APPROPRIATEZZA DELL'IMAGING NEI TUMORI DEL RETTO

Attualità nei trattamenti integrati del carcinoma del Retto localmente avanzato:
verso la preservazione d'organo

Il punto di vista del radioterapista oncologo

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ART
Advanced Radiation Therapy

ESTRO
Institutional member
2016

INCONTRO CON GLI ESPERTI XIV EDIZIONE
APPROPRIATEZZA DELL'IMAGING NELLA DIAGNOSTICA E RADIOTERAPIA DEI TUMORI GASTROINTESTINALI

Presidente Onorario
Prof. Giampiero AUSILI CÉFARO

Presidenti del Congresso
Prof. Antonio Raffaele COTRONEO
Prof. Domenico GENOVESI

23 e 24 FEBBRAIO 2017
Sala Convegni Ce.S.I.
Fondazione Università
"G. d'Annunzio" Chieti-Pescara
Via Luigi Polacchi, 11 Chieti Scalo

pCR and Organ Preservation

- **The meaning of CR**

- How to achieve CR

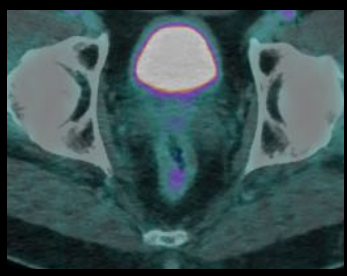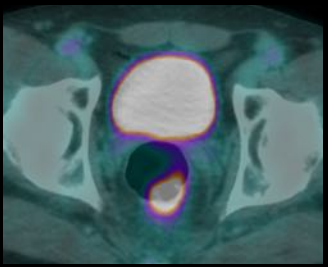- What to irradiate

- How to predict

pCR after CRT

Protocol	pCR	Concomitant CT	Cumulative pCR
EORTC 22921	13.7*		
FFCD 9203	11.4	5FU	
STAR	16		≈ **15%**
ACCORD	19.2	5FU and oxaliplatin	
NASBP R04	20.9		
CAO-ARO-AIO 04	16.5		

*pT0

The meaning of CR after CRT

LC-CRT

pCR and long term outcomes: RCT

				Hazard ratio
R1	6/15	7/9		0·40 (0·13–1·25)
TNM stage				
ypT0N0	9/104	6/81		1·20 (0·43–3·36)
Stage I	19/148	30/176		0·72 (0·40–1·28)
Stage II	40/154	48/148		0·74 (0·49–1·13)
Stage III	57/154	71/169		0·89 (0·63–1·28)
Type of surgery				
Low anterior resection	98/398	105/416		0·98 (0·74–1·29)
Intersphincteric resection	5/31	10/30		0·46 (0·16–1·35)
Abdominoperineal resection	45/151	67/152		0·58 (0·39–0·85)
Total				
All	**159/613**	**198/623**		**0·79 (0·64–0·98)**

0·2   0·5   1·0   2·0 3·0 4·0
Hazard ratio

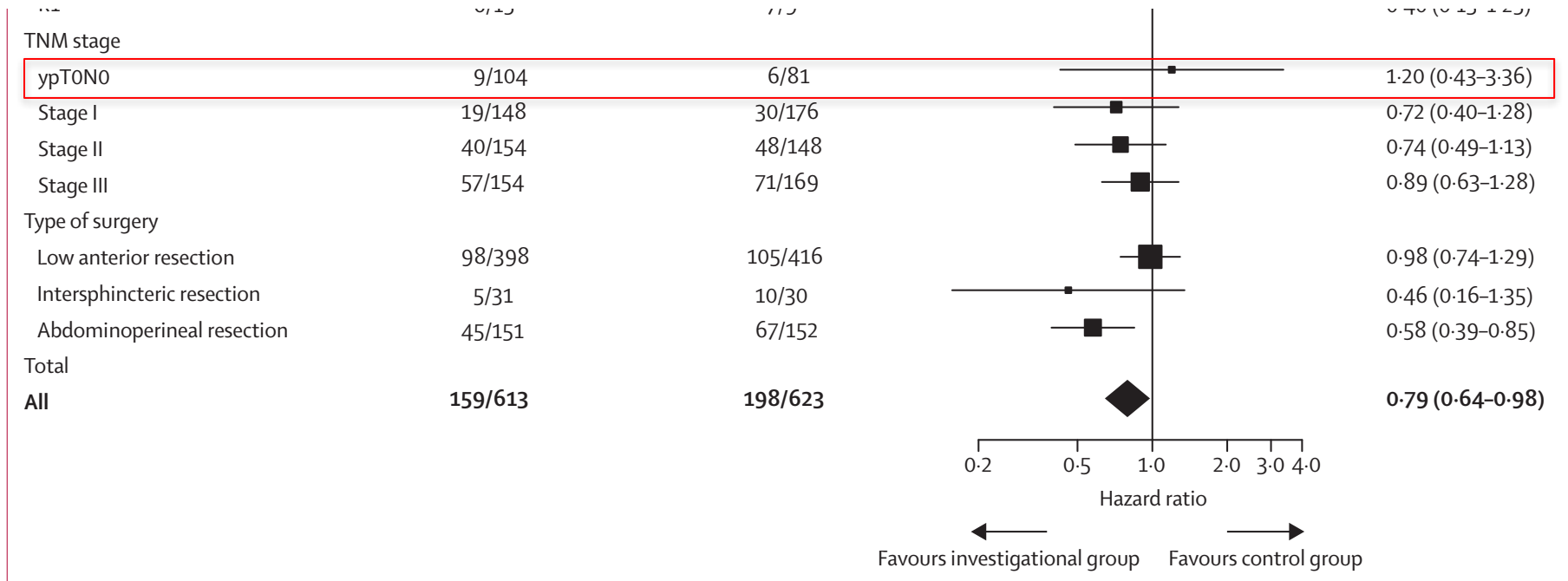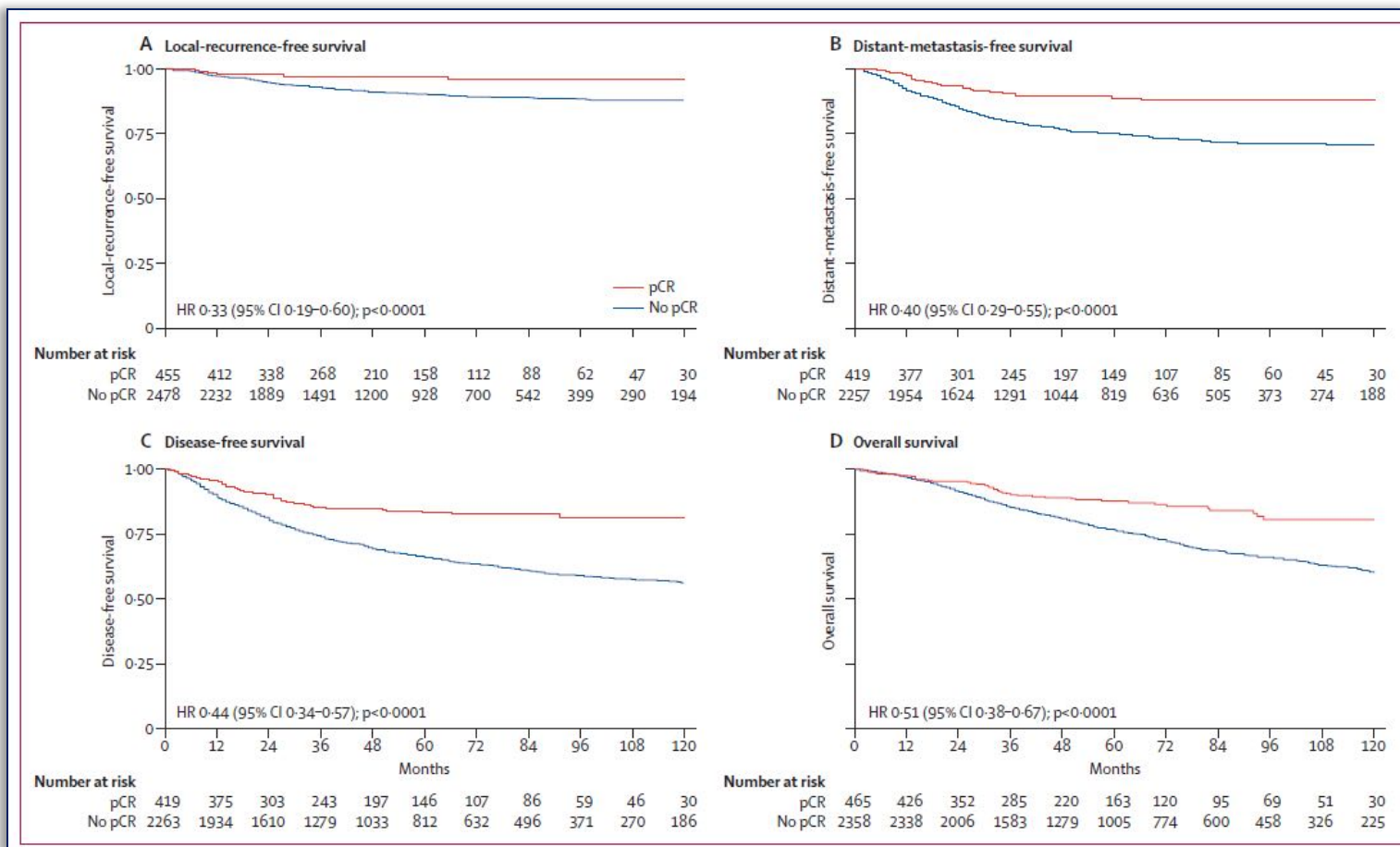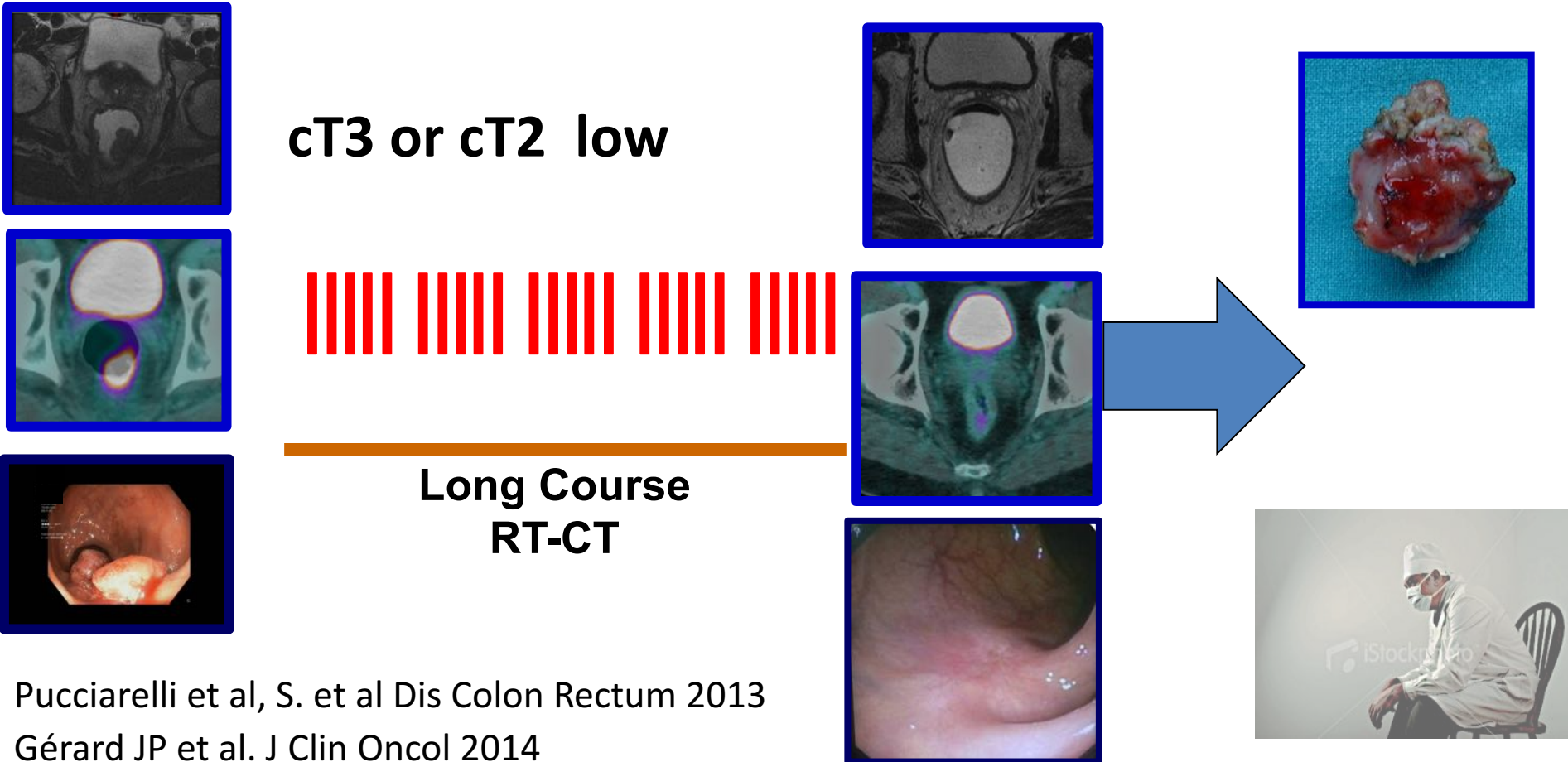Favours investigational group   Favours control group

Figure 4: Disease-free survival in the intention-to-treat population by patient subgroups according to pretreatment and surgical or pathological factors after preoperative chemoradiotherapy

Rodel C et al. Lancet Oncol 2015

pCR and long term outcomes: pooled analyses

A Local-recurrence-free survival
HR 0·33 (95% CI 0·19–0·60); p<0·0001

B Distant-metastasis-free survival
HR 0·40 (95% CI 0·29–0·55); p<0·0001

C Disease-free survival
HR 0·44 (95% CI 0·34–0·57); p<0·0001

D Overall survival
HR 0·51 (95% CI 0·38–0·67); p<0·0001

Maas M et al. Lancet Oncol 2010
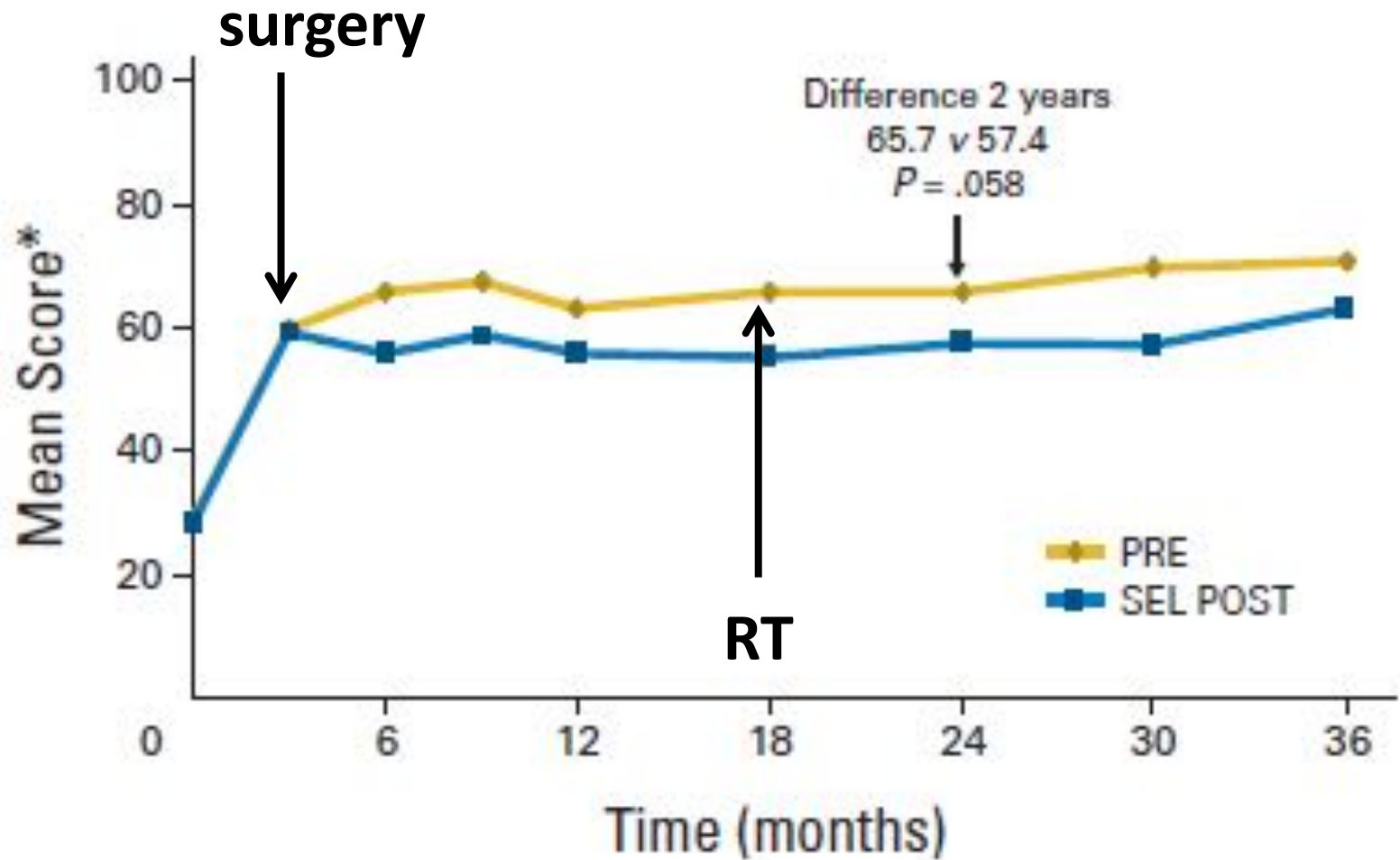
Surgery descalation

cT3 or cT2 low

Long Course
RT-CT

cCR

Pucciarelli et al, S. et al Dis Colon Rectum 2013
Gérard JP et al. J Clin Oncol 2014
Vuong T et al. Semin Colon Rectal Surg 2010
Maas M et al J Clin oncol 2011
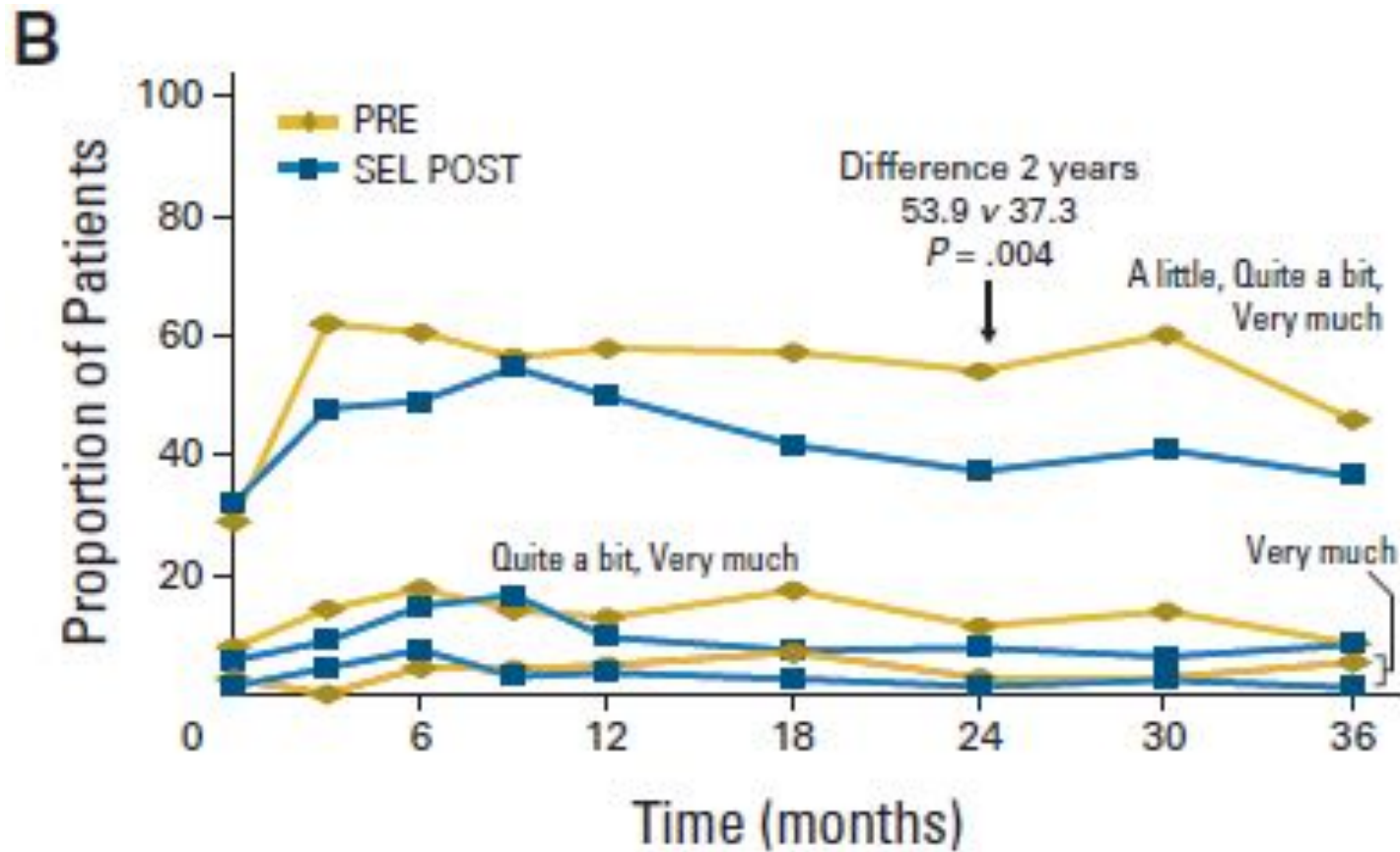Appelt A. Lancet Oncol 2015

Sexual function (male*)

*Only 11% of women completed the questionnaire at 2 yrs

Stephens et al JCO 2010

Sphincter function
Unintentional release of stool

Stephens et al JCO 2010

pCR and Organ Preservation

- The meaning of CR

- **How to achieve CR**

- What to irradiate

- How to predict

How to achieve CR

- **Chemotherapy** intensification

- **Radiotherapy** intensification

- **TIME** CRT ⟶┈┈┈▸ Surgery

CT intensification

During RT

'New' CT agents

Target therapies

Sequence of therapies

Total Neoadjuvant Therapy

CT intensification during RT: 'New agents'

ypCR	OXAL −	OXAL +	
ACCORD 12	14 %	19 %	p=ns
STAR	16 %	16 %	p=ns
CAO/ARO/AIO-04	13 %	17 %	p=.038
PETAAC 6	11.5 %	13 %	p=ns

G3 + Acute toxicity			
ACCORD 12	11 %	25 %	p<.001
STAR	8 %	24 %	p<.001
CAO/ARO/AIO-04	20 %	24 %	p<.001
PETAAC 6	15 %	37 %	p<.001

Gerard JP et Al - JCO - 2010, Aschele C et Al, CO – 2011, Rödel C et Al – Lancet Oncol -2012, Schmoll J –ECCO - 2013
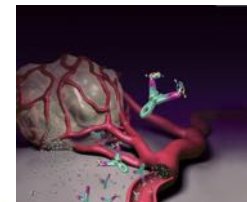
Gemelli ART ESTRO
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Università Cattolica del Sacro Cuore

Target therapies

Clinical trials with EGFR-Inhibition in RC

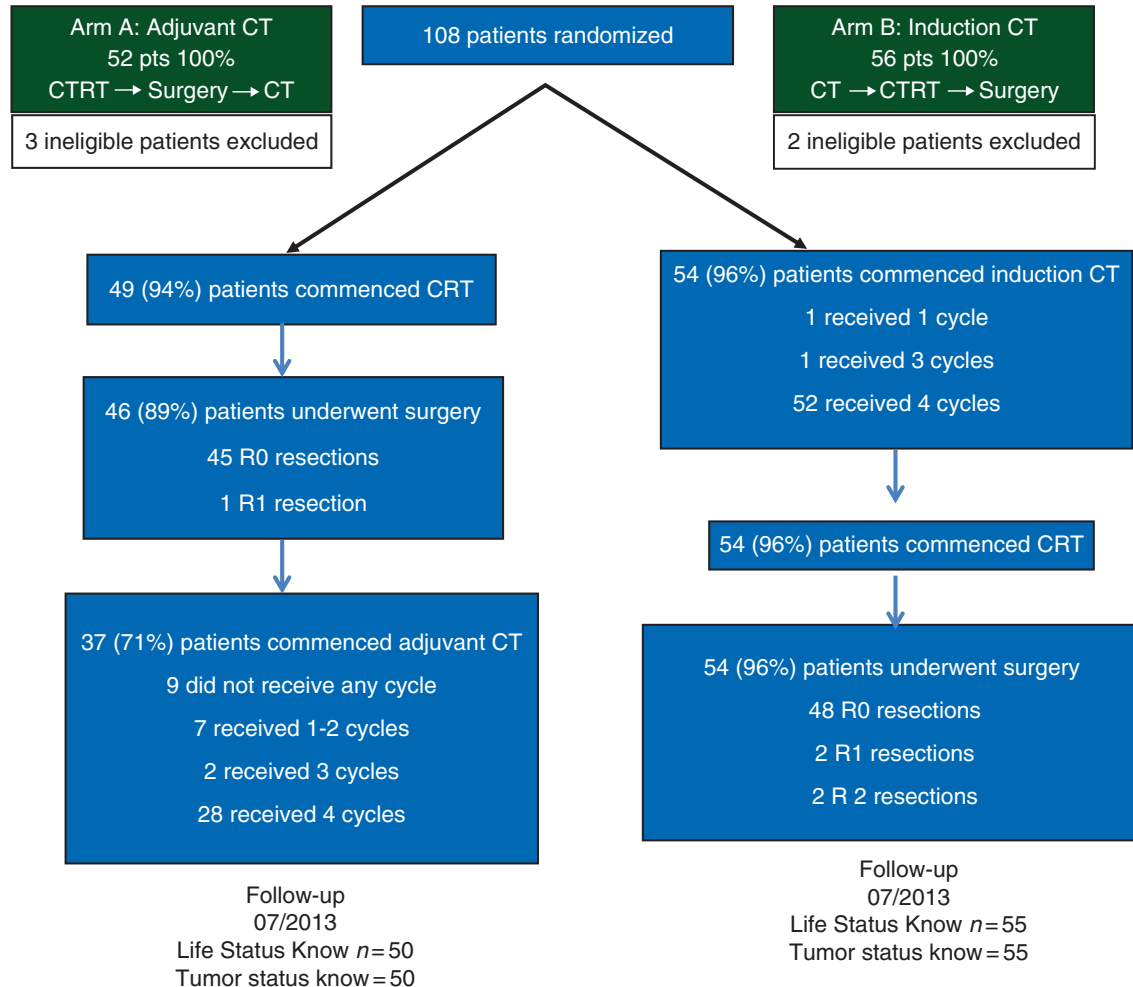| Series	n	Treatment	pCR
Bertolini, 2007	40	RT + 5-FU + *Cetuximab*	8%
Machiels, 2007	30	RT + Cape + *Cetuximab*	5%
Rödel, 2008	48	RT + Capox+ *Cetuximab*	9%
Hofheinz, 2008	50	RT + Capiri+ *Cetuximab*	8%

Target therapies

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

By the Courtesy of C.Rodel – ESTRO Course 2016

CT intensification:
Total Neoadjuvant Treatment

Arm A: Adjuvant CT
52 pts 100%
CTRT → Surgery → CT

3 ineligible patients excluded

108 patients randomized

Arm B: Induction CT
56 pts 100%
CT → CTRT → Surgery

2 ineligible patients excluded

49 (94%) patients commenced CRT

46 (89%) patients underwent surgery

45 R0 resections

1 R1 resection

37 (71%) patients commenced adjuvant CT

9 did not receive any cycle

7 received 1-2 cycles

2 received 3 cycles

28 received 4 cycles

Follow-up
07/2013
Life Status Know $n = 50$
Tumor status know $= 50$

54 (96%) patients commenced induction CT

1 received 1 cycle

1 received 3 cycles

52 received 4 cycles

54 (96%) patients commenced CRT

54 (96%) patients underwent surgery

48 R0 resections

2 R1 resections

2 R 2 resections

Follow-up
07/2013
Life Status Know $n = 55$
Tumor status know $= 55$

Fernandez-Martoz C et al. JCO 2010

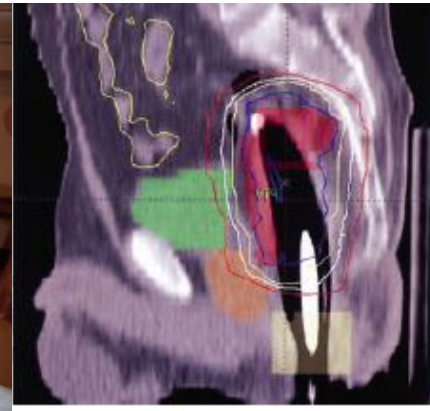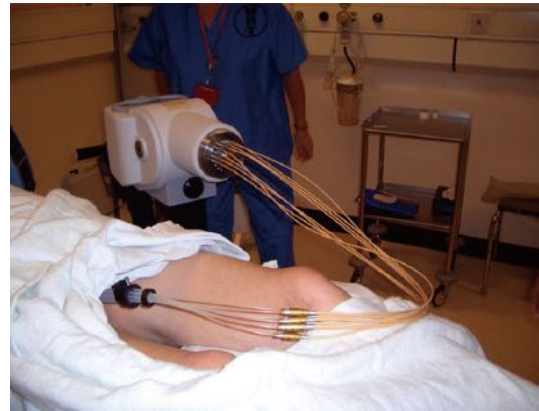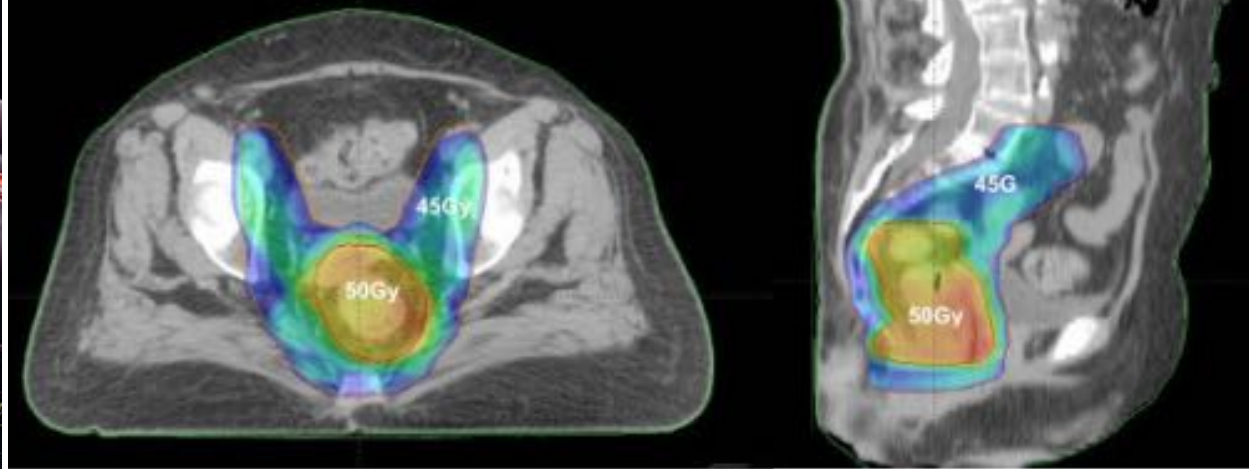# Preoperative treatment intensification: Total Neoadjuvant Treatment

Table 3. End Points for the Total Patient Group

End Point	Arm A: Post-operative Adjuvant CT (n = 52)		Arm B: Induction CT (n = 56)		P^*
	No.	%	No.	%	
pCR	7	13	8	14	.94
95% CI, %	5.6 to 25.8		6.4 to 26.2		
Downstaging	30	58	24	43	.13
95% CI, %	43.2 to 71.3		29.7 to 56.8		
R0 resection rates	45	87	48	86	.40
TRG†					
4: complete regression	7	15	8	15	.88
3: > 50% of tumor mass	22	48	20	37	
2: ≥ 25%-50% of tumor mass	11	24	13	24	
1: < 25% of tumor mass	2	4	3	6	
0: no regression	1	2	3	6	
Not otherwise specified	3	7	7	13	

Fernandez-Martoz C et al. JCO 2010

How to achieve CR

- **Chemotherapy** intensification

- **Radiotherapy** intensification

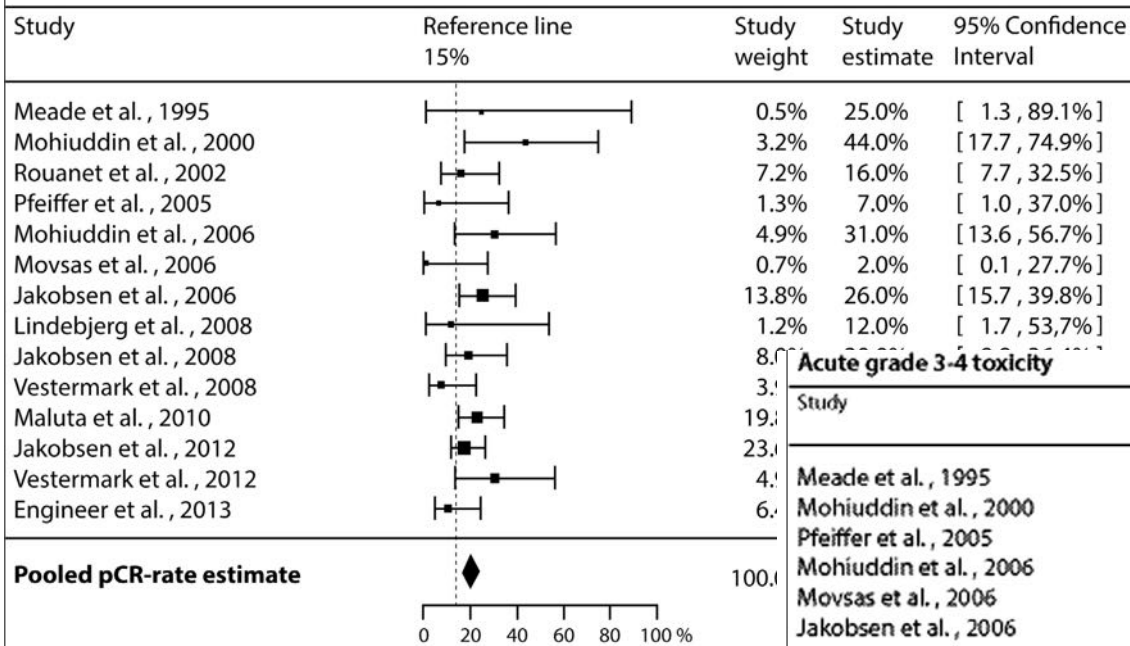- **TIME** CRT ⎯⎯⎯⎯→------→ Surgery

RT intensification

Reliability of RT for cure

D50,TRG1=   **92.0 Gy**
D50,TRG1-2=   **72.1 Gy**

Appelt AL et al. Int. J Radiat Oncol Biol Phys 2013
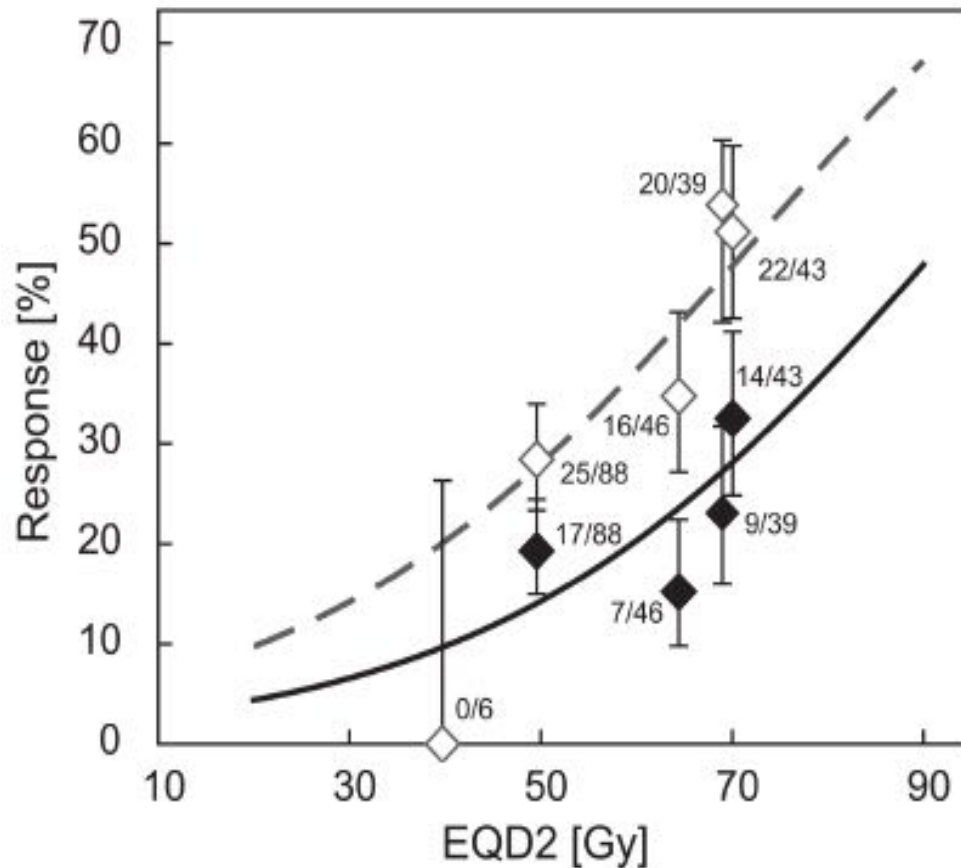
RT intensification: dose≥ 60Gy

pCR-rate

Study	Reference line 15%	Study weight	Study estimate	95% Confidence Interval
Meade et al. , 1995		0.5%	25.0%	[1.3 , 89.1%]
Mohiuddin et al. , 2000		3.2%	44.0%	[17.7 , 74.9%]
Rouanet et al. , 2002		7.2%	16.0%	[7.7 , 32.5%]
Pfeiffer et al. , 2005		1.3%	7.0%	[1.0 , 37.0%]
Mohiuddin et al. , 2006		4.9%	31.0%	[13.6 , 56.7%]
Movsas et al. , 2006		0.7%	2.0%	[0.1 , 27.7%]
Jakobsen et al. , 2006		13.8%	26.0%	[15.7 , 39.8%]
Lindebjerg et al. , 2008		1.2%	12.0%	[1.7 , 53,7%]
Jakobsen et al. , 2008		8.		
Vestermark et al. , 2008		3.		
Maluta et al. , 2010		19.		
Jakobsen et al. , 2012		23.		
Vestermark et al. , 2012		4.		
Engineer et al. , 2013		6.		
Pooled pCR-rate estimate		100.		

pCR 20%

G3-4 TOX 10%

Acute grade 3-4 toxicity

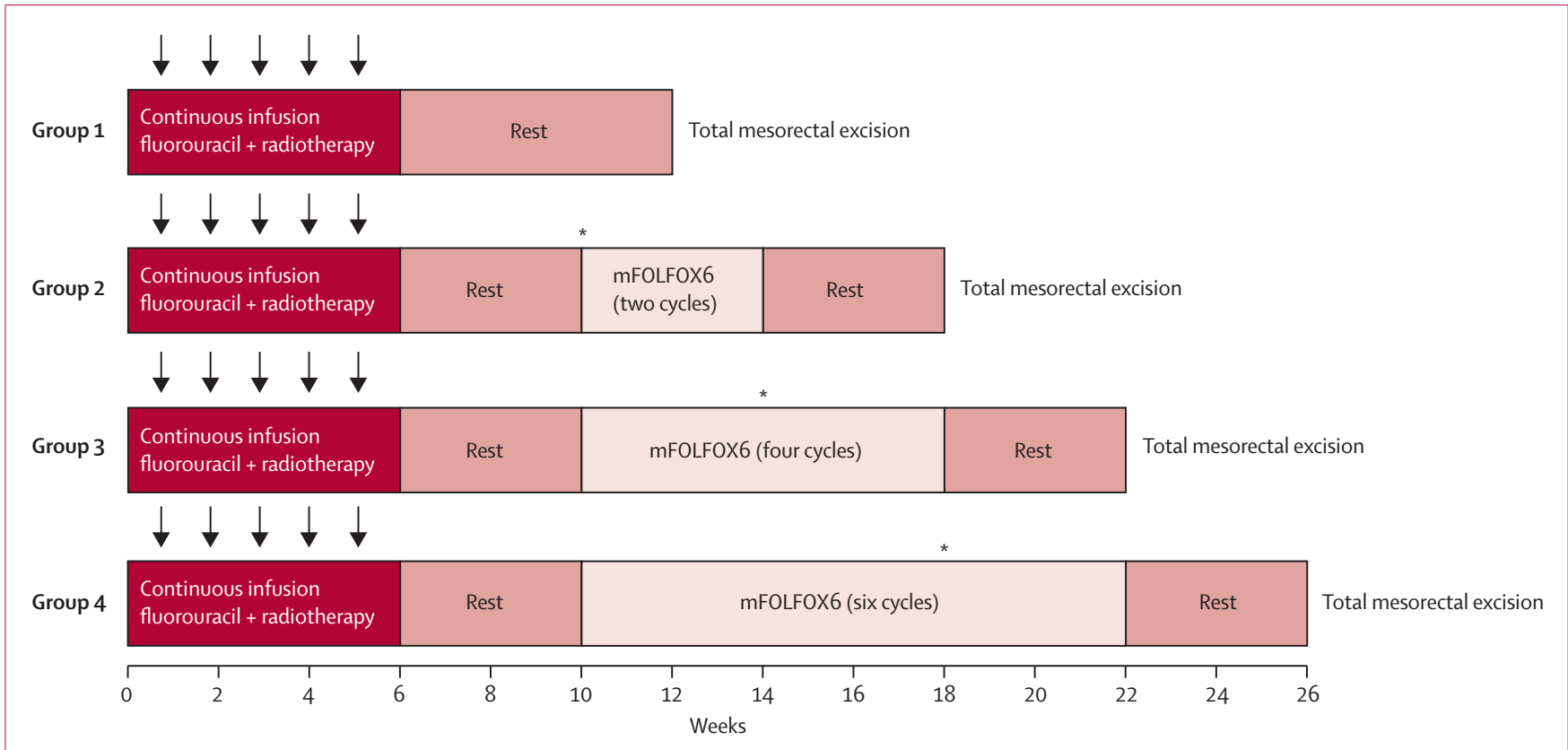| Study		Study weight	Study estimate	95% Confidence Interval
Meade et al. , 1995		3.5%	25.0%	[1.3 , 89.1%]
Mohiuddin et al. , 2000		9.4%	33.3%	[11.1 , 66.7%]
Pfeiffer et al. , 2005		6.5%	7.1%	[1.0 , 37.0%]
Mohiuddin et al. , 2006		11.6%	43.8%	[22.5 , 67.6%]
Movsas et al. , 2006		10.2%	14.3%	[4.7 , 36.1%]
Jakobsen et al. , 2006		10.6%	6.0%	[1.9 , 17.0%]
Jakobsen et al. , 2008		9.2%	5.7%	[1.4 , 20.2%]
Vestermark et al. , 2008		9.2%	5.6%	[1.4 , 19,7%]
Maluta et al. , 2010		6.7%	1.3%	[0.2 , 8.80%]
Jakobsen et al. , 2012		13.5%	10.1%	[5.7 , 17.3%]
Engineer et al. , 2013		9.2%	4.5%	[1.1 , 16.4%]
Pooled toxicity estimate		100.0%	10.3%	[5.4 , 18.6%]

Burbach et al. Radiother Oncol 2014

RT intensification

Interact Trial

Xelac — Concomitant Boost 10 Gy
Capecitabine 1600 mg/m2 chrono
45 Gy

Random

Oxaliplatin 130 mg/m^2
Capecitabine 1300 mg/m2 chrono
45 Gy   5 Gy

Xelox

Interact Trial: analysis 01/14

Valentini V et al. ESTRO-33-2014

RT intensification

Interact Trial

Accrual: 527 pts

	Xelac	Xelox
Randomized	270	257
Evaluable	265	253

Pts evaluable: 518 pts

Interact Trial: analysis 01/14

Valentini V et al. ESTRO-33-2014

RT intensification

	Xelac (%)	Xelox (%)	p
TRG			
TRG1	31.4	30.8	ns
TRG 1-2	60.2	51.0	ns
pCR	**24.4**	**23.8**	**ns**

Interact Trial: analysis 01/14

Modified from Valentini V et al. ESTRO-33-2014

RT intensification

Outcome:
Acute CRT G3+ Toxicity

	Xelac (%)	Xelox (%)	p
Hemat	8.4	18.4	0.002
GI	15	27.8	0.001
Skin	31.2	25.2	ns
GU	20.6	17.5	ns
Liver	5.6	5.4	ns
Neuropathy	3.8	20.5	0.001

Interact Trial: analysis 01/14

Valentini V et al. ESTRO-33-2014

How to achieve CR

- **Chemotherapy** intensification

- **Radiotherapy** intensification

- **TIME** CRT ⎯⎯⎯⎯→┄┄┄→ Surgery

Preoperative treatment intensification: Total Neoadjuvant Treatment

RC→ 12 cm from AV
   cT3-4, N0; cT, N1-2

Primary end-point: ypCR

Garcia-Aguilar J et al. Lancet Oncol 2015

Preoperative treatment intensification: Total Neoadjuvant Treatment

Primary end-point: ypCR

RC→ 12 cm from AV
   cT3-4, N0; cT, N1-2
259 enrolled patients

	Group 1 (n=60)	Group 2 (n=67)	Group 3 (n=67)	Group 4 (n=65)	p value
Pathological complete response	11 (18%)	17 (25%)	20 (30%)	25 (38%)	0·0036
Partial response	44 (73%)	50 (75%)	46 (69%)	39 (60%)	..
Stable disease	5 (8%)	0	1 (1%)	1 (2%)	..

Data are number (%). p value tests the null hypothesis of equal proportions across study groups.

Table 3: **Pathological tumour response**

	Group 1 (n=60)	Group 2 (n=67)	Group 3 (n=67)	Group 4 (n=65)	p value
Time from start of chemoradiation to surgery (weeks)	14·2 (4·3)	17·1 (2·9)	21·0 (2·7)	25·2 (4·0)	0·0001
Time from end of chemoradiation to surgery (weeks)	8·5 (4·2)	11·1 (2·9)	15·4 (2·6)	19·3 (4·2)	0·0001
Sphincter-saving surgery	46 (77%)	50 (75%)	50 (75%)	44 (68%)	0·68
Ileostomy	38/46 (83%)	43/50 (86%)	47/50 (94%)	38/43 (88%)*	0·33
Resection with negative margins	59 (98%)	67 (100%)	64 (96%)	64 (100%)†	0·089
Number of nodes examined	12 (2–31)	14 (2–30)	13 (2–30)	11 (1–47)	0·20
Pelvic fibrosis‡	2·4 (1·7)	3·9 (2·6)	4·4 (2·4)	3·9 (2·4)	0·0001
Technical difficulty§	4·6 (2·7)	4·9 (2·8)	5·1 (2·5)	4·8 (2·4)	0·80
Estimated blood loss (mL)	200 (50–1200)	225 (25–1500)	200 (50–1000)	150 (0–1000)	0·62

Data are mean (SD), number (%), n/N (%), or median (range). p values test the null hypothesis of equal means or proportions across study groups. *Information on whether an ileostomy was created or not was not available for one patient. †Data missing for one patient. ‡Scale ranges from 1 (none) to 10 (maximum). §Scale ranges from 1 (easy) to 10 (difficult).

Table 2: **Surgical results**

Garcia-Aguilar J et al. Lancet Oncol 2015

Time effect?

Pooled analysis of RCT:

Accord 12/0405

EORTC 22921

FFCD 9203

CAO/ARO/AIO-94

CAO-ARO-AIO-04

INTERACT and TROG 01.04

5247 pts → 3078 → 440 (14%) had pCR

Median Surgery Time → 6 wks

	Shorter Interval Group $\leq$ 6 wks (1953 pts)	**Longer Interval Group** >6 wks (1125 pts)	**p**
pCR	**11%**	**19%**	**.01**

Valentini V ECCO 2017

Time effect?

Cumulative pCR along time

Plateau @ 16 months

95% @ 11 months
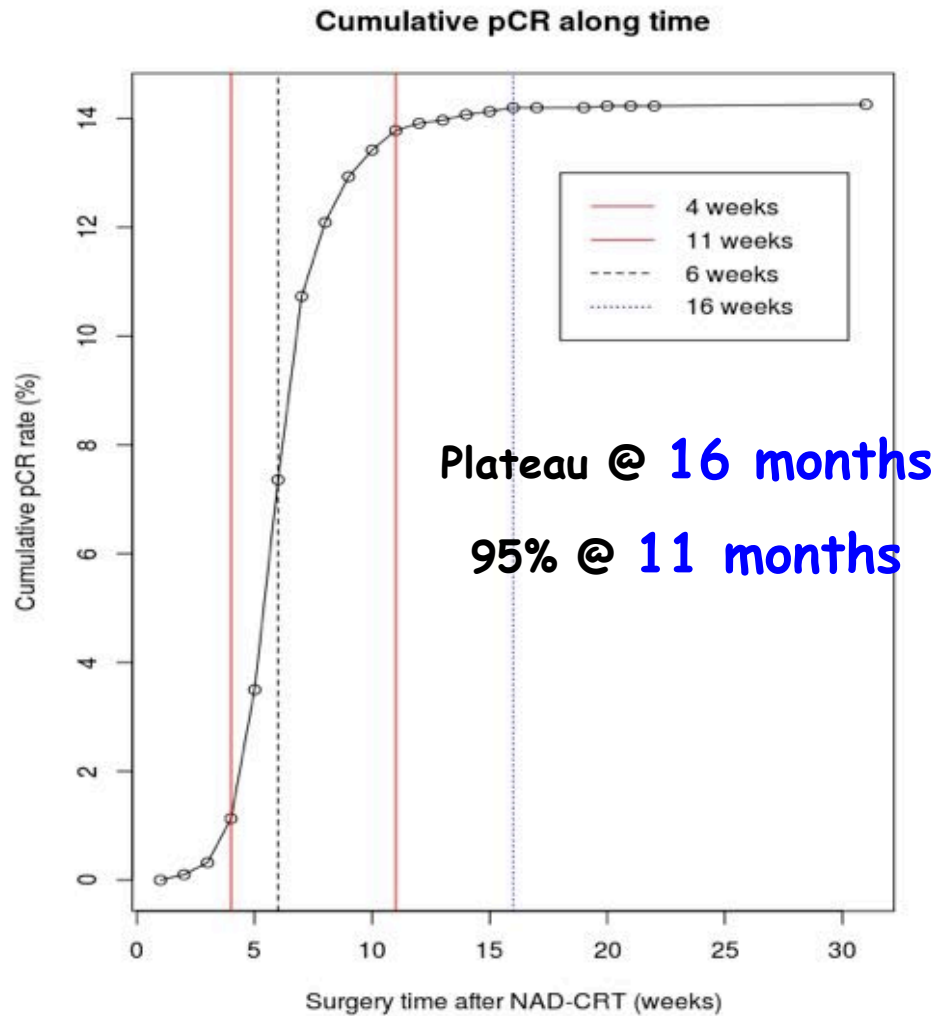
Time effect?

Table 1: Significant covariates of univariate logistic regression model			
Covariates	Coefficients	P-Value	Outcome
Surgery time after NAD-CRT (weeks)	0,019	<0.01	An increase of weeks after NAD-CRT increases pCR rate
Radiotherapy Dose	0,007	<0.01	An increase in radiotherapy dose increases pCR rate
Neoadjuvant chemotherapy Oxaliplatin based	0,056	<0.01	Neoadjuvant chemotherapy Oxaliplatin based increases pCR rate
Longer interval group	0,072	<0.01	Have surgery after 6 weeks increases pCR rate
Surgery time after NAD-CRT (weeks)	-0,015	<0.01	An increase of weeks after NAD-CRT decreased post-surgical complications

Valentini V ECCO 2017

Time effect?

- Retrospective pooled analysis 2094 pts from 21 Italian Centers

- Median time to surgery→ 9 weeks

- Cumulative pCR → 22.3%

	≤ 6 wks	7-12 wks	≥ 13 wks	p
pCR AIRO	**12.6%**	**23.0%**	**31.1%**	**<0.001**
pCR Garcia- Aguilar	18% (8.1 wks)	25% (11 wks)	30% (15 wks)	**0.036**

Macchia G et al. on behalf of AIRO-GI submitted

pCR and Organ Preservation

- The meaning of CR

- How to achieve CR

- **What to irradiate**

- How to predict

What to irradiate

3D Conformal RT

GTV + corresp mesorectum

IMRT-IGRT

GTV + margin

Myerson et al IJROBP 2009
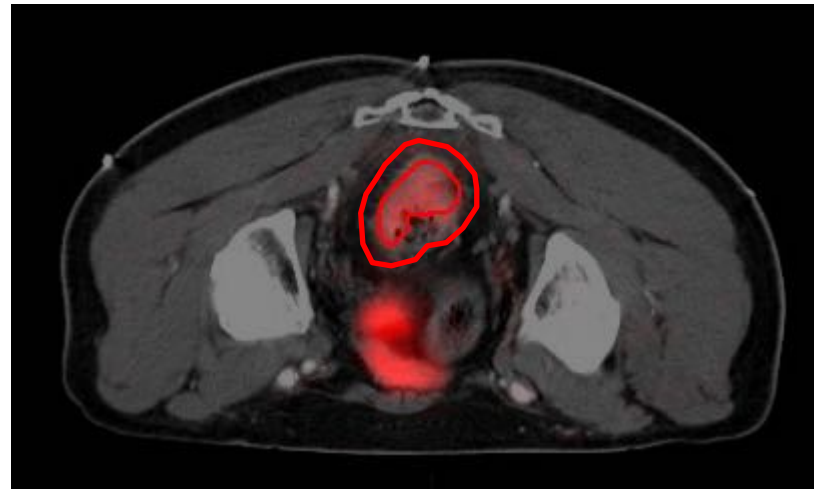
Imaging modality for GTV
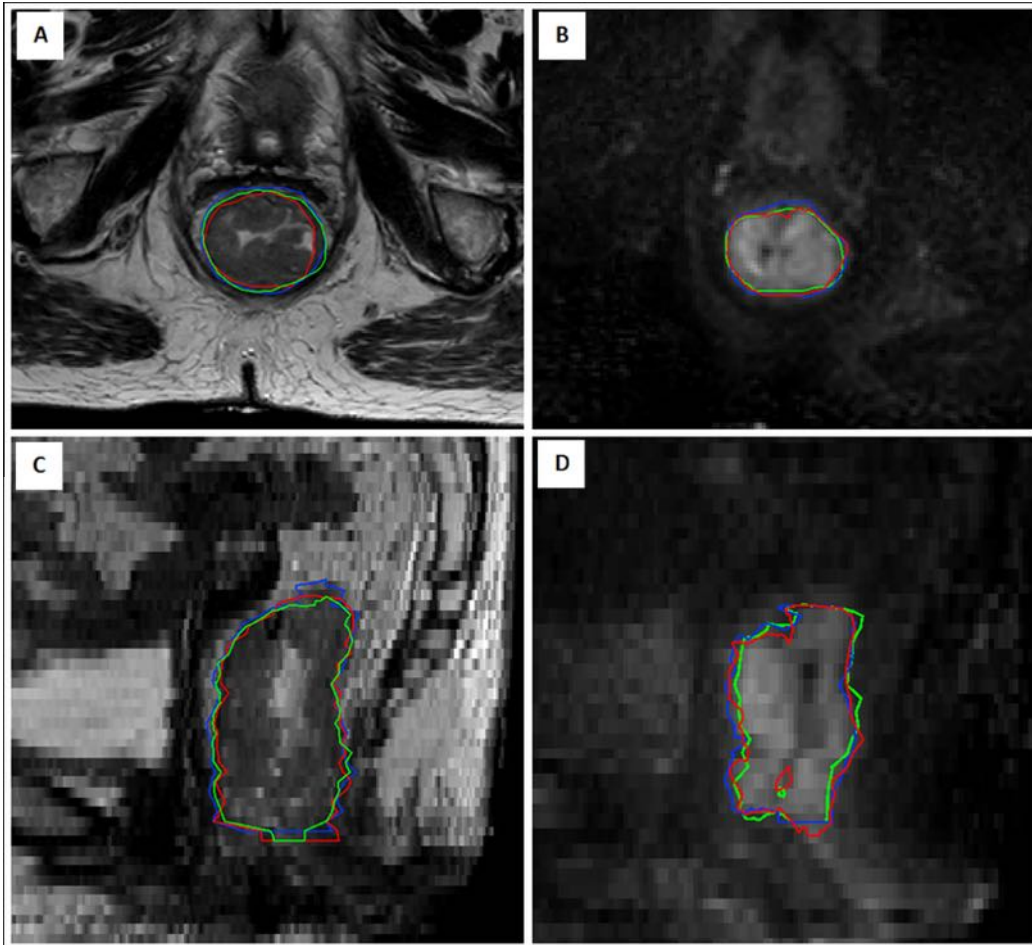
24 pts
3 observer

GTV on:
- **T2w**
- **DWI**
- **Combi T2-DWI**

Bonnetain F et al. Eur J Cancer 2016

Imaging modality for GTV

D   All volumes per modality

	N	Mean	SD	Min	Max
T2	72	63.16	33.39	9.38	153.40
DWI	69	41.94	25.49	7.60	115.18
Combi	69	54.63	29.54	10.12	131.68

A   Conformity index per modality

	N	Mean	SD	Min	Max
T2	24	.699	.078	.55	.84
DWI	23	.707	.104	.38	.85
Combi	23	.690	.074	.53	.81

B   HDmax per modality

Distance parameters (mm)

HDmax	N	Mean	SD	Min	Max
T2	24	18.59	7.00	9.16	31.41
DWI	23	14.42	9.15	4.03	49.10
Combi	23	15.42	6.24	8.01	30.27
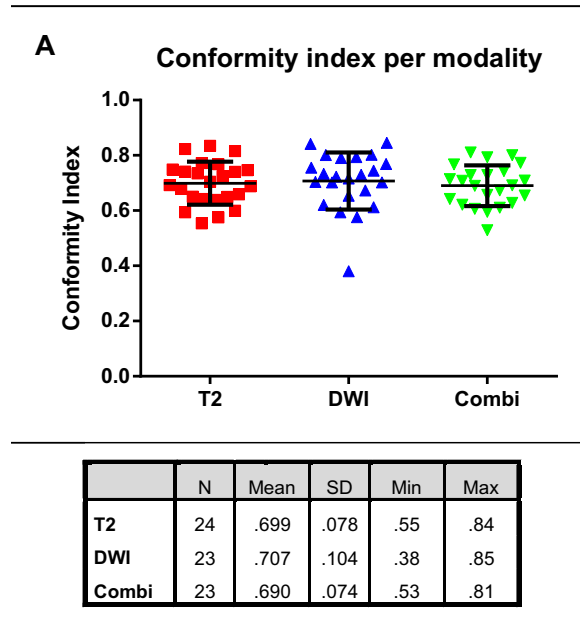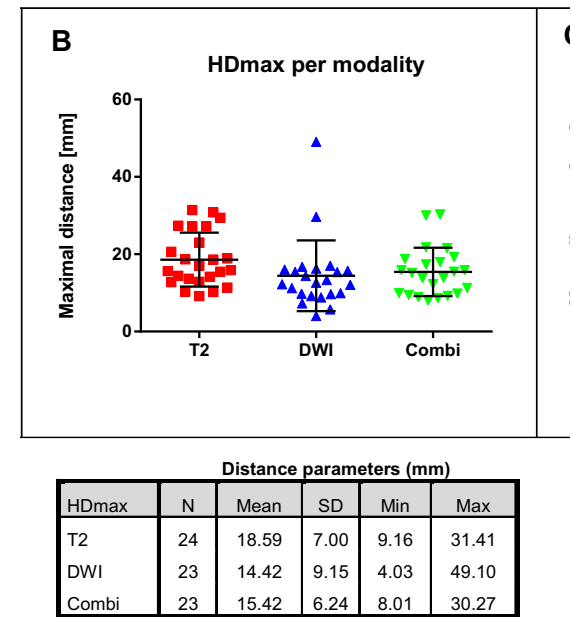
volume   **overlapping**   **margins**

Target motion

Shape variation
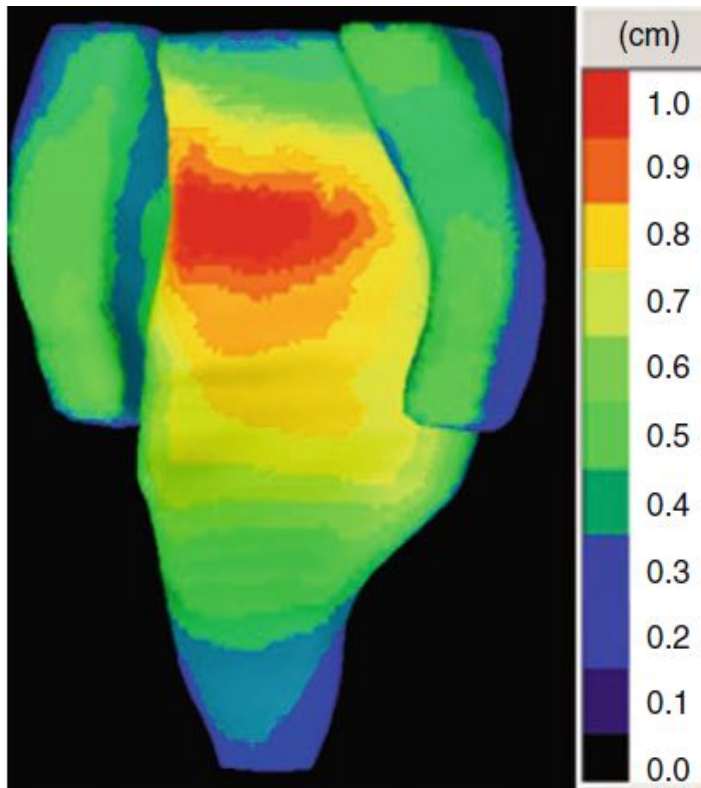
Set-up

- **Prone up to 0.24 cm**
- **left-right direction**

- **Supine < 0.1 cm**

Nijkamp J et al. Radiother Oncol 2009

IMAGE GUIDED RADIOTHERAPY

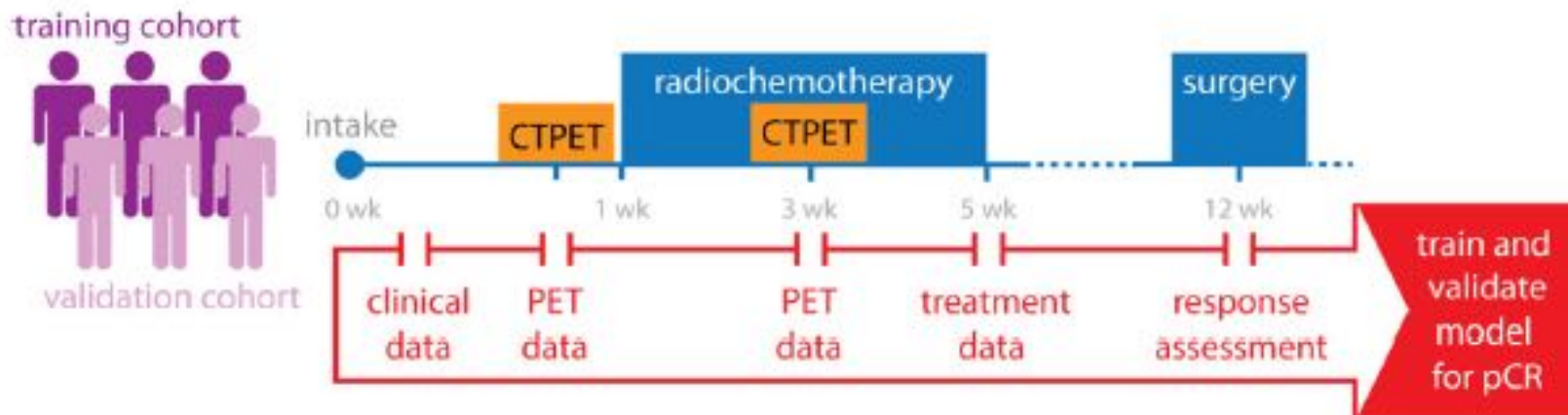BEFORE　　　　　　TREATMENT　　　　　　AFTER

MRI HYBRID Machines

pCR and Organ Preservation

- The meaning of CR

- How to achieve CR

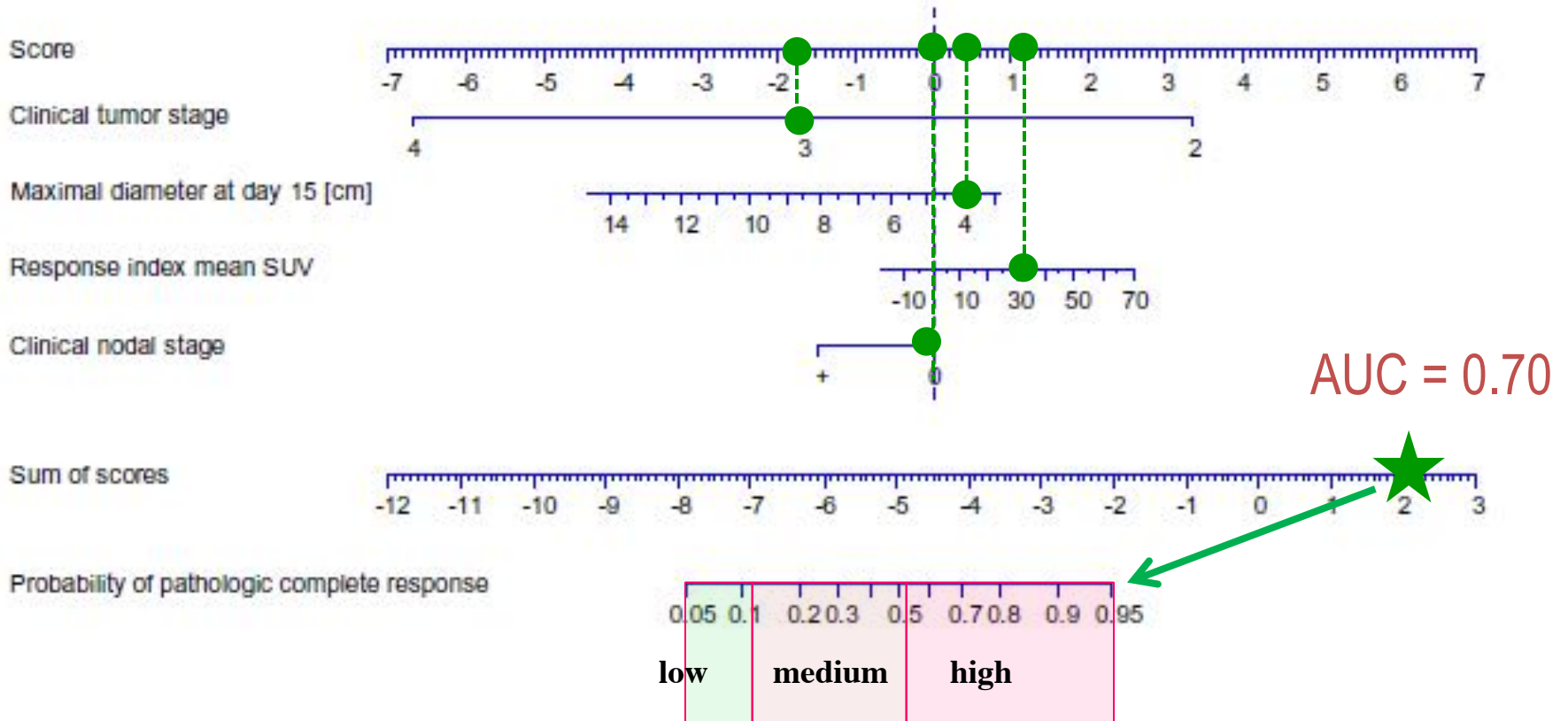- What to irradiate

- **How to predict**

Nomograms for pCR
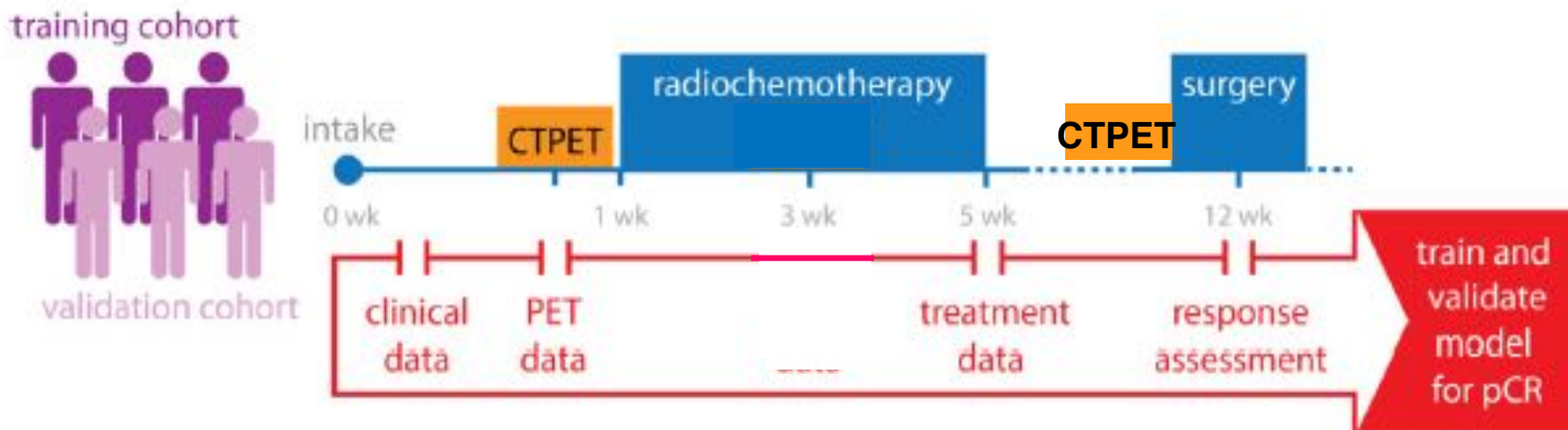
Van Stiphout R, Valentini V et al. Radiother Oncol 2011

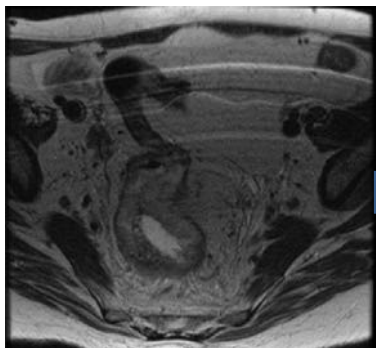Van Stiphout R, Valntini V. et al. Radiother Oncol 2014
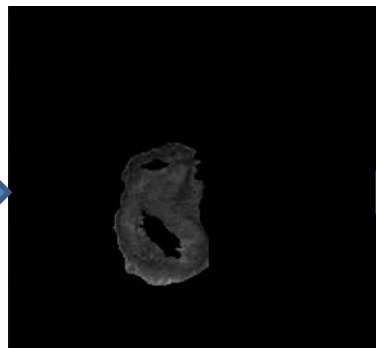
Nomogram

pCR (ypT0N0)

AUC = 0.70

Van Stiphout R, Valentini V et al. Radiother Oncol 2014

Radiomic in rectal cancer: a model for pCR prediction
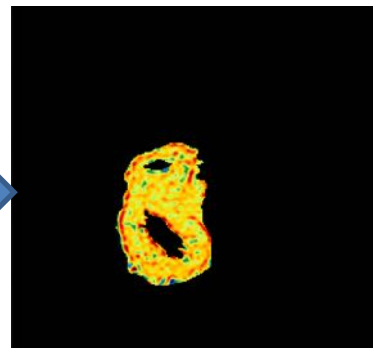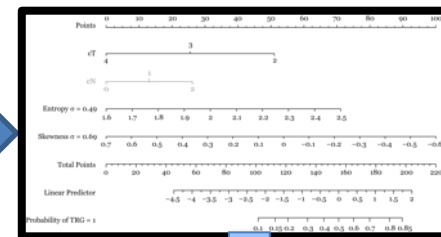

MRI

ROI extraction

Filter Application

Data analysis (Moddicon): Model development/validation

EXTERNAL VALIDATION

Datamining Radiomics

KBO Labs
Knowledge Based Oncology Labs

Dinapoli N. et al. ESTRO 35, Turin 2016

To remember

- The meaning of CR   surg reduction

- How to achieve CR   RT; TIME

- What to irradiate   GTV-MR

- How to predict   nomograms