Giuditta Chiloiro

The rectal cancer journey: what have we not to forget?

Gemelli | ART

History of rectal cancer

Rectal cancer has been a recognized disease for millennia.

It was considered incurable until the 18th century, when **Giuseppe Morgagni** proposed the first techniques to remove the rectum.

Jacques LisFranc performed the **first successful excision** of a rectal tumor in 1826.

A.S. Galler et al. / Surgical Oncology 20 (2011) 223–230

History of rectal cancer surgery

Miles described a combined abdominoperineal approach→ high mortality and local failures of 50%

1908

1940

Dixon proposed AR negligible impact on 5-year LRR of 20%-40%

LR rate 20%-50%

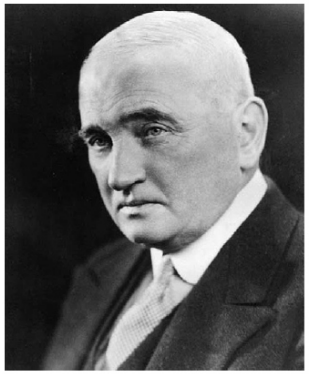
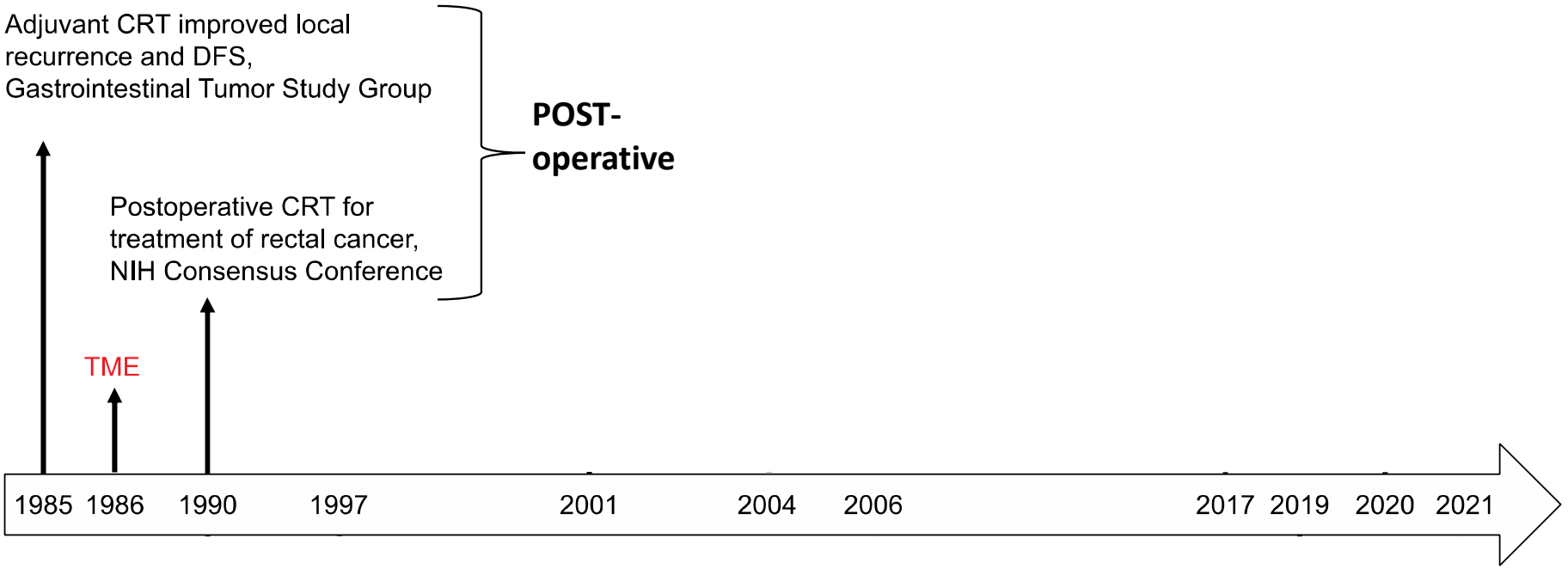


Image 3. Sir William Ernest Miles [9].

Pioneer POSToperative RT



Group Trial 22921

Pioneer POSToperative RT

Local Control

Overall Survival

Trial	Randomization	Local control	DFS	OS
National Surgical Adjuvant Breast and Bowel Project (NSABP) R-01 trial *J Natl Cancer Inst 1988*	**S → adj CT** vs **S → adj CRT** vs **S → adj RT** vs **S alone**	**yes**	**no**	**no**
Gastrointestinal Study Group (GITSG) 7175 trial *GITSG group* **N.Engl.J. Med - 1985**	**S → adj CT** vs **S → adj CRT** Vs **S →adj CRT+ 5FU CT** vs **S → adj RT** vs **S alone**	**yes**	**yes**	**yes**
North Central Cancer Treatment Group (NCCTG) 794751 *N Engl J Med 324:709-715, 1991*	**S → adj CRT** vs **S → adj RT** vs **S alone**	**yes**	**yes**	**yes**

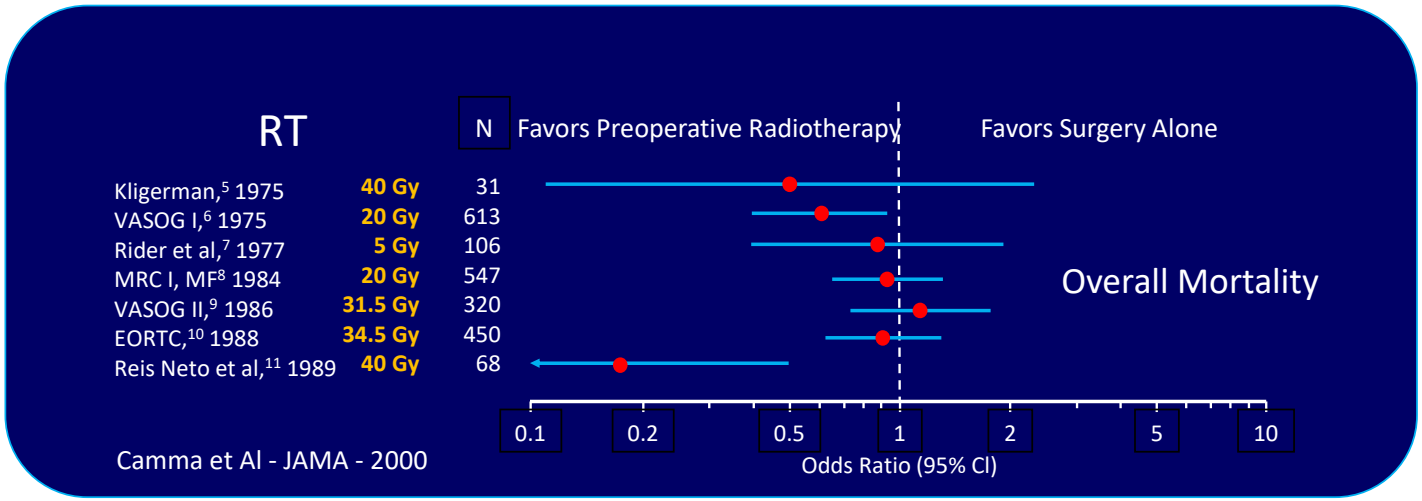
Pioneer POSToperative RT

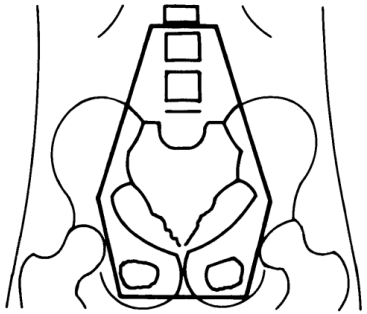
Local Control

LR rate 30%

Trial	Randomization	Local control	DFS	OS
National Surgical Adjuvant Breast and Bowel Project (NSABP) R-01 trial *J Natl Cancer Inst 1988*	**S → adj CT** vs **S → adj CRT** vs **S → adj RT** vs **S alone**	**Adj CRT** **Adj RT**	**no**	**no**
Gastrointestinal Study Group (GITSG) 7175 trial *GITSG group*- **N.Engl.J. Med - 1985**	**S → adj CT** vs **S → adj CRT** Vs **S →adj CRT+ 5FU** **CT** vs **S → adj RT** vs **S alone**	**Adj CRT** **Adj RT**	**Adj CRT**	**Adj CRT**
North Central Cancer Treatment Group (NCCTG) 794751 *N Engl J Med 324:709-715, 1991*	**S → adj CRT** vs **S → adj RT** vs **S alone**	**Adj CRT**	**Adj CRT**	**Adj CRT**

Pioneer PREoperative RT





2.3 Gy /die
34.5 total dose

+ 5FU

Boulis-Wassif et al- Cancer - 1984

3.12 Gy twice/week
37.4 total dose

+ 5FU & MTX

Hempel Sparso et al - Cancer - 1984

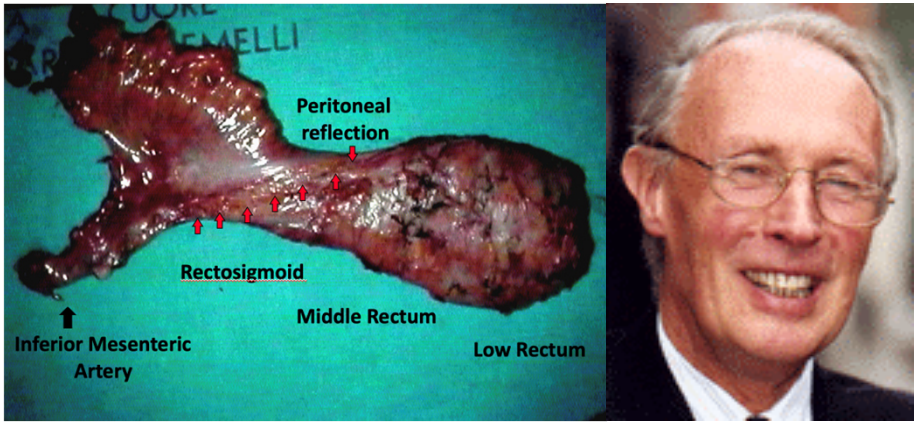
Take home messages

Pioneer RT

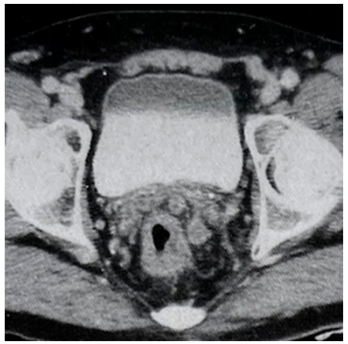
- **RT in rectal cancer** not so common
- **Post-operative RT** preferred
- **Intermediate pre-operative doses** evaluated
- **Large fields + intensive concomitant chemotherapy** to be avoided

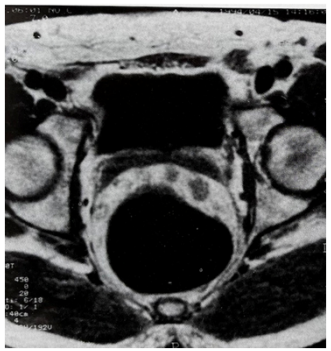
LR rate 30%

90’ Standardization

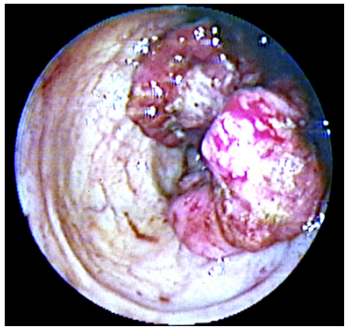


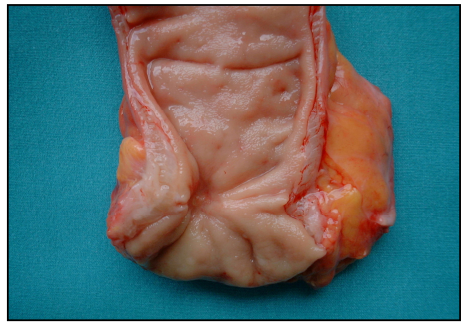
Standardized Surgery





Standardized Staging





Tumor Response

1° generation: PREoperative RT

Adjuvant CRT improved local recurrence and DFS, Gastrointestinal Tumor Study Group

Postoperative CRT for treatment of rectal cancer, NIH Consensus Conference

POST-operative

TME

1985 1986 1990 1997 2001 2004 2006 2017 2019 2020 2021

Preoperative CRT improves local recurrence and survival, Swedish Rectal Cancer trial

Preoperative SCRT superior local control compared to postoperative CRT, Multicenter RCT Uppsala University Sweden

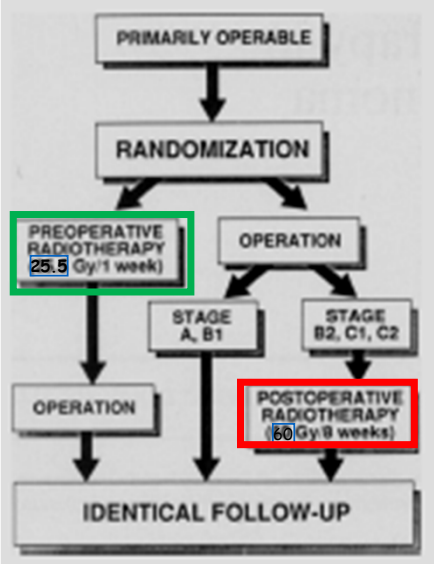
PRE-operative

PREoperative RT

Theoretical benefits of neoadjuvant RT:

- tumors with intact vasculature
- less risk of surgical tumor seeding
- increased frequency of sphincter-sparing surgery

Pre-RT > Post-RT



UPPSALA Trial	471	Pts

Survival		Local control	
Pre – Post 5y %		Pre – Post 5y %	
42 - 38	ns	86 - 77	0.02

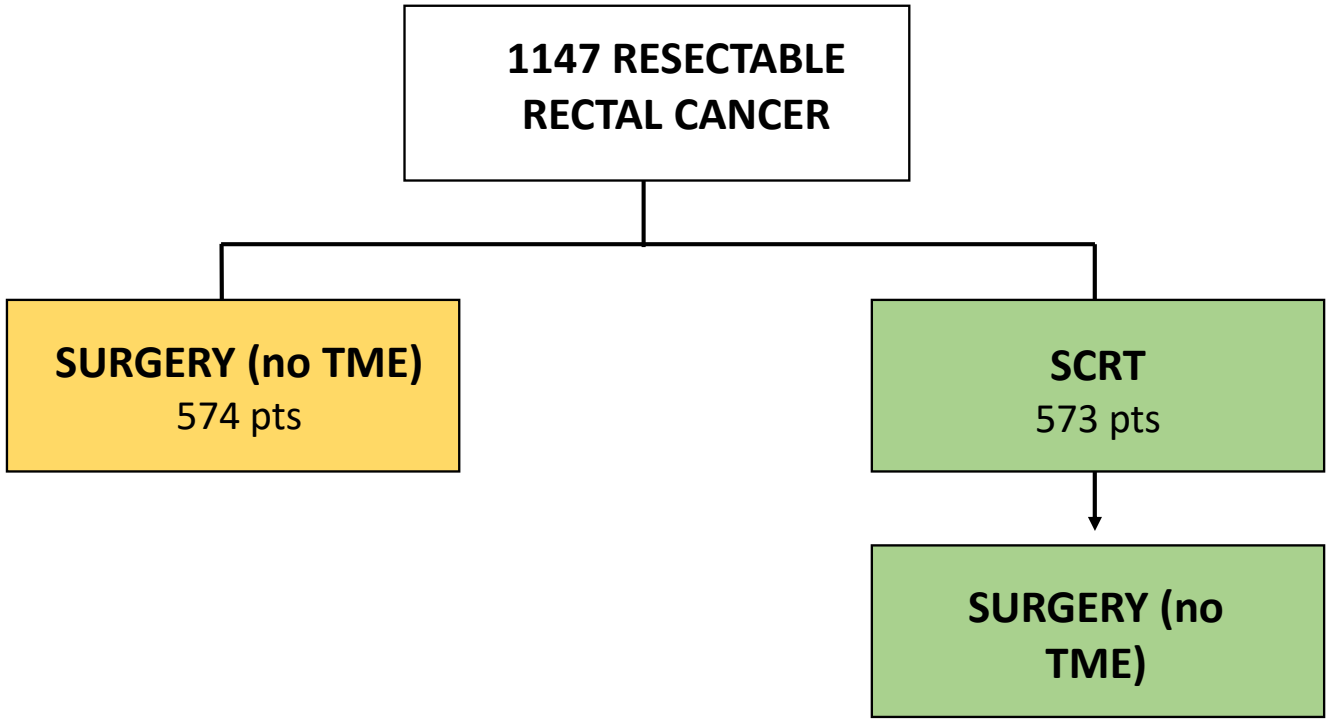
Pahlman L et al. Ann Aurg 1990

1° generation: PREoperative RT

Trial	Randomization	Local control	DFS	OS	Toxicity
Swedish trial *Swedish Rectal cancer Trial NEJM 1997*	**5x5→ S** vs **S alone**	**yes**	**yes**	**yes**	↑
Dutch trial *Kapiteijn E NEJM 2001*	**5x5→ S** vs **S alone**	**yes**	**no**	**no**	↑
British trial **MRC-CR07** *Sebag-Montefiore D. Lancet 2009*	**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)	↑

Before TME
Swedish trial

1147 RC patients
Primary end-points: local recurrence; overall survival



Cedermark B, et al. *N Engl J Med* 1997

Adjuvant CRT improved local recurrence and DFS, Gastrointestinal Tumor Study Group

Postoperative CRT for treatment of rectal cancer, NIH Consensus Conference

TME

1985 1986 1990 1997 2001 2004 2006 2017 2019 2020 2021

Preoperative CRT improves local recurren
Swedish Rect

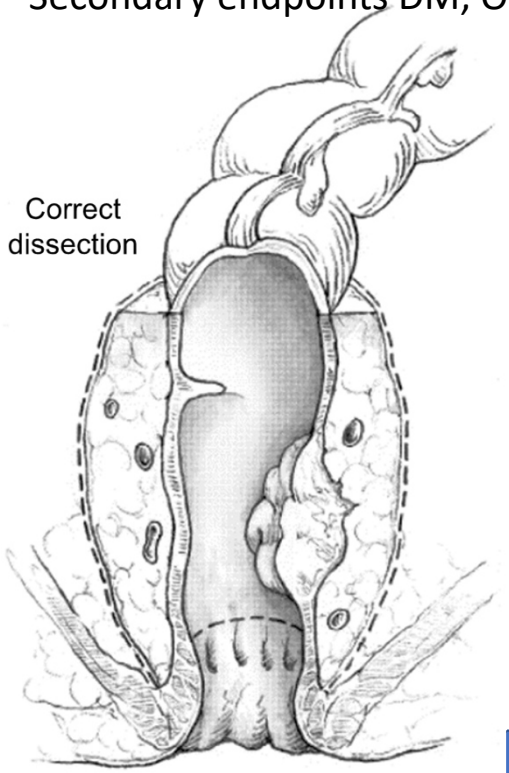
Dutch Colorectal Cancer trial

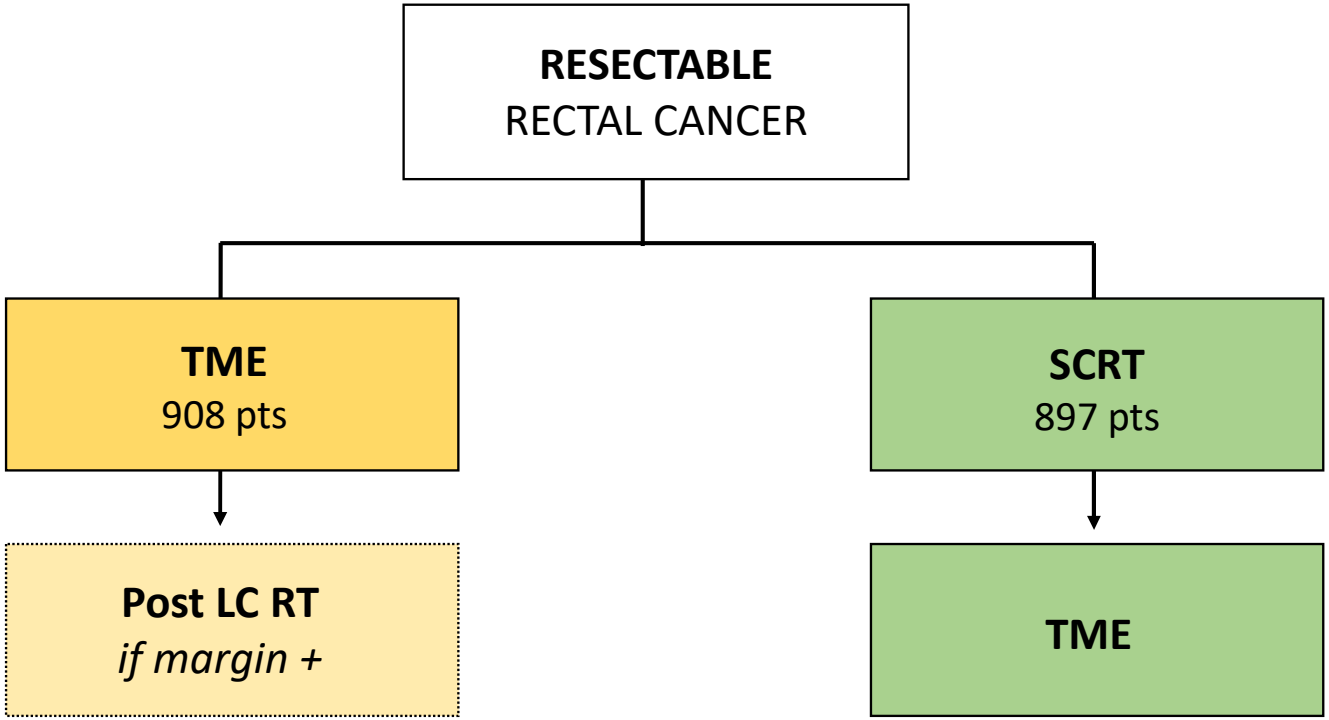
PRE-operative SC-RT + TME

Preoperative SCRT superior local
compared to postoperative CRT,
Multicenter RCT Uppsala Universi
Sweden

With TME

1805 RC pts
All STAGES
Primary endpoint **LC**
Secondary endpoints DM, OS, CSS

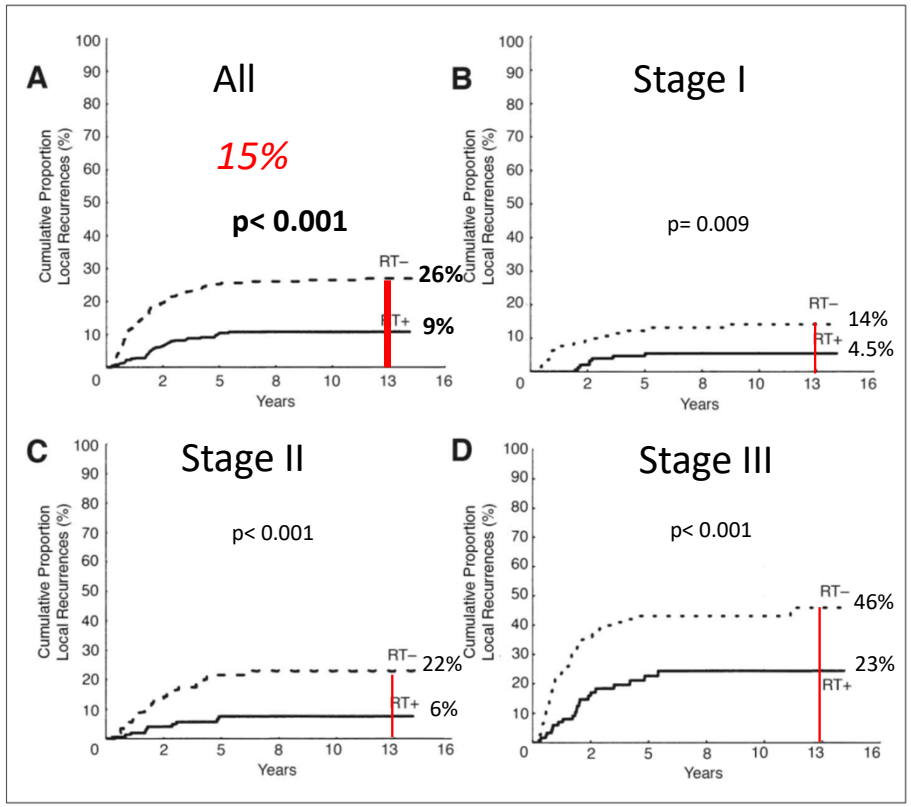




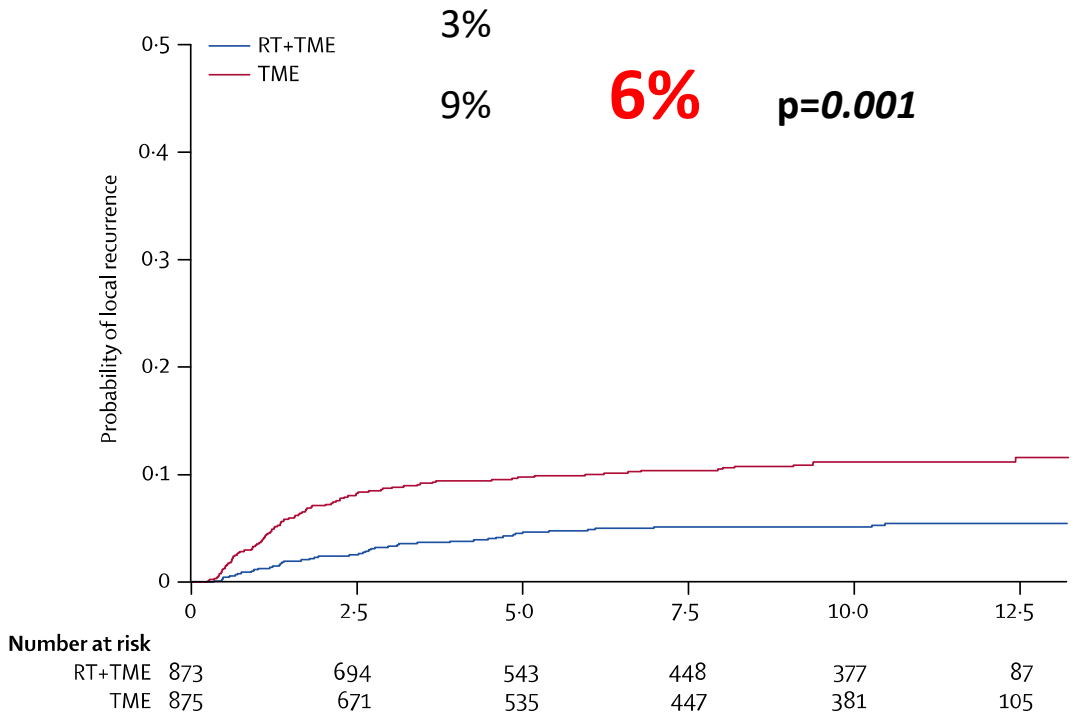
Kapiteijn E et al. *N Engl J Med 2001*

Local control

NO TME

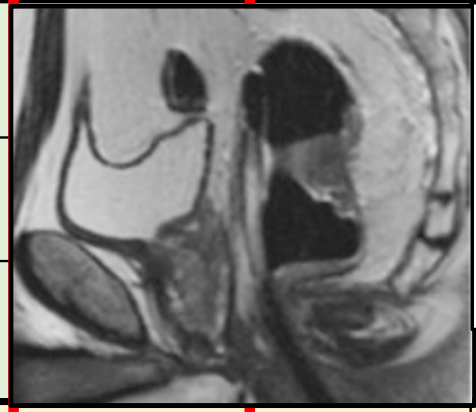


TME



1° generation: PREoperative RT

Local Control

Trial	Randomization	Local control	DFS	OS	Toxicity
Swedish trial *Swedish Rectal cancer Trial NEJM 1997*	**5x5→ S** vs **S alone**			**T1-T3 resectable NO DOWNSTAGING**	
Dutch trial *Kapiteijn E NEJM 2001*	**5x5→ S** vs **S alone**				
British trial **MRC-CR07** *Sebag-Montefiore D. Lancet 2009*	**5x5→ S** vs **S alone**				↓
German trial **CAO-ARO-AIO-94** *Sauer R. NEJM 2004*	**Preop CRT** vs **post-op CRT**	**yes**	**no**	**no**	↓
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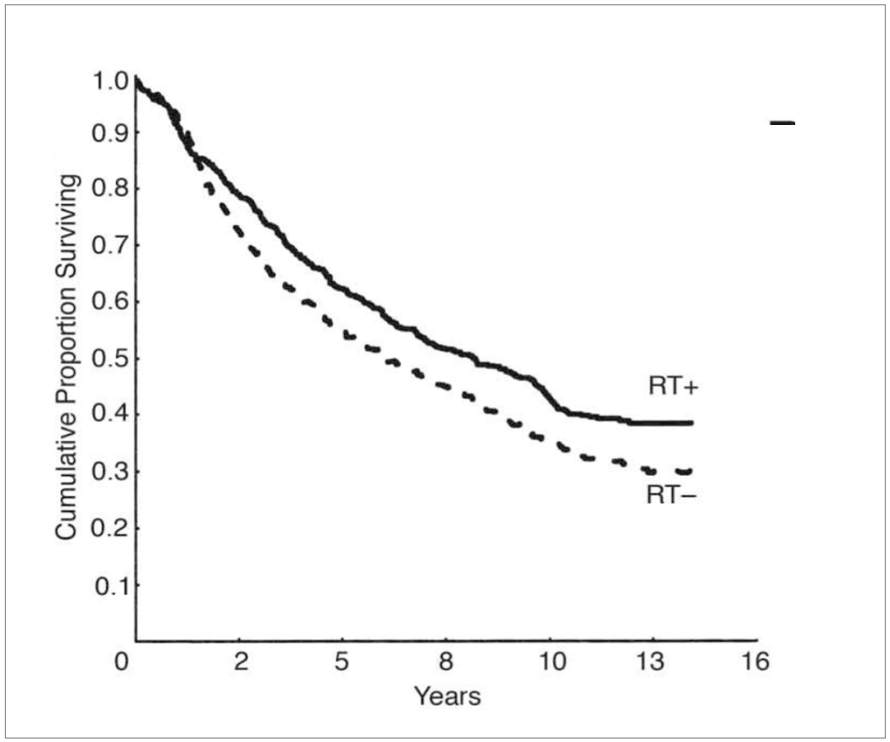
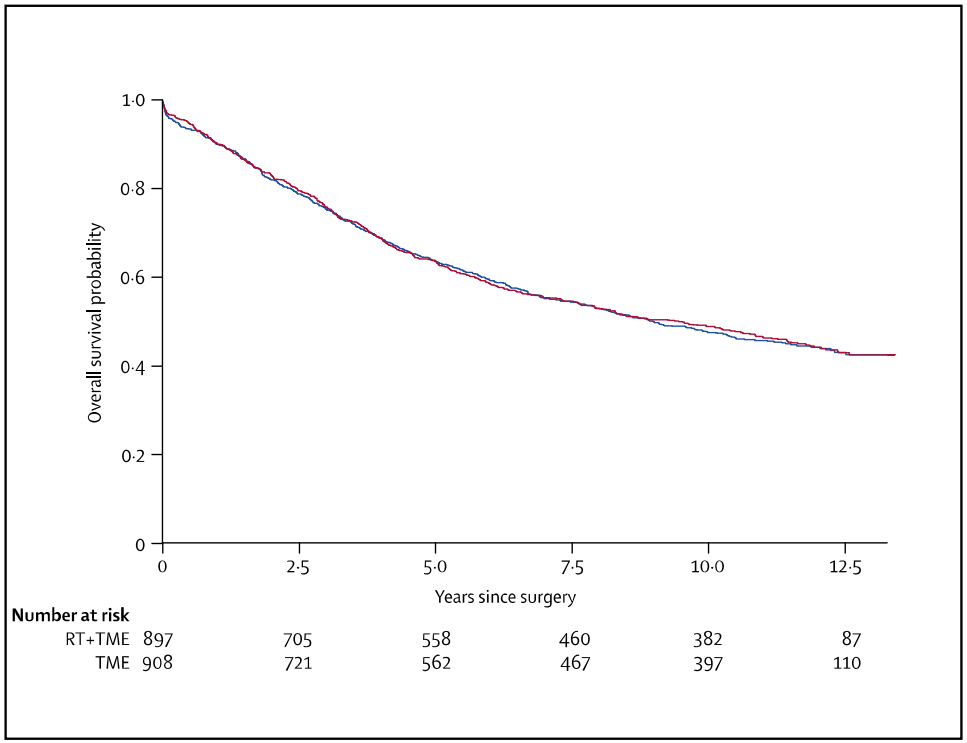
Overall Survival

NO TME



Overall Survival gain 48%→ 58% **10%**
p=*0.004*

TME



OS → NO gain in all patients

Folkesson J, et al. *J Clin Oncol 2015* Van Gijn W, et al. *Lancet Oncol 2011*

1° generation: PREoperative RT

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Adjuvant CRT improved local recurrence and DFS, Gastrointestinal Tumor Study Group

Postoperative CRT for treatment of rectal cancer, NIH Consensus Conference

TME

1985 1986 1990 1997 2001 2004 2006 2017 2019 2020 2021

Preope… local re… Swedis…

Dutch Colorectal Cancer trial

PRE-operative SC-RT + TME

Preoperative SCRT superior local compared to postoperative CRT, Multicenter RCT Uppsala University Sweden

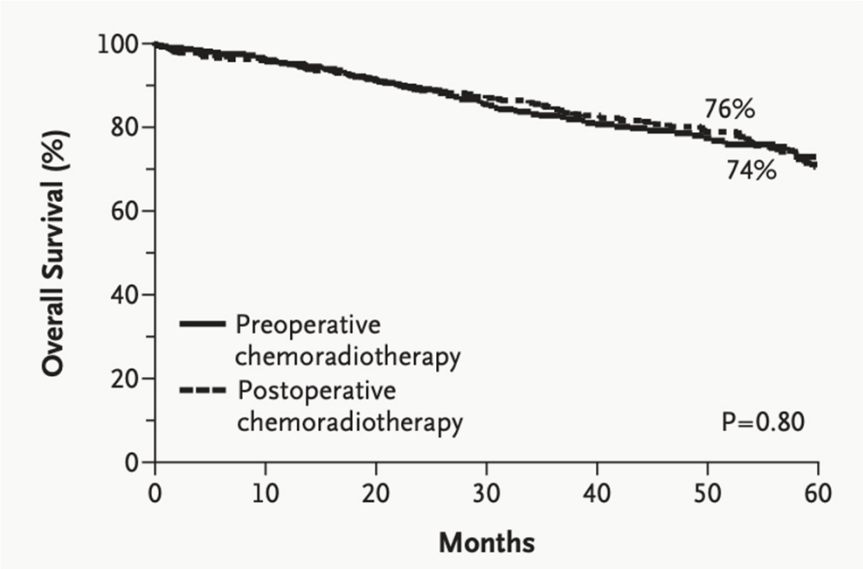
Preoperative CRT superior to postoperative CRT for locoregional control, German Rectal Cancer trial

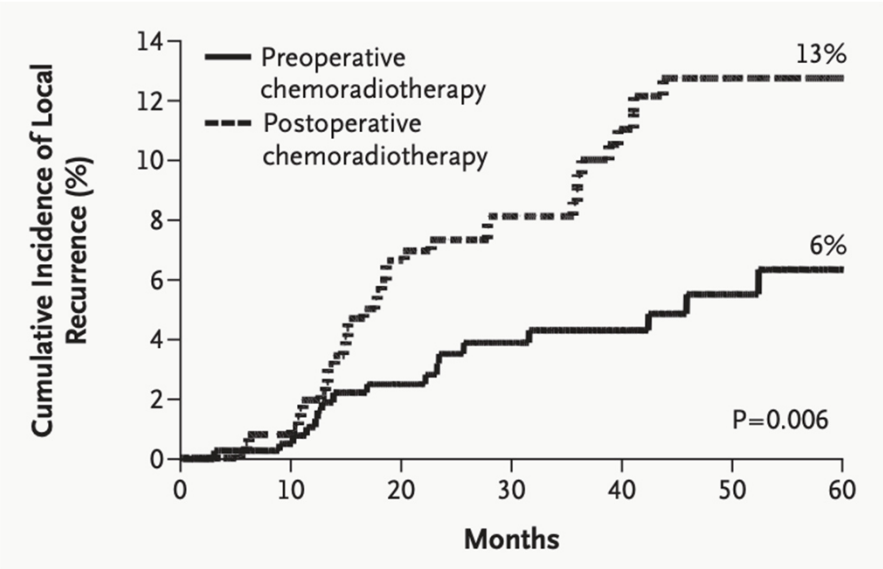
PRE-operative LC-CRT

1° generation: PREoperative RT

CAO/ARO/AIO-94

Pre-ChemoRT > Post-ChemoRT





N Engl J Med 2004

1° generation: PREoperative RT

Local Control

Trial	Randomization	Local control	DFS	OS	Toxicity
Swedish trial *Swedish Rectal cancer Trial NEJM 1997*	**5x5→ S** vs **S alone**	**yes**	**yes**	**yes**	↑
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EORTC trial *Bosset JF et al NEJM 2006*	**Preop CRT** vs **preop RT**				
Scandinavian trial *Braendengen M JCO 2008*	**Preop CRT** vs **preop RT**				

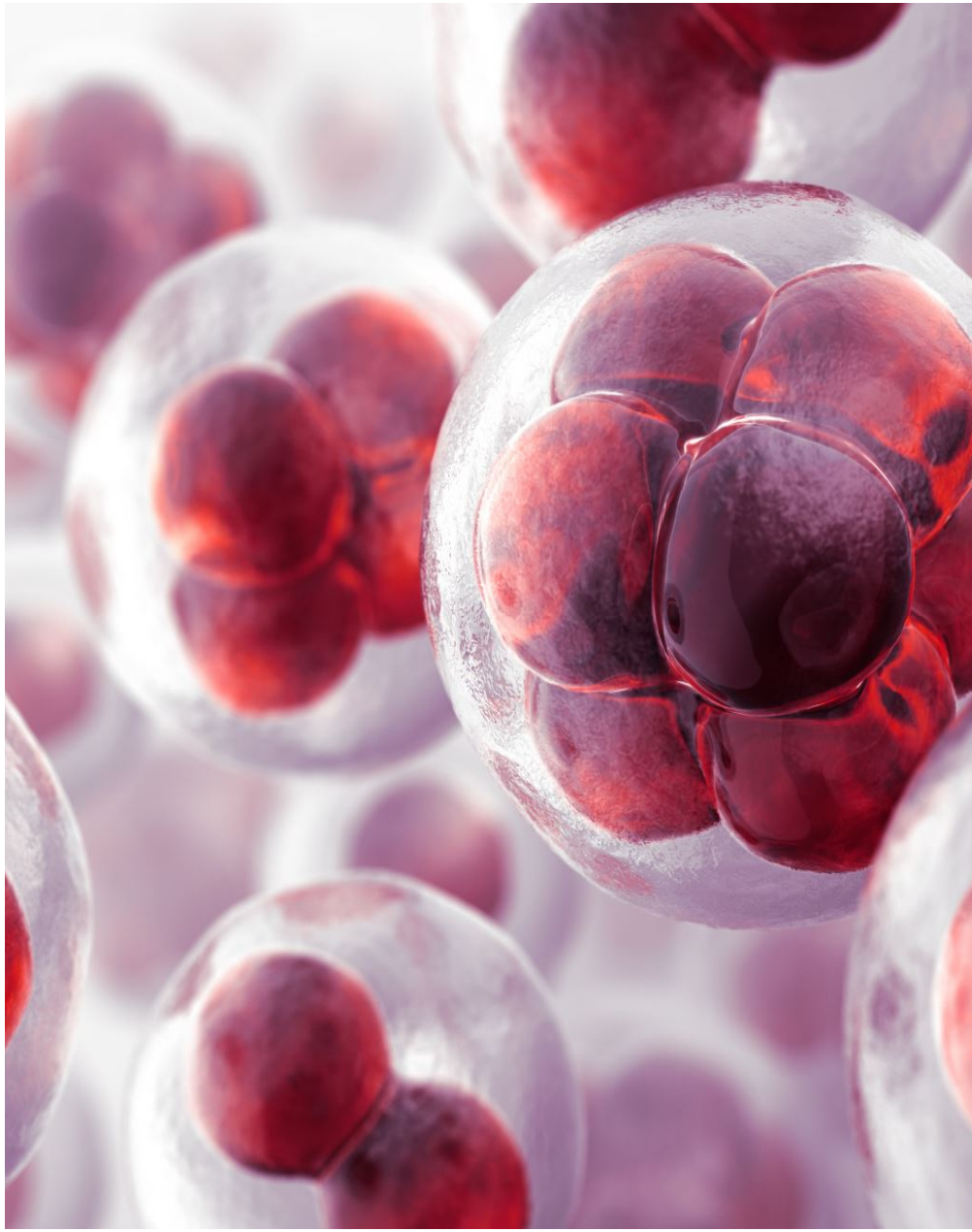
T3-T4

DOWNSTAGING

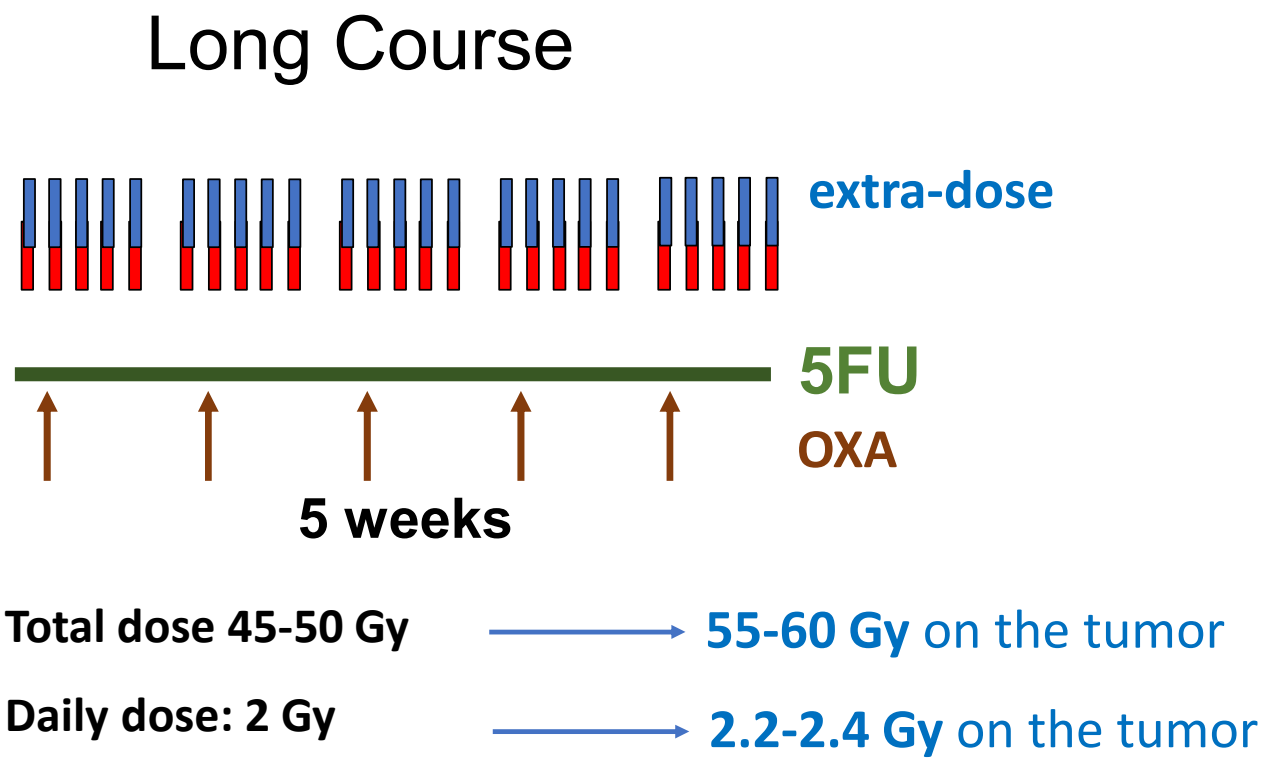
Take home messages

1° generation RT

- **Preop Short Course RT:**
  - Improves LC and OS if NO TME
  - No downstaging
- **Preop ChemoRT:** **LR rate 3-5%**
  - Improves LC
  - Downstaging
  - **Tumor response** as a broad spectrum of rectal cancer disease



2° generation: INTEnsification Trials



2° generation: INTEnsification Trials

Tumor Response

Trial	Randomization	pCR	Toxicity	Compliance
ACCORD 12 *Gérard JP. JCO 2010*	**RTCT OXA-5FU-HD** vs **RTCT 5FU**	**25%** vs 11%	↑	↓
NSABP R04 *O'Connell M. JCO 2014*	**RTCT OXA-5FU-HD** vs **RTCT 5FU**	**20%** vs18%	↑	↓
STAR 01 *Aschele C. JCO 2011*	**RTCT OXA-5FU** vs **RTCT 5FU**	**16%** vs 16%	↑	↓
CAO-ARO-AIO 04 *Rödel C. Lancet Onc 2012*	**RTCT OXA -5FU** vs **RTCT 5FU**	**17%** vs 13%	=	=
INTERACT *Valentini V. R&O 2019*	**RTCT OXA-5FU** vs **RTCT 5FU HD**	**26%** vs26%	↑	=
PETACC-6 *Schmoll HJ. JCO 2020*	**RTCT OXA -5FU** vs **RTCT 5FU**	**14%** vs 11%	↑	↓

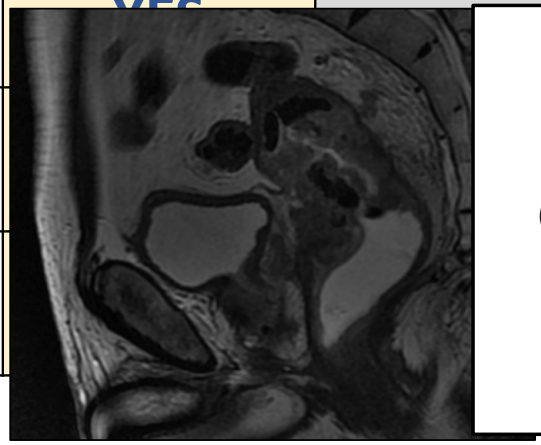
2° generation: INTEnsification Trials

Tumor Response

Trial	Randomization	pCR	Toxicity	Compliance
ACCORD 12 *Gérard JP. JCO 2010*	**RTCT OXA-5FU-HD** vs **RTCT 5FU**			
NSABP R04 *O'Connell M. JCO 2014*	**RTCT OXA-5FU-HD** vs **RTCT 5FU**			
STAR 01 *Aschele C. JCO 2011*	**RTCT OXA-5FU** vs **RTCT 5FU**			
CAO-ARO-AIO 04 *Rödel C. Lancet Onc 2012*	**RTCT OXA -5FU** vs **RTCT 5FU**			
INTERACT *Valentini V. R&O 2019*	**RTCT OXA-5FU** vs **RTCT 5FU HD**			
PETACC-6 *Schmoll HJ. JCO 2020*	**RTCT OXA -5FU** vs **RTCT 5FU**			

T3-T4
Low Tumor

DOWNSTAGING



T3-T4
HR
(MRF+,mucinous, EMVI)

DOWNSTAGING

2° generation: INTEnsification Trials

Tumor Response

Trial	Randomization	pCR	Toxicity	Compliance
ACCORD 12 *Gérard JP. JCO 2010*	**RTCT OXA-5FU-HD** vs **RTCT 5FU**	**NO**	↑	↓
NSABP R04 *O'Connell M. JCO 2014*	**RTCT OXA-5FU-HD** vs **RTCT 5FU**	**NO**	↑	↓
STAR 01 *Aschele C. JCO 2011*	**RTCT OXA-5FU** vs **RTCT 5FU**	**NO**	↑	↓
CAO-ARO-AIO 04 *Rödel C. Lancet Onc 2012*	**RTCT OXA -5FU** vs **RTCT 5FU**	**YES**	=	=
INTERACT *Valentini V. R&O 2019*	**RTCT OXA-5FU** vs **RTCT 5FU HD**	**NO**	↑	=
PETACC-6 *Schmoll HJ. JCO 2020*	**RTCT OXA -5FU** vs **RTCT 5FU**	**NO**	↑	↓

RT Dose INTEnsification Trials

INTERACT ITALIAN TRIAL

Radiotherapy and Oncology 134 (2019) 110–118

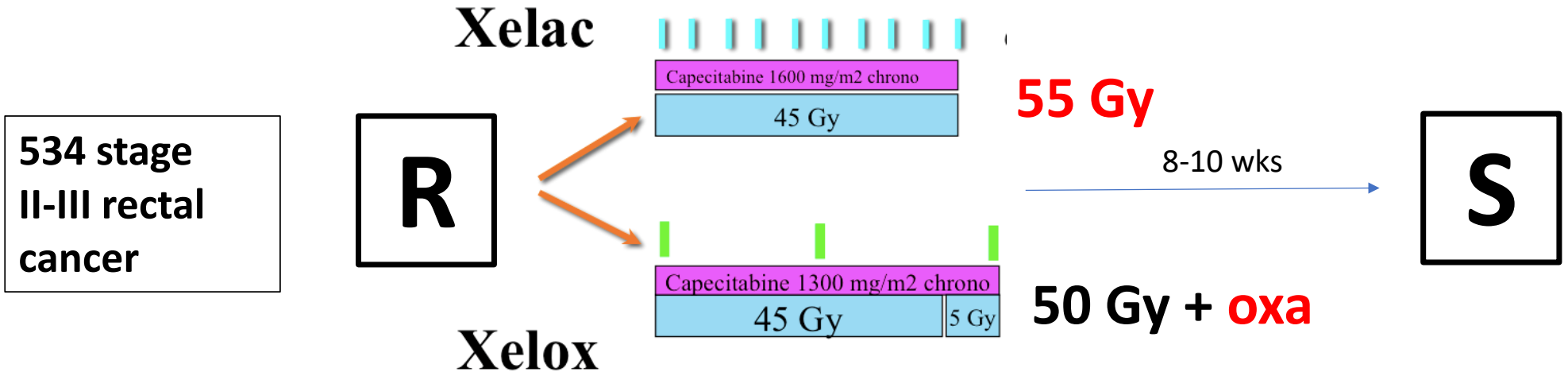
Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

The INTERACT Trial: Long-term results of a randomised trial on preoperative capecitabine-based radiochemotherapy intensified by concomitant boost or oxaliplatin, for cT2 (distal)–cT3 rectal cancer



Valentini V et al. Radiother Oncol 2019

RT Dose INTEnsification Trials

INTERACT ITALIAN TRIAL

Tumor Response

	XELAC	XELOX	p
TRG1	32.3%	32.9%	ns
TRG1-2	61%	52.3%	0.039
pCR	26%	26%	ns

Acute toxicity

Toxicity	XELAC	XELOX	p
Hemat	8.7%	18%	0.011
GI	16.9%	10.2%	0.054
Neuro	1.7%	21%	0.001

Valentini V et al. Radiother Oncol 2019

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TME

1985 1986 1990 1997 2001 2004 2006 2017 2019 2020 2021

Preope local re Swedis

Dutch Colorectal Cancer trial

PRE-operative SC-RT + TME

PRE-operative SC-RT delayed TME

Delayed surgery following SCRT, Stockholm III trial

Preoperative SCRT superior local compared to postoperative CRT, Multicenter RCT Uppsala University Sweden

Preoperative CRT superior to postoperative CRT for locoregional control, German Rectal Cancer trial

PRE-operative LC-CRT

Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial

Johan Erlandsson, Torbjörn Holm, David Pettersson, Åke Berglund, Björn Cedermark, Calin Radu, Hemming Johansson, Mikael Machado, Fredrik Hjern, Olof Hallböök, Ingvar Syk, Bengt Glimelius, Anna Martling

Stockholm III RCT for operable rectal cancers

455 pts

5 x 5 → **S** **pT0 = 1.7%**

228 pts

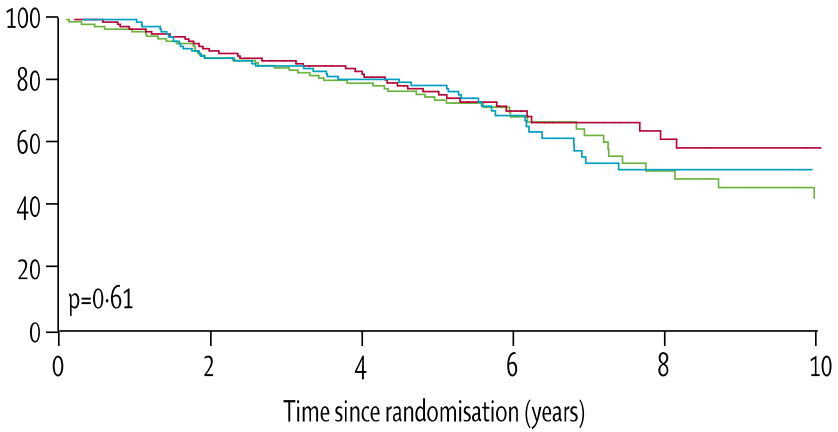
5 x 5 → **S** **pT0 = 11.8%**

227 pts

Petterson D et al. Br J Surg 2015

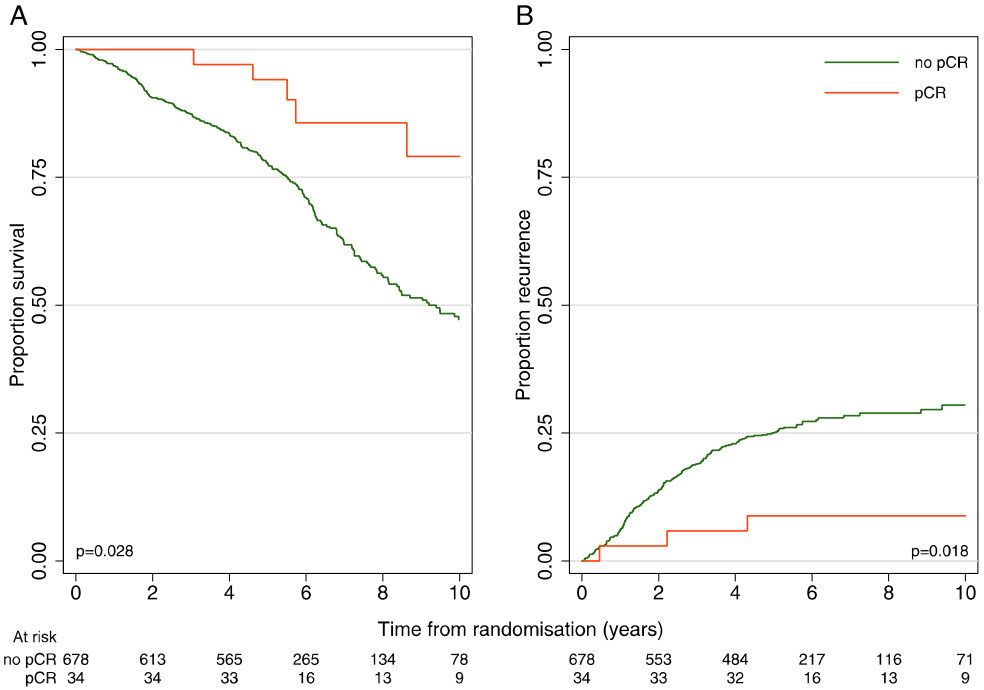
SCRT and delayed Surgery: Overall Survival

All



NO difference

OS LR



Better OS and **TR** in pts with pCR

Erlandsson J et al. *Radiother Oncol 2019*

Radiotherapy and Oncology 154 (2021) 154–160

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Timing to achieve the highest rate of pCR after preoperative radiochemotherapy in rectal cancer: a pooled analysis of 3085 patients from 7 randomized trials

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Pooled analysis of RCT:

Accord 12/0405

EORTC 22921

FFCD 9203

CAO/ARO/AIO-94

CAO-ARO-AIO-04

INTERACT and TROG 01.04

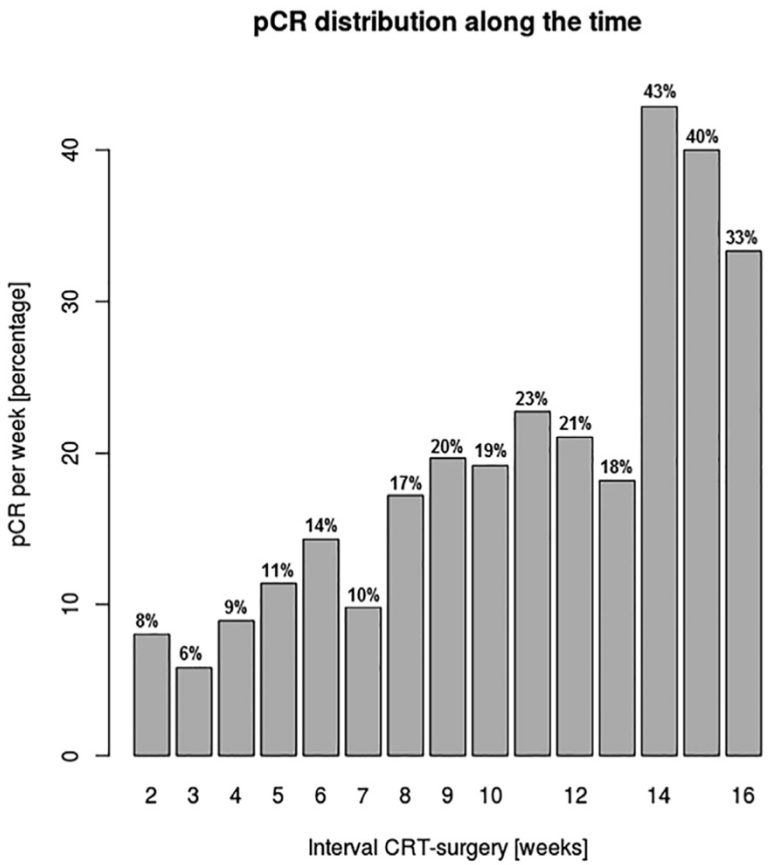
3078 pts → pCR 440 (14%)

Median Surgery Time → 6 wks

	Short Interval Group ≤ 6 wks (1953 pts)	Long Interval Group >6 wks (1125 pts)	p-value
pCR	11%	19%	0.01

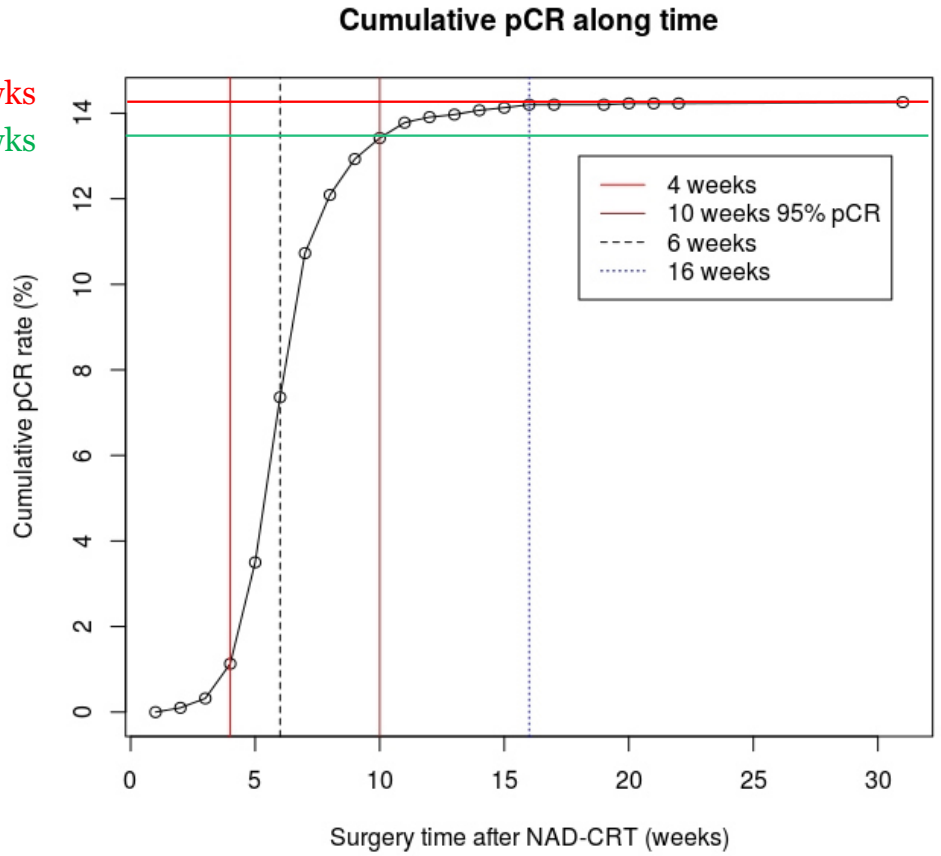
Gambacorta MA et al. Radiother Oncol 2020

The TIME effect

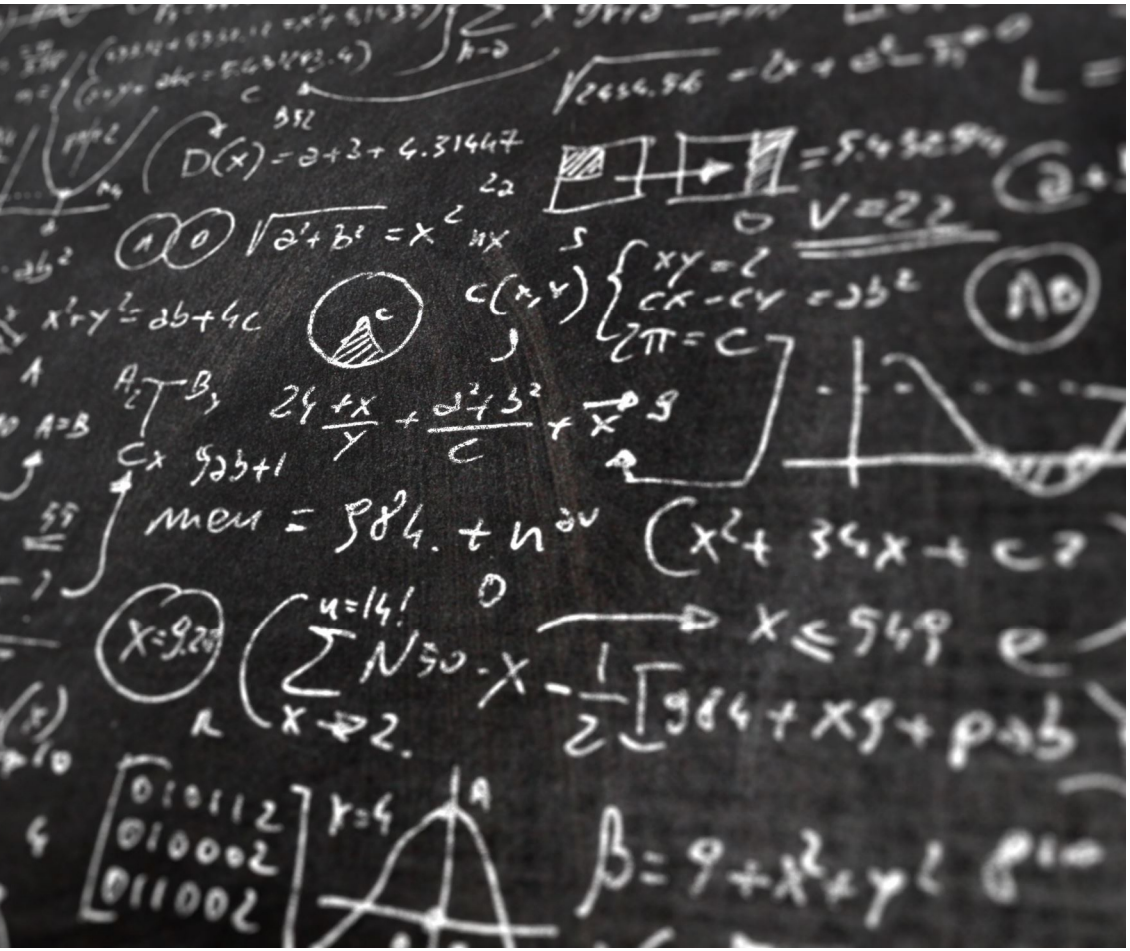


Plateau → 16 wks

95% of pCR→ 10 wks



Take home messages



2° generation RT

- **Preop ChemoRT Intensification** improves downstaging and pCR
- **pCR rate of 25%**
- **Preop Short Course RT and Delay surgery** same LC, better tolerance and downstaging

Adjuvant CRT improved local recurrence and DFS, Gastrointestinal Tumor Study Group

Postoperative CRT for treatment of rectal cancer, NIH Consensus Conference

TME

Dutch C
Cancer t

1985 1986 1990 1997 2001 2004 2006 2017 2019 2020 2021

Preoperative CRT improves local recurrence and survival, Swedish Rectal Cancer trial

Preoperative SCRT superior local control compared to postoperative CRT, Multicenter RCT Uppsala University Sweden

TNT-era

Induction vs Consolidation TNT, German Group CAO/ARO/AIO-12

SCRT + transanal endoscopic microsurgery for low grade rectal cancer, Trec trial

RAPIDO trial for HR RC SCRT + CT and TME

Rationale for TNT

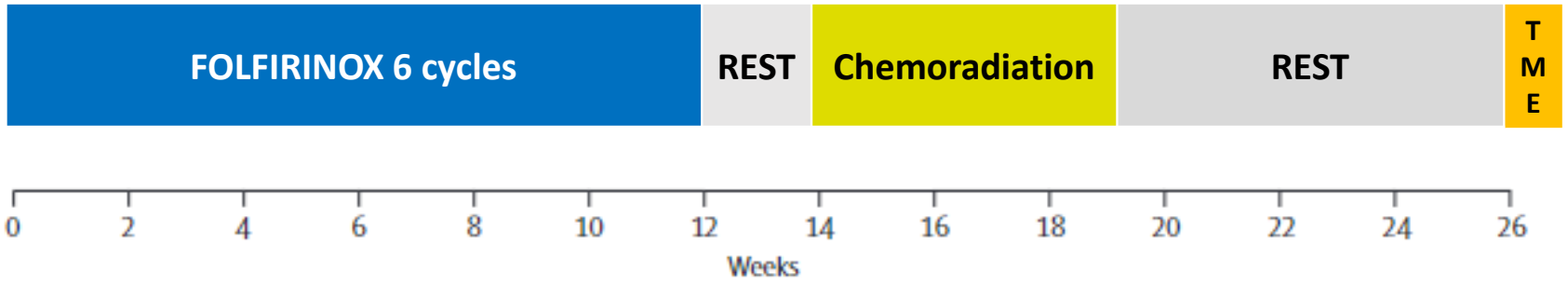
Earlier use of systemic therapy: **micrometastases**

Maximal downstaging: **better primary tumor local control**

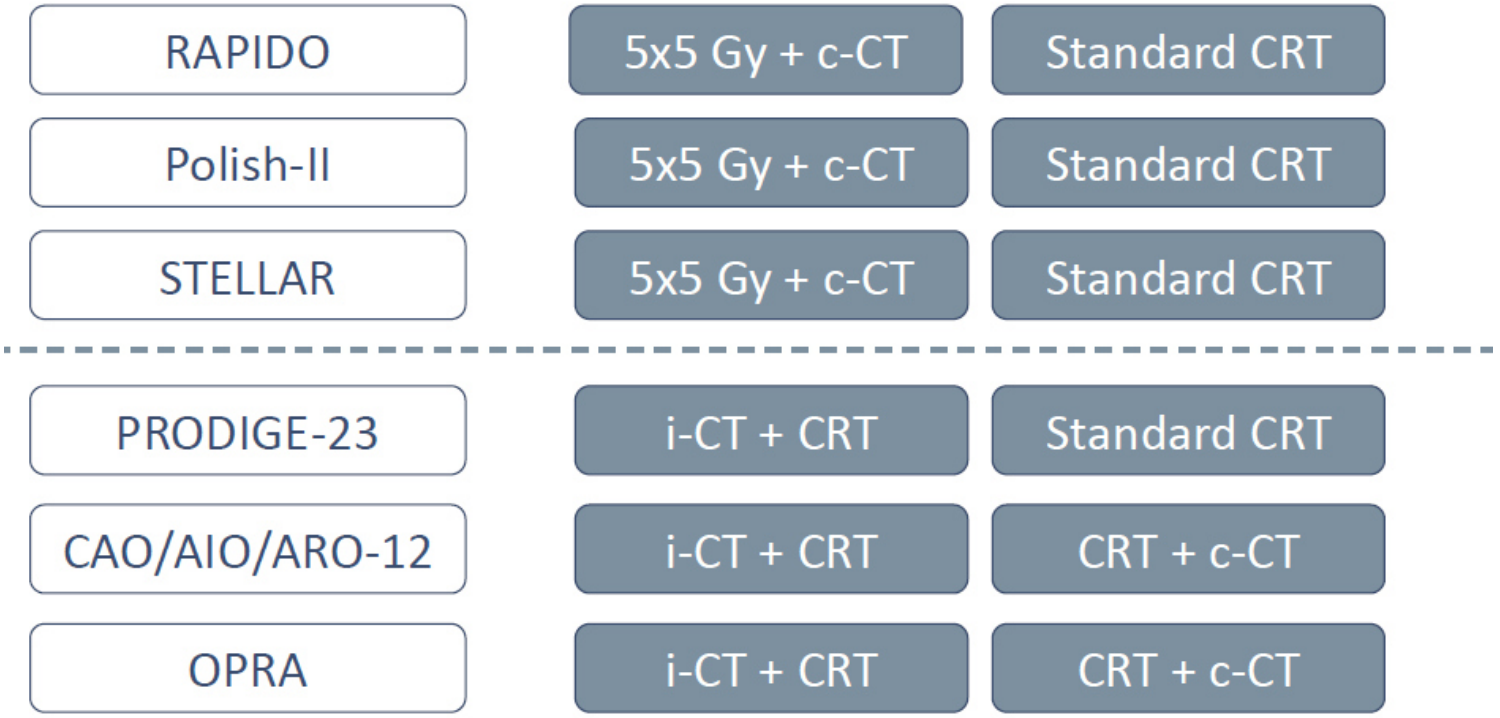
TNT: SCRT vs LCRT

RAPIDO trial

PRODIGE-23 trial



3° generation: Total Neoadjuvant Therapy



RAPIDO pCR

	TNT	**Standard**
pCR	**28%**	14%

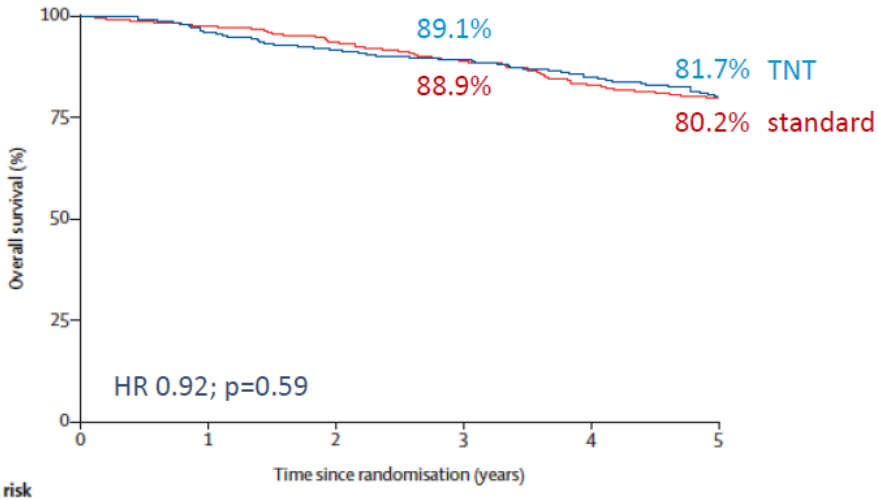
Bahadoer RR *Lancet Oncol 2021*

DFS

	5x5 Gy + c-CT	Standard CRT	Best arm DFS
RAPIDO	76%	70%	5x5 Gy + c-CT
Polish-II	53%	52%	similar
STELLAR	64%	62%	similar

	i-CT + CRT	Standard CRT	Best arm DFS
PRODIGE-23	76%	69%	i-CT + CRT
CAO/AIO/ARO-12	73%	73%	similar
OPRA	77%	78%	similar

RAPIDO trial: Outcomes

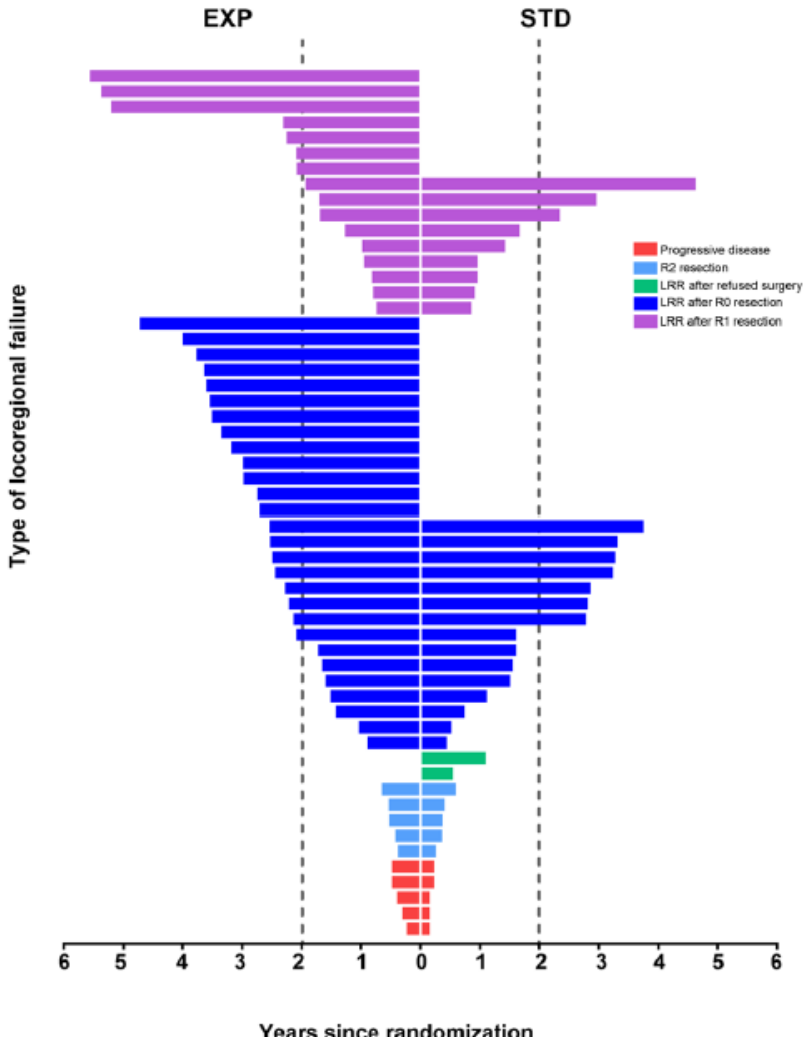


Number at risk (number censored)						
Standard of care group	450 (0)	450 (2)	438 (3)	418 (8)	392 (169)	214 (208)
Experimental group	462 (0)	462 (1)	442 (2)	421 (9)	403 (181)	216 (217)

Bahadoer RR *Lancet Oncol 2021*

RAPIDO trial: LR

12%



8%

More LR in the experimental arm

Dijkstra E, Ann Surg 2023

Take home messages

3° Generation TNT

- Better DFS **3yDFS 76%**
- Decreased **5yDM ≈ 23%**
- Increased LR in SC RT **12%**
- Increased pCR

Adjuvant CRT improved local recurrence and DFS, Gastrointestinal Tumor Study Group

Postoperative CRT for treatment of rectal cancer, NIH Consensus Conference

TME

Dutch Colorectal Cancer trial

Preoperative CRT superior to postoperative CRT for locoregional control, German Rectal Cancer trial

Delayed surgery following SCRT, Stockholm III trial

1985 1986 1990 1997 2001 2004 2006 2017 2019 2020 2021

FUTURE

Preoperative CRT improves local recurrence and survival, Swedish Rectal Cancer trial

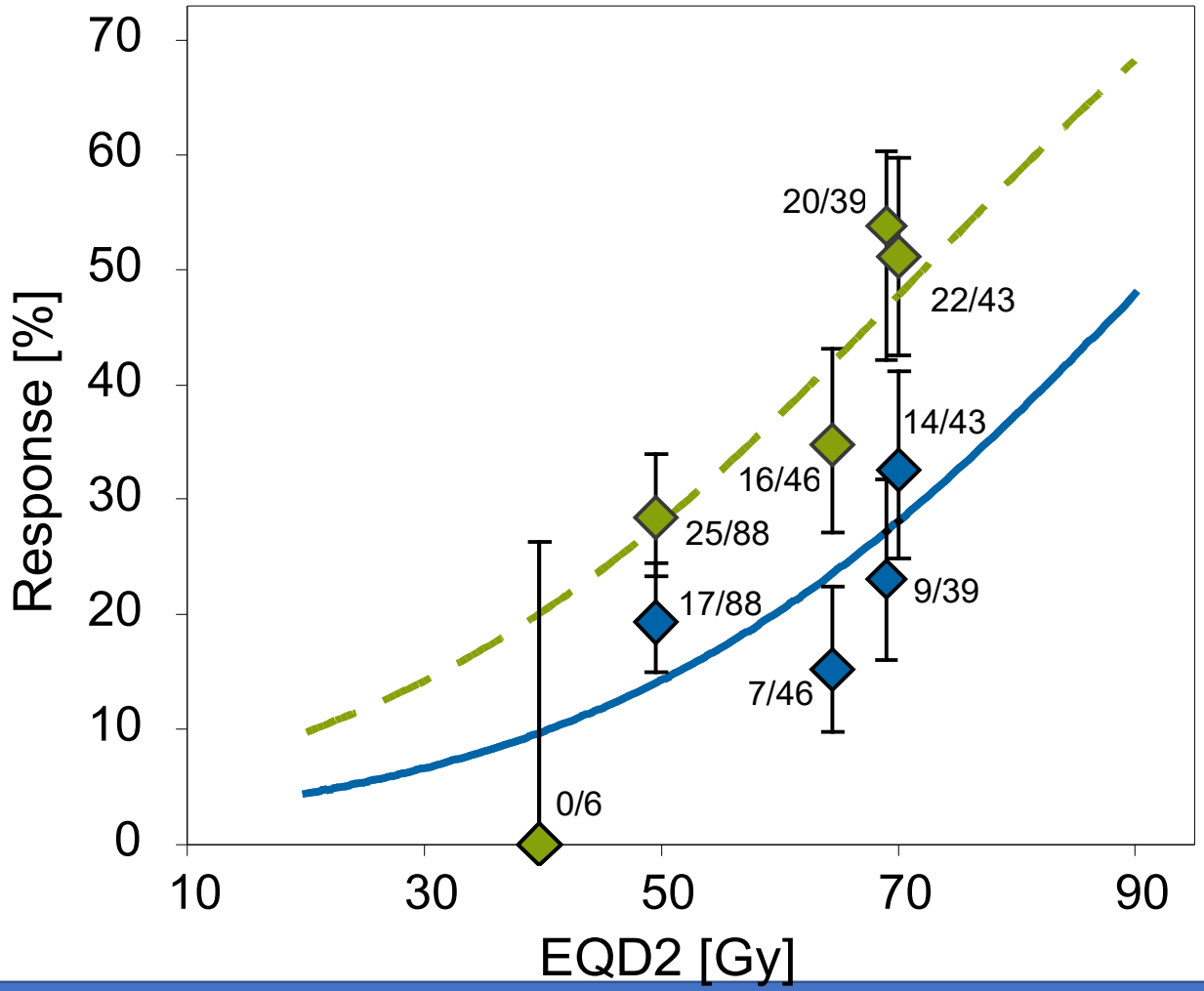
Preoperative SCRT superior local control compared to postoperative CRT, Multicenter RCT Uppsala University Sweden

Induction vs Consolidation TNT, German Group CAO/ARO/AIO-12

SCRT + transanal endoscopic microsurgery for low grade rectal cancer, Trec trial

RAPIDO trial for HR RC SCRT + CT and TME

DOSE



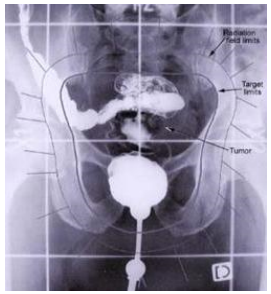
Blue: TRG1 (complete response)
Green: TRG1-2 (major response)

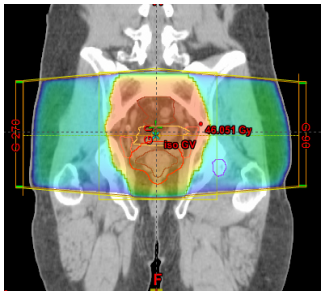
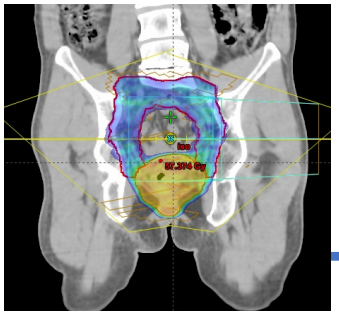
Appelt et al, *IJROBP 2013*

What has changed in RT?

MACHINES

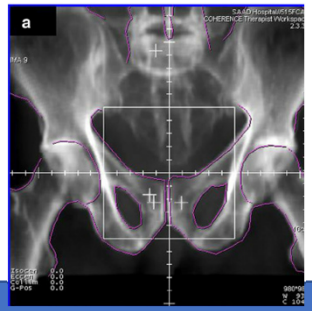


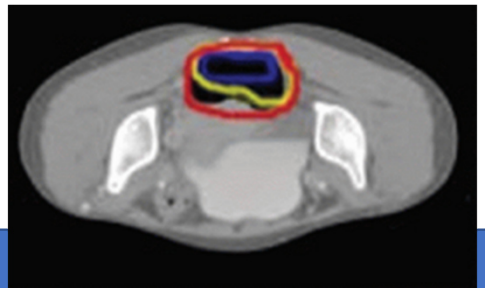
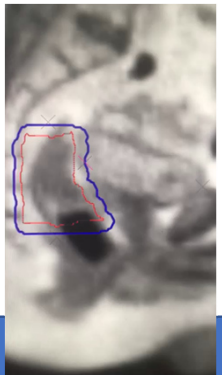



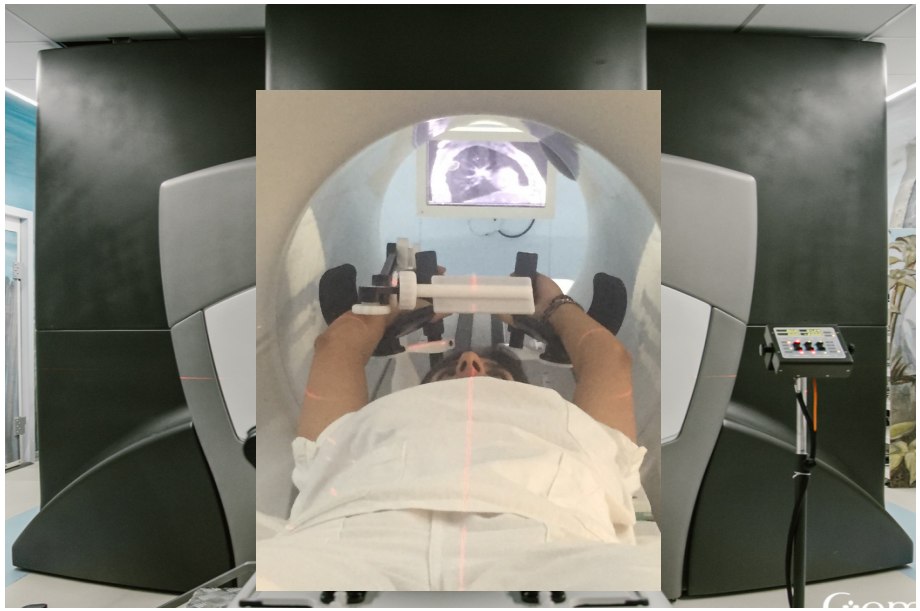
TECHNIQUES

IMAGING



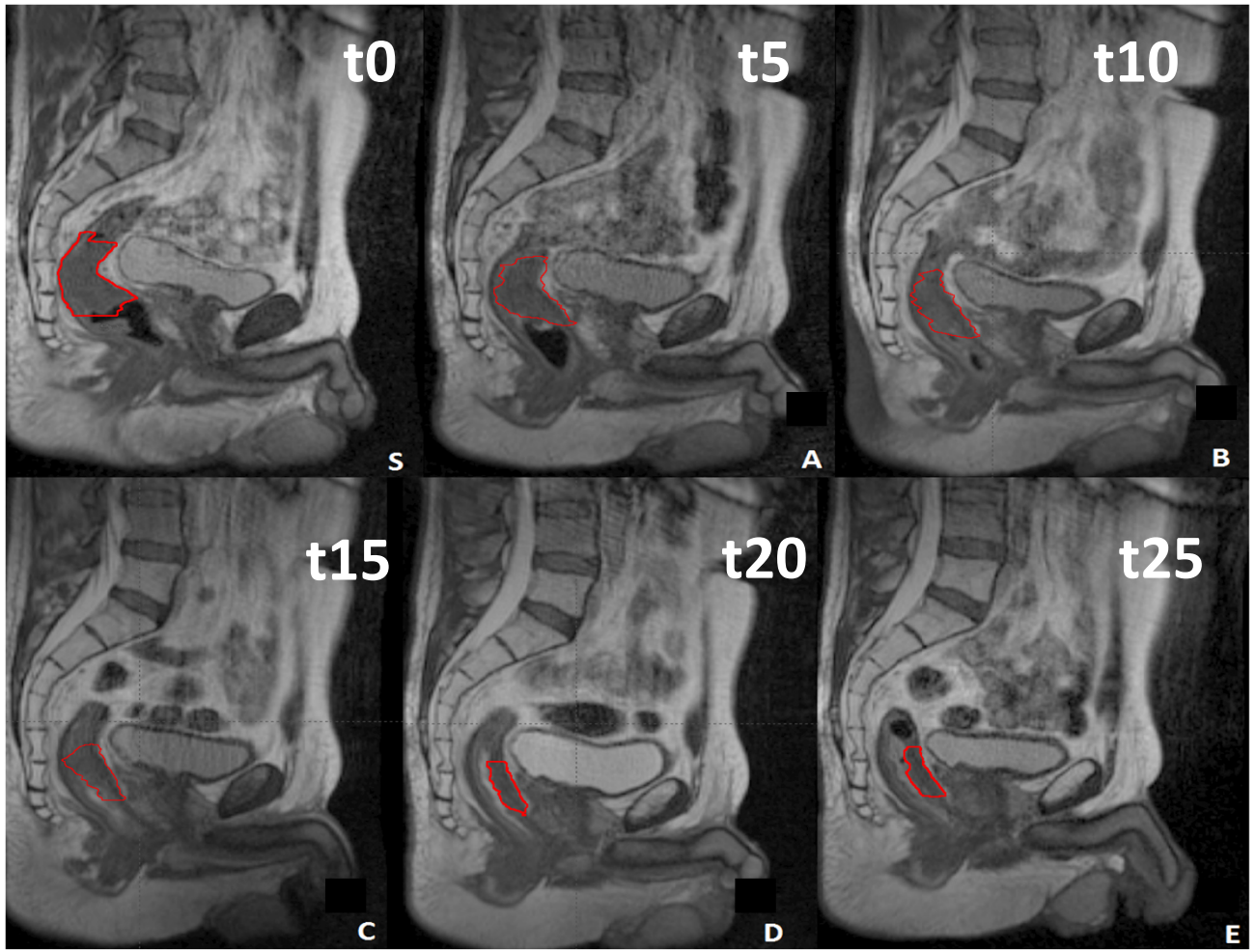
Target visualization: MRI-Guided RT



Direct TUMOR visualization:

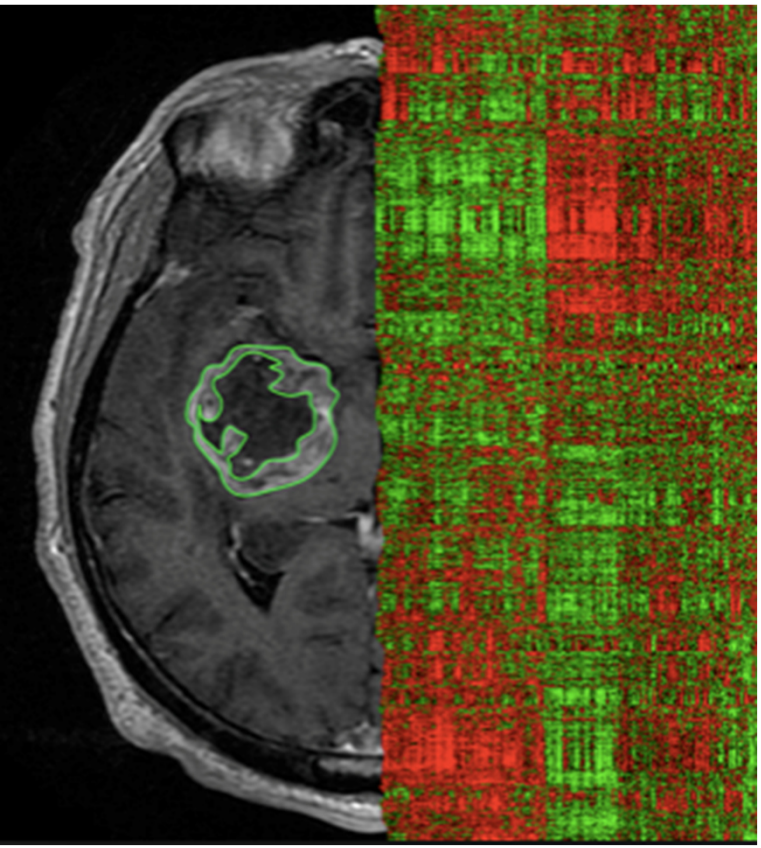
- During each fraction
- Throughout the treatment
- By doctor
- By patient
- Gated dose delivering

Adaptive Radiation Therapy



Boldrini L et al. Radiol Med 2018

Radiomics

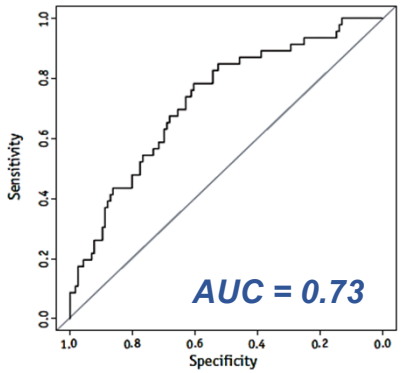


- Not invasive
- Repeatable
- Analyzes entire tumor volume
- Uses already available diagnostic and therapeutics images
- Cheap

Delta volumes and radiomics for CR prediction

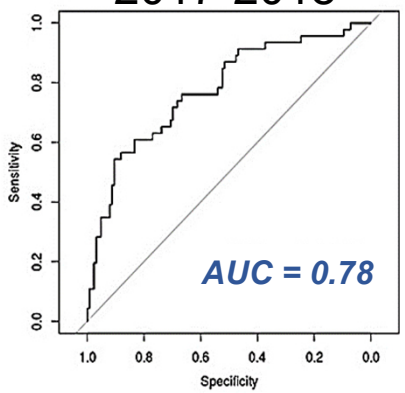
GEMELLI.ART published experiences

2017



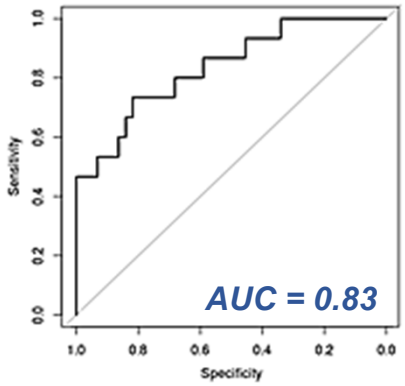
1.5T MRI Radiomics

2017-2018



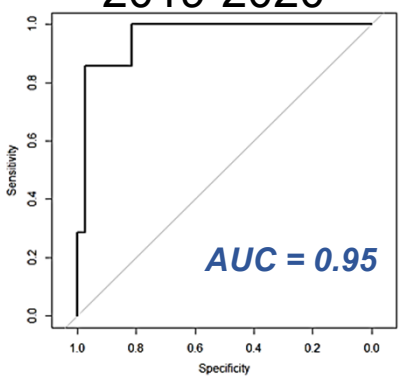
Fractals Radiomics

2018-2019



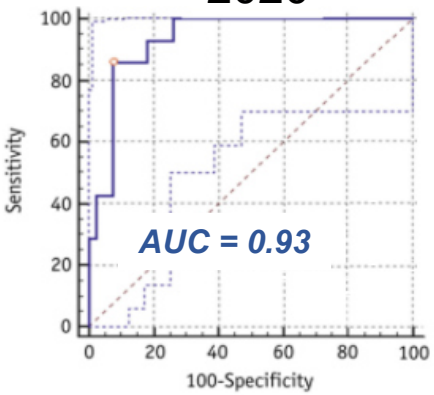
1.5-3T MRI Radiomics

2019-2020



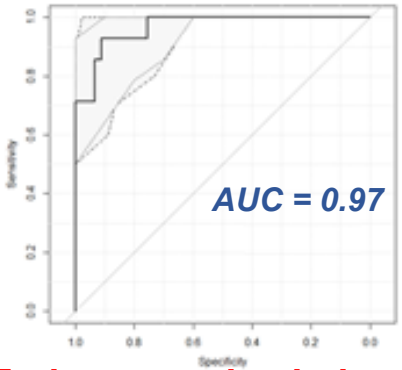
Delta Radiomics

2020



Early regression index

2021



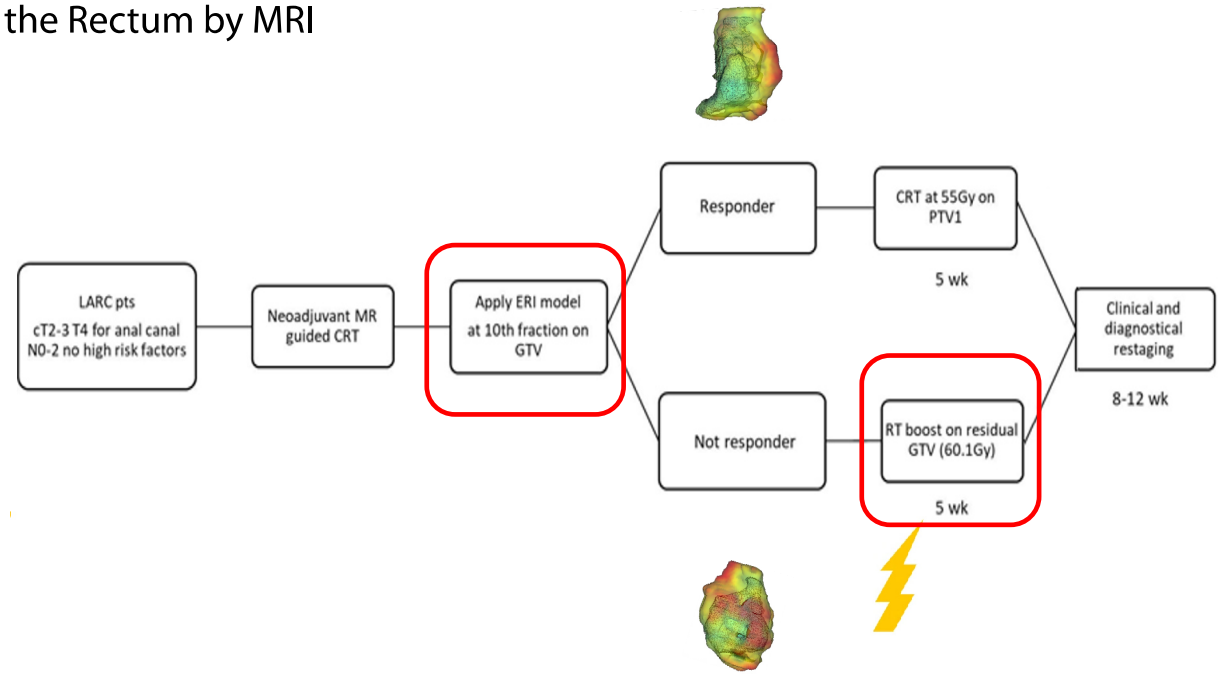
Early regression index + Radiomics

Gemelli ART
Advanced Radiation Therapy
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Future: personalization

STUDY PROTOCOL Open Access

THUNDER 2: THeragnostic Utilities for Neoplastic DisEases of the Rectum by MRI guided radiotherapy



Chiloiro *et al. BMC Cancer* (2022) 22:67
https://doi.org/10.1186/s12885-021-09158-9

The rectal cancer journey: what have we not to forget?

RADIOTHERAPY

- Alone → Local Control
- RT-CT → Tumor Response
- TNT → Distant Metastases

FUTURE

- Treatment personalization
- Treatment modulation