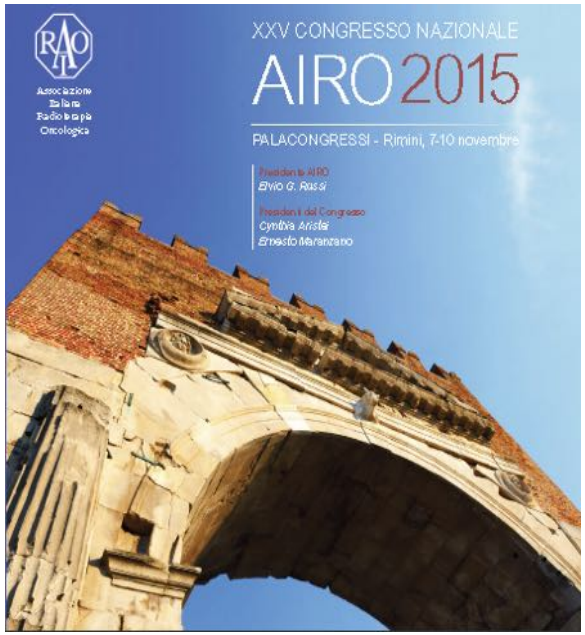


SALA DELLA PIAZZA

14.00 - 15.30 **WORKSHOP**

Intensificazione dei trattamenti neoadiuvanti nel carcinoma del retto e fattori predittivi di risposta

Moderatori: F. Valvo, V. Valentini

Cosa i pazienti si aspettano dall'intensificazione del trattamento - **M.A. Gambacorta**
L'intensificazione della chemioterapia - **A. De Paoli**
L'intensificazione della radioterapia: quali volumi irradiare e la verifica della loro corretta irradiazione durante la terapia - **G. Mantello**
L'intensificazione della radioterapia: la scelta della dose e del frazionamento - **M. Lupattelli**
Fattori predittivi e modellistica della risposta al trattamento - **V. Valentini**
Discussione

L'intensificazione della radioterapia: la scelta della dose e del frazionamento

M. Lupattelli
SC Radioterapia Oncologica
Perugia

Stemma dell'Ospedale di S. Maria della Misericordia di Perugia

DICHIARAZIONE

Relatore: Marco Lupattelli

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)**
- Titolarietà 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

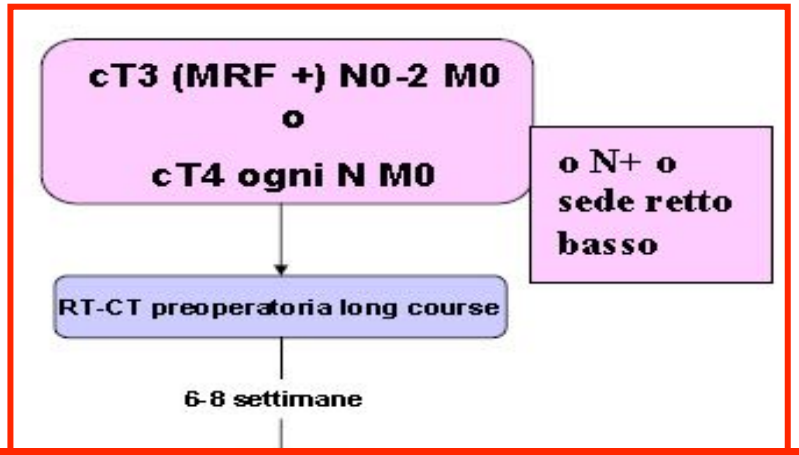
EURECCA consensus conference highlights about rectal cancer clinical management: The radiation oncologist's expert review

Radiother Oncol 2014

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

[a] *Department of Radiation Oncology, Cattedra di Radioterapia, Università Cattolica S. Cuore, Rome, Italy;* [b] *Department of Radiology, Oncology and Radiation Science, Uppsala University, Sweden;* [c] *Department of Radiation Oncology, University Hospitals Leuven Campus Gasthuisberg, Belgium;* [d] *Department of Clinical Oncology, Leiden University Medical Center, The Netherlands;* [e] *Radiation Oncology, University Hospital of Frankfurt, Germany;* [f] *Department of Sur gery, Leiden University Medical Center, The Netherlands;* [g] *Radiation Oncology Section, Department of Surgery, Radiology and Dentistry, University of Perugia, Italy*

Results: 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. Moderate consensus was achieved for cT3 anyNM0 disease. In this frame, agreement was reached on either SCRT followed by immediate surgery or LCRTCT with delayed surgery for mesorectal fascia (MRF) negative tumors at presentation. LCRTCT was recommended for tumor shrinkage in MRF+ at presentations but if patients were not candidates for chemotherapy, SCRT with delayed surgery is an option/alternative. LCRTCT was recommended for cT4 anycNM0. SCRT offers the advantages of less acute toxicity and lower costs, and LCRTCT tumor shrinkage and down-staging, with 13–36% pathological complete response (pCR) rates.



Fallimento terapeutico correlato a ripresa a distanza nel 25-30% pazienti con neoplasia localmente avanzata

- dose: 45-50.4 Gy totali
- frazioni: 25-28 fr.1.8 Gy/die (II,A)
- boost (non mandatorio fino a 55.4 Gy) (II,C). La brachiterapia o la IORT sono modalità alternative ai fasci esterni di somministrazione di boost locale (III,C). Il loro utilizzo può essere preso in considerazione, ove la tecnica sia disponibile, all'interno di studi clinici, solamente negli stadi avanzati.
- *Chemioterapia concomitante con fluoropirimidine* (I,A) (infusione continua di 5-Fluorouracile 225 mg/mq/die o capecitabina 825 mg/mq/bid per os per tutta la durata della RT).

Perché intensificare RT ?

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

Monique Maas, Patty J Nelemans, Vincenzo Valentini, Prajnan Das, Claus Rödel, Li-Jen Kuo, Felipe A Calvo, Julio García-Aguilar, Rob Glynne-Jones, Karin Haustermans, Mohammed Mohiuddin, Salvatore Pucciarelli, William Small Jr, Javier Suárez, George Theodoropoulos, Sebastiano Biondo, Regina G H Beets-Tan, Geerard L Beets

Interpretation Patients with pCR after chemoradiation have better long-term outcome than do those without pCR. pCR might be indicative of a prognostically favourable biological tumour profile with less propensity for local or distant recurrence and improved survival.

Correlazione dose-risposta

Dati letteratura: cT3-4; recidive

- Dose ≥ 55Gy →risposta clinica Overgaard 1984
- Dose ≥ 55Gy e 5FU PVI → pRC Mohiuddin 2000
- Dose 50Gy →pRC, LC, OS Chan 2000
- Dose ≥ 46Gy → pRC, LC, OS Wiltshire 2006

- Dose ≥ 45Gy, 5FU PVI, polichemioterapia (pRC) Sanghera 2008

Published in final edited form as:
Int J Radiat Oncol Biol Phys. 2013 January 1; 85(1): 74–80. doi:10.1016/j.ijrobp.2012.05.017.

Radiation dose-response model for locally advanced rectal cancer after pre-operative chemoradiotherapy

Ane L. Appelt, M.Sc.[1,2], **John Pløen, M.D.**[1], **Ivan R. Vogelius, Ph.D.**[3], **Søren M. Bentzen, Ph.D., D.Sc.**[4], and **Anders Jakobsen, D.M.Sc.**[1,2]

Purpose. In the present study we estimated radiation dose-response curves for various grades of tumour regression after preoperative CRT.

Methods and Materials—A total of 222 patients, treated with consistent chemotherapy and radiotherapy techniques, were considered for the analysis. Radiotherapy consisted of a combination of external beam radiotherapy and brachytherapy.

Conclusions—This study has demonstrated a significant dose-response relationship for tumour regression after preoperative CRT for locally advanced rectal cancer for tumour dose levels in the range of 50.4 to 70 Gy, which is higher than the dose-range usually considered.

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

2014

Systematic review

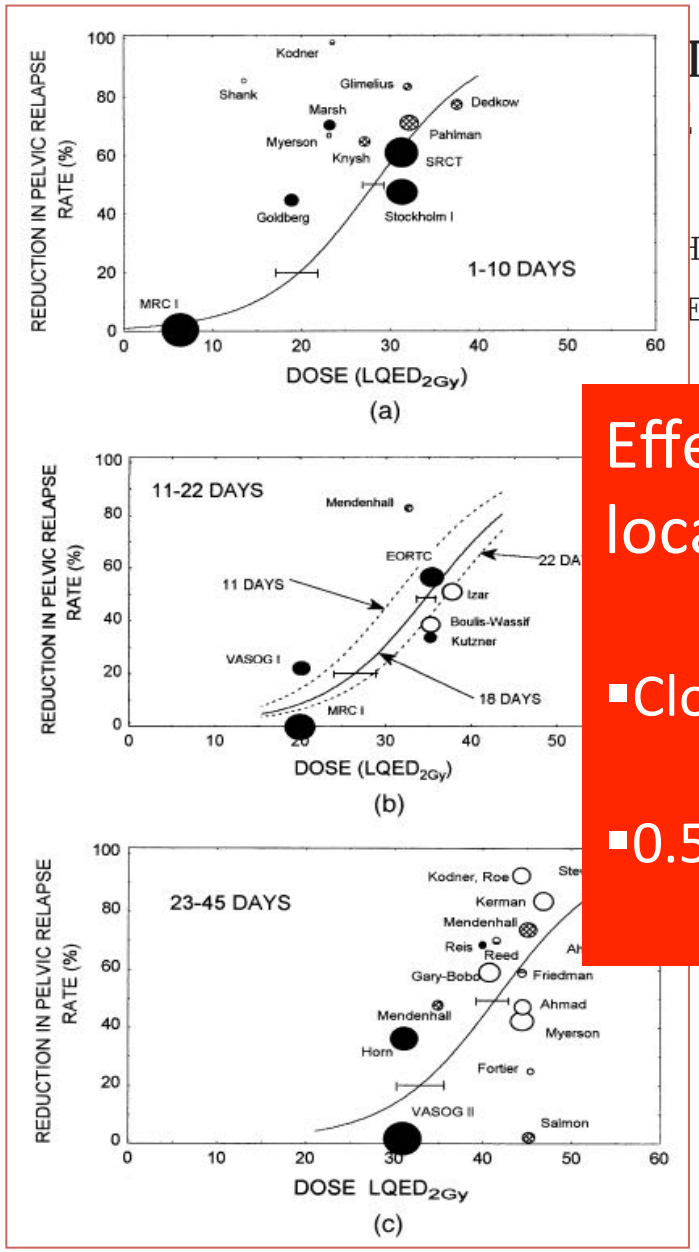
Impact of radiotherapy boost on pathological complete response in patients with locally advanced rectal cancer: A systematic review and meta-analysis

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

Results: The search identified 3377 original articles, of which 18 met our inclusion criteria (1106 patients). Fourteen studies were included for meta-analysis (487 patients treated with ⩾60 Gy). pCR-rate ranged between 0.0% and 44.4%. Toxicity ranged between 1.3% and 43.8% and resectability-rate between 34.0% and 100%. Pooled pCR-rate was 20.4% (95% CI 16.8–24.5%), with low heterogeneity (I^2 0.0%, 95% CI 0.00–84.0%). Pooled acute grade ⩾3 toxicity was 10.3% (95% CI 5.4–18.6%) and pooled resectability-rate was 89.5% (95% CI 78.2–95.3%).

Conclusion: Dose escalation above 60 Gy for locally advanced rectal cancer results in high pCR-rates and acceptable early toxicity. This observation needs to be further investigated within larger randomized controlled phase 3 trials in the future.

IJROBP 1998



ICROSCOPIC RECTAL CANCER AS A
TO PREOPERATIVE RADIATION THERAPY

H.D.,*‡ JEREMY M.G. TAYLOR, PH.D.,*† AND
EY WITHERS, M.D., D.SC.*

Effect of overall treatment duration on local control:

- Clonogen doubling time as short as 4-5 days
- 0.54 Gy/die of protraction

Intensificazione dose

PRO: dati letteratura e radiobiologici

Frazionamento convenzionale?
NO, per dati radiobiologici

Intensificazione dose

- Dose totale più elevata in tempo minore (dose singola > 1.8Gy)

- Concomitant boost – CB (3CRT)

- Simultaneous integrated boost – SIB (IMRT)

3DCRT-CONCOMITANT BOOST

CLINICAL INVESTIGATION Rectum

A PHASE I/II TRIAL OF THREE-DIMENSIONALLY PLANNED CONCURRENT BOOST RADIOTHERAPY AND PROTRACTED VENOUS INFUSION OF 5-FU CHEMOTHERAPY FOR LOCALLY ADVANCED RECTAL CARCINOMA

IJROBP 2001

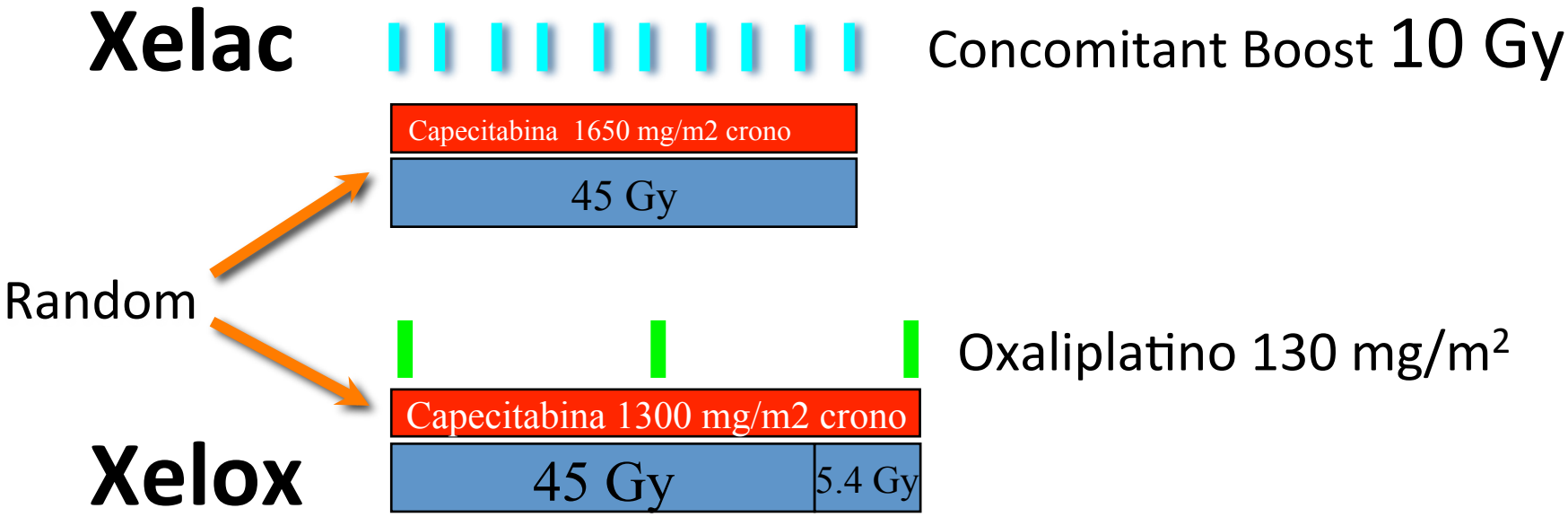
ROBERT J. MYERSON, M.D.,* VINCENZO VALENTINI, M.D.,† ELISA H. BIRNBAUM, M.D.,‡
NUMA CELLINI, M.D.,† CLAUDIO COCO, M.D.,§ JAMES W. FLESHMAN, M.D.,‡
MARIA ANTONIETTA GAMBACORTA, M.D.,† DOMENICO GENOVESI, M.D.,† IRA J. KODNER, M.D.,‡
JOEL PICUS, M.D.,‖ GARY A. RATKIN, M.D.,‖ AND THOMAS E. READ, M.D.‡

Methods and Materials: 37 patients with unresectable or recurrent rectal cancer, received 45 Gy/25 fractions to the pelvis with a 3D planned concomitant boost of 0.9 Gy per fraction delivered twice a week concurrently (total dose 54Gy) plus 5-FU P.V.I.

Results. Resectability rate 78%, pCR 24%
3y LC 63%, 3y OS 82%
severe acute toxicity 24%
compliance 100%

Studio INTERACT

Analisi 01/14



Obiettivi.

Primario: valutazione risposta patologica

Secondario: tossicità, DFS e OS

Casistica: 527 pz – cT3 N0-2, MRF +/-; cT2 N+ retto inferiore

Studio INTERACT: risultati

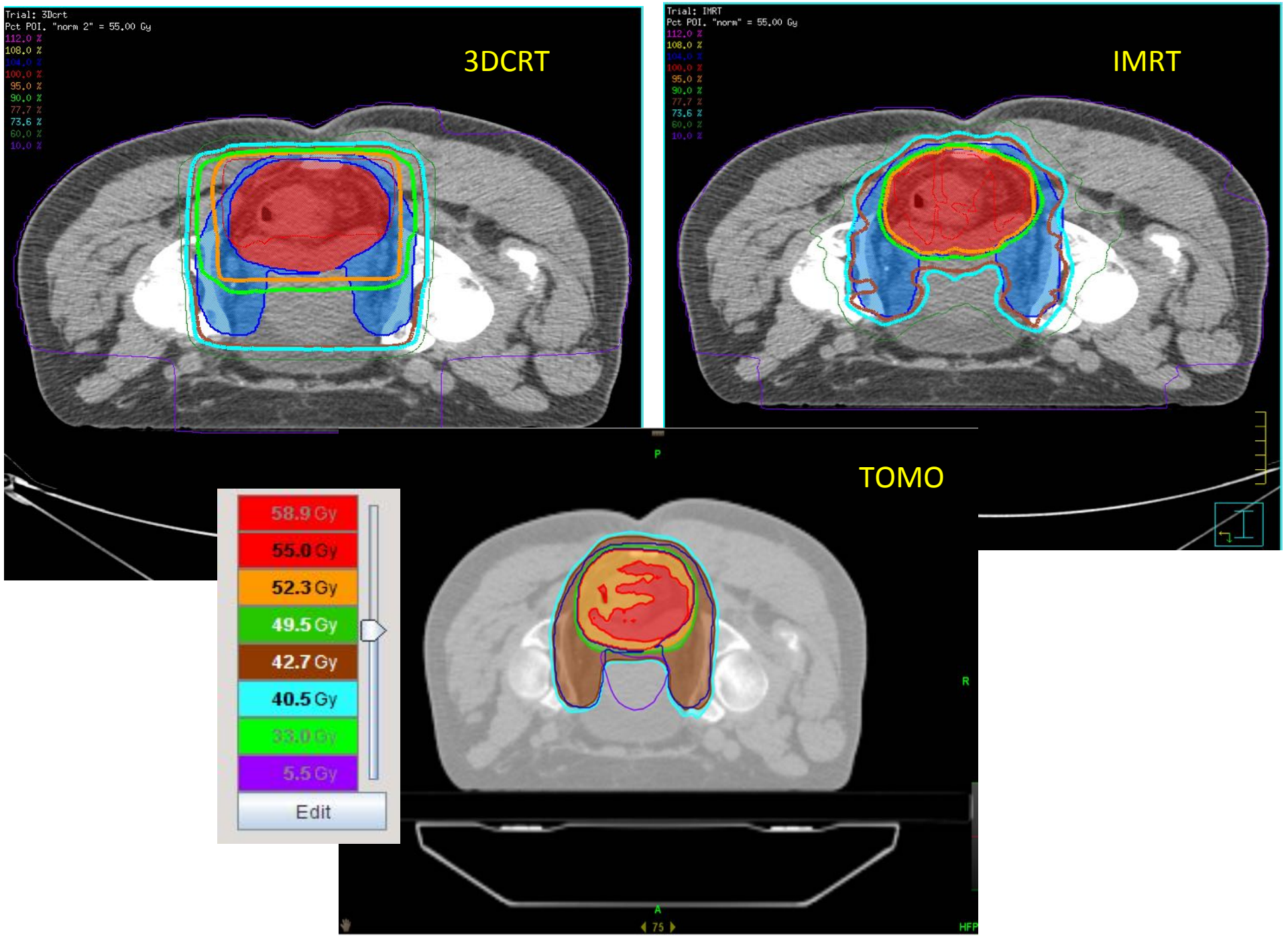
Variabile	XELAC	XELOX	p
TRG 1	31.4%	30.8%	NS
TRG 1-2	60.2%	51%	NS
Cor			
Cor			1
Tos			
Tossicità GI ≥ 3	15%	27.8%	0.001
Tossicità neurologica ≥ 3	3.8%	20.5%	0.001
Controllo locale, DFS, OS			NS

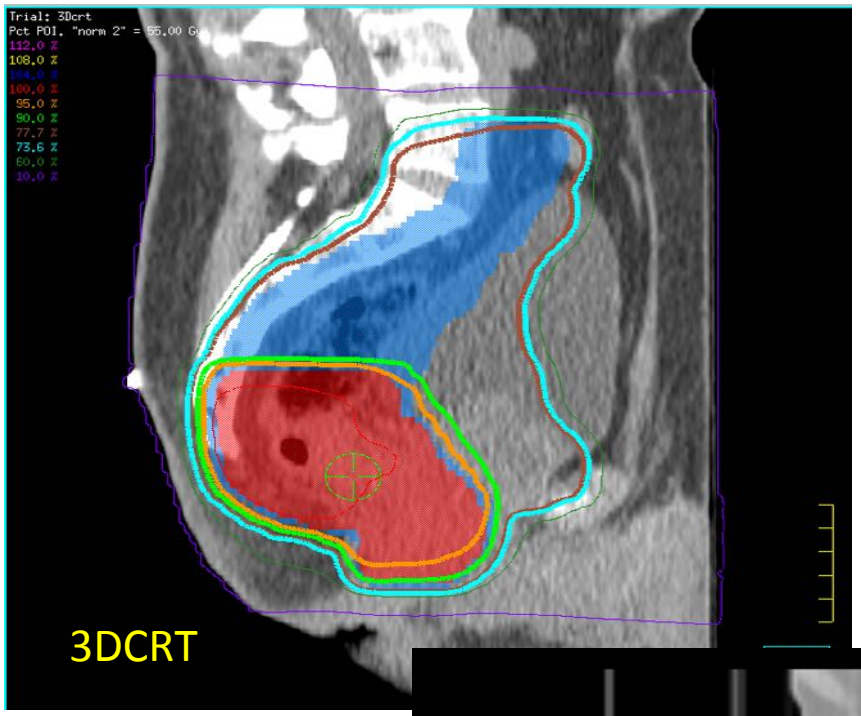
Braccio XELAC
trattamento di riferimento

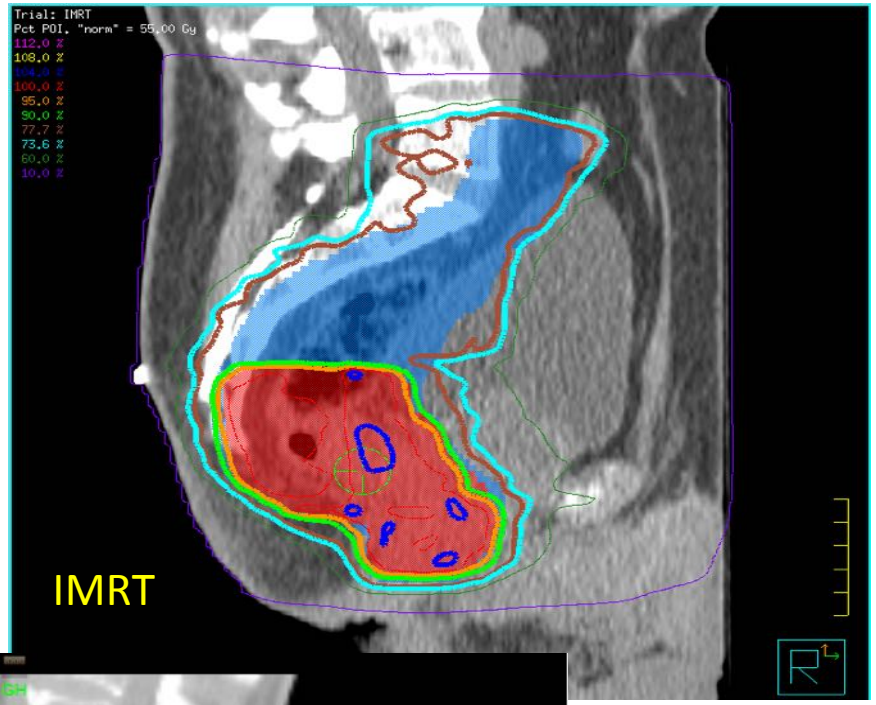
IMRT-Simultaneous Integrated Boost

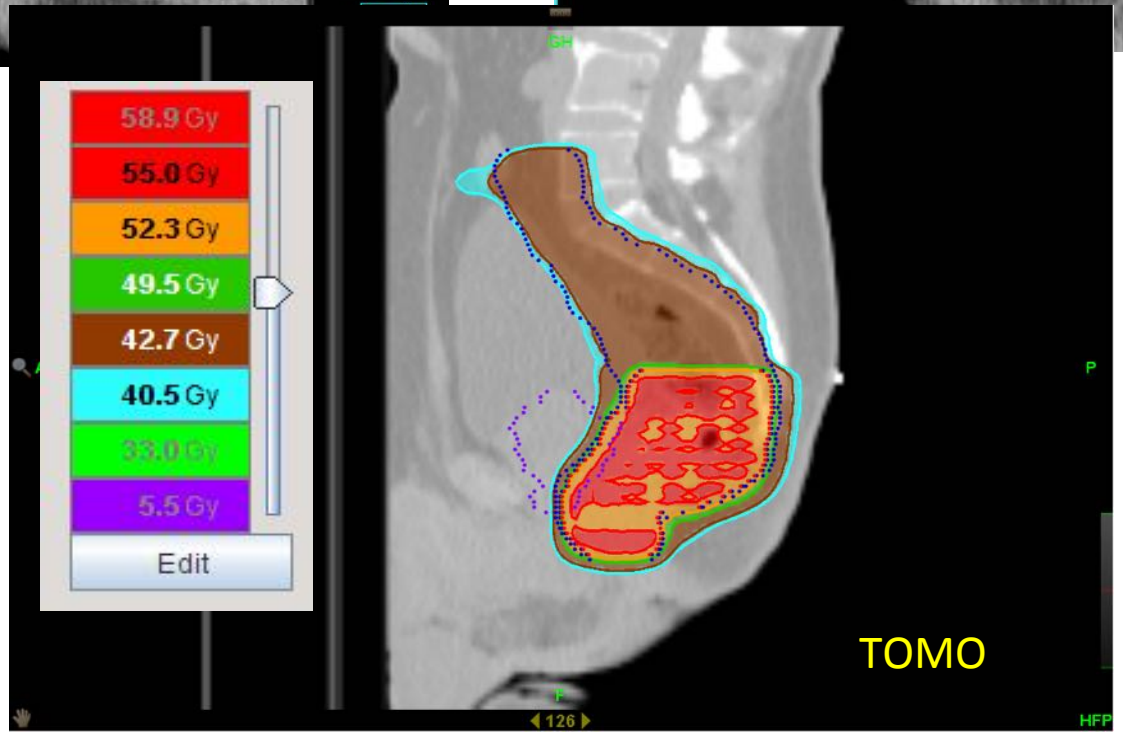
Studi di confronto dosimetrico 3D vs IMRT

LAVORI	Copertura PTV	C.I.	H.I.	Tessuti sani	Tenue	Vescica
Arbea 2010 IMRT vs 3DCRT	IMRT	IMRT	ND	V5 3D; V20 IMRT	IMRT	IMRT
Richetti 2010 RA vs 3DCRT	RA	RA	RA	RA	RA	RA
Mok 2011 IMRT vs 3DCRT	IMRT	IMRT	IMRT	V5 3D, altro IMRT	IMRT	IMRT
Cilla 2012 VMAT, IMRT, 3D	Nessuna Differenza	VMAT	ND	V5 3D; V20 VMAT	VMAT - IMRT	VMAT - IMRT
Shang 2014 IMRT vs VMAT	DA-VMAT	DA-VMAT	-	V5-10 IMRT	IMRT	IMRT
Liu 2015 RA, IMRT, 3D	IMRT-RA	IMRT-RA	IMRT-RA	IMRT-RA	IMRT-RA	IMRT-RA
Yu 2015 Tomo vs 3DCRT	TOMO	TOMO	TOMO	-	TOMO	TOMO


Trial: 3Dcrt
Pct POI. "norm 2" = 55.00 Gy
112.0 %
108.0 %
104.0 %
100.0 %
95.0 %
90.0 %
77.7 %
73.6 %
60.0 %
10.0 %
3DCRT
Trial: IMRT
Pct POI. "norm" = 55.00 Gy
112.0 %
108.0 %
104.0 %
100.0 %
95.0 %
90.0 %
77.7 %
73.6 %
60.0 %
10.0 %
IMRT
TOMO
58.9 Gy
55.0 Gy
52.3 Gy
49.5 Gy
42.7 Gy
40.5 Gy
33.0 Gy
5.5 Gy
Edit
P
R
A
75
HFP


Trial: 3Dcrt
Pct POI, "norm 2" = 55.00 Gy
112.0 %
108.0 %
100.0 %
95.0 %
90.0 %
77.7 %
73.6 %
3DCRT


Trial: IMRT
Pct POI, "norm" = 55.00 Gy
112.0 %
108.0 %
100.0 %
95.0 %
90.0 %
77.7 %
73.6 %
IMRT


58.9 Gy
55.0 Gy
52.3 Gy
49.5 Gy
42.7 Gy
40.5 Gy
33.0 Gy
5.5 Gy
Edit
TOMO
126
HFP

Tossicità acuta: confronto 3D vs IMRT

- Riduzione Volume tenue fino al 60% IMRT vs 3DCRT
  (Duthoy 2004, Nuyttens 2004, Guerrero 2006, Tho 2006)

- Ferrigno 2010: ↓ diarrea grado 2; ↑ Grado 0

- Samuelian 2012: 92 pz ↓ tox GE (32 vs 62%);
  grado 3 (3 vs 20%)

- Parekh 2013: 48 pz ↓diarrea globalmente (30 vs 61%), diarrea ≥ 2 (40 vs 75%) e diarrea ≥ 3 (0 vs 10%)

Predictors of Acute Gastrointestinal Toxicity During Pelvic Chemoradiotherapy in Patients With Rectal Cancer

2014

T. Jonathan Yang,[1] Jung Hun Oh,[2] Christina H. Son,[1] Aditya Apte,[2] Joseph O. Deasy,[2] Abraham Wu,[1] Karyn A. Goodman[1]

RESULTS: The median age was 60; 76 patients were women; 98 were treated with intensity-modulated radiotherapy (IMRT) and 79 with 3D conformal RT (3DCRT). A higher rate of grade 2+ diarrhea was observed in the women, starting at week 4 (24% women vs. 11% men, $P = .01$; week 5: 33% vs. 12%, $P = .002$), as well as in all the patients treated with 3DCRT (22% vs. 12% IMRT, $P = .03$; week 5: 32% vs. 11%, $P = .001$). On multivariate analysis, the normal tissue complication probability (NTCP) model including bowel V45 (bowel volume receiving ≥45 Gy) showed that being female, and use of 3DCRT, was most predictive of grade 2+ diarrhea (area under the curve [AUC] = 0.76; $R_S = 0.35$; $P < .001$). A higher rate of grade 2+ proctitis was seen in patients <60 years of age starting at week 3 (21% vs. 9%, $P = .02$; week 4: 35% vs. 16%, $P = .003$). The NTCP model including anal canal V15 and younger age was most predictive of grade 2+ proctitis (AUC = 0.67; $R_S = 0.25$; $P < .001$).

NRG Oncology Radiation Therapy Oncology Group 0822: A Phase 2 Study of Preoperative Chemoradiation Therapy Using Intensity Modulated Radiation Therapy in Combination With Capecitabine and Oxaliplatin for Patients With Locally Advanced Rectal Cancer

IJROBP 2015

Methods and Materials: Patients with T3 or T4 rectal cancer received 45 Gy with IMRT in 25 fractions, followed by a 3-dimensional conformal boost of 5.4 Gy in 3 fractions with CAPOX. Seventy-one patients provided 80% probability to detect at least a 12% reduction in the specified GI toxicity with the treatment of CAPOX and IMRT, at a significance level of .10 (1-sided).

Results: Seventy-nine patients were accrued, of whom 68 were evaluable. Thirty-five patients (51.5%) experienced grade 2 GI toxicity, 12 patients (17.6%) experienced grade 3 or 4 diarrhea.

Conclusion: The use of IMRT in neoadjuvant chemoradiation for rectal cancer did not reduce the rate of GI toxicity.

Criticità:
- Tipo RT (associazione IMRT-3DC)
- Non usati constraints di dose tenue standard (V15 <120-150cc)

IMRT– SIB: vantaggi

- Erogazione simultanea di dosi differenti a volumi diversi nella stessa frazione
- Riduzione del tempo di trattamento (singola frazione e complessiva)
- Possibilità di ipofrazionamento

Autore	No. pz	Stadio	Radioterapia	Compliance RT-CT	pRC	Tox ≥ 3	OS
Ballonoff 2008	8	T3-T4 N0/N+	45Gy/25fr/1.8 55Gy/25fr/2.2	100%	38%	13%	2y 100%
De Ridder 2008	24/ 13	T3-T4 MRF +	46Gy/23 fr/2 55.2Gy/23fr/2.4	100% (no CT)	NR	No	
Arbea 2011	100	T3-T4 N+	47.5Gy/19fr/2.5 47.5Gy/20fr/2.4	97% - 80%	13%	25%	5y 87%
Li 2012	63	T3-T4 N+	41.8Gy/22fr/1.9 50.6Gy/22fr/2.3	100%	31%	14%	2y 96%
Passoni 2013	25	T3-T4 N+	45.6Gy/18fr	96% - 92%	30%	12%	NR
Hernando 2014	74	T2-T4 N+	45Gy/25fr/1.8 57.5Gy/25fr/2.3	99%	31%	17.6%	3y 86%
Zhu 2014	78	T3-T4 N0/N+	50Gy/25fr/2 55Gy/25fr/2.2	100% - 62%	24%	14%	3y 77%
Wang 2015	260	T3-T4 N0/N+	41.8Gy/22fr/1.9 50.6Gy/22fr/2.3	96%	18.5%	6%	3y 92%

dose totale
47.5-57.5Gy/20-25fr/2.2-2.5Gy

as

Complicanze postoperatorie
7-25%

Radio-chemioterapia standard: compliance e tossicità

Variabile	Percentuale
Compliance RT	92-100
Compliance chemioterapia	50-93
Tossicità acuta ≥3 globale	14-28
Rischio morte	1
Complicanze post-operatorie	25-36
Diarrea cronica severa	5-10
Occlusione intestinale	30 (1/3 chirurgia)

Phase II trial

2014

Preoperative intensity-modulated and image-guided radiotherapy with a simultaneous integrated boost in locally advanced rectal cancer: Report on late toxicity and outcome

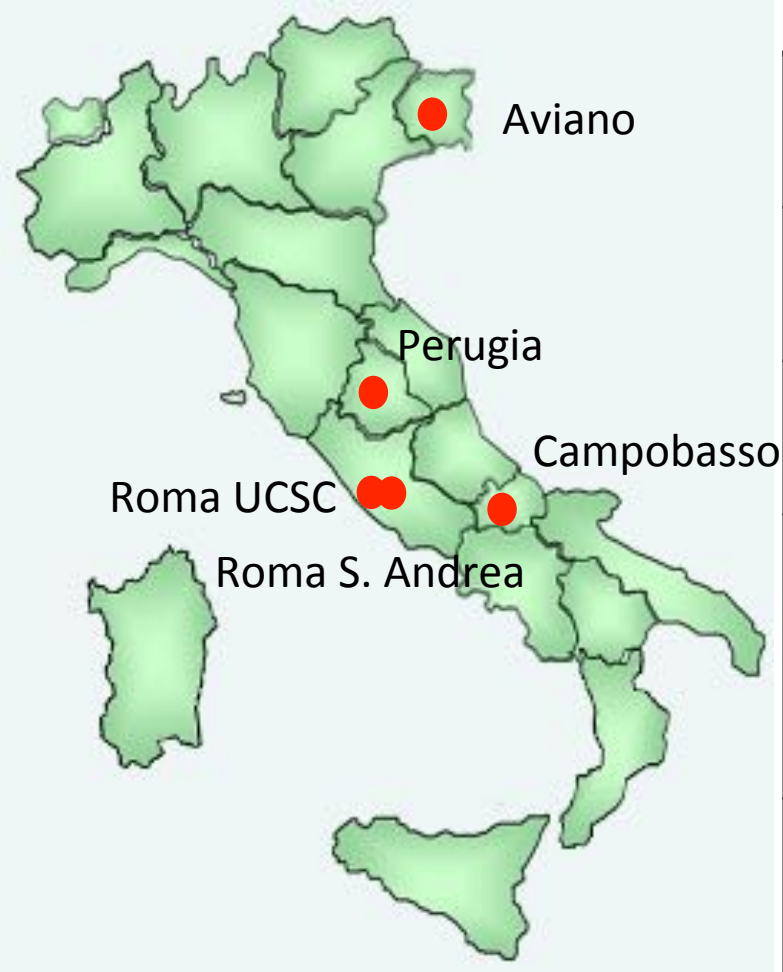
Benedikt Engels [a,*], Nele Platteaux [a], Robbe Van den Begin [a], Thierry Gevaert [a], Alexandra Sermeus [b], Guy Storme [a], Dirk Verellen [a], Mark De Ridder [a]

[a] Department of Radiotherapy; and [b] Department of Gastroenterology, UZ Brussel, Vrije Universiteit Brussel, Belgium

Results: The absolute incidence of grade ≥ 3 late gastrointestinal and urinary toxicity was 9% and 4%, respectively, with a 13% rate of any grade ≥ 3 late toxicity. Th) and overall su , R1 resection a

Parametri	Engels	Letteratura
Tox tardiva GI	9%	9% (Sauer 2004)
Diarrea ≥ 2	5%	9.6% (Bosset 2006)
Chirurgia per occlusione tenue	3.6%	1.4-2% (Bosset 2006, Sauer 2004)
Morti tox	1.9%	1.3-3.2% (Bujko, Bosset, Sauer)
Tox GU ≥ 3	7%	2% (Sauer 2004)
Secondi tumori	6.6%	11.7-14% (Birgisson 2005, Van Gijn 2011)

Intensificazione della dose di radioterapia nel trattamento radiochemioterapico preoperatorio del carcinoma del retto localmente avanzato. Risultati preliminari di una pooled analysis.



Risultati	No. / %
Tossicità ematologica G3	2 / 3%
Tossicità G.E. G3	9 / 13%
Risposta valutabile	38
Downstaging	31 / 82%
TRG1	8 / 21%
Compliance	
RT	100%
chemioterapia	77%

CONSIDERAZIONI (I)

- 3DCRT 50.4Gy + fluoropirimidina → standard
- Basi radiobiologiche, fattibilità, tossicità acuta, "short-term outcomes"→ intensificazione della dose
- Necessità di ulteriori studi prospettici per migliore definizione dose/frazionamento

CONSIDERAZIONI (II)

- Necessità di dati ulteriori su tossicità tardiva
- Intensificazione: 3D o IMRT in base a parametri clinico-dosimetrici e disponibilità tecnologica, anche se IMRT……
- Intensificazione se fattori prognostici negativi (T3N+; MRF + o T4N0/N+)