GRANDANGOLO IN RADIOTERAPIA ONCOLOGICA
Neoplasie dell' apparato gastrointestinale

ASLCagliari
SISTEMA SANITARIO DELLA SARDEGNA

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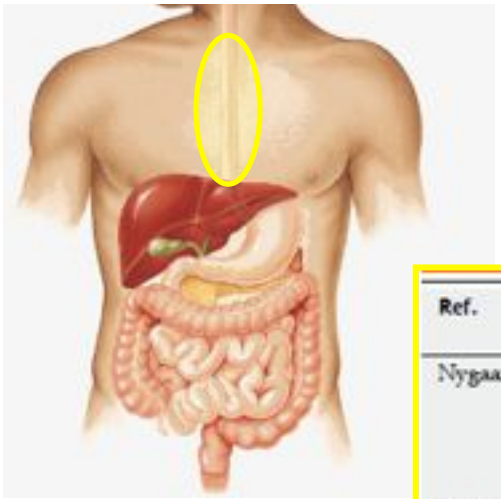


Does neoadjuvant CRT improve survival?

Esophageal cancer

Ref.	n	Histology	Treatment	R0	pCR	Op mortality	MS	3 YS	Locoregional failure
Nygaard *et al*[50], 1992		Sq	S	37%	-	5 (3.4)	Approximately 0.6 yr	Approximately 9%	-
			CB → S	41%		6 (4.0)	Approximately 0.7 yr	Approximately 2%	
			R → S	40%		4 (2.7)	Approximately 0.9 yr	Approximately 20%	
			CB + R → S	55% (Gp 4 vs 1, $P = 0.08$)		8 (5.4)	Approximately 0.7 yr	Approximately 18%	
Walsh *et al*[51], 1996	113	A	CF + R → S	-	25%	5 (10.4)	16	32%	-
			S	-	0%	2 (3.7)	11 mo	6%	-
							$P = 0.01$	$P = 0.01$	
Bosset *et al*[52], 1997	282	Sq	C + R → S	-	26%	17 (12.3)	18.6 mo	36%	-
			S	-	0%	5 (3.6)	18.6 mo	34%	-
								See text	
Urba *et al*[53], 2001	100	75% A	CFV + R → S	90%	28%	1 (2.1)	16.9 mo	30%	19%
		25% Sq	S	90%	0%	2 (4)	17.6 mo NS	16%	42%
									$P = 0.02$
Burmeister *et al*[54], 2005	256	37% Sq	CF + R → S	80%	16%	5 (4.8)	22.2 mo	35%	15%
		62% A	S	59%	0%	6 (5.5)	19.3 mo	30%	19%
		1% mixed/ other						See text	
Tepper *et al*[55], 2008	56	25% Sq	CF + R → S	-	33%	0 (0)	4.5 yr	39%	13%
		75% A	S		0%	1 (3.8)	1.8 yr	16%	15%
							$P = 0.002$	5 YS	
Cao *et al*[56], 2009	366	Sq	CFM → S	87%	1.7%	0%	Approximately 42 mo	Approximately 69%	-
			R → S	98%	15%	0%	Approximately 42 mo	69%	
			CFM + R → S	98%	22%	0%	Approximately 60 mo	74%	
			S	73%	0%	0%	Approximately 42 mo	53%	
								$P = 0.013$	
van Hagen *et al*[58], 2012 multicenter phase III randomized **CROSS Trial**	366 T1-3 N0-1 M0	23% Sq 75% A 2% other	JT + R → S	92%	29%	6 (4)	49.4 mo	58%	-
			S	69%	0%	8 (4)	24 mo	44%	
								$P = 0.03$	

improved DFS of 22% at 5 years and improved OS of 13% with a pCR = 29%

Patricia Tai, Edward Yu. World J Gastrointest Oncol 2014; 6(8): 263-274

Lloyd S, Chang BW. J Gastrointest Oncol. 2014;5:156-65

Cellini F. Radiation Oncology 2014, 9:45

418 ptz available for analysis
combining patients
phase II trial and phase III CROSS trial

resectable Esophageal or GEJ cancer (T2-3N0-1M0)
75% Adenocarcinoma

VOLUME 32 · NUMBER 5 · FEBRUARY 10 2014
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

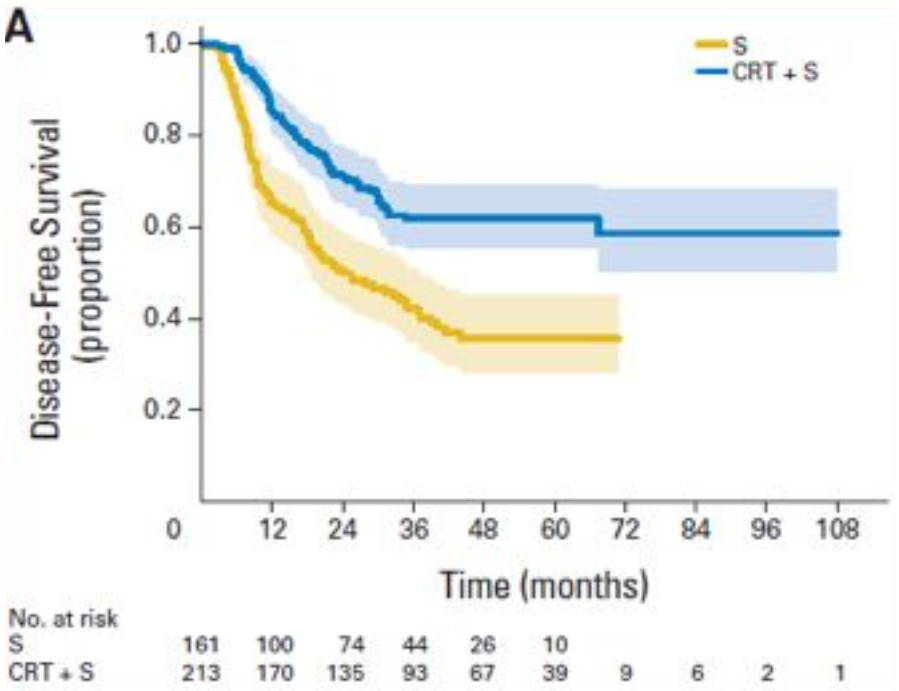
Patterns of Recurrence After Surgery Alone Versus Preoperative Chemoradiotherapy and Surgery in the CROSS Trials

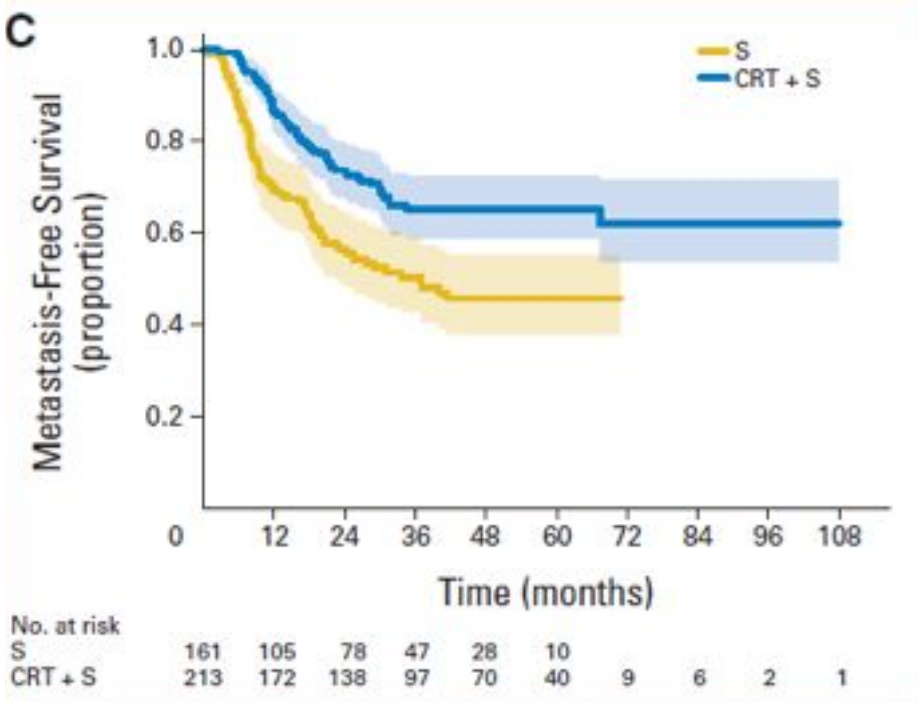
Weekly Carboplatin and Paclitaxel for 5 wk and concurrent RT (41.4 Gy/23 f), followed by surgery.

PTV: GTV + proximal and distal margin of 4 cm (3 cm in case of tumor extension into the stomach) and + 1.5 cm radial margin.

minimum follow-up = 24 ms (median, 45 ms)

overall recurrence rate: **57.1%** vs **34.7%**





van Hagen P. N Engl J Med. 2012; 31;366:2074-84.
Oppedijk V. J Clin Oncol. 2014;32:385-9

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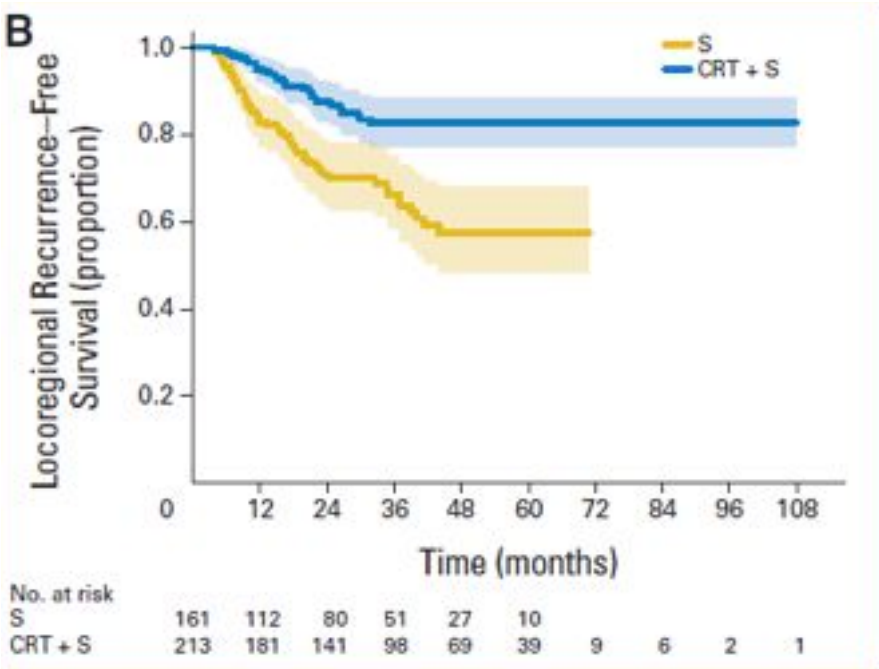
minimum follow-up = 24 ms (median, 45 ms)

LRR: **34%** vs **14%** (*P .001*)
peritoneal carcinomatosis: ***14%*** *vs* ***4%*** *(P .001).*



LRR:
- *5% within the target volume,*
- *2% in the margins*
- *6% outside the radiation target volume.*

Tumor Recurrences in Relation to Radiation Target Volumes in Patients Undergoing CRT Plus Surgery (n = 213)

Recurrence	Infield	Outfield	Borderline	Unknown	Total
LRR only	2	2	2	1	7
Distant only	0	43	0	1	44
LRR plus distant	9	11	3	0	23
Total	11	56	5	2	74

Only 1% had an isolated infield recurrence after CRT plus surgery.

van Hagen P. N Engl J Med. 2012; 31;366:2074-84
Oppedijk V. J Clin Oncol. 2014;32:385-9

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Univariable and Multivariable Cox Regression Analyses for LRRs in Patients Undergoing Resection (n = 374)

Factor	LRR Incidence (%)		Univariable		Multivariable	
	S Arm	CRT + S Arm	HR	95% CI	HR	95% CI
Method of resection (TTE *v* THE)	20 *v* 17	6 *v* 8	0.83	0.54 to 1.29	NA	
Tumor length (≤ 5.0 *v* > 5.0 cm)	23 *v* 39	16 *v* 11	0.89	0.54 to 1.46	NA	
Clinical T stage (T1-2 *v* T3-4)	31 *v* 35	5 *v* 17	1.32	0.76 to 2.29	NA	
Clinical nodal stage (N0 *v* N1)	31 *v* 35	10 *v* 18	1.50	0.93 to 2.41	NA	
Pathologic nodal stage (N0 *v* N1)	**22 *v* 38**	**10 *v* 23**	**3.66**	**2.2 to 5.85**	**2.85**	**1.59 to 5.11**
Involved margins (R0 *v* R1)	34 *v* 36	13 *v* 29	**2.29**	**1.38 to 3.76**	NA	
Histology (SCC *v* AC)	47 *v* 30	15 *v* 14	0.70	0.44 to 1.12	**0.49**	**0.29 to 0.82**
Sex (male *v* female)	33 *v* 34	12 *v* 20	1.12	0.67 to 1.87	NA	
Treatment arm (S *v* CRT + S)	27	14	**0.37**	**0.23 to 0.59**	**0.50**	**0.29 to 0.86**
pCR after CRT (no *v* yes)*	NA	7 *v* 17	0.36	0.13 to 1.05	NA	

Consistent with the concept of spatial cooperation
the addition of neoadjuvant CRT
provided benefits in local, regional, and distant disease control
relative to surgery alone.

van Hagen P. N Engl J Med. 2012; 31;366:2074-84
Oppedijk V. J Clin Oncol. 2014;32:385-9

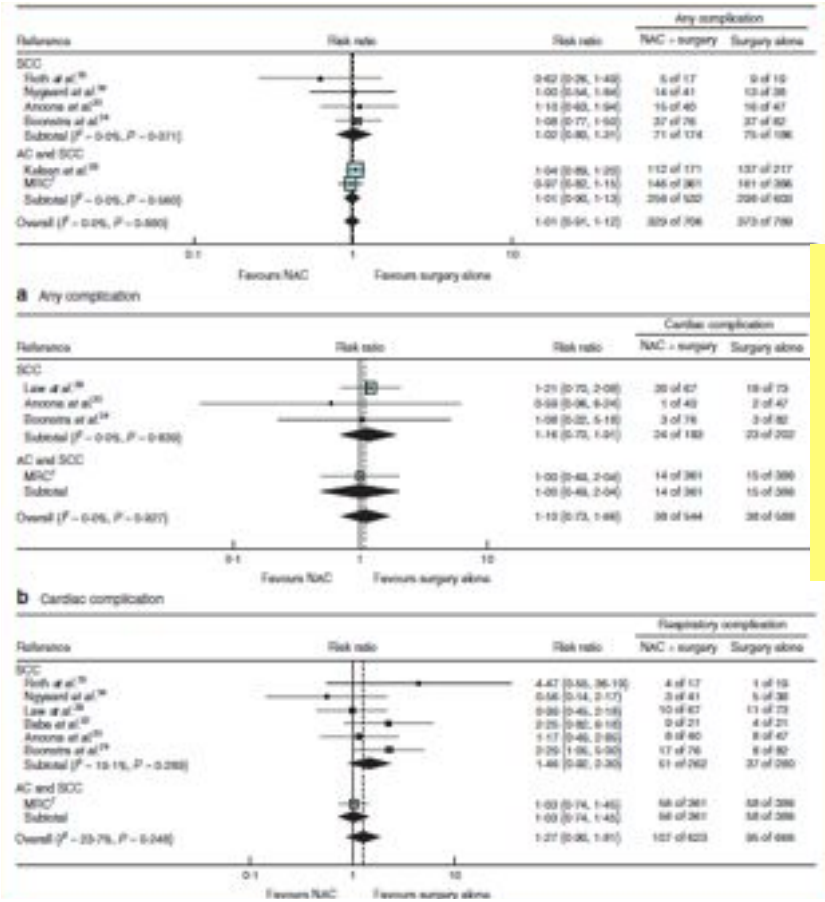
Can neoadjuvant therapies contribute to subsequent postoperative morbidity and mortality?

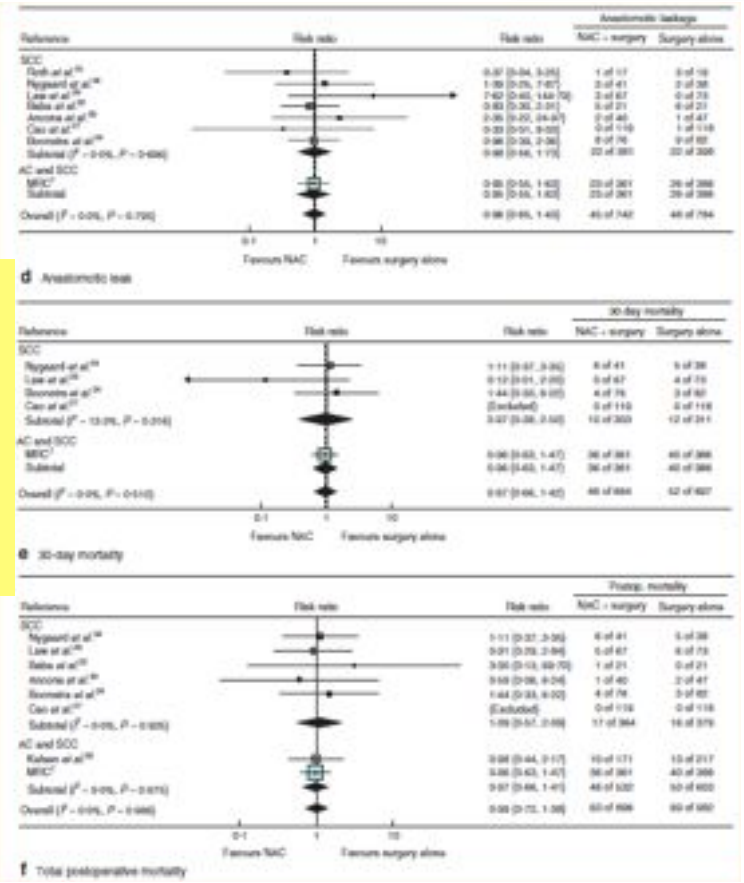
Meta-analysis of postoperative morbidity and perioperative mortality in patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal and gastro-oesophageal junctional cancers

neoadjuvant CT plus S vs S alone

Studies included in meta-analysis
$n = 23$

Since 1994



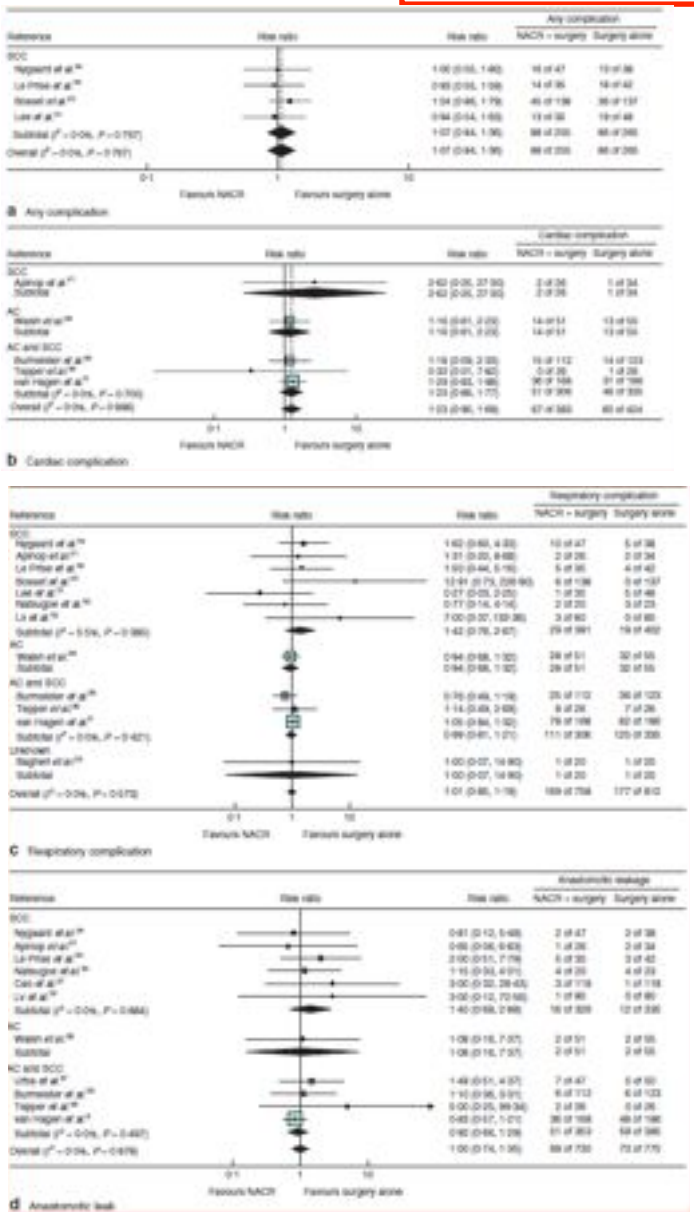


no evidence to suggest that **neoadjuvant CT increased** the risk of any type of postoperative Complication.

Kumagai K. Br J Surg. 2014;101:321-38.

Can neoadjuvant therapies contribute to subsequent postoperative morbidity and mortality?

neoadjuvant CRT plus S vs S alone



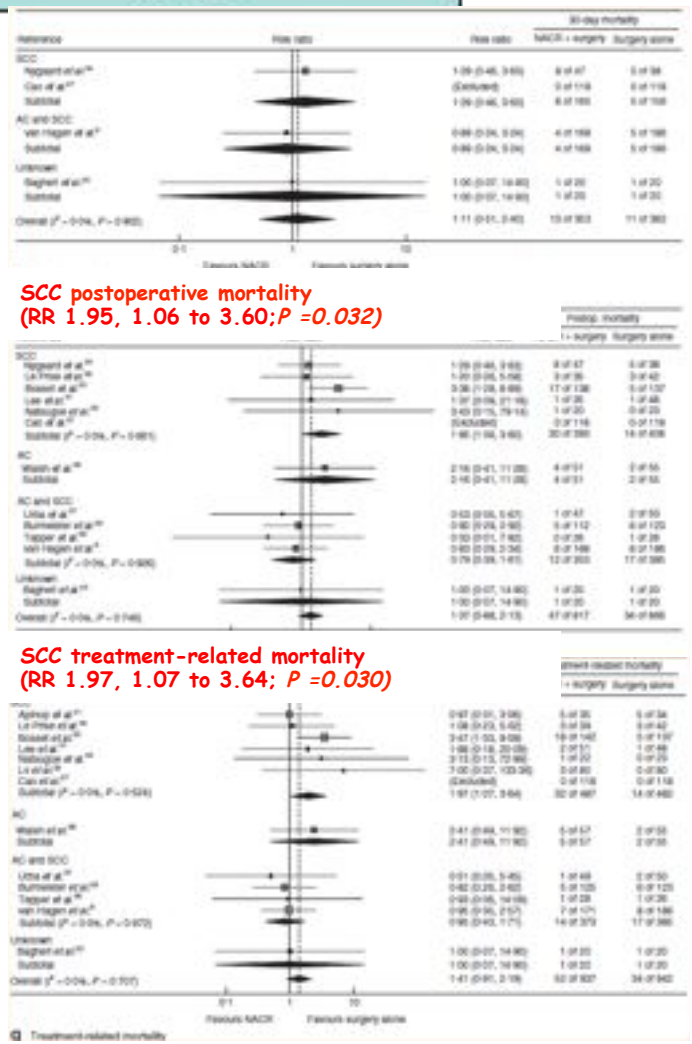
no evidence to suggest that **neoadjuvant CRT increased** the risk of any type of postoperative Complication.

SCC higher risk of total postoperative mortality and treatment-related mortality compared with surgery alone

no difference with **ADK**

Since 1994

Studies included in meta-analysis
$n = 23$



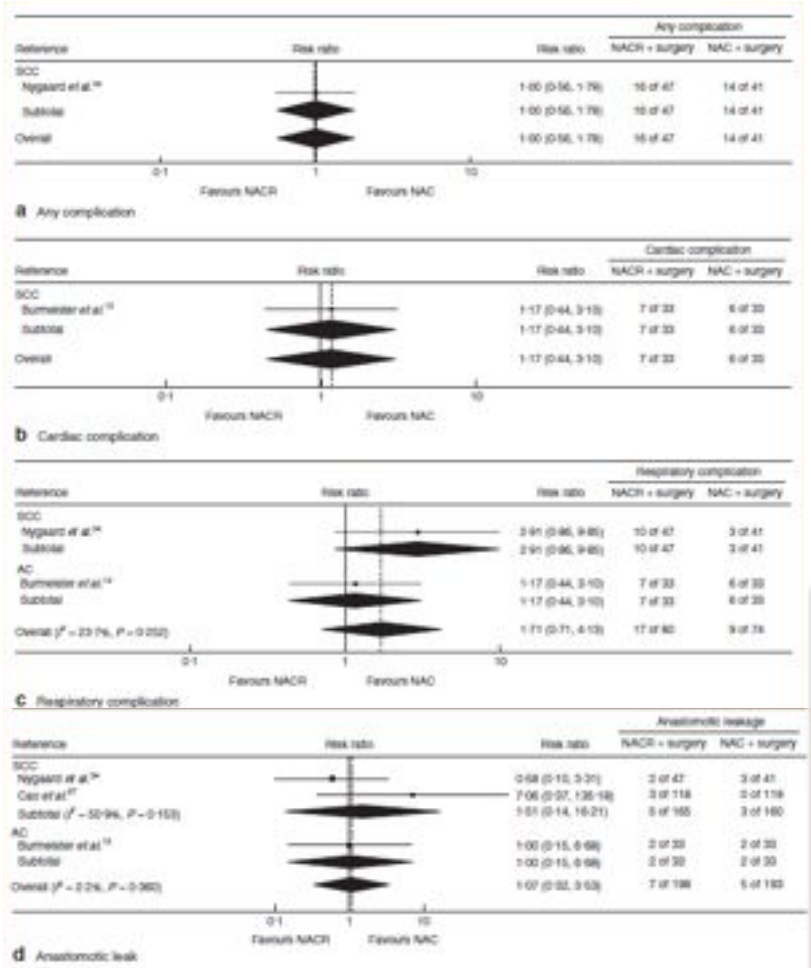
SCC postoperative mortality
(RR 1.95, 1.06 to 3.60; *P =0.032*)

SCC treatment-related mortality
(RR 1.97, 1.07 to 3.64; *P =0.030*)

Kumagai K. Br J Surg. 2014;101:321-38.

Can neoadjuvant therapies contribute to subsequent postoperative morbidity and mortality?

Direct comparison and Adjusted indirect comparison method of **neoadjuvant CRT plus S and neoadjuvant CT plus S** (common control group = S alone).



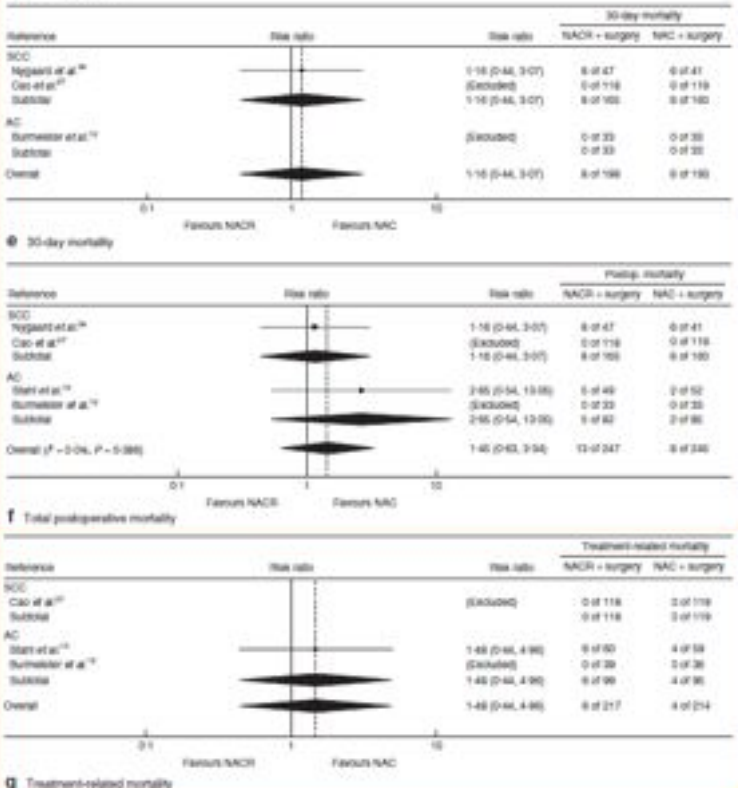
no evidence to suggest that **neoadjuvant CRT increased** the risk of any type of postoperative Complication.

No difference for SCC

Limitations:
- Only article in English
- Some studies included pts with stomach cancer
- Variation in definition and classification of complications and their severity

Studies included in meta-analysis
n = 23

Since 1994



Kumagai K. Br J Surg. 2014;101:321-38.

Induction CT followed by preoperative CRT: what benefit?

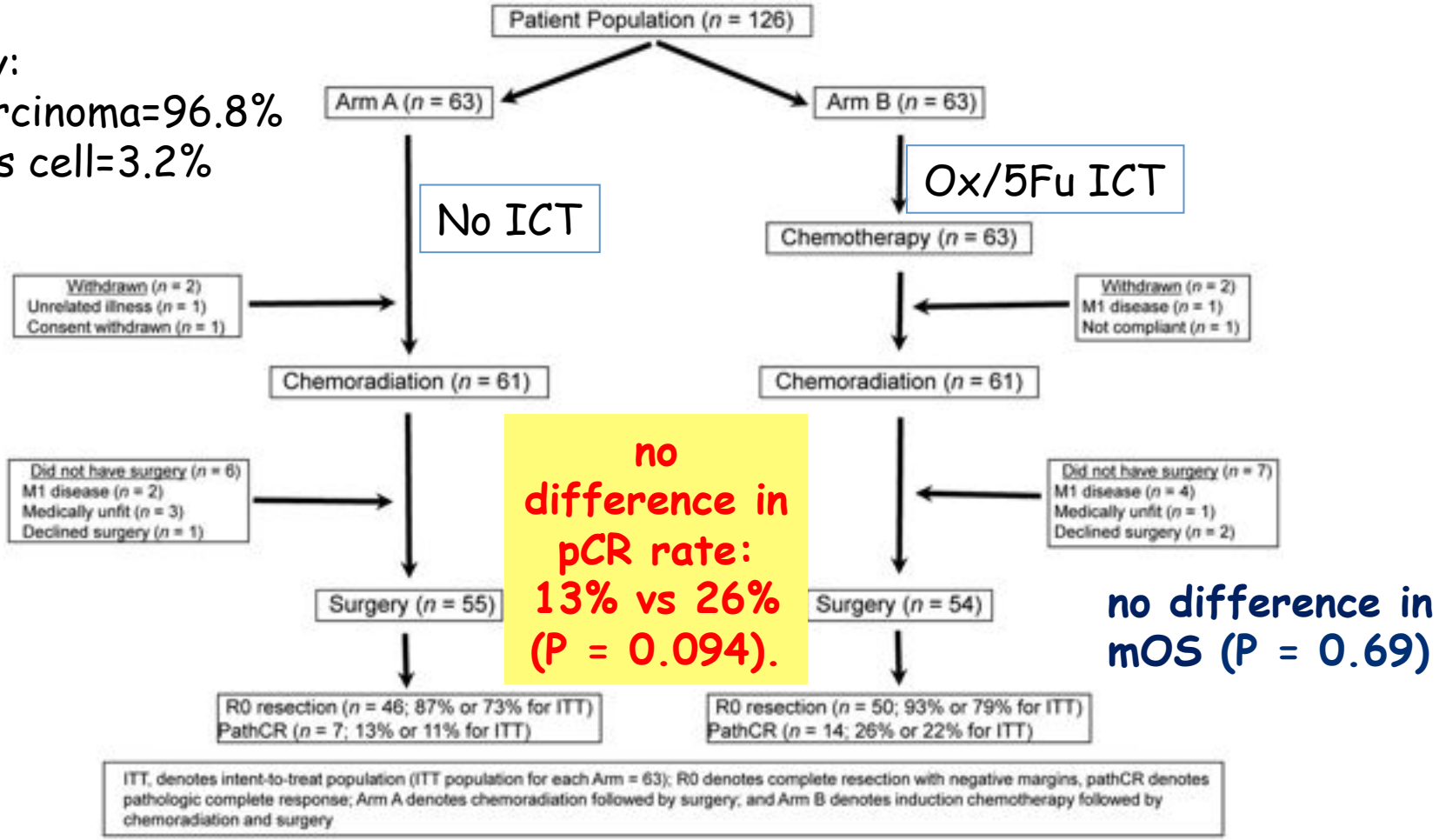
Treatment Intensification
Resectable disease

Annals of Oncology 24: 2844–2849, 2013
doi:10.1093/annonc/mdt339
Published online 23 August 2013

Primary objective: pCR rate.
Secondary objectives: OS, R0 resection rate, and safety (including 30-day surgical mortality).

Histology:
Adenocarcinoma=96.8%
Squamous cell=3.2%

A phase II randomized trial of induction chemotherapy versus no induction chemotherapy followed by preoperative chemoradiation in patients with esophageal cancer



no difference in pCR rate: 13% vs 26% (P = 0.094).

no difference in mOS (P = 0.69)

J. A. Ajani. Annals of Oncology 24: 2844–2849, 2013

A Phase II Study with Cetuximab and Radiation Therapy for Patients with Surgically Resectable Esophageal and GE Junction Carcinomas

Hoosier Oncology Group G05-92

Treatment Intensification
Resectable disease

pCR

Targeted Therapies:
Cetuximab

phase II, open-label, single-arm, multicenter study; **39 ptz**
resectable Esophageal or GEJ cancer
78% Adenocarcinoma

and
concurrent RT (50.4 Gy in 28 fx)

pCR rate =
36.6% by intention-to-treat and
48% for patients who underwent esophagectomy

TABLE 4. Grade 3 Toxicities ≥5% Irrespective of Causality Attributed

	Grade 3	
CTCAE	N	%
Anorexia	3	7
Dehydration	3	7
Dysphagia	7	17
Dyspnea	2	5
Fatigue	2	5
Hypernatremia	2	5

TABLE 5. Pathologic Complete Remission by Initial Clinical Stage and Histology

Stage or Histology	pCR	%
IIA	7/10	70
IIB	2/7	29
III	6/22	27
IVA	0/2	0
Adenocarcinoma	9/32	28
Squamous cell	6/9	67

pCR, pathologic complete response.

Becerra CR. J Thorac Oncol. 2013;8:1425-9

Treatment Intensification
Resectable disease

Preoperative Chemoradiation Therapy in Combination With Panitumumab for Patients With Resectable Esophageal Cance The PACT Study

International Journal of Radiation Oncology biology • physics
www.redjournal.org

pCR

phase II, multicenter study; **90 ptz**
resectable Esophageal or GEJ cancer
80% Adenocarcinoma

Targeted Therapies: **Panitumumab**

Carboplatin and Paclitaxel
and concurrent RT(41.4 Gy in 23 fx)

The addition of panitumumab to CRT with carboplatin and paclitaxel was safe and well tolerated but could not improve pCR rate to the preset criterion of 40%.

Table 3 Pathology assessment of tumor regression grades

TRG	AC		SCC		Other		Total	
1 (pCR)	10	14%	7	47%	2	100%	19	22%
2	14	20%	4	27%	0	0%	18	21%
3	32	46%	4	27%	0	0%	36	41%
4/5	14	20%	0	0%	0	0%	14	16%
Total	70	80%	15	17%	2	2%	87	100%

Abbreviations: AC = adenocarcinoma; pCR = pathologic complete remission; SCC = squamous cell carcinoma; TRG = tumor regression grade.
The primary endpoint was TRG 1 (pCR) of all patients (n = 19 [22%]).

Kordes S. Int J Radiat Oncol Biol Phys. 2014;90:190-6

Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial

Unresectable disease

RT: 50 Gy/ 25 fx

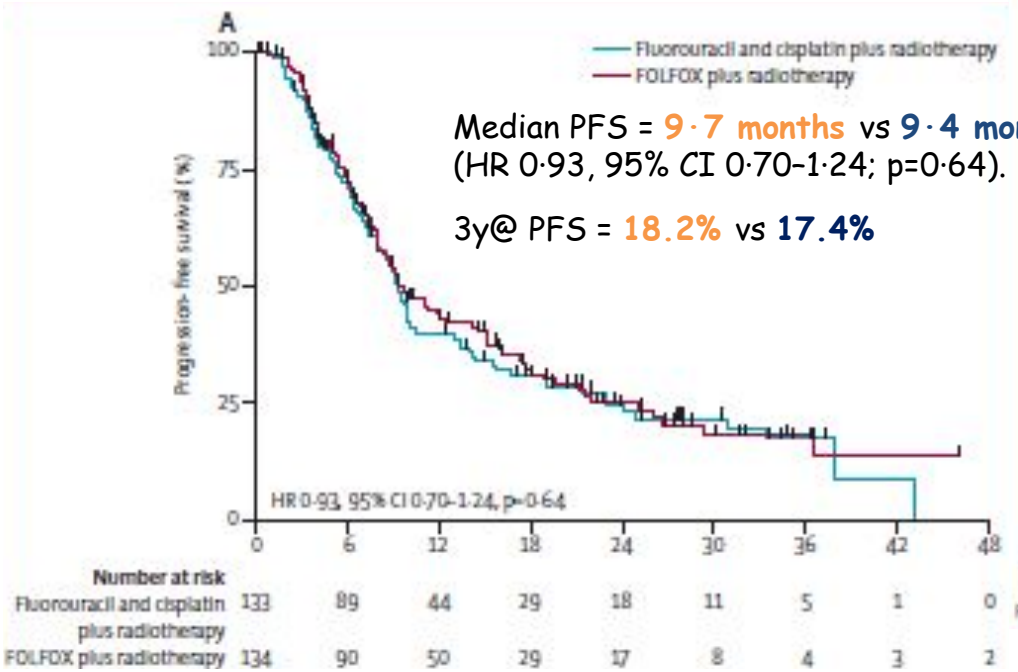
THE LANCET Oncology

Thierry Conroy, Marie-Pierre Galais, Jean-Luc Raoul, Olivier Bouché, Sophie Gourgou-Bourgade, Jean-Yves Douillard, Pierre-Luc Etienne, Valérie Boige, Isabelle Martel-Lafay, Pierre Michel, Carmen Llacer-Moscardo, Eric François, Gilles Créhange, Meher Ben Abdelghani, Beata Juzyna, Laurent Bedenne, Antoine Adenis, for the Fédération Francophone de Cancérologie Digestive and UNICANCER-GI Group

Histology:
Adk=86%
SCC=14%

Primary endpoint = PFS

Median follow-up = 25.3 months

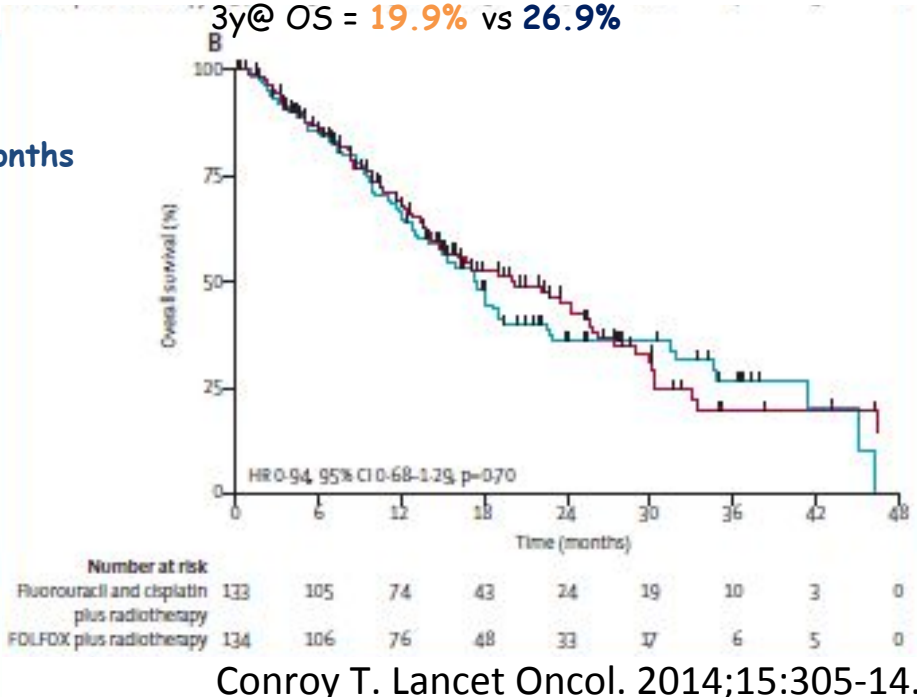


Median PFS = 9·7 months vs 9·4 months
(HR 0·93, 95% CI 0·70–1·24; p=0·64).

3y@ PFS = 18.2% vs 17.4%

Median OS = 20·2 months vs 17·5 months
(HR 0·94, 95% CI 0·68–1·29; p=0·70)

3y@ OS = 19.9% vs 26.9%



Conroy T. Lancet Oncol. 2014;15:305-14.

No significant differences were recorded in the rates of most frequent grade 3 or 4 adverse events between the treatment groups.

	FOLFOX group (n=131)			Fluorouracil and cisplatin group (n=128)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Haematological						
Neutropenia	30 (23%)	29 (22%)	9 (7%)	32 (25%)	26 (20%)	11 (9%)
Febrile neutropenia	0	5 (4%)	2 (2%)	1 (1%)	6 (5%)	3 (2%)
Neutropenia and infection	1 (1%)	2 (2%)	0	0	1 (1%)	2 (2%)
Lymphopenia	4 (3%)	14 (11%)	7 (5%)	4 (3%)	11 (9%)	11 (9%)
Leucopenia	38 (29%)	25 (19%)	3 (2%)	41 (32%)	20 (16%)	11 (9%)
Anaemia	68 (52%)	6 (5%)	1 (1%)	69 (54%)	12 (9%)	2 (2%)
Thrombocytopenia	52 (40%)	6 (5%)	3 (2%)	53 (41%)	2 (2%)	8 (6%)
Hyponatraemia	14 (11%)	3 (2%)	0	22 (17%)	5 (4%)	0
Hyperkalaemia	11 (8%)	1 (1%)	0	20 (16%)	1 (1%)	0
Hypocalcaemia	14 (11%)	0	0	13 (10%)	1 (1%)	0
Non-haematological						
Aphagia/dysphagia	16 (12%)	32 (24%)	6 (5%)	12 (9%)	31 (24%)	0
Asthenia	47 (36%)	23 (18%)	0	47 (37%)	12 (9%)	1 (1%)
Oesophagitis	19 (15%)	8 (6%)	1 (1%)	18 (14%)	11 (9%)	0
Erythema/epidermitis	9 (7%)	0	1 (1%)	17 (13%)	1 (1%)	0
Weight loss	42 (32%)	5 (4%)	0	40 (31%)	5 (4%)	0
Anorexia	25 (19%)	6 (5%)	0	19 (15%)	4 (3%)	0
Mucositis	20 (15%)	6 (5%)	1 (1%)	30 (23%)	2 (2%)	0
Vomiting	28 (21%)	4 (3%)	1 (1%)	39 (31%)	3 (2%)	0
Nausea	62 (47%)	3 (2%)	0	74 (58%)	4 (3%)	0
Odynophagia	17 (13%)	2 (2%)	0	8 (6%)	3 (2%)	0
Denutrition	0	2 (2%)	0	0	2 (2%)	0

Sensory neuropathy: 24 [18%] vs 1 [1%], p<0·0001,
increases in AST concentrations (14 [11%] vs 2 [2%], p=0·002),
increases in ALTconcentrations (11 [8%] vs 2 [2%], p=0·012)

Oesophageal/epigastric pain	16 (12%)	4 (3%)	0	13 (10%)	2 (%)	0
Paraesthesia	61 (47%)	0	0	2 (2%)	1 (1%)	0 **p<0·0001**

Alopecia: 2 [2%] vs 12 [9%], p=0·005

Renal insufficiency	1 (1%)	0	0	4 (3%)	1 (1%)	1 (1%) **p=0·011**

Data are n (%). FOLFOX=fluorouracil, leucovorin, and oxaliplatin.

Conroy T. Lancet Oncol. 2014:15:305-14

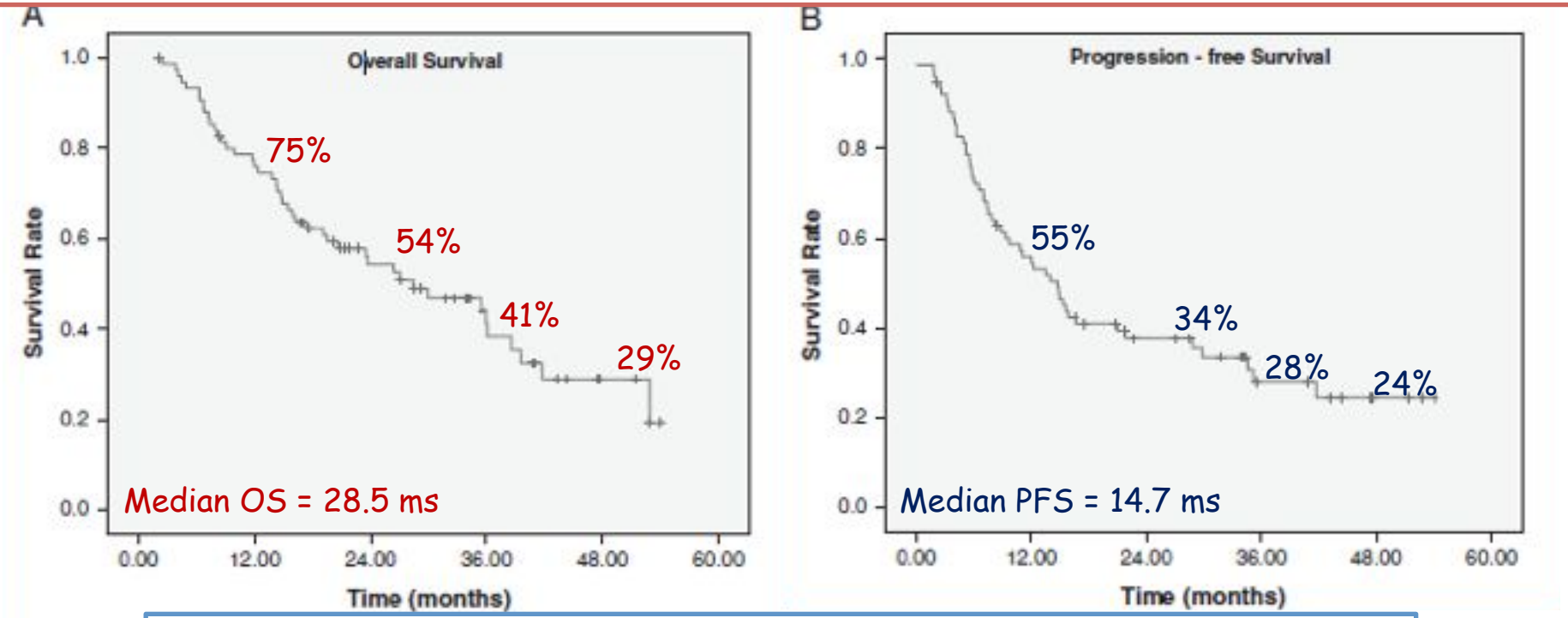
A Phase II Study of Concurrent Chemoradiotherapy With Paclitaxel and Cisplatin for Inoperable Esophageal Squamous Cell Carcinoma

Unresectable disease

76 enrolled pts
89.5% and 63.2%pts completed ≥2 cycles and all 4 cycles of CT, respectively

Median follow-up = 36 months

BETTER than the result of **RTOG9405 (5-FU + CDDP) => (1- 2-y@ OS =66% and 40%)** and equal to the result of **RTOG0113 (5-FU+ PTX) => (1- 2-y@ OS =76% and 56%)**

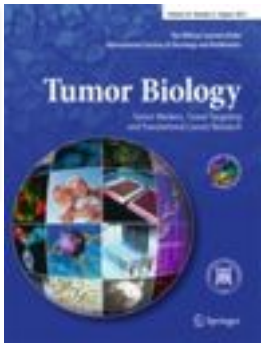


The main toxicities were grade 3 and 4 leukopenia and neutropenia.
Grade 3 and 4 leukopenia in 43.4% and 14.5% of the cases, respectively.
Grade 3 and 4 neutropenia in 30.3% and 31.6% of the cases, respectively.

Hua-Rong Tang. Am J Clin Oncol 2014;in press

RT in gastric carcinoma

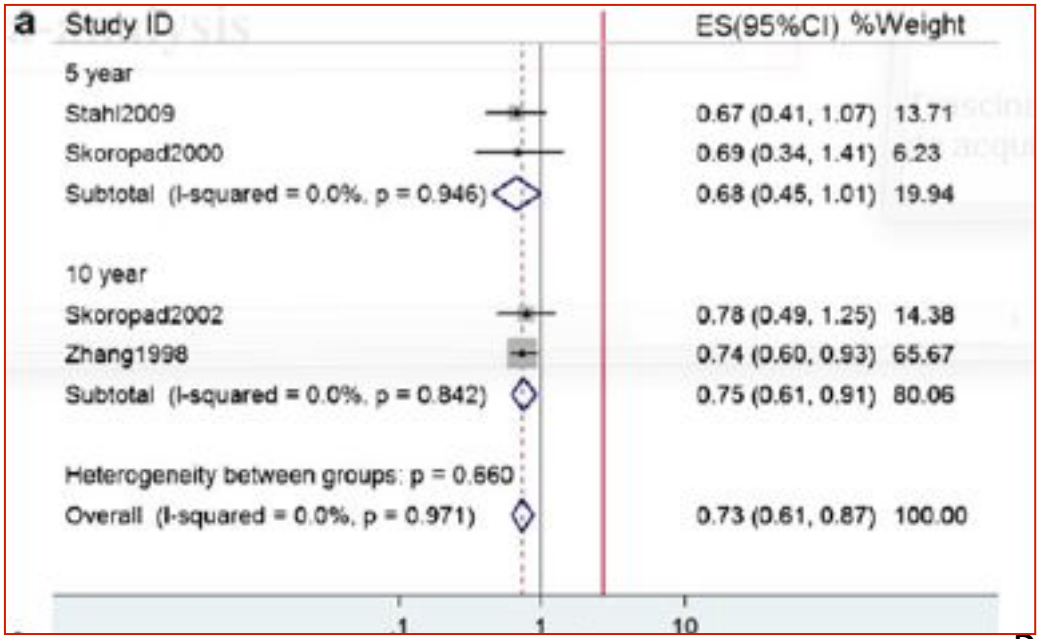
both in the preoperative and postoperative RT



Radiotherapy for gastric cancer: a systematic review and meta-analysis

Randomized controlled trials based on English-language peer-reviewed studies published before 1 May 2013. **16 trials** published between 1979 and 2012, involving a total of **3,716 patients**, 1,865 in study group and 1,827 in control.

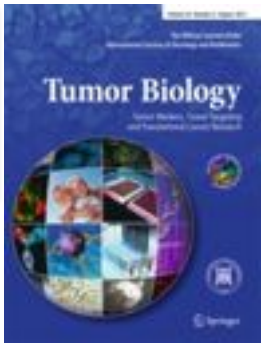
In the subgroup of patients receiving **preoperative RT (4 Trials)**, a significant benefit was found on 10-y@ OS with a HR of 0.75 (95 % CI, 0.61 to 0.91); however, the benefit on 5-y@ OS was not proven (HR, 0.68; 95%CI, 0.45 to 1.01).



Pang X. Tumor Biol 2014

RT in gastric carcinoma

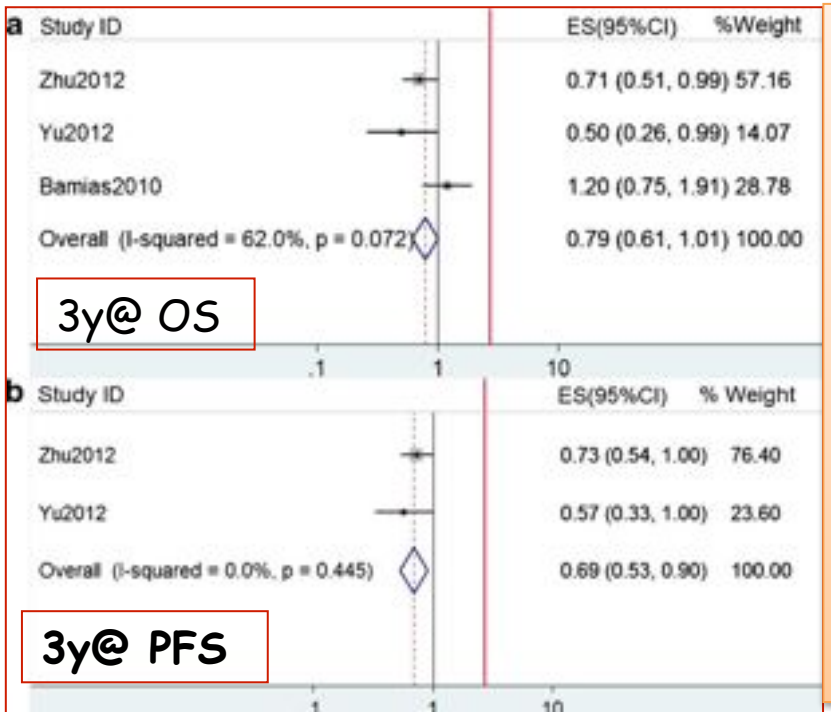
both in the preoperative and postoperative RT



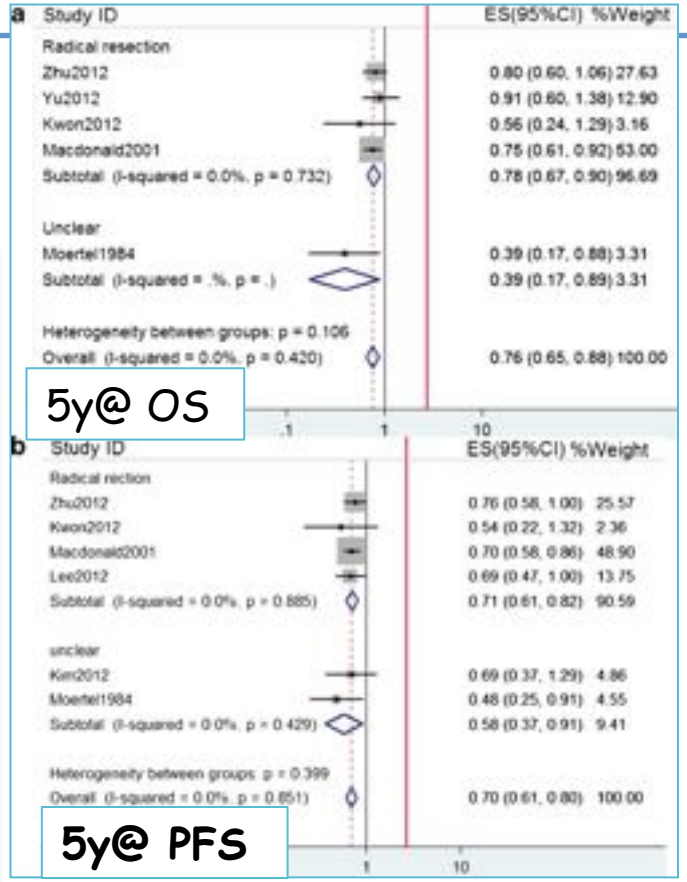
Radiotherapy for gastric cancer: a systematic review and meta-analysis

Randomized controlled trials based on English-language peer-reviewed studies published before 1 May 2013. **16 trials** published between 1979 and 2012, involving a total of **3,716 patients**, 1,865 in study group and 1,827 in control.

In the subgroup of patients receiving **postoperative RT (7 trials)**, survival benefits were found on 3- and 5-y@ **PFS**
HR of 0.69 (95 %CI, 0.53 to 0.90) and
HR of 0.70 (95 %CI, 0.61 to 0.80)



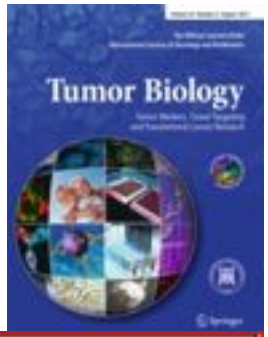
The results **need further examination** due to the time span of the included trials (**from 1979 to 2012**), the **different criteria for staging**, and different **techniques applied** for radiotherapy across trials.



Pang X. Tumor Biol 2014

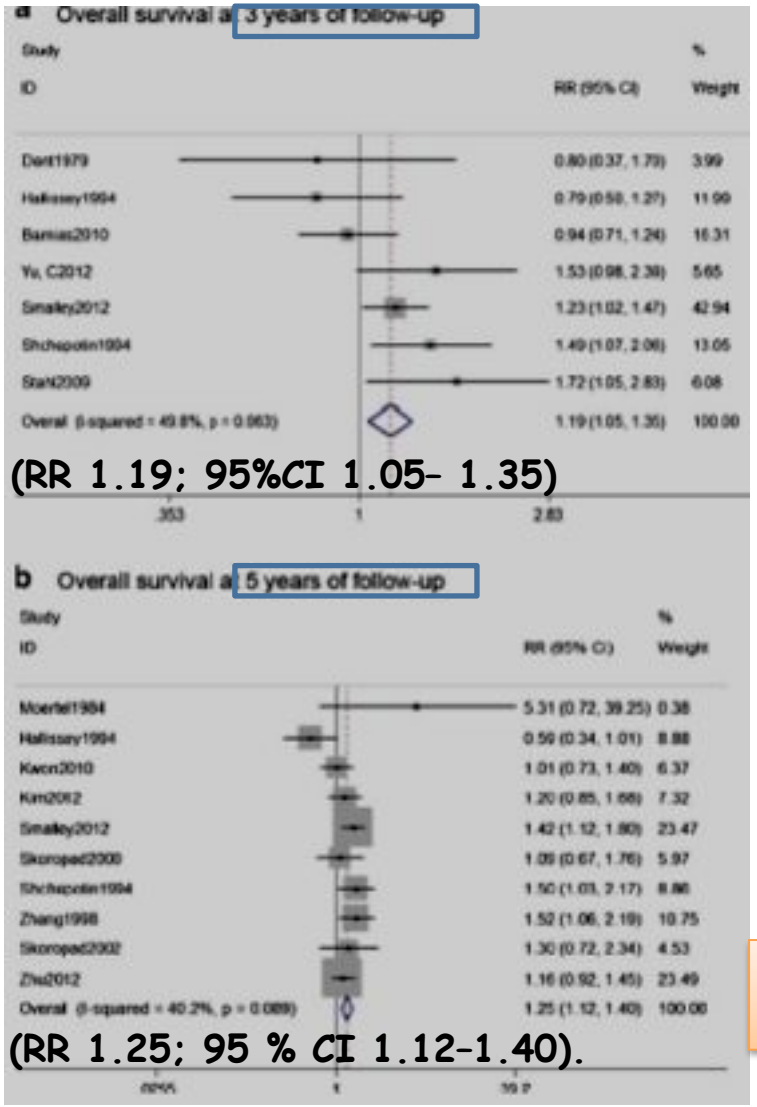
RT in **resectable** gastric carcinoma

Benefit of radiotherapy on survival in resectable gastric carcinoma: a meta-analysis



Adjuvant RT significantly increased the 3-y@ and 5-y@ survival

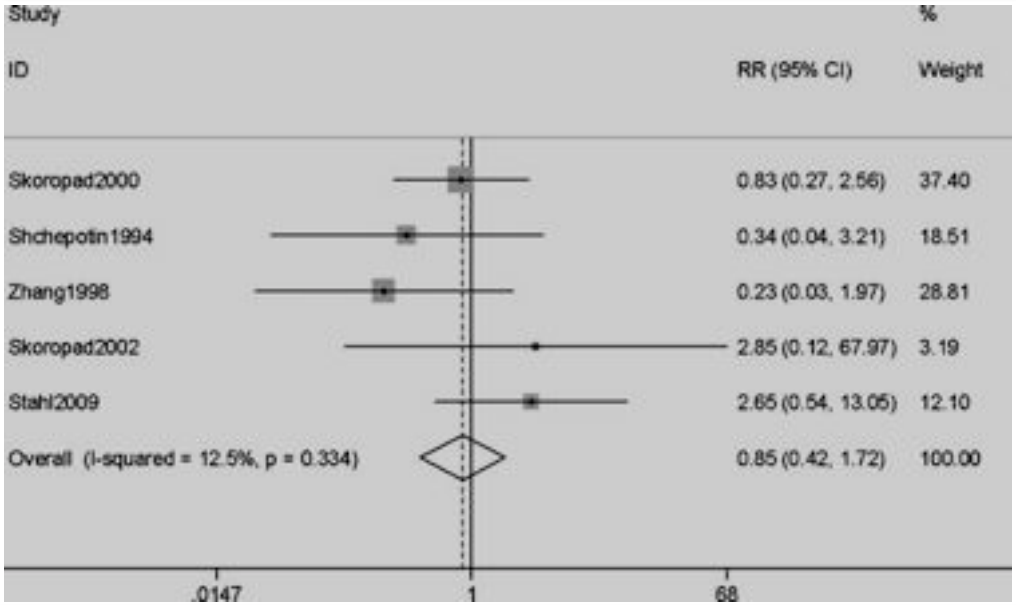
14 RCTs (2853 patients) included in analysis



(RR 1.19; 95%CI 1.05– 1.35)

(RR 1.25; 95 % CI 1.12–1.40).

No significant effect of preoperative RT on increase of postoperative mortality
[RR 0.85 (95 % CI 0.42–1.72), I2= 12.5 %, P=0.334]



Available evidence is insufficient to determine the benefit of postoperative RT after a D2 lymphadenectomy and R0

Li LL, et al. Tumour Biol. 2014;35:4957-66.

CRT postoperatoria rispetto alla sola CT adiuvante

RADIATION ONCOLOGY—REVIEW ARTICLE

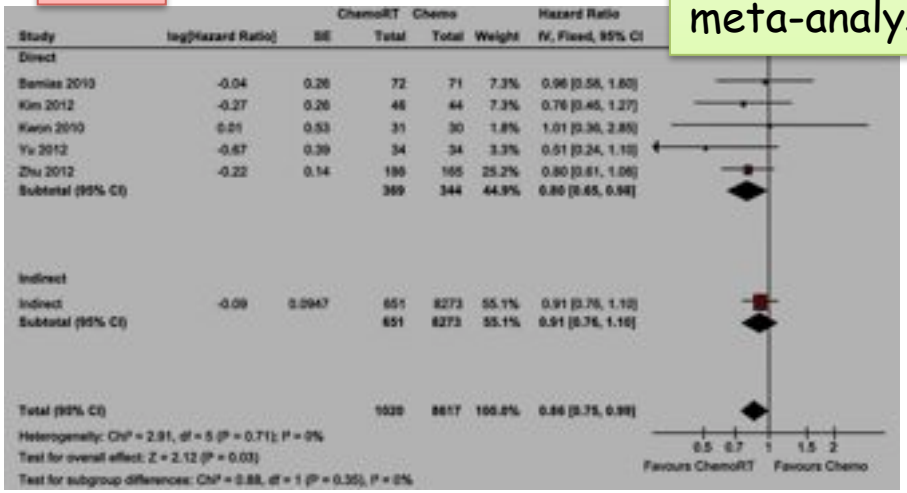
Postoperative chemo-radiotherapy versus chemotherapy for resected gastric cancer: A systematic review and meta-analysis

6 trials comparing postoperative CTRT with CT (*n = 1171*).
direct and indirect comparison meta-analysis

Postoperative CRT significantly improved both DFS and OS when compared with CT.

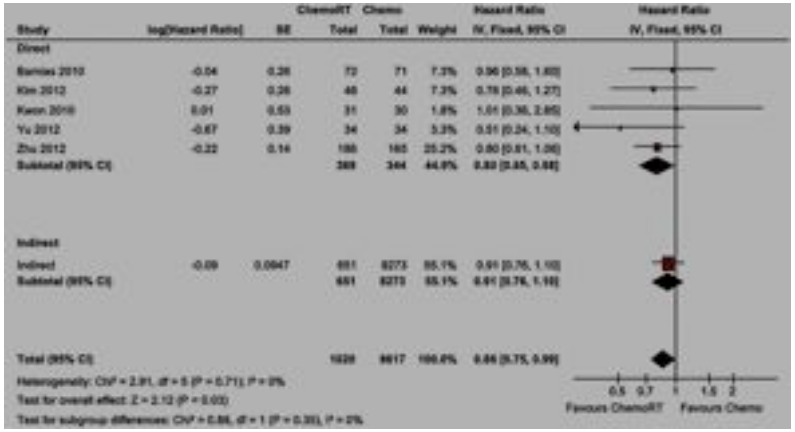
There were no significant differences in toxicity between the two groups.

OS



(HR 0.80, 95% CI 0.65–0.98, *P = 0.03*)

DFS



(HR 0.76, 95% CI 0.63–0.91, P = 0.003)

NO statistically significant difference in effects on OS between subgroups defined by use of D2 resection, IMRT, 5FU or platinum based CT

Table 2. Subgroup effects on overall survival

Subgroups	Patients	Hazard ratio	95% CI	Interaction P
D2 lymph node dissection				
Mandatory	502	0.80	0.63 to 1.02	0.99
Non-mandatory	211	0.79	0.52 to 1.21	
Intensity-modulated radiotherapy techniques				
Yes	419	0.76	0.59 to 0.99	0.61
No	294	0.87	0.62 to 1.23	
5-fluorouracil chemotherapy				
Yes	570	0.77	0.62 to 0.97	0.42
No	143	0.96	0.58 to 1.60	
Platinum chemotherapy				
Yes	204	0.97	0.61 to 1.53	0.42
No	509	0.76	0.61 to 0.96	

Soon YY. J Med Imaging Radiat Oncol. 2014;58:483-96

Oncology

Clinical Study

Oncology 2014;86:79–85
DOI: 10.1159/000354641

Received: April 4, 2013
Accepted after revision: July 19, 2013
Published online: January 15, 2014

Chemoradiation Therapy versus Chemotherapy Alone for Gastric Cancer after R0 Surgical Resection: A Meta-Analysis of Randomized Trials

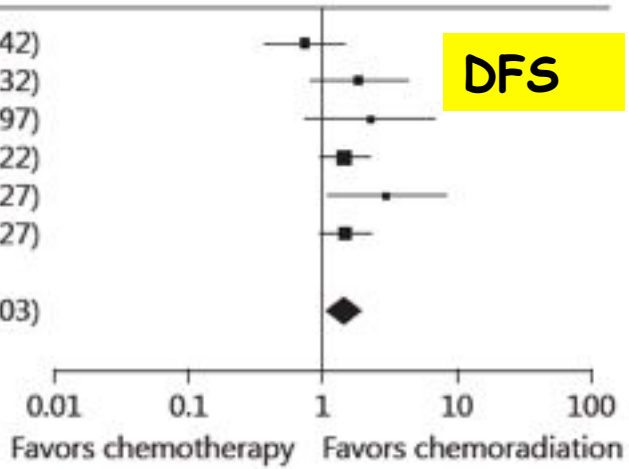
6 trials comparing postoperative CTRT with CT (*n = 1171*).

R0 Resection
Stage IIA-IIIC and/ or pN+

Improvement in DFS among patients treated with CRT vs CT alone in the adjuvant treatment of surgically resected gastric cancer

Study or subgroup	Chemotherapy events	Chemotherapy total	Chemoradiation events	Chemoradiation total	Weight, %	Odds ratio M-H, random (95% CI)
Bamias [17], 2010	37	71	43	72	16.3	0.73 (0.38–1.42)
Kim [18], 2012	24	44	18	46	11.4	1.87 (0.81–4.32)
Kwon [19], 2010	12	30	7	31	7.0	2.29 (0.75–6.97)
Lee [20], 2012	72	228	55	230	29.0	1.47 (0.97–2.22)
Yu [21], 2012	24	34	15	34	8.5	3.04 (1.12–8.27)
Zhu [22], 2012	106	165	102	186	27.8	1.48 (0.96–2.27)
Total (95% CI)		572		599	100.0	1.48 (1.08–2.03)
Total events	275		240			

Heterogeneity: $\tau^2 = 0.05$, $\chi^2 = 7.16$, d.f. = 5 ($p = 0.21$), $I^2 = 30\%$
Test for overall effect: $Z = 2.44$ ($p = 0.01$)



Min C. Oncology. 2014;86:79-85.

CT-RT after R1 Resection

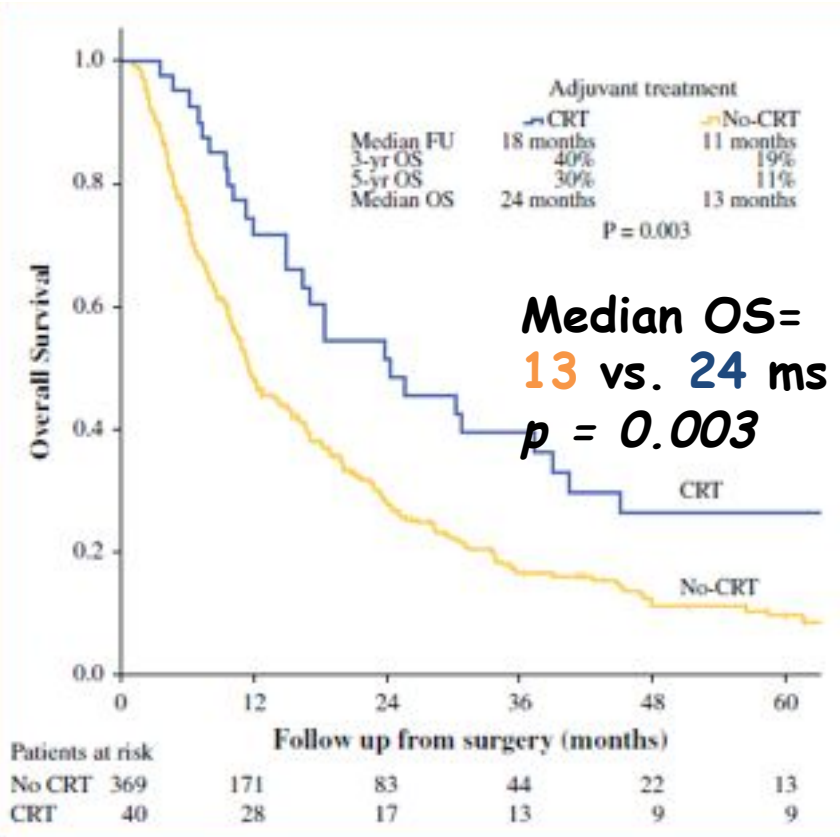
Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Does Adjuvant Chemoradiotherapy Improve the Prognosis of Gastric Cancer After an R1 Resection? Results from a Dutch Cohort Study

Comparison of the survival of 409 patients after R1 resection who did not receive adjuvant CRT (no-CRT group, N = 369) with the survival of resected patients who had adjuvant CRT (CRT group, N = 40)

In the multivariable analysis, adjuvant CRT was an independent prognostic factor for improved OS (HR 0.54; 95 % CI 0.35–0.84).



Median OS= 13 vs. 24 ms
p = 0.003

Stiekema J.Ann Surg Oncol. 2014 Aug 28. [Epub ahead of print]

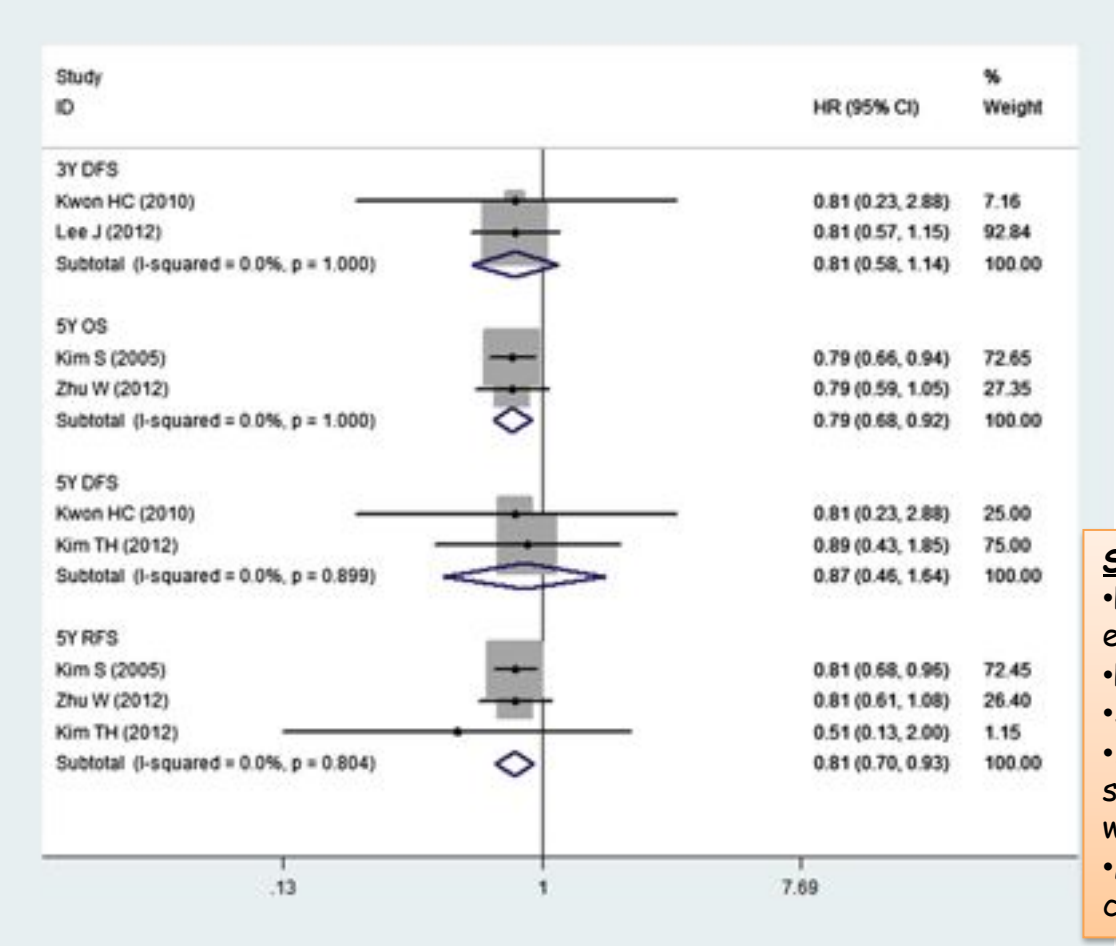
CT-RT after D2 lymphadenectomy

6 studies involving 2135 pts

Review

Is postoperative adjuvant chemoradiotherapy efficacious and safe for gastric cancer patients with D2 lymphadenectomy? A meta-analysis of the literature

EJSO
the Journal of Cancer Surgery



Postoperative adjuvant CRT may be associated with longer 5-y@ OS and 5-y@ RFS in patients with D2 lymphadenectomy, but might not improve 5-y@ DFS compared to non-CRT.

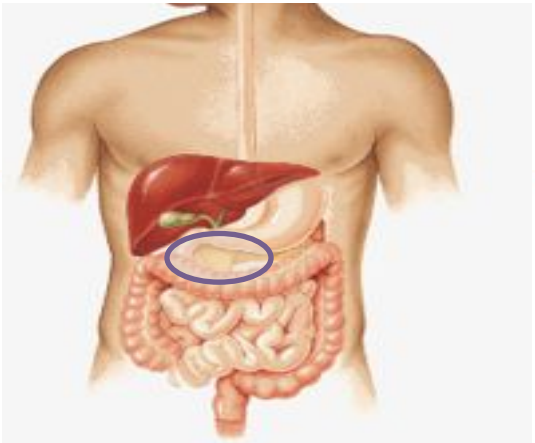
Methodologically high-quality comparative studies are needed for further evaluation.

Several limitations:

- Poor quality of the included trials, not described all end-points for each study
- Postoperative CRT protocols are not all the same
- Small number of studies
- Due to the limited number of the trials, the subgroup analysis based on the different protocols was not performed
- Most of the studies were conducted in Asian countries

Liang JW. Eur J Surg Oncol. 2014. [Epub ahead of print].

Pancreatic cancer



ELSEVIER

Seminars in
RADIATION
ONCOLOGY

Volume 24, Number 2

April 2014

Pancreaticobiliary Malignancies: Past, Present, and Future

Neoadjuvant vs Adjuvant Therapy for Resectable Pancreatic Cancer: The Evolving Role of Radiation

Sarah Hoffe, MD, Nikhil Rao, MD, and Ravi Shridhar, MD, PhD

Review Article

Neoadjuvant Therapy in Pancreatic Cancer: An Emerging Strategy

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2014, Article ID 183852, 9 pages
http://dx.doi.org/10.1155/2014/183852

Alessandro Bittoni, Matteo Santoni, Andrea Lanese, Chiara Pellei, Kalliopi Andrikou, and Cascinu Stefano

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J.M. Herman. Semin Radiat Oncol. 2014;24:61-66

Hoffe S. Semin Radiat Oncol. 2014;24:113-25.

REVIEW

17 studies, 3,088 pts CRT vs non-CRT

Effect of chemoradiotherapy and neoadjuvant chemoradiotherapy in resectable pancreatic cancer: a systematic review and meta-analysis

Several limitations:

- many phase II studies were excluded for lack of control groups
- Poor quality of the included trials
- only 6 randomized controlled trials
- only 3 rare, old and small size studies investigating neoadjuvant CRT vs adjuvant CRT

OS data for the comparison between CRT and non-CRT

A

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.1.1 neo-ad CRT								
Allendorf 2008	47	59	119	149	-2.98	41.42	6.0%	0.93 [0.69, 1.26]
Golcher 2008	10	21	30	58	-1.27	15.42	2.2%	0.92 [0.56, 1.52]
Papalezova 2012	43	76	44	68	-4.82	35.9	5.2%	0.87 [0.63, 1.21]
Satoi 2009	8	18	21	30	-5.11	11.25	1.6%	0.63 [0.35, 1.14]
Vento 2007	12	22	15	25	-1.12	11.7	1.7%	0.91 [0.51, 1.61]
Subtotal (95% CI)		**196**		**330**			**16.7%**	**0.88 [0.73, 1.05]**
Total events	120		229					
Heterogeneity: Chi² = 1.37, df = 4 (P = 0.85); I² = 0%								
Test for overall effect: Z = 1.42 (P = 0.15)								
1.1.2 ad CRT								
EORCT 1999	63	104	72	103	-7.41	51.75	7.5%	0.87 [0.66, 1.14]
ESPAC-1 2004	125	145	112	144	7.43	72.75	10.5%	1.11 [0.88, 1.39]
ESPAC1-plus 2001	27	33	29	36	1.1	13.6	2.0%	1.08 [0.64, 1.84]
GITSG 1985	15	21	19	22	-2.04	10.74	1.5%	0.83 [0.45, 1.50]
GITSG1987	17	30	19	22	-5.35	12.69	1.8%	0.66 [0.38, 1.14]
Hsu 2010	384	583	360	509	-19.35	271.75	39.2%	0.93 [0.83, 1.05]
Morak 2008	38	59	44	61	-3.4	29.99	4.3%	0.89 [0.62, 1.28]
Piperd 2010	21	39	6	13	1.5	9.75	1.4%	1.17 [0.62, 2.18]
Schmidt 2012	53	64	64	68	4.59	32.97	4.8%	1.15 [0.82, 1.62]
Smeenk 2005	21	33	14	21	-0.6	12.83	1.8%	0.95 [0.55, 1.65]
Van Laethem 2010	26	45	25	45	0.88	22.5	3.2%	1.04 [0.69, 1.57]
Yeo 1997	47	120	16	53	9.57	36.67	5.3%	1.30 [0.94, 1.79]
Subtotal (95% CI)		**1276**		**1097**			**83.3%**	**0.98 [0.90, 1.06]**
Total events	837		780					
Heterogeneity: Chi² = 9.45, df = 11 (P = 0.58); I² = 0%								
Test for overall effect: Z = 0.54 (P = 0.59)								
Total (95% CI)		**1472**		**1427**			**100.0%**	**0.96 [0.89, 1.03]**
Total events	957		1009					
Heterogeneity: Chi² = 11.98, df = 16 (P = 0.75); I² = 0%								
Test for overall effect: Z = 1.08 (P = 0.28)								
Test for subgroup differences: Chi² = 1.16, df = 1 (P = 0.28), I² = 13.7%								

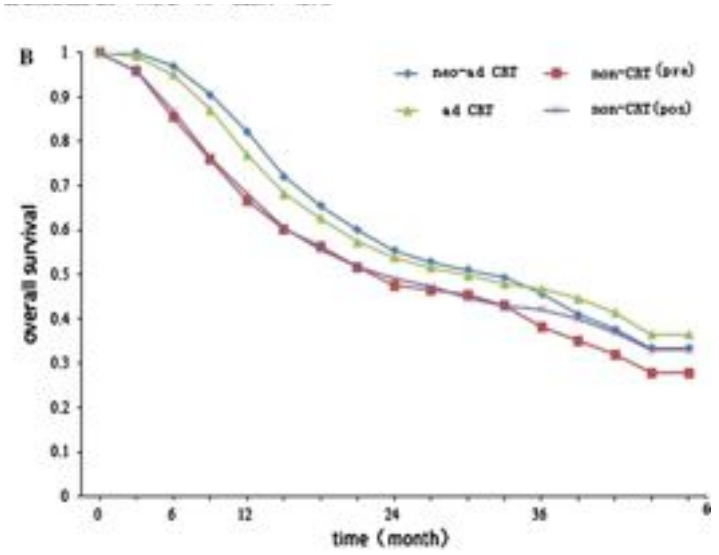
Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI

0.5 0.7 1 1.5 2

Favours experimental Favours control

HR of 0.96 (95 % CI 0.89–1.03; *P = 0.28).*

no clear evidence that adding CT to RT improved OS or PFS after a follow-up >5y@



C. P. Xu. J Cancer Res Clin Oncol (2014) 140:549–559

REVIEW

Effect of chemoradiotherapy and neoadjuvant chemoradiotherapy in resectable pancreatic cancer: a systematic review and meta-analysis

Several limitations:

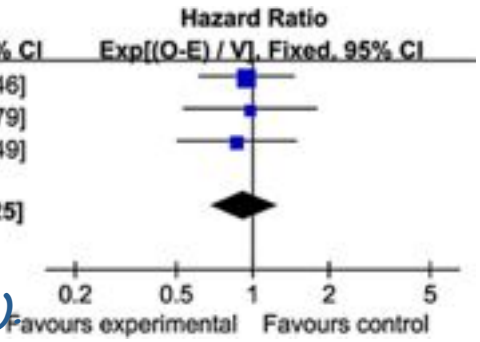
- many phase II studies were excluded for lack of control groups
- Poor quality of the included trials
- only 6 randomized controlled trials
- only 3 rare, old and small size studies investigating neoadjuvant CRT vs adjuvant CRT

OS: 3 studies, 189 pts neoadjuvant CRT vs postop CRT

	neoadjuvant CRT		adjuvant CRT					Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI	Exp[(O-E) / V], Fixed, 95% CI
Chao 2010	44	53	29	33	-1.16	20.34	46.4%	0.94 [0.61, 1.46]	
Pendurthi 1998	19	25	14	18	-0.24	10.47	23.9%	0.98 [0.53, 1.79]	
Spitz 1997	28	41	15	19	-1.88	12.98	29.6%	0.87 [0.50, 1.49]	
Total (95% CI)		**119**		**70**			**100.0%**	**0.93 [0.69, 1.25]**	
Total events	91		58						

Heterogeneity: Chi² = 0.10, df = 2 (P = 0.95); I² = 0%

Test for overall effect: Z = 0.50 (P = 0.62)



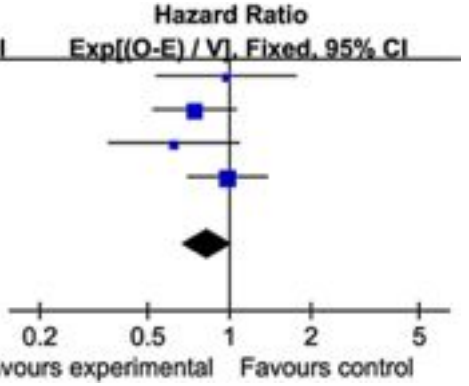
HR 0.93 (95 % CI 0.69–1.25, *P = 0.62*)

DFS: 4 studies, 399 pts neoadjuvant CRT vs postop CRT

	CRT		Non-CRT					Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI	Exp[(O-E) / V], Fixed, 95% CI
GITSG 1985	13	21	14	22	-0.3	10.74	12.5%	0.97 [0.53, 1.77]	
Morak 2008	44	95	38	61	-8.91	30.07	34.9%	0.74 [0.52, 1.06]	
Satoi 2009	12	27	26	41	-5.79	12.28	14.3%	0.62 [0.36, 1.09]	
Schmidt 2012	37	64	40	68	-0.57	32.97	38.3%	0.98 [0.70, 1.38]	
Total (95% CI)		**207**		**192**			**100.0%**	**0.83 [0.68, 1.03]**	
Total events	106		118						

Heterogeneity: Chi² = 2.57, df = 3 (P = 0.46); I² = 0%

Test for overall effect: Z = 1.68 (P = 0.09)



HR 0.83 (95 % CI 0.68–1.03, *P = 0.09*)

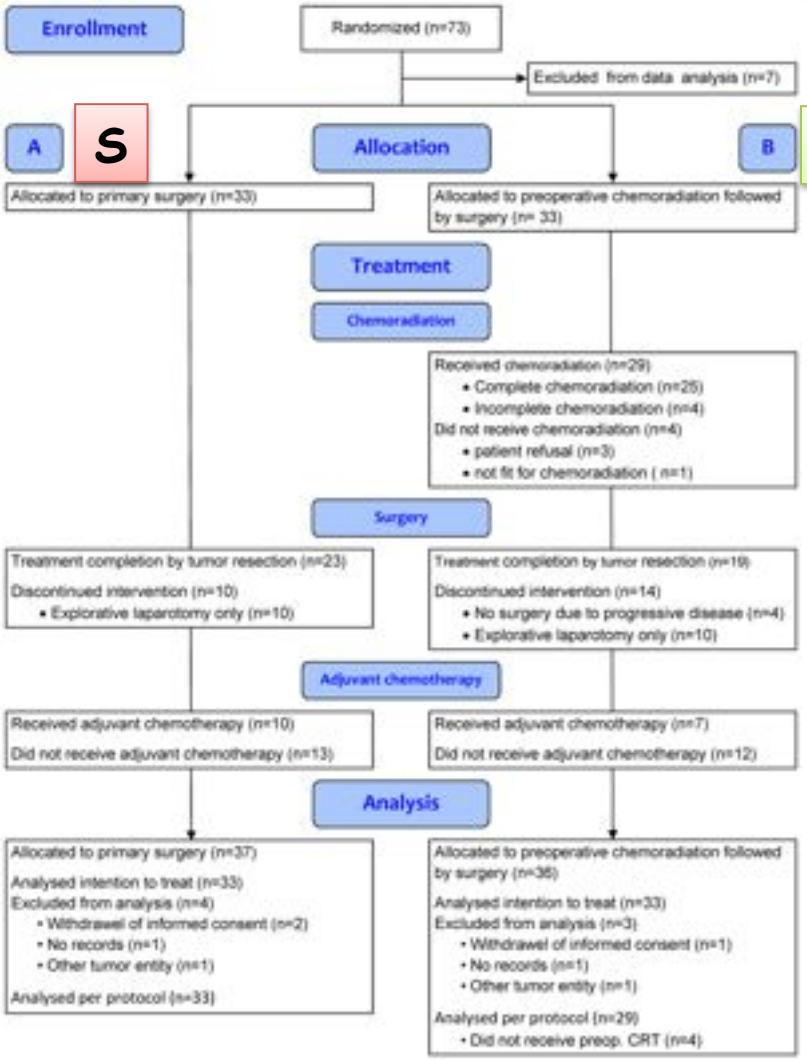
C. P. Xu. J Cancer Res Clin Oncol (2014) 140:549–559

ORIGINAL ARTICLE

Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer

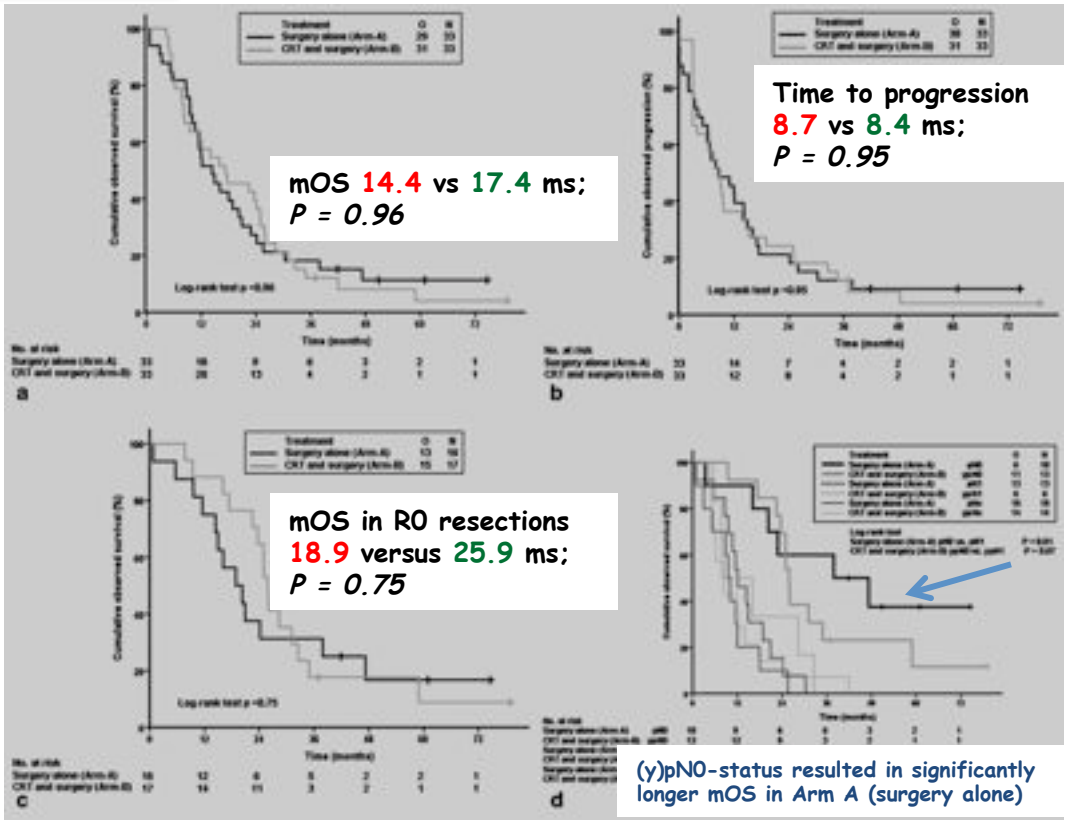
Results of the first prospective randomized phase II trial.

254 pts required to detect a 4.33 month improvement in median overall survival (mOS)



NeoCRT

The trial was stopped after 73 pts due to the slow recruiting;
66 pts were eligible for analysis



(y)pN0-status resulted in significantly longer mOS in Arm A (surgery alone)

H Golcher. Strahlenther Onkol 2014 in press

ORIGINAL ARTICLE

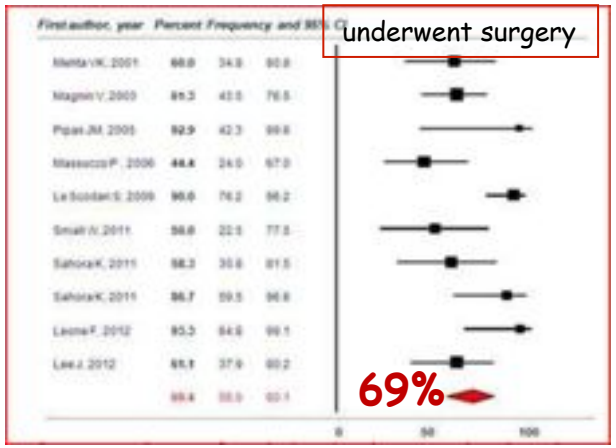
JOP. J Pancreas (Online) 2013 Nov 10; 14(6):618-625.

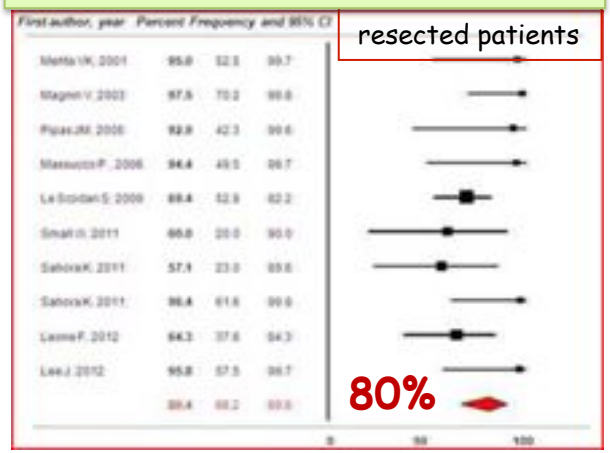
Neoadjuvant Chemo-Radiotherapy for Patients with Borderline Resectable Pancreatic Cancer: A Meta-Analytical Evaluation of Prospective Studies

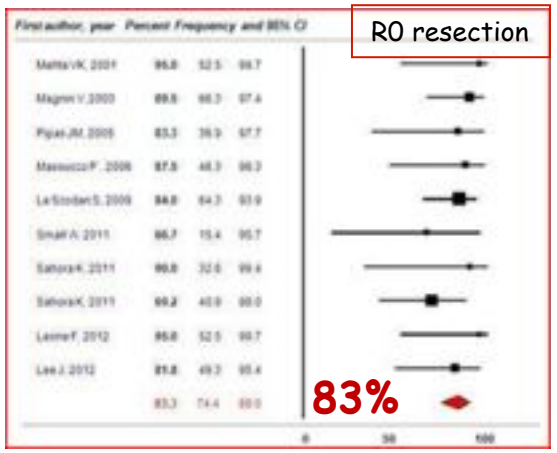
10 studies published between 2001 and 2012, 182 pts

Primary outcome: surgical exploration and resection rates;
Secondary outcomes: tumor response, therapy induced toxicity, and survival

mean of median survival = 22 ms







Tumor response (RECIST criteria) = 6 studies
- complete/partial response = 16% (95% CI: 9-28%)
- stable lesions = 69% (95% CI: 60-76%)
- progressive disease = 19% (95% CI: 13-25%)

Grade 3-4 toxicity was estimated at 32% (95% CI: 21-45%)

Downstaging is uncommon.
A benefit of this regimen could be to spare surgery to patients with progressive disease during the CRT frame-time.

Festa V. JOP. 2013;14:618-25.

Clinical Investigation: Gastrointestinal Cancer

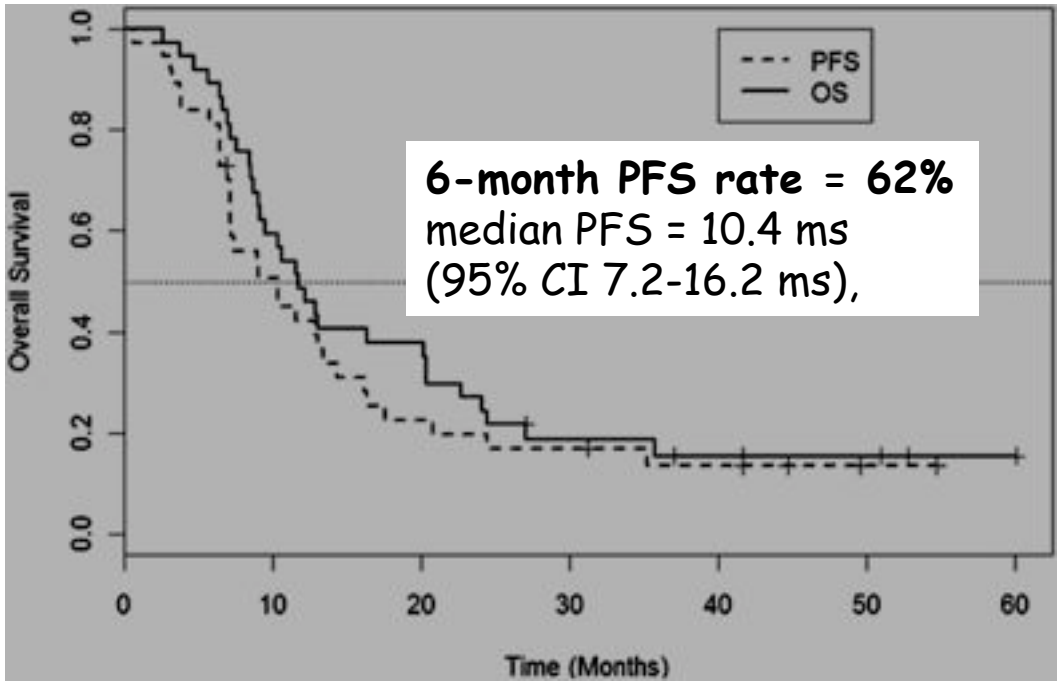
Phase 2 Trial of Induction Gemcitabine, Oxaliplatin, and Cetuximab Followed by Selective Capecitabine-Based Chemoradiation in Patients With Borderline Resectable or Unresectable Locally Advanced Pancreatic Cancer

Treatment Intensification

Targeted Therapies: **Cetuximab**

Primary objective = rate of PFS at 6 months.
Secondary objectives =tolerance and toxicity, radiologic response rate, R0 resection rate, and OS.

37 evaluable pts



6-month PFS rate = 62%
median PFS = 10.4 ms
(95% CI 7.2-16.2 ms),

median OS =11.8 ms
(95% CI 9.2-20.4 ms).

LAPC median OS = 9.3 ms
(95% CI 8.6-13.1 ms);

BRPC the median OS = 24.1 ms
(95% CI 12.2-N)

R0 surgical resection = 29.7%
(BRPC;= 69.2%; LAPC= 8.3%).

Esnaola NF. Int J Radiat Oncol Biol Phys. 2014;88:837-44.

Clinical Investigation

Multi-institutional Pooled Analysis on Adjuvant Chemoradiation in Pancreatic Cancer

Alessio G. Morganti, MD,*,† Massimo Falconi, MD,‡
Ruud G.P.M. van Stiphout, MSc,§ Gian-Carlo Mattiucci, MD,*
Sergio Alfieri, MD,‖ Felipe A. Calvo, MD,¶ Jean-Bernard Dubois, MD,#
Gerd Fastner, MD,** Joseph M. Herman, MD, MSc,††
Bert W. Maidment III, MD,‡‡ Robert C. Miller, MD,§§
William F. Regine, MD,‖‖ Michele Reni, MD,¶¶
Navesh K. Sharma, DO, PhD,‖‖ Edy Ippolito, MD,##
and Vincenzo Valentini, MD*

Impact of adjuvant CRT on OS

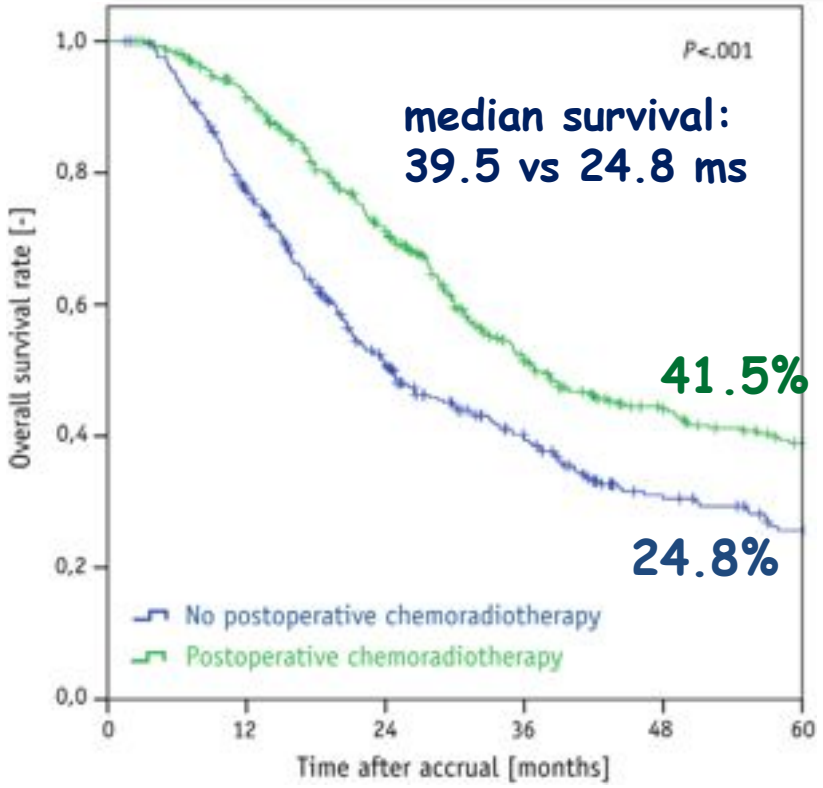
International Journal of Radiation Oncology biology • physics
www.redjournal.org

multicenter retrospective review
of 955 consecutive pts
with macroscopically negative margins
resection (R0-1),
cT1-4; N0-1; M0.
RT (median = 50.4 Gy, continuous course)

Table 1 Adjuvant Series Investigating Radiation Questions as well as Chemotherapy Questions

Study	Arm	N	RT (Y/N)	Dose	MS (m)	5-y OS	P
RT question							
GITSG	Observation	22	N		11	5	S
	CRT	21	Y	40 (a)	20	19	
EORTC	Observation	54	N		12.6	22	NS
	CRT	60	Y	40 (a)	17.1	25	
ESPAC-1 (2 × 2)	Observation	144	N			20	0.009
	CRT	145	Y	40 (a)		10	
	Observation	142	N			9	0.05
	Chemotherapy	147	N			21	
ESPAC-1 (pooled)	Observation	178	N		16.1		0.24
	CRT	175	Y	40 (a)	15.5		
	Observation	235	N		14		0.0005
	Chemotherapy	238	N		19.7		
GERCOR	Gemcitabine	45	N		24		NS
	Gemcitabine + CRT	45	Y	50.4	24		
Chemotherapy question							
RTOG 9704	CRT + 5-FU	230	Y	50.4	17.1	18	0.08
	CRT + Gemcitabine	221	Y	50.4	20.5	22	
CONKO-001	Observation	161	N		20.2	9	0.005
	Gemcitabine	133	N		22.8	21	
ESPAC-3	5-FU	551	N		23		0.39
	Gemcitabine	537	N		23.6		

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; GERCOR, Groupe Coordinateur Multidisciplinaire en Oncologie; GITSG, Gastrointestinal Tumor Study Group; MS, median survival; NS, not statistically significant; OS, overall survival; S, statistically



Hoffe S. Semin Radiat Oncol. 2014;24:113-25

A.G. Morganti. Int J Radiation Oncol Biol Phys, 2014 ; 90(4):911-917

Clinical Investigation

Multi-institutional Pooled Analysis on Adjuvant Chemoradiation in Pancreatic Cancer

Impact of adjuvant CRT on OS

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Negative impact of:
- microscopic residual disease (R1 resection),
- positive lymph nodes,
- higher pT stage,
- Tumor diameter ≥ 20 mm.

Positive impact of adjuvant CRT and of >10 pancreatic resection per year

RT (median = 50.4 Gy, continuous course)

Table 3 Multivariate Cox analysis

	HR	CI_upper	CI_lower	*P* value
Microscopic residual disease (R0)	1.17	1.07	1.28	<.001
pT stage (pT1)	1.23	1.11	1.37	<.001
pN stage (pN0)	1.27	1.15	1.41	<.001
Adjuvant CRT (no)	0.72	0.60	0.87	.001
Tumor diameter (low)	1.14	1.05	1.23	.002
Pancreatic resections per year (<10)	0.87	0.78	0.97	.014
Sex (male)	0.91	0.84	1.00	.053
Grading (G1)	1.09	0.99	1.19	.078
Tumor site (head)	0.93	0.83	1.05	.246
Adjuvant CT (no)	1.05	0.95	1.16	.347
Adjuvant RT (no)	1.08	0.88	1.32	.465
Type of resection (PD)	1.00	0.90	1.11	.988
Age (low)	1.00	0.91	1.10	.997

Abbreviations: CI = confidence interval; CRT = concurrent chemoradiation therapy; CT = chemotherapy; HR = hazard ratio; PD = pancreatico-duodenectomy; RT = radiation therapy.
Hazard ratios with their confidence intervals are reported. Variables are ranked according to their *P* value in the Cox analysis. For each variable, the reference level is indicated in parentheses.

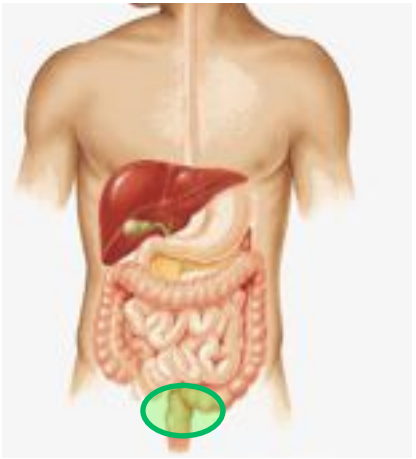
Table 4 Subanalysis of all predictor values of 2-year overall survival (OS), 5 year OS, and median survival time, including log-rank test

		Overall survival						
Variable		2-Year (%)		5-Year (%)		Median (mo)		
Adjuvant CRT	Value	No	Yes	No	Yes	No	Yes	*P* value
Age	<50	60.8	69.3	39.2	26.5	30.1	38.0	.941
	50-70	50.4	72.3	21.8	41.5	24.0	38.7	<.001*
	>70	48.7	79.9	22.6	51.8	23.0	65.0	.001*
Sex	Male	47.0	71.1	16.4	41.2	21.5	36.9	<.001*
	Female	56.3	75.5	32.0	41.2	31.3	42.0	.005*
Tumor site	Head	48.0	74.2	22.4	40.9	23.2	39.0	<.001*
	Body	75.0	53.3	36.1	44.4	44.1	35.0	.352
	Tail	50.0	61.5	50.0	34.2	16.9	49.8	.846
Type of resection	PD	49.5	71.7	23.6	36.0	23.8	36.9	<.001*
	DP	60.7	78.6	33.8	55.2	39.1	66.0	.170
	Total	47.7	56.1	8.9	42.1	21.4	24.4	.139
Grading	1	56.0	66.4	24.2	48.4	28.7	38.7	.108
	2	54.2	71.2	24.9	38.3	26.5	39.5	.006*
	3	41.4	75.8	20.1	43.2	20.8	48.0	<.001*
	4	–	91.2	–	60.4	–	72.0	–
Microscopic residual disease	No	55.7	76.4	29.7	46.1	28.7	49.0	<.001*
	Yes	38.8	62.2	11.0	24.8	19.8	31.	<.001*
Tumor diameter	<20 mm	68.8	75.2	44.4	30.9	50.8	36.9	.372
	≥20 mm	47.2	53.9	20.2	18.3	22.3	25.4	.617
pT stage	1	92.9	100	67.5	70.9	116.8	102.0	.828
	2	44.1	90.9	35.9	70.0	21.5	88.0	.001*
	3	49.7	66.6	20.9	31.3	24.0	32.5	<.001*
	4	50.6	60.0	27.0	27.8	27.8	32.0	.520
pN stage	N0	63.4	83.4	43.2	59.6	36.4	81.0	.020*
	N+	46.2	67.3	17.1	29.6	21.9	32.5	<.001*
Adjuvant chemotherapy	No	46.4	83.0	22.8	63.2	21.4	81.0	<.001*
	Yes	53.5	63.5	24.9	22.7	26.5	30.8	.359
Pancreatic resections per year	<10	41.5	53.4	29.6	27.3	19.8	24.7	.265
	≥10	52.4	77.2	23.6	44.5	25.0	48.0	<.001*
Pancreatic irradiations per year	<10	37.0	55.6	15.4	22.2	16.9	27.3	.001*
	≥10	57.7	83.7	27.3	52.2	31.5	67.0	<.001*

Abbreviations: CRT = concurrent chemoradiation; CT = chemotherapy; DP = distal pancreatectomy; PD = pancreatico-duodenectomy; RT = radiation therapy.
Data are stratified for postoperative chemoradiation (no vs yes).
* *P*<.05 is significant.

A.G. Morganti. Int J Radiation Oncol Biol Phys, 2014 ; 90(4):911-917

Rectal cancer



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DOI: 10.3748/wjg.v20.i32.11249

World J Gastroenterol 2014 August 28; 20(32): 11249-11261
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Multidisciplinary treatment of rectal cancer in 2014: Where are we going?

at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

ELSEVIER

Review

Current treatment of rectal cancer adapted to the individual patient

CrossMark

The well-recognized benefits of RT or CRT, in term of reduced local recurrence, increase rate of sphincter saving procedures, however need to be balanced against the risk of increased faecal incontinence, genitourinary disorders, impaired sexual function and bowel disorders.

Vignali A. World J Gastroenterol. 2014;20:11249-11261.
Cerezo L. Rep Pract Oncol Radiother. 2013;18:353-62.

ORIGINAL ARTICLE – COLORECTAL CANCER

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

Neoadjuvant Radiotherapy for Rectal Cancer: Meta-analysis of Randomized Controlled Trials

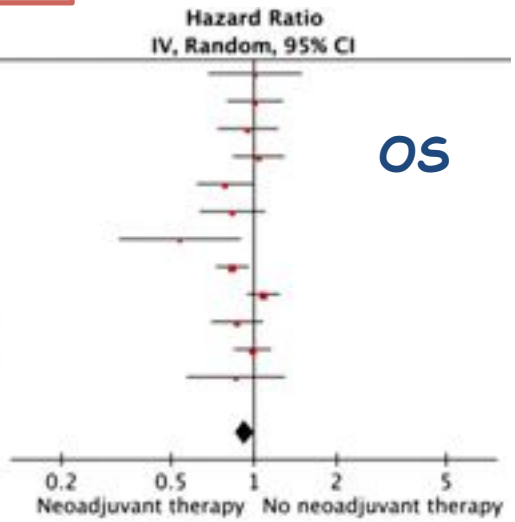
neoadjuvant therapy vs surgery alone

17 and 5 relevant trials , 8,568 and 2,393 pts

a

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Dahl	0.01	0.2	3.6%	1.01 [0.68, 1.49]
Goldberg	0.01	0.12	8.1%	1.01 [0.80, 1.28]
GTCCG/EORTC	-0.05	0.13	7.2%	0.95 [0.74, 1.23]
MRC 1a	0.04	0.11	9.1%	1.04 [0.84, 1.29]
MRC 2	-0.24	0.12	8.1%	0.79 [0.62, 1.00]
NWRCT	-0.18	0.14	6.5%	0.84 [0.63, 1.10]
Peteren	-0.62	0.26	2.3%	0.54 [0.32, 0.90]
SRCT	-0.18	0.07	14.8%	0.84 [0.73, 0.96]
Stockholm I	0.08	0.07	14.8%	1.08 [0.94, 1.24]
Stockholm II	-0.14	0.11	9.1%	0.87 [0.70, 1.08]
TME Trial	-0.01	0.08	13.1%	0.99 [0.85, 1.16]
Toronto	-0.15	0.21	3.3%	0.86 [0.57, 1.30]
Total (95% CI)			**100.0%**	**0.93 [0.85, 1.00]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 16.90$, df = 11 (P = 0.11); $I^2 = 35\%$
Test for overall effect: Z = 1.89 (P = 0.06)



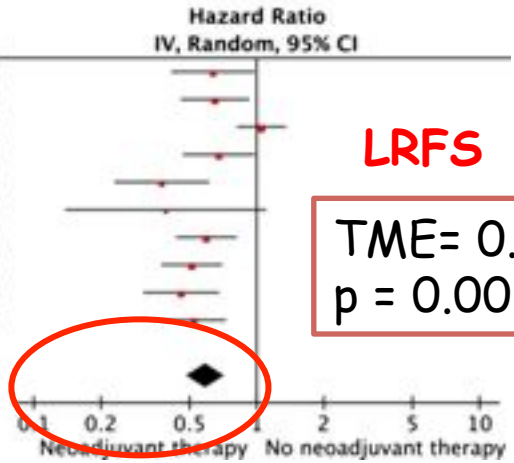
OS

The pooled analysis showed a strong advantage **also of neoadjuvant CRT regarding LRFS** (HR 0.53; 95% CI 0.39–0.72; P<0.001; I2 = 0%).

b

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Goldberg	-0.45	0.22	9.4%	0.64 [0.41, 0.98]
GTCCG/EORTC	-0.43	0.18	10.9%	0.65 [0.46, 0.93]
MRC 1a	0.05	0.13	12.9%	1.05 [0.81, 1.36]
MRC 2	-0.39	0.19	10.5%	0.68 [0.47, 0.98]
NWRCT	-0.98	0.25	8.4%	0.38 [0.23, 0.61]
Petersen curative	-0.94	0.53	3.1%	0.39 [0.14, 1.10]
SRCT Curative	-0.52	0.16	11.7%	0.59 [0.43, 0.81]
Stockholm I	-0.67	0.16	11.7%	0.51 [0.37, 0.70]
Stockholm II	-0.78	0.2	10.1%	0.46 [0.31, 0.68]
TME Trial curative	-0.65	0.17	11.3%	0.52 [0.37, 0.73]
Total (95% CI)			**100.0%**	**0.59 [0.48, 0.72]**

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 26.36$, df = 9 (P = 0.002); $I^2 = 66\%$
Test for overall effect: Z = 5.06 (P < 0.00001)



LRFS

TME= 0.55 (0.38, 0.80), p = 0.002; n = 2

Rahbari NN. Ann Surg Oncol. 2013;20:4169-82.

ORIGINAL ARTICLE – COLORECTAL CANCER

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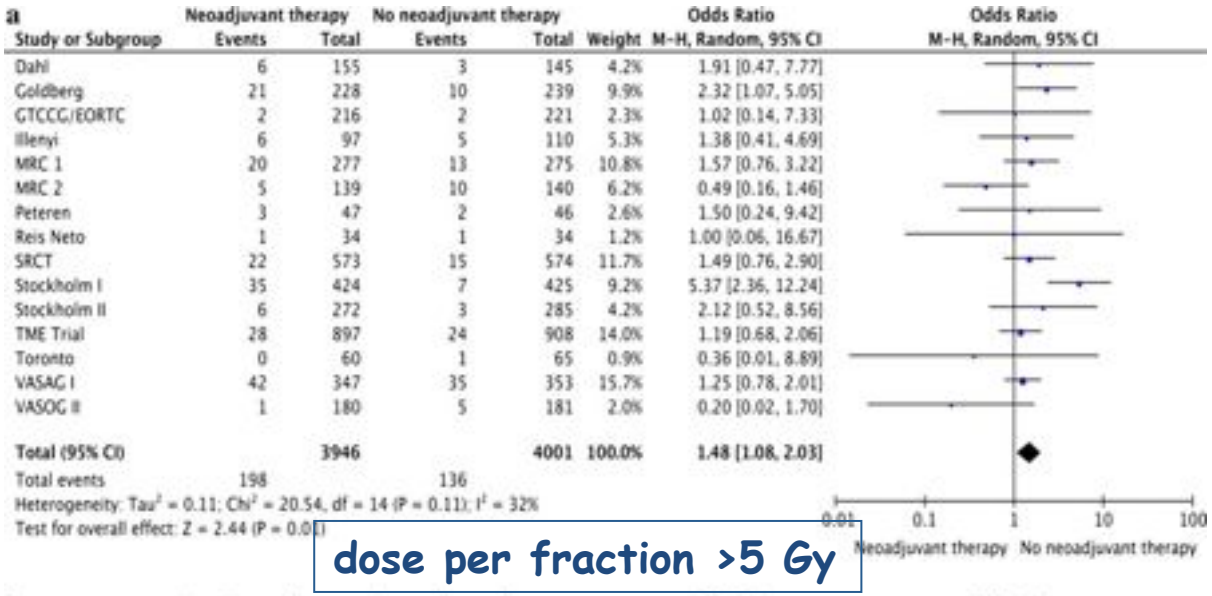


a

Study or Subgroup	Neoadjuvant therapy Events	Total	No neoadjuvant therapy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Dahl	6	155	3	145	4.2%	1.91 [0.47, 7.77]
Goldberg	21	228	10	239	9.9%	2.32 [1.07, 5.05]
GTCCG/EORTC	2	216	2	221	2.3%	1.02 [0.14, 7.33]
Illenyi	6	97	5	110	5.3%	1.38 [0.41, 4.69]
MRC 1	20	277	13	275	10.8%	1.57 [0.76, 3.22]
MRC 2	5	139	10	140	6.2%	0.49 [0.16, 1.46]
Peteren	3	47	2	46	2.6%	1.50 [0.24, 9.42]
Reis Neto	1	34	1	34	1.2%	1.00 [0.06, 16.67]
SRCT	22	573	15	574	11.7%	1.49 [0.76, 2.90]
Stockholm I	35	424	7	425	9.2%	5.37 [2.36, 12.24]
Stockholm II	6	272	3	285	4.2%	2.12 [0.52, 8.56]
TME Trial	28	897	24	908	14.0%	1.19 [0.68, 2.06]
Toronto	0	60	1	65	0.9%	0.36 [0.01, 8.89]
VASAG I	42	347	35	353	15.7%	1.25 [0.78, 2.01]
VASOG II	1	180	5	181	2.0%	0.20 [0.02, 1.70]
Total (95% CI)		**3946**		**4001**	**100.0%**	**1.48 [1.08, 2.03]**
Total events	198		136			

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 20.54$, df = 14 (P = 0.11); $I^2 = 32\%$
Test for overall effect: Z = 2.44 (P = 0.0[illegible])

Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Neoadjuvant therapy No neoadjuvant therapy

dose per fraction >5 Gy

b

Study or Subgroup	Neoadjuvant therapy Events	Total	No neoadjuvant therapy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
SRCT	241	573	190	574	19.1%	1.47 [1.15, 1.87]
Stockholm I	112	424	81	425	15.7%	1.52 [1.10, 2.11]
Stockholm II	111	272	79	285	14.6%	1.80 [1.26, 2.56]
TME Trial	336	897	297	908	21.0%	1.23 [1.02, 1.50]
Toronto	0	60	1	65	0.4%	0.36 [0.01, 8.89]
VASAG I	184	347	187	353	16.8%	1.00 [0.74, 1.35]
VASOG II	63	180	77	181	12.3%	0.73 [0.48, 1.11]
Total (95% CI)		**2753**		**2791**	**100.0%**	**1.25 [1.02, 1.54]**
Total events	1047		912			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 16.04$, df = 6 (P = 0.01); $I^2 = 63\%$
Test for overall effect: Z = 2.16 (P = 0.03)

Odds Ratio M-H, Random, 95% CI
0.05 0.2 1 5 20
Neoadjuvant therapy No neoadjuvant therapy

Despite the increase in perioperative morbidity and mortality, **there was no significant difference in the incidence of anastomotic leakage**

Rahbari NN. Ann Surg Oncol. 2013;20:4169-82.

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase III randomised trial

Cap45 vs Capox50

SELECTIVE USE OF PREOPERATIVE RT

Results in the elderly with locally advanced rectal cancer from the ACCOR12/PRODIGE 2 phase III trial: Tolerance and efficacy

Benefit of neoadjuvant CRT between the elderly (>70 years; n = 142) and younger patients (<70 years; n = 442)

	Age <70 years (n = 442)	Age ≥70 years (n = 142)	p
Radiotherapy			
Median duration (day)	37	37	0.75
Range	6–67	22–55	
Planned dose (%)			
No	22 (5.0)	8 (5.6)	0.76
Yes	419 (95.0)	134 (94.4)	
Missing	1	0	
Treatment stop			
No	434 (98.6)	136 (95.8)	0.03
Yes	6 (1.4)	6 (4.2)	
Missing	2	0	
Chemotherapy			
Dose modification (%)			
No	192 (44.4)	61 (43.6)	0.85
Yes	240 (55.6)	79 (56.4)	
Missing	10	2	
Delayed (%)			
No	314 (71.9)	112 (79.4)	0.12
Yes	117 (27.1)	29 (20.6)	
Missing	11	1	
Grade 3/4 toxicities (%)			
Overall	70 (15.8)	36 (25.6)	0.01
Hematologic	18 (4.1)	7 (4.9)	0.66
Non-hematologic	60 (13.6)	30 (21.1)	0.03
Diarrhea	31 (7.2)	14 (10.1)	0.26

The relative number of interventions per surgery type ($p = 0.18$), R0 resection rate (88.6% vs. 90.6%; $p = 0.54$) and pCR (14.7% vs. 16.9%; $p = 0.55$) were nearly identical between the two categories.

Francois E. Radiother Oncol. 2014:110:144-9.

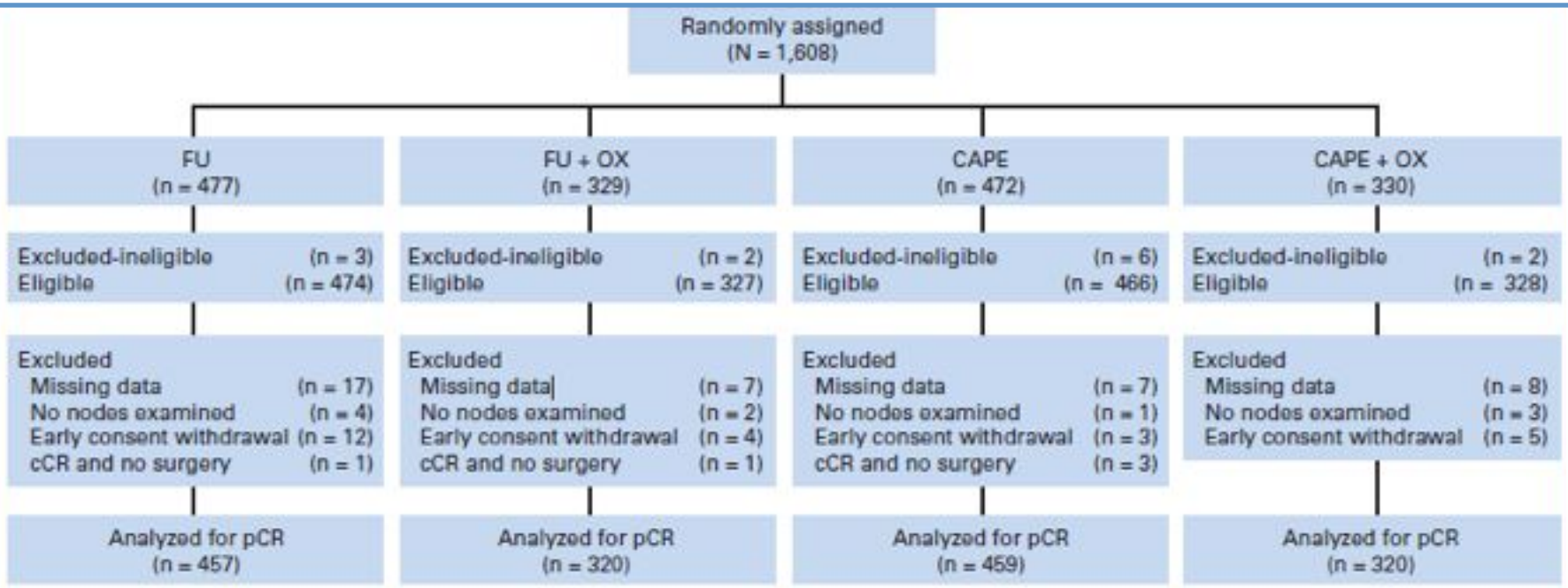
Treatment Modulation
CapOX

VOLUME 32 · NUMBER 18 · JUNE 20 2014
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Capecitabine and Oxaliplatin in the Preoperative Multimodality Treatment of Rectal Cancer: Surgical End Points From National Surgical Adjuvant Breast and Bowel Project Trial R-04

From September 2004 to August 2010,

Primary endpoint: locoregional failure (this will be presented in a future article).
Secondary end points: **pCR, sphincter-sparing surgery, surgical downstaging,** and toxicity (focus of this article)



O'Connell MJ. J Clin Oncol. 2014;32:1927-34.

Treatment Modulation
CapOX

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From September 2004 to August 2010

**pCR,
sphincter-sparing surgery,
surgical downstaging**

Outcomes for FU Compared With Capecitabine

Table 2. Comparison of FU With CAPE: NSABP R-04

End Point	FU (± OX)			CAPE (± OX)			*P*
	No. of Patients	%	95% CI (%)	No. of Patients	%	95% CI (%)	
pCR	138 of 777	17.8	15.1 to 20.6	161 of 779	20.7	17.9 to 23.7	.14
SSS	463 of 780	59.4	55.8 to 62.8	462 of 779	59.3	55.8 to 62.8	.98
SD	43 of 202	21.3	15.9 to 27.6	44 of 209	21.1	15.7 to 27.2	.95
Grade 3-5 diarrhea*	75 of 639	11.7	9.3 to 14.5	75 of 641	11.7†	9.3 to 14.4	1.0

Outcomes for Oxaliplatin Versus No Oxaliplatin

Table 3. OX Versus No OX: NSABP R-04*

End Point	No OX (FU or CAPE)			OX (FU or CAPE)			*P*
	No. of Patients	%	95% CI (%)	No. of Patients	%	95% CI (%)	
pCR	113 of 636	17.8	14.9 to 21.0	125 of 640	19.5	16.5 to 22.8	.42
SSS	388 of 636	61.0	57.1 to 64.8	372 of 644	57.8	53.8 to 61.6	.24
SD	39 of 166	23.5	17.2 to 30.7	30 of 168	17.9	12.4 to 24.5	.20
Grade 3-5 diarrhea	44 of 636	6.9	5.1 to 9.2	106 of 644	16.5†	13.7 to 19.6	<.001

O'Connell MJ. J Clin Oncol. 2014;32:1927-34.

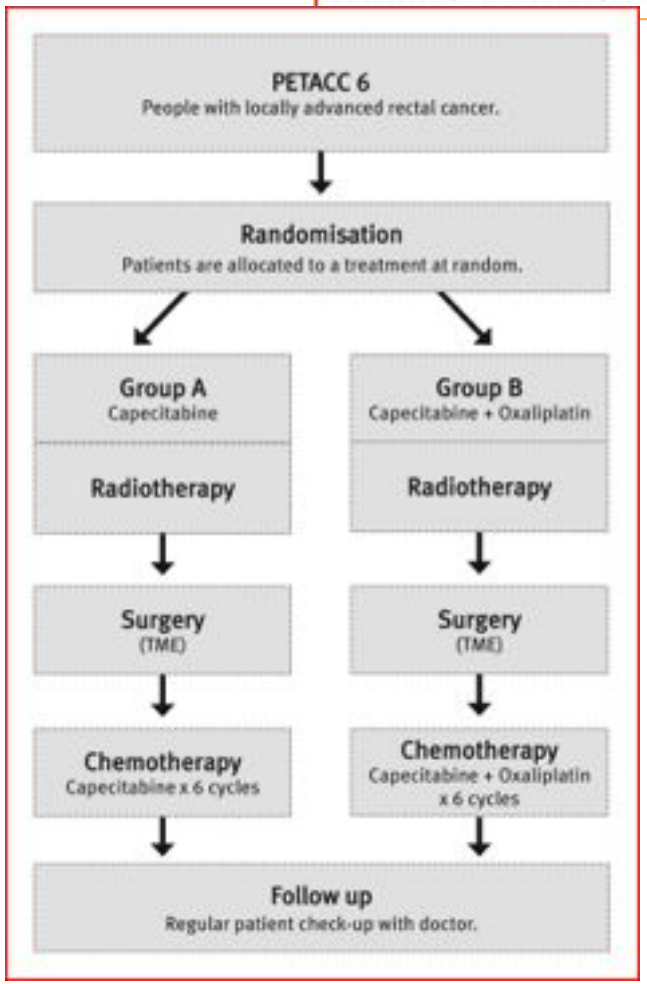
ESTRO 33
4 - 8 April 2014
Vienna, Austria

Treatment Modulation CapOX

ASCO 50th ANNUAL MEETING
SCIENCE & SOCIETY
MAY 30-JUNE 3, 2014
McCORMICK PLACE | CHICAGO, ILLINOIS

FIRST RESULTS OF THE PETACC-6 RANDOMIZED PHASE III TRIAL IN LOCALLY ADVANCED RECTAL CANCER

K. Haustermans[1], H.J. Schmoll[2], T. Price[3], B. Nordlinger[4], R.D. Hofheinz[5], J.F. Daisne[6], J. Janssens[7], P. Schmidt[8], H. Reinel[9], E. Van Cutsem[10].



primary endpoint: disease-free survival

secondary endpoints:
- pathological down-staging (ypT0-2N0) rate, complete remission (ypT0N0) rate,
- sphincter preservation
- R0 resection rate

An interim analysis of the **EORTC-PETACC-6** trial indicated that adding oxaliplatin to capecitabine plus radiotherapy did **not improve DFS** compared with capecitabine plus radiotherapy alone (44.3 Gy in arm 1 and 44.4 Gy in arm 2).

14 studies (487 patients treated with ≥60 Gy)

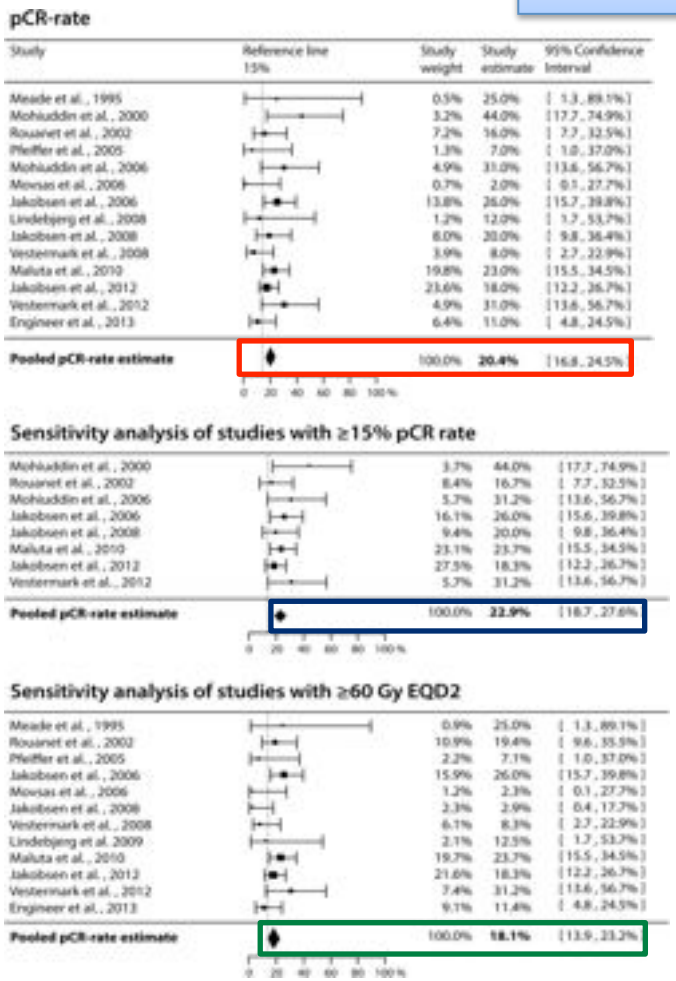
Treatment Modulation
RT BOOST

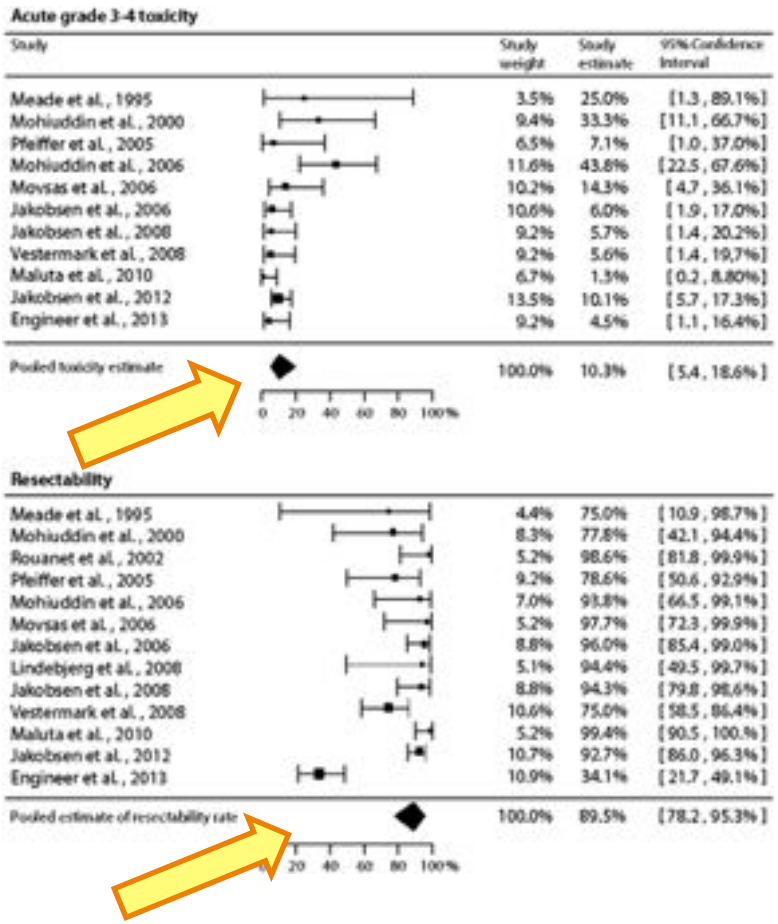
pCR

Original article

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

Total RT dose between 60 and 75 Gy (EQD2 58.4–66.3 Gy),
As an accumulation of standard EBRT (45–54 Gy) and boost dose (6–30 Gy).





Burbach J P M. Radiother Oncol. 2014. S0167-8140(14)00372-7

Time modulation after Radiotherapy

frontiers in ONCOLOGY

REVIEW ARTICLE
published: 07 April 2014
doi: 10.3389/fonc.2014.00050

Optimal time intervals between pre-operative radiotherapy or chemoradiotherapy and surgery in rectal cancer?

pCR

Is a longer interval between the end of neoadjuvant CRT and S associated with a better rate of pCR in rectal cancer?

Increasing the Interval Between Neoadjuvant Chemoradiotherapy and Surgery in Rectal Cancer

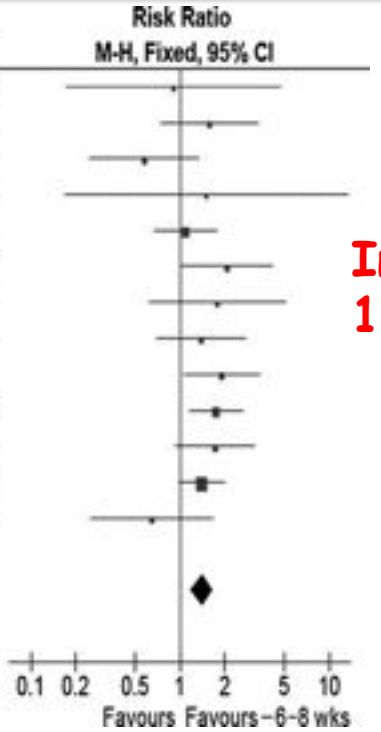
A Meta-Analysis of Published Studies

13 trials, 3584 pts, and overall interval longer than 6 to 8 weeks

Study or Subgroup	> 6-8 weeks Events	Total	< 6-8 weeks Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Stein 2003	2	14	3	19	1.3%	0.90 [0.17, 4.71]	2003
Moore 2004	14	73	10	82	4.9%	1.57 [0.74, 3.32]	2004
Habr-Gama 2008	8	129	13	121	6.9%	0.58 [0.25, 1.34]	2008
Tran 2006	3	32	1	16	0.7%	1.50 [0.17, 13.30]	2008
Lim 2008	27	180	30	217	14.0%	1.08 [0.67, 1.76]	2008
Tulchinsky 2008	29	84	8	48	5.2%	2.07 [1.03, 4.16]	2008
Evans 2011	8	45	5	50	2.4%	1.78 [0.63, 5.04]	2011
Garcia-Aguilar 2011	17	67	11	60	6.0%	1.38 [0.71, 2.71]	2011
de Campos-Lobato 2011	28	94	13	83	7.1%	1.90 [1.06, 3.42]	2011
Wolthuis 2012	43	155	32	201	14.4%	1.74 [1.16, 2.62]	2012
Una Cidon 2012	21	58	12	57	6.2%	1.72 [0.94, 3.16]	2012
Sloothak 2013	183	1281	32	312	26.5%	1.39 [0.98, 1.99]	2013
Fang 2013	9	74	6	32	4.3%	0.65 [0.25, 1.67]	2013
Total (95% CI)		**2286**		**1298**	**100.0%**	**1.42 [1.19, 1.68]**	
Total events	392		176				

Heterogeneity: $\chi^2 = 12.18, df = 12 (P = 0.43); I^2 = 2\%$

Test for overall effect: $Z = 4.00 (P < 0.0001)$



Increased pCR from 13.7% to 19.5% (by 6%)

F Petrelli. Ann Surg 2013;00:1–8

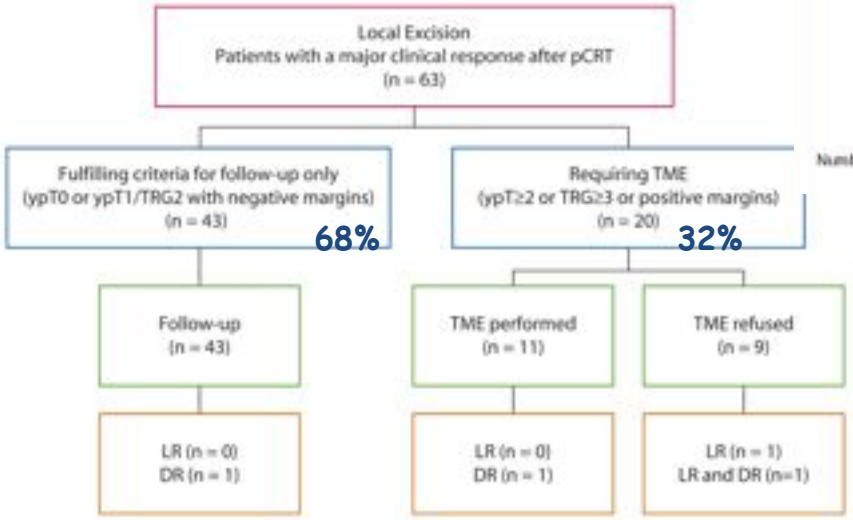
Surgery modulation after Radiotherapy

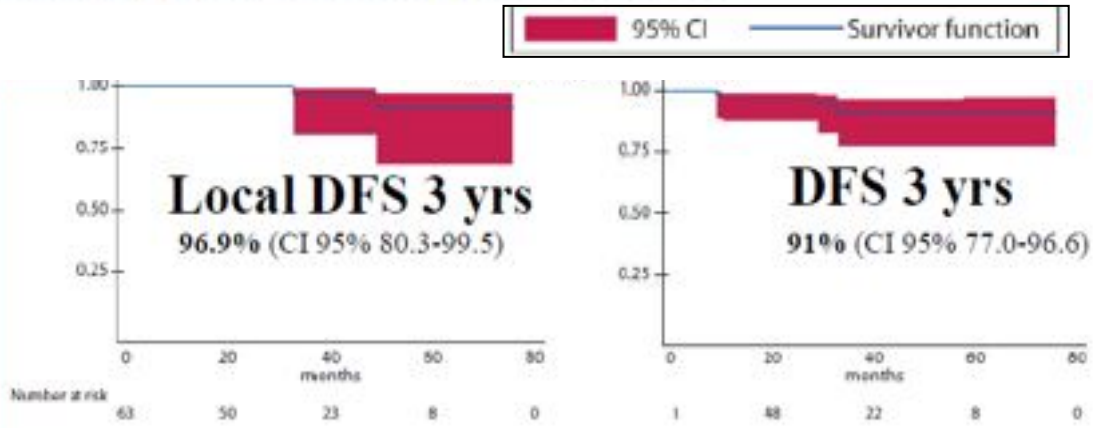
DISEASES OF THE COLON & RECTUM

Organ preservation
TEM and
outcomes

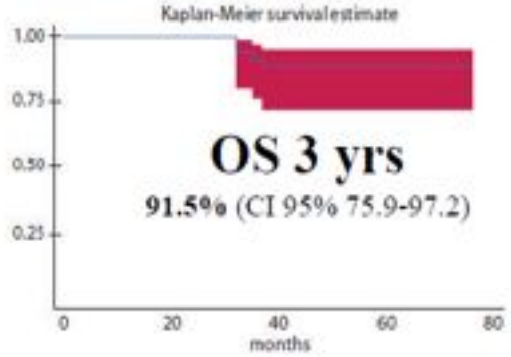
Local Excision After Preoperative Chemoradiotherapy for Rectal Cancer: Results of a Multicenter Phase II Clinical Trial

Prospective multicenter study
63 pts, T3 or low lying T2





Limitations:
Short follow-up and
small sample size



Low rate of local recurrence in the whole group

Pucciarelli S. Dis Colon Rectum. 2013;56:1349-56.

Surgery modulation after Radiotherapy

RECTAL CANCER
WHEN NOT TO OPERATE
An International Consensus Meeting
Champalimaud Foundation • Lisbon, Portugal
14th - 15th February 2014

Organ preservation

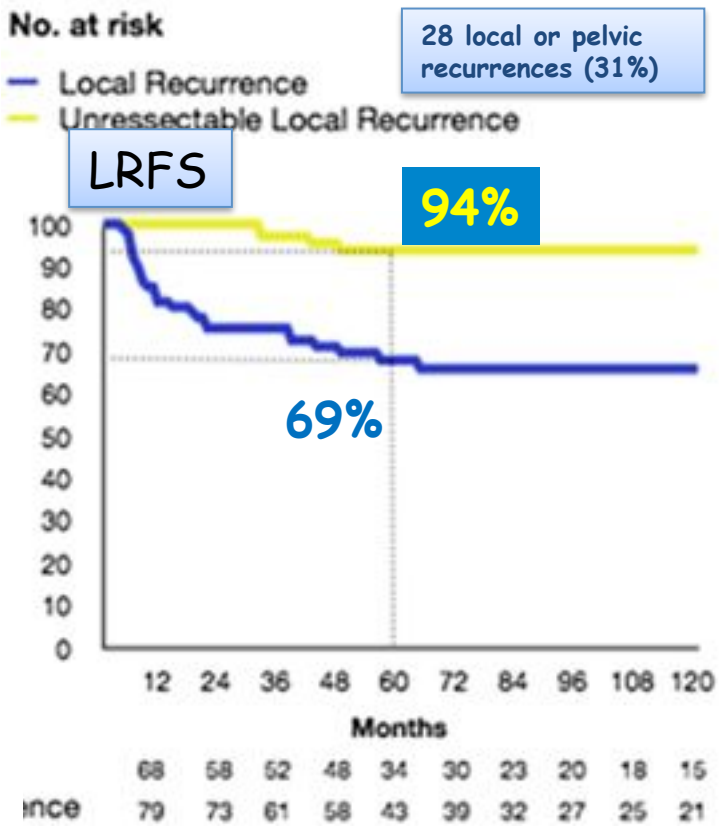
Wait and See

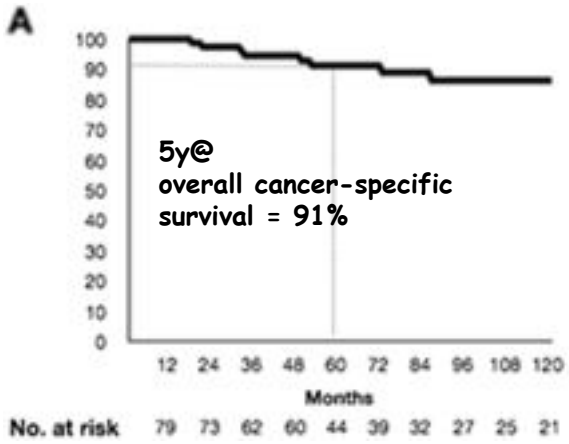
International Journal of Radiation Oncology biology • physics
www.redjournal.org

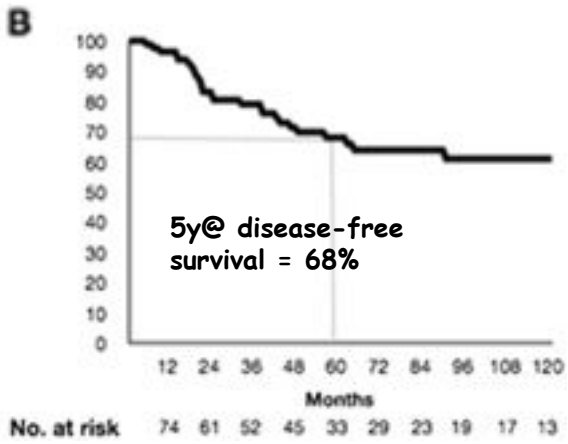
Clinical Investigation: Gastrointestinal Cancer

Local Recurrence After Complete Clinical Response and Watch and Wait in Rectal Cancer After Neoadjuvant Chemoradiation: Impact of Salvage Therapy on Local Disease Control

Between 1991 and 2011, 183 pts with distal rectal cancer underwent neoadjuvant CRT. After assessment of response at least 8 weeks after completion of CRT, **90 pts were considered to have initial cCR (49%)** and were referred to **no immediate surgery (Watch and Wait)**.







Habr-Gama A. Dis Colon Rectum. 2013;56:1109-17.

Post-operative 5Fu based Chemotherapy

THE LANCET Oncology

Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study

Jean-François Bosset, Gilles Calais, Laurent Mineur, Philippe Maingon, Suzana Stojanovic-Rundic, René-Jean Bensadoun, Etienne Bardet, Alexander Beny, Jean-Claude Ollier, Michel Bolla, Dominique Marchal, Jean-Luc Van Laethem, Vincent Klein, Jordi Giralt, Pierre Clavère, Christoph Glanzmann, Patrice Cellier, Laurence Collette, for the EORTC Radiation Oncology Group

1011 patients
median follow-up of **10.4 y@** to assess a possible longterm benefi t of adjuvant CT on **OS and DFS**.

p= 0.0017

	No adjuvant chemotherapy		Adjuvant chemotherapy	
	Radiotherapy (N=252)	Chemoradiotherapy (N=253)	Radiotherapy (N=253)	Chemoradiotherapy (N=253)
Local relapse				
At 5 years	21·9% (16·7–27·1)	10·9% (7·0–14·8)	13·7% (9·4–17·9)	10·7% (6·9–14·5)
At 10 years	22·4% (17·3–27·6)	11·8% (7·8–15·8)	14·5% (10·1–18·9)	11·7% (7·7–15·6)
Distant metastases				
At 5 years	36·9% (30·9–42·9)	32·1% (26·3–37·9)	33·5% (27·6–39·3)	29·8% (24·1–35·4)
At 10 years	39·6% (33·5–45·8)	33·4% (27·5–39·3)	35·9% (29·9–41·9)	34·1% (28·2–40·1)

Data are % (95% CI).

Table 2: Cumulative incidence of local relapse and distant metastases

10 y@ OS

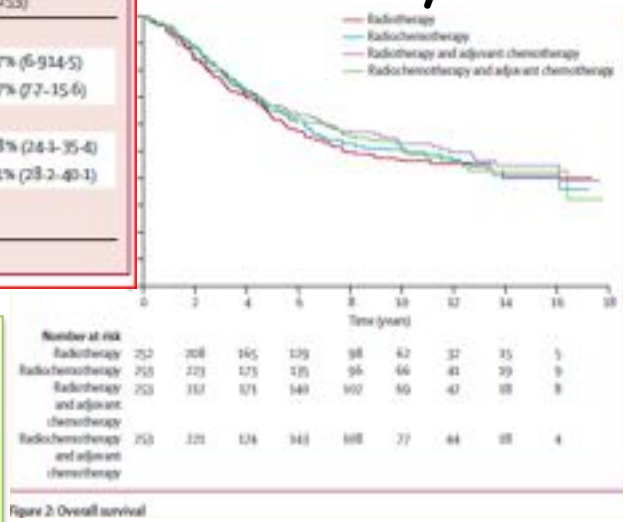


Figure 2: Overall survival

10 y@ DFS

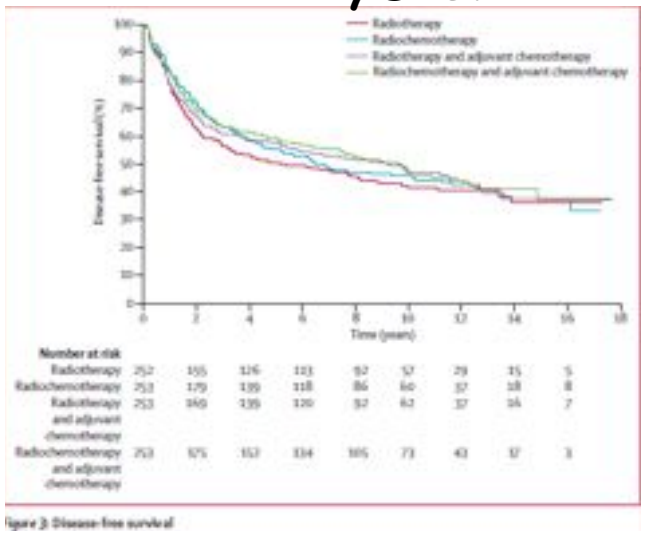


Figure 3: Disease-free survival

The EORTC 22921 trial showed a significant benefit on local control by adding CT to preoperative RT.

no difference in 10-year OS & DFS
between preoperative RT vs preoperative RCT

no difference in 10-year OS & DFS with or without adjuvant CT

Bosset JF.Lancet Oncol. 2014 Feb;15(2):184-90.

Post-operative 5Fu based Chemotherapy

THE LANCET Oncology

Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study

Jean-François Bosset, Gilles Calais, Laurent Mineur, Philippe Maingon, Suzana Stojanovic-Rundic, René-Jean Bensadoun, Etienne Bardet, Alexander Beny, Jean-Claude Ollier, Michel Bolla, Dominique Marchal, Jean-Luc Van Laethem, Vincent Klein, Jordi Giralt, Pierre Clavère, Christoph Glanzmann, Patrice Cellier, Laurence Collette, for the EORTC Radiation Oncology Group

1011 patients median follow-up of **10.4 y@** to assess a possible longterm benefi t of adjuvant CT on **OS and DFS**.

Are there subgroups of patients that might benefit from adjuvant CT?

Comments concerning some limitations of the study:

- the subgroup analysis comparing benefit of chemotherapy in relation to the location of the tumour within the rectum was not repeated
- less than 50% of the patients received the chemotherapy as planned per protocol, thus compromising the survival of the 40% of patients with pathological stage III disease→ subgroup analyses of overall survival and disease-free survival by chemotherapy dose intensity received
- staging was done clinically and by CT scan with or without endorectal ultrasound → the possibility of overstaging to be high, which might contribute to the absence of perceived benefit of adjuvant chemotherapy.

Bosset JF.Lancet Oncol. 2014 Feb;15(2):184-90.

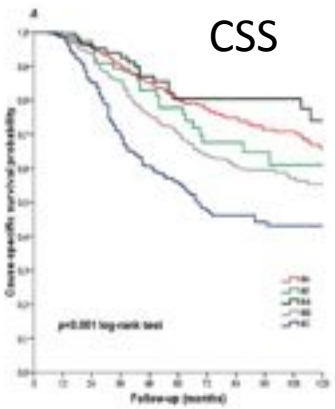
Post-operative RT-Chemotherapy

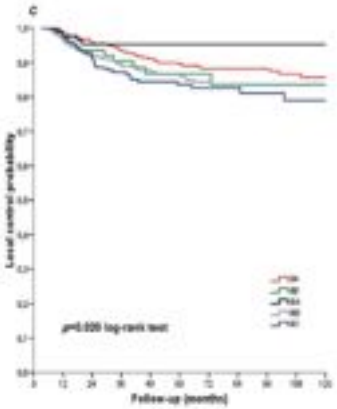
Postoperative 5-FU based Radiochemotherapy in Rectal Cancer: Retrospective Long Term Results and Prognostic Factors of a Pooled Analysis on 1,338 Patients

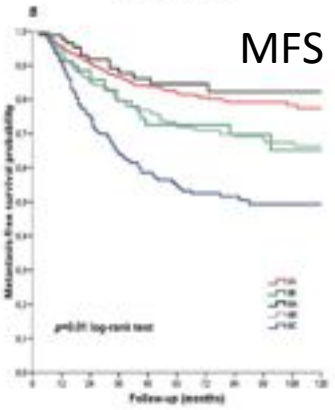
DOMENICO GENOVESI[1*], ROBERT J. MYERSON[2], GIAMPIERO AUSILI CÈFARO[1], ANNAMARIA VINCIGUERRA[1], ANTONIETTA AUGURIO[1], MARIANNA TRIGNANI[1], MONICA DI TOMMASO[1], MARIANNA NUZZO[1], MARCO LUPATTELLI[3], CYNTHIA ARISTEI[3], RITA BELLAVITA[3], LUCIANO SCANDOLARO[4], DORIAN COSENTINO[4], GIUSEPPE PANI[5], LUIGI ZICCARELLI[6], MARIA A. GAMBACORTA[7], MARIA C. BARBA[7], ERNESTO MARANZANO[8], FABIO TRIPPA[8], PIERA SCIACERO[9], RITA NIESPOLO[10], CRISTINA LEONARDI[11], TIZIANA IANNONE[12], MARIA ELENA ROSETTO[13], VINCENZO FUSCO[14], PIERO SANPAOLO[14], ANTONELLA MELANO[15], FRANCESCA VALVO[16], CARLO CAPIRCI[17], ANTONINO DE PAOLI[18], MARTA DI NICOLA[19], GIOVANNA MANTELLO[20] and VINCENZO VALENTINI[7], ON BEHALF OF THE G.I. A.I.R.O. WORKING GROUP

5y@
LC = 87%,
DFS = 61.6 %
MFS = 72%
CSS = 70.4%
OS = 84.1%

10y@
LC = 84.1%,
DFS = 52.1 %
MFS = 67.2%
CSS = 57.5%
OS = 53.4%







Impact of pStage

Table IV. *Multivariate analysis of factors having an influence on cause specific survival and metastases free survival as identified by Cox's proportional hazard model. The items in brackets are the referent (hazard risk equal to 1).*

Cause specific survival	HR[a]; 95% CI	*p*-Value
Age at surgery (years) (≤ 65)		
>65	HR:1.37; CI:1.02-1.85	0.037
pT (T1-T2)		
T3	HR:1.77; CI:0.89-3.53	0.105
T4	HR:3.42; CI:1.52-7.68	0.003
pN (N0)		
N1	HR:1.96; CI:1.35-2.84	<0.001
N2	HR:2.61; CI:1.77-3.85	<0.001
Tumor location (low rectum)		
Mid rectum	HR:0.77; CI:0.54-1.11	0.170
Upper rectum/sigmoid junction	HR:0.55; CI:0.38-0.80	0.002
Number of lymph nodes removed (≤12)		
>12	HR:0.76; CI:0.56-0.93	0.049
Metastasis free survival		
pT (T1-T2)		
T3	HR:1.71; CI:0.74-3.95	0.210
T4	HR:3.25; CI:1.03-5.98	0.047
pN (N0)		
N1	HR:1.37; CI:0.90-2.10	0.141
N2	HR:2.69; CI:1.76-4.11	<0.001

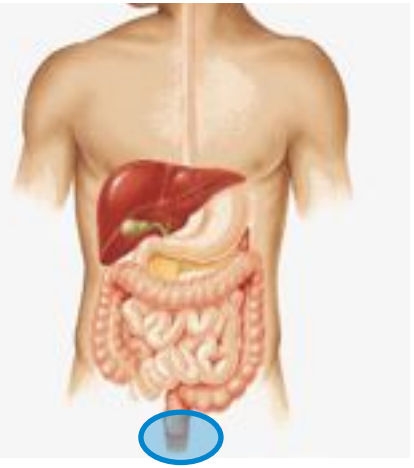
[a]HR=Hazard ratio estimated by Cox proportional hazards model.

Genovesi D. Anticancer Res. 2013;33:4557-66.

2014
IL FUMIR
COMPIE 40
ANNI

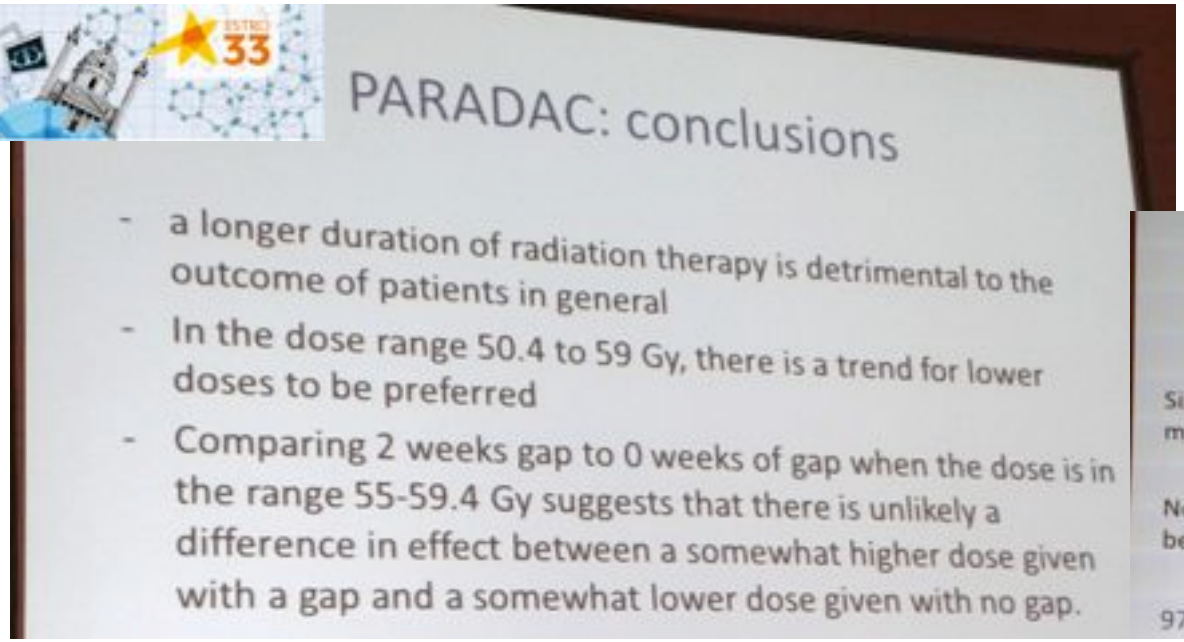
Nigro N,
Dis Colon Rectum - 1974

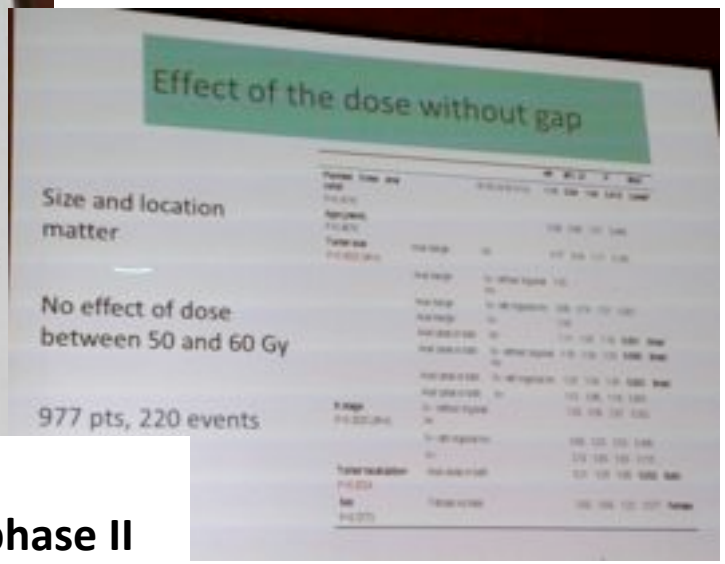
Anal cancer
Evidenze consolidate



MIND THE TIME ……..

Tempo totale /gap





PARADAC
Project surveying and pooling data on RT parameters in phase II and III trials in anal cancer (O. Matzinger & J. Lorent).

courtesy by G. Mantello

ACT II

Anal cancer
Evidenze consolidate

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.

MIND THE TIME ……..

Tempo di Risposta

		Absolute risk difference (95% CI)	
Pts with CR		CR rate %	MMC
Week 11	429	65.6	57.9
Week 18	527	75.4	76.2
Week 26	582	83.5	84.0

CR 26 w = + 29%

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

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

R. Glynne-Jones,. Journal Of Clinical Oncology Vol 30, No 15_Suppl 2012: 4004

per approfondire ....

clinical practice guidelines

Annals of Oncology 24 (Supplement 6): vi61–vi68, 2013
doi:10.1093/annonc/mdt342

Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

doi:10.1093/annonc/mdt344

Gastric cancer†: ESMO–ESSO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Annals of Oncology 00: 1–11, 2014
doi:10.1093/annonc/mdu159

Anal cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

LUNEDÌ 10 NOVEMBRE 2014

AULA MORGAGNI

10.00 - 11.20 **SIMPOSIO AIRO-SIRM**
La malattia metastatica epatica
Moderatori: L. Rubaltelli, M. Scorsetti

Il ruolo dell'imaging: stadiazione, valutazione della risposta e follow-up - **P. Sartori**
Il ruolo della radiologia interventistica - **C. Aliberti**
Il ruolo della SBRT - **F. Alongi**
Discussione

GIUNZIONE ESOFAGO-GASTRICA

A. De Paoli (Aviano); F. Cellini (Roma Campus); G.C. Mattiucci (Roma UCSC); D. Genovesi (Chieti); F.Mauriti (Pesaro); M La Macchia (Ancona)

LAB CONTOURING
Coordinatori: D. Genovesi, U. Ricardi

AULA GIOTTO

Domenica

10.00 - 11.30 **Linfomi** - V. De Sanctis, G. Simontacchi
13.30 - 15.00 **Giunzione esofago-gastrica** - F. Cellini, G. Mattiucci

Lunedi

10.00 - 11.30 **Linfomi** - P. Ciammella, A.R. Filippi
13.30 - 15.00 **Giunzione esofago-gastrica** - A. Augurio, G. Mantello

Aggiornamento 2014

GRANDANGOLO IN RADIOTERAPIA ONCOLOGICA
Neoplasie dell' apparato gastrointestinale

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U.O. Radioterapia sperimentale
Presidio Ospedaliero Oncologico "A. Businco",
Cagliari

Grazie per l'attenzione