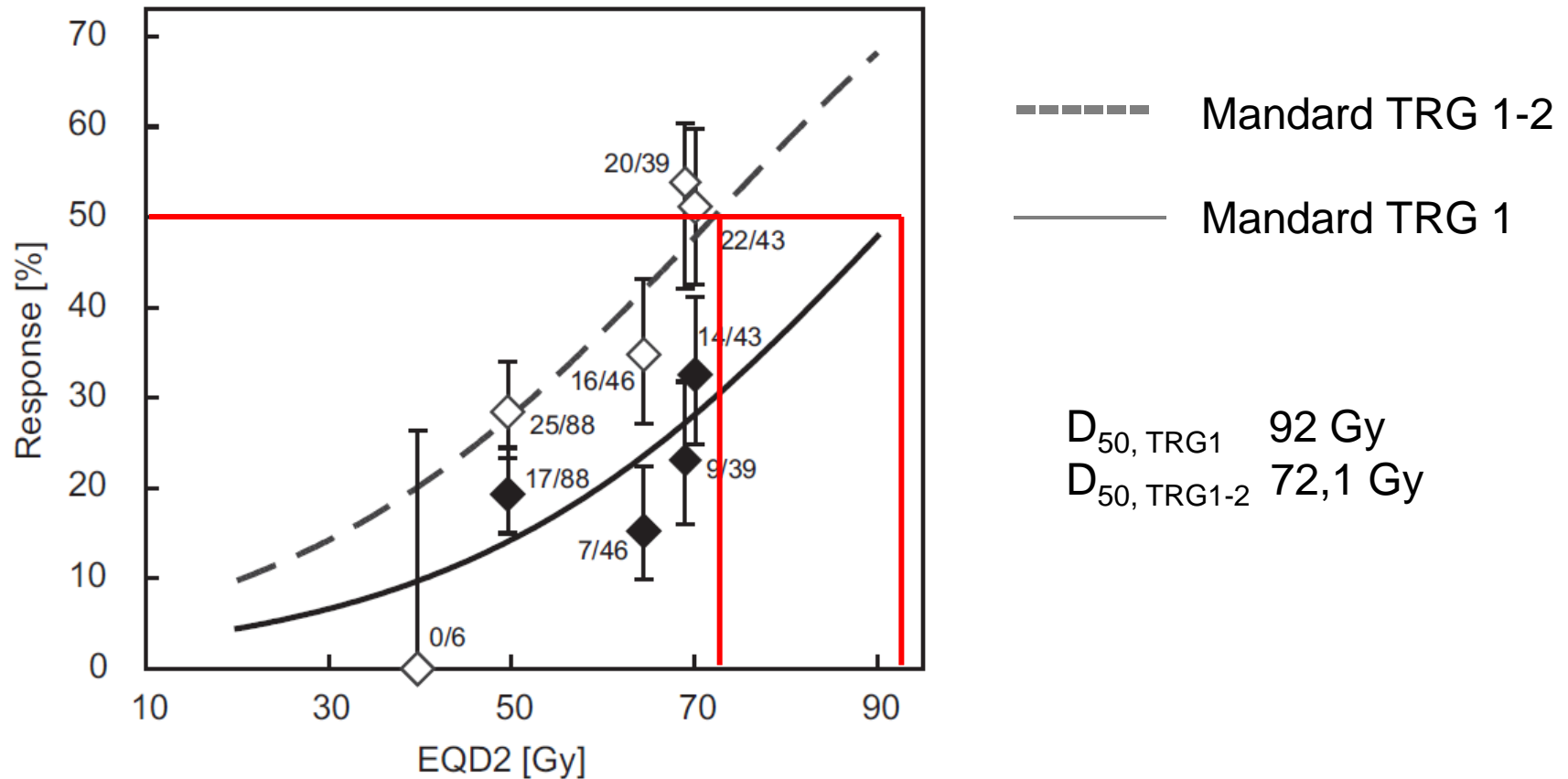
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# RT dose escalation

## Dose-response per TRG



# RT dose escalation: how?

**EBRT boost**



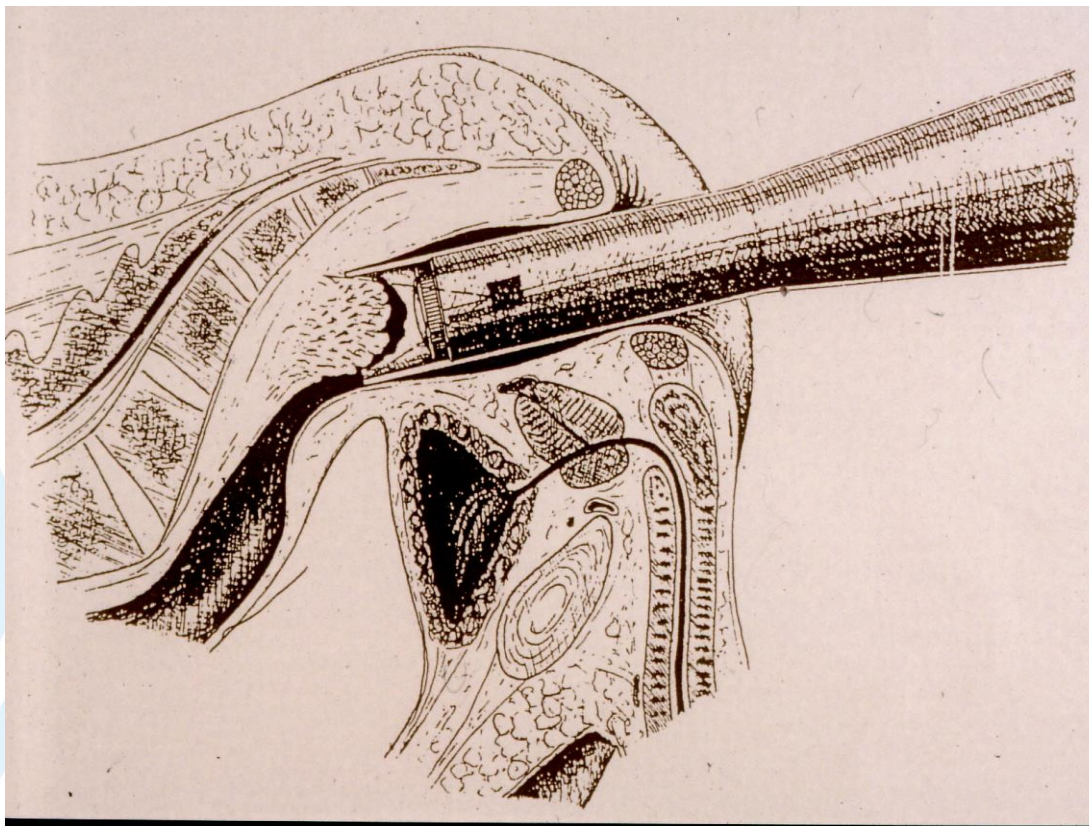
**Contact RT**



**HDR brachy**



# Contact RT



- Dose prescribed at the surface of the tumour
- Steep fall-off of dose with depth (50% at 5 mm, 25% at 10 mm)
- Delivery of large doses per fraction (approximately 30 Gy)
- Gradual destruction of exophytic tumours layer per layer in a few fractions  
3-4 fractions (90-120 Gy)  
4-6 weeks overall treatment time

# Contact RT

- Lyon R96-02
- Dose-escalation randomized phase III trial

Low rectal cancer  
cT2-3NxM0  
Not more than 2/3 of rectum  
(n=88)

EBRT 39Gy/ 3Gy  
(n= 43)

EBRT 39Gy/ 3Gy  
+ contact RT boost 85 Gy/ 3fr  
(n= 45)

# Contact RT

## Clinical CR:

11 patients EBRT + CXR vs. 1 patient EBRT ( $p < 0,05$ )

## Pathological response

Characteristic	EBRT (n=43)	EBRT + CXR (n=38*)	P-value
Mean tumour diameter (cm)	3,2	2,6	0.03
Complete sterilization	3	8	
Few residual cells	12	15	
Complete sterilization + few residual cells	28	23	0.027
SSS	19	34	0.004

\* 7 patients did not undergo surgery (6 cCR, 1 peritoneal carcinosis)

# Contact RT

## Surgical complications

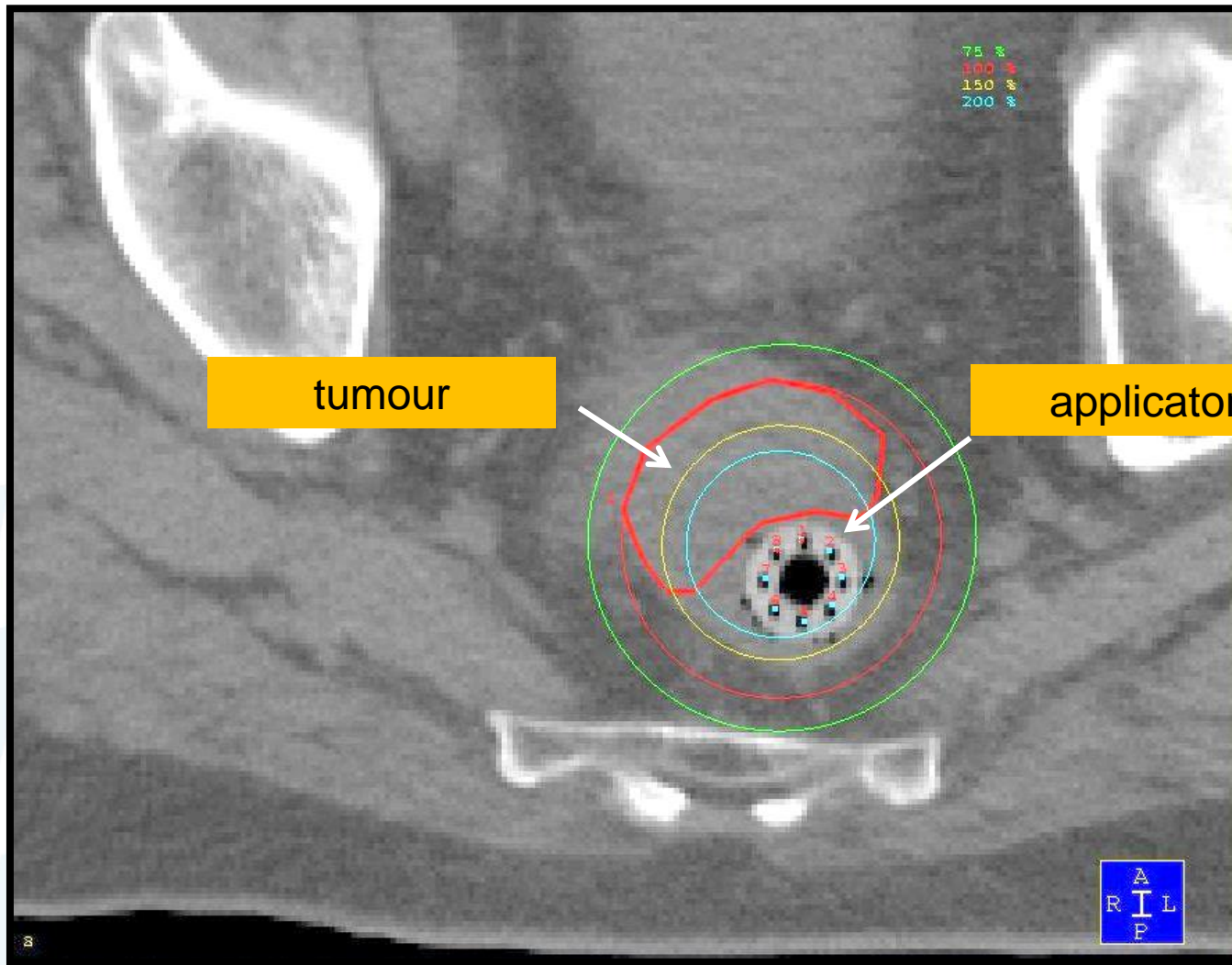
Complications	EBRT (n=43)	EBRT + CXR (n=38*)
Postoperative death (< 60 d)	1	0
Fistula (AR)	2/19	3/24
Abscess	3	1
Hemorrhage	1	0
Peritonitis	2	2
Reoperation within 2 months	4	4
Hospitalization time (median No. days)	16	17

**Surgical complications and acute toxicity are comparable**

\* 7 patients did not undergo surgery (6 cCR, 1 peritoneal carcinosis)



# Brachytherapy



# Brachytherapy

## Endorectal BT as boost

- Danish Colorectal Cancer Group
- Dose-escalation randomized phase III trial

Standard CRT  
(50,4 Gy in 28 fx)  
N = 123  
(T3: 102; T4: 21)

Pts with  
resectable T3  
and T4 tumours;  
CRM  $\leq$  5mm on  
MRI

Standard CRT +  
HDR brachy boost  
(10 Gy in 2 fx)  
N = 120  
(T3: 102; T4: 18)



# Brachytherapy

**Table 4** Effect in T3 tumors according to treatment arm

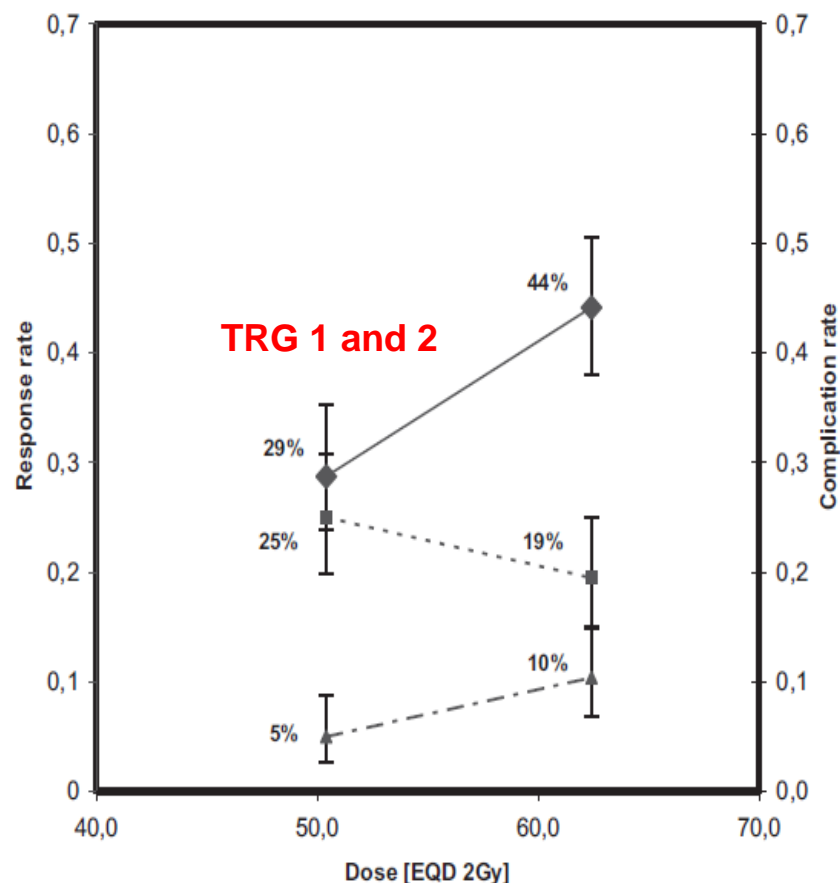
Variable	Arm A (n)	Arm B (n)	P value
R0 resection	83 (90)	87 (99)	<.05
Major response TRG1+2	23 (28)	35 (44)	<.05
Major response according to tumor diameter			
<3.7 cm	14 (33)	23 (58)	<.03
>3.7 cm	8 (28)	11 (31)	>.1

Abbreviation: TRG = tumor regression grade.

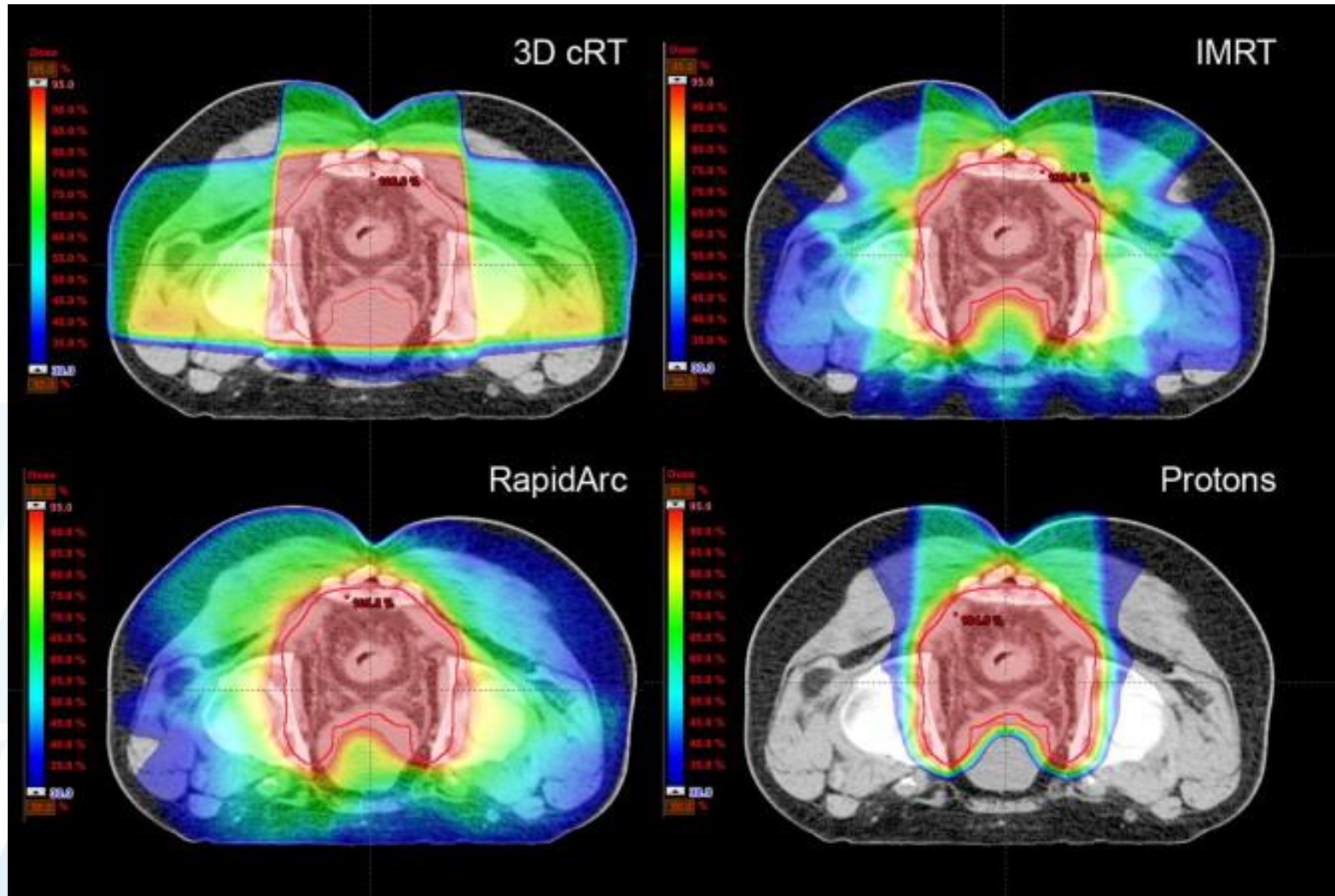
Data in parentheses are percentages.

- Higher radiation dose increases the rate of major response (TRG1-2) by 50% in T3 tumours
- Endorectal boost is feasible, with no significant increase in toxicity or surgical complications

## T3 tumours

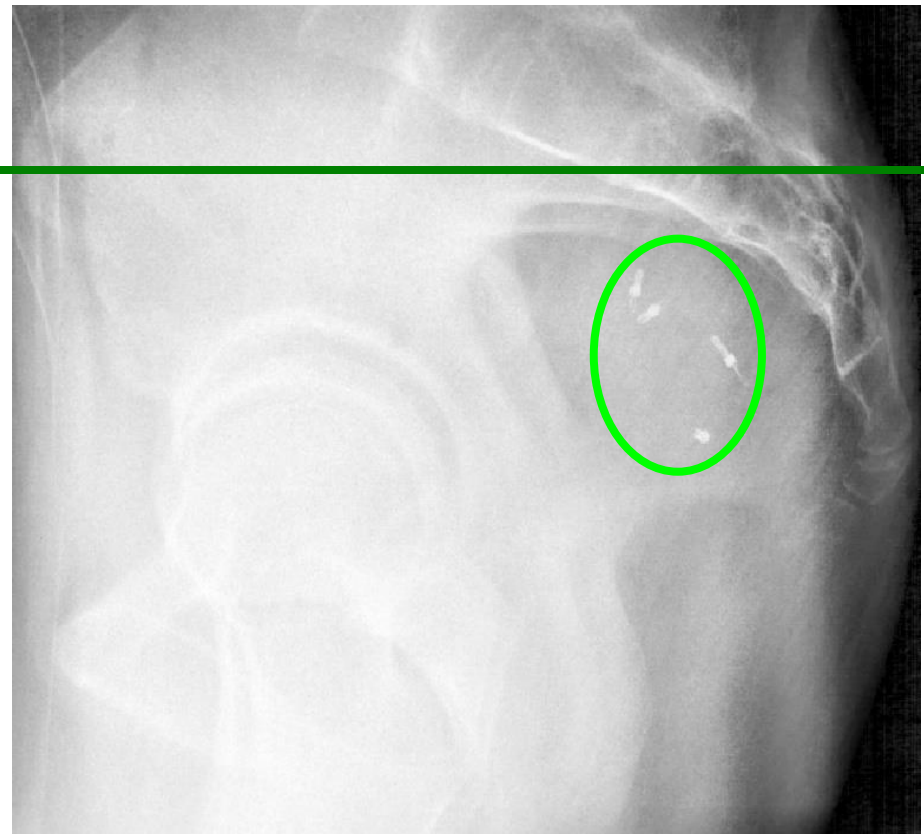
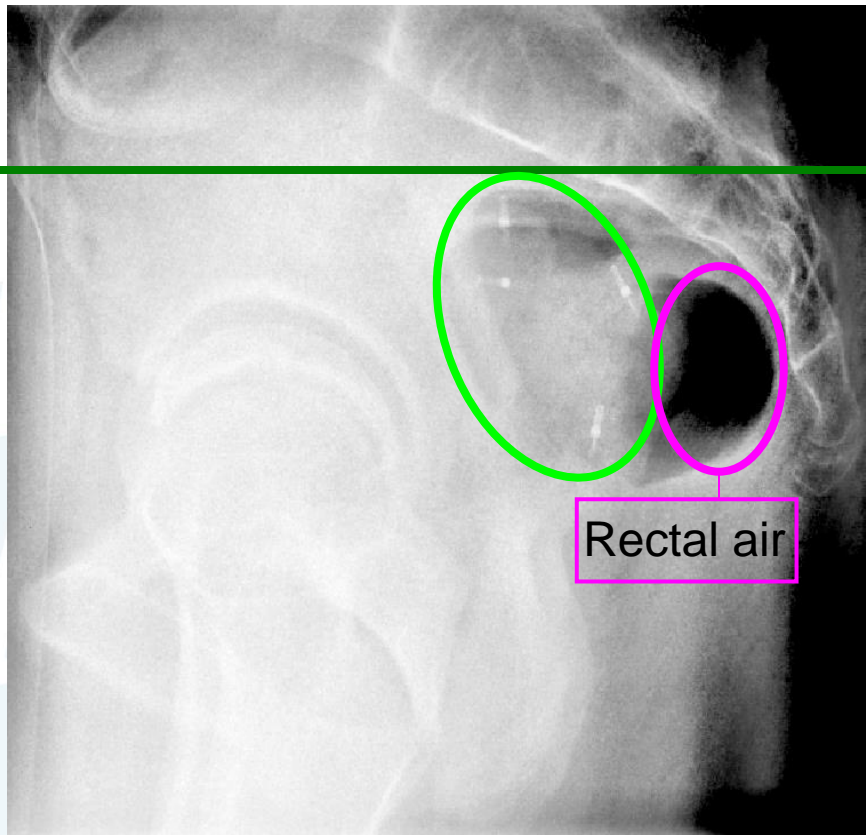


# Conformal RT

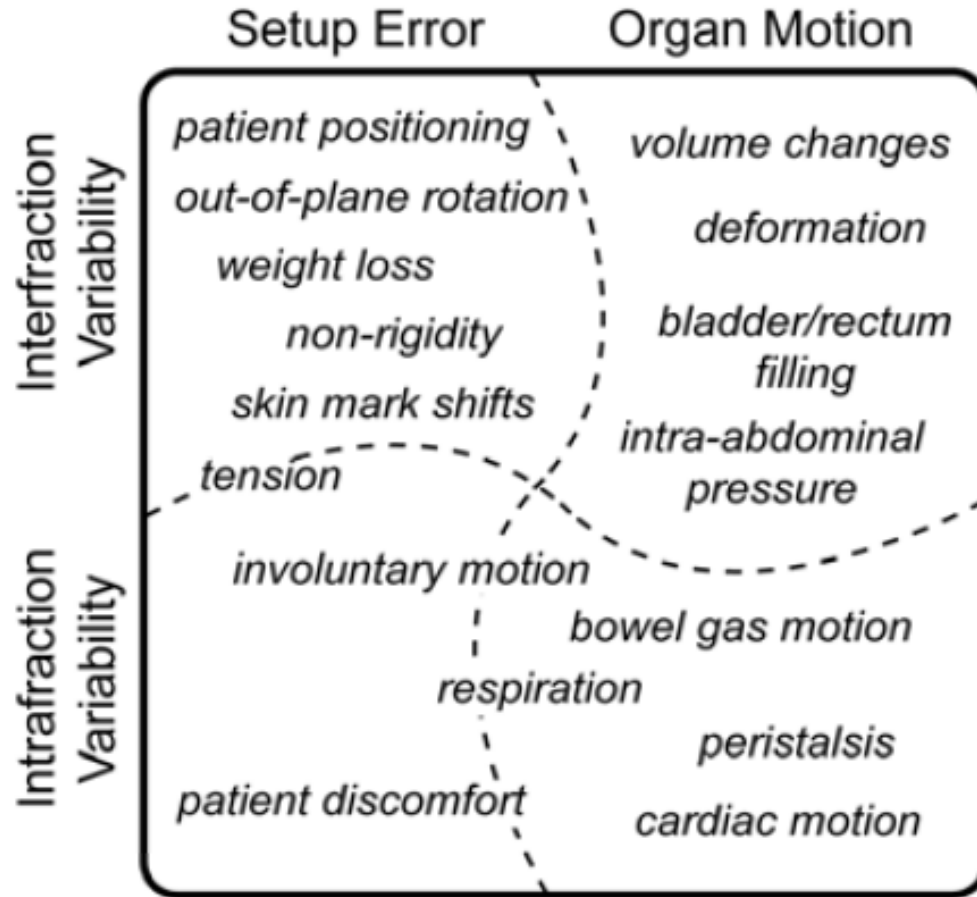


# RT dose escalation: challenges

## IGRT with kV-EPID and fiducial markers



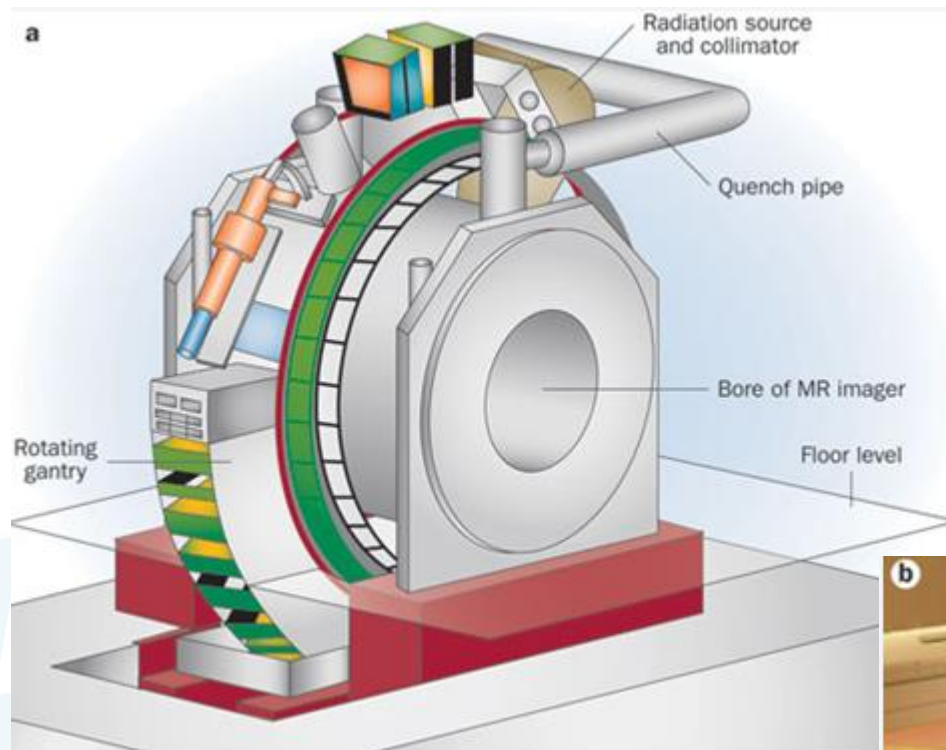
# RT dose escalation: challenges



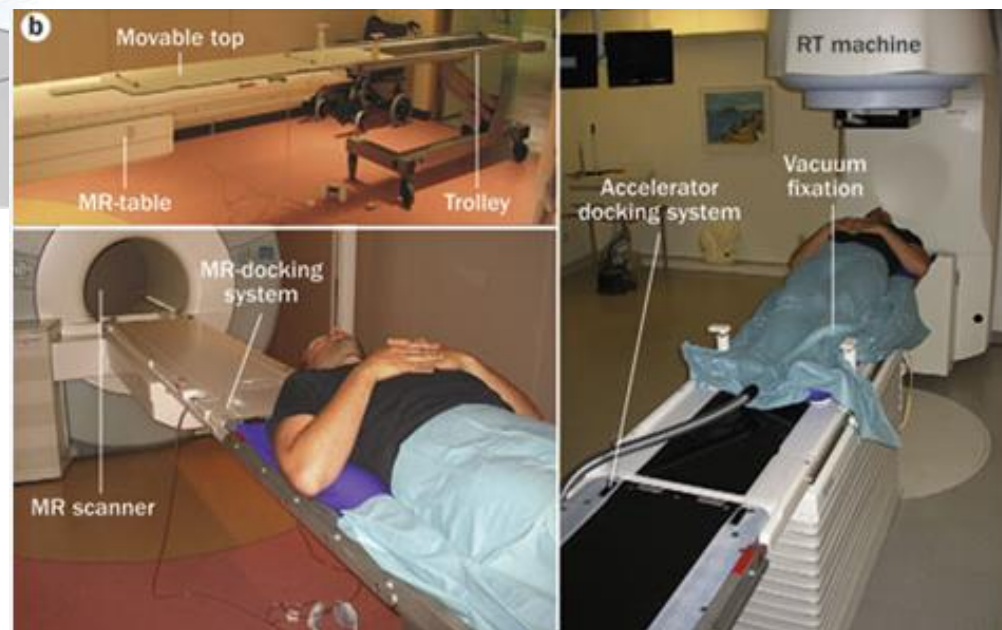
- Set-up variation
- Internal organ displacement
- Volume change and deformation



# IGRT technologies



MRI-guided radiotherapy



# RT dose escalation

- Organ preservation is appealing...
- ... and oncological outcome in responders seems good ...

## How to increase the response rate?

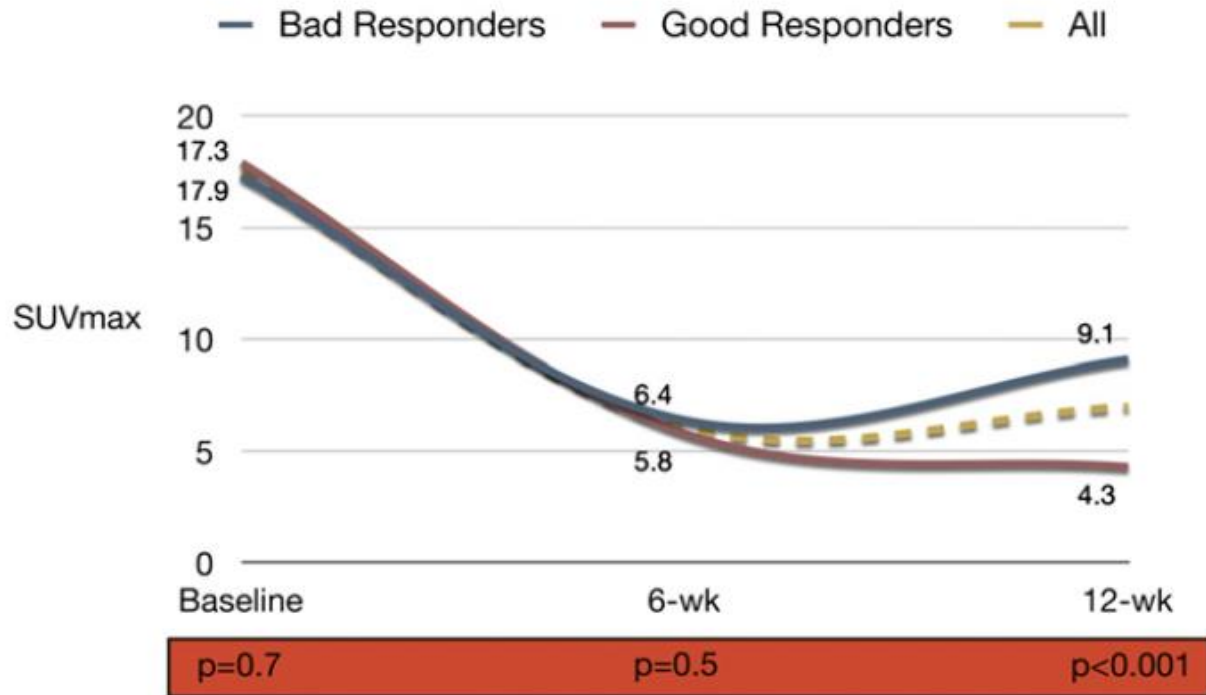
- increasing the dose of radiation?
- longer interval to surgery?
- addition of chemotherapy?
- addition of molecular agents?

# Longer interval

91 patients

cT2-4N0-2M0 distal rectal cancer

PET baseline, after 6 and 12 weeks



# Longer interval

**Table 2** Outcomes of patients with increased activity between 6 and 12 weeks from CRT completion

Early SUVmax	Increased activity ("bad")	Decreased activity ("good")	<i>P</i>
<i>n</i>	46 (50.5%)	45 (49.5%)	
TRG (TRG3 + TRG4)*	6 (15.8%)	14 (45.2%)	.008
Complete response (cCR or pCR)	3 (6.5%)	17 (37.8%)	.001
Final tumor size (cm)*	4.3 ± 2.1	3.3 ± 1.7	.03

*Abbreviations:* cCR = clinical complete response; CRT = chemoradiation therapy; pCR = pathological complete response; TRG = tumor regression grade.

\* Tumor regression grade and final tumor size were available only for patients managed by surgical excision of the primary tumor.

Bad responders less

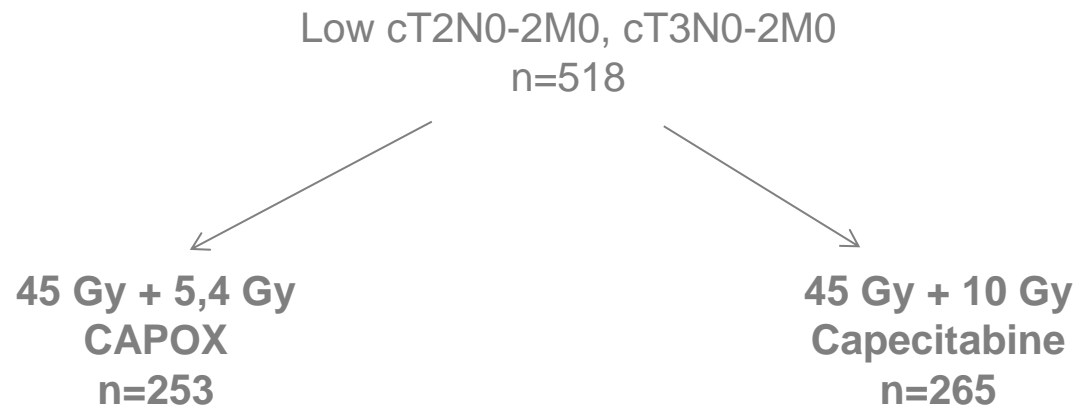
- CR
- Dworak TRG 3-4
- Tumoural downsizing



SUV variation may help to identify patients who benefit from longer interval between CRT and surgery



# INTERACT trial



	CAPOX	RT boost	p value
Hematologic toxicity	↑		0.002
Gastrointestinal toxicity	↑		0.001
Neurologic toxicity	↑		<0.001
Sphincter saving	85 %	85 %	0.8
TRG 1	28 %	29 %	0.113
ypT0N0	26 %	23,5 %	

# RAPIDO trial

- Rectal Cancer And Pre-operative Induction Therapy Followed by Dedicated Operation trial
- Randomized multicentre Phase III study

## Arm A = control

→ Long course  
chemo-RT  
(5 weeks)  
→ Surgery  
→ (adjuvant  
chemo)

Pts with primary  
high risk rectal  
cancer  
N = 885

## Arm B = exp

→ 5 x 5Gy  
→ 6 cycles of  
capecitabine +  
oxaliplatin  
→ Surgery

# Conclusions

- There is a steep dose response relationship in rectal cancer
- Highly conformal RT techniques and better imaging allow for radiation dose escalation
- Rays and drugs are a powerful combination
- Further research on the optimal radiation dose/fractionation, time interval to surgery, drugs and dosing is ongoing...

On to the next speaker

