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**Work Shop**

**NOVITÀ PER UN "PERCORSO PREFERENZIALE"  
NELLE STRATEGIE DIAGNOSTICO-TERAPEUTICHE  
DEL CANCRO COLORETTALE**



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***Napoli, 22.06.2017***  
***La Radioterapia Neoadiuvante***

***Biagio Pecori***  
***UOSD RT Addome - INT G. Pascale Napoli***

Dopo **CHRT** le percentuali di **pCR** ammontano a circa il **15-27%**

la pCR è associato con una **prognosi favorevole** rispetto a : controllo locale, recidive a distanza , DFS ed OS

I pazienti con pCR hanno una migliore prognosi a lungo termine rispetto ai pazienti che non presentano pCR ciò può essere indicativo di un **più favorevole profilo biologico** del tumore con minore propensione alla recidiva (locale o a distanza) ed una migliore sopravvivenza

Questo dato è clinicamente rilevante perchè è correlato alla necessità di evitare ulteriori trattamenti adiuvanti ai pazienti che rispondono bene e di **intensificarlo** a coloro che **non rispondono**

Maas M . Et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data  
Lancet Oncology 2010; 11: 835-44



# migliorare la risposta: lo sviluppo di nuove armi

Modificare il trattamento chemioterapico nelle associazioni CHTRT potenziandolo farmacologicamente anche con nuove associazioni di farmaci

Modificare il trattamento radioterapico nelle associazioni CHTRT , aumentando la dose RT, anche con nuove metodiche per risparmiare gli organi a rischio e ridurre la tossicità

Modificare l'intervallo preoperatorio dopo trattamento RT esclusivo (fondamentalmente short course radiotherapy) o modificarne il frazionamento



# Nuove associazioni CHT con RT convenzionale

Risposte Pat	pCR	Major Resp	T downstg.	N downst.
	<b>39% (24)</b>	32% (20)	82 % (51)	77% (40)

Complicanze post chir	Maggiori (corr chirurg)
30% (19)	13% (8)

Toxicity	First series (n = 31)						Second series (n = 32)						Whole series (n = 63)					
	All Grade		Grade 3		Grade 4		All Grade		Grade 3		Grade 4		All Grade		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<b>Hematologic</b>																		
neutropenia	17	55	5	16	7	22	21	65	10	31	3	9	38	60	15	24	10	16
Febrile neutropenia	5	16	0		2	6	6	19	3	9	1	3	11	17	3	5	3	5
Thrombocytopenia	5	16	0		0		4	12	0		0		9	14	0		0	
Anemia	0		0		0		1	3	0		0		1	2	0		0	
<b>Gastrointestinal</b>																		
Nausea/vomiting	15	48	0		0		17	53	0		0		32	51	0		0	
Colitis	3	9	0		0		2	6	0		0		5	8	0		0	
Diarrhea	13	42	6	19	0		17	53	2	6	0		30	48	8	13	0	
Stomatitis	0		1	3	0		2	6	0		0		3	5	1	2	0	
Proctitis	5	16	0		0		9	28	0		0		14	22	0		0	
<b>Metabolic/laboratory</b>																		
Hyperbilirubinemia	0		0		0		1	3	0		0		1	2	0		0	
Transaminases	4	13	0		0		6	19	0		0		10	16	0		0	
<b>Skin toxicity</b>	3	9	0		0		4	12	0		0		7	11	0		0	
<b>Fatigue</b>	4	13	0		0		2	6	0		0		6	9	0		0	
<b>Fever</b>	3	9	0		0		1	3	0		0		4	6	0		0	
<b>Sensory neuropathy</b>	5	16	0		0		5	16	0		0		10	16	0		0	

Sessantatré pazienti T4, cN1-2, o cT3N0 ≤ 5 cm dal margine anale e/o con un CRM ≤ 5 mm, tre cicli bisettimanali di chemioterapia OXA, 100 mg/m<sup>2</sup>; raltitrexed (RTX), 2.5 mg/m<sup>2</sup> on day 1, and 5-fluorouracil (5-FU), 900 mg/m<sup>2</sup> (31 p) or 800 mg/m<sup>2</sup> (32 p); levo-folinic acid (LFA), 250 mg/m<sup>2</sup> on day 2, concomitante a RT pelvica (45 Gy)

Short Course RT (5x5Gy) chirurgia in 1 sett.

Aumenta il controllo locale e riduce del 50% le recidive (Swedish rectal cancer trial 2005)

non permette downstaging né è associata a pCR (0%)



Si può migliorare?

Short course RT e delayed surgery

Stesso trattamento RT SHORT esclusivo ma tempi chirurgici differenti, non 2-3 gg dopo RT ma dopo 6-8 settimane

## Short-course preoperative radiotherapy with delayed surgery in rectal cancer – A retrospective study

Radu C. et al. *Radiotherapy and Oncology* 2008;87: 343-349

Short-course radiotherapy, with elective delay prior to surgery, in patients with unresectable rectal cancer who have poor performance status or significant co-morbidity<sup>☆</sup>

Hatfield P. et al. *Radiotherapy and Oncology* 2009 ; 92: 210-214

**Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer**

Pettersson D. et al. *British Journal of Surgery* 2010; 97: 580-587

Radu 46 Pts	Hatfield 41 Pts
RO = 88%	RO = 85%
pCR = 8%	pCR = 8%
N- = 67%	N- = 65%

## Preoperative short-course radiotherapy with delayed surgery in primary rectal cancer

D. Pettersson<sup>1</sup>, T. Holm<sup>1</sup>, H. Iversen<sup>1</sup>, L. Blomqvist<sup>1</sup>, B. Glimelius<sup>2,3</sup> and A. Martling<sup>1</sup>

British Journal of Surgery 2012; 99: 577-583

-SRT-delay schedule is a feasible alternative **not only for older patients**, and those with severe co-morbidity and advanced tumours;

**-Younger patients** with less co-morbidity and tumours that were not locally advanced also fared well with this treatment.

-Potential advantages of **SRT-delay** compared with immediate surgery are **fewer postoperative complications and a downstaging effect**..





EURECCA consensus conference highlights about rectal cancer clinical management: The radiation oncologist's expert review



Vincenzo Valentini<sup>a</sup>, Bengt Glimelius<sup>b</sup>, Karin Haustermans<sup>c</sup>, Corrie A.M. Marijnen<sup>d</sup>, Claus Rödel<sup>e</sup>, Maria Antonietta Gambacorta<sup>a,\*</sup>, Petra G. Boelens<sup>f</sup>, Cynthia Aristei<sup>g</sup>, Cornelis J.H. van de Velde<sup>f</sup>

**Conclusions:** The starting-point of the present EURECCA document is that adding SCRT or LCRTCT to TME improved loco-regional control but did not increase overall survival in any single trial which, in any case, had improved with the introduction of total mesorectal excision (TME) into clinical practice.

...if patients were not candidates for chemotherapy, SCRT with delayed surgery is an option/alternative.

LCRTCT was recommended for cT4 anycN0.

SCRT offers the advantages of less acute toxicity and lower costs, and LCRTCT tumor shrinkage and downstaging, with 13–36% pathological complete response (pCR) rates.

August 22, 2016

RESEARCH ARTICLE

# Evaluation of Tumor Response after Short-Course Radiotherapy and Delayed Surgery for Rectal Cancer

Daniela Rega<sup>1\*</sup>, Biagio Pecori<sup>2</sup>, Dario Scala<sup>1</sup>, Antonio Avallone<sup>3</sup>, Ugo Pace<sup>1</sup>, Antonella Petrillo<sup>4</sup>, Luigi Aloj<sup>5</sup>, Fabiana Tatangelo<sup>6</sup>, Paolo Delrio<sup>1</sup>

sixty-seven patients cT3N0 <12 cm from the anal verge and with circumferential resection margin > 5 mm (MRI); cT2, any N, < 5 cm from anal verge; tumors with enlarged nodes and/or CRM+ve who resulted unfit for chemoradiation

TRG evaluation at different interval to surgery after RT: <6 wk ; 6-8 wk or >8 wk

Pathologic downstaging is higher when surgery is performed after more than 8 weeks the end of neoadjuvant radiotherapy

An interval between 8 and 10 weeks may be ideal for the tumor to shrink and eventually disappear and is not long enough to increase the risk of tumor progression

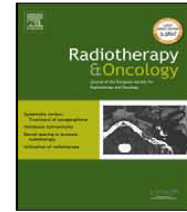




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## Radiotherapy and Oncology

journal homepage: [www.thegreenjournal.com](http://www.thegreenjournal.com)



Rectal cancer

### Preoperative radiotherapy and local excision of rectal cancer with immediate radical re-operation for poor responders: A prospective multicentre study <sup>☆</sup>

Krzysztof Bujko <sup>a,\*</sup>, Piotr Richter <sup>b</sup>, Fraser M. Smith <sup>c</sup>, Wojciech Polkowski <sup>d</sup>, Marek Szczepkowski <sup>e</sup>, Andrzej Rutkowski <sup>a</sup>, Adam Dziki <sup>f</sup>, Lucyna Pietrzak <sup>a</sup>, Milena Kołodziejczyk <sup>a</sup>, Jerzy Kuśnierz <sup>a</sup>, Tomasz Gach <sup>b</sup>, Jan Kulig <sup>b</sup>, Grzegorz Nawrocki <sup>a</sup>, Jakub Radziszewski <sup>a</sup>, Ryszard Wierzbicki <sup>d</sup>, Teresa Kowalska <sup>g</sup>, Wiktor Meissner <sup>h</sup>, Andrzej Radkowski <sup>i</sup>, Krzysztof Paprota <sup>j</sup>, Marcin Polkowski <sup>k</sup>, Anna Rychter <sup>l</sup>

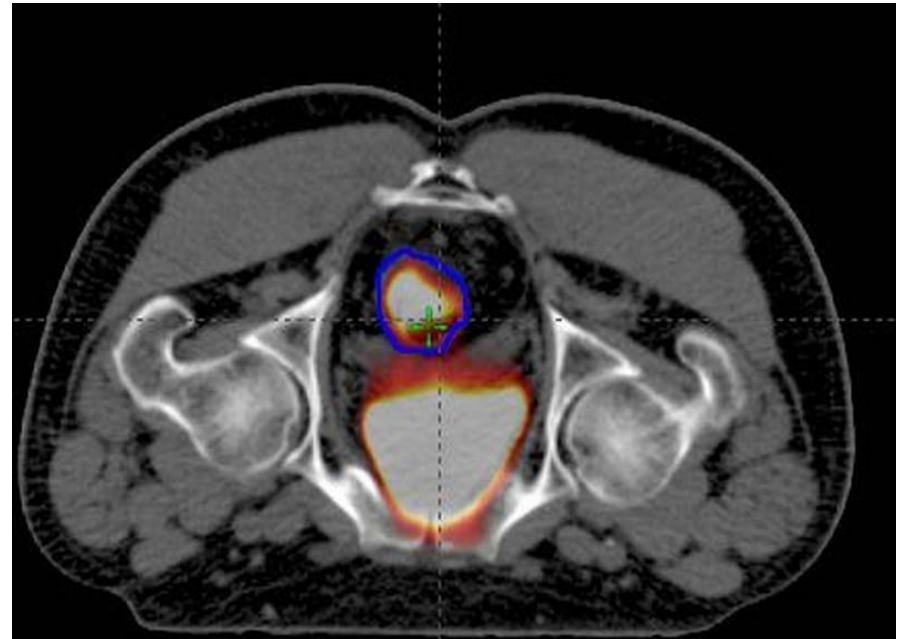
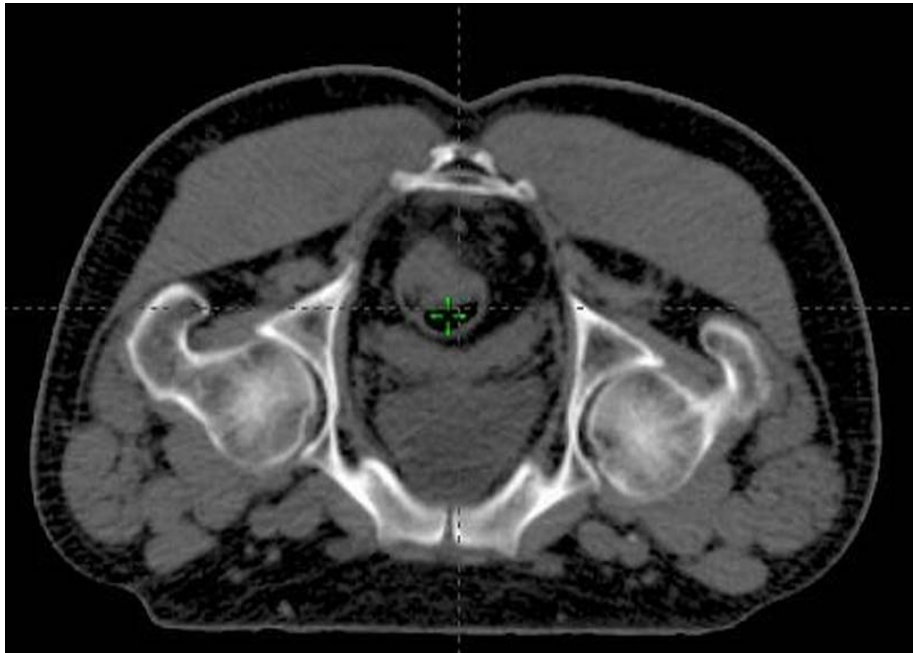
89 patients; median age 69; G1-2 rectal adenocarcinoma <3–4 cm; unfavourable cT1N0 (23.6%), cT2N0 (62.9%) or borderline cT2/cT3N0 (13.5%)

5 X 5 Gy plus 4 Gy boost or 55 8 Gy in 31 fractions with 5-FU and leucovorin Local excision  
6-8 week interval between radiation and surgery

acceptable local recurrence rate (10%) after preoperative radiotherapy and local excision of small, radiosensitive tumours in elderly patients.

short-course radiation can be safely used in patients unfit for chemotherapy

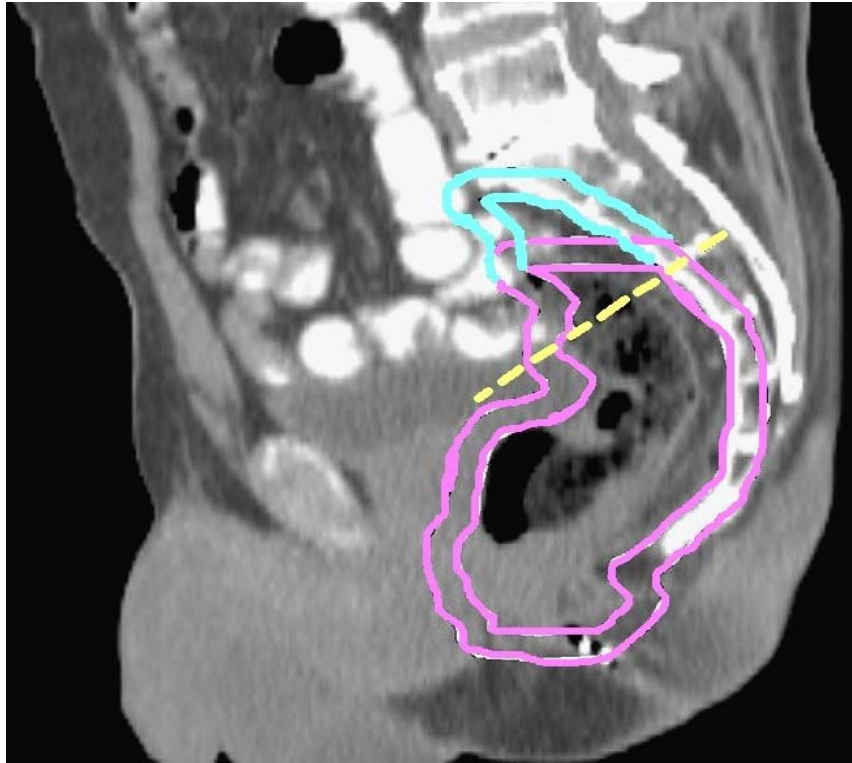
RT target localization procedure: precise assessment of T is difficult with CT only



# Better definition of T= reduction of treatment volume

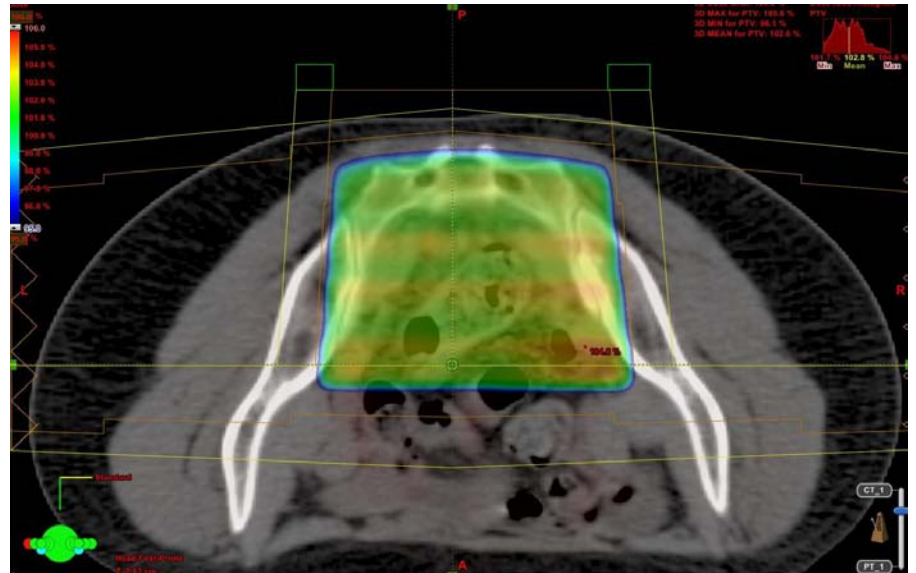
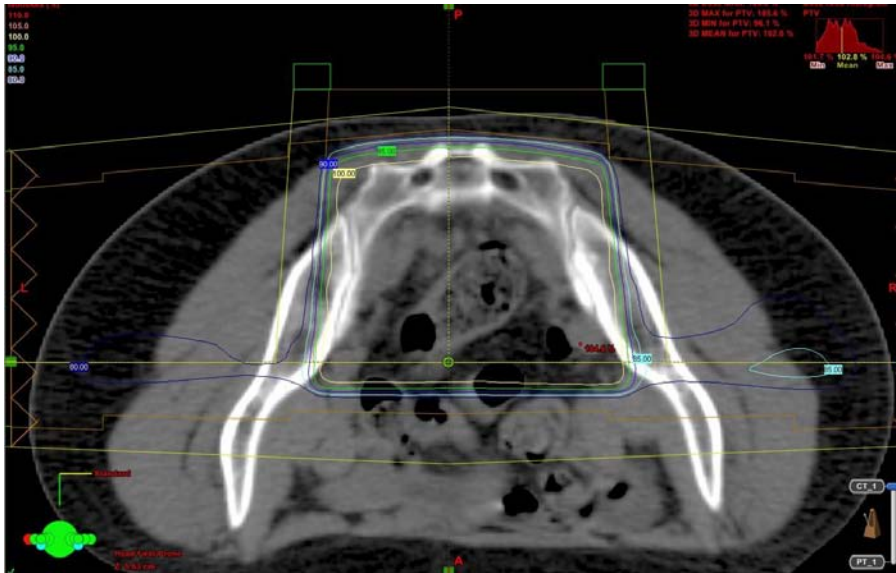
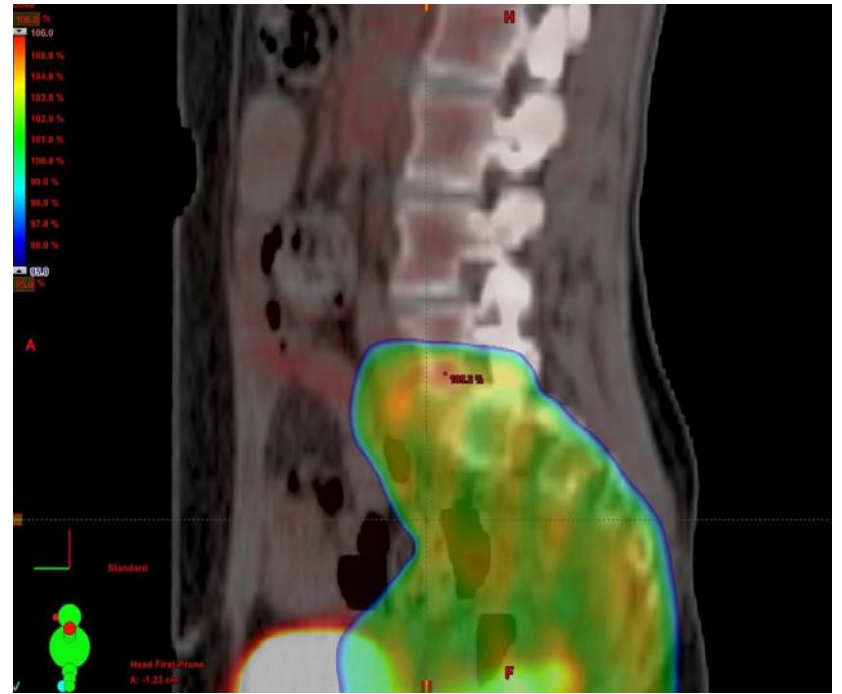


# SHORT RT: which volumes can we save ?

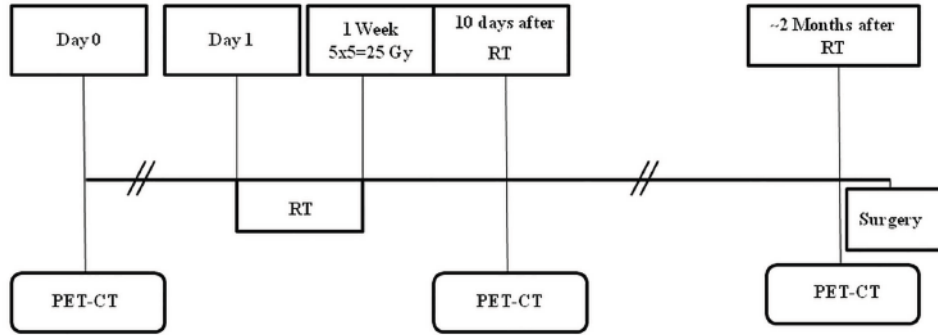


The cranial border of the CTV can safely be lowered for patients without expected nodal or CRM involvement, yielding a significant **60% reduction of dose to the small bowel** reduction without risk of recurrence . Therefore, a significant reduction of acute and late toxicity can be expected

Nijkamp J et al. Int. J. Radiation Oncology Biol. Phys., 2; 1-8, 2010



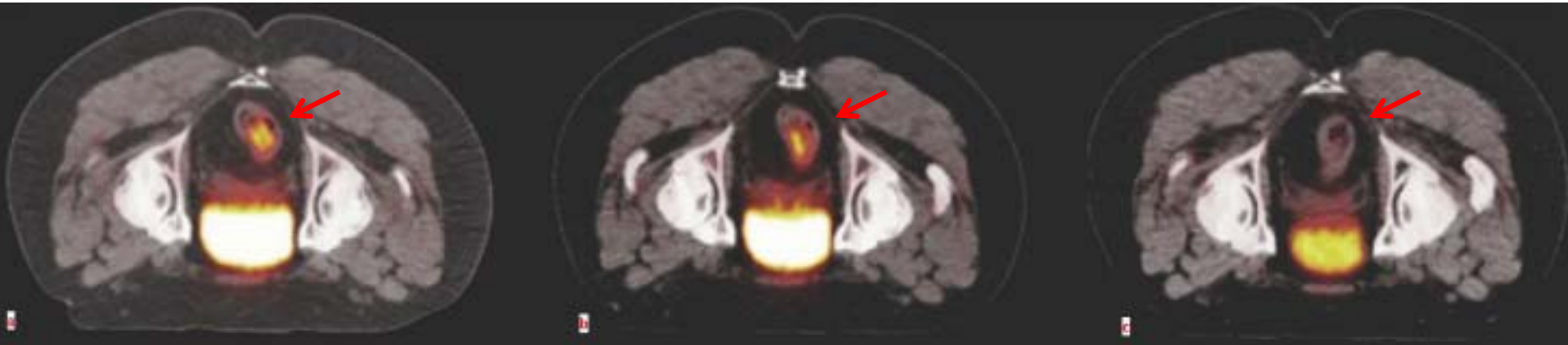
Sequential PET/CT with [18F]-FDG Predicts Pathological Tumor Response to Preoperative Short Course Radiotherapy with Delayed Surgery in Patients with Locally Advanced Rectal Cancer Using Logistic Regression Analysis



$$\frac{1}{1 + e^{-X}}$$

$$X = -13.4911 - .3198 * (TLG_{Early}) + 37.8934 * (OverallReduction_{TLG}).$$

$$OverallReduction_{TLG} = \frac{TLG_{Baseline} - TLG_{Delayed}}{TLG_{Baseline}}$$



	TLG Basal	TLG Early	TLG Delayed	Score Resp	Probability Responder	Score Compl	Probability Complete Responder
Pt. A	90	66,7	32	-2,142526	0,10503167	-8,3652574	0,00023276
Pt. B	76,21	5,50	2,00	2,8440459	0,94501009	1,74280812	0,8510434





# Rectal cancer : tumours position = identification of anterior peritoneal reflection

- ▶ **identification of the APR** is useful for choosing the optimal treatment for each patient in relation to the risk of **undertreatment** or **overtreatment**, only tumours **with an extraperitoneal** extension, need to be treated by neoadjuvant chemoradiation
- ▶ **important treatment implications** : extraperitoneal and intraperitoneal cancers are characterized by peculiar routes of lymphatic spread. Lateral drainage of the extraperitoneal portion of the tumor to the internal iliac nodes, through the middle or inferior rectal lymphatics, is considered the primary cause of the high rate of pelvic recurrence
- ▶ increasing clinical evidence show that **chemoradiation**, is not useful for intraperitoneal cancers.
- ▶ rectal cancers **above the PR** are often surrounded by loops of the small bowel, with an increased risk of **morbidity** from **radiation** enteritis.
- ▶ **risk of undertreatment** and local failure, if a tumor with a prominent intraperitoneal location, but with inferior edge below the PR is treated only surgically.
  - ▶ **rigid rectoscopy**, measure the distance between the inferior edge of the tumor and the anal verge, but the optimal cut-off distance to discriminate extra- vs intraperitoneal tumors **remains to be defined**. Many constitutional factors may influence the distance of the peritoneal reflection from the anal verge, **including age, sex, height, weight and parity**

Folkesson J, Birgisson H, Pahlman L et al. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol* 2005; 23: 5644–50

Nijkamp J, Kusters M, Beets-Tan RG et al. Three-dimensional analysis of recurrence patterns in rectal cancer: the cranial border in hypofractionated preoperative radiotherapy can be lowered. *Int J Radiat Oncol Biol Phys* 2011;80: 103–10



## **Radiotherapy dose lead to a substantial prolongation of survival in patients with locally advanced rectosigmoid junction cancer: a large population based study**

**Xu Guan<sup>1,\*</sup>, Zheng Jiang<sup>2,\*</sup>, Tianyi Ma<sup>1</sup>, Zheng Liu<sup>2</sup>, Hanqing Hu<sup>1</sup>, Zhixun Zhao<sup>1</sup>, Dawei Song<sup>1</sup>, Yinggang Chen<sup>1</sup>, Guiyu Wang<sup>1</sup>, Xishan Wang<sup>1,2</sup>**

**Received:** December 19, 2015

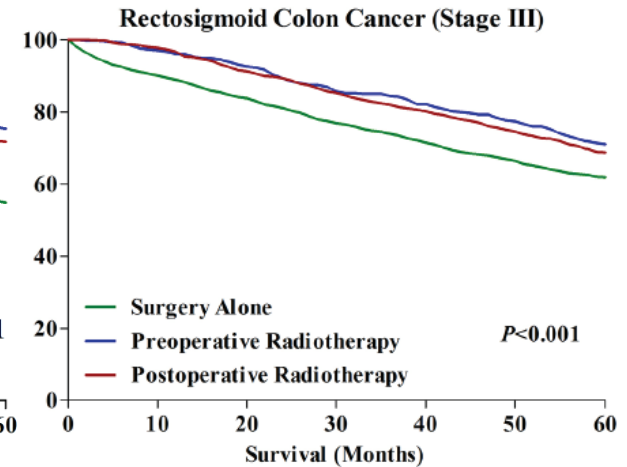
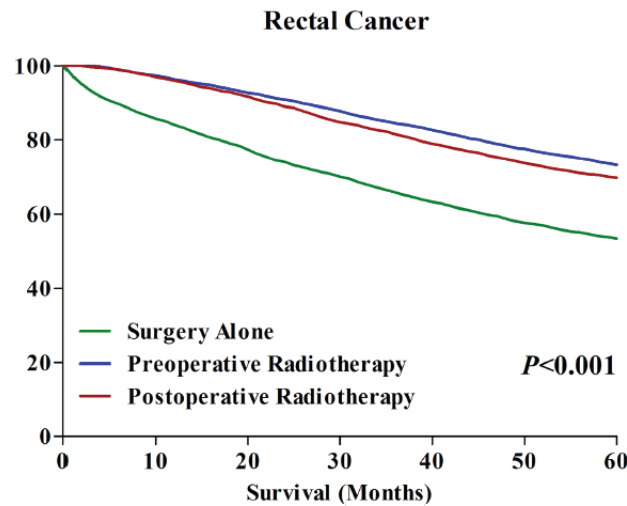
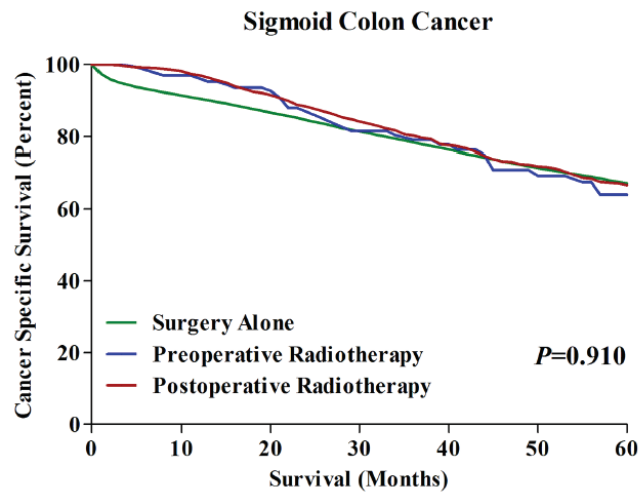
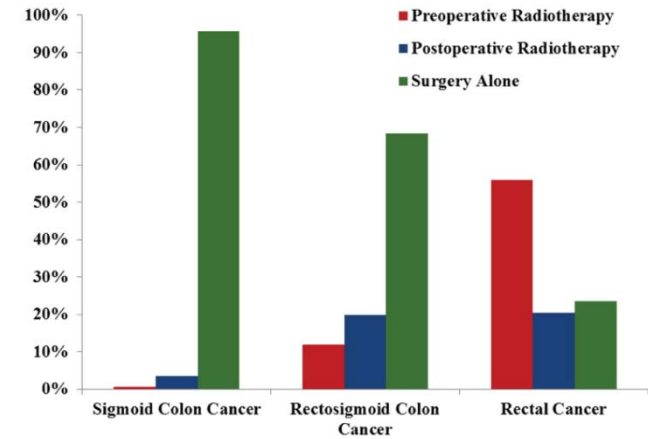
**Accepted:** March 28, 2016

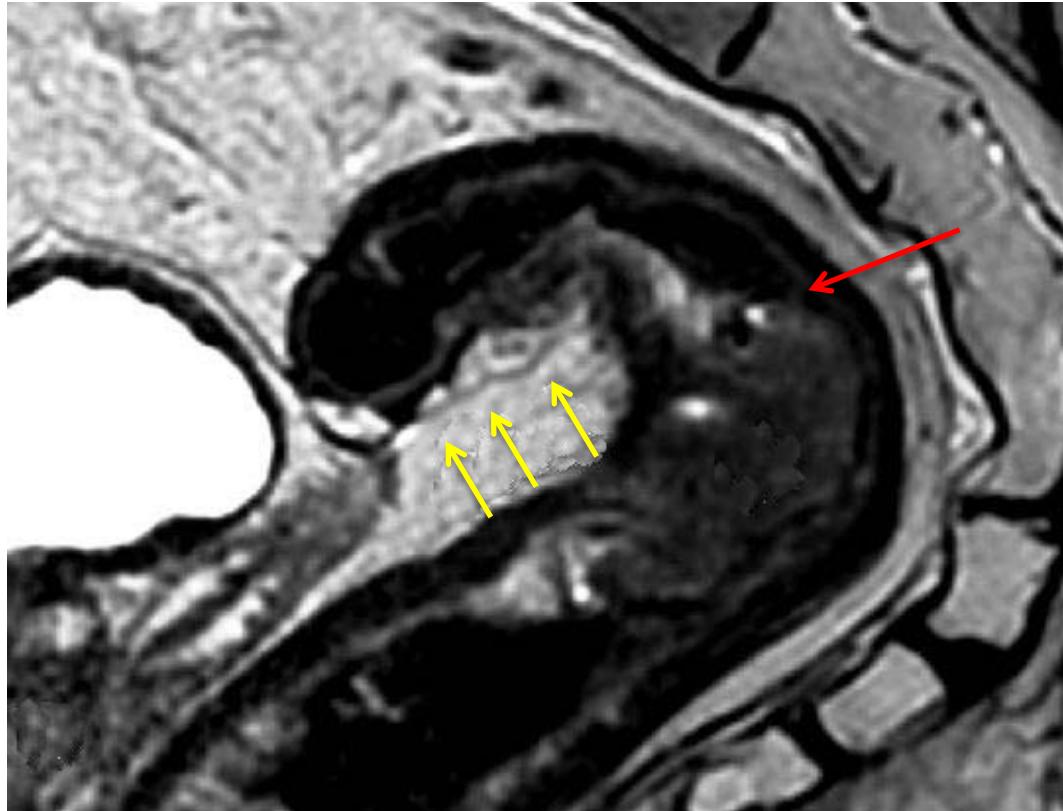
**Published:** April 7, 2016

“.....locally advanced rectosigmoid junction cancer patients could obtain potential long-term survival benefits from radiotherapy”

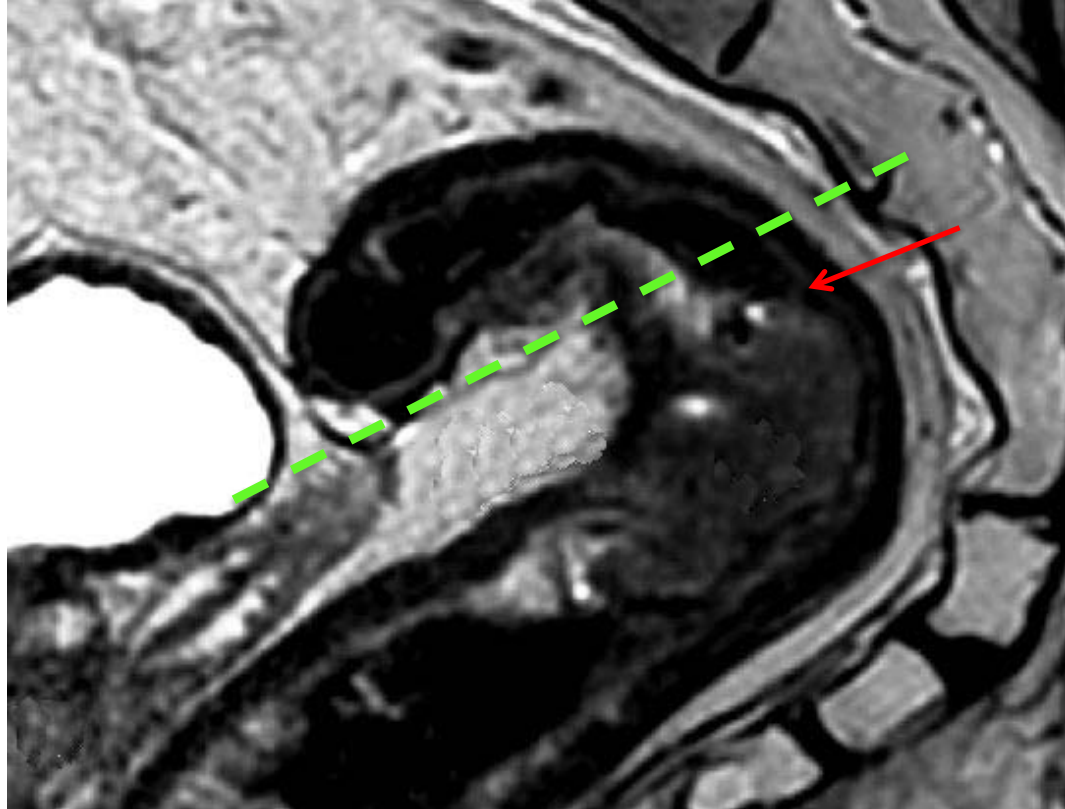


Characteristics	Sigmoid colon cancer	Rectosigmoid colon cancer	Rectal cancer	All patients
	N=24266 (%)	N=10074 (%)	N=19592 (%)	N=53932 (%)
<b>Tumor size (cm)</b>				
< 2	1135 (4.7)	415 (4.1)	1335 (6.8)	2885 (5.4)
2-5	12565 (51.8)	4702 (46.7)	8318 (42.5)	25585 (47.4)
≥ 5	9175 (37.8)	4228 (42.0)	6666 (34.0)	20069 (37.2)
Unknown	1391 (5.7)	729 (7.2)	3273 (16.7)	5393 (10.0)
<b>Therapy</b>				
Preoperative radiotherapy	136 (0.6)	1194 (11.8)	10977 (56.0)	12307 (22.8)
Postoperative radiotherapy	865 (3.5)	1992 (19.8)	4026 (20.6)	6883 (12.8)
Surgery alone	23265 (95.9)	6888 (68.4)	4589 (23.4)	34742 (64.4)





— Rectal Cancer RT



— Rectal Cancer RT



## Pathological response = TRG 1

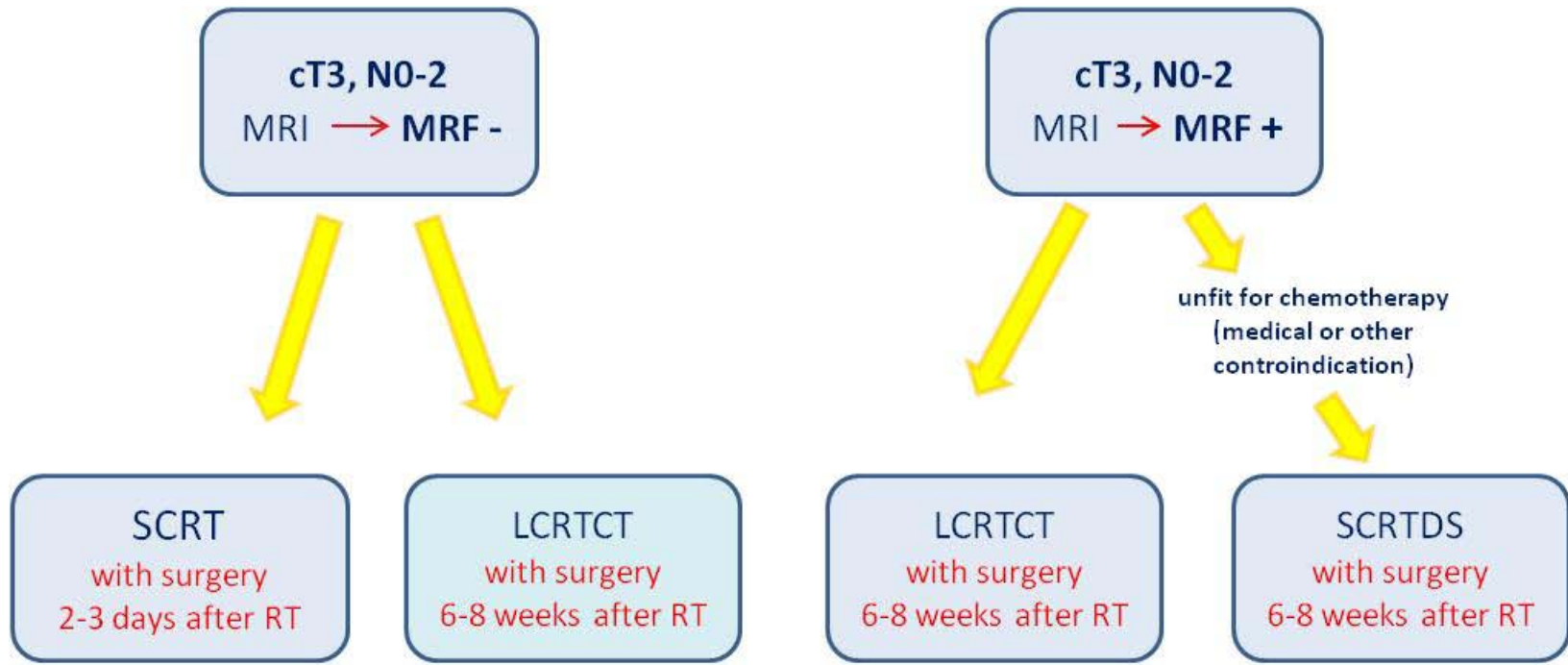
Pre-treatment



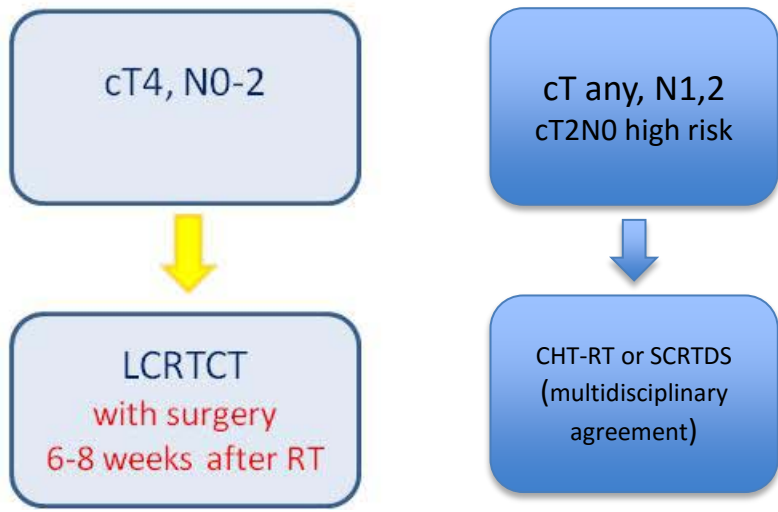
8 weeks after -treatment



Patient 41 y, cT3N2b (IIIC stage),  
2 Gy x 25 Gy = RT-CHT (Cap)



SCRT= Short Course RT=5x5Gy  
LCRT= long Course RT-CHT= 25x 1,8-2,0 Gy  
SCRTDS= Short Course RT+delayed surgery



**INDIVIDUALIZED**

Tailoring Treatments  
by  
Prognostic/Predictive  
Features

DISEASE CONTROL  
SIDE-EFFECT CONTROL

**ADAPTIVE**

Tailoring Treatments  
by continuous  
monitoring

**MODELLING**

Prediction by  
Multidimensional  
Large Database