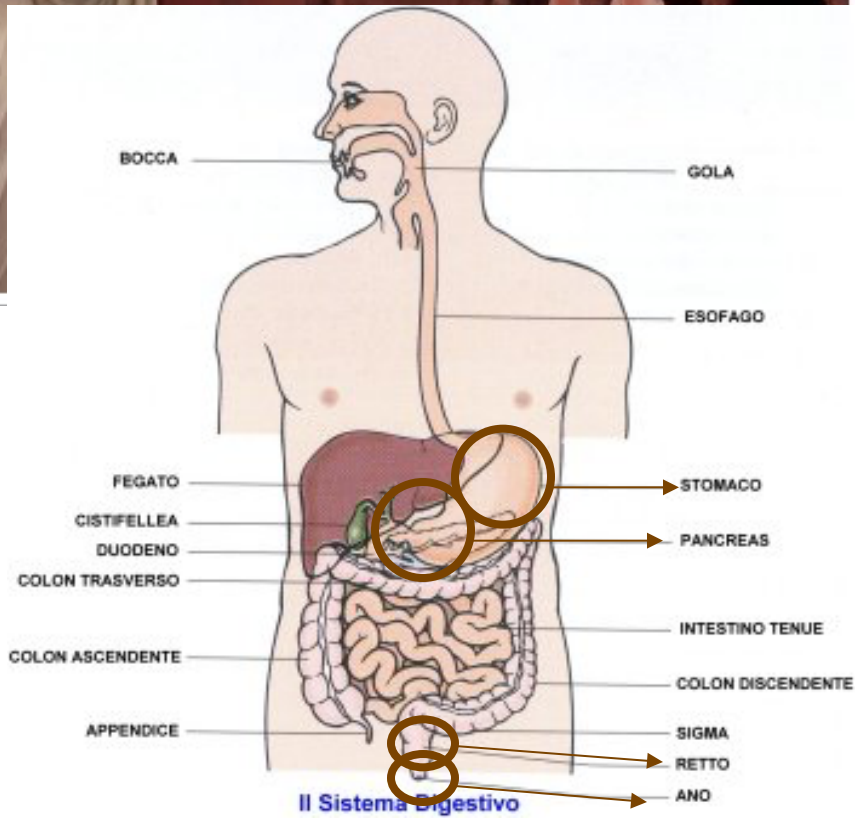
NEOPLASIE DEL GASTROENTERICO

GIOVANNA MANTELLO



stomaco

2012: quali nuove evidenze a supportare

Ruolo radioterapia adiuvante

?

VOLUME 30 · NUMBER 19 · JULY 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPO

INT 0116

Updated Analysis of SWOG-Directed Intergroup Study 0116: A Phase III Trial of Adjuvant Radiochemotherapy Versus Observation After Curative Gastric Cancer Resection

Stephen R. Smalley, Jacqueline K. Benedetti, Daniel G. Haller, Scott A. Hundahl, Norman C. Estes, Jaffer A. Ajani, Leonard L. Gunderson, Bryan Goldman, James A. Martenson, J. Milburn Jessup, Grant N. Stemmermann,† Charles D. Blanke, and John S. Macdonald

update, with a more than 10-year median follow-up

STRONG PERSISTENT BENEFIT FROM RADIOCHEMOTHERAPY

Conclusion

Intergroup 0116 (INT-0116) demonstrates strong persistent benefit from adjuvant radiochemotherapy. Toxicities, including second malignancies, appear acceptable, given the magnitude of RFS and OS improvement. LRF reduction may account for the majority of overall relapse reduction. Adjuvant radiochemotherapy remains a rational standard therapy for curatively resected gastric cancer with primaries T3 or greater and/or positive nodes.

INT 0116

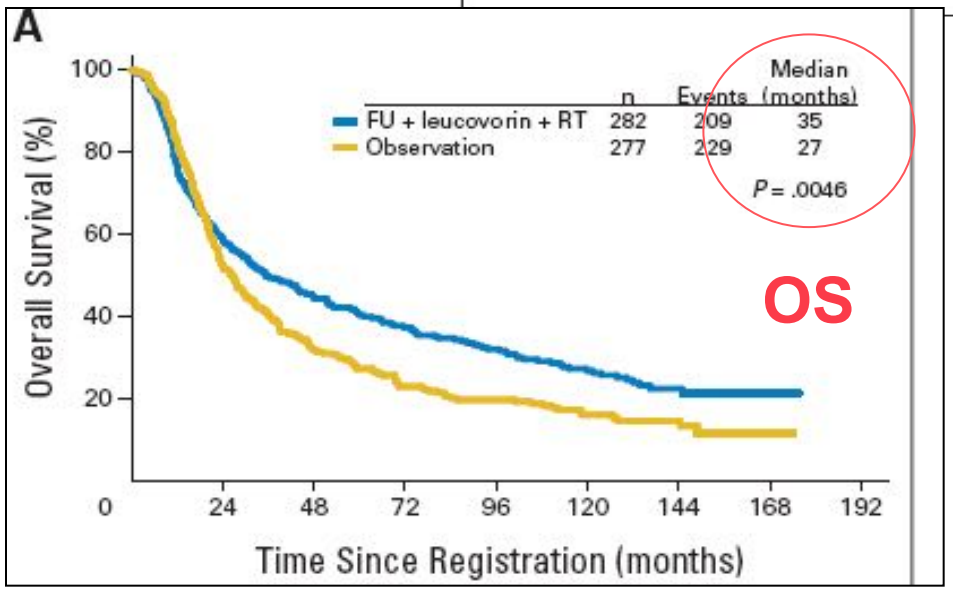
Table 2. Patterns of Failure by Arm

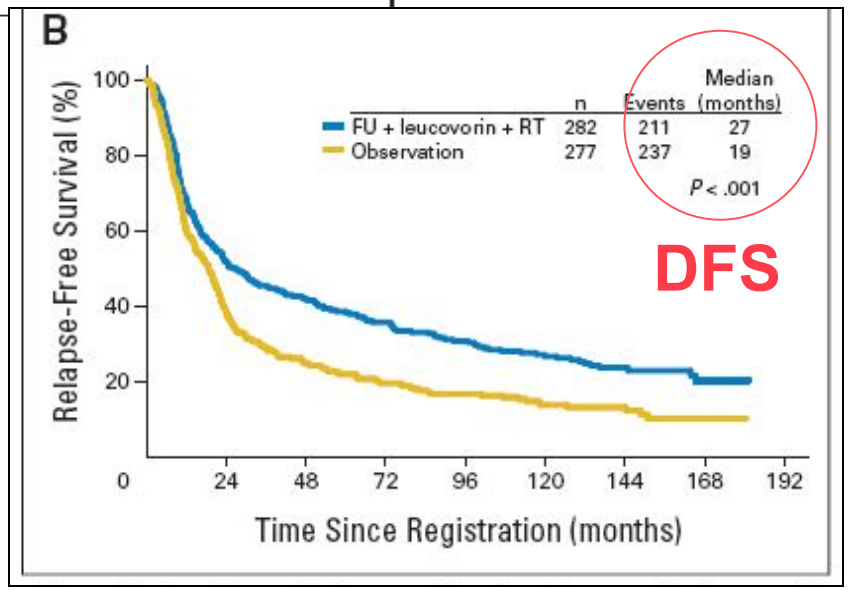
P<0.001

Relapse Status	Radiochemotherapy No.	Radiochemotherapy %	Control (surgery alone) No.	Control (surgery alone) %	Total No.	Total %
No relapse*	135	48	67	24	202	36
Relapse*	147	52	210	76	357	64
Sites of relapse (% of those randomly assigned)*						
Local	7	2	21	8	28	5
Regional	62	22	109	39	171	31
Distant	46	16	49	18	95	17
Unknown site	32	11	31	11	63	11
Total	282		277		559	

*Indicates statistically significant comparisons. $P < .001$ for relapse v no relapse (χ^2); $P = .012$ for sites of relapse (among those with sites reported, χ^2 test for trend).

Riduce la % di recidive locoregionali

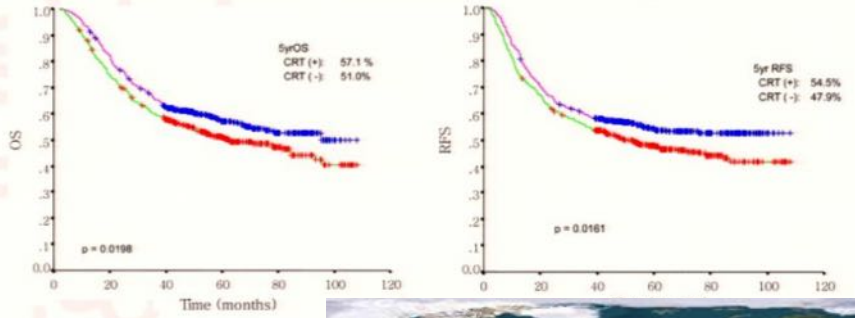




Does adjuvant chemoradiotherapy just compensate for poor surgery?

Role of adjuvant chemoradiotherapy in D2-resected gastric cancer patients

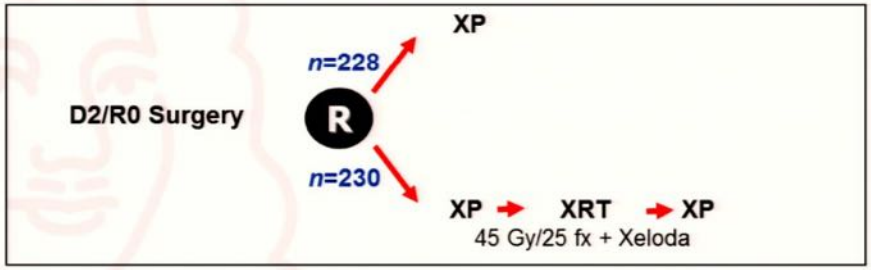
- observational study
- n=544: postoperative CRT (INT-0116) after curative D2 resection
  n=446: surgery only
- median duration of OS 95.3 vs. 62.6 months (p=0.02)
  DFS 75.6 vs. 52.7 months (p<0.02)



ARTIST trial

Adjuvant chemoradiotherapy vs. chemotherapy

ARTIST Trial



- Median number of lymph nodes dissected in both arms: 40!
- Median number of involved lymph nodes was only 3
- 59.6 vs. 57.8% had IB or II disease

Lee et al. JCO 2012

mod VERHEIJ M ESTRO31 2012

VOLUME 30 · NUMBER 3 · JANUARY 20 2012

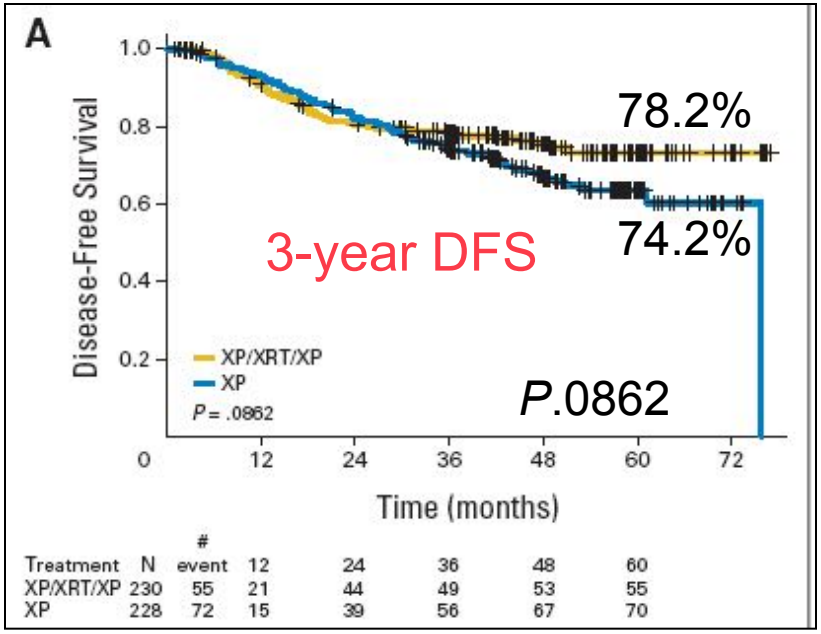
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL R

ARTIST

Phase III Trial Comparing Capecitabine Plus Cisplatin Versus Capecitabine Plus Cisplatin With Concurrent Capecitabine Radiotherapy in Completely Resected Gastric Cancer With D2 Lymph Node Dissection: The ARTIST Trial

Jeeyun Lee, Do Hoon Lim, Sung Kim, Se Hoon Park, Joon Oh Park, Young Suk Park, Ho Yeong Lim, Min Gew Choi, Tae Sung Sohn, Jae Hyung Noh, Jae Moon Bae, Yong Chan Ahn, Insuk Sohn, Sin Ho Jung, Cheol Keun Park, Kyoung-Mee Kim, and Won Ki Kang



Fup mediano 53.2 mesi

Table 3. Pattern of Recurrence

Pattern of Recurrence*	XP Arm		XP/XRT/XP Arm		*P*
Locoregional recurrence†	19	8.3	11	4.8	.3533
Distant metastasis‡	56	24.6	47	20.4	.5568

There were no significant differences in the percentage of locoregional recurrence or distant metastases between treatment arms

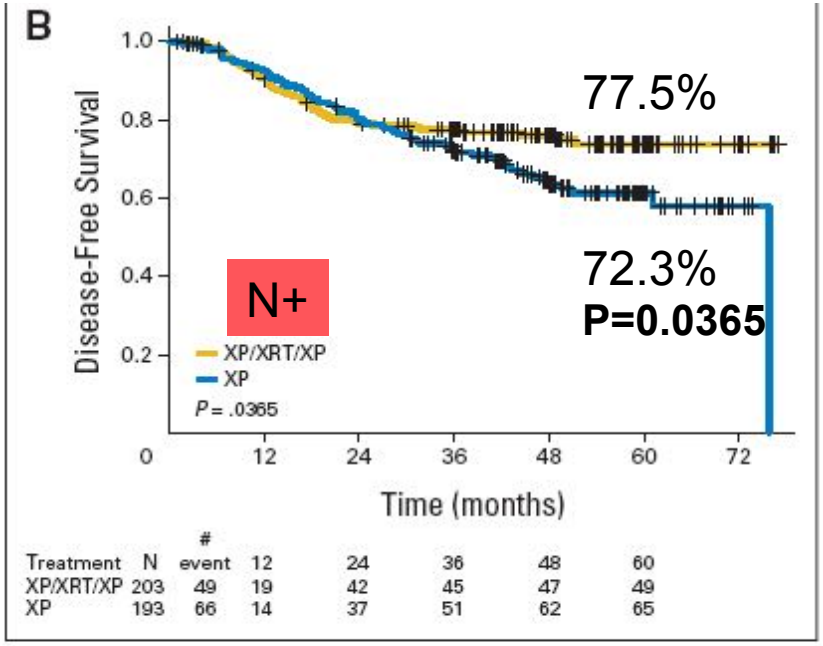
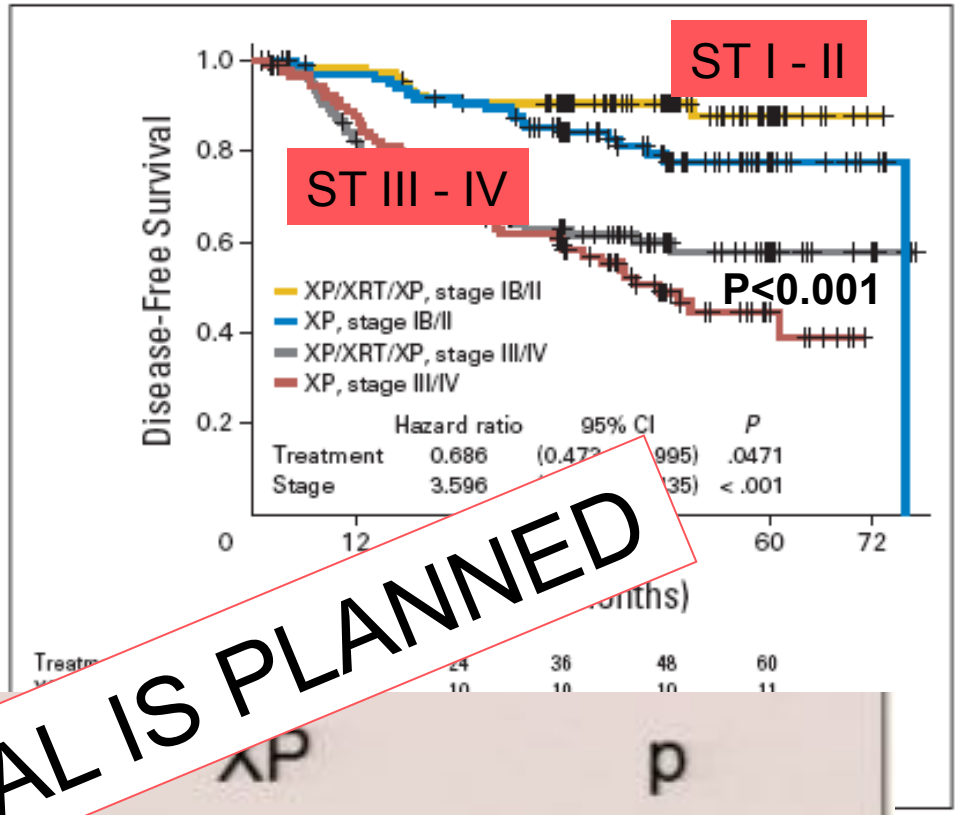


Fig 2. Disease-free survival in (A) all patients and (B) lymph node–positive patients. XP, capecitabine plus cisplatin; XRT, radiotherapy with capecitabine.



ARTIST-2 TRIAL IS PLANNED

	XP	p
3-yr DFS	74.2%	n.s.
3-yr D	72.3%	0.0365

In a subgroup analysis of **396 patients with N+,** there was a statistically significant prolongation in DFS in the XP/XRT/XP arm

(*Am J Clin Oncol* 2012;35:216–221)

Adjuvant Radiation Therapy Increases Overall Survival in Node-Positive Gastric Cancer Patients With Aggressive Surgical Resection and Lymph Node Dissection

A SEER Database Analysis

Ravi Shridhar, MD, PhD, George W. Dombi, PhD,† Jill Weber, MS,‡ Sarah E. Hoffe, MD,* Kenneth Meredith, MD,‡ and Andre Konski, MD§*

To ***examine the outcomes of patients*** with gastric cancer ***who received adjuvant radiation*** therapy

11.630 pazienti **1973 - 2004**

TABLE 2. Analysis of Effect of Radiation on Survival by AJCC Stage

AJCC Stage	Median Survival (m)* No RT	RT	HR†	95% CI	*P*
I	80	96	1.061	0.901-1.251	0.4828
IA	113	NR	1.182	0.611-2.285	0.6201
IB	56	96	0.824	0.693-0.979	0.0281
T2N0	58	95	0.921	0.756-1.118	0.4013
T1N1	43	100	0.548	0.377-0.796	0.0016
II	23	37	0.782	0.709-0.863	<0.0001
III	14	22	0.797	0.724-0.876	<0.0001
IIIA	16	23	0.795	0.715-0.885	<0.0001
IIIB	11	17	0.765	0.617-0.949	0.0147
IV	10	18	0.703	0.616-0.801	<0.0001

*Median survival derived from Kaplan-Meier analysis.
†No RT group set as reference for Cox proportional hazard model.
AJCC indicates American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; NR, not reached; RT, radiation therapy.

TABLE 3. Impact of Radiation on Survival by AJCC N-stage and Lymph Node Dissection

AJCC N-stage	Median Survival (m)* No RT	RT	HR†	95% CI	*P*
N0	87	70	1.272	1.098-1.473	0.0013
<15 LN removed	75	56	1.267	1.077-1.492	0.0044
≥15 LN removed	129	70	1.326	0.943-1.865	0.1047
N1	26	33	0.759	0.701-0.822	<0.0001
<15 LN removed	22	29	0.742	0.677-0.813	<0.0001
≥15 LN removed	39	52	0.892	0.701-0.969	0.0191
N2	15	20	0.740	0.662-0.826	<0.0001
<15 LN removed	12	17	0.694	0.588-0.820	<0.0001
≥15 LN removed	20	22	0.806	0.695-0.936	0.0046
N3	12	18	0.605	0.494-0.739	<0.0001
<30 LN removed	12	14	0.701	0.547-0.899	0.0052
≥30 LN removed	13	23	0.480	0.341-0.676	<0.0001

*Median survival derived from Kaplan-Meier analysis.
†No RT group set as reference for Cox proportional hazard model.
AJCC indicates American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; LN, lymph nodes; RT, radiation therapy.

Conclusions: There is a correlation between survival and radiation therapy in node-positive gastric cancer patients and is independent of the extent of surgical resection and lymph node dissection.

Surgery + postoperative chemoradiotherapy

- 3 Dutch phase I/II trials (2001-2007); n=94

versus

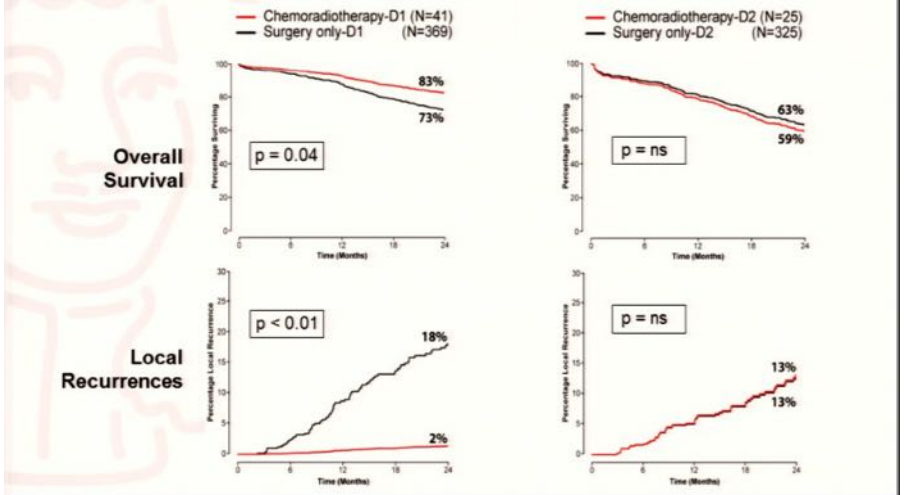
Surgery only

- Dutch Gastric Cancer Group Trial (1989-1993); n=649
- D1 (limited) vs D2 (extended) lymph node dissection

Retrospective comparison of patients

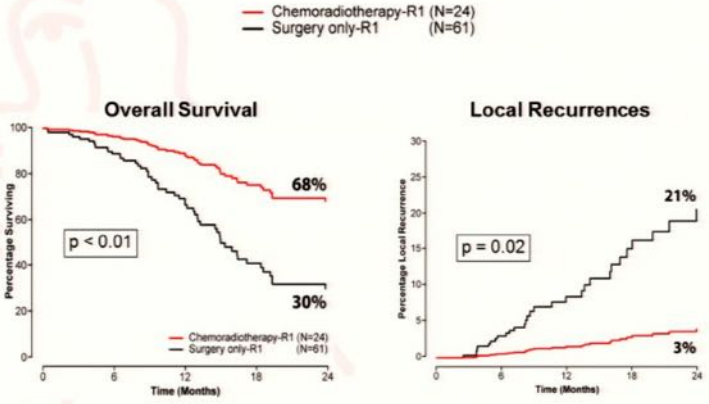
Hartgrink et al. JCO 2004, Jansen et al. IJROBP 2007, Jansen et al. Br J Cancer 2007, Jansen et al. Ann Oncol 2009

Following D1 dissection, postoperative chemoradiotherapy improves overall survival and reduces local recurrences



Verheij et al. JCO/ASTRO 2010

Following R1 resection, postoperative chemoradiotherapy improves overall survival and reduces local recurrences as compared to surgery only



Verheij et al. JCO/ASTRO 2010

mod VERHEIJ M ESTRO31 2012

Jansen EP Recent Results Cancer Res.2012

Dikken et al. BMC Cancer 2011, 11:329
http://www.biomedcentral.com/1471-2407/11/329

ONGOING

BMC Cancer

STUDY PROTOCOL Open Access

Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS)

Johan L Dikken[1,2], Johanna W van Sandick[3], HA Maurits Swellengrebel[3], Pehr A Lind[4], Hein Putter[5], Edwin PM Jansen[2], Henk Boot[6], Nicole CT van Grieken[7], Cornelis JH van de Velde[1], Marce[illegible], Annemieke Cats[6*]

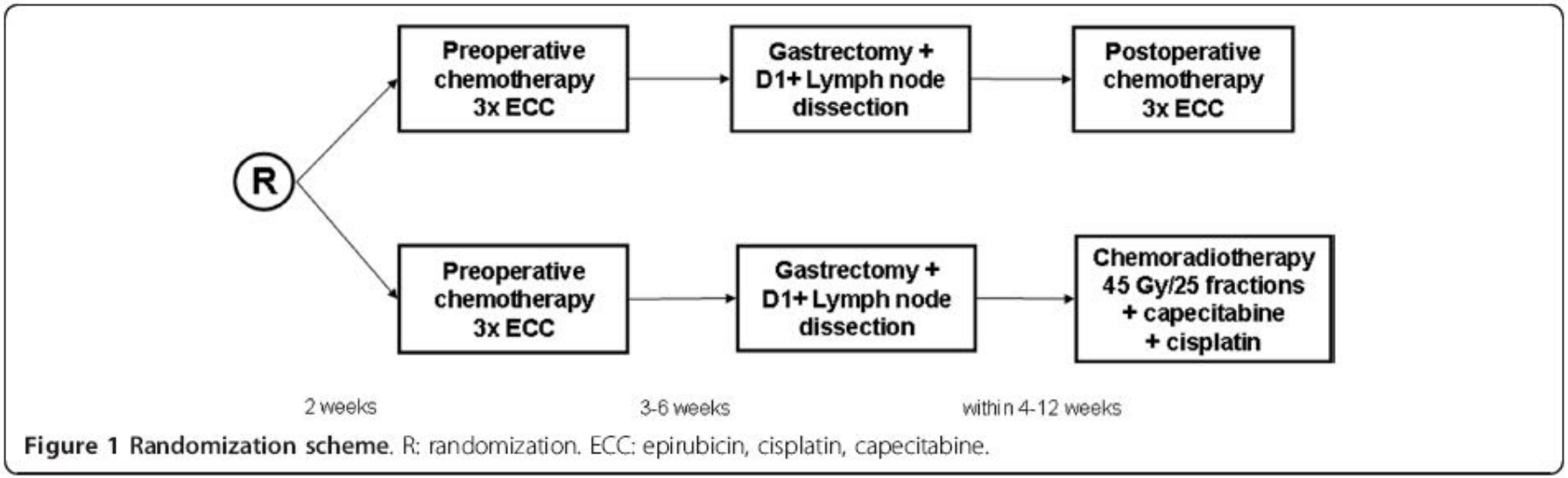


Figure 1 Randomization scheme. R: randomization. ECC: epirubicin, cisplatin, capecitabine.

REALTA' NON CONFRONTABILI?

Gastric Cancer: Nagoya Is Not New York

John S. Macdonald, *Aptium Oncology, Los Angeles, CA*

See accompanying article on page 4387

JCO 2011

Gastric Cancer: Apples Will Always Be Apples

JCO 2012

Jaffer A. Ajani, Mariela A. Blum, Jeannelyn S. Estrella, Prajnan Das, and Keith F. Fournier

EVIDENZE NON "ESPORTABILI"?

- **POST-OPERATIVE CHEMORADIATION IMPROVES OUTCOME (SWOG-INT 0116) (1b,A)**
  - Only **N+ /stage III, after D2** (ASIAN STUDIES - ARTIST)→ **ARTIST 2**
  - ALWAYS ,but especially **N+ and R1 patients, after D1** (Western studies DUTCH, trials – SEER 2012) → **CRITICS**

- **PERIOPERATIVE CHEMOTHERAPY (MAGIC) IMPROVES OUTCOME (1b,A)**

pancreas

2012: quali nuove evidenze a supportare

Ruolo Radioterapia Adiuvante

Ruolo Radioterapia neo-adiuvante

?

2012 = Analisi del passato per “organizzare il futuro”

ATTIVAZIONE NUOVI TRIALS

DEFINIZIONE DI LINEE GUIDA

nonostante

Printed by giovanna mantello on 8/31/2012 6:01:20 PM. For personal use only. Not approved for distribution. Copyright © 2012 National Comprehensive Cancer Network, Inc

NCCN National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2012
Pancreatic Adenocarcinoma

→ Si RT ADIUVANTE

Currently there is no consensus around the world on what constitutes "standard" adjuvant therapy for pancreatic cancer.

This controversy derives from several studies, each fraught with its own limitations dose, technique, volumes… , equipment (1973) , no QA

Standards of care vary with regard to geography and economy:

→ **chemo-radiotherapy followed by chemotherapy or vice versa is considered the optimal therapy in North America**

→ **chemotherapy alone is the current standard in Europe.**

L.Bujanda *World J Gastroenterol* 2012
A.G. Morganti ESTRO 2012

RUOLO RT ADIUVANTE

Tabella 1 **Studi randomizzati: neoplasie resecabili**

Trial	*Trattamento*	*N° pazienti*	*Recidiva locale (%)*	*Metastasi (%)*	*Sopravvivenza*		
					libera da malattia a 2 anni (%)	*globale a 5 anni (%)*	*mediana (mesi)*
GITSG	RT + CT (5FU a bolo, durante e dopo RT per 2 anni)	21	47	40	48	14	20
	Osservazione	22	33	52	14	4	11
EORTC	RT + CT (5FU i.c. durante RT)	218 (114 pancreas)	36	49	37	20 (pancreas)	17.1 (pancreas)
	Osservazione		36	49	38	10 (pancreas)	12.6 (pancreas)
ESPAC-1	RT + CT (5FU a bolo durante RT)	73	62 in tutti i gruppi di pazienti	61 in tutti i gruppi di pazienti		7	13.9
	RT + CT (5FU a bolo durante RT seguito da acido folinico e 5FU per 6 mesi)	75				29	21.6
	CT (FUFA: 5FU e acido folinico mensilmente per 6 mesi)	72				13	19.9
	Osservazione	69				11	16.9

n.s.

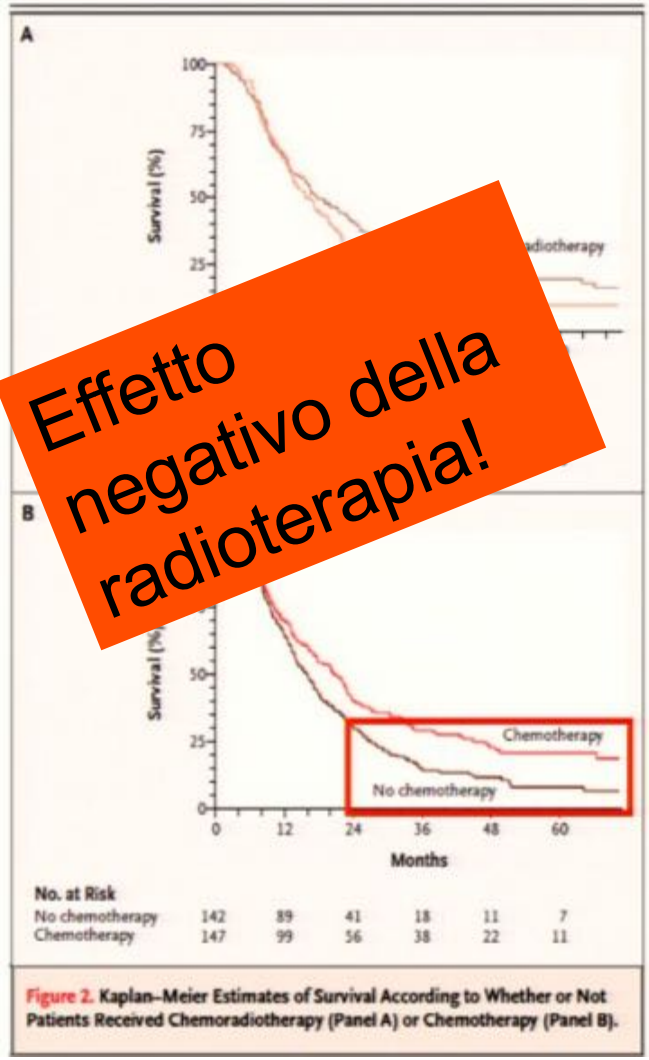
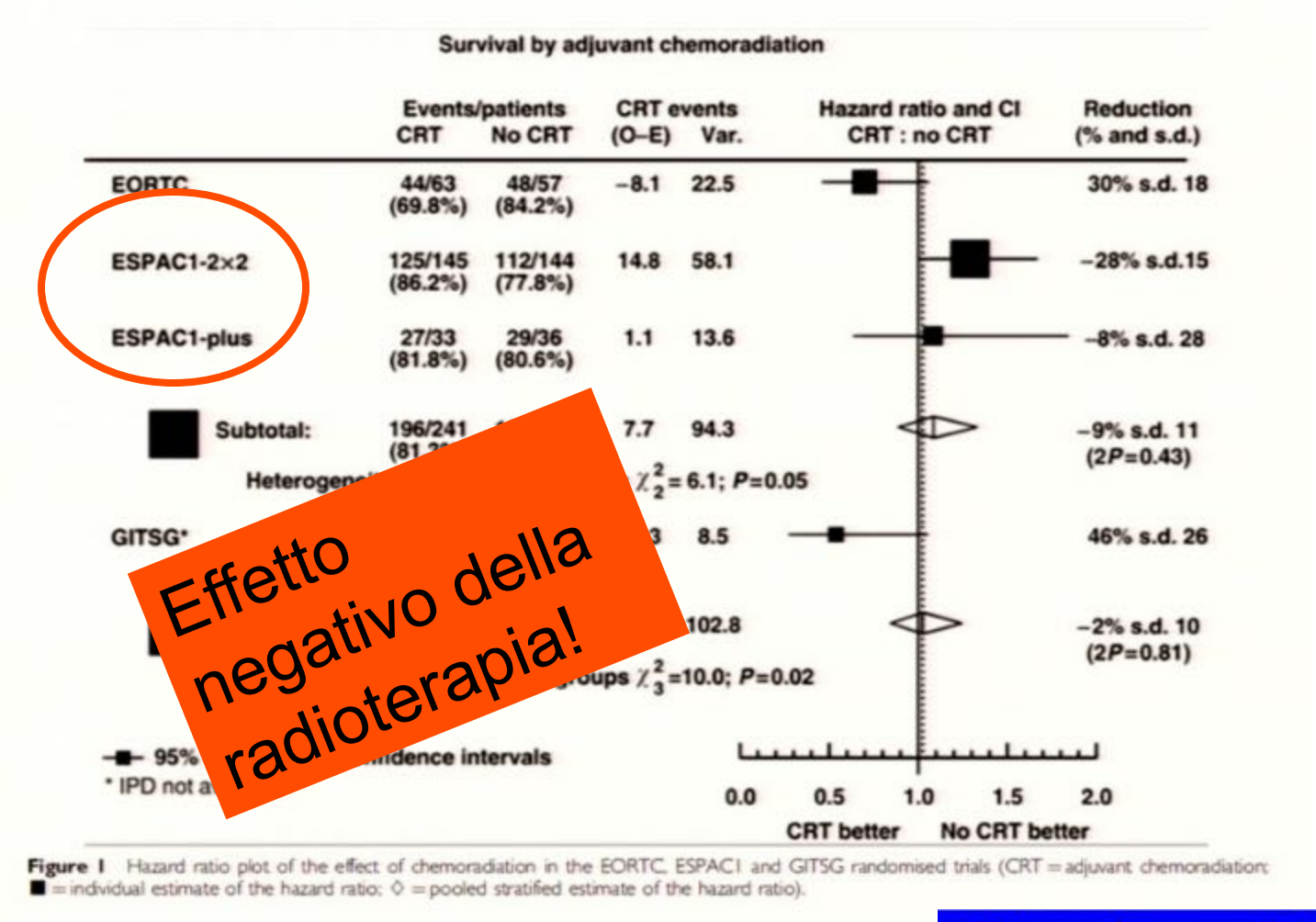


Figure 2. Kaplan–Meier Estimates of Survival According to Whether or Not Patients Received Chemoradiotherapy (Panel A) or Chemotherapy (Panel B).

Effetto negativo della radioterapia!

RUOLO RT ADIUVANTE

metaanalisi



Effetto negativo della radioterapia!

Figure 1 Hazard ratio plot of the effect of chemoradiation in the EORTC, ESPAC1 and GITSG randomised trials (CRT = adjuvant chemoradiation; ■ = individual estimate of the hazard ratio; ◊ = pooled stratified estimate of the hazard ratio).

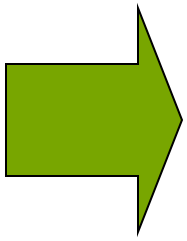
Stocken DD et al.,
BJC 2005

RUOLO RT ADIUVANTE

study type		survival	comment
randomized studies	GITSG 1985	improved	
	EORTC 1999	improved	NS
	ESPAC 2004	reduced	NS
retrospective stud.	UCSC 2001	improved	NS
	John Hopkins 2008	improved	
	Mayo 2008	improved	
	You 2009	improved	N+ & R1
meta-analysis	Stocken 2005	not improved	
	Khanna 2006	improved	
pooled analysis	Merchant 2009	improved	N+
	Hsu 2010	improved	
tumor registry	Lim 2003	improved	
	Hazard 2007	improved	> T2 and/or N+
	Vanderveen 2009	improved	N+ or G3
	Mc Dade 2010	improved	

Mod A.G. MORGANTI ESTRO31 2012

La radioterapia adiuvante puo' migliorare l'outcome



Necessita' di
nuovi trial clinici
Linee guida e QA

QA NEI TRIAL CLINICI

RADIATION THERAPY ONCOLOGY GROUP
RTOG 97-04
SWOG/ECOG R9704

A PHASE III STUDY OF PRE AND POST CHEMORADIATION 5-FU VS. PRE AND POST CHEMORADIATION GEMCITABINE FOR POSTOPERATIVE ADJUVANT TREATMENT OF RESECTED PANCREATIC ADENOCARCINOMA

SCHEMA

S **Nodal Status**
1. Uninvolved
T 2. Involved

R **Tumor Diameter**
1. < 3 cm
A 2. ≥ 3 cm

T **Surgical Margins**
1. Negative
I 2. Positive
3. Unknown
F

Y

R

A **Arm 1**: Pre-CRT 5-FU + Chemoradiation *(CRT)* *(5-FU/RT)* + Post-CRT 5-FU

N

D

O **Arm 2:** Pre-CRT Gemcitabine + Chemoradiation *(CRT)* *(5-FU/RT)* + Post-CRT Gemcitabine

M

I

Z

E

GEM >5FU

QA NEI TRIAL CLINICI

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. 809–816, 2012

FAILURE TO ADHERE TO PROTOCOL SPECIFIED RADIATION THERAPY GUIDELINES WAS ASSOCIATED WITH DECREASED SURVIVAL IN RTOG 9704—A PHASE III TRIAL OF ADJUVANT CHEMOTHERAPY AND CHEMORADIOTHERAPY FOR PATIENTS WITH RESECTED ADENOCARCINOMA OF THE PANCREAS

Ross A. Abrams, M.D.,* Kathryn A. Winter, M.S.,† William F. Regine, M.D.,‡ Howard Safran, M.D.,§ John P. Hoffman, M.D.,‖ Robert Lustig, M.D.,† Andre A. Konski, M.D.,¶ Al B. Benson, M.D.,** John S. Macdonald, M.D.,†† Tyvin A. Rich, M.D.,‡‡ and Christopher G. Willett, M.D.§§

R-D

(b)

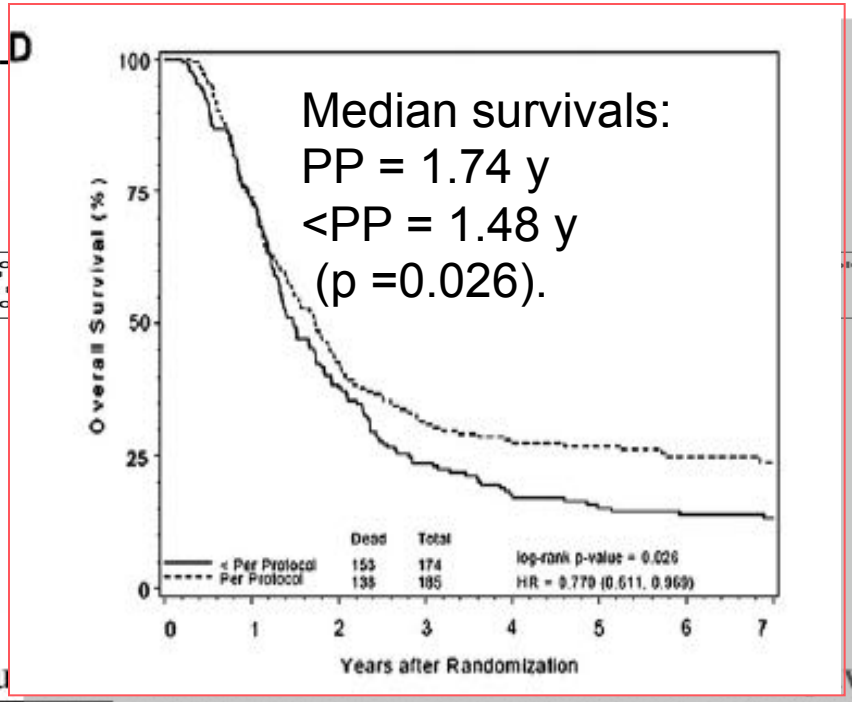


Table 5. Multivariate analysis for overall survival (continued): head of pancreas patients only (n = 359)

Adjustment variables	Comparison	Adjusted HR	p value†
Treatment	Gemcitabine vs. 5-FU	0.79 (0.62–0.99)	0.043
Nodal involvement	No vs. yes	1.47 (1.13–1.91)	0.0036
Tumor diameter	<3 vs. ≥3 cm	1.25 (0.98–1.59)	0.070
Surgical margin status	Negative	Reference level	–
	Positive	1.07 (0.82–1.40)	0.64
	Unknown	0.94 (0.69–1.27)	0.68
RT QA score	<PP vs. PP	0.75 (0.60–0.95)	0.016

Conclu vant protocol for pancreatic adenocarcinoma to evaluate the impact of adherence to specified RT protocol guidelines on protocol outcomes. Failure to adhere to specified RT guidelines was associated with reduced survival and, for patients receiving gemcitabine, trend toward increased nonhematologic toxicity. © 2012 Elsevier Inc.

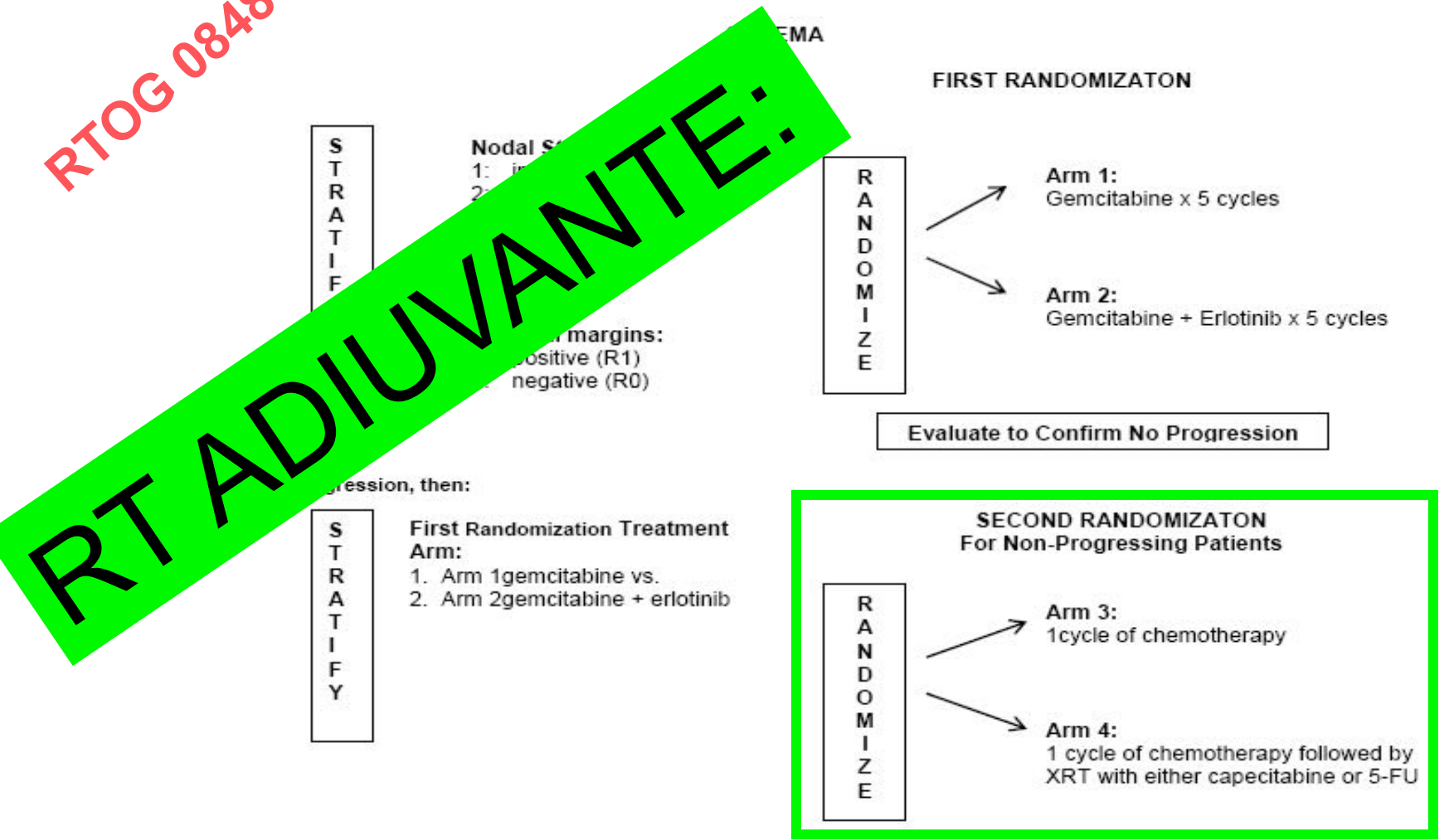
QA NEI TRIAL CLINICI

RTOG 0848

RT ADIUVANTE:

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0848
A Phase III Trial Evaluating Both Erlotinib and Chemoradiation as Adjuvant Treatment for Patients with Resected Head of Pancreas Adenocarcinoma



QA NEI TRIAL CLINICI

RT NEL LOCALMENTE AVANZATO

GERCOR LAP 07

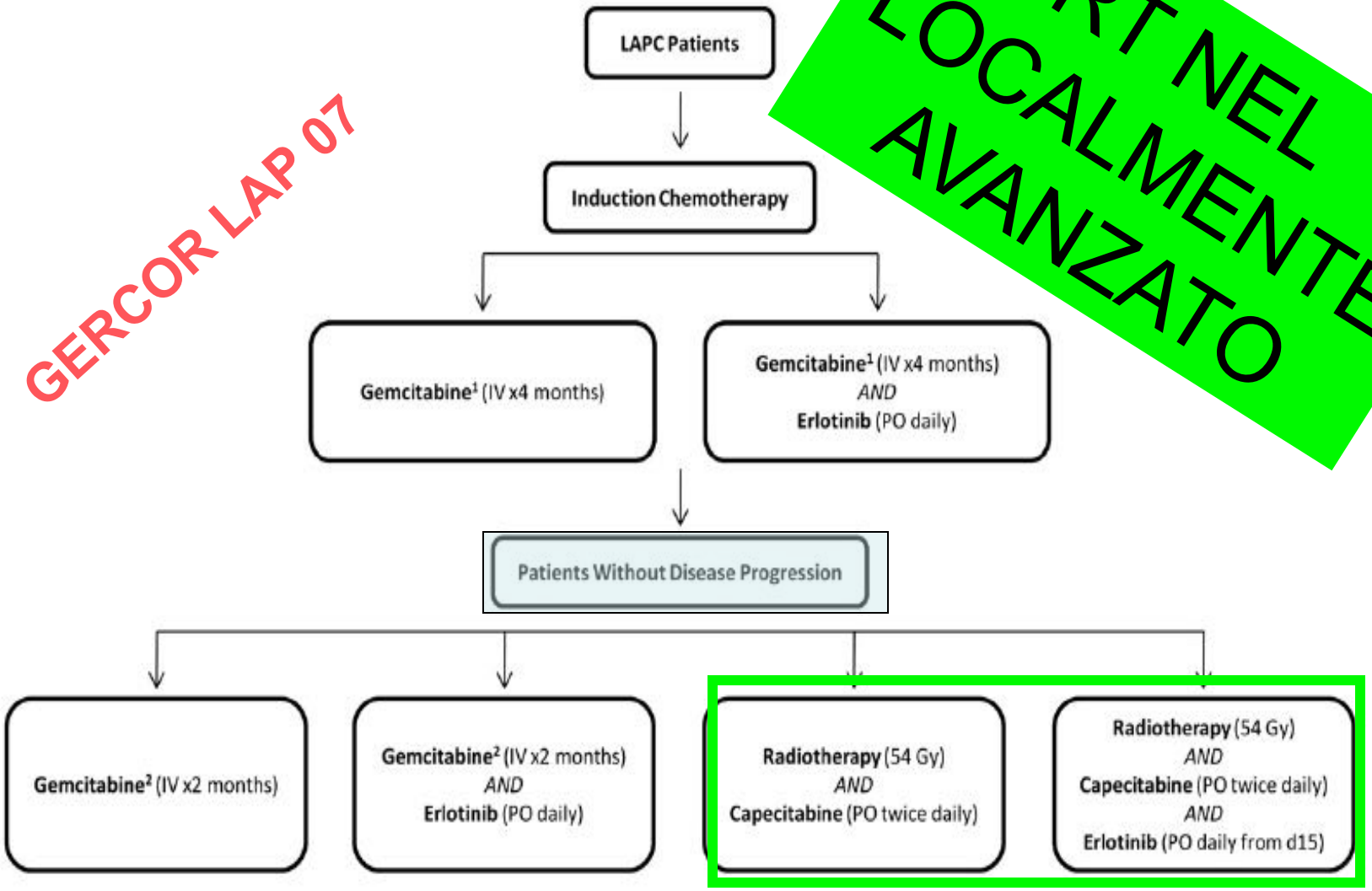


Fig. GERCOR LAP 07 Phase III Trial. Chemoradiation therapy flow diagram. 1 = d1, 8, 15, 22, 29, 36, 43; d57, 64, 71, 85, 92, 99. 2 = d113, 120, 127; d141, 148, 155. Gemcitabine dose schedule: 1 = days 1, 8, 15, 22, 29, 36, 43; 57, 64, 71, 85, 92, 99. 2 = days 113, 120, 127; 141, 148, 155".

QA NEI TRIAL CLINICI

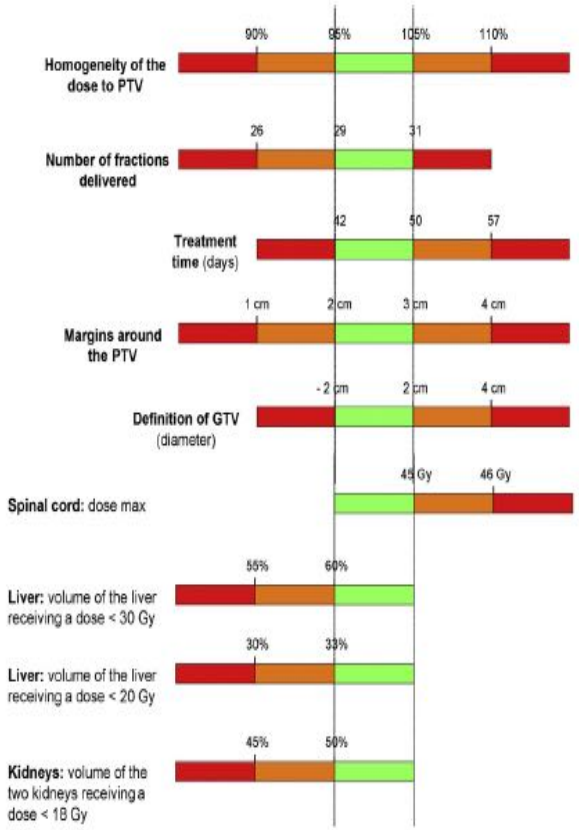
Critical Review

Int J Radiation Oncol Biol Phys, Vol. 83, No. 5, pp. 1355–1364, 2012

Radiotherapy Technical Considerations in the Management of Locally Advanced Pancreatic Cancer: American-French Consensus Recommendations

Florence Huguet, M.D., Ph.D.,* Karyn A. Goodman, M.D.,† David Azria, M.D., Ph.D.,‡ Severine Racadot, M.D.,§ and Ross A. Abrams, M.D.¶

green = per protocol

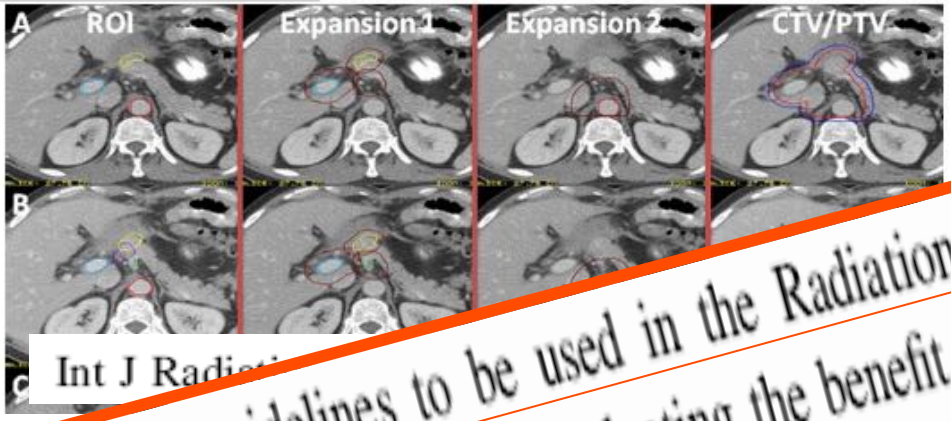


An expert panel convened in May 2008 with members of RTOG and GERCOR to prepare the guidelines.

MEDLINE 1980 – 2011
ASCO – ASTRO 2005 - 2011

This kind of QA is used in the ongoing LAP07 trial

QA NEI TRIAL CLINICI



Int J Radiat

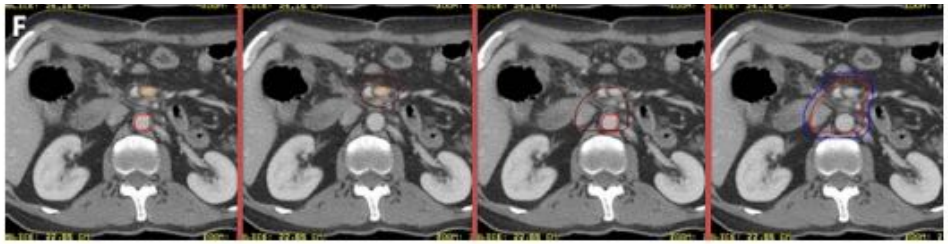
Purpose: To develop contouring guidelines to be used in the Radiation Therapy Oncology Group protocol 0848, a Phase III randomized trial evaluating the benefit of adjuvant chemoradiation in patients with resected head of pancreas cancer.

Radiati… …anel

…linical Target

…reatment of Pancreatic

…oodman, M.D.,* William F. Regine, M.D.,† Laura A. Dawson, M.D.,‡
Edgar Ben-Josef, M.D.,§ Karin Haustermans, M.D.,‖ Walter R. Bosch, D.Sc.,¶
Julius Turian, Ph.D,** and Ross A. Abrams, M.D.**



RADIOTERAPIA NEO-ADIUVANTE : quale ruolo?

ESTRO 31
MAY 2012 • 9-13

OC-0456

NEOADJUVANT CHEMORADIOTHERAPY VS SURGERY FOR PANCREATIC CANCER. A MULTI-CENTRE RANDOMISED PHASE II TRIAL

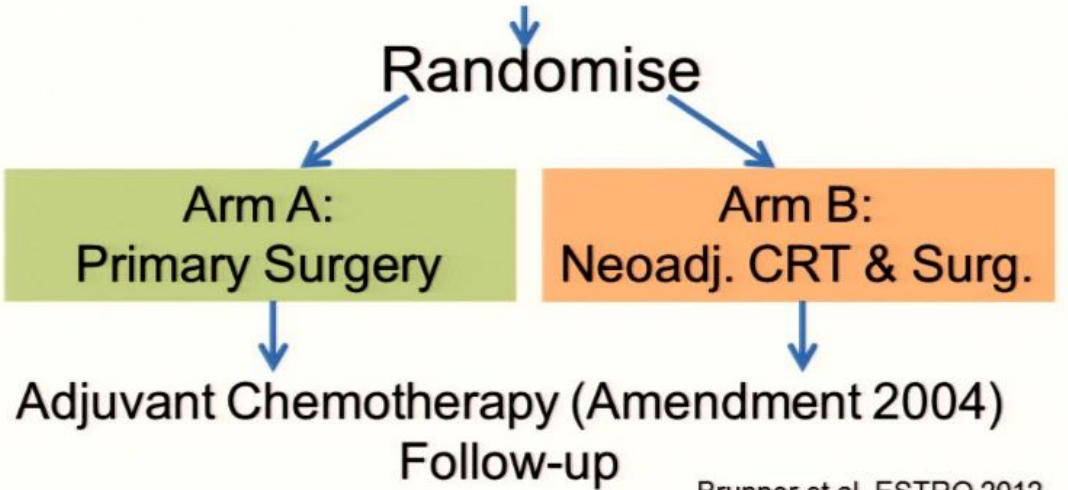
T. Brunner[1], H. Golcher[2], H. Witzigmann[3], L. Marti[4], W. Bechstein[5], C. Bruns[6], J. Hauss[7], S. Merkel[2], R. Fietkau[8], W. Hohenberger[2]

[1]*University of Oxford, Oncology, Oxford, United Kingdom*
[2]*University Hospitals Erlangen, Surgery, Erlangen, Germany*
[3]*Krankenhaus Dresden Friedrichstadt, Surgery, Dresden, Germany*
[4]*Kantonsspital St. Gallen, Surgery, St. Gallen, Switzerland*
[5]*University Hospitals Frankfurt, Surgery, Frankfurt am Main, Germany*
[6]*University Hospitals Munich Großhadern, Surgery, Munich, Germany*
[7]*University Hospitals Leipzig, Surgery, Leipzig, Germany*
[8]*University Hospitals Erlangen, Radiation Oncology, Erlangen, Germany*

CA RESECABILE

centre p II RCT

- Histologically confirmed PDAC of the head
- Tumour contact ≤ 180° at peripancreatic vessels
- No distant mets



Brunner et al. ESTRO 2012

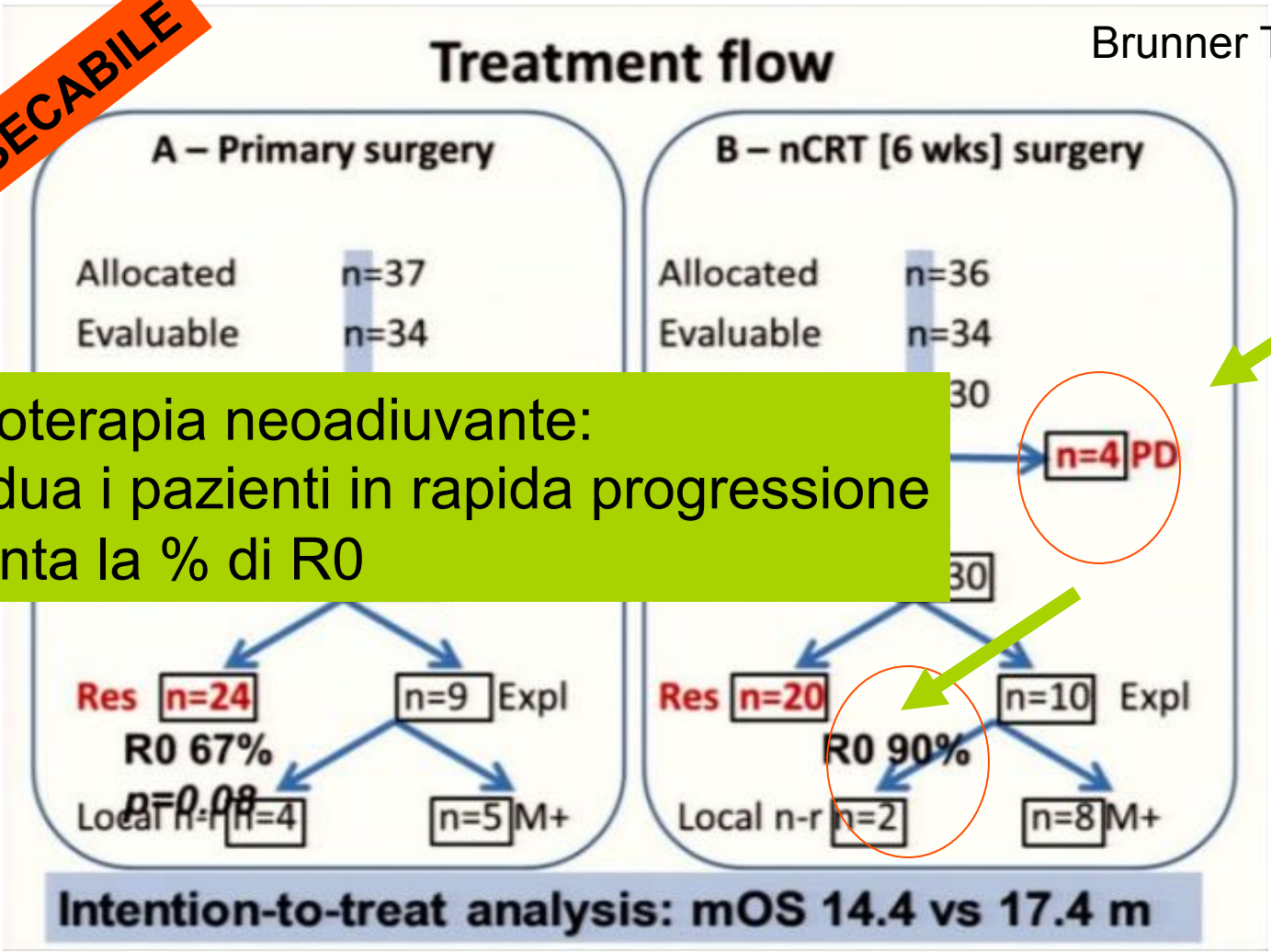
RADIOTERAPIA NEO-ADIUVANTE : quale ruolo?

webcast by streamdis.eu

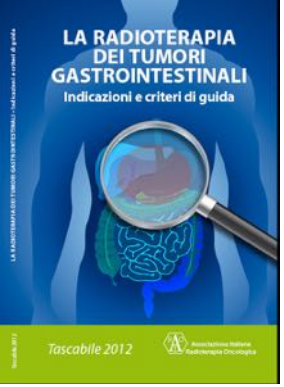
ESTRO 31
MAY 2012 • 9-13

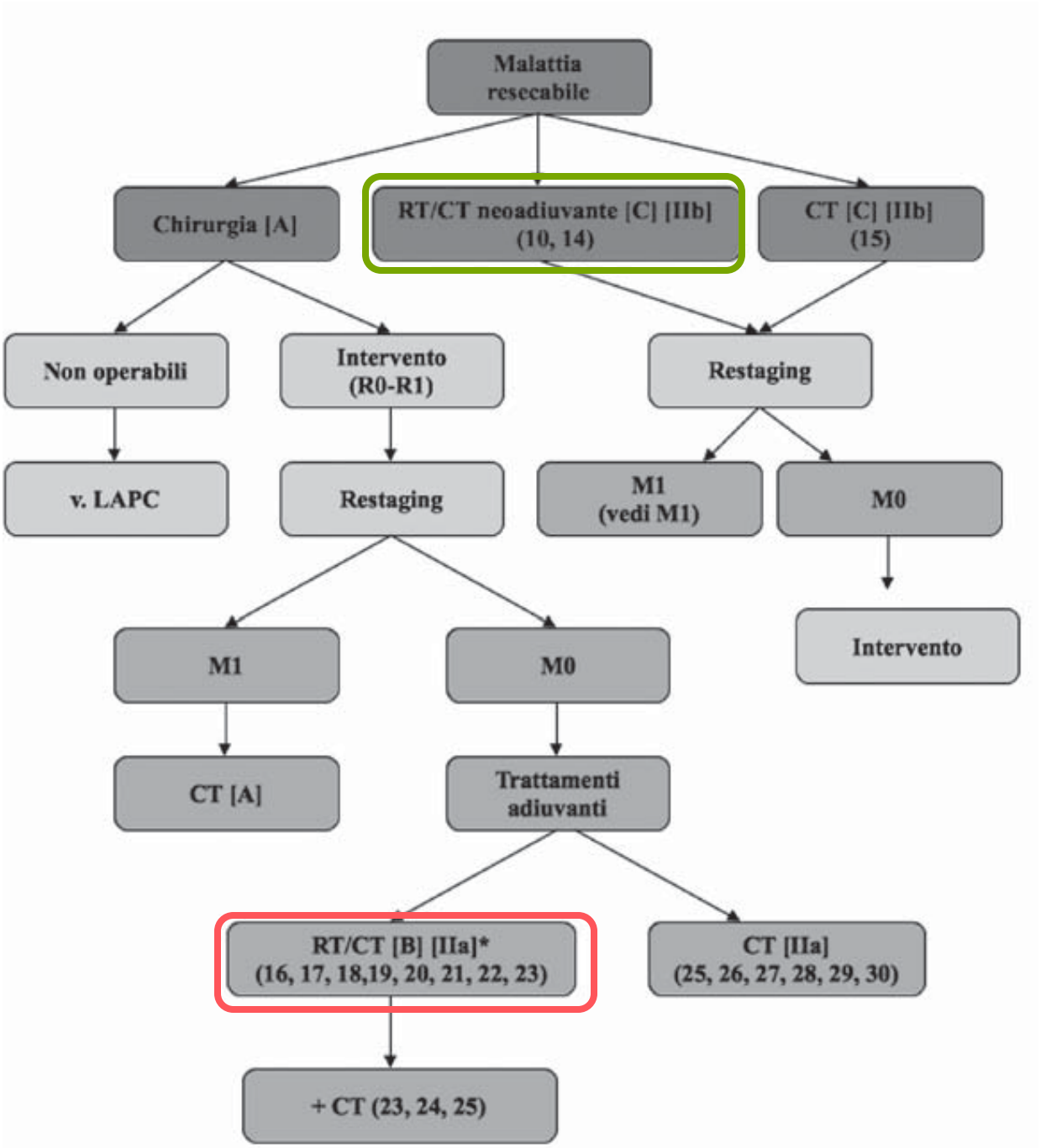
CA RESECABILE

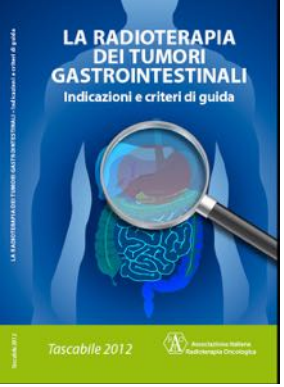
Brunner T, UK - Oxford



La radioterapia neoadiuvante:
- individua i pazienti in rapida progressione
- aumenta la % di R0


LA RADIOTERAPIA DEI TUMORI GASTROINTESTINALI
Indicazioni e criteri di guida
Tascabile 2012


Malattia resecabile
Chirurgia [A]
RT/CT neoadiuvante [C] [IIb] (10, 14)
CT [C] [IIb] (15)
Non operabili
Intervento (R0-R1)
Restaging
v. LAPC
Restaging
M1 (vedi M1)
M0
Intervento
M1
M0
CT [A]
Trattamenti adiuvanti
RT/CT [B] [IIa]* (16, 17, 18,19, 20, 21, 22, 23)
CT [IIa] (25, 26, 27, 28, 29, 30)
+ CT (23, 24, 25)


LA RADIOTERAPIA DEI TUMORI GASTROINTESTINALI
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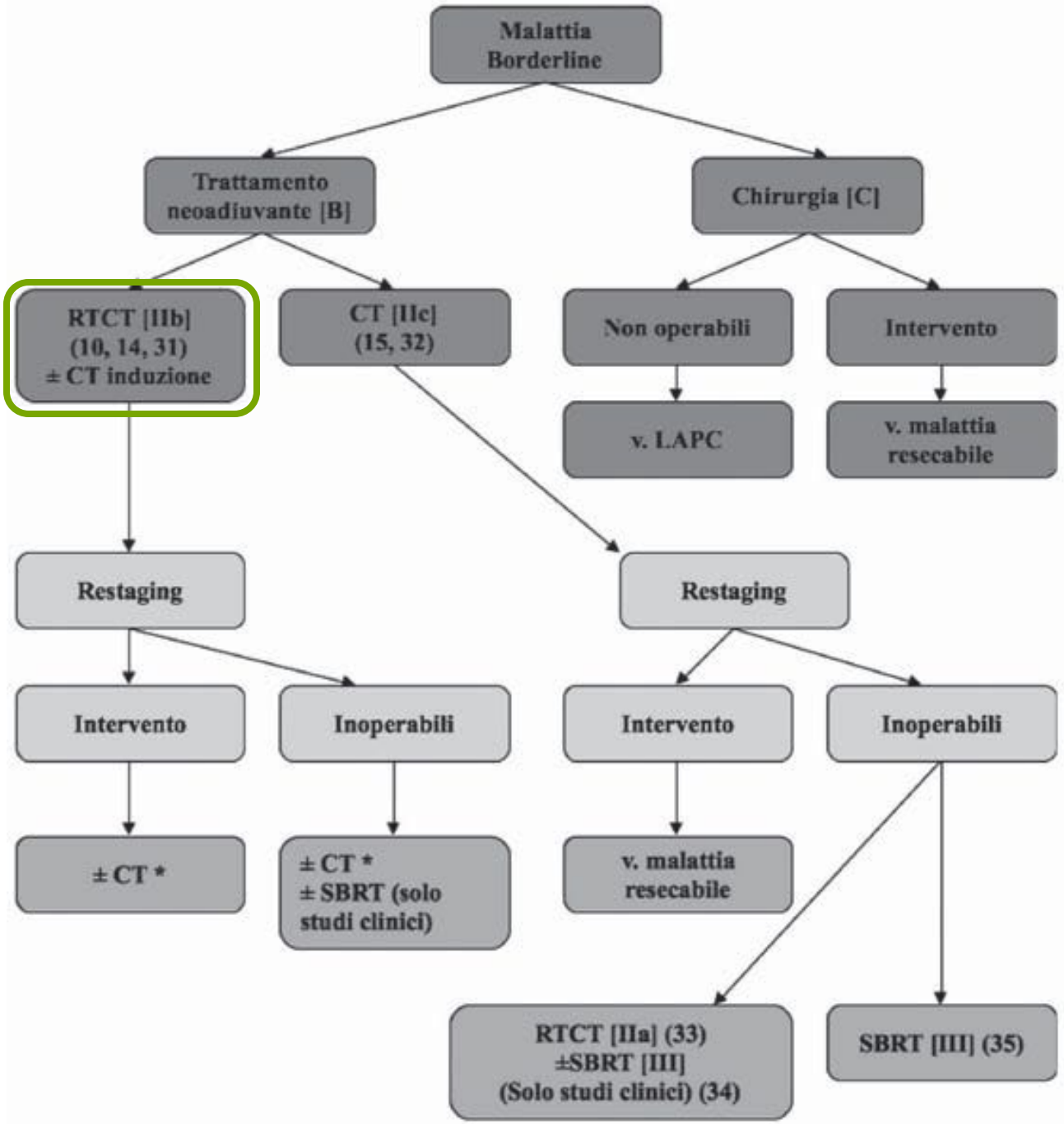
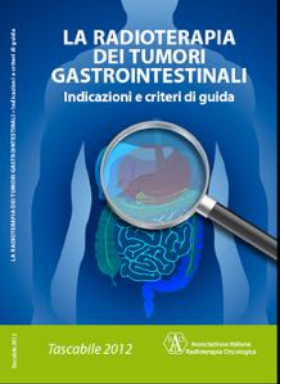
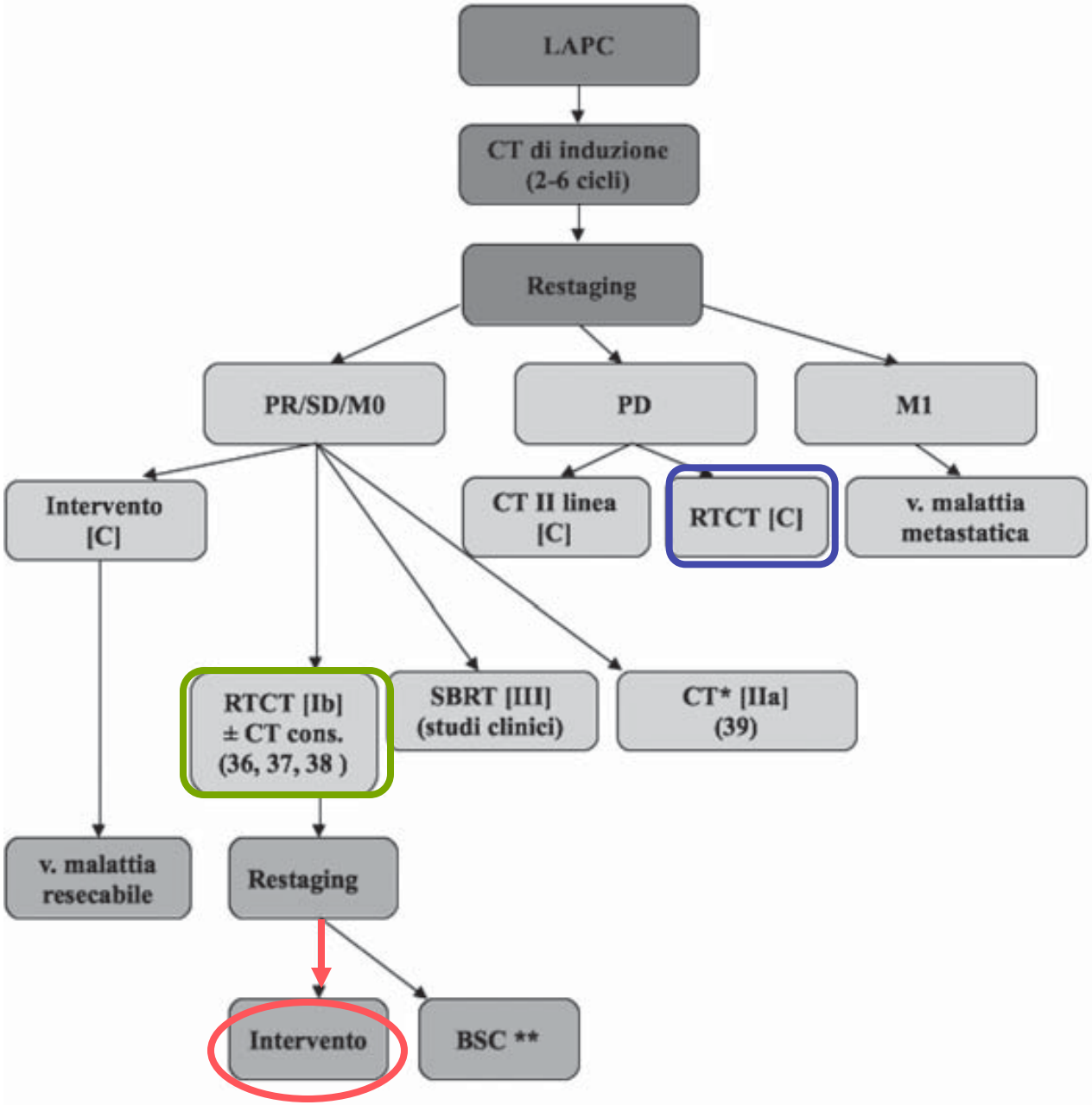
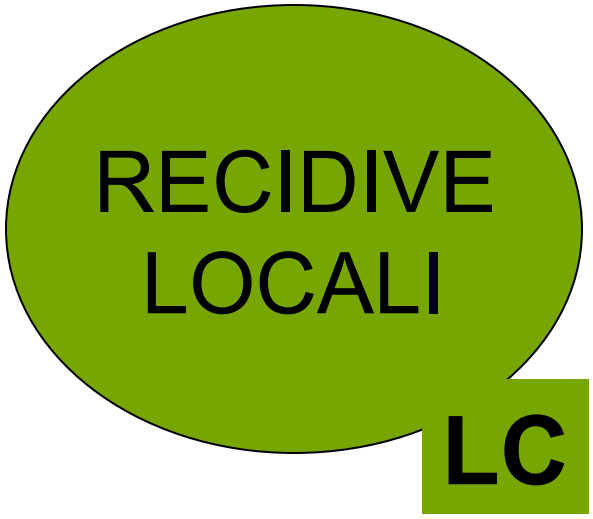

Malattia Borderline
Trattamento neoadiuvante [B]
Chirurgia [C]
RTCT [IIb] (10, 14, 31) ± CT induzione
CT [IIc] (15, 32)
Non operabili
Intervento
v. LAPC
v. malattia resecabile
Restaging
Restaging
Intervento
Inoperabili
Intervento
Inoperabili
± CT *
± CT * ± SBRT (solo studi clinici)
v. malattia resecabile
RTCT [IIa] (33) ±SBRT [III] (Solo studi clinici) (34)
SBRT [III] (35)


LA RADIOTERAPIA
DEI TUMORI
GASTROINTESTINALI
Indicazioni e criteri di guida
Tascabile 2012


LAPC
CT di induzione
(2-6 cicli)
Restaging
PR/SD/M0
PD
M1
Intervento
[C]
CT II linea
[C]
RTCT [C]
v. malattia
metastatica
RTCT [Ib]
± CT cons.
(36, 37, 38)
SBRT [III]
(studi clinici)
CT* [IIa]
(39)
v. malattia
resecabile
Restaging
Intervento
BSC **

retto



2012: quali nuove evidenze ?

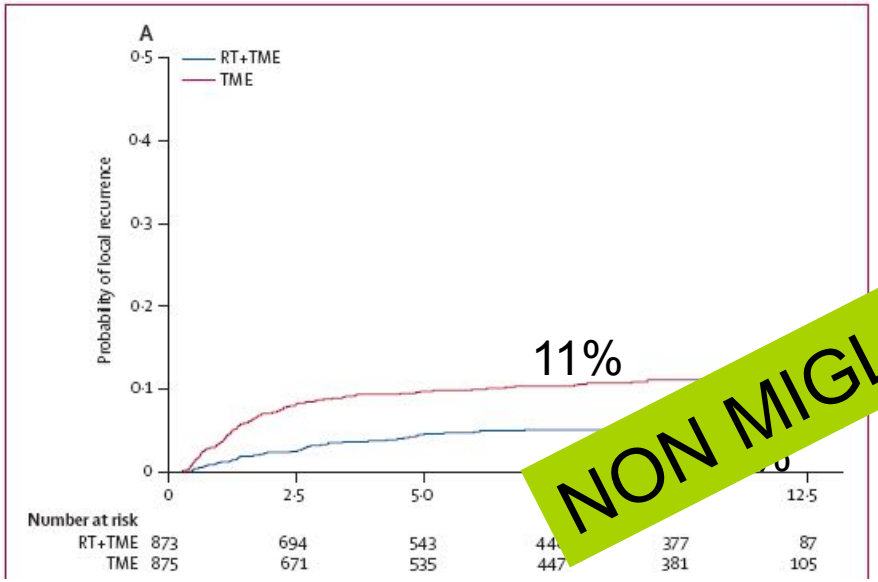
RT+TME = TME ?

DUTCH trial

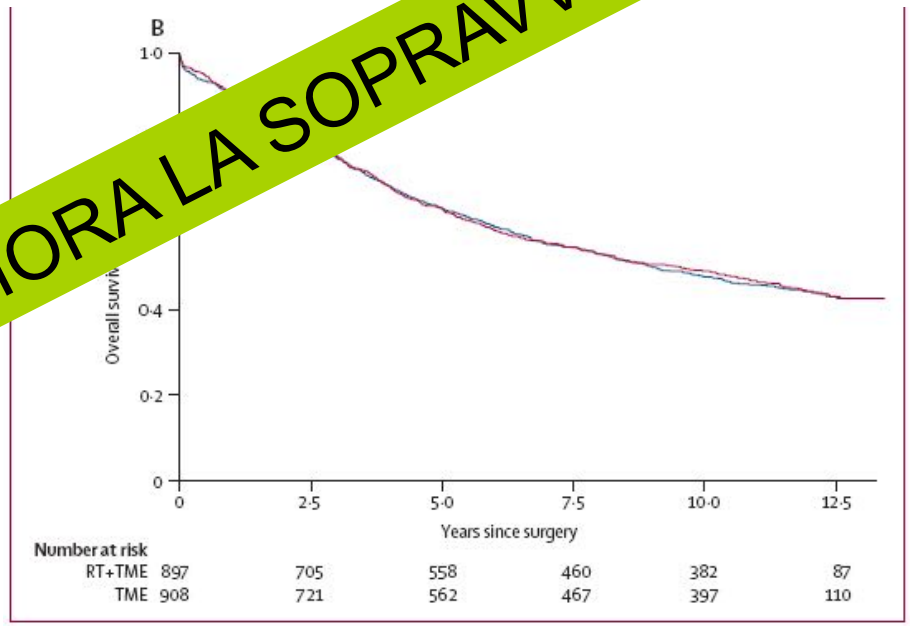
Lancet Oncol 2011; 12: 575–82

Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial

Willem van Gijn, Corrie A M Marijnen, Iris D Nagtegaal, Elma Meershoek-Klein Kranenbarg, Hein Putter, Theo Wiggers, Harm J T Rutten, Lars Påhlman, Bengt Glimelius, Cornelis J H van de Velde, for the Dutch Colorectal Cancer Group



NON MIGLIORA LA SOPRAVVIVENZA



RTCHEM = RT ?

EORTC 22921
FFCD 9203

European Journal of Cancer (2012) 48, 1781–1790

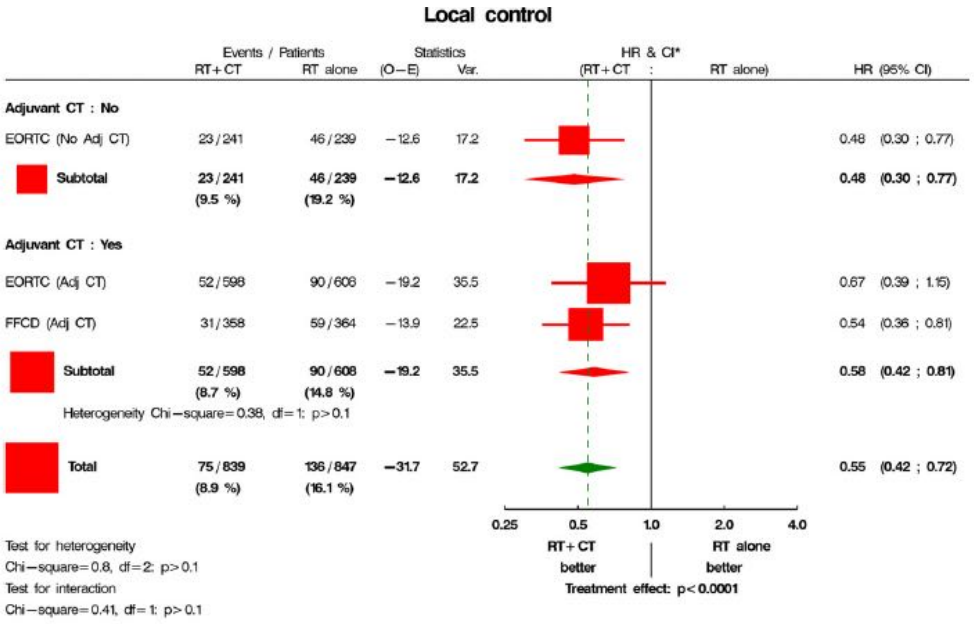
Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

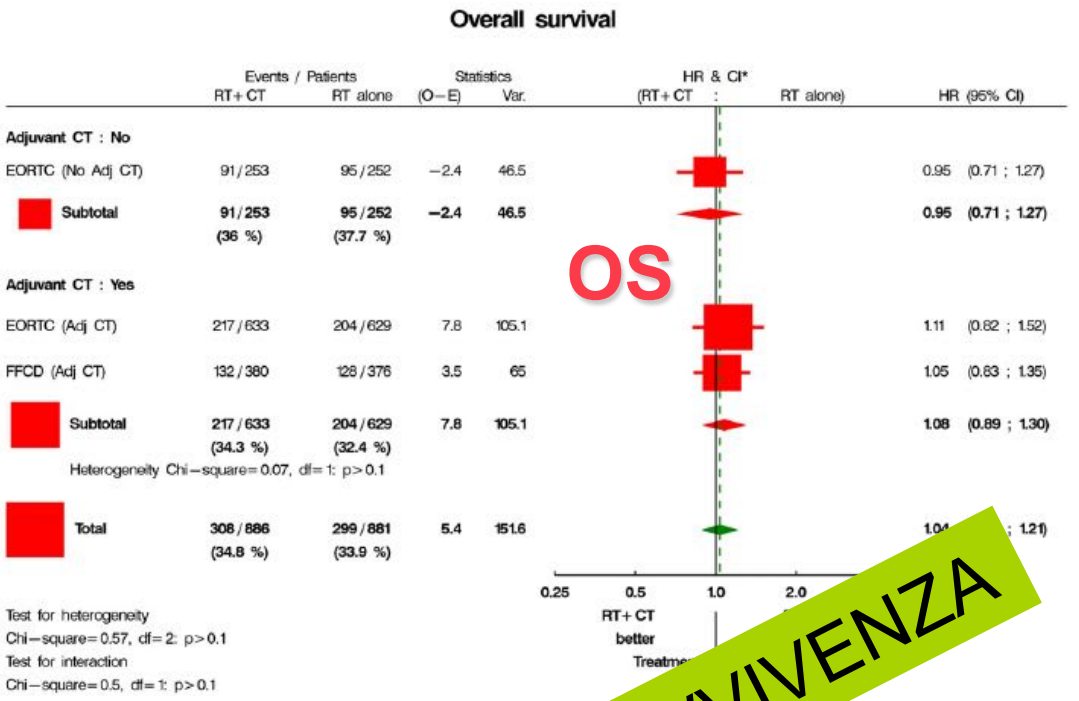
What is the clinical benefit of preoperative chemoradiotherapy with 5FU/leucovorin for T3-4 rectal cancer in a pooled analysis of EORTC 22921 and FFCD 9203 trials: Surrogacy in question?

F. Bonnetain [a,*], J.F. Bosset [b], J.P. Gerard [c], G. Calais [d], T. Conroy [e], L. Mineur [f], O. Bouché [g], P. Maingon [h], O. Chapet [i], L. Radosevic-Jelic [j], N. Methy [a], L. Collette [k]

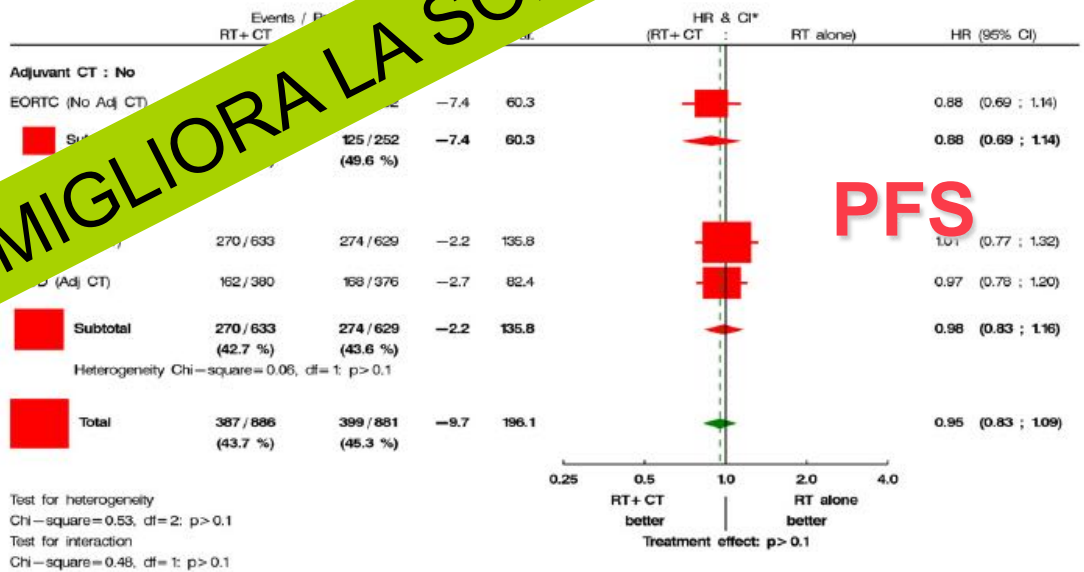


RTCHEM = RT ?

EORTC 22921
FFCD 9203



NON MIGLIORA LA SOPRAVVIVENZA



RTCHEM preop = RTCHEM postop ?

VOLUME 30 · NUMBER 16 · JUNE 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

CAO/ARO/AIO 94

Preoperative Versus Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial After a Median Follow-Up of 11 Years

Rolf Sauer, Torsten Liersch, Susanne Merkel, Rainer Fietkau, Werner Hohenberger, Clemens Hess, Heinz Becker, Hans-Rudolf Raab, Marie-Therese Villanueva, Helmut Witzigmann, Christian Wittekind, Tim Beissbarth, and Claus Rödel

See accompanying editorial on page 1901; listen to the podcast by Dr Hong at www.jco.org/podcasts

RTCHEM preop = RTCHEM postop ?

CAO/ARO/AIO 94

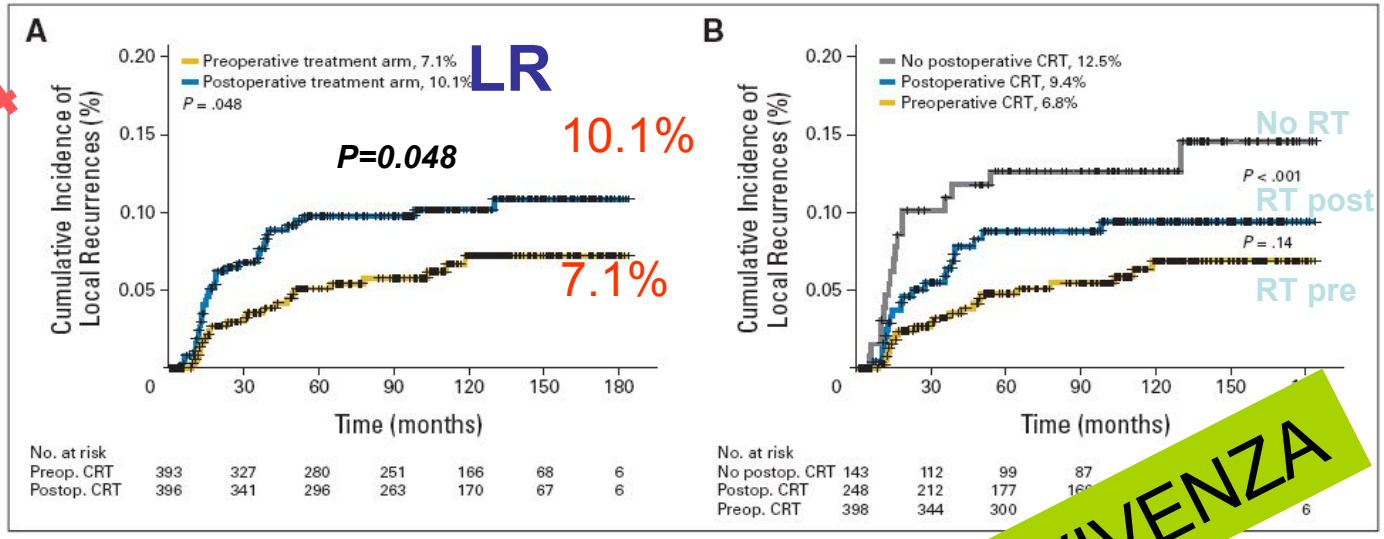


Fig 3. Cumulative incidence of local recurrences after macroscopically complete local tumor resection in the … (A) and according to treatment received (B). CRT, chemoradiotherapy; preop, preoperative; postop, postoperative.

NON MIGLIORA LA SOPRAVVIVENZA

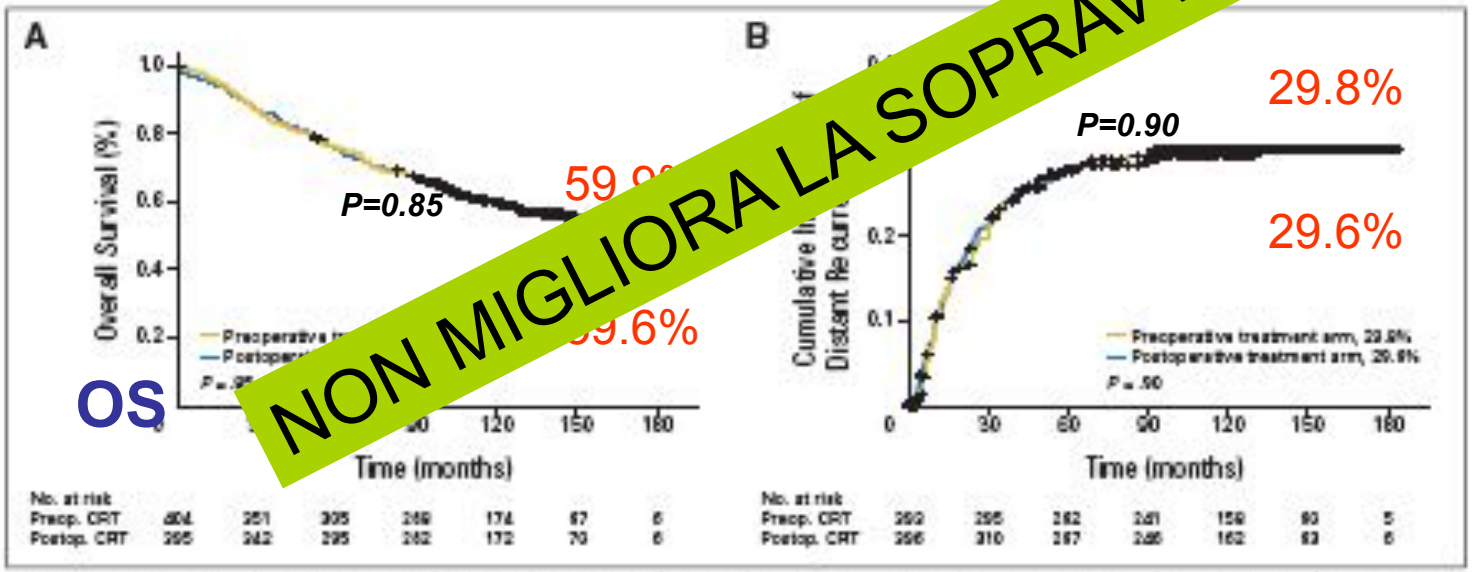


Fig 2. (A) Overall survival and (B) cumulative incidence of distant recurrences in the intention-to-treat population. CRT, chemoradiotherapy; preop, preoperative;

Up date studi “storici”:

→ la radioterapia preoperatoria migliora il controllo locale ma non OS e DFS

OXALIPLATINO

Quale ruolo ?

OXALIPLATINO MIGLIORA L'OUTCOME ?

ACCORD 12

Published Ahead of Print on October 29, 2012 as 10.1200/JCO.2012.42.8771
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2012.42.8771

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Clinical Outcome of the ACCORD 12/0405 PRODIGE 2 Randomized Trial in Rectal Cancer

Jean-Pierre Gérard, David Azria, Sophie Gourgou-Bourgade, Isabelle Martel-Lafay, Christophe Hennequin, Pierre-Luc Etienne, Véronique Vendrely, Eric François, Guy de La Roche, Olivier Bouché, Xavier Mirabel, Bernard Denis, Laurent Mineur, Jean-François Berdah, Marc-André Mahé, Yves Bécouarn, Olivier Dupuis, Gérard Lledo, Jean-François Seitz, Laurent Bedenne, Béata Juzyna, and Thierry Conroy

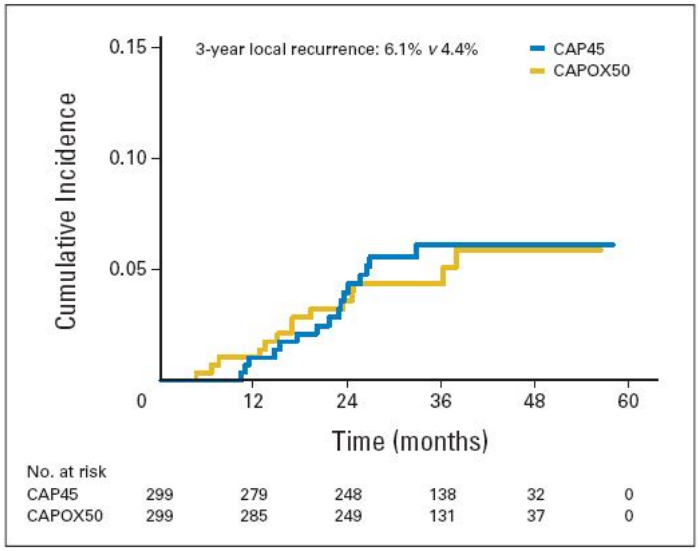


Fig 2. Intention-to-treat analysis of cumulative incidence of local recurrence (Kaplan-Meier estimate and log-rank test). CAP45, 45-Gy radiation therapy for 5 weeks with concurrent capecitabine; CAPOX50, 50-Gy radiation therapy for 5 weeks with concurrent capecitabine and oxaliplatin.

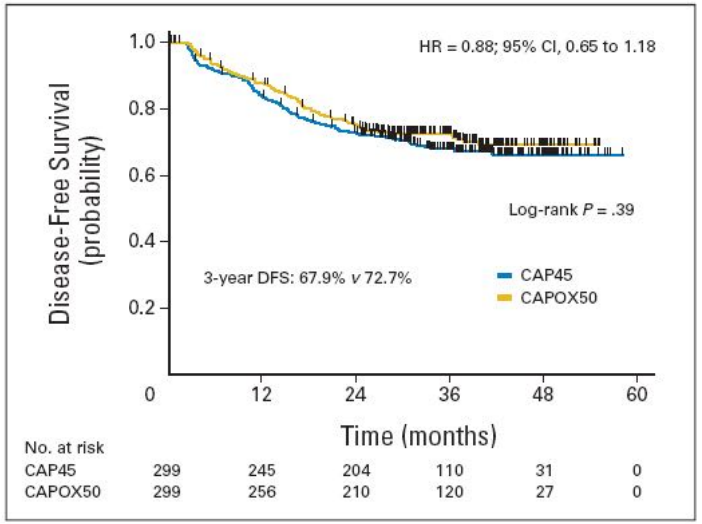


Fig 3. Intention-to-treat analysis of disease-free survival (DFS; Kaplan-Meier estimate and log-rank test). CAP45, 45-Gy radiation therapy for 5 weeks with concurrent capecitabine; CAPOX50, 50-Gy radiation therapy for 5 weeks with concurrent capecitabine and oxaliplatin; HR, hazard ratio.

3y local recurrence

3y DFS

OXALIPLATINO MIGLIORA L'OUTCOME ?

ACCORD 12

Event	CAP45 (n = 299)	CAPOX50 (n = 299)
Recurrence		
Local recurrence alone	5	5
Local recurrence with distant metastasis	11	9
Total local recurrence	16	14
Distant metastasis (alone or with local recurrence)		
Metastasis	73	66
Liver (alone or with other site)	40	
Lung (alone or with other site)	31	
Other site (no liver, no lung)		
Second cancer		
Death		
Total		
Resulting from rectal cancer		
Resulting from surgery		1
Resulting from		7
Toxicity		
	171	165
	48	52
	48	47
	19	15
	1	1
Missing	0	4

Abbreviations: CAP45, 45-Gy radiation therapy for 5 weeks with concurrent capecitabine; CAPOX50, 50-Gy radiation therapy for 5 weeks with concurrent capecitabine and oxaliplatin.

Conclusion
At 3 years, no significant difference in clinical outcome was achieved with the intensified CAPOX regimen. When compared with other recent randomized trials, these results indicate that concurrent administration of oxaliplatin and RT is not recommended.

pCR (P
C
% (*P* .09),

pCR + nearly CR
CAP45 28.9%
Versus
CAPOX50 39.4% (*P* .008).

In summary, surgery with total mesorectal excision remains the cornerstone of treatment of locally advanced rectal cancer. Neoadjuvant treatment with CT-RT is standard management, and various regimens have been tested in randomized studies. Because the ACCORD 12 trial showed no clinical benefit at 3-year follow-up with the addition of oxaliplatin, and taking into consideration other recent phase III trials, this CT regimen should not be recommended concurrently with irradiation.

OXALIPLATINO MIGLIORA L'OUTCOME ?

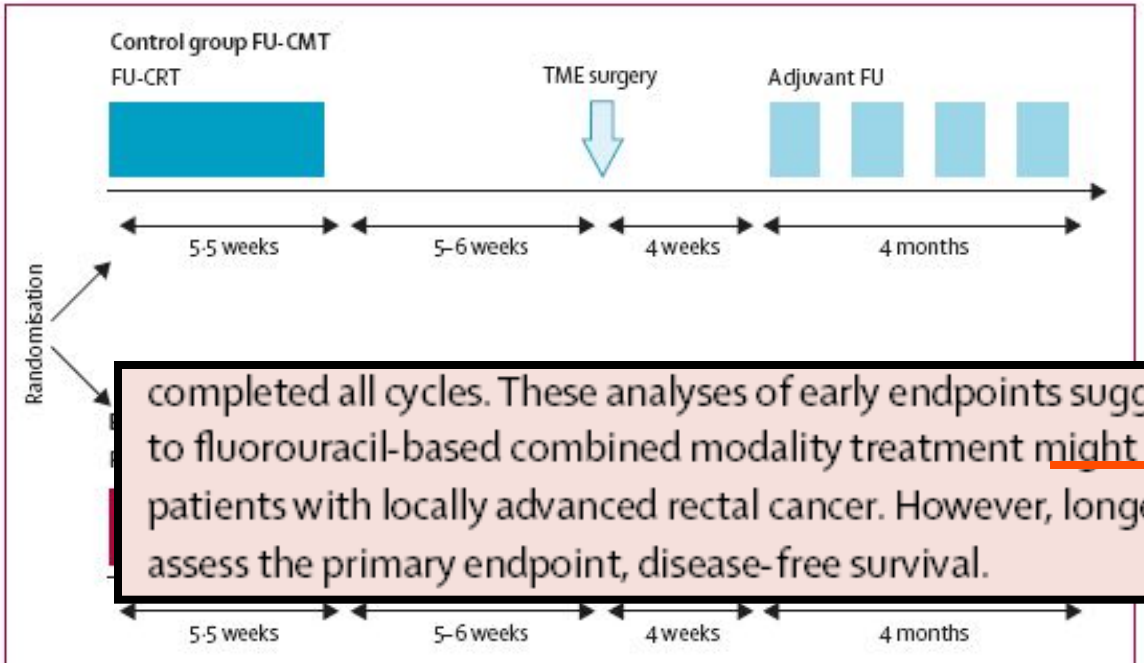
1236 pazienti

CAO/ARO/AIO 04

Lancet Oncol 2012; 13: 679–87

Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial

Claus Rödel, Torsten Liersch*, Heinz Becker, Rainer Fietkau, Werner Hohenberger, Torsten Hothorn, Ullrich Graeven, Dirk Arnold, Marga Lang-Welzenbach, Hans-Rudolf Raab, Heiko Sülberg, Christian Wittekind, Sergej Potapov, Ludger Staib, Clemens Hess, Karin Weigang-Köhler, Gerhard G Grabenbauer, Hans Hoffmanns, Fritz Lindemann, Anke Schlenska-Lange, Gunnar Folprecht, Rolf Sauer, on behalf of the German Rectal Cancer Study Group*



pCR
19% (5FU+OX)
vs
14% (5FU)

completed all cycles. These analyses of early endpoints suggest that addition of oxaliplatin to fluorouracil-based combined modality treatment might be an attractive option for patients with locally advanced rectal cancer. However, longer follow-up is needed to assess the primary endpoint, disease-free survival.

OXALIPLATINO MIGLIORA L'OUTCOME ?

METAANALISI

ARTICLE IN PRESS

European Journal of Cancer (2012) xxx, xxx–xxx

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejcancer.info

Short term results of neoadjuvant chemoradiotherapy with fluoropyrimidine alone or in combination with oxaliplatin in locally advanced rectal cancer: A meta analysis

Xin An [a,b,h], Xi Lin [a,c,h], Feng-Hua Wang [a,b,h], Karyn Goodman [d,h], Pei-Qiang Cai [a,e], Ling-Heng Kong [a,f], Yu-Jing Fang [a,f], Yuan-Hong Gao [a,g], Jun-Zhong Lin [a,f], De-Sen Wan [a,f], Zhi-Zhong Pan [a,f,*], Pei-Rong Ding [a,f,*]

[a] *State Key Laboratory of Oncology in South China, Guangzhou, P.R. China*

Table 1
Trials comparing pre-operative chemoradiotherapy with FU and OX versus FU alone in locally advanced rectal cancer.

Study	Regimen	No. of patients
ACCORD[12]	Arm 1: Cape (1600 mg/m^2 5 d/week) + 45 Gy	299
	Arm 2: Cape (1600 mg/m^2 5 d/week)/OX (50 mg/m^2/week) + 50 Gy	299
AIO-04[15]	Arm 1: 5-fluorouracil (1000 mg/m^2 d 1–5, 29–33) + 50.4 Gy	637
	Arm 2: 5-fluorouracil (250 mg/m^2 d 1–14, 22–35)/OX(50 mg/m^2/week) + 50.4 Gy	628
NSABP R-04[14]	Arm 1: 5-fluorouracil (CIV 225 mg/m^2 5 d/week) or Cape (825 mg/m^2 bid) + 4600 cGy + 540–1080 cGy	622
	Arm 2: 5-fluorouracil (CIV 225 mg/m^2 5 d/week) or Cape (825 mg/m^2 bid + OX 50 mg/m^2/ week) + 4600 cGy + 540–1080 cGy	631
STAR-01[13]	Arm 1: 5-fluorouracil (225 mg/m^2) + 50.4 Gy	379
	Arm 2: 5-fluorouracil (225 mg/m^2)/OX (60 mg/m^2/week) + 50.4 Gy	368

Abbreviations: FU, fluoropyrimidine (5-fluorouracil or Capecitabine); OX, oxaliplatin; CIV, continuous intravenous infusion; Cape, capecitabine.

Study or Subgroup	Ox/Fu Events	Ox/Fu Total	Fu alone Events	Fu alone Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ACCORD 12/0405	55	299	40	299	13.7%	1.46 [0.94, 2.27]
CAO/ARO/AIO-04	103	628	81	637	28.2%	1.35 [0.98, 1.84]
NSABP R-04	121	578	111	580	36.7%	1.12 [0.84, 1.49]
STAR-01	59	368	62	379	21.5%	0.98 [0.66, 1.44]
Total (95% CI)		**1873**		**1895**	**100.0%**	**1.20 [1.01, 1.42]**
Total events	338		294			

Heterogeneity: Chi² = 2.57, df = 3 (P = 0.46); I² = 0%
Test for overall effect: Z = 2.07 (P = 0.04)

Odds Ratio M-H, Fixed, 95% CI

Fig. 1. Forest plot of odds rati

Interpretation: Adding weekly OX to FU in neoadjuvant CRT of LARC appeared to modestly increase the pCR rate and reduced the rate of intra-abdominal or peri-operative metastases in this meta analysis. Although OX/FU significantly increased grade 3/4 toxicity, it did not result in more surgical complications or postoperative deaths within 60 d. The concept of combination of OX and FU in the pre-operative setting for LARC still seems promising, either with a modified schedule, or as induction therapy prior to CRT or after CRT, prior to surgery.

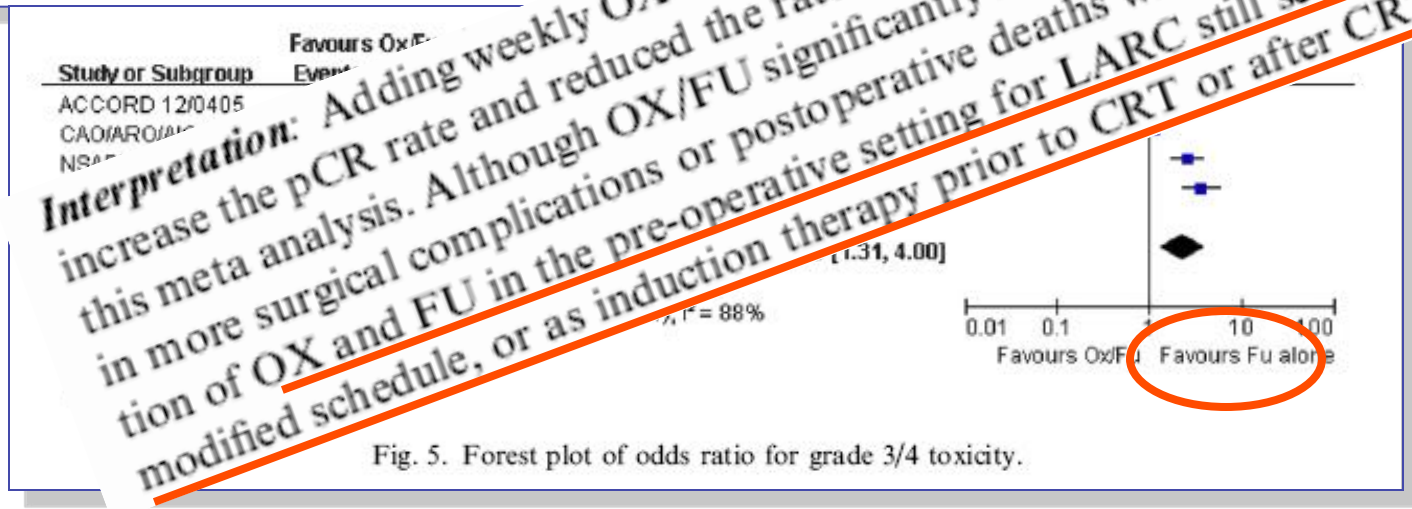


Fig. 5. Forest plot of odds ratio for grade 3/4 toxicity.

Tossicita'

Study or Subgroup	Ox/Fu Events	Ox/Fu Total	Fu alone Events	Fu alone Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ACCORD 12/0405	14	299	22	299	30.7%	0.62 [0.31, 1.23]
CAO/ARO/AIO-04	21	628	34	637	47.8%	0.61 [0.35, 1.07]
STAR-01	2	368	15	379	21.5%	0.13 [0.03, 0.58]
Total (95% CI)		**1295**		**1315**	**100.0%**	**0.51 [0.34, 0.77]**
Total events	37		71			

Heterogeneity: Chi² = 3.89, df = 2 (P = 0.14); I² = 49%
Test for overall effect: Z = 3.23 (P = 0.001)

Odds Ratio M-H, Fixed, 95% CI

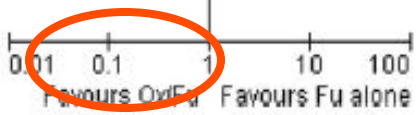
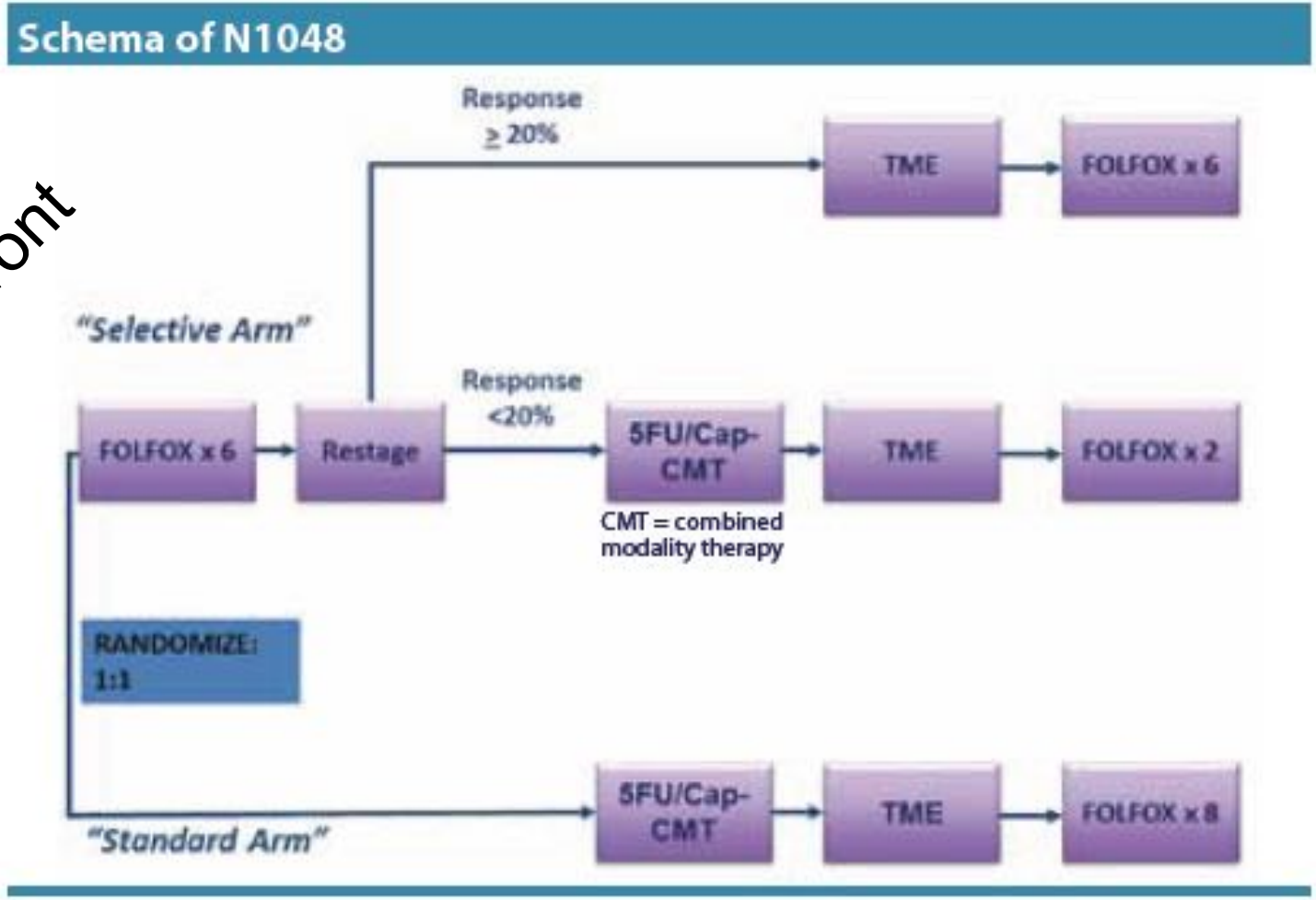


Fig. 3. Forest plot of odds ratio for peri-operative metastases.

Meta peri-operatorie

PROSPECT TRIAL

Up front



GOODMAN ASCO 2012

I farmaci biologici

Quale ruolo ?

I FARMACI BIOLOGICI MIGLIORANO L'OUTCOME ?

VOLUME 30 · NUMBER 14 · MAY 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

EXPERT - C

Multicenter Randomized Phase II Clinical Trial Comparing Neoadjuvant Oxaliplatin, Capecitabine, and Preoperative Radiotherapy With or Without Cetuximab Followed by Total Mesorectal Excision in Patients With High-Risk Rectal Cancer (EXPERT-C)

Alice Dewdney, David Cunningham, Josep Tabernero, Jaume Capdevila, Bengt Glimelius, Andres Cervantes, Diana Tait, Gina Brown, Andrew Wotherspoon, David Gonzalez de Castro, Yu Jo Chua, Rachel Wong, Yolanda Barbachano, Jacqueline Oates, and Ian Chau

To evaluate the addition of cetuximab to neoadjuvant chemotherapy before chemoradiotherapy in high-risk rectal cancer.

Table 3. Radiologic Response

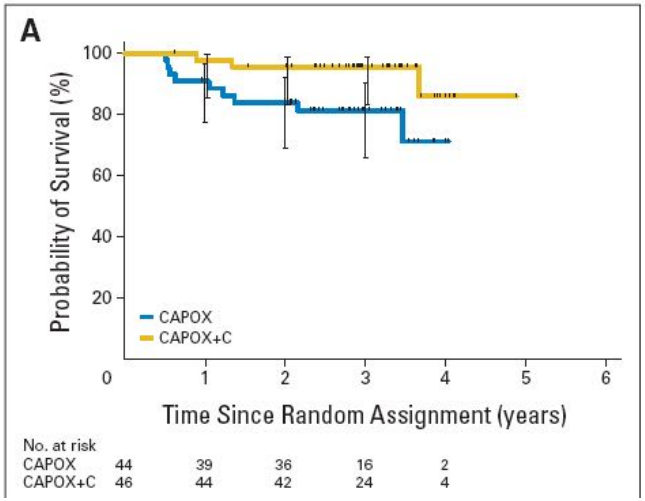
Response	Wild-Type Patients: CAPOX (n = 44) No.	%	Wild-Type Patients: CAPOX+C (n = 46) No.	%	P	All Treated Patients: CAPOX (n = 81) No.	%	All Treated Patients: CAPOX+C (n = 83) No.	%	P
Neoadjuvant chemotherapy										
CR	1	2	5	11		2	3	6	8	
PR	21	48	27	59		38	51	43	56	
SD	20	46	12	26		33	44	27	35	
PD	1	2	0	0		2	3	1	1	
Unknown*	1	2	2	4		6	7	6	7	
Overall response†	22	51	32	71	.038	40	54	49	64	.41
Chemoradiation										
CR	2	5	7	16		7	9	9	11	
PR	30	70	34	77		50	66	55	72	
SD	6	14	3	7		14	19	11	14	
PD	4	9	0	0		4	5	1	1	
Unknown*	1	2	2	4		6	8	7	8	
Overall response†	32	75	41	93	.065	57	76	64	84	.23

Abbreviations: CAPOX, capecitabine/oxaliplatin; CAPOX+C, capecitabine/oxaliplatin plus cetuximab; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
*Patients for whom no best response was provided by the investigator.
†Overall response = CR+PR.

the addition of cetuximab did not improve the primary end point of CR (9% *v* 11%), or PFS

Cetuximab significantly improved RR (after chemotherapy, 51% *v* 71%, *P* .038; after chemoradiation, 75% *v* 93%; *P* .028) and OS (*P* .034).

Skin toxicity and diarrhea were more frequent in the CAPOX-C arm.



in patients with high-risk rectal cancer. However, despite an improvement in the secondary end points of RR and OS in patients with *KRAS/BRAF* wild-type rectal cancer, the primary end point of improved CR was not met, and we do not currently recommend the routine use of cetuximab in this patient population. On the basis of these results, there are sufficient data to indicate that cetuximab has some biologic activity in this setting, and further evaluation in combination with alternative chemotherapy backbones may yield more promising results.

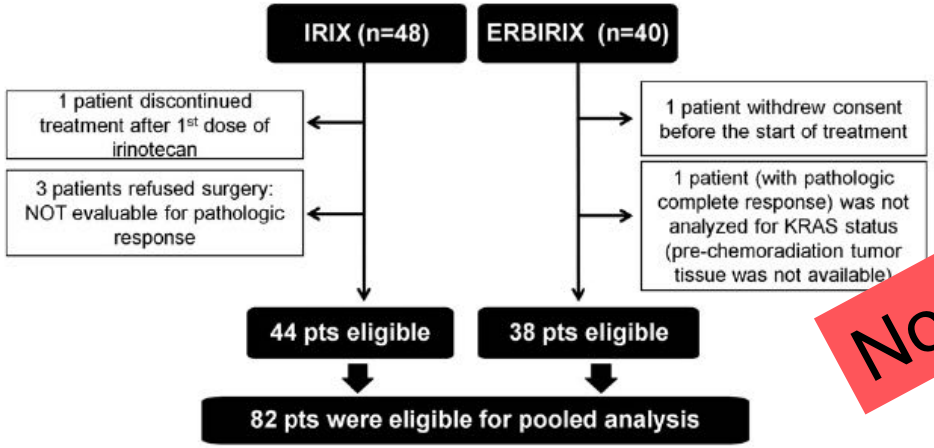
I FARMACI BIOLOGICI MIGLIORANO L'OUTCOME ?

Int J Radiation Oncol Biol Phys, Vol. ■, No. ■, pp. 1–7, 2012

KRAS Mutation Status and Clinical Outcome of Preoperative Chemoradiation With Cetuximab in Locally Advanced Rectal Cancer: A Pooled Analysis of 2 Phase II Trials

Sun Young Kim, MD,* Eun Kyung Shim, RN,* Hyun Yang Yeo, PhD,† Ji Yeon Baek, MD,* Yong Sang Hong, MD,‡ Dae Yong Kim, MD, PhD,*,† Tae Won Kim, MD, PhD,‡ Jee Hyun Kim, MD, PhD,§ Seock-Ah Im, MD, PhD,‖ Kyung Hae Jung, MD, PhD,‡ and Hee Jin Chang, MD, PhD*,†

*Center for Colorectal Cancer, Research Institute and Hospital, National Cancer Center, Goyang, Korea; †Division



Non vantaggioso

Fig. 3. Patient selection for the pooled analysis.

Conclusions: In patients with *KRAS* wild-type locally advanced rectal cancer, the addition of cetuximab to the chemoradiation with irinotecan plus capecitabine regimen was not associated with improved clinical outcome compared with chemoradiation without cetuximab. © 2012 Elsevier Inc.

pCR

Quale outcome ?

pCR MIGLIORA L'OUTCOME?

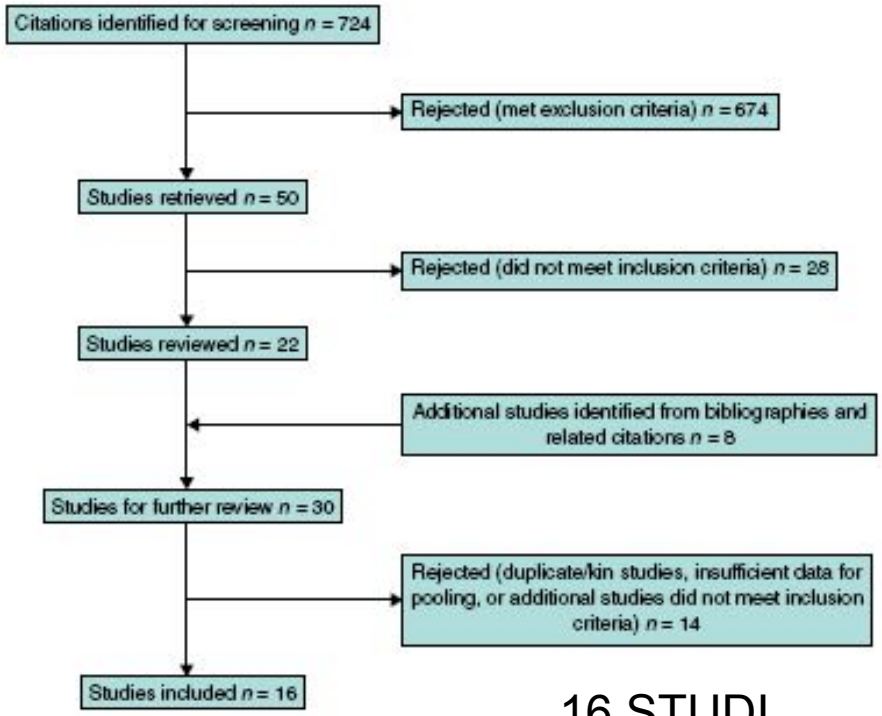
Meta-analysis

British Journal of Surgery 2012; 99: 918–928

Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer

S. T. Martin, H. M. Heneghan and D. C. Winter

Institute for Clinical Outcomes, Research and Education (iCORE) and Department of Colorectal Surgery, St Vinc Dublin, Ireland



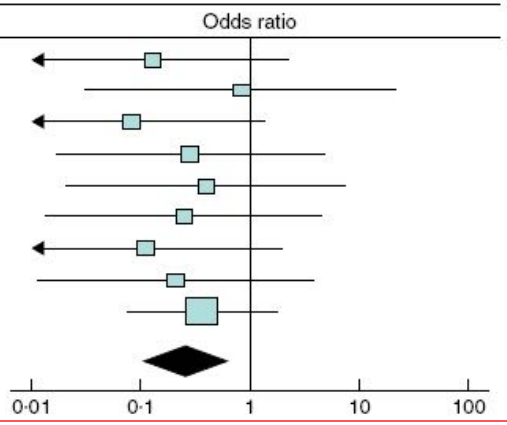
16 STUDI
3363 PAZIENTI

Reference	No. of patients (% men)	Follow-up (months)	Mean age (years)	Preoperative stage (%)	pCR*	a
Avallone *et al.*[14] (2011)	63 (51)	60	58	TNM: I, 0; II, 16; III, 84; IV, 0	24 (38)	< 5
Capirci *et al.*[15]‡ (2008)	536 (66)	46	61·8	TNM: I, 6; II, 44; III, 45; IV, 0; unknown, 5	536 (100)‡	
Chan *et al.*[5] (2005)	128 (73)	60	62	T3, 86·7; T4, 13·3	32 (25·0)	
Ciccocioppo *et al.*[16] (2009)	40 (65)	72	63	All TNM II/III	7 (18)	
De Campos-Lobato *et al.*[6] (2011)	238 (73)	54	57	TNM: I, 0; II, 65; III, 35; IV, 0	54 (22·7)	
Hong *et al.*[17] (2011)	40 (69)	60	59	TNM: I, 0; II, 19; III, 81; IV, 0	11 (28)	
Kim *et al.*[18] (2011)	420 (66)	56	58	TNM: I, 0; II, 18; III, 82; IV, 0	58 (13·8)	
Pucciarelli *et al.*[19] (2004)	106 (62)	40	60	TNM: I, 0; II, 29; III, 71; IV, 0	19 (17·9)	
Rödel *et al.*[20] (2005)	385 (73)	41	< 61: 53% > 61: 47%	TNM: I, 0; II, 40; III, 60; IV, 0	40 (10·4)	
Roh *et al.*[21] (2009)	113 (69)	40	< 60: 43% > 60: 57%	All TNM II/III	17 (15·0)	
Ruo *et al.*[22] (2002)	69 (68)	69	57	All TNM II/III	10 (14)	
Shivnani *et al.*[23] (2007)	100 (56)	52·4	61	TNM: I, 1; II, 46; III, 53; IV, 0	25 (25·0)	< 8
Smith *et al.*[8] (2010)	562 (60)	87	59	TNM: I + II, 59; III, 41; IV, 0	100 (17·8)	
Valentini *et al.*[24] (2008)	165 (64)	67	63	TNM: I, 1; II, 20; III, 79; IV, 0	17 (10·3)	
Wheeler *et al.*[25] (2004)	65 (NR)	41	65	T3, 68; T4, 32	9 (14)	
Yeo *et al.*[26] (2010)	333 (67)	43	56	TNM: I, 0; II, 31; III, 69; IV, 0	304 (91·3)	
Overall	3363 (65·0)	55·5	60	TNM: I, 1·0; II, 34·1; III, 64·8; IV, 0·1	1263 (24·4)¶	

pCR MIGLIORA L'OUTCOME?

Reference	Odds ratio	P
Chan *et al.*[5]	0·13 (0·01, 2·23)	0·158
Hong *et al.*[17]	0·83 (0·03, 21·80)	0·909
de Campos-Lobato *et al.*[6]	0·08 (0·01, 1·39)	0·084
Rödel *et al.*[20]	0·28 (0·02, 4·82)	0·382
Ruo *et al.*[22]	0·39 (0·02, 7·50)	0·534
Shivnani *et al.*[23]	0·25 (0·01, 4·71)	0·356
Valentini *et al.*[24]	0·11 (0·01, 1·95)	0·134
Wheeler *et al.*[25]	0·21 (0·01, 3·85)	0·292
Yeo *et al.*[26]	0·37 (0·07, 1·81)	0·216
Overall	0·25 (0·10, 0·59)	0·002

Test for heterogeneity: $Q = 1·9$, 8 d.f., $P = 0·981$, $I^2 = 0\%$

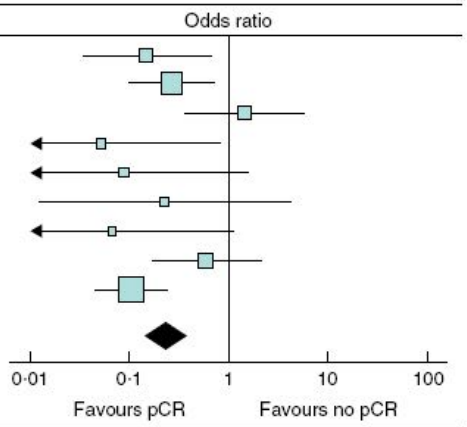


a Local recurrence

RECIDIVE LOCALI

Reference	Odds ratio	P
Chan *et al.*[5]	0·15 (0·03, 0·65)	0·012
de Campos-Lobato *et al.*[6]	0·27 (0·10, 0·71)	0·008
Pucciarelli *et al.*[19]	1·44 (0·36, 5·84)	0·607
Rödel *et al.*[20]	0·05 (0·00, 0·84)	0·037
Roh *et al.*[21]	0·09 (0·01, 1·54)	0·097
Ruo *et al.*[22]	0·22 (0·01, 4·14)	0·315
Shivnani *et al.*[23]	0·07 (0·00, 1·13)	0·061
Valentini *et al.*[24]	0·59 (0·16, 2·16)	0·423
Yeo *et al.*[26]	0·11 (0·05, 0·25)	< 0·001
Overall	0·23 (0·11, 0·47)	< 0·001

Test for heterogeneity: $Q = 14·63$, 8 d.f., $P = 0·067$, $I^2 = 45\%$



b Distant recurrence

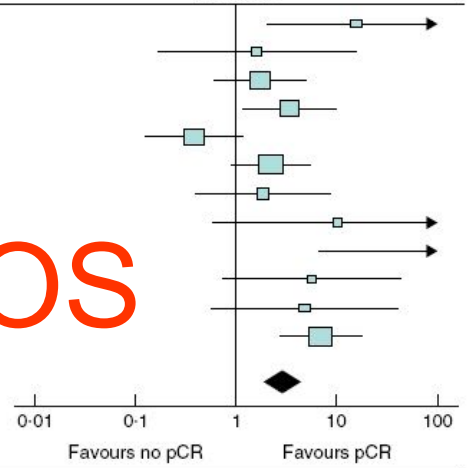
METASTASI

Fig. 2 Forest plots showing **a** local recurrence and **b** distant disease recurrence in patients wit
complete response (pCR) to chemoradiotherapy. A random-effects model was used for meta-
95 per cent confidence intervals

pCR MIGLIORA L'OUTCOME?

Reference	Odds ratio	*P*
Chan *et al.*[5]	15·50 (2·02, 118·73)	0·008
Ciccocioppo *et al.*[16]	1·62 (0·17, 15·72)	0·680
Kim *et al.*[18]	1·72 (0·59, 5·01)	0·317
de Campos-Lobato *et al.*[6]	3·36 (1·14, 9·88)	0·027
Pucciarelli *et al.*[19]	0·38 (0·12, 1·18)	0·095
Rödel *et al.*[20]	2·22 (0·90, 5·45)	0·083
Roh *et al.*[21]	1·85 (0·39, 8·79)	0·439
Ruo *et al.*[22]	10·11 (0·56, 181·57)	0·116
Shivnani *et al.*[23]	113·93 (6·65, 1951·68)	0·001
Valentini *et al.*[24]	5·63 (0·72, 43·90)	0·099
Wheeler *et al.*[25]	4·80 (0·56, 41·13)	0·152
Yeo *et al.*[26]	6·86 (2·63, 17·86)	< 0·001
Overall	3·28 (1·66, 6·51)	0·001

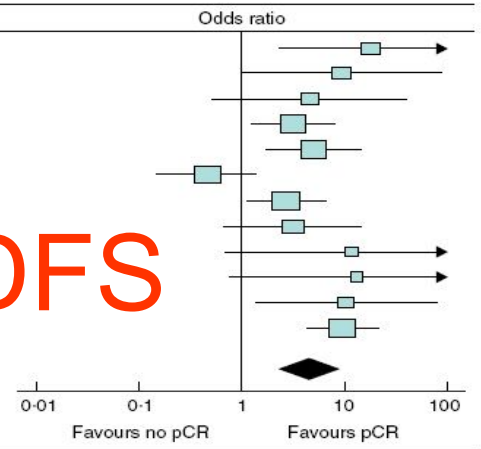
Test for heterogeneity: $Q = 27·6$, 11 d.f., $P = 0·004$, $I^2 = 60\%$



a Overall survival

Reference	Odds ratio	*P*
Chan *et al.*[5]	17·79 (2·33, 136·01)	0·006
Ciccocioppo *et al.*[16]	9·23 (0·99, 85·78)	0·051
Hong *et al.*[17]	4·50 (0·50, 40·65)	0·180
Kim *et al.*[18]	3·10 (1·20, 8·02)	0·019
de Campos-Lobato *et al.*[6]	5·06 (1·74, 14·70)	0·003
Pucciarelli *et al.*[19]	0·45 (0·15, 1·38)	0·162
Rödel *et al.*[20]	2·65 (1·08, 6·50)	0·033
Roh *et al.*[21]	3·09 (0·66, 14·40)	0·151
Ruo *et al.*[22]	11·73 (0·66, 210·11)	0·094
Shivnani *et al.*[23]	13·07 (0·75, 226·77)	0·078
Valentini *et al.*[24]	10·25 (1·32, 79·40)	0·026
Yeo *et al.*[26]	9·46 (4·20, 21·31)	< 0·001
Overall	4·33 (2·31, 8·09)	< 0·001

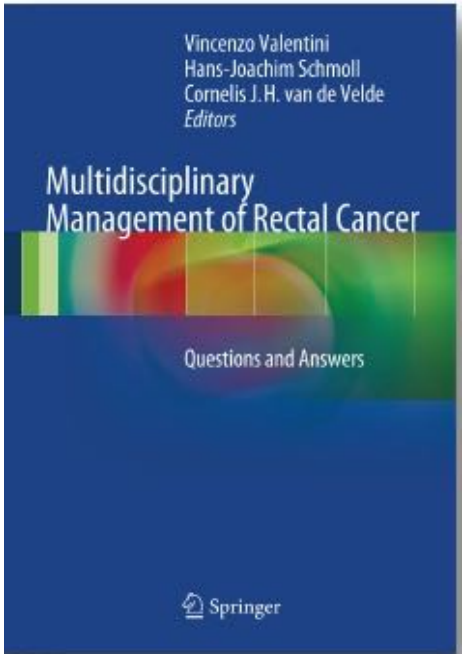
Test for heterogeneity: $Q = 25·0$, 11 d.f., $P = 0·009$, $I^2 = 56\%$



b Disease-free survival

Fig. 3 Forest plots showing **a** overall and **b** disease-free survival in patients with *versus* those without a pathological complete response (pCR) to chemoradiotherapy. A random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals

retto



METASTASI

DFS
OS

RECIDIVE LOCALI

LC

TME vs RT+TME

RT vs RTCHEM

RT postop vs RT preop

OXALIPLATINO/ UP FRONT

CETUXIMAB

>pCR

Canale anale

FU.

MI.

R

MIGLIORARE
DFS E CFS

RIDURRE TOSSICITA’

CHEM
INDUZIONE ?

Dose /volume/tecnica ?

CHEM
CONS ?

INTENSIFICAZIONE RADIOTERAPIA E CHEMIOTERAPIA

ACCORD 03

VOLUME 30 · NUMBER 16 · JUNE 1 2012

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

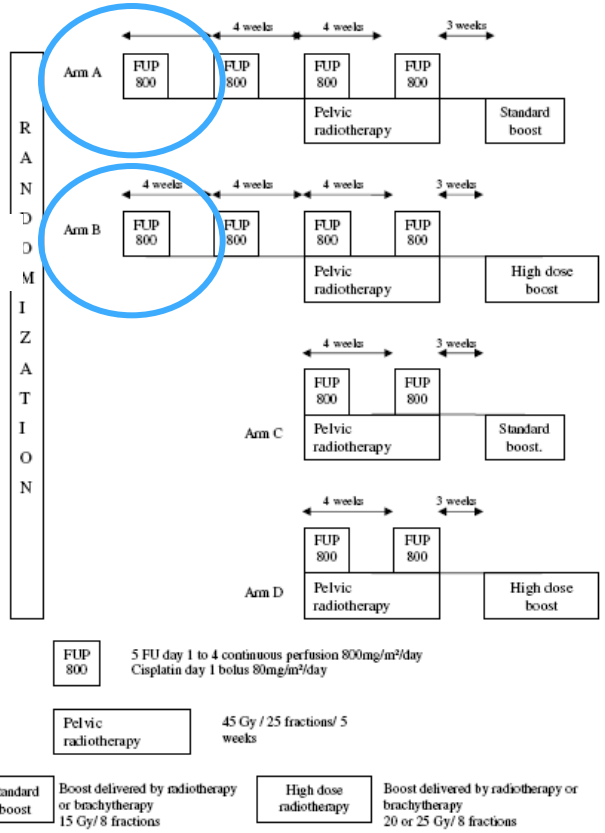
JCO 2012

Induction Chemotherapy and Dose Intensification of the Radiation Boost in Locally Advanced Anal Canal Carcinoma: Final Analysis of the Randomized UNICANCER ACCORD 03 Trial

Didier Peiffert, Laetitia Tournier-Rangeard, Jean-Pierre Gérard, Claire Lemanski, Eric François, Marc Giovannini, Frédérique Cvitkovic, Xavier Mirabel, Olivier Bouché, Elisabeth Luporsi, Thierry Conroy, Christine Montoto-Grillot, Françoise Mornex, Antoine Lusinchi, Jean-Michel Hannoun-Lévi, Jean-François Seitz, Antoine Adenis, Christophe Hennequin, Bernard Denis, and Michel Ducreux

Didier Peiffert, Laetitia Tournier-Rangeard, Elisabeth Luporsi, Thierry Conroy, EA 4360 Centre, Alexis Vautrin and Nancy University, Vandoeuvre-lès-Nancy, France; Jean-Pierre Gérard, Eric François, Jean-Michel Hannoun-Lévi, Centre Antoine Lacassagne, Nice, France; Michel Ducreux, Institut Gustave Roussy, Villejuif, France; Claire

L. Tournier-Rangeard et al. / Radiotherapy and Oncology 87 (2008) 391–397



Chem di induzione

Intensificazione RT

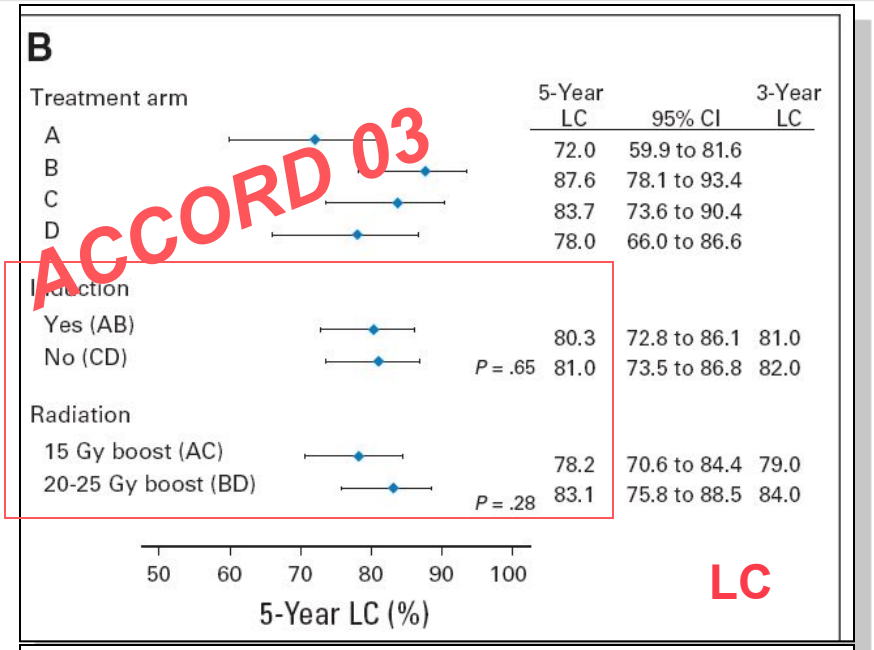
Intensificazione RT

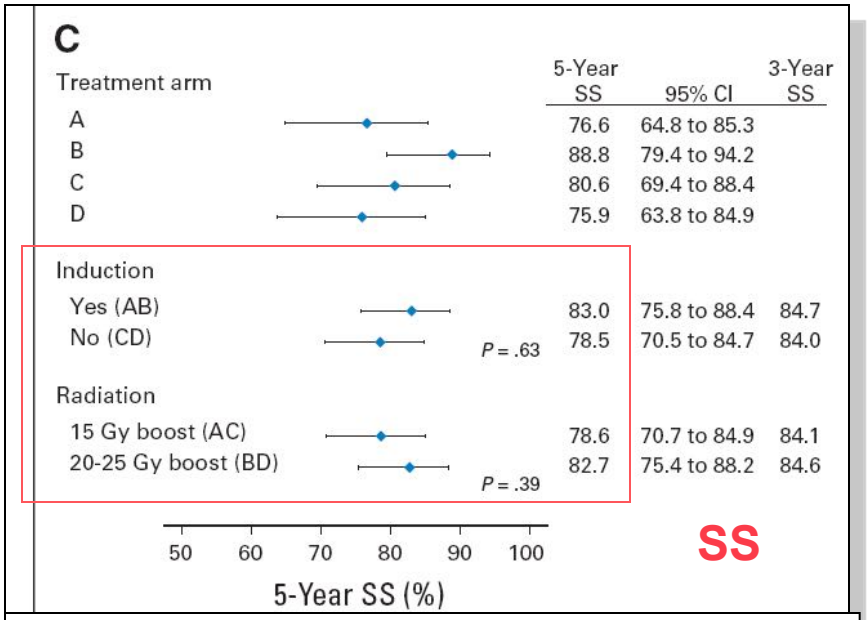
End point :

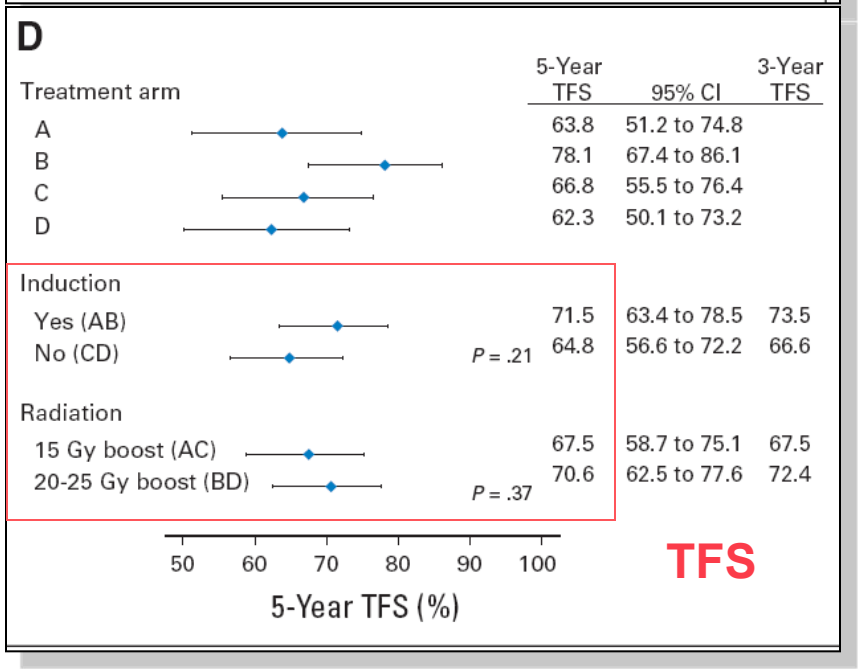
Colostomy
Free Survival

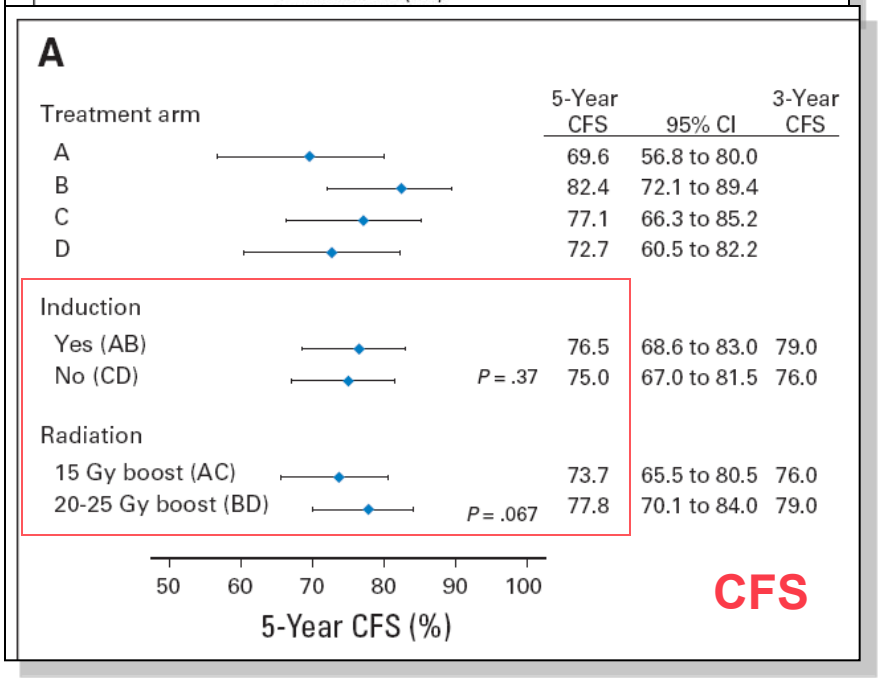
INTENSIFICAZIONE RADIOTERAPIA E CHEMIOTERAPIA

ACCORD 03



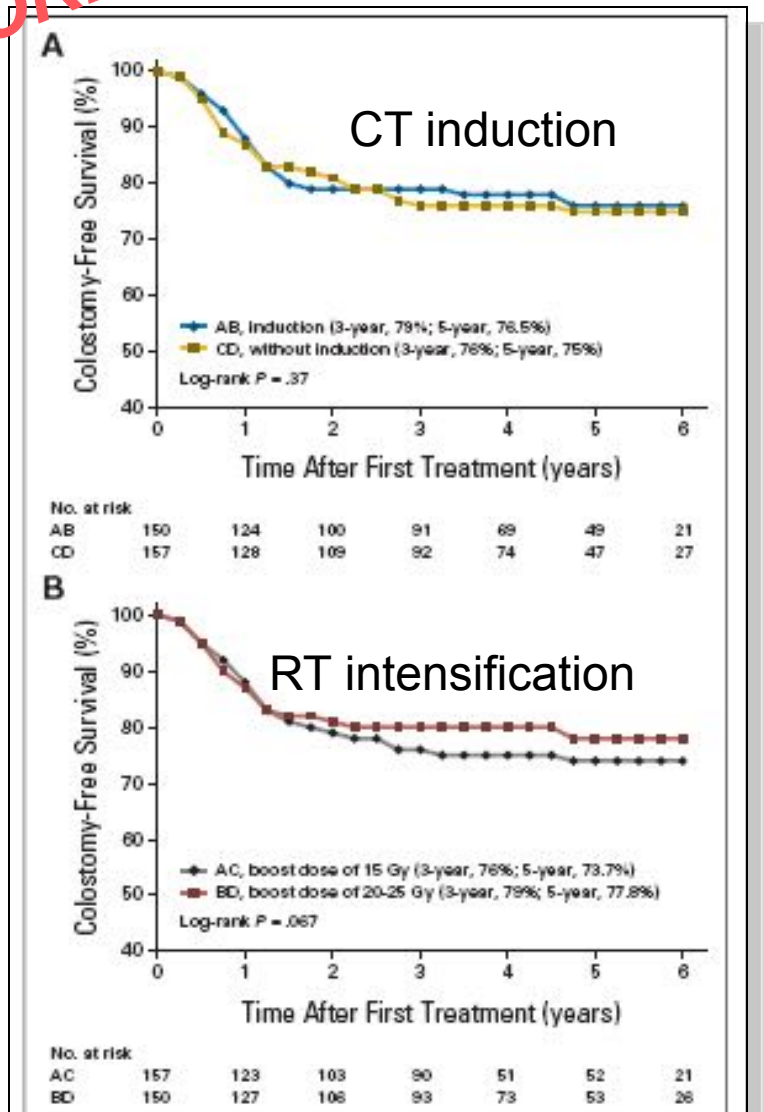






INTENSIFICAZIONE RADIOTERAPIA E CHEMIOTERAPIA

ACCORD 03

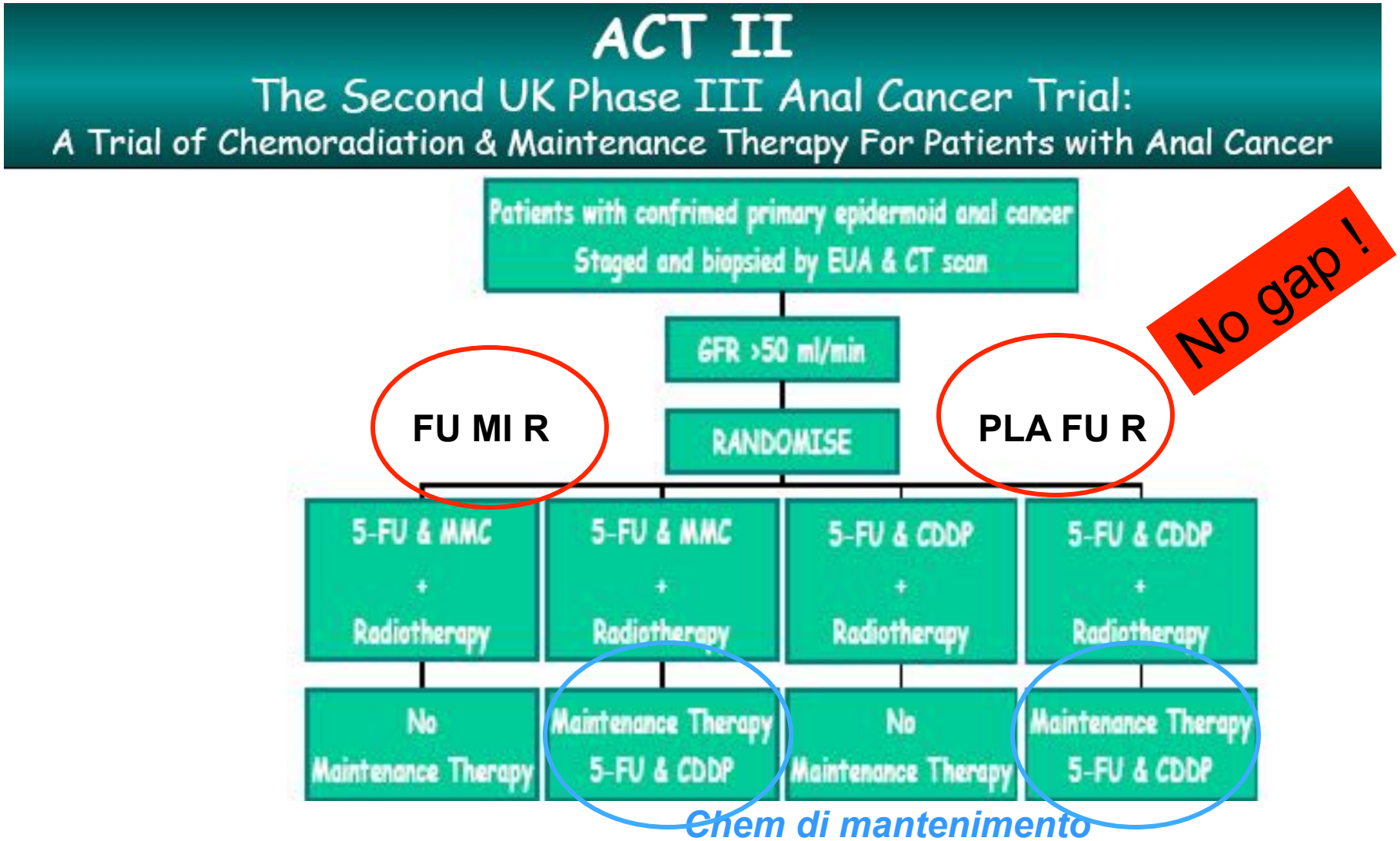


CHEM induzione
o
Intensificazione RT

NO VANTAGGIO

per CFR

CHEMIOTERAPIA DI MANTENIMENTO



CHEMIOTERAPIA DI MANTENIMENTO

ASCO 2009

A randomized trial of chemoradiation using mitomycin or cisplatin, with or without maintenance cisplatin/5FU in squamous cell carcinoma of the anus (ACT II).

Conclusions:

- CR (95%) and RFS (75%) at 3 yrs

(excellent outcome influenced by the absence of a gap in the RT schedule).

- **no difference** in CR rates between MMC and CDDP
- **no difference** in RFS rates **with or without maintenance chemotherapy**.

VALUTAZIONE DELLA RISPOSTA CLINICA

ASCO 2012

Optimum time to assess complete clinical response (CR) following chemoradiation (CRT) using mitomycin (MMC) or cisplatin (CisP), with or without maintenance CisP/5FU in squamous cell carcinoma of the anus: Results of ACT II.

Robert Glynne-Jones, Roger James, Helen Meadows, Rubina Begum, David Cunningham, John Northover, Jonathan A. Ledermann, Sandra Beare, Latha Kadalayil, David Sebag-Montefiore and ACT II Study Group

	Pts with CR	Absolu difference CR rate %
Week 11	429	65.6
Week 18	527	75.4
Week 26	582	83.5

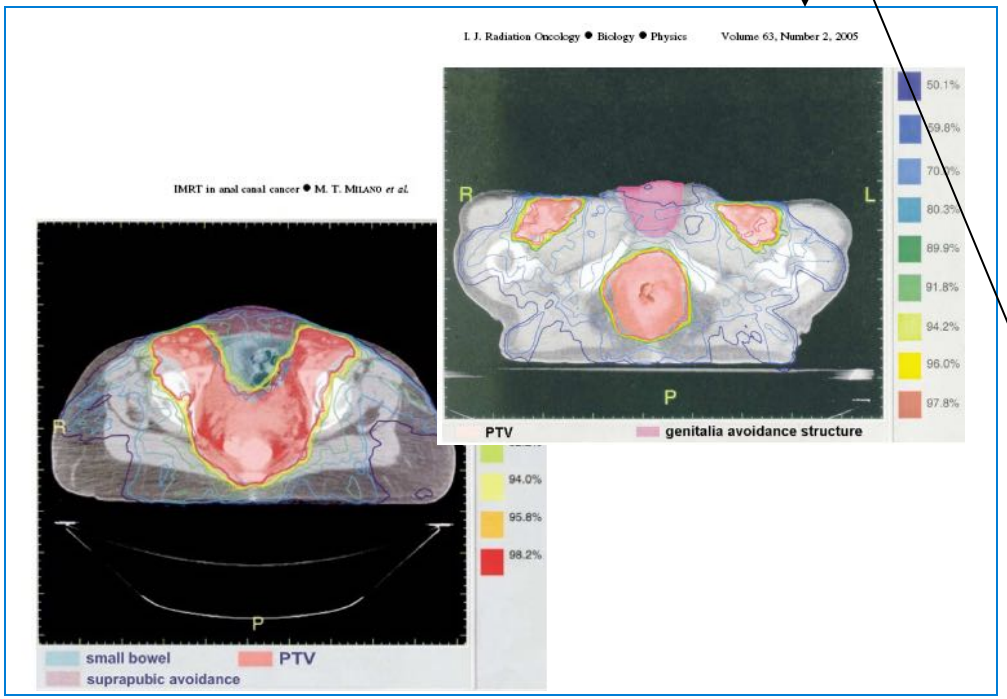
CR 26 w = + 29%

202/695 (29%) pts not in CR at 11 weeks were CR at 26 weeks

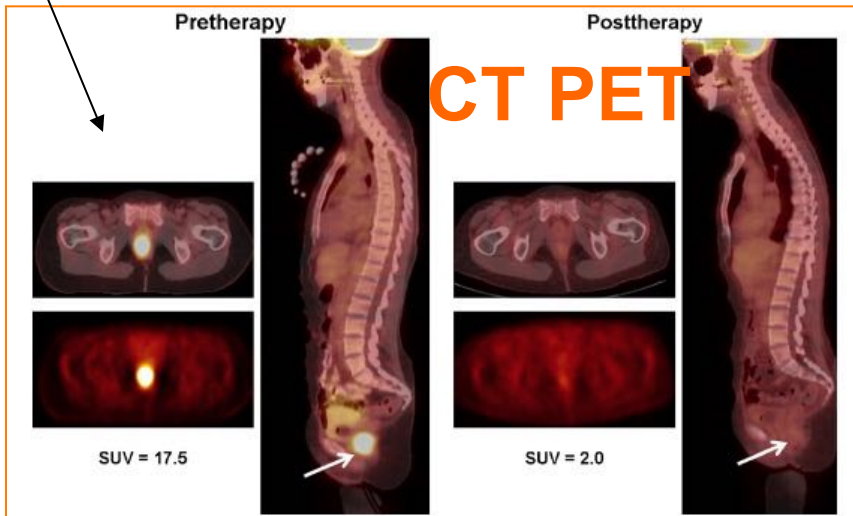
Optimum time to assess complete clinical response (CR) = 26 weeks

Ottimizzazione tecnica e volumi RT

FUMIR +



IMRT



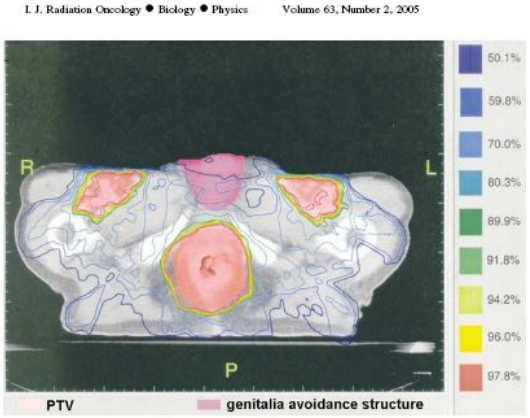
Ottimizzazione tecnica RT : IMRT

RTOG

0529

FU MI + IMRT

ONGOING



RTOG 0529

A Phase II Evaluation of Dose-Painted IMRT in Combination with 5-Fluorouracil and Mitomycin-C for Reduction of Acute Morbidity in Carcinoma of the Anal Canal

SCHEMA (5/31/07)

5-FU + Mitomycin-C and IMRT		
R	**5-FU + Mitomycin-C**	**IMRT**
E		
G	• Mitomycin-C on days 1 and 29	The prescription dose scheme will depend on staging as
I		follows: (see Section 6.0 for complete details)
S	• 5-FU by **96-hour** continuous infusion (M-F)	• T2N0: 28 fractions over 5.5 weeks
T	beginning on day 1 and	• T3N0 or T4N0: 30 fractions over 6 weeks
E	again on day 29	• N+: 30 fractions over 6 weeks
R	**Note:** Days 1 and 29 are based on calendar days	

See Section 5.0 for pre-registration requirements.

Ottimizzazione volumi RT:LINEE GUIDA

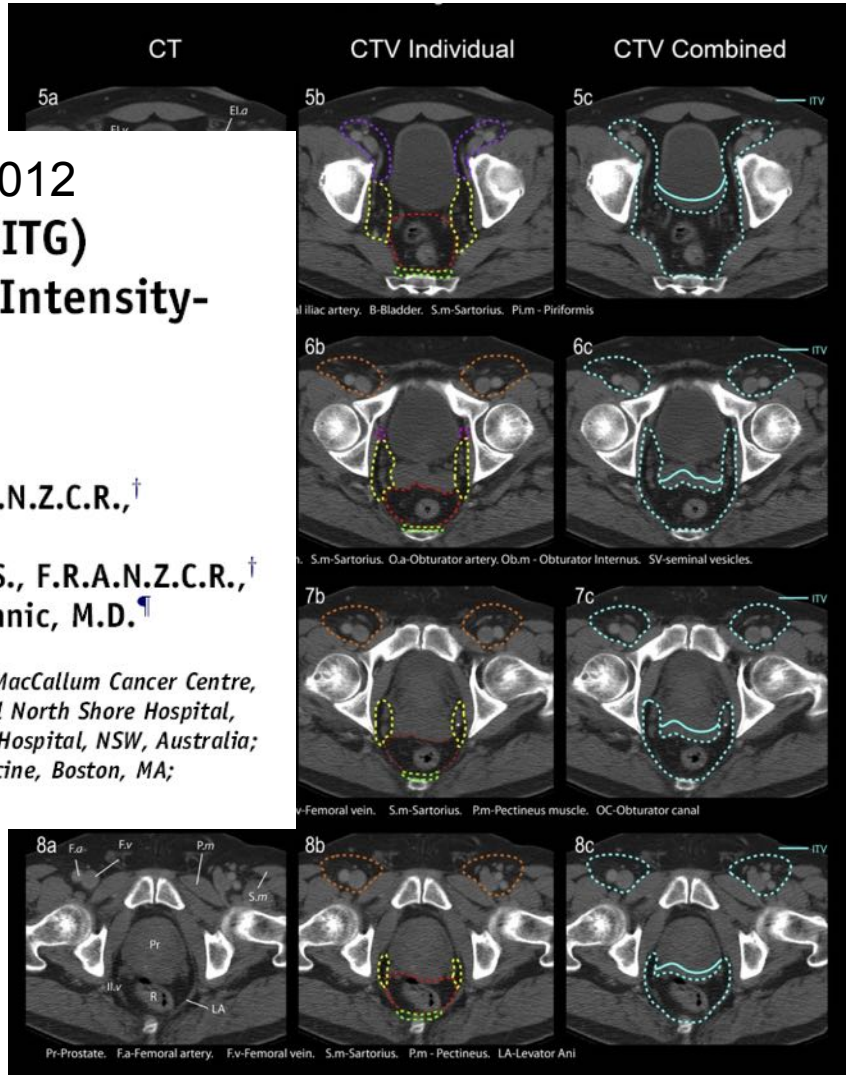
IJROBP 2012

Report

Australasian Gastrointestinal Trials Group (AGITG) Contouring Atlas and Planning Guidelines for Intensity-Modulated Radiotherapy in Anal Cancer

Michael Ng, M.B.B.S.(Hons), F.R.A.N.Z.C.R.,* Trevor Leong, M.B.B.S., M.D., F.R.A.N.Z.C.R.,†,‖ Sarat Chander, M.B.B.S., F.R.A.N.Z.C.R.,† Julie Chu, M.B.B.S., F.R.A.N.Z.C.R.,† Andrew Kneebone, M.B.B.S., F.R.A.N.Z.C.R.,‡,** Susan Carroll, M.B.B.S., F.R.A.N.Z.C.R.,§,** Kirsty Wiltshire, M.B.B.S., F.R.A.N.Z.C.R.,† Samuel Ngan, M.B.B.S., F.R.C.S.Ed., F.R.A.N.Z.C.R.,†,‖ and Lisa Kachnic, M.D.¶

*Radiation Oncology Victoria, Victoria, Australia; †Department of Radiation Oncology, Peter MacCallum Cancer Centre, Victoria, Australia; ‡Department of Radiation Oncology, Northern Sydney Cancer Centre, Royal North Shore Hospital, NSW, Australia; §Department of Radiation Oncology, Sydney Cancer Centre, Royal Prince Alfred Hospital, NSW, Australia; ¶Department of Radiation Oncology, Boston Medical Center, Boston University School of Medicine, Boston, MA; ‖University of Melbourne, Australia; and **University of Sydney, Australia



Ottimizzazione volumi RT: Irradiazione profilattica linf. inguinali

l. Phys., Vol. 82, No. 5, pp. 1988–1995, 2012
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0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2011.02.010

CLINICAL INVESTIGATION **Gastrointestinal Cancer**

ANAL CANAL CANCER: MANAGEMENT OF INGUINAL NODES AND BENEFIT OF PROPHYLACTIC INGUINAL IRRADIATION (CORS-03 STUDY)

CÉCILE ORTHOLAN, M.D., PH.D.,*† MICHEL RESBEUT, M.D.,‡§‡‡
JEAN-MICHEL HANNOUN-LEVI, M.D., PH.D.,*‡‡ ERIC TEISSIER, M.D.,¶‡‡ JEAN-PIERRE GERARD, M.D.,*

IJROBP 2012

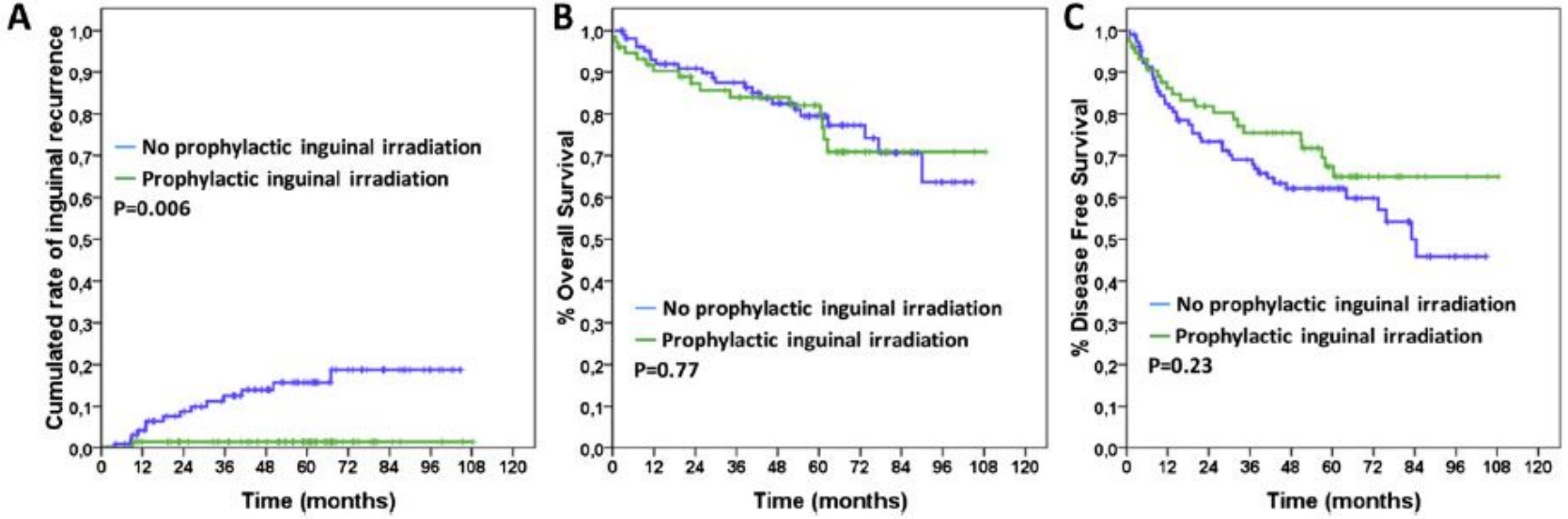


Fig. 4. Cumulated rate of inguinal recurrence (A), overall survival (B), and disease-specific survival (C) curves according to prophylactic inguinal irradiation (Kaplan-Meier method).

Conclusion: PII with a dose of 45 Gy is safe and highly efficient to prevent inguinal recurrence and should be recommended for all T3-4 tumors. For early-stage tumors, PII should also be discussed, because the 5-year inguinal recurrence risk remains substantial when omitting PII (about 10%). © 2012 Elsevier Inc.

Ottimizzazione RT:
- ricerca nuovi farmaci
- inclusione HIV+

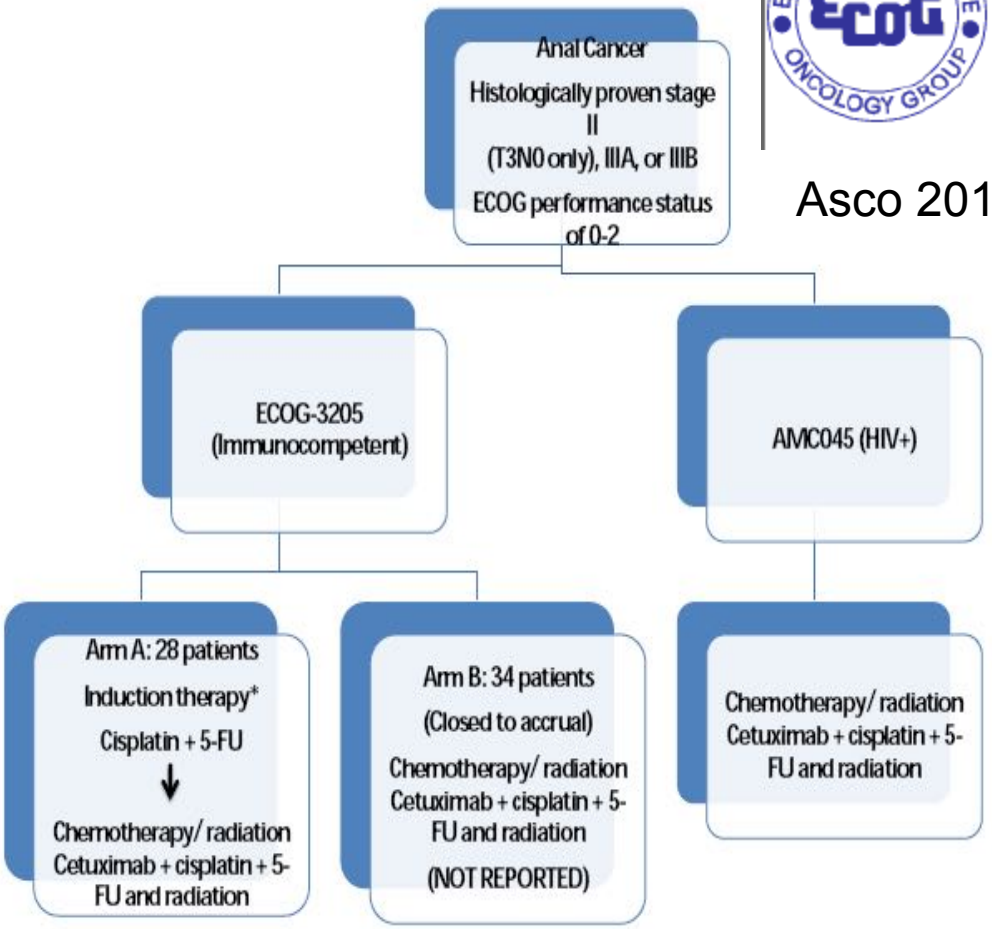
ONGOING

Table 5. Prospective Phase I and II trials—not reported or ongoing

Phase II Trials	No.	Design	RT Dose	CR	Median F/U	3-year DFS	3-year CFS	OS
RTOG-0529 Phase II completed accrual March 2008 (69)	63	5FU 1000 mg/m^2 days 1–4, 29–33 2 doses of MMC 10 mg/m^2 days 1 and 29	IMRT dose according to T stage 50.4 Gy/28# T2N0 54Gy/30# for T3/ T4N0	34/61 67% at 8 weeks	No data	No data	No data	No data
ECOG E3205	62	NACT cisplatin/5FU x2 induction then 5FU/cisplatin/ cetuximab during RT in immunocompetent	54 Gy/30# for T3/ T4N0	ind + PLAFUR-C		No data	No data	No data
cetuximab								
AMC045 NCT003244415	47	5FU 1000 mg/m^2 days 1–4, cisplatin day 1, 29 cetuximab during RT in HIV +	54 Gy/30# for T3/ T4N0	PLAFUR-C (HIV+)	No data	No data	No data	No data
FNCLCC NCT00955140	77	Cisplatin and 5FU with cetuximab	65 Gy	Study ongoing	No data	No data	No data	No data
TOTAL	245							

Abbreviations: No = number; RT = radiotherapy; CR = complete clinical response; DFS = disease-free survival; CFS = colostomy-free survival; OS = overall survival; IMRT = intensity-modulated radiotherapy; ECOG = Eastern Cooperative Oncology Group; AMC = AIDS Malignancy Consortium; 5FU = 5-fluorouracil; Cis = cisplatinum; MMC = mitomycin C; F/U = follow-up; NACT = neoadjuvant chemotherapy; HIV = human immunodeficiency virus.

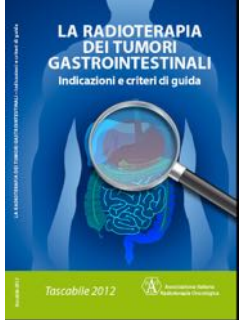
Ottimizzazione RT:
- ricerca nuovi farmaci
- inclusione HIV+



Asco 2012

	ECOG 3205	AMC 045
Number	28	45
Stage I II III	 11% (3/28) 50% (14/28) 39% (11/28)	 24% (11/45) 42% (19/45) 34% (15/45)
Completed therapy per protocol	79% (22/28)	82% (37/45)
Adverse Effect Type I Type II	 4% (1/28) 4% (1/28)	 4% (5/45) 1% (1/45)
Failure at 2 years	25.7% (7/27) •13% progression •6% unrelated deaths •4% Grade 5 •4% Unknown	17.7 (8/45) •7% progression •4% unrelated deaths •4% grade 5 •2% Unknown
Local Failure	**11% (3/27)**	**7% (3/45)** **(all disease progression included; LF alone data not available at this time)**
Progression Free Survival (95% CI) 1 year 2 year	 96% (89%, 100%) 92% (90%, 100%)	 84% (67.6%, 92.5%) 80.0% (67.6%, 92.5%)
Overall Survival (95% CI) 1 year 2 year	 96% (93%, 100%) 93% (83%, 100%)	 92% (78%-94.5%) 89% (73%-95%)
Colostomy Rate at 2 years	14% (4/28)	7% (3/45)

Ca canale anale : TAKE HOME EVIDENCES (1)



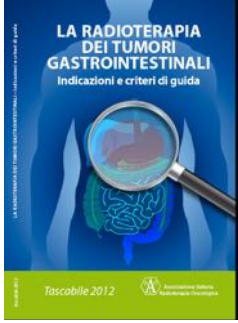
- Il **CDDP** rappresenta una valida alternativa alla MMC soprattutto laddove sia necessario evitare la tossicità ematologica. (fase II Rich TA 1993, Doci R 1996, Martenson JA 1997, Gerard JP1998, Peiffert D 1997 e fase III ACT II) **(Ib,B)**

  E3205, AMC045 (HIV+)

- L'utilizzo di una **chemioterapia di mantenimento** dopo la fase di radiochemioterapia concomitante non modifica la sopravvivenza libera da recidiva pertanto non e' consigliato. (fase III UK ACT II) **(Ib,B)**

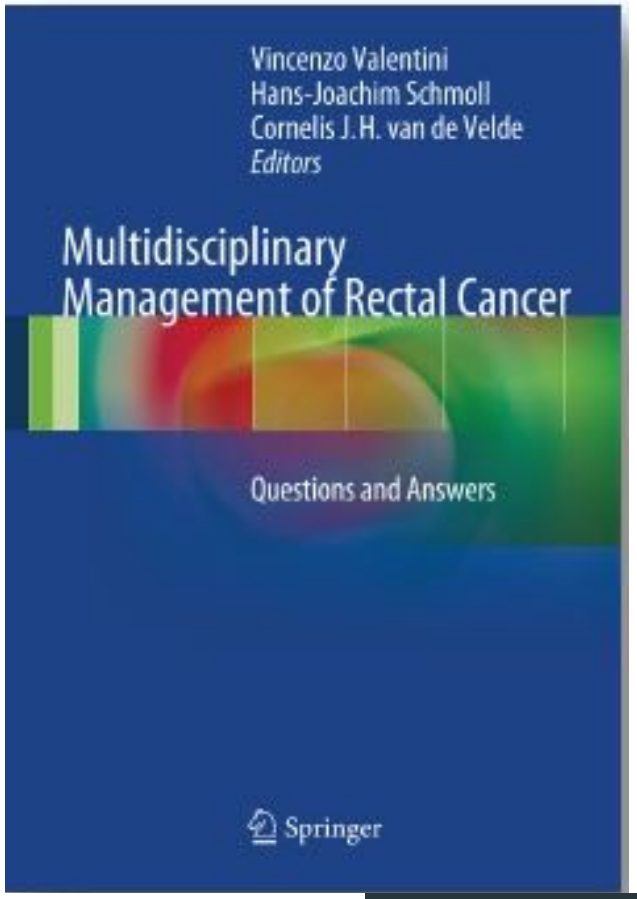
- La **chemioterapia di induzione** con CDDP+5FU ha portato a risultati contrastanti (fase III RTOG 98-11, **ACCORD 03**) pertanto il suo impiego non puo' essere considerato uno standard di trattamento. (Ib,B)

Ca canale anale : TAKE HOME EVIDENCES (2)



- **L'irradiazione profilattica del volume inguinale** con una dose di 45 Gy aumenta il controllo locale e deve pertanto essere raccomandata nei casi T3- T4. (fase III CORS – 03) **(Ib,A)**
  - Nei pazienti con malattia allo stadio iniziale , la scelta rimane discutibile; in questi casi deve comunque essere considerato il rischio di recidiva locale pari al 10%.
- **Una dose totale di radioterapia superiore a 59 Gy** nel trattamento combinato non ha dimostrato beneficio aggiuntivo (fase III ACCORD-03). **(Ib,B)**
- La **valutazione della risposta clinico-strumentale** deve essere effettuata dopo 12 settimane dal termine del trattamento radio chemioterapico **(Ib,A)**
  - **La chirurgia di salvataggio dovrebbe essere proposta dopo 26 settimane** (rev ACT II 2012) **(Ib,B)**

…PER APPROFONDIRE…



MARTEDÌ 20 NOVEMBRE 2012

In contemporanea

AUDITORIUM

8.30 - 9.30 **SIMPOSIO**

Radioterapia e trattamenti sistemici nel carcinoma del pancreas: update

Moderatori: C. De Renzis (Messina), M.G. Trovò (Aviano)

La chirurgia: come, quando e quale - **V. Ziparo** (Roma)
Il ruolo della radioterapia e le interazioni radio-chemioterapiche - **A.G. Morganti** (Campobasso)
La radioterapia: dal planning alla delivery - **D. Genovesi** (Chieti)