



XXXII CONGRESSO NAZIONALE AIRO
XXXIII CONGRESSO NAZIONALE AIRB
XII CONGRESSO NAZIONALE AIRO GIOVANI

AIRO2022

Radioterapia di precisione per un'oncologia innovativa e sostenibile

BOLOGNA, 25-27 NOVEMBRE
PALAZZO DEI CONGRESSI

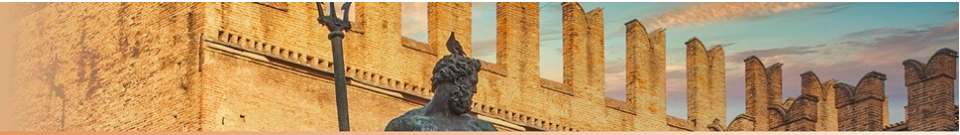
VENERDI, 26 NOVEMBRE 2022

“SESSIONE 7 - LA PERSONALIZZAZIONE DEL TRATTAMENTO NEL TUMORE DEL RETTO LOCALMENTE AVANZATO”.

12.15 a.m.
12.30 a.m.

COME MIGLIORARE GLI OUTCOMES NEGLI STADI SFAVOREVOLI

E. Meldolesi

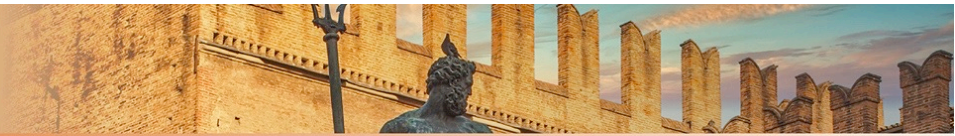


DICHIARAZIONE

Relatore: ELISA MELDOLESI

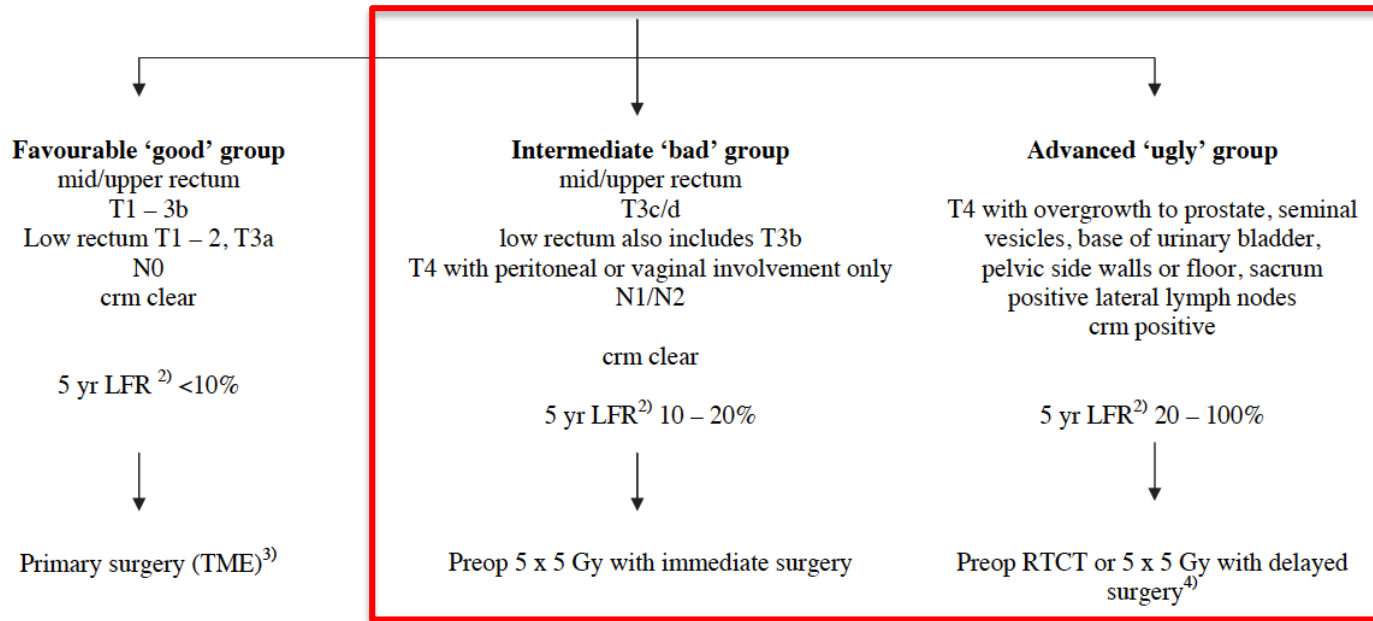
Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro



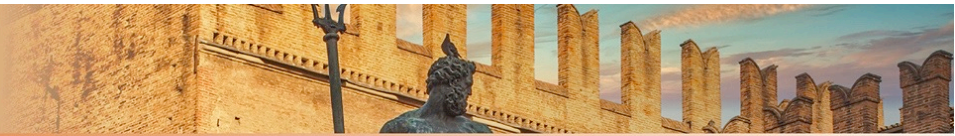
TUMORE DEL RETTO LOCALMENTE AVANZATO: STADI SFAVOREVOLI

The 'good', the 'bad', and the 'ugly' rectal cancers 7



- cT4
- MRF+
- MVI +
- N extramesorettali
- Mucinosi

Lennart Blomqvist et al. Acta Oncol. 2008;47(1):5-8

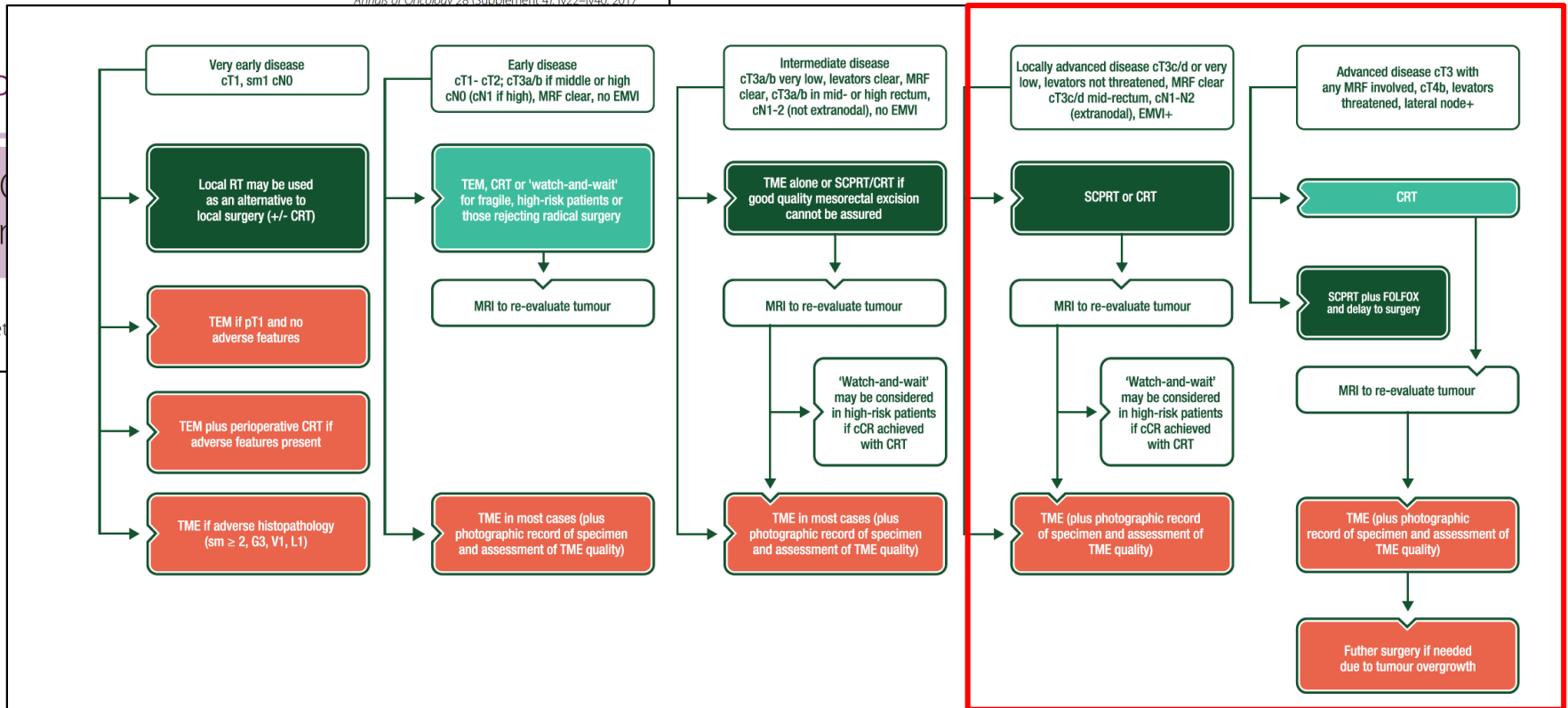


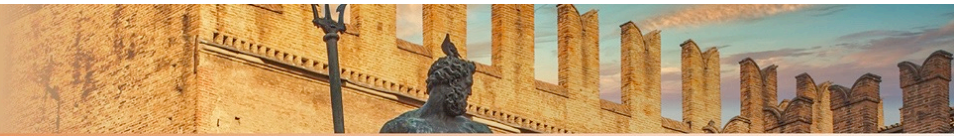
CLINICAL PRACTICE GUIDELINES

Rectal cancer: ESMO for diagnosis, treatment

R. Glynne-Jones¹, L. Wyrwicz², E. Tiret³
 the ESMO Guidelines Committee*

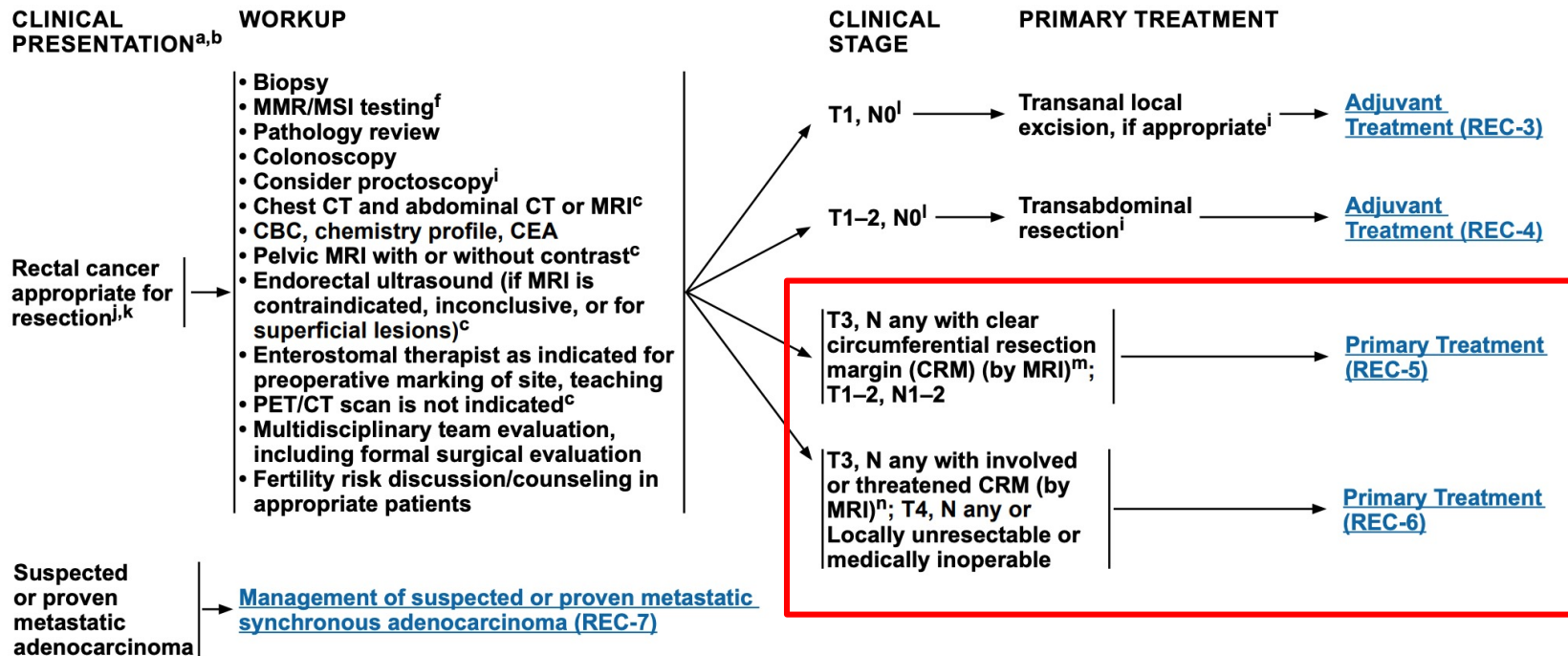
Annals of Oncology 28 (Supplement 4): iv22-iv40, 2017





NCCN Guidelines Version 1.2022 Rectal Cancer

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)





European Journal of Cancer (2014) 50, 1.e1-1.e34



Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

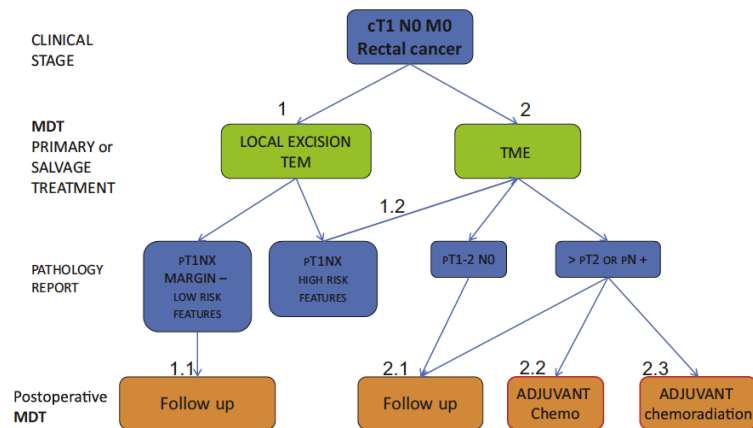


Position Paper

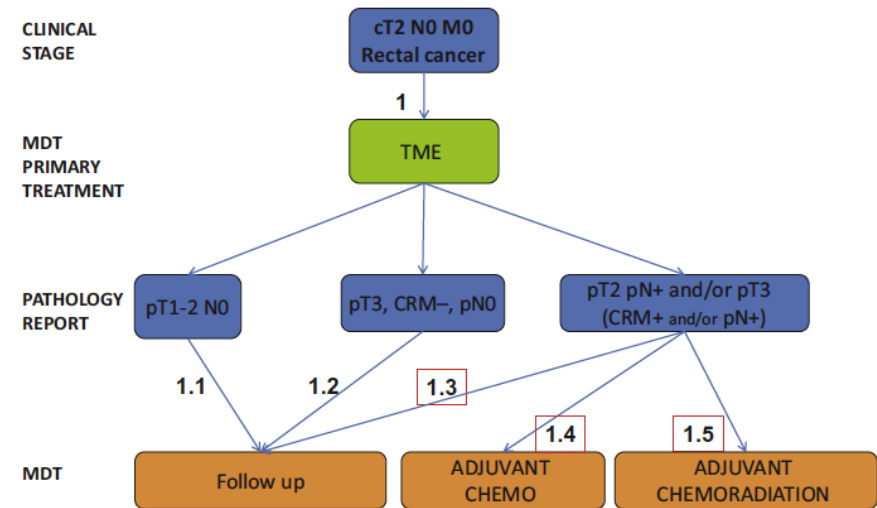
EURECCA colorectal: Multidisciplinary management:
 European consensus conference colon & rectum ☆

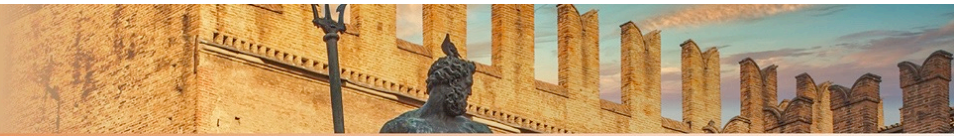


TREATMENT STRATEGY: cT1 N0 M0

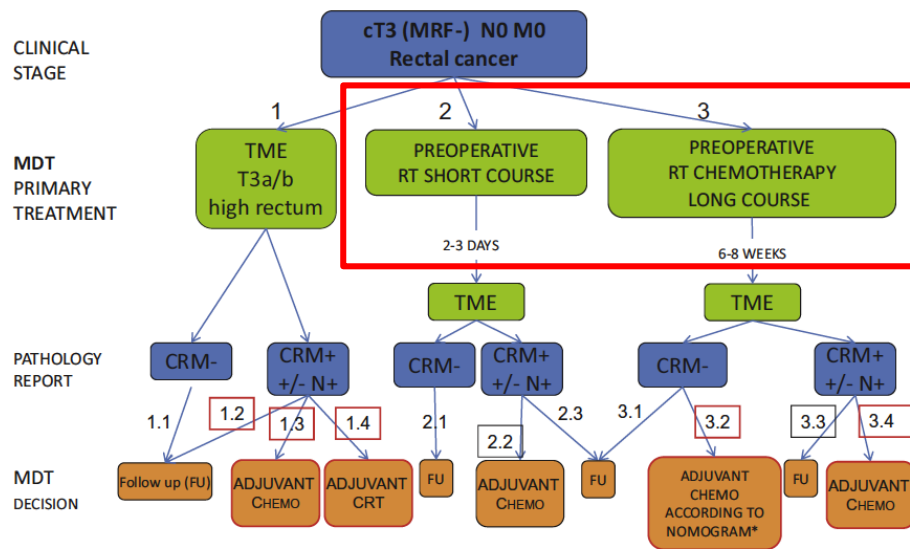


TREATMENT STRATEGY: cT2 N0 M0





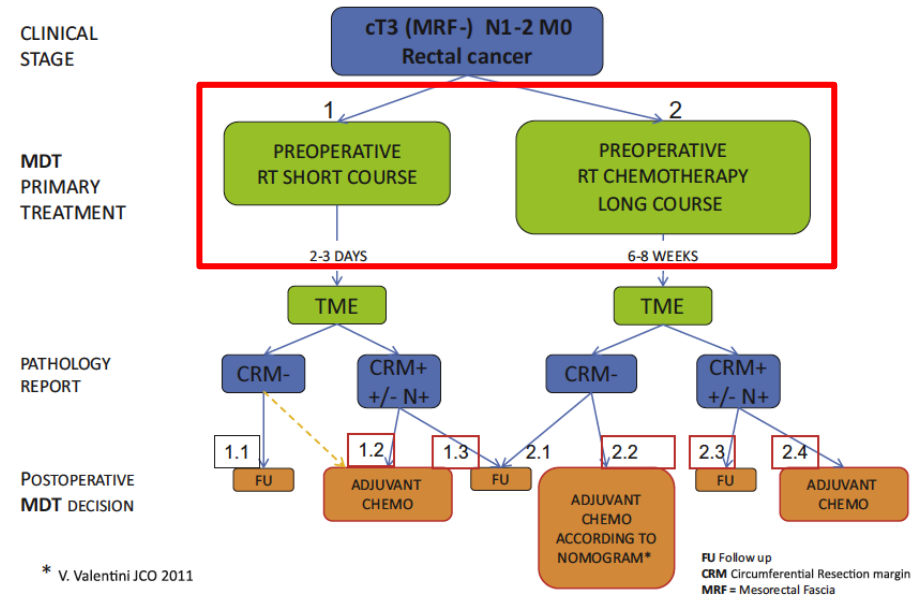
TREATMENT MODALITIES: cT3 (MRF -) NO M0



* V. Valentini JCO 2011

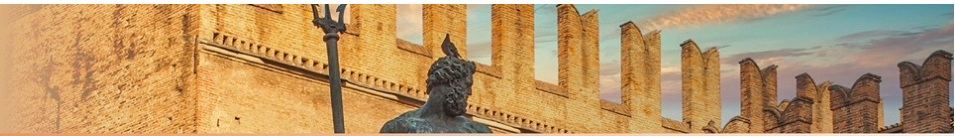
MRF = Mesorectal Fascia FU follow up CRT Chemoradiation

TREATMENT MODALITIES: cT3 (MRF -) N1-2 M0

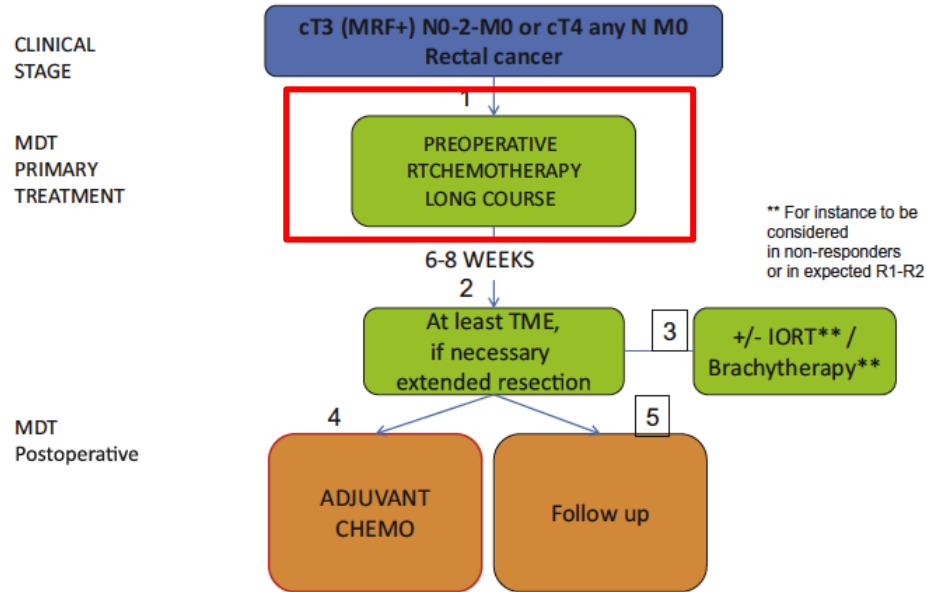


* V. Valentini JCO 2011

FU Follow up
 CRM Circumferential Resection margin
 MRF = Mesorectal Fascia



TREATMENT MODALITIES: cT3 (MRF+) N0-2-M0 or cT4 any N M0





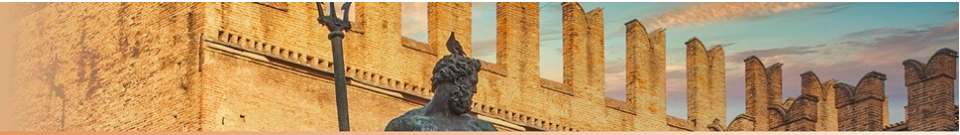
Radiation Therapy for Rectal Cancer: An ASTRO Clinical Practice Guideline

Table 3. Recommendations for neoadjuvant RT indications

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with rectal cancer, pelvic MRI with a rectal cancer protocol is recommended for preoperative clinical T and N staging.	Strong	Moderate 4-7
2. For patients with stage II-III rectal cancer, neoadjuvant RT is recommended.	Strong	High 8-15
3. For patients with stage II rectal cancer at lower risk of locoregional recurrence, omission of neoadjuvant RT is conditionally recommended after discussion with a multidisciplinary team. <u>Implementation remark:</u> Lower risk is defined as a cT3a/b N0 tumor that is >10 cm from the anal verge* and with mrCRM ≥ 2 mm and no mrEMVI.	Conditional	Moderate 6,7,12,16
4. For patients with cT1-2N0 rectal cancer who may need an APR, neoadjuvant chemoradiation is conditionally recommended to improve the chance of sphincter preservation.	Conditional	Expert Opinion 17-19
5. For patients with rectal cancer where radiation is indicated, RT should be performed preoperatively rather than postoperatively.	Strong	High 9-11,17-19

Abbreviations: APR = abdominoperineal resection; KQ = key question; mrCRM = MRI-determined circumferential resection margin; mrEMVI = MRI-determined extramural vascular invasion; MRI = magnetic resonance imaging; RT = radiation therapy.

* cT3a/b = 1 to 5 mm extramural tumor spread; tumor height should be surgeon defined.



COME MIGLIORARE GLI OUTCOMES NEGLI STADI SFAVOREVOLI?

- 1) Intensificazione della dose di Radioterapia
- 2) Intensificazione della terapia sistemica
- 3) Immunoterapia





Contents lists available at [ScienceDirect](#)

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Systematic review

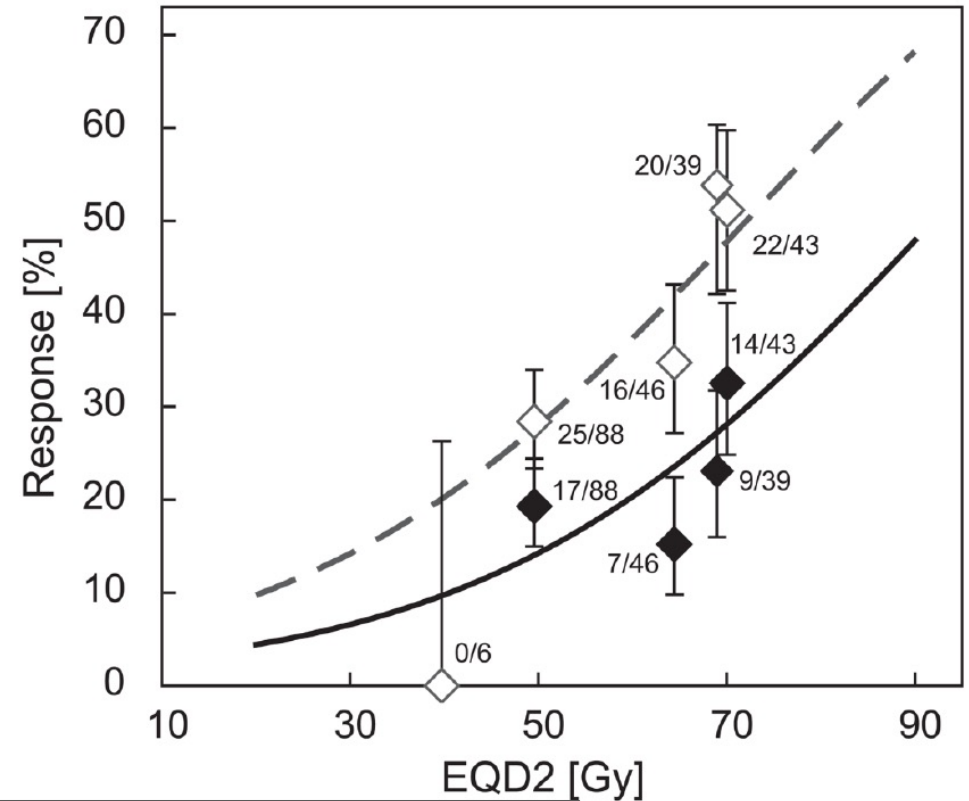
Impact of radiotherapy boost on pathological complete response in patients with locally advanced rectal cancer: A systematic review and meta-analysis

 CrossMark

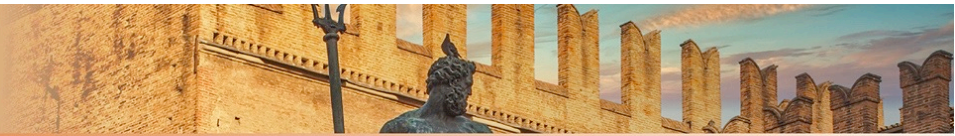
Johannes Peter Maarten Burbach^{a,*}, Annemarie Maria den Harder^{b,1}, Martijn Intven^a, Marco van Vulpen^a, Helena Marieke Verkooijen^c, Onne Reerink^a

Radiat Oncol; 2014 Burbach et al.

«Dose escalation above 60 Gy for LARC results in high pCR-rate (0-44%)»



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



Preoperative intensification



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)
Radiotherapy and Oncology
 journal homepage: www.thegreenjournal.com

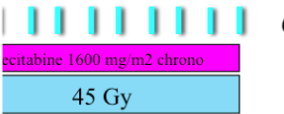


The INTERACT Trial: Long-term results of a randomised trial on preoperative capecitabine-based radiochemotherapy intensified by concomitant boost or oxaliplatin, for cT2 (distal)-cT3 rectal cancer

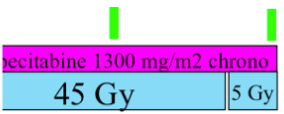


534 resectable
T3 N0-1
Low T2 N1

R

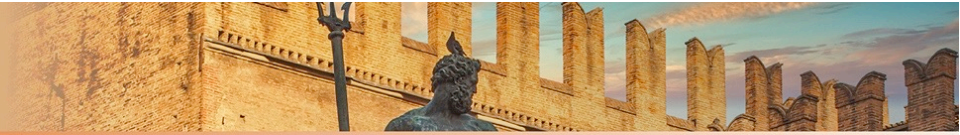


55 Gy + cape



50 Gy + cape-oxa

Valentini V et al. Radiother Oncol 2019



INTERACT ITALIAN TRIAL

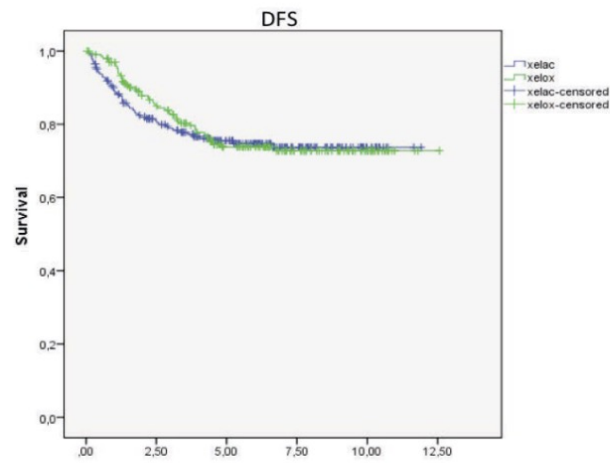
Tumor Response

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

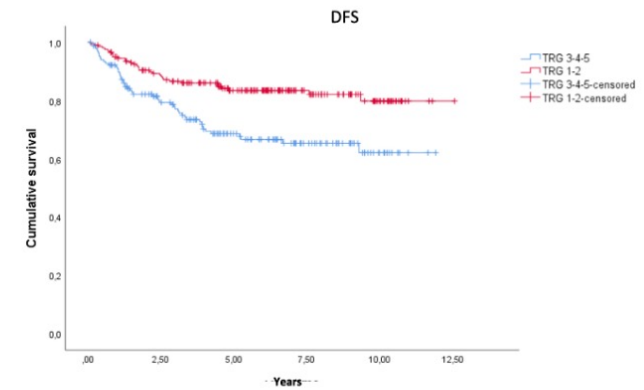
Acute toxicity

INTERACT ITALIAN TRIAL

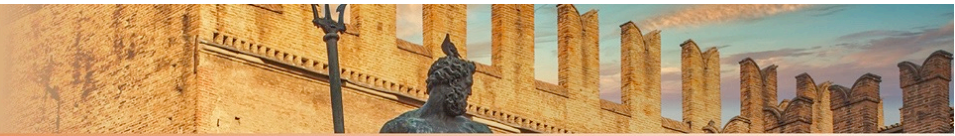
All patients



According to TRG



Valentini V et al. Radiother Oncol 2019



[Cancers \(Base\)](#). 2022 Apr; 14(7): 1643.

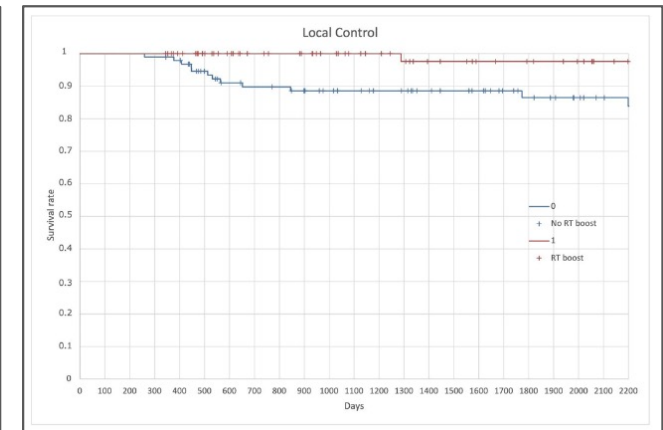
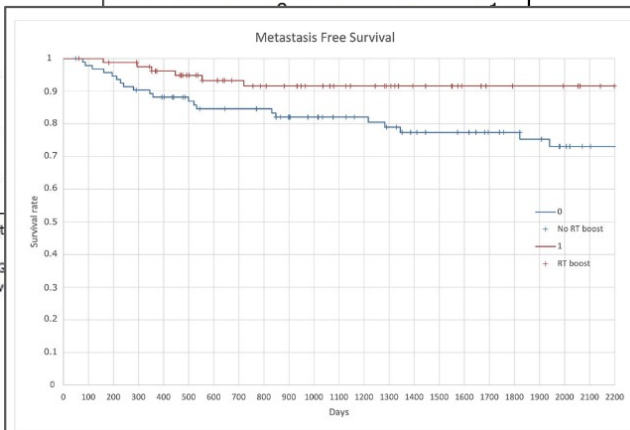
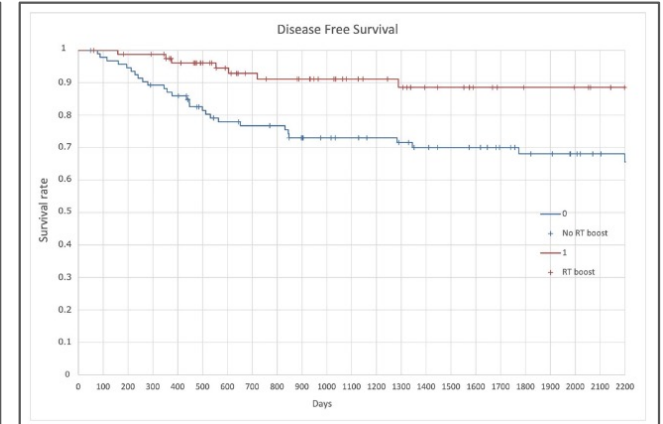
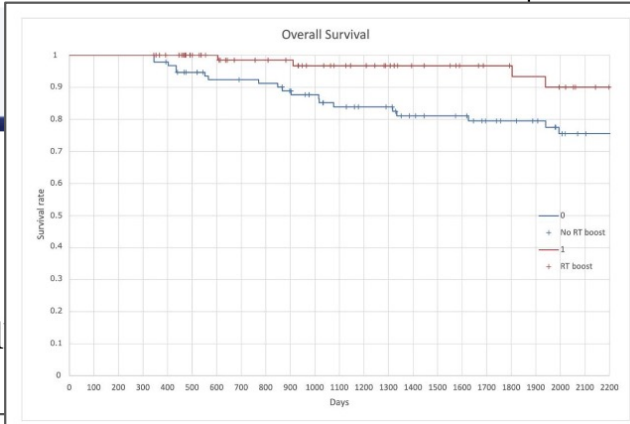
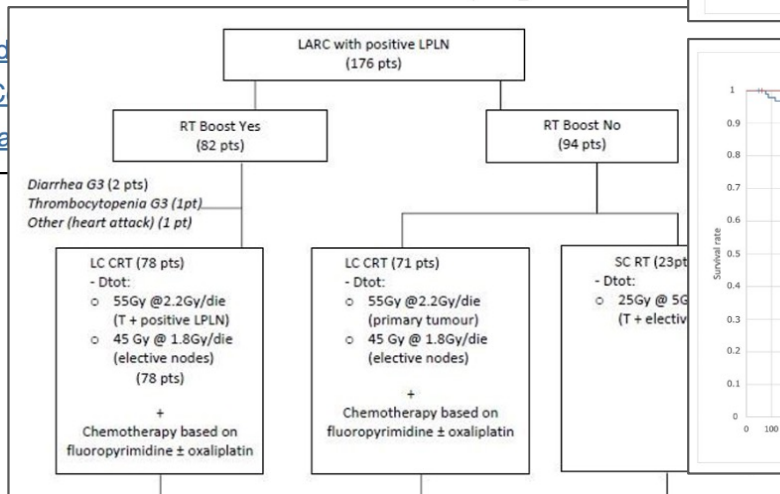
Published online 2022 Mar 24. doi: [10.3390/cancers14071643](https://doi.org/10.3390/cancers14071643)

The Role of Simultaneous Integrated Boost in Local Patients with Positive Lateral Pelvic Lymph Nodes

[Elisa Meldani](#)

[Claudio Cazzaniga](#)

[Valeria Mariani](#)





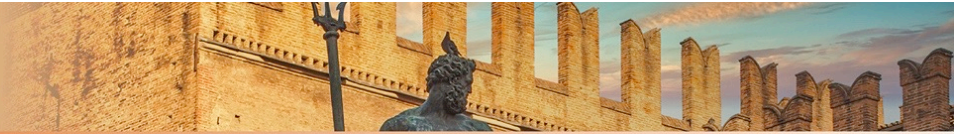
Radiomics

“High-throughput extraction of large amounts of image features from radiographic images [...] with the intent of creating mineable databases”

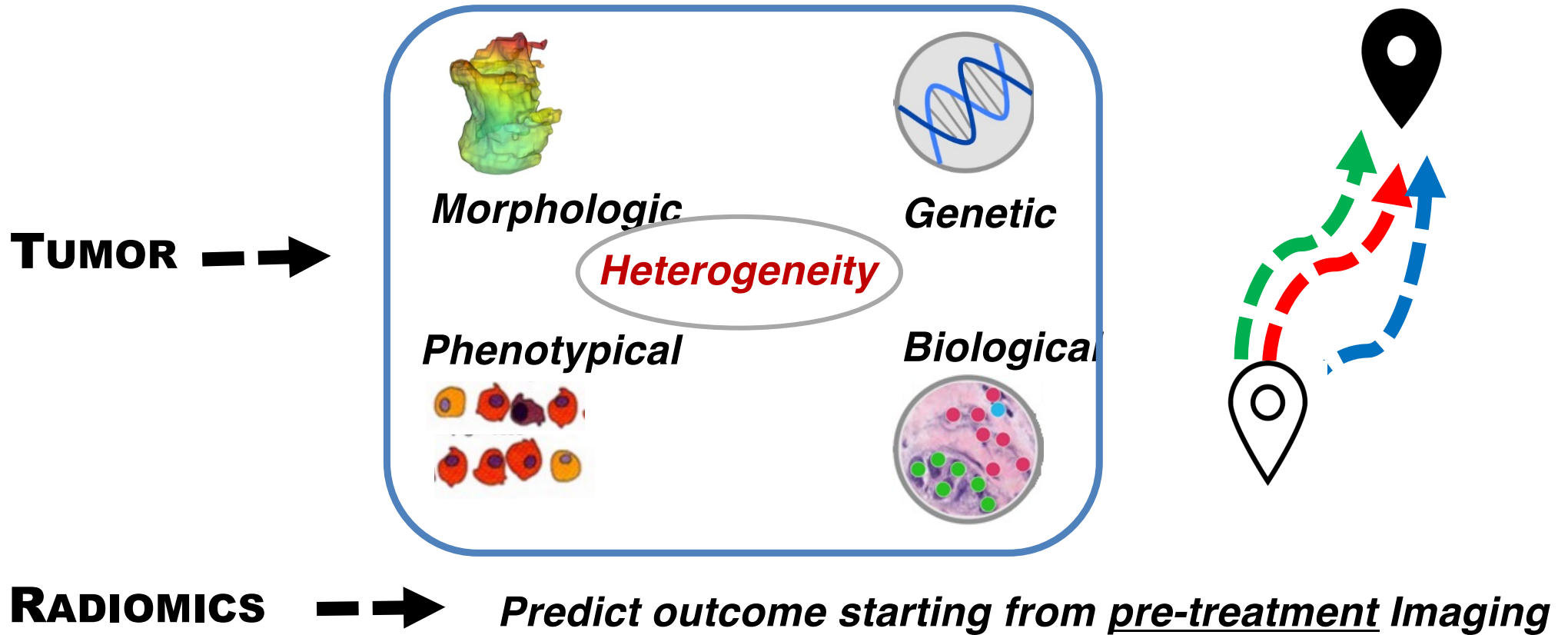
P. Lambin et al. Eur J Cancer 2012 Mar;48(4):441-6.

“The goal of Radiomics is to convert images into mineable data, with high fidelity and high throughput”

V. Kumar et al. Magnetic Resonance Imaging 30 (2012) 1234-1248.



Lambin *et al.* 2012 Eur J Cancer. 48:441-6.





The question of time Delta Radiomics

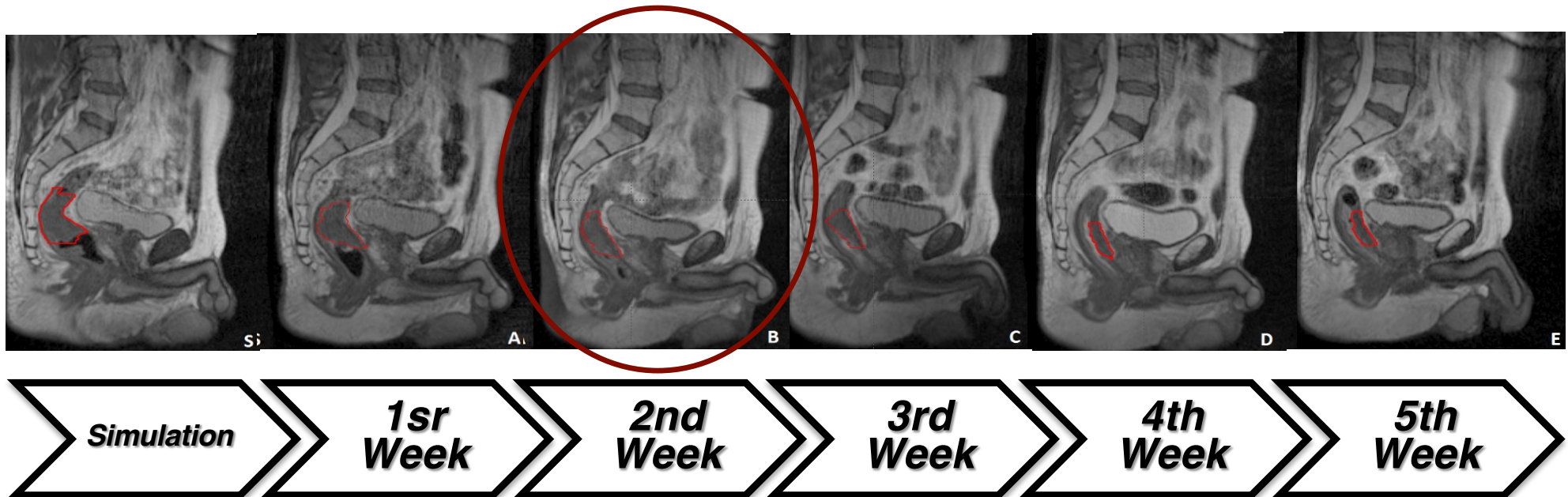


Study the temporal variation of the radiomics features allows to model the response of each patient



Boldrini et al. Rad Med, 2018

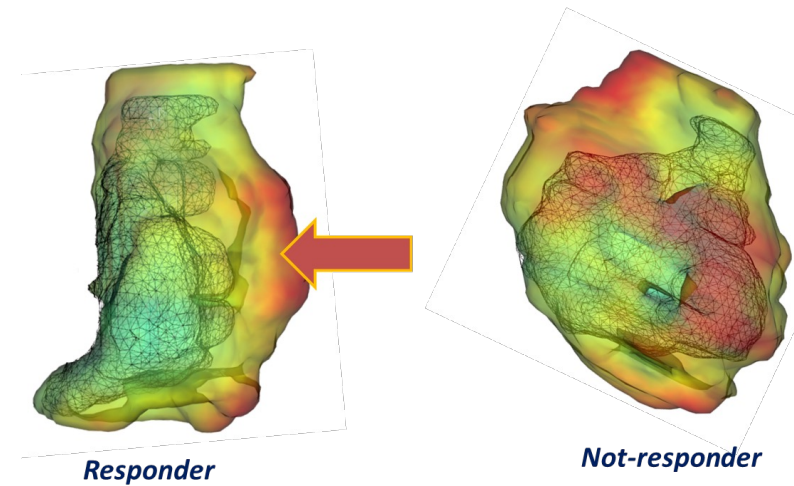
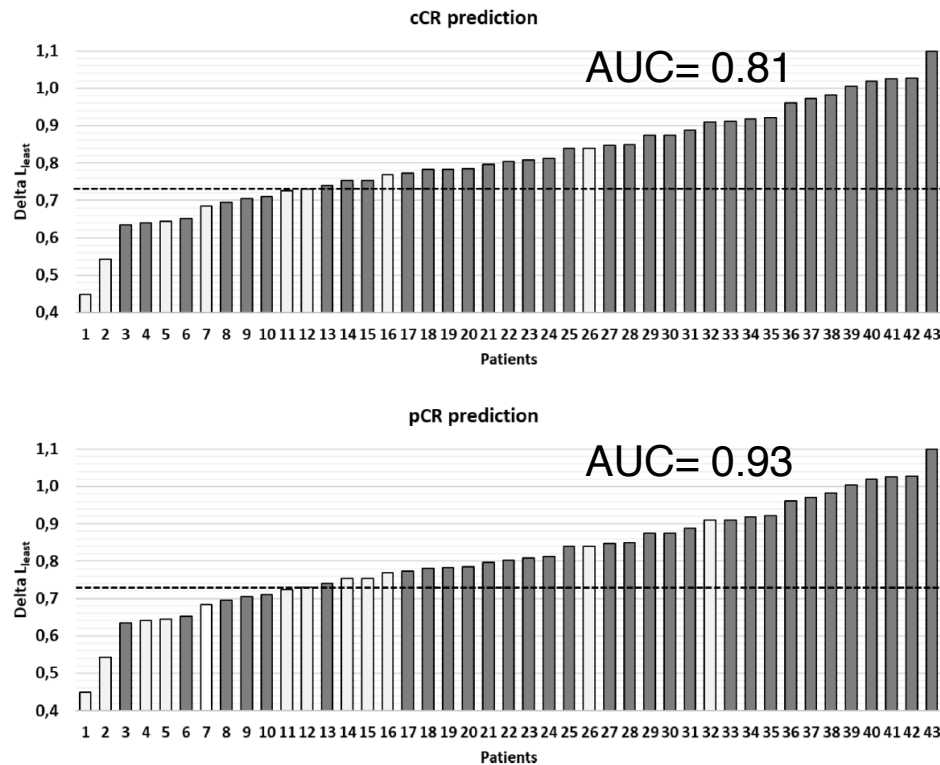
- 6 MRI per patient , 0.35 T MR
- 175 sec TRUFI acquisition (*TRUe Fast Imaging with steady state Precession*) T2*/T1
- Resolution = 1.5x1.5x1.5 mm³ GTV contoured by 2 Radiation Oncologists
- Clinical complete response prediction cCR,



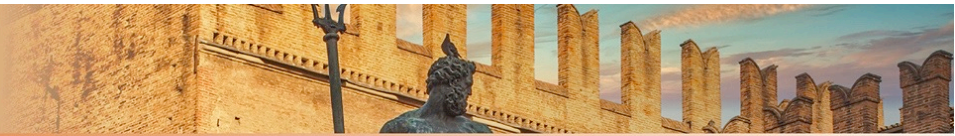


Cusumano D et al. Phys Med, 2021

Results of first study confirmed on an external validation cohort of 43 patients



Best ΔL_{Least} cut-off values = 0.73



Early Regression Index



Contents lists available at [ScienceDirect](#)

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Original article

A TCP-based
neo-adjuvan

Claudio Fiorino
Giovanni M. Ca
Monica Ronzon
Nadia G. Di Mu

^a Medical Physics; ^b Radiot

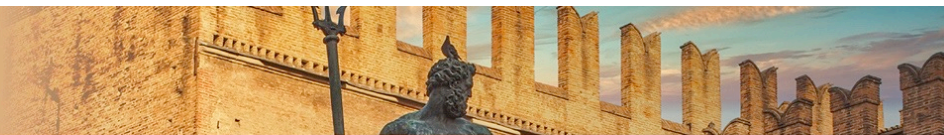
External Validation of Early Regression Index (ERI TCP) as Predictor of Pathologic Complete Response in Rectal Cancer Using Magnetic Resonance-Guided Radiation Therapy

Davide Cusumano ¹, Luca Boldrini ², Poonam Yadav ³, Gao Yu ⁴, Bindu Musurunu ³,
 Giuditta Chiloiro ¹, Antonio Piras ¹, Jacopo Lenkowicz ¹, Lorenzo Placidi ¹, Sara Broggi ⁵,
 Angela Romano ¹, Martina Mori ¹, Brunella Barbaro ¹, Luigi Azario ¹,
 Maria Antonietta Gambacorta ¹, Marco De Spirito ¹, Michael F Bassetti ³, Yingli Yang ⁴,
 Claudio Fiorino ⁵, Vincenzo Valentini ¹

**From
cCR**



**To
pCR**



Is this index applicable to low tesla MRgRT images?

$$ERI = -\ln \left[1 - \left(\frac{V_{mid}}{V_{pre}} \right)^{V_{pre}} \right]$$

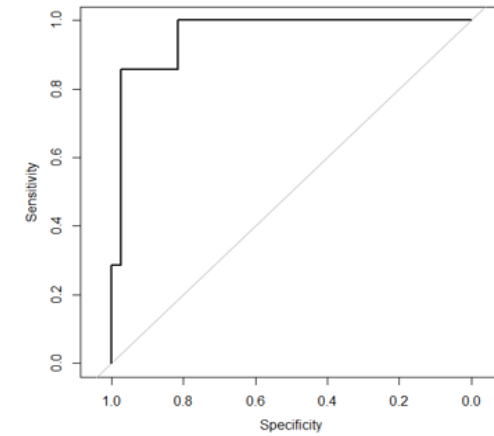
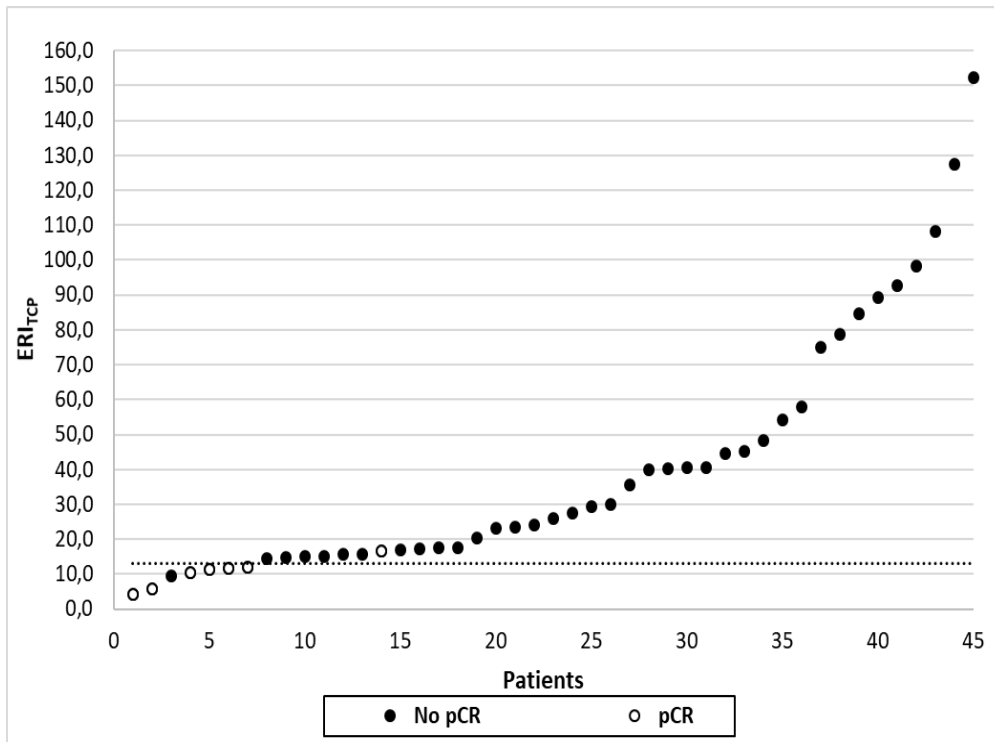
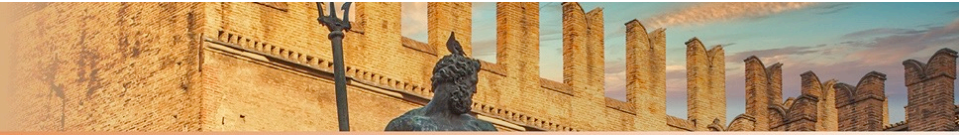
V_{pre} GTV volume during simulation

V_{mid} GTV volume at the **9th** fraction of RT

ERI (*Early tumor Regression Index*)

values < 13.1 predicts pCR with an AUC of ROC curve = 0.81

High resolution T2-weighted MRI images – obtained with 1.5 Tesla scanners



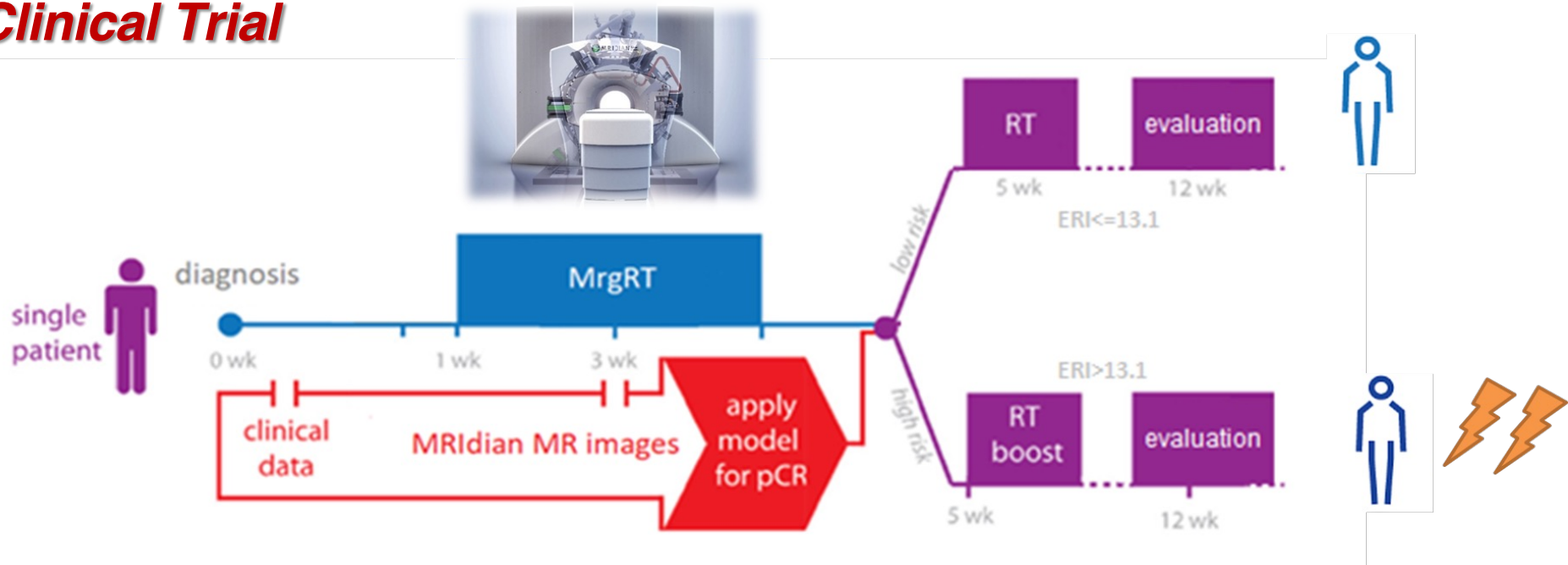
AUC = 0.95
Sensitivity = 0.86
Specificity = 0.97
Accuracy = 0.95

Cusumano et al IJROBP 2020

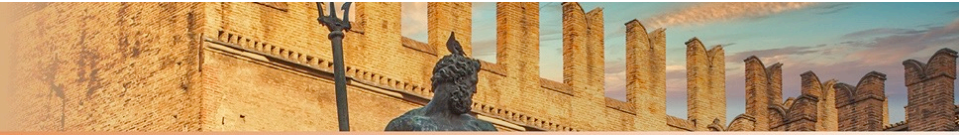


Thunder 2 - Phase 2 Clinical Trial

Chiloiro G, BMC 2022

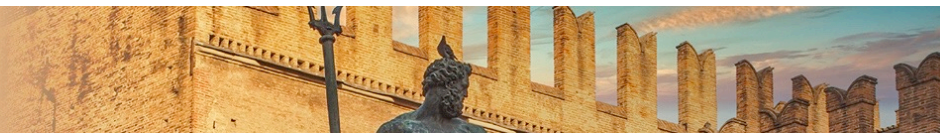


CT with 5-FU or oral capecitabine (5-FU 225 mg/mq/day in c.i.; Capecitabine 1650 mg/m2/day chronomodulated)



COME MIGLIORARE GLI OUTCOMES NEGLI STADI SFAVOREVOLI?

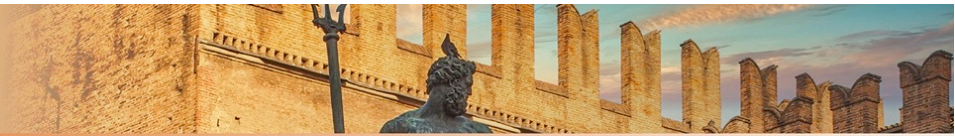
- 1) Intensificazione della dose di Radioterapia
- 2) Intensificazione della terapia sistemica
- 3) Immunoterapia



NAME	SCHEME	N°
ACCORD 12/0405 PRODIGE 02	CAP45 VS CAPOX50	598 (293+291)
STAR-01	5-FU VS 5-FU + OXA	747 (379+378)
PETACC-6	CAPE VS CAPOX	1094 (547 + 547)
NSABP R-04 (NCT00058474)	5-FU/CAPE VS 5-FU/CAPE + OXA	1608 (940+655)

Randomized phase III trials:

- Investigated the addiction of oxaliplatin to NCRT or perioperative chemo(radio)therapy
- They did NOT demonstrate benefit of additional oxaliplatin



ORIGINAL ARTICLE

Impact of age on the impact of preoperative chemotherapy on overall survival of the CAO/ARO/AR

R.-D. Hofheinz^{1*}, D. Arnold²,
W. Hohenberger⁷, M. Ghadimi
on behalf of the German Recto

NAME

CAO/ARO/AIO-04

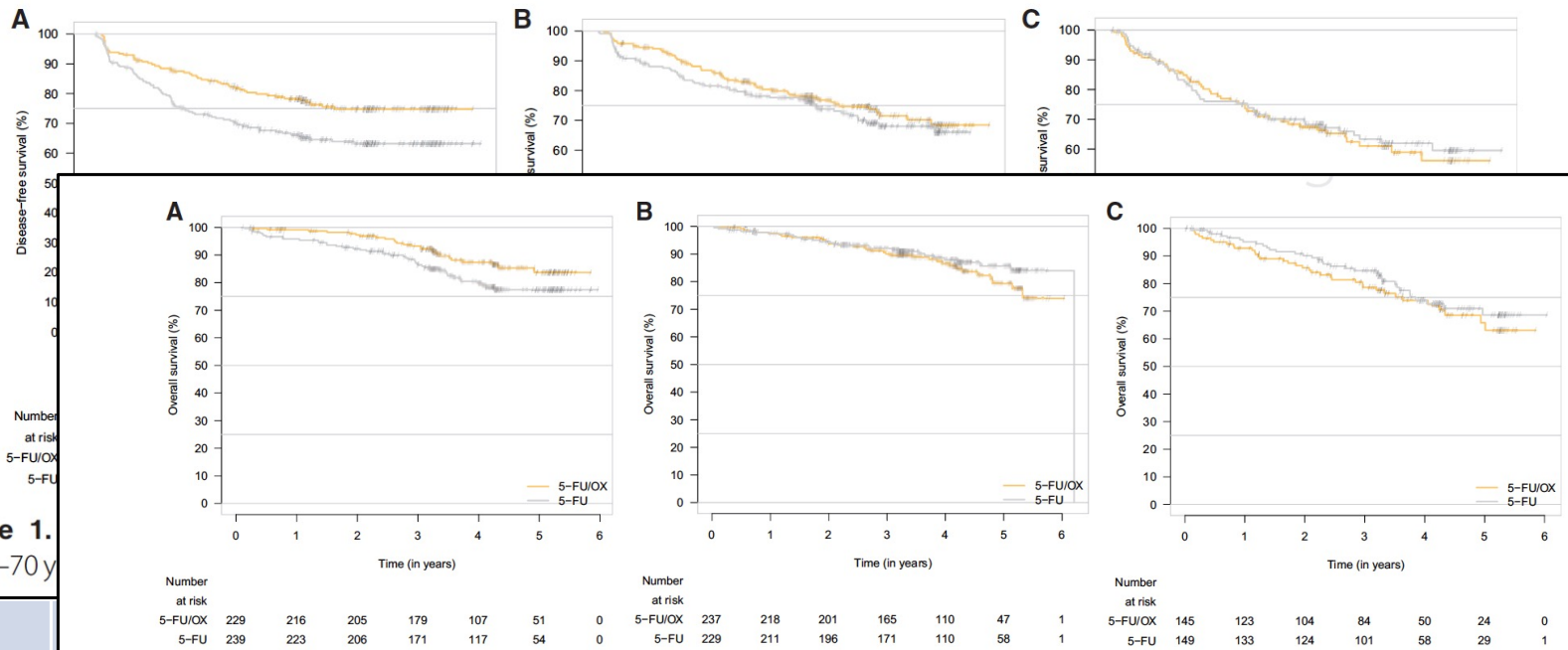
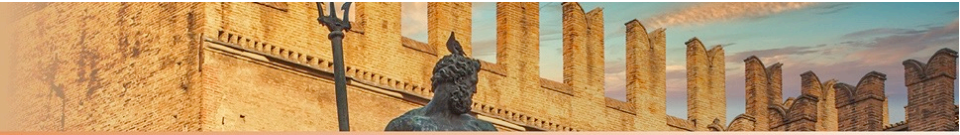


Figure 2. Kaplan-Meier analysis of overall survival according to age groups and treatment arms. Patients aged (A) <60 years, (B) 60-70 years, and (C) >70 years.



Total Neoadjuvant Therapy (TNT): adding more systemic therapy before or after CRT

Study, year	RT dose	Study arm	N	pCR	Toxicity	DFS	OS
Fernandez-Martos et al. [31], 2015	-	CRT then surgery and adjuvant CAPOX vs. induction CAPOX then CRT then surgery	108	13% vs. 14%	ND	5-yr: 64% vs. 62%; p = 0.85	5-yr: 78% vs. 75%; p = 0.64
Fernandez-Martos et al. [32], 2019	50.4 Gy	mFOLFOX6 + aflibercept vs. mFOLFOX6 alone	180	22.6% vs. 13.8% (p = 0.15)	Hypertension: 24.3% vs. 1.5% Postoperative complications: 15.5% vs. 12.9%	ND	ND
Fokas et al. [28], 2019	50.4 Gy in 28 fx	Induction FOLFOX vs. consolidation FOLFOX	311	17% vs. 25%	37% vs. 27%	ND	ND
Masi et al. [33], 2019	50.4 Gy	Single arm: induction FOLFOXIRI + BEV	49	0.364	Neutropenia: 41.6% Diarrhea: 12.5%	2-yr: 80.45%	ND
OPRA trial [35], 2020	54 Gy	Induction vs. consolidation FOLFOX or CAPOX	324	ND	ND	3-yr DFS: 78% vs. 77%; p = 0.9 3-yr MFS: 81% vs. 83%; p = 0.86	ND
Conroy et al. [36], 2020	50 Gy	CRT alone vs. induction mFOLFIRINOX then CRT	461	11.7% vs. 27.5% (p < 0.001)	ND	3-yr DFS: 68.5% vs. 75.7% 3-yr MFS: 71.7% vs. 78.8%	3-yr OS: 87.7% vs. 90.8%



COME MIGLIORARE GLI OUTCOMES NEGLI STADI SFAVOREVOLI?

- 1) Intensificazione della dose di Radioterapia
- 2) Intensificazione della terapia sistemica
- 3) Immunoterapia

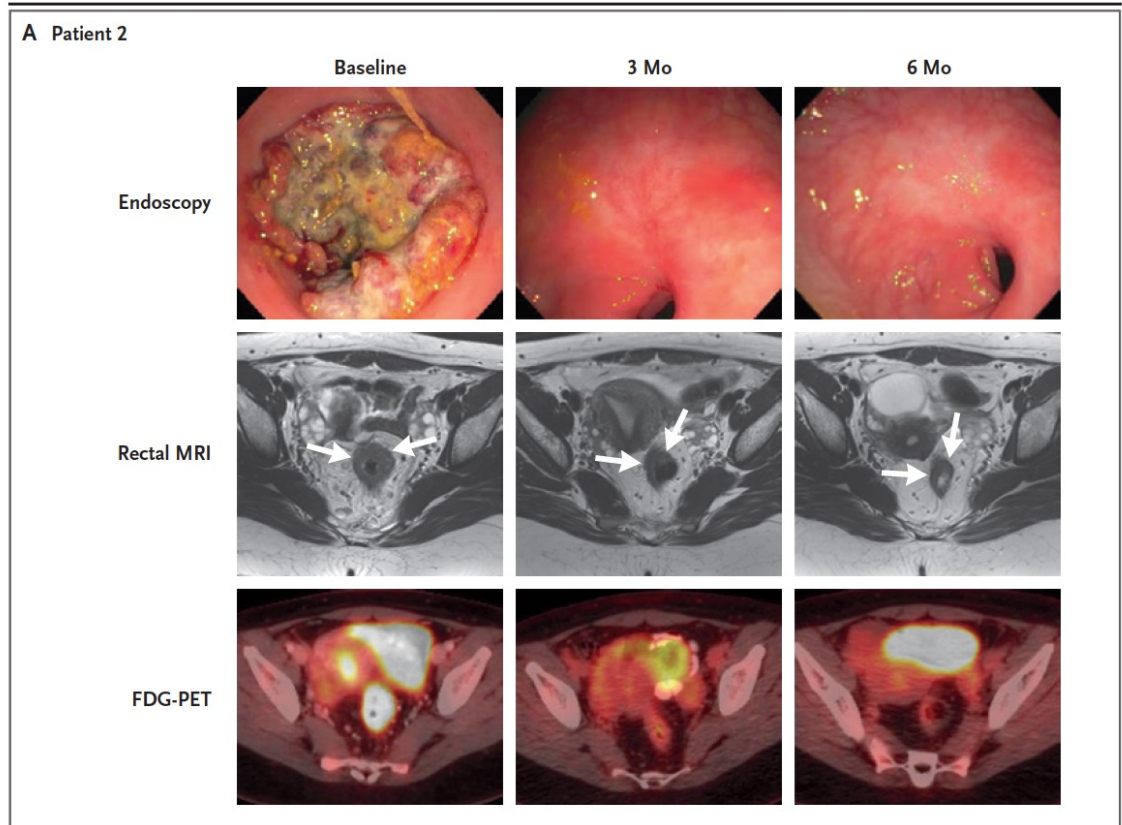
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

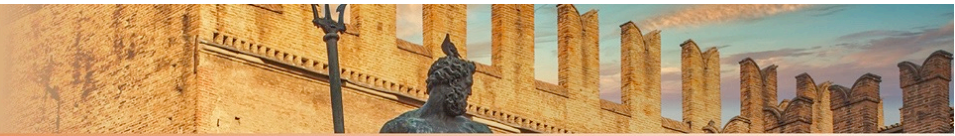
PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.

«A single-agent dostarlimab, an anti-PD-1 monoclonal antibody, was administered every 3 weeks for 6 months in patients with mismatch repair–deficient stage II or III rectal adenocarcinoma (5 to 10% of rectal adenocarcinomas)»



N Engl J Med. 2022 Jun 23;386(25):2363-2376.

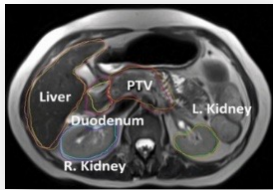


The Adaptive of the Future

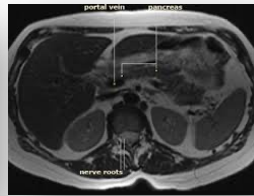
ADAPTIVE TREATMENT



Simulation



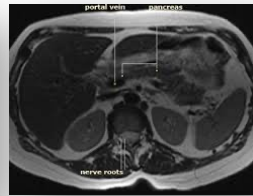
1st Fx



2nd Fx



3rd Fx



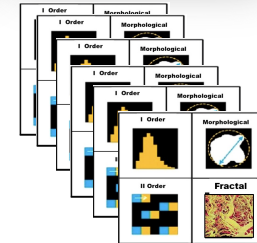
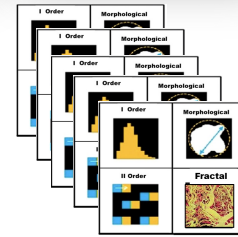
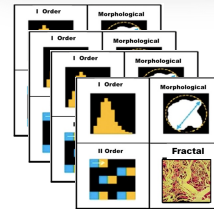
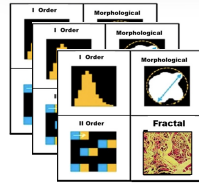
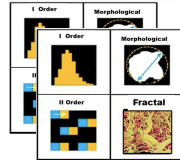
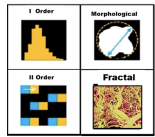
4th Fx



5th Fx



RADIOMICS ANALYSIS



PREDICTIVE ANALYSIS



OUTCOME PREDICTION



RESPONDER

NOT-RESPONDER

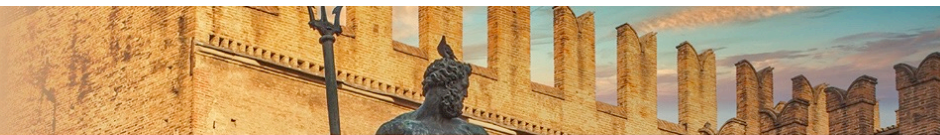
Alternative Approaches



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Thank you!!