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Multidisciplinary session on rectal cancer

Expert: **Prof Maria Antonietta Gambacorta**, A. Gemelli University Polyclinic Foundation, Rome, Italy

Expert: **Dr Katia Roque Perez**, Instituto Nacional de Enfermedades Neoplasicas, Lima, Peru

Discussant: **Prof Ramon Andrade Bezerra de Mello**, Nine of July University, Sao Paulo, Brazil

Discussant: **Dr Zaher Lakkis**, University Hospital of Besançon, Besançon, France

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Multidisciplinary managment on Rectal Cancer

Katia Roque Pérez, M.D.
Instituto Nacional de Enfermedades Neoplásicas
Sociedad Peruana de Oncología Medica
Lima – Perú

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Standar treatment

Short course RT (SCR)

Long-course chemoradiotherapy (LCRT)

Total mesorectal excision (TME)

Adjuvant fluoropyrimidine-based chemotherapy.

ypN+tumor after preoperative chemoradiotherapy (CRT) / R1 resection

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SCRT vs LCRT ?

	N	pCR	CM+	PFS 4y	OS 4-5y	LR 4-3y	DiR 4y
Bujkio	155 vs 157	0.7% vs 16.1%	12.9%; vs 4.4% P= 0.017	**58.4 vs 55.6 (p = 0.820)**	**67.2 vs 66.2 (p = 0.960)**	**9.0 vs 14.2 (p = 0.170)**	
Ngan	163 vs 163	1% vs 15%	5% vs 4%	73% vs 70%	74 vs 70% (p= 0.62)	**7.5% vs 4.4% (p= 0.24**	27% vs 30% (p=0.92)

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Bujko et al. Br J Surg 2006; 93:1215-1223.
Ngan SY et al. J Clin Oncol 2012; 30:3827-3833.

Prognostic Value of pCR

- Meta-analysis 27 articles, based on 17 different datasets
- 5-year disease-free survival.
- 484 of 3105 included patients had a pCR.

5-year rate	pCR (n=484)	Others (n=2621)	HR	p
Locoregional recurrence	2.8%	9.7%	0.33	<0.0001
Distant recurrence	88.8%	74.9%	0.40	<0.0001
DFS	83.3%	65.6%	0.44	<0.0001
OS	87.6%	76.4%	0.51	<0.0001

Maas M. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol*. 2010;11(9):835-844.

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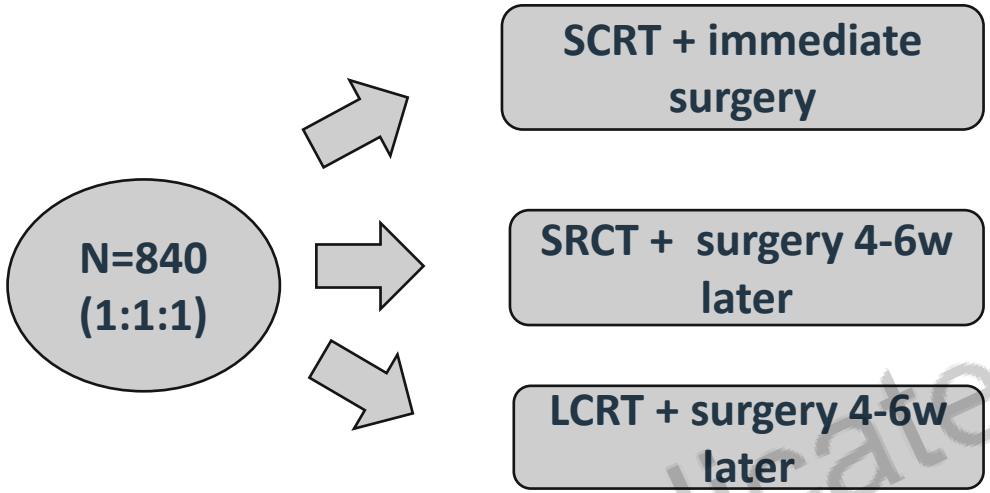
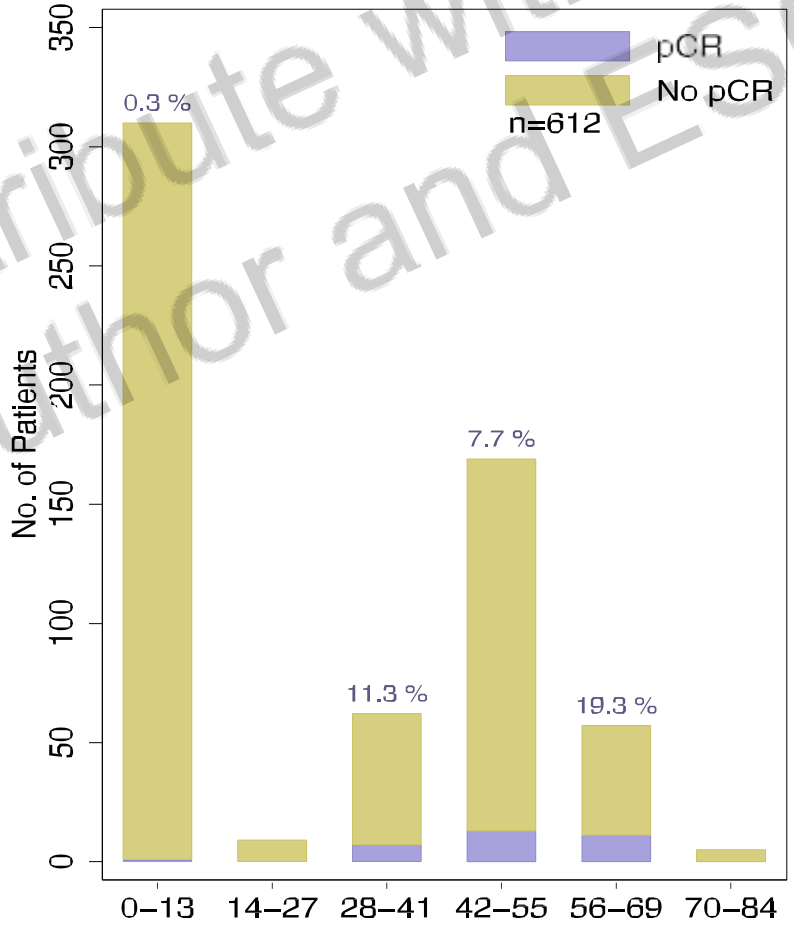
SRT and delayed Surgery: Stockholm III





- No different significantly in disease outcomes (LR, DiR and OS)
- Lower rate of postoperative complications (41 vs 53%, p 0.001)
- Greater tumor regression and a higher rate of pCR (11.8% vs 1.7%)

Erlandsson J et al. Lancet Oncol 2017; 18:336-346.

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SCRT – Consolidation CT: Polish II

SCRT + 3 cycles FOLFOX versus CRT (with 5FU and Oxaliplatin)

Less acute toxicity ; p=0.006

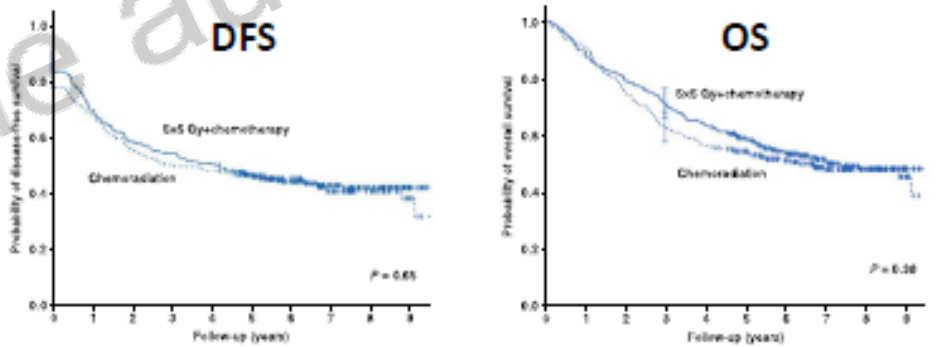
R0 resection 77% vs 71% ; p=0.07

pCR 16% vs 12% ; p=0.17

Median follow-up 7.0 years

No difference for locoregional and distant recurrences

No difference in DFS and OS



Bujko K et al, Ann Oncol 2016 ; Cisel B et al, Ann Oncol 2019

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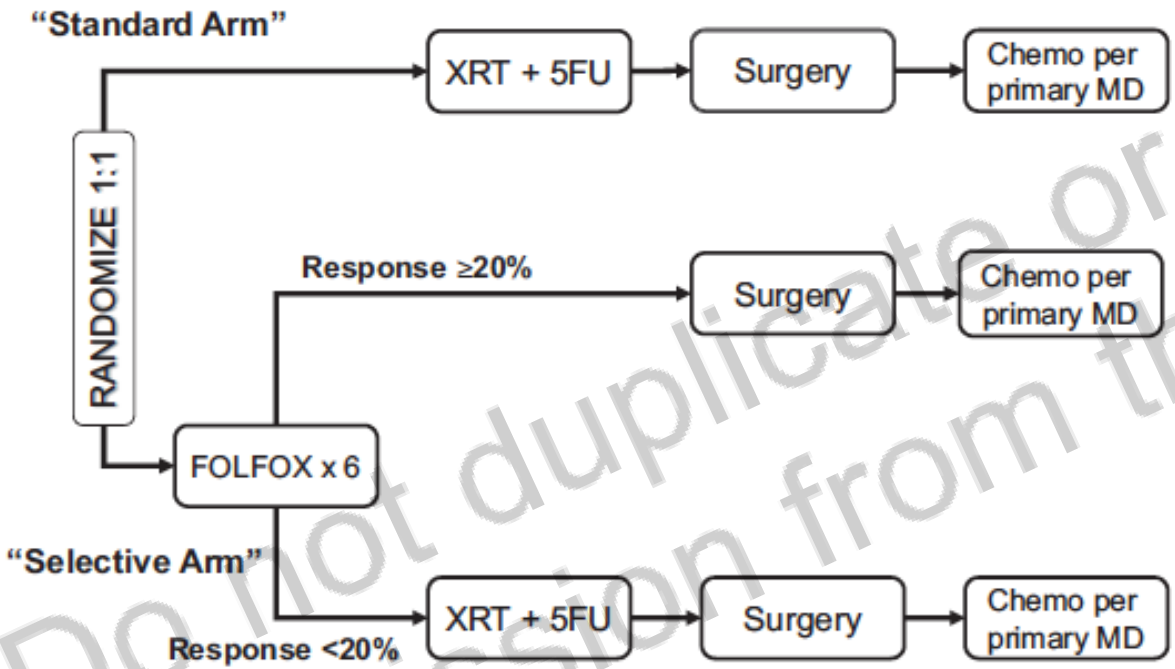
Do all patients with LARC need radiation?

PROSPECT TRIAL



- Phase II/III trial
- Selective RT in patients with intermediate-risk LARC (T1/2N1, T3N0, or T3N1)

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What is the optimal timing of systemic chemotherapy?

SPANISH GCR3

N=108
(A 52- B 56)

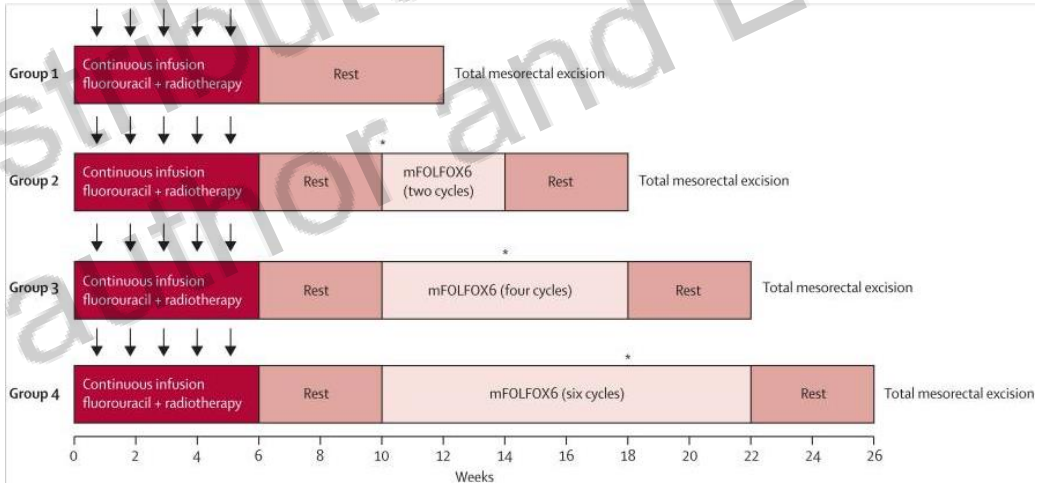
CRT + surgery + 4 CAPOX

4 CAPOX+ CRT+ surgery

- No different significantly in disease outcomes (5y DFS, OS, LR and DiR)
- Lower acute toxicity and improved compliance with induction CT compared with adjuvant CT

2010 ; Fernandez-MartosC et al, Ann Oncol2015

NCT 00335816



- pCR was higher in group 4 (38%, 30%, 25% and 18%; p 0.0036)
- No difference in sphincher saving surgery, R0 resection, technical difficulty and grade 3-4 operative complications.

Garcia-AguilarJ et al, Lancet Oncol2015

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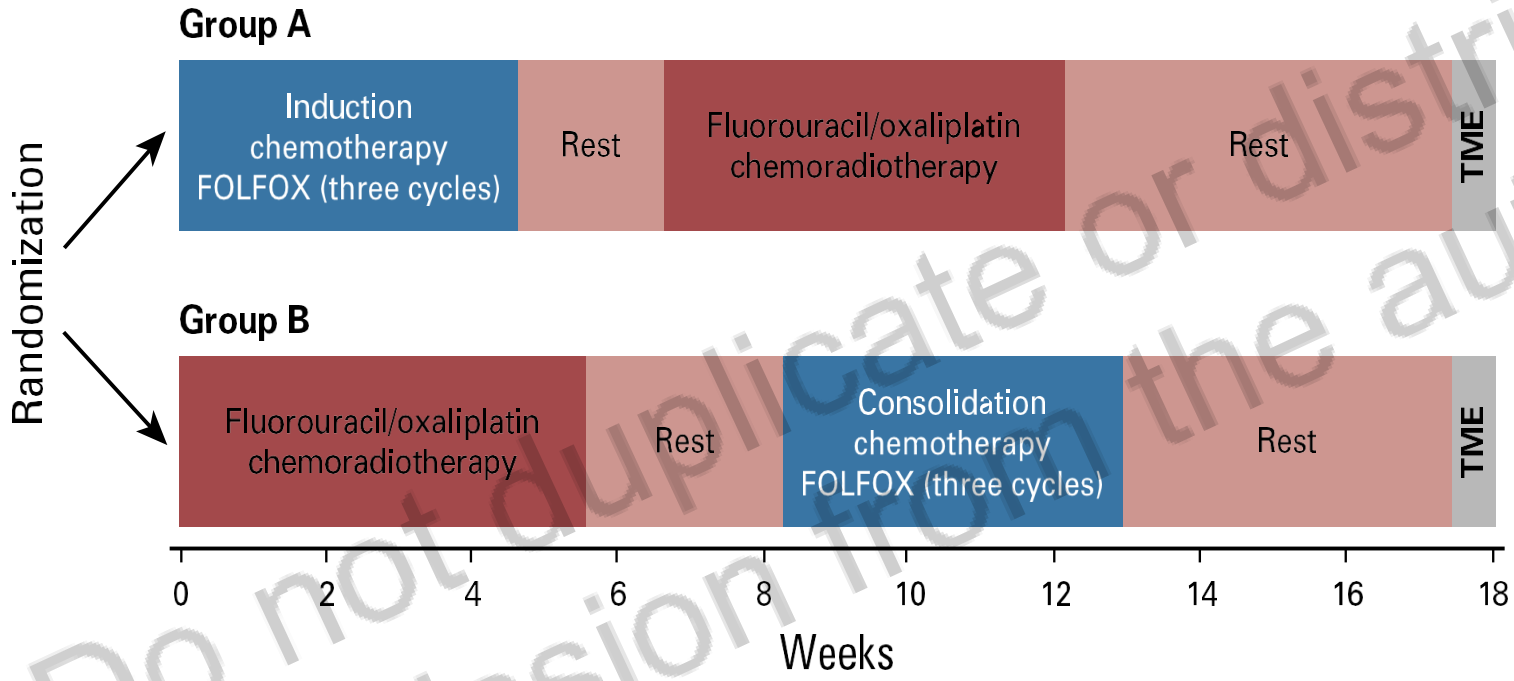
Induction vs consolidation CT?

CAO / ARO / AIO-12



Fokas E et al, J Clin Oncol 2019

- pCR ITT population :
- 17% in group A ($P = 0.210$) vs 25% in group B ($P < 0.001$).
- Group B: Less grade 3-4 toxicities(37% vs 27%) and better compliance during CRT

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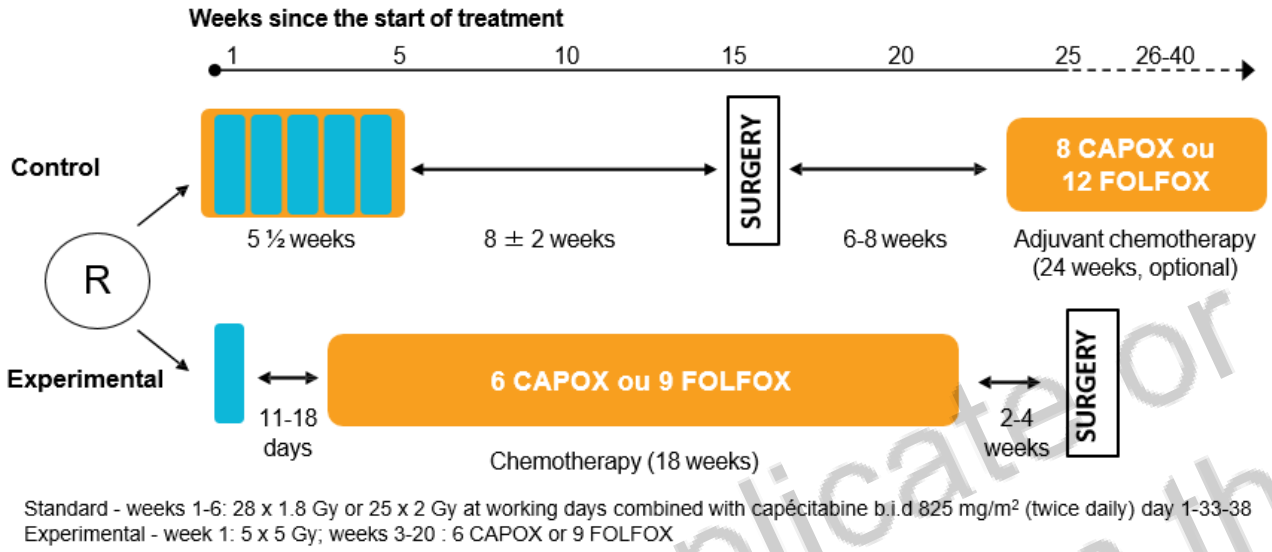
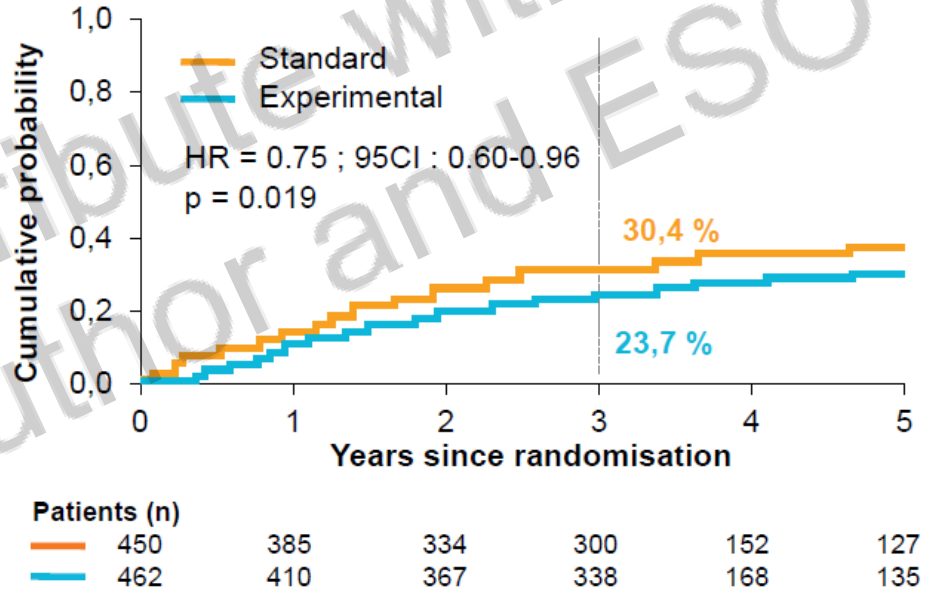
RAPIDO TRIAL



Standard - weeks 1-6: 28 x 1.8 Gy or 25 x 2 Gy at working days combined with capécitabine b.i.d 825 mg/m² (twice daily) day 1-33-38
Experimental - week 1: 5 x 5 Gy; weeks 3-20 : 6 CAPOX or 9 FOLFOX



- Phase III trial
- HR LARC: T4a/b, extramural vascular invasión+, N2, mesorectal fascia+, enlarged lateral lymph nodes)
- Primary End point: disease-related treatment failure(DrTF): DiM, LRR, new primary colorectal cáncer or treatment related death.

- TNT arm: higher rate of pCR (28% vs 14%) and a lower 3-year rate of distant recurrence (20% vs 27%, p 0.005).
- No significance OS (89.1 vs88.8%) and LRR (8.7 vs 6%)

Bahadoer RR et al, Lancet Oncol 2020

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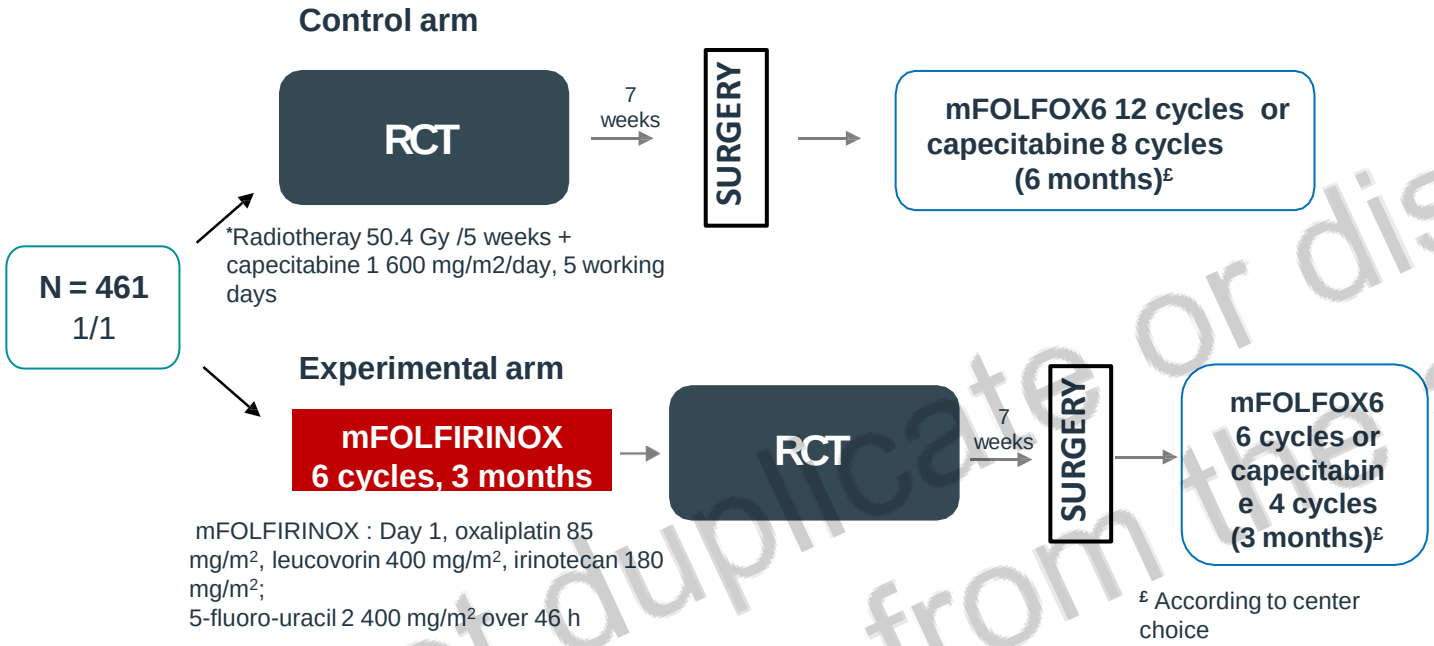
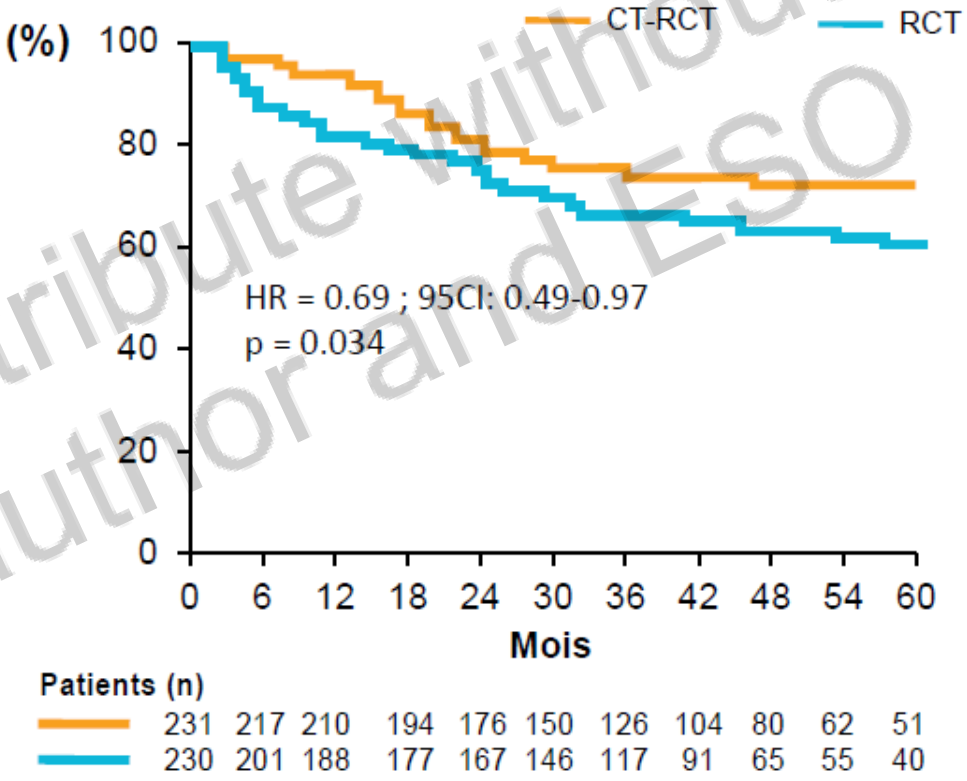
PRODIGE 23 TRIAL





- Phase III trial: LARC < 15cm anal margin.
- Primary End point: DFS

Conroy T et al, Lancet Oncol 2021

- pCR was higher (28 vs 12%) and 3-year DFS: 76% vs 69% (HR 0.69, 95% CI 0.49–0.97; p=0·034).
- Dim 21.2 vs 28.3% (p 0.017), LR 4.8 vs 7% (p NS) and OS 88 vs 91% (p 0.07)

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Do all patients need resection?

International Watch & Wait Database (IWWD)

- Retrospective analysis of a data base, from 47 different institutes (15 countries)
- 880 of 1009 included patients with a cCR.

88% occurred in the first 2 years and 97% was located in the bowel wall.

3-year		CI
Locoregional recurrence	25.2%	22.2-28.5
Distant recurrence	8%	
DFS 5y	94%	91-96
OS	95%	80.9-87.7

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Take Home message

- Multidisciplinary management is essential.
- pCR is a prognostic factor.
- Neoadjuvant chemotherapy is now validated in LARC
- TNT approach offers an improvement in the rate of pCR,
- Treatment has to be selected accordingly with risk factors.
- A longer follow up is necessary for OS data.

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Thanks!

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Multidisciplinary session on rectal cancer
The role of radiotherapy

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Maria Antonietta Gambacorta

Radiation Oncologist
Fondazione Policlinico Universitario A. Gemelli

Associate Professor
Università Cattoplica del Sacro Cuore

Rome-Italy

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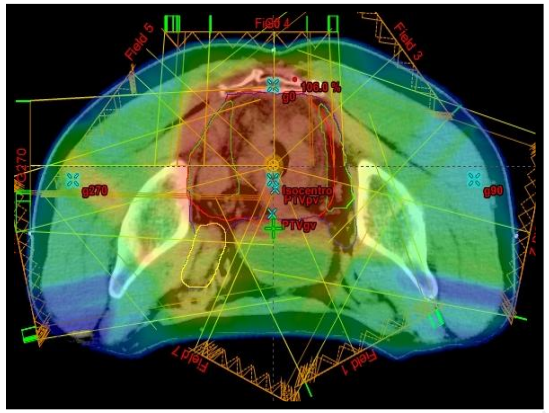
Gemelli ART Advanced Radiation Therapy

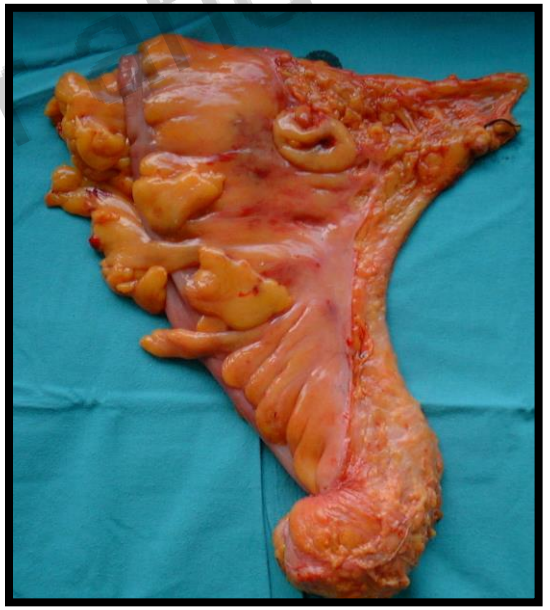
Rectal cancer management



Radiotherapy

TME Surgery

Chemotherapy
(high risk factors)



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Aim of neo/adjuvant treatments

- Oncological Outcomes

- Quality of Life

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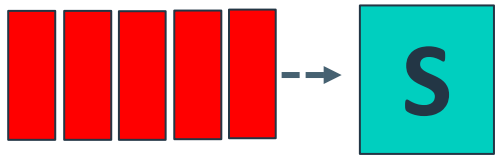
Radiotherapy schedules

Short course



RT DOSE: 25 Gy; 5 Gy/day ~ 40 Gy @ 2 Gy/day

Long course

RT DOSE: 45-50 Gy; 2 Gy/day

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What we learned from RCT

Trial	Randomization	Local control	DFS	OS	Toxicity
Swedish trial	**5x5→ S** vs **S alone**	**yes**	**yes***	**yes***	↑
Dutch trial	**5x5→ S** vs **S alone**	**yes**	**no**	**no**	↑
British trial **MRC-CR07** *Sebag-Montefiore D. Lancet Oncol*	**5x5→ S** vs **S alone**	**yes**	**yes**	**no**	↑
German trial **CAO-ARO-AIO-94** *Sauer R NEJM 2004*	**Preop CRT** vs **post-op CRT**	**yes**	**no**	**no**	↓
French trial **FFCD** *Gérard JP et al JCO 2006*	**Preop CRT** vs **preop RT**	**yes**	**no**	**no**	↑
EORTC trial *Bosset JF et al NEJM 2006*	**Preop CRT** vs **preop RT**	**yes**	**no**	**no**	↑
Scandinavian trial *Braendengen M JCO 2008*	**Preop CRT** vs **preop RT**	**yes**	-	**yes°** (CSS)	↑

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* before TME

° unresectable

What we learned from RCT

Trial	Randomization	Local control	DFS	OS	Toxicity
Swedish trial	**5x5→ S** vs S alone	**Included T1-T4 pts** **Treatment T3 resectable**			
Dutch trial	**5x5→ S** vs S alone				
British trial	**5x5→ S** vs S alone				
German trial	**Preop CRT** vs post-op CRT	**Included T3-T4 pts** **Treatment T3 resectable, HR T3 MRF+, T4 unresectable**			
French trial *Gérard JP et al JCO 2006*	**Preop CRT** vs preop RT				
EORTC trial *Bosset JF et al NEJM 2006*	**Preop CRT** vs preop RT				
Scandinavian trial	**Preop CRT** vs preop RT				

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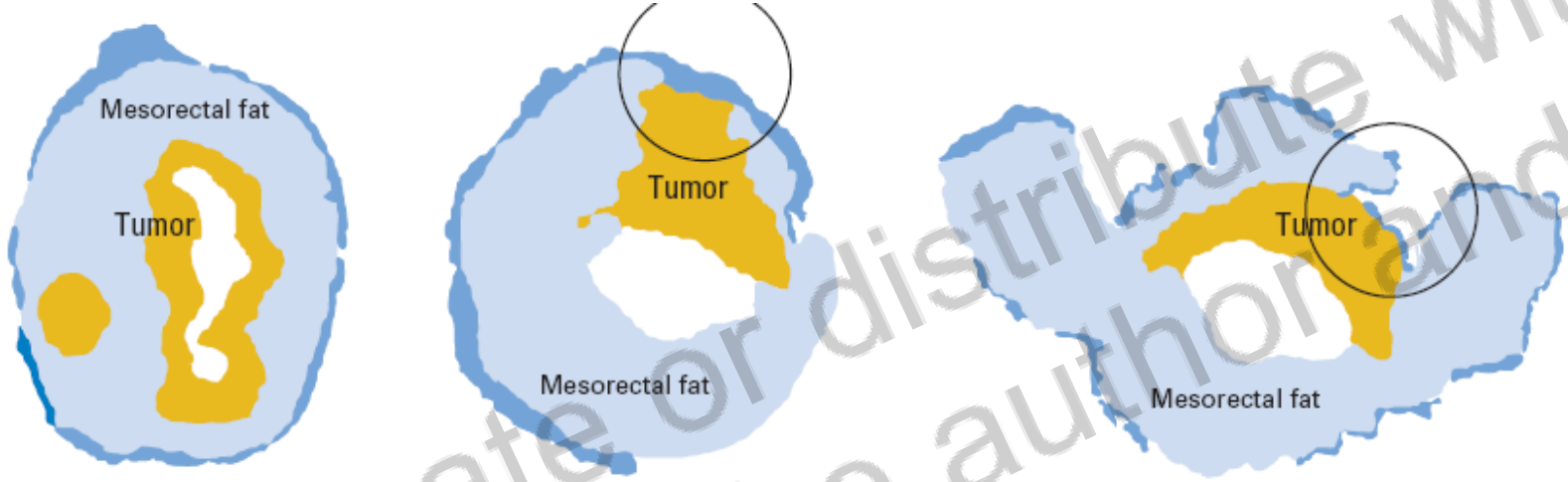
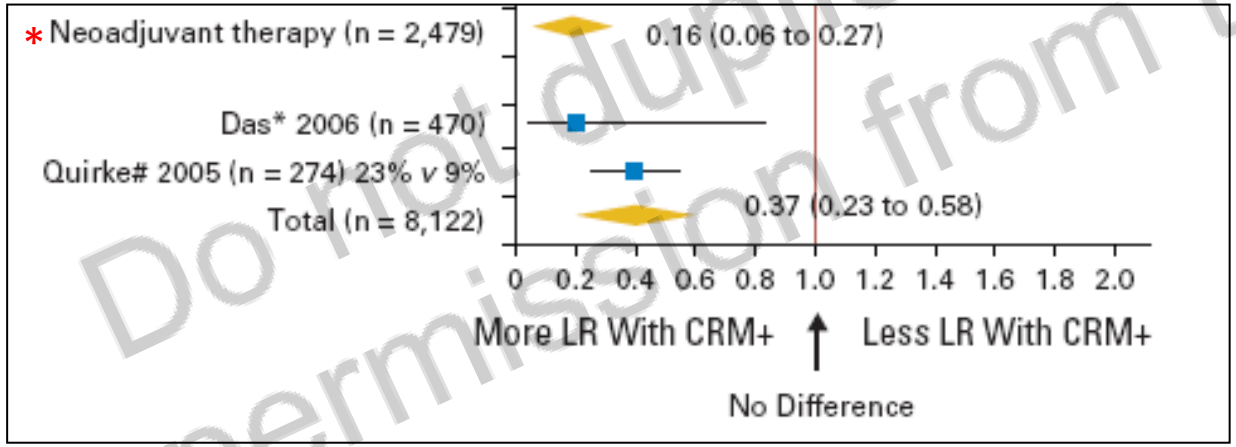
R0 RESECTION

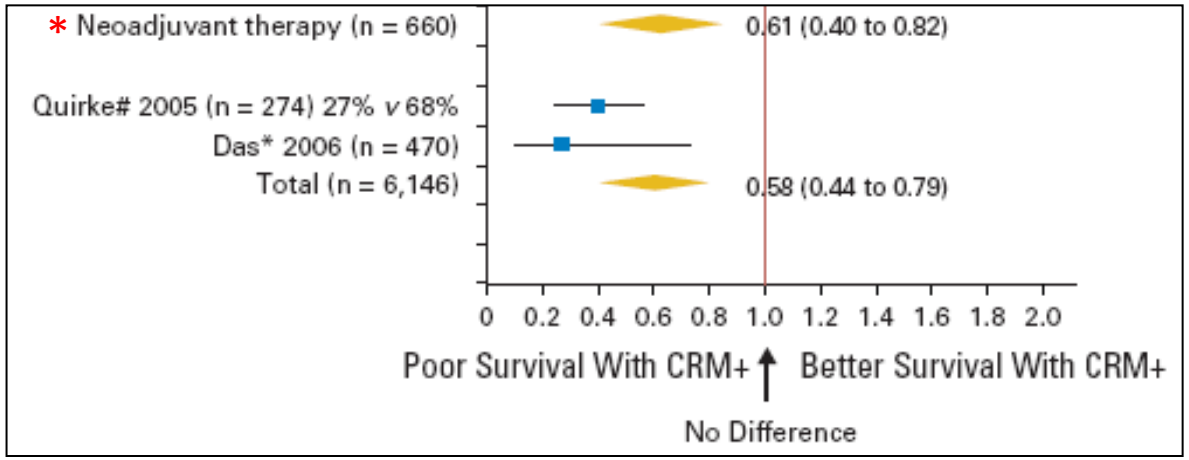
Circumferential Resection Margin



LOCAL RECURRENCE



OVERALL SURVIVAL



* **Neoadjuvant therapy: SHORT COURSE**

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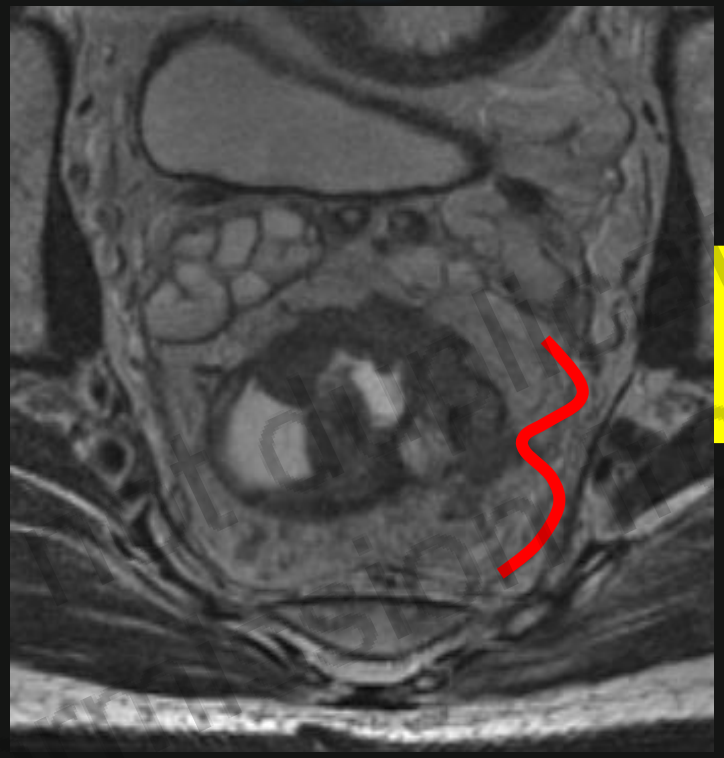
Nagtegaal I D et al , JCO 2008

R0 RESECTION

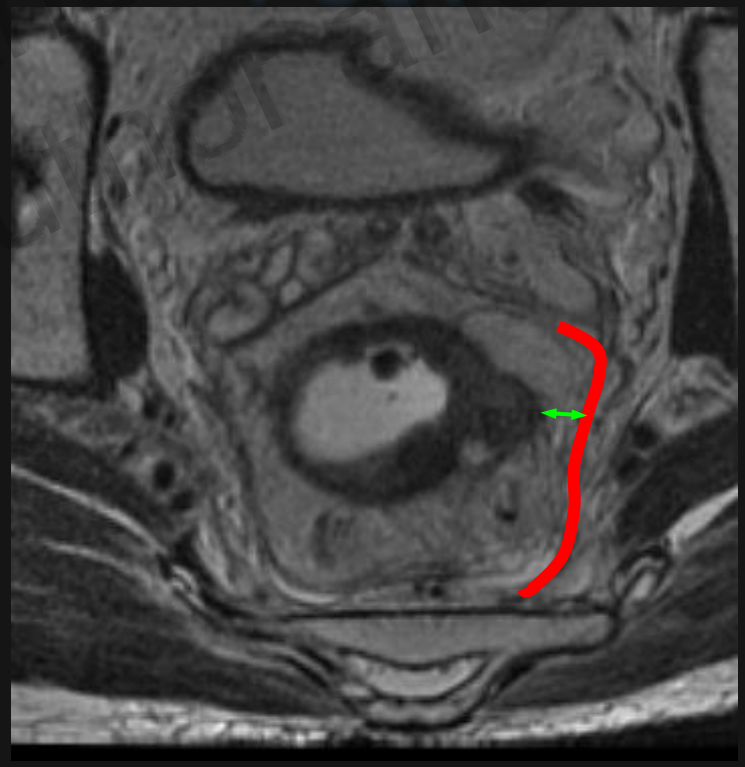
*Meso**Rectal** Fascia* (MRF+)

PRE



CRT

POST



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DOWN-STAGING

Long term outcomes
Unresectable

	RT-CT	RT	p
R0 resection	**84 %**	**68%**	**.009**
ypCR	16%	7%	.04
ypT stage	74	59	.001
Acute Toxicity G3+	28%	6%	.001
Local recurrence R0-1	**5%**	**7%**	**.03**
Distant metastases	**29%**	**36%**	**.04**

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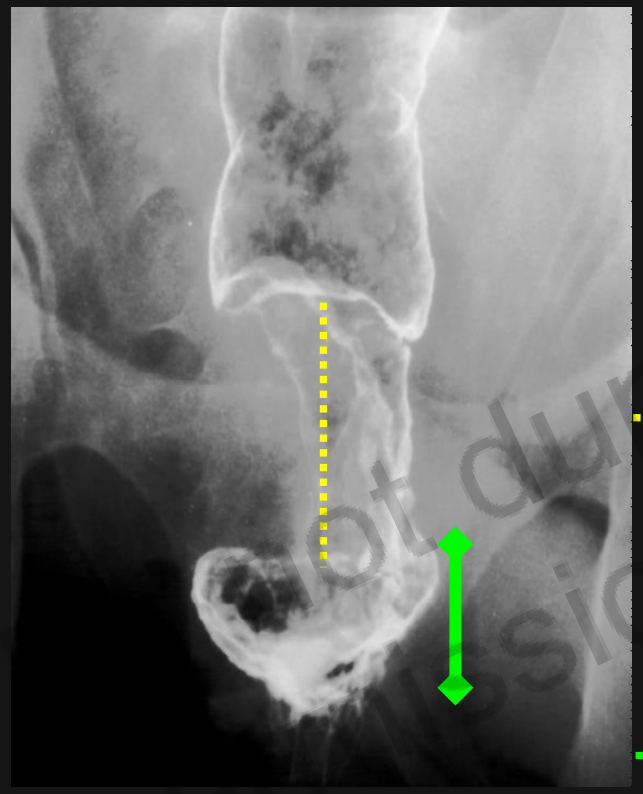
Braendengen M et al, JCO 2008

SPHINCER PRESERVATION

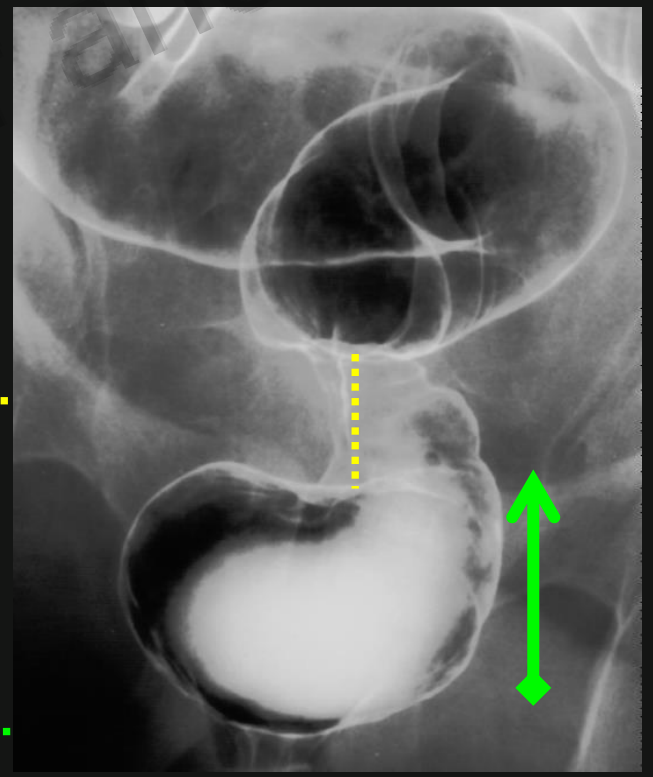
PRE



Tumor lenght

Distance from the anal-rectal junction

POST



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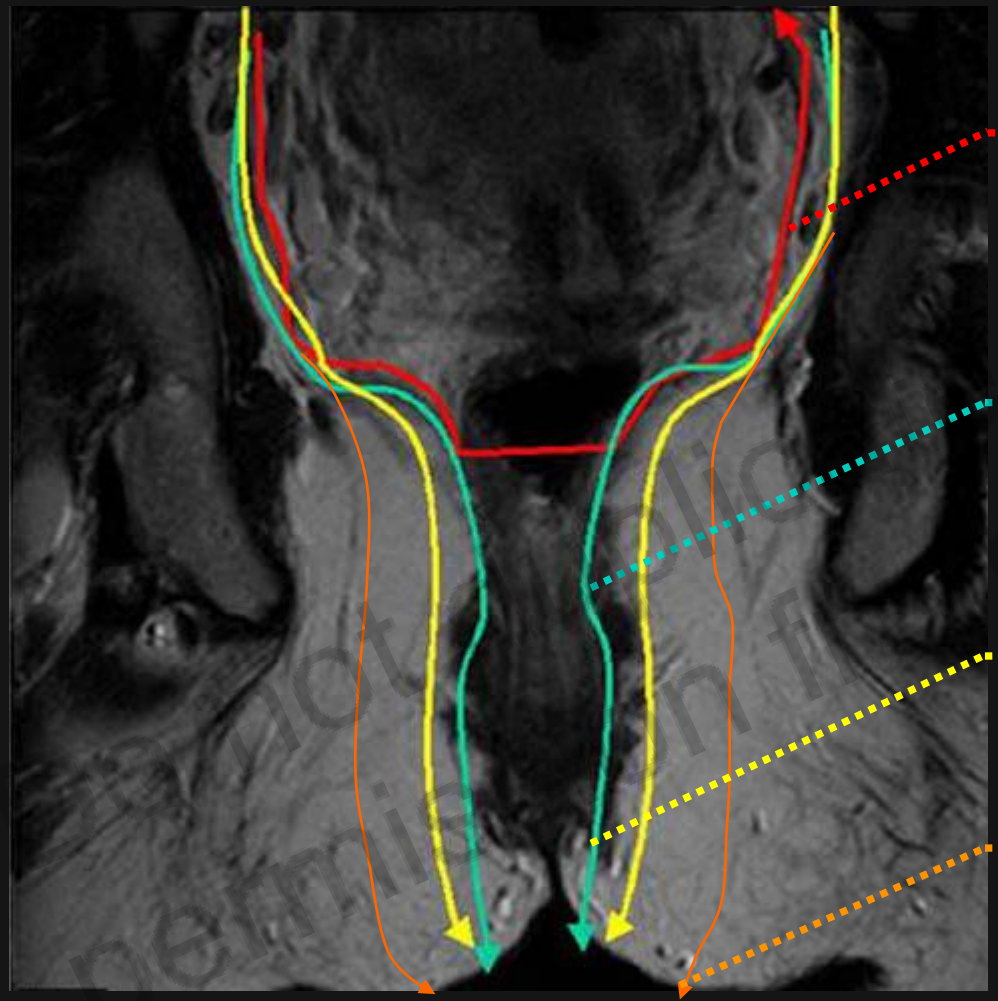
SPHINCER PRESERVATION



Low Anterior Resection

Intrasphincteric Resection

Abdomino-Perineal Resection

Extra-Levator APR

Mod from Shihab OC et al. Eur. Radiol. 2009

Sphincter preservation in trials

cT3-cT4 resectable
Long Course

TRIAL	Sphincter preservation		p	
	RT	CRT		
EORTC 22921	51	53	ns	*Bosset JF Eur J Can 2004*
FFCD 9203	52	53	ns	*Gerard JP J Clin Oncol 2006*
Polish Trial	57	52	ns	*Buijko K Radiother Oncol 2004*
Rome experience	85	90	ns	*Gambacorta MA Tumori 2007*
ACCORD	75	75	ns	*Gerard JP J Clin Oncol 2010*

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BUT...

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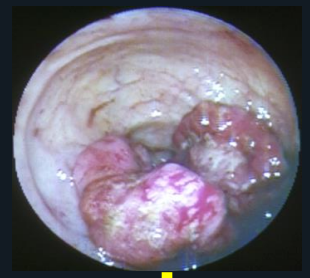
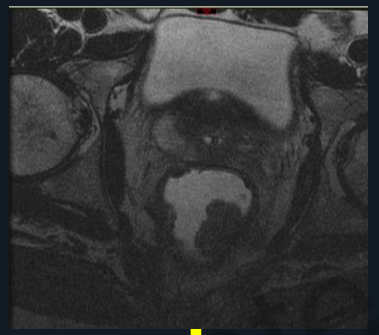
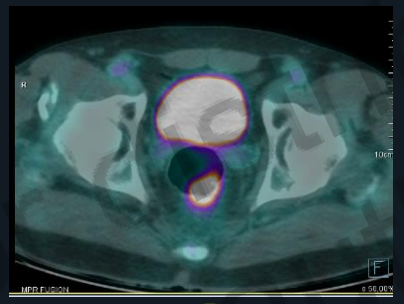
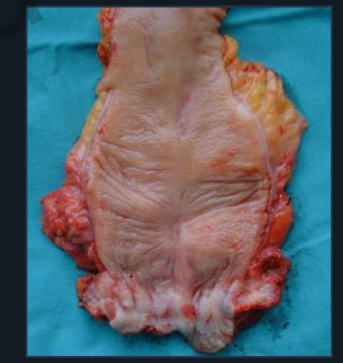
Complete Response

PRE









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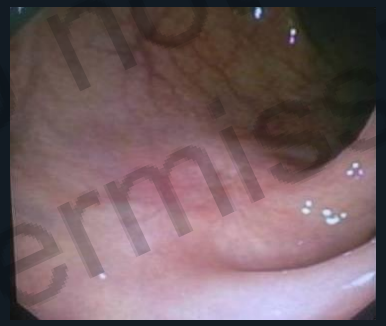

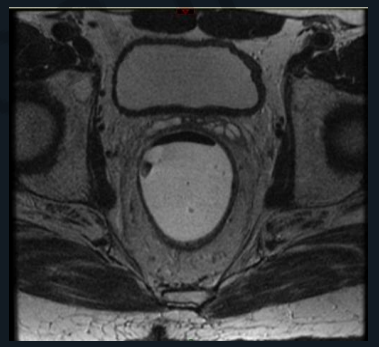

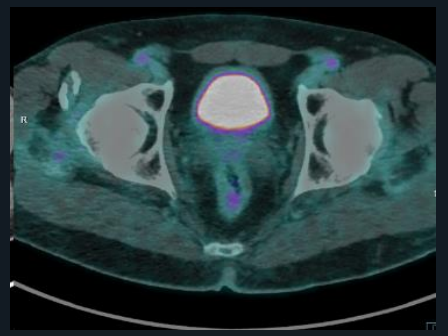

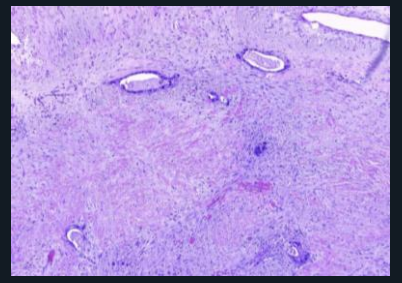

pCR: 20-40%

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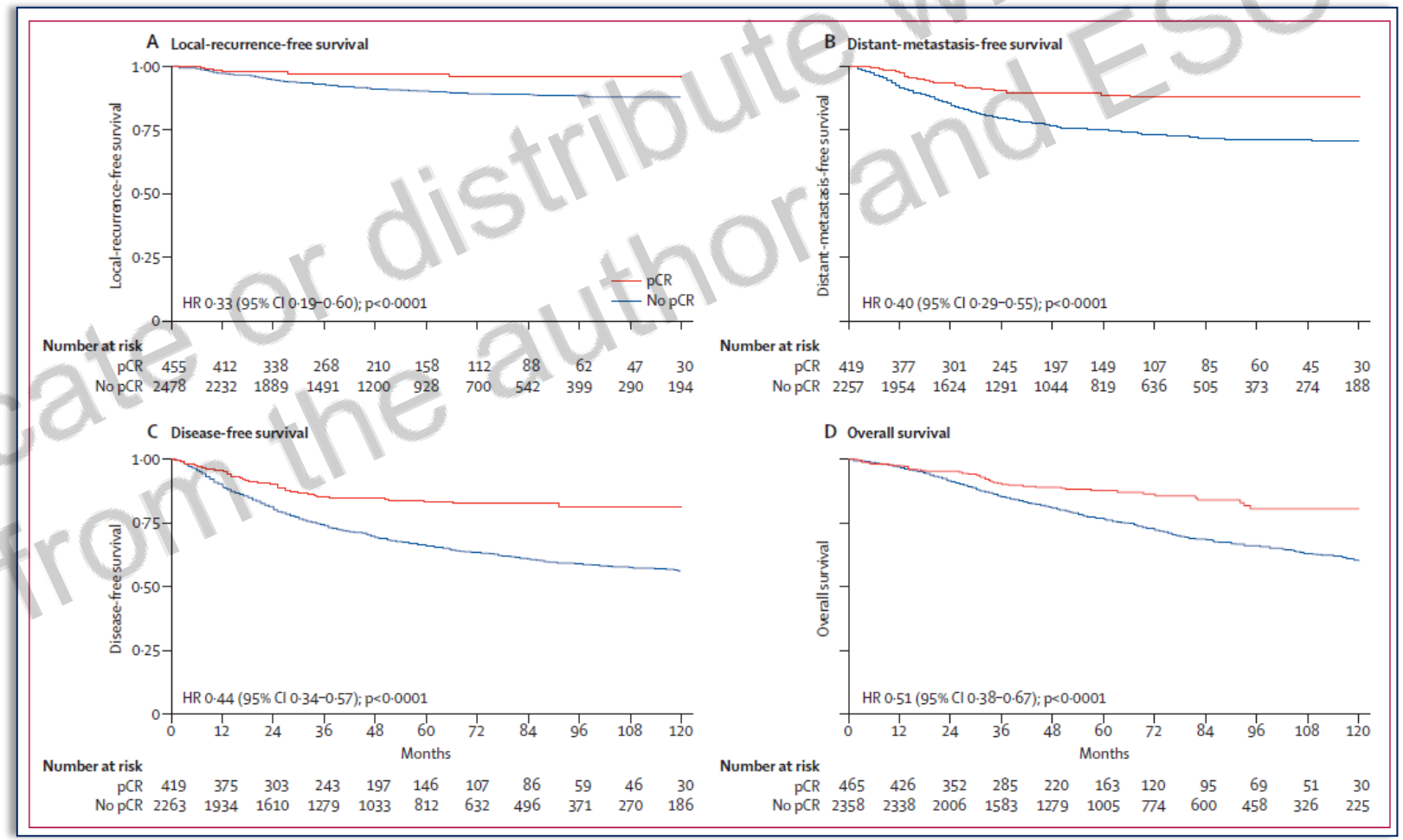
Meaning of Complete Response

- **3105 patients** treated with preoperative CRT
- **484 pCR (15%)**

Complete Responders

NO Complete Responders



Maas M et al. Lancet Oncol 2010

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Second generation studies

oxaliplatin randomized trials

Neoadjuvant oxaliplatin	Number of patients	pCR	DFS		Acute toxicity	compliance
			diff	p		
ACCORD 12	584	x	4.3%	0.25	↑	↓
NSABP R04	1284	x	5%	0.34	↑	↓
STAR 01	739	x	3.6%	0.37	↑	↓
CAO-ARO-AIO 04*	1236	↑	4.7%	0.03	=	=*
CHINESE	206	x	10.6%	0.08	↑	↓
PETACC-6	1094	x	Full paper pending		↑	↓
FORWARK	475	↑	Follow-up continues		↑	=

*% of Adherence to RT
% of Adherence to standard RTCT (only 5FU)

Lower oxaliplatin dose/cycles compared to other trials

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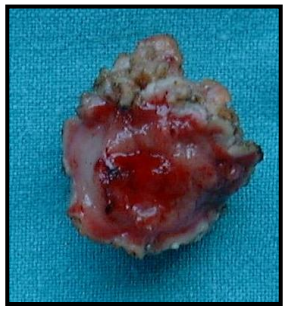
Organ Preservation

CR and nCR → Organ Preservation

NOM→ watch and wait



LE→ TEM, TAMIS

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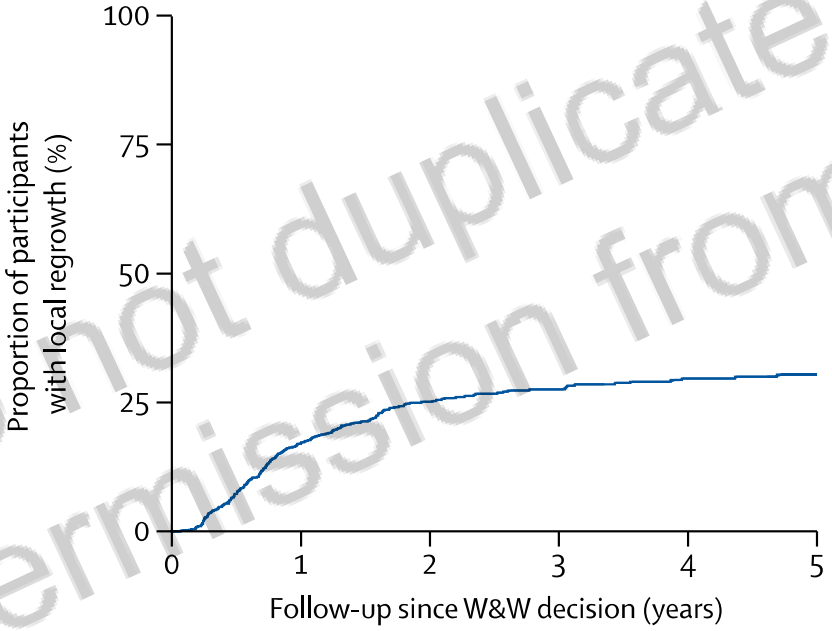
Outcomes of NOM

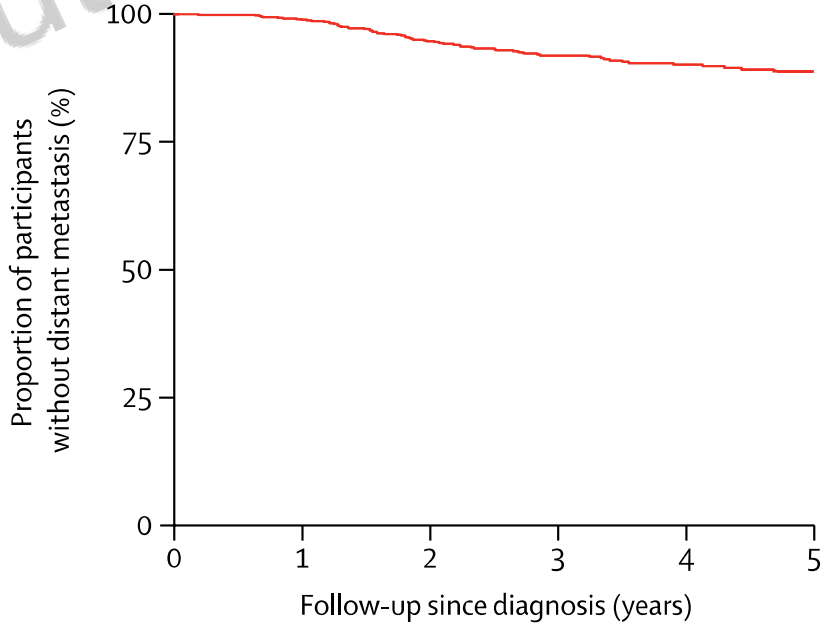
study	pts	Re-growth	Time	Salvage	DM	DFS	DSS	OS
IWWD pooled analysis *Van der Valk Lancet 2018*	**880**	**25.2%** 97% bowel wall	**88%** in the first 2 years	**93%** Of 115 Salvaged with TME	**8.1%** **18% regrowth** 5% cCR	**nr**	**94%** 84%regrowth 97.3% in cCR	**85%** 75.4% regrowth 87.9% in cCR

A



Number at risk	880	594	417	308	224	152
(number censored)	(0)	(150)	(125)	(97)	(76)	(70)

B



Number at risk	880	777	581	415	302	223
(number censored)	(0)	(95)	(166)	(151)	(106)	(75)

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How to improve CR and decrease metastases

- Oncological Outcomes
- Quality of Life

1. CT intensification→ TNT
2. RT Dose escalation
3. Timing between RT and surgery
4. CRT for early tumors

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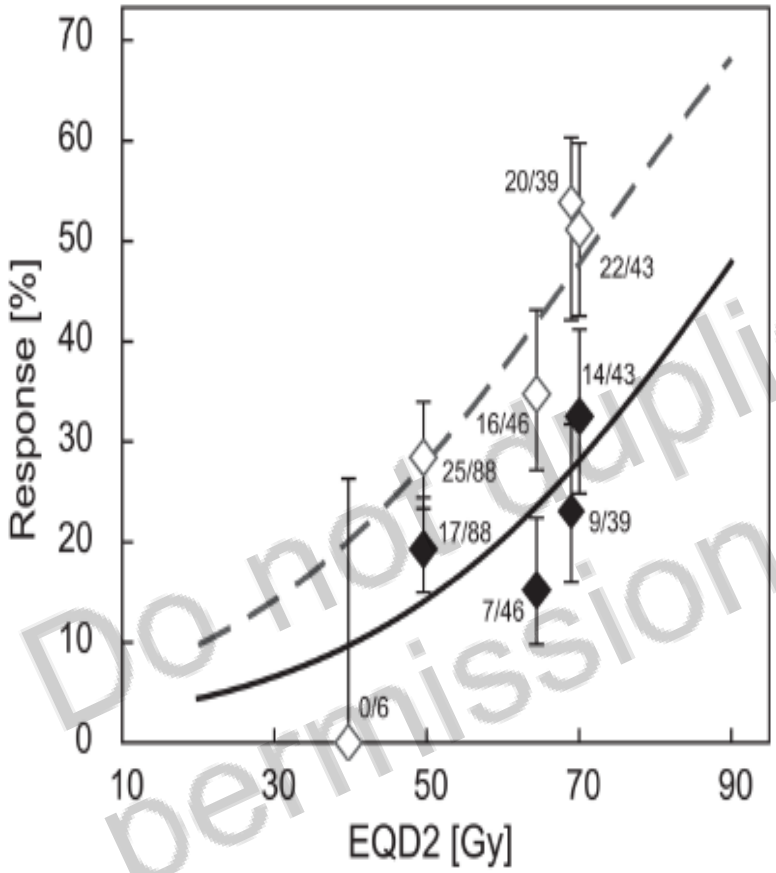
1. Dose escalation

D50 TRG1→ 92.0 Gy

D50 TRG1-2→72.1 Gy



External Beam RADIOTHERAPY

Metanalysis 18 studies (1106 patients)

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		8.0%	20.0%	[9.8 , 36.4%]
Vestermark et al., 2008		3.9%	8.0%	[2.7 , 22.9%]
Maluta et al., 2010		19.8%	23.0%	[15.5 , 34.5%]
Jakobsen et al., 2012		23.6%	18.0%	[12.2 , 26.7%]
Vestermark et al., 2012		4.9%	31.0%	[13.6 , 56.7%]
Engineer et al., 2013		6.4%	11.0%	[4.8 , 24.5%]

Dose ≥ 60 Gy → pCR 20.4%

G3 tox 10.3%; R0 89.5%

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Appelt AL et al. Int. J Radiat Oncol Biol Phys 2013

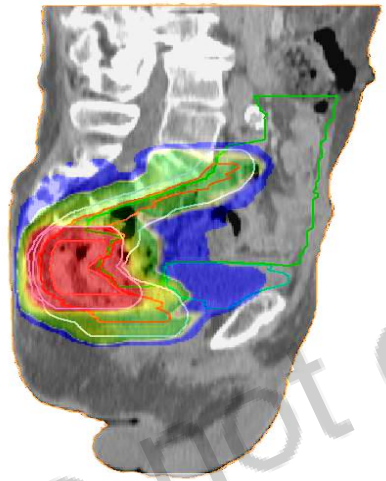
Burbach et al. Radiother Oncol 2014

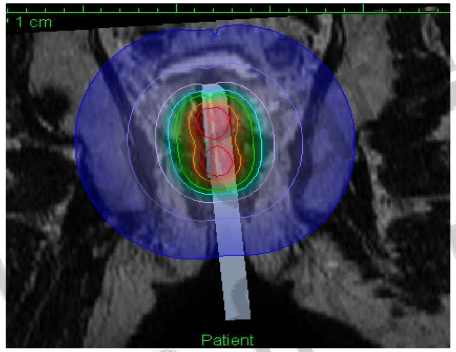
Radiotherapy dose intensification

External beam + LOCAL THERAPIES

Brachytherapy

Early Tumors





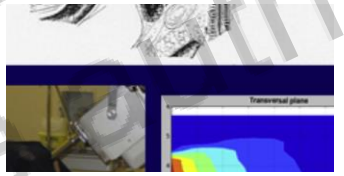
EBRT 60 Gy + **brachy: 5 Gy**

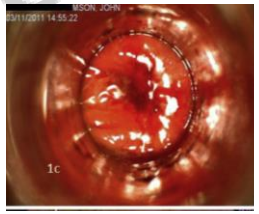
cCR @ 2 years 58% (WW)

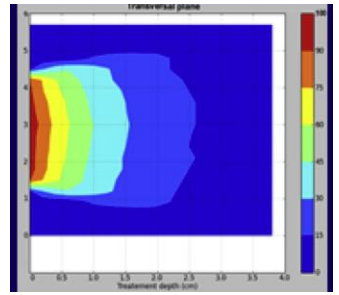
Appelt A et al. Lancet Oncol 2015

Contact Therapy

All tumors Unfit patients







CBX: 90 Gy

+/- EBRT according to stage
pre or post according to tumor diameter

cCR @ 24% (WW)

Dhadda AS et al. Clinical Oncol 2017

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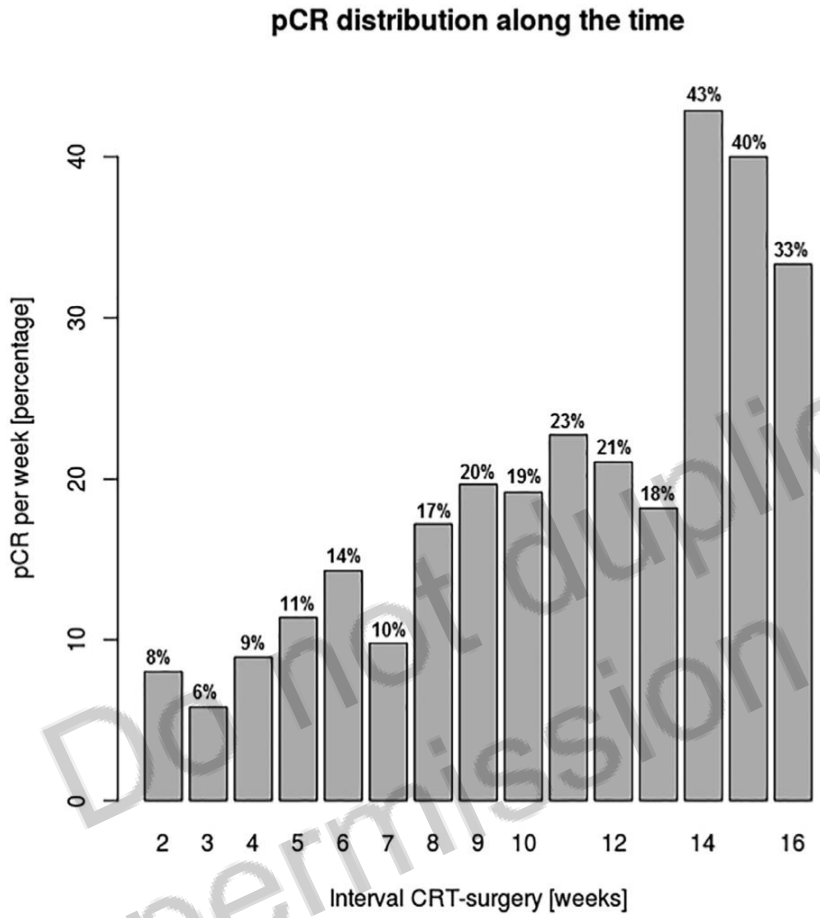
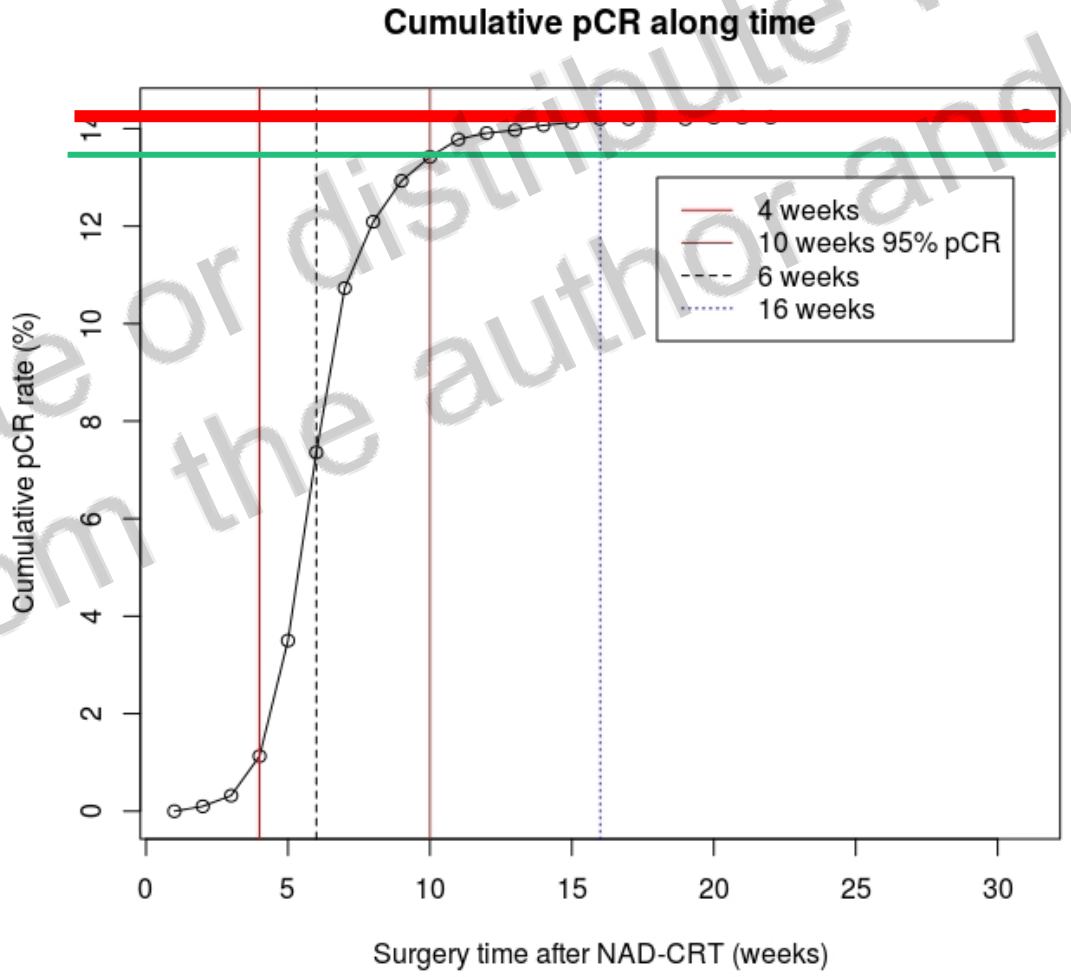
3. Timing

CRT-surgery interval





Plateau → 16 wks

95% of pCR→ 10 wks

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Gambacorta et al. Radiother Oncol 2021

ADVANCES in RADIOTHERAPY

Delivery: IMRT→VMAT

Modulation of the dose

On-board imaging: IGRT→ MRgRT

Visualization of the target and Organ at Risk

Adaptive RADIOTHERAPY

Volume and dose adaptation

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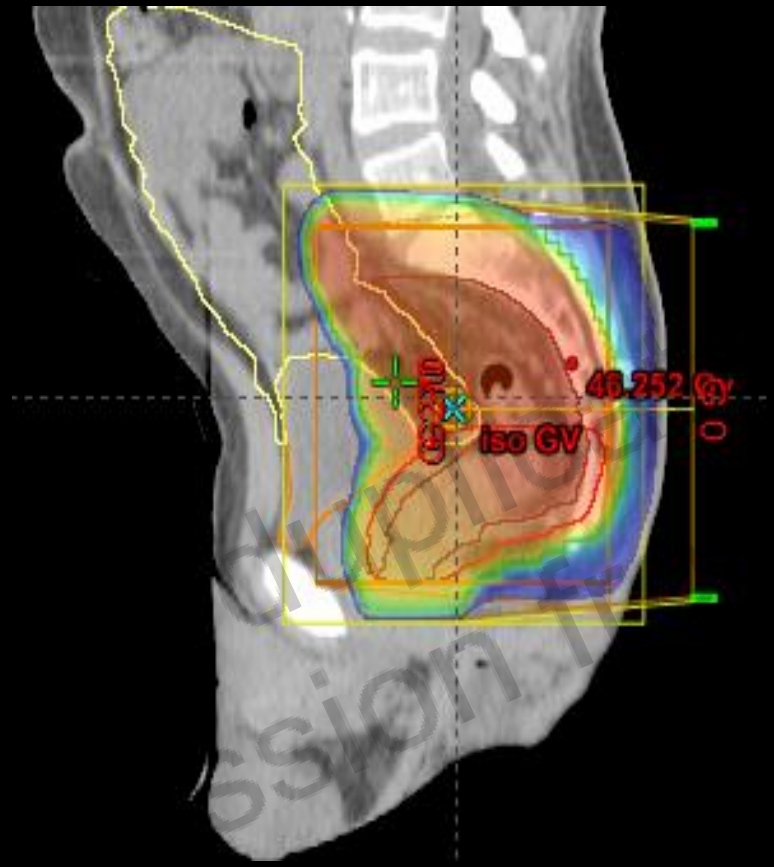
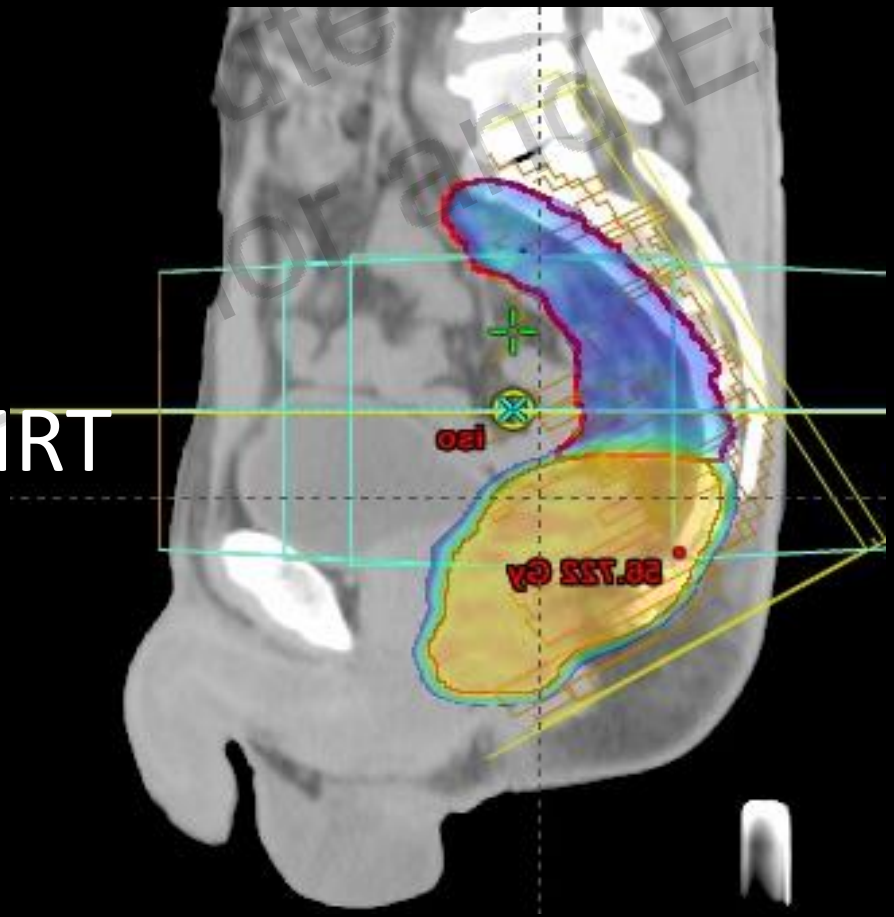
New RT technologies: DOSE distribution

3D



Spare noremal tissues

IMRT

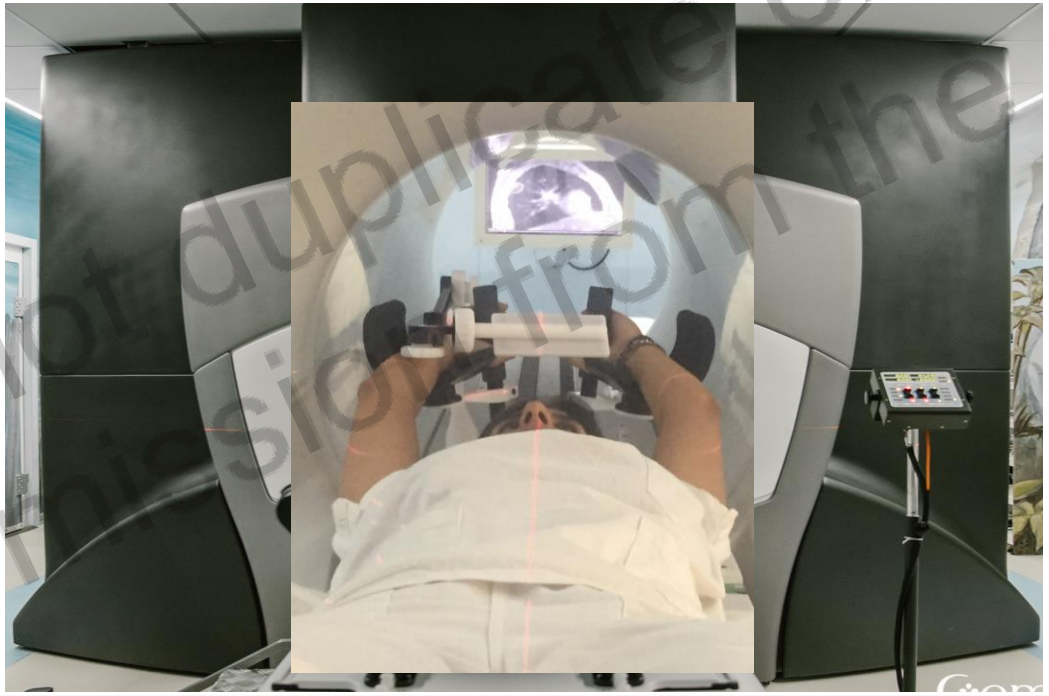


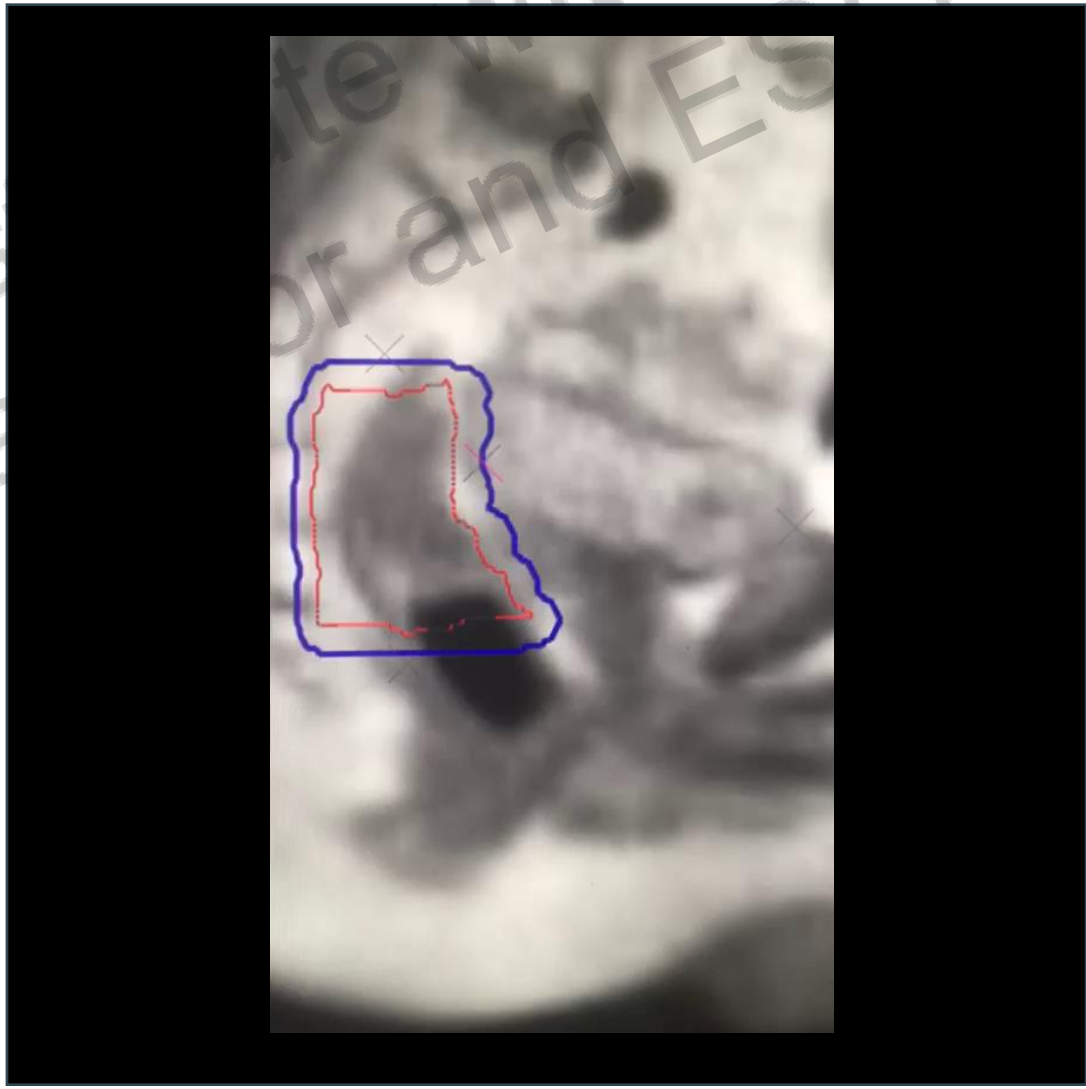
Modulate the dose

Target visualization: MRI-Guided RT

Direct TUMOR visualization:

- During each fraction
- Throughout the treatment
- By doctor
- By patient
- Gated dose delivering





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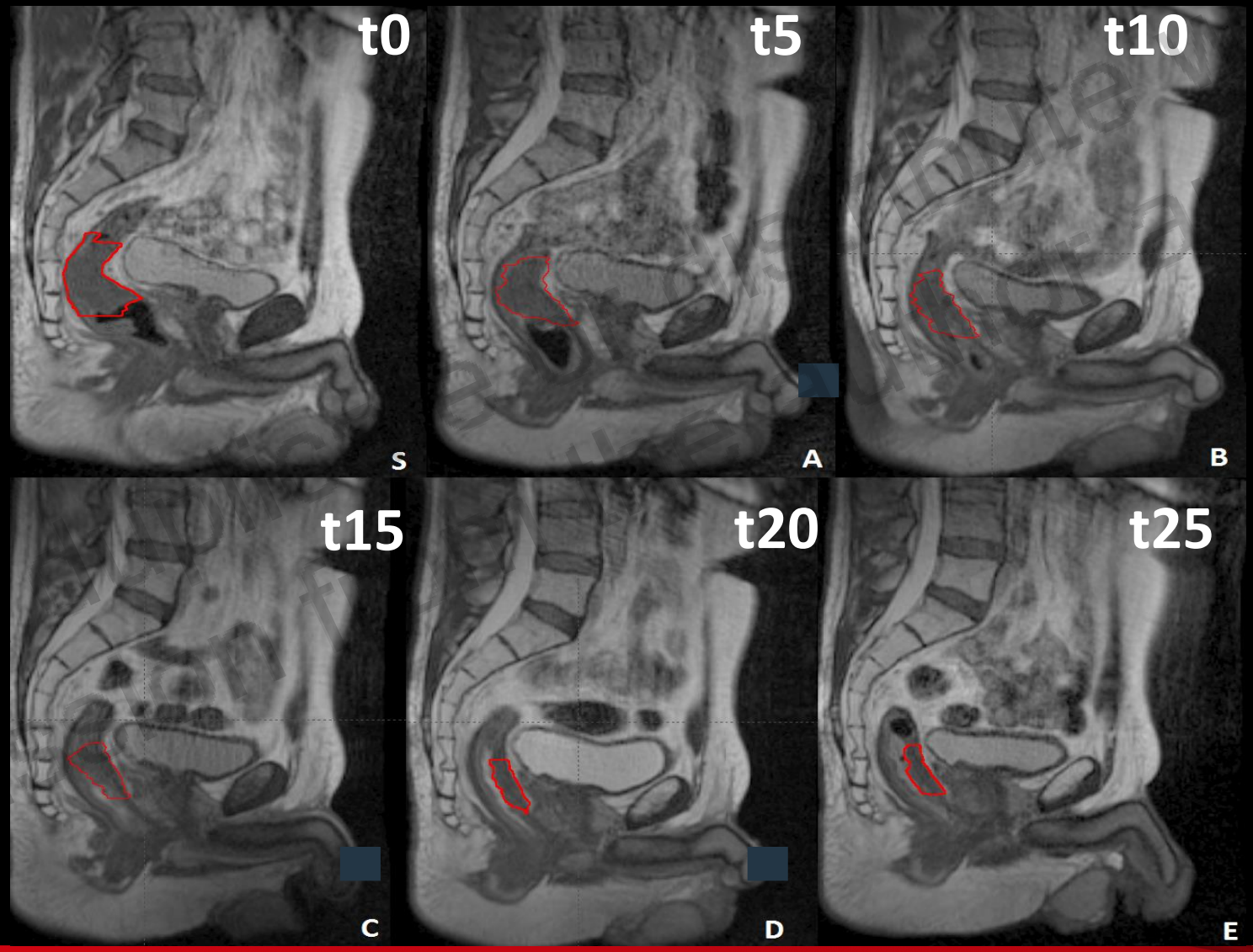
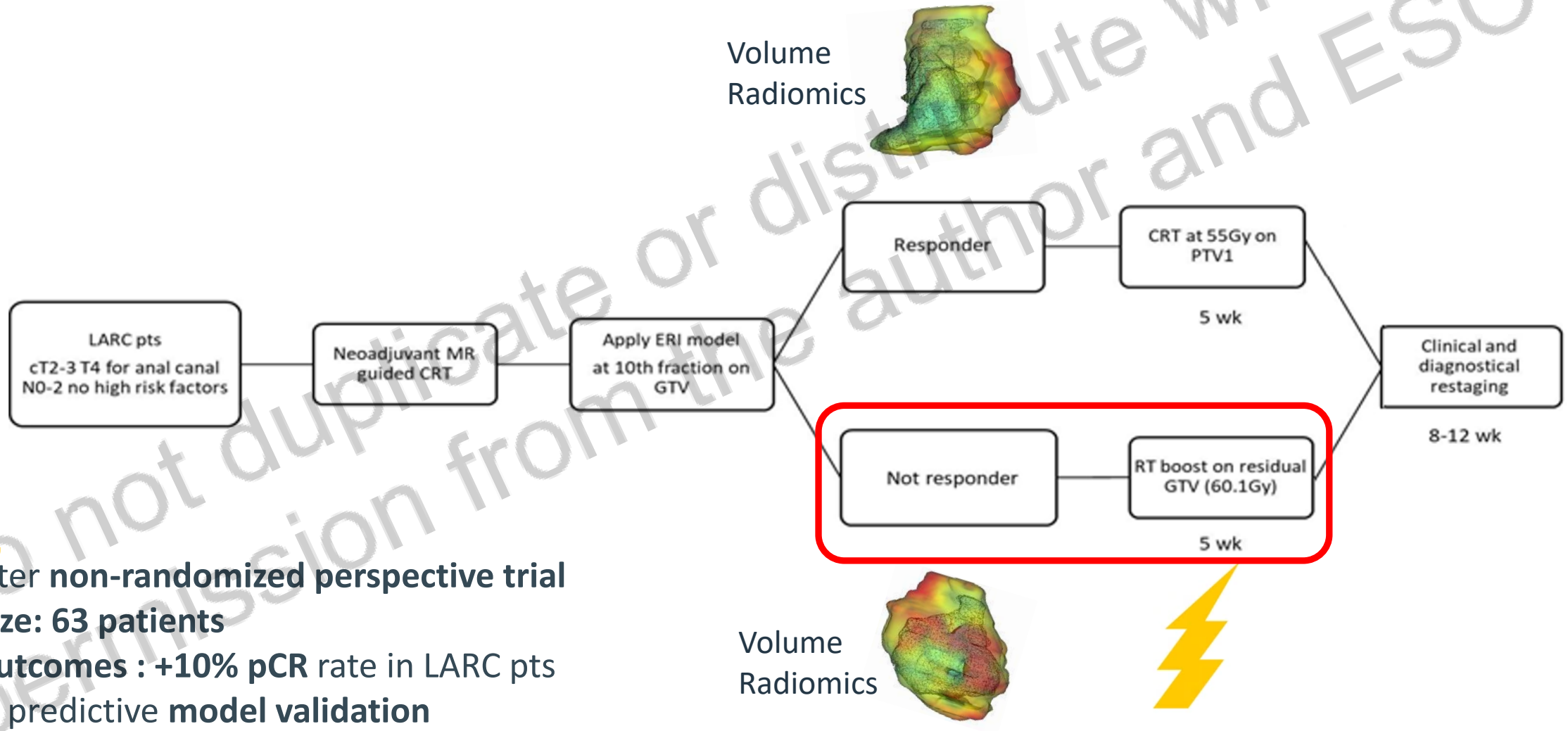
Adaptive Radiation Therapy



Boldrini L et al. Radiol Med 2018

THUNDER-2 trial: THeragnostic Utilities for Neoplastic Diseases of the rEctum by MRI guided Radiotherapy



Single center **non-randomized perspective trial**
Sample size: 63 patients
Primary outcomes : +10% pCR rate in LARC pts
Radiomics predictive **model validation**

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Take home messages…the role of RT

- Radiotherapy increases local control
- CR after CRT is related to better outcomes
- CR patients may avoid SURGERY with improved QoL
- Preoperative intensification (TNT, RT dose) may increase CR and decrease DM
- New RT technologies: dose modulation and adaptation

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