Chemotherapy in carcinoma rectum

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RECTAL CANCER

Progress in ***multimodal therapy*** is one of the best examples of success stories of Clinical Research in the last 2 decades.

Carcinoma rectum

- From 1975 to 1989, postoperative pelvic RT combined with FU-based chemotherapy (CT) was evaluated in the United States in patients with Dukes' B and C rectal cancer. The combined therapy resulted in a significant benefit for local control, distant metastases, and survival compared with surgery alone.

Gastrointestinal Tumor Study Group: Prolongation of the disease-free interval in surgically treated rectal carcinoma. N Engl J Med 312:165- 172, 1985

Local-Regional Failure

local-regional failure is the only or 1st site of recurrence in patients with curative resected rectal cancer

- Stage I 5% to 10%
- Stage II up to 25% to 30%
- Stage III up to 50% or higher

NIH Consensus Conference on Adjuvant Therapy for Patients with Colon and Rectal Cancer, JAMA, Sept. 19, 1990

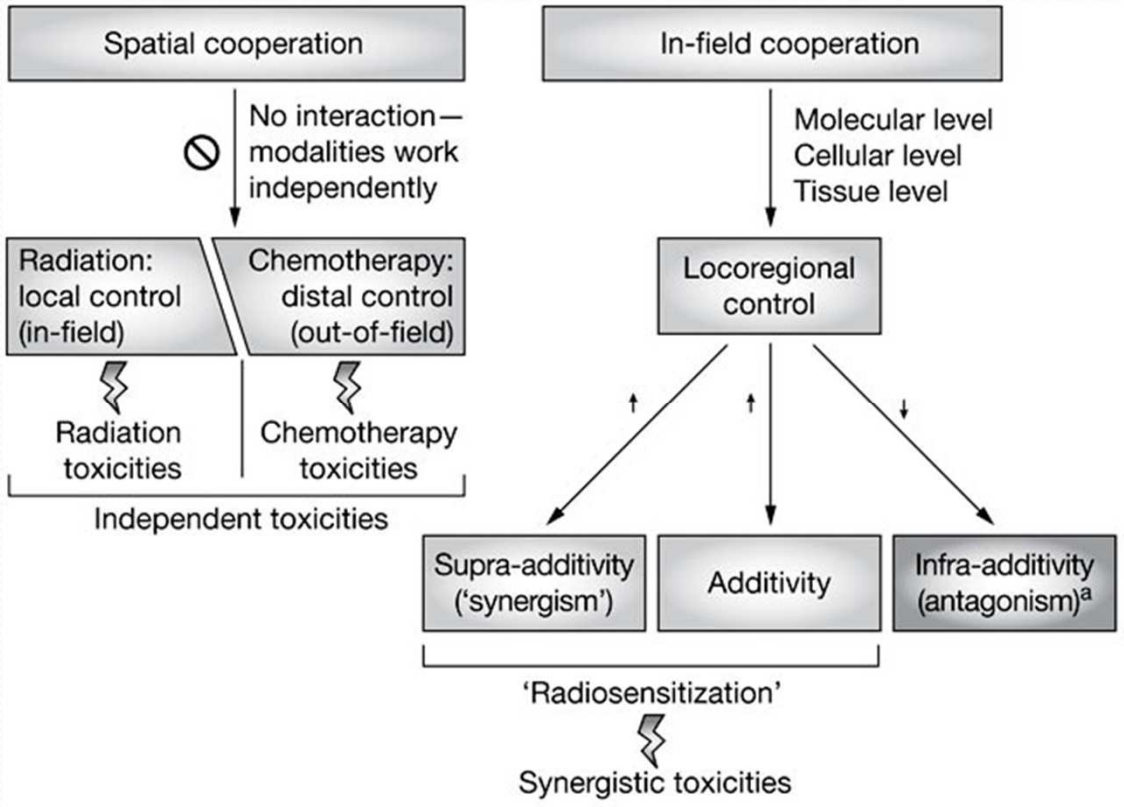
Carcinoma rectum

- From 1975 to 1989, postoperative pelvic RT combined with FU-based chemotherapy (CT) was evaluated in the United States in patients with Dukes' B and C rectal cancer. The combined therapy resulted in a significant benefit for local control, distant metastases, and survival compared with surgery alone.

Moertel C, Childs D, Reitemeier R, et al: Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. Lancet 2:865-867, 1969

Krook JE, Moertel CG, Gunderson LL, et al: Effective surgical adjuvant therapy for highrisk rectal carcinoma. N Engl J Med 324:709-715,1991

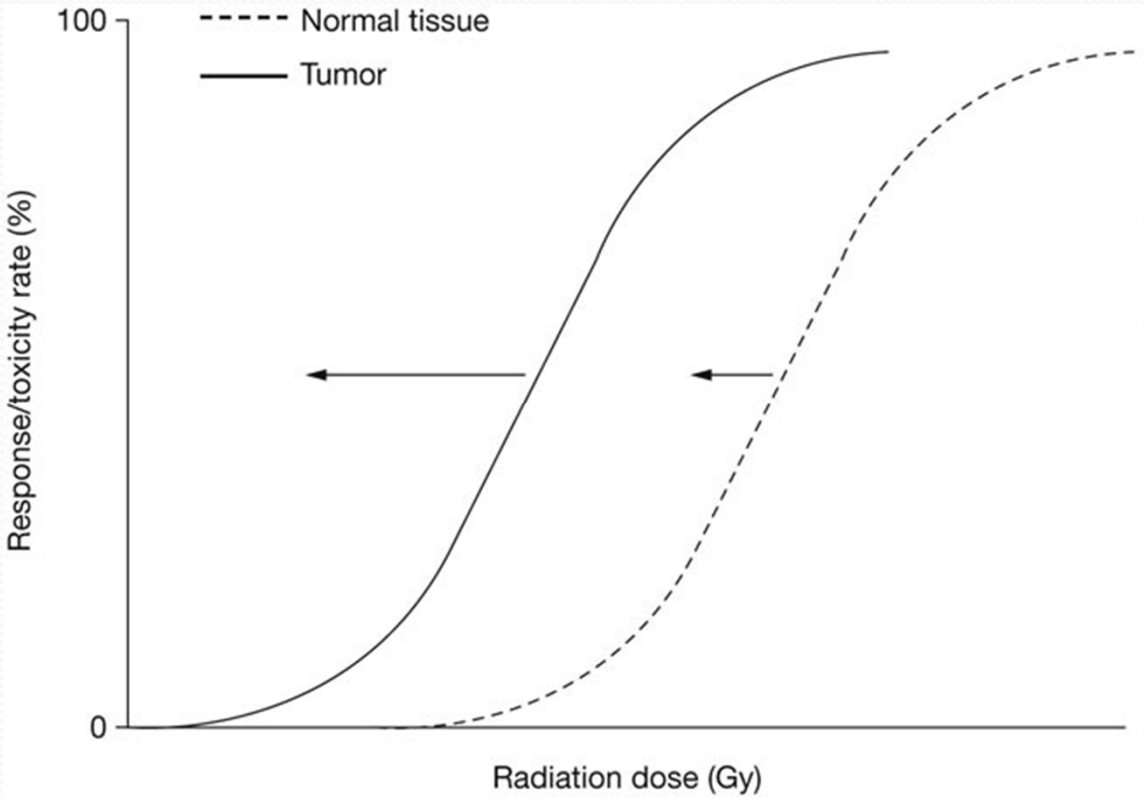
Rationale for adding chemotherapy to radiation



Seiwert TY *et al.* (2007) The concurrent chemoradiation paradigm—general principles
Nat Clin Pract Oncol **4**: 86–100 doi:10.1038/ncponc0714

nature CLINICAL PRACTICE ONCOLOGY

Figure 3 Schematic dose–response curves for tumor and normal tissue damage with radiation



Seiwert TY *et al.* (2007) The concurrent chemoradiation paradigm—general principles
Nat Clin Pract Oncol **4**: 86–100 doi:10.1038/ncponc0714

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ONCOLOGY

Carcinoma rectum

- In 1989, N I H Consensus Conference stated that postoperative chemo radiotherapy (RT-CT) should be regarded as standard treatment for patients with stage II and III rectal cancer.

National Institutes of Health: NIH Consensus Conference: Adjuvant therapy for patients with colon and rectal cancer. JAMA 264:1444- 1450, 1990

Carcinoma rectum

- ***preoperative (preop) RT alone, demonstrated its value on local control and, on survival.***
- Swedish scheme delivered 25 Gy in 5 fractions over 1 week immediately followed by surgery, and conventional schemes delivered 40 to 50 Gy in 20 to 25 fractions over 4 to 5 weeks followed 3 to 4 weeks later by surgery.

Compared with surgery alone, preop RT halved the local failure rates, irrespective of the scheme.

Long course Vs Short course

- Better down staging
- Sphincter preservation
- Decreased morbidity
- Combine chemo along with it
- T3/T4, N+

- Patient convenience
- Lower cost
- T1-T3,Nx

Short Course (25 Gy/5 fr)

- Surgery within 1 wk
- Sphinter preservation - not the end point
- No Chemo along with RT
- Only in Resectable rectal cancer

Conventional schedule (45 Gy/25 fr+/-boost)

Proper Counseling

- It increases operability and sphincter presentation
- Decreases tumor seeding
- Decreases - A/c toxicity
- Increases radio sensitivity due to better oxygenation
- Surgery done after 4-8 wks
- Chemo increases pCR

Conventional Pre – OP RT

- ✓ 12 RCT
- ✓ 2 meta analysis
- ✓ Increased Sphincter preservation
- ✓ Increased Tumor down staging

REVIEW

Preoperative Radiotherapy for Resectable Rectal Cancer

A Meta-analysis

Local recurrence	**P <0.001**
Distant recurrence	**P=0.54**
OS	**P=.03**

JAMA. 2000;284:1008-1015

Carcinoma rectum

- In early 1990s, it became clear that preop RT-CT was a relevant issue for clinical research.
- The European Organisation for Research and Treatment of Cancer (EORTC) Radiotherapy Group demonstrated that an FU dose of 350 mg/m2/d could be safely administrated in combination with a leucovorin (LV) dose of 20 mg/m2/d delivered the first and fifth weeks of a 45-Gy dose of pelvic RT in patients with unresectable or locally recurrent rectal cancer.

Bosset JF, Pavy JJ, Hamers HP, et al: Determination of the optimal dose of 5-fluorouracil when combined with low dose D,L-leucovorin and irradiation in rectal cancer: Results of three consecutive phase II studies—EORTC Radiotherapy Group. Eur J Cancer 29A:1406-1410, 1993

Carcinoma rectum

In 1993, the EORTC initiated a four-arm randomized trial (EORTC 22921) to examine the value of pre op RT-CT versus pre op RT alone and the value of additional CT versus none with respect to overall survival and progression-free survival in the same patient group.

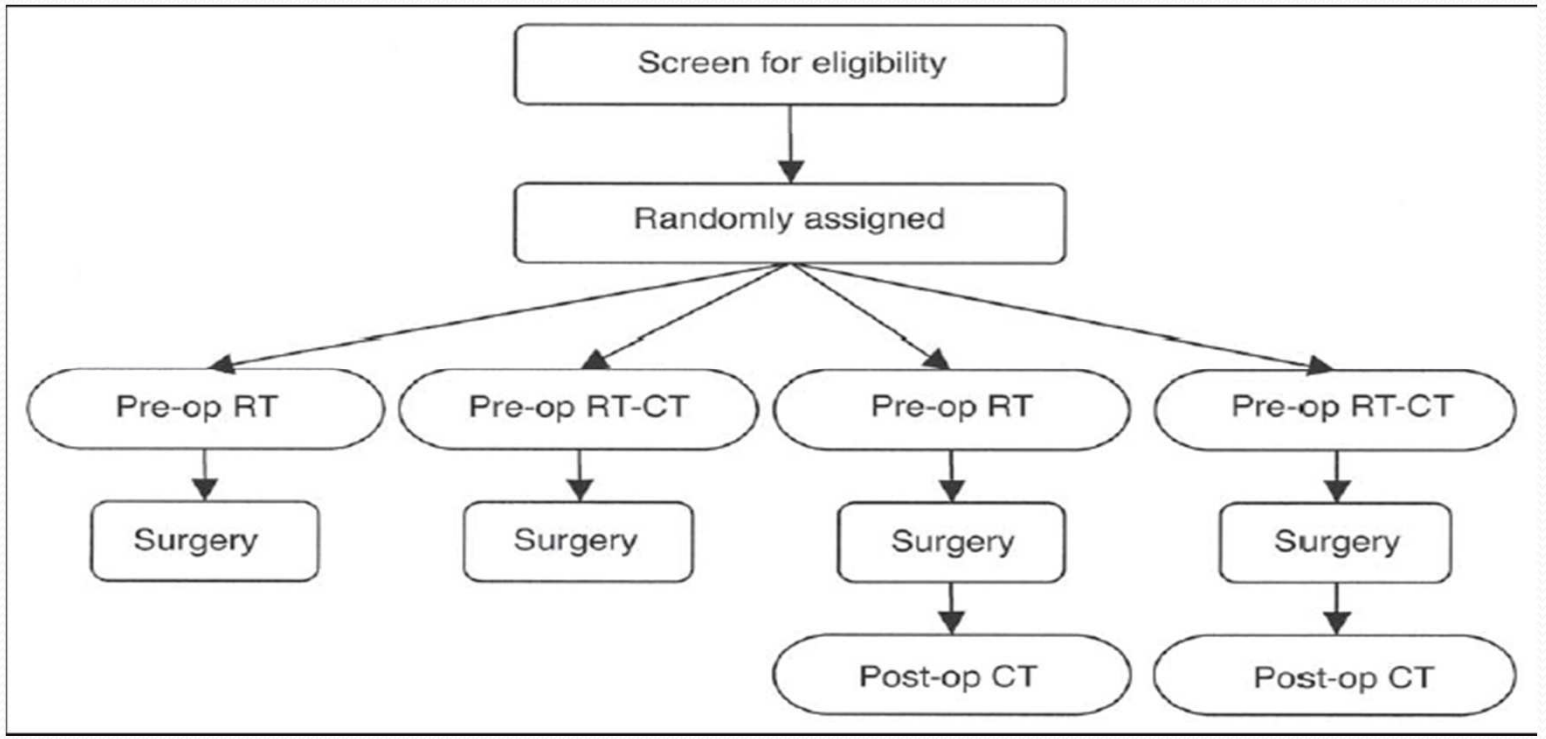
VOLUME 23 · NUMBER 24 · AUGUST 20 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Enhanced Tumorocidal Effect of Chemotherapy With Preoperative Radiotherapy for Rectal Cancer: Preliminary Results—EORTC 22921

Jean-François Bosset, Gilles Calais, Laurent Mineur, Philippe Maingon, Ljiljana Radosevic-Jelic, Alain Daban, Etienne Bardet, Alexander Beny, Antoine Briffaux, and Laurence Collette



Carcinoma rectum

- Pre op RT-CT has been previously recommended after the observation that patients with a pathologic tumour response had a favourable outcome.

- The randomized German study showed improved local control and reduced toxicity with pre op RT-CT compared with postoperative RT-CT.

Sauer R, Becker H, Hohenberger W, et al: Preoperative versus postoperative chemo radiotherapy for rectal cancer. N Engl J Med 351: 1731-1739, 2004

Cochrane review

2013

Authors' conclusions

Compared to preoperative RT alone, preoperative CRT enhances pathological response and improves local control in resectable stage II and III rectal cancer, but does not benefit disease free or overall survival. The effects of preoperative CRT on functional outcome and quality of life are incompletely understood and should be addressed in future trials.

RECTAL CARCINOMA – RECENT ADVANCES -- OVERALL

1.sphincter saving procedures –from 15% to 50% -- no colostomy (improved qol)

2. overall five year survival – up from 30% to 60%

3. depth of invasion – decreased by 40%-60% with adjuvant treatment.

4. lymph node status and rec. free survival - same

Pre OP Chemo RT Vs Post OP Chemo RT

- INT 0147
- NSABP-R- 03
- German Trial CAO/ARO/AIO-94

Characteristics	Pre OP RT	Post OP Chemo RT
Tumour down Staging	+	-
Increased tumour resectability	+	-
Increased sphinter preservation	+	-
Increased compliance	+	-
Less A/c and C/c toxicity	+ +	-
Increased survival	+	-
Treatment based on pathologic finding	-	+

Compliance with Therapy

	Pre-OP Chemo RT	Post OP Chemo RT	P Value
Chemo	89%	50%	<0.001
RT	92%	54%	<0.001

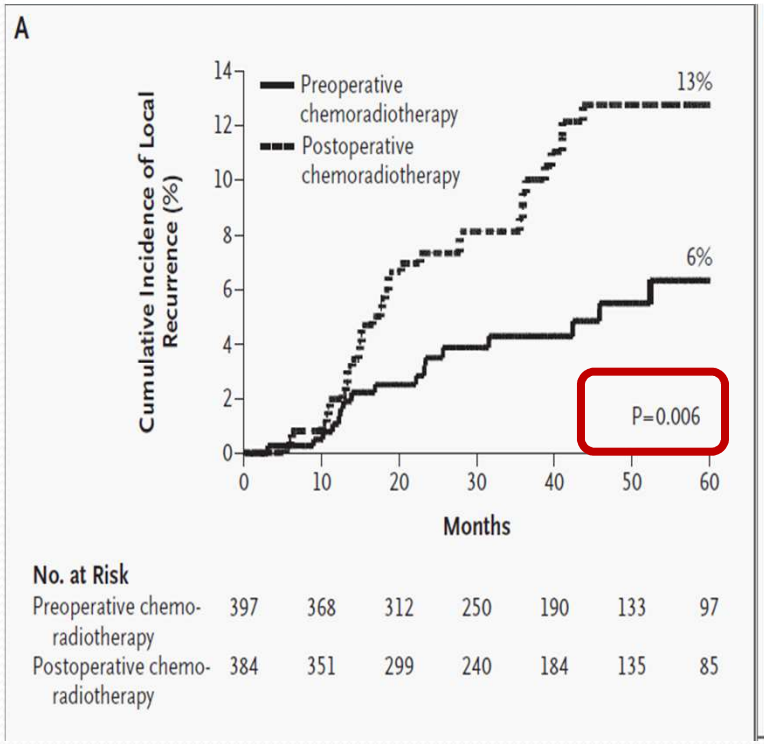
N Engl J Med 2004;351:1731-40.

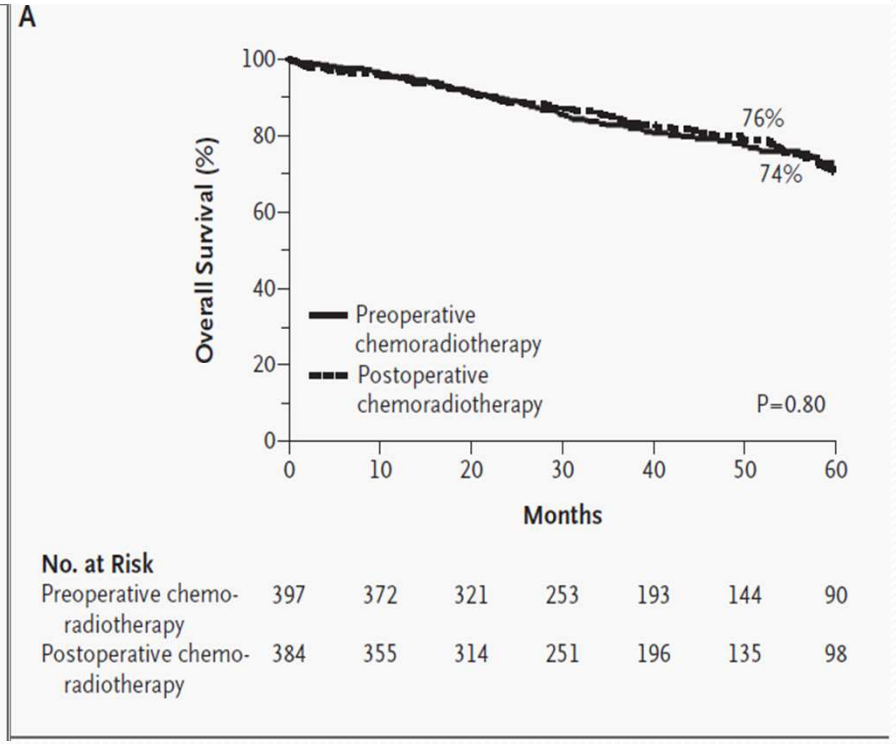
ORIGINAL ARTICLE

Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer

Rolf Sauer, M.D., Heinz Becker, M.D., Werner Hohenberger, M.D., Claus Rödel, M.D., Christian Wittekind, M.D., Rainer Fietkau, M.D., Peter Martus, Ph.D., Jörg Tschmelitsch, M.D., Eva Hager, M.D., Clemens F. Hess, M.D., Johann-H. Karstens, M.D., Torsten Liersch, M.D., Heinz Schmidberger, M.D., and Rudolf Raab, M.D., for the German Rectal Cancer Study Group*

N Engl J Med 2004;351:1731-40.





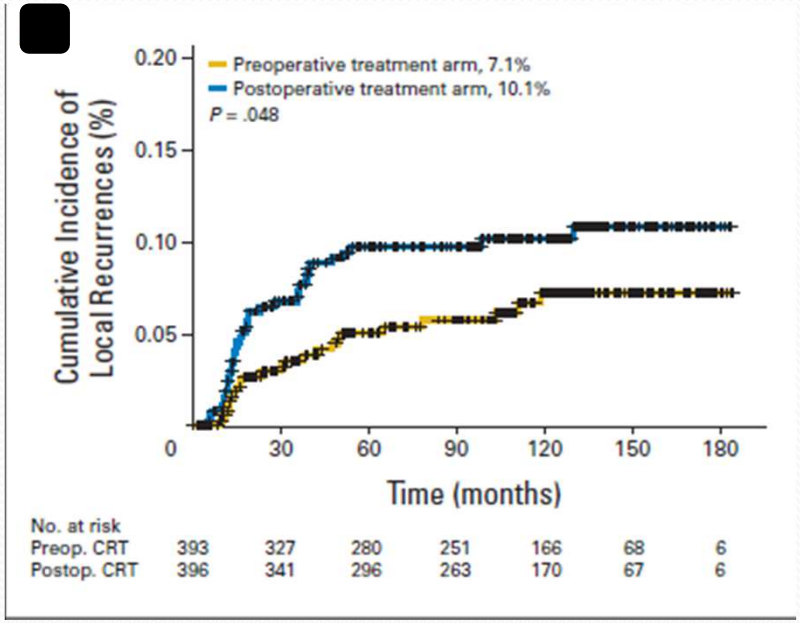
VOLUME 30 · NUMBER 16 · JUNE 1 2012

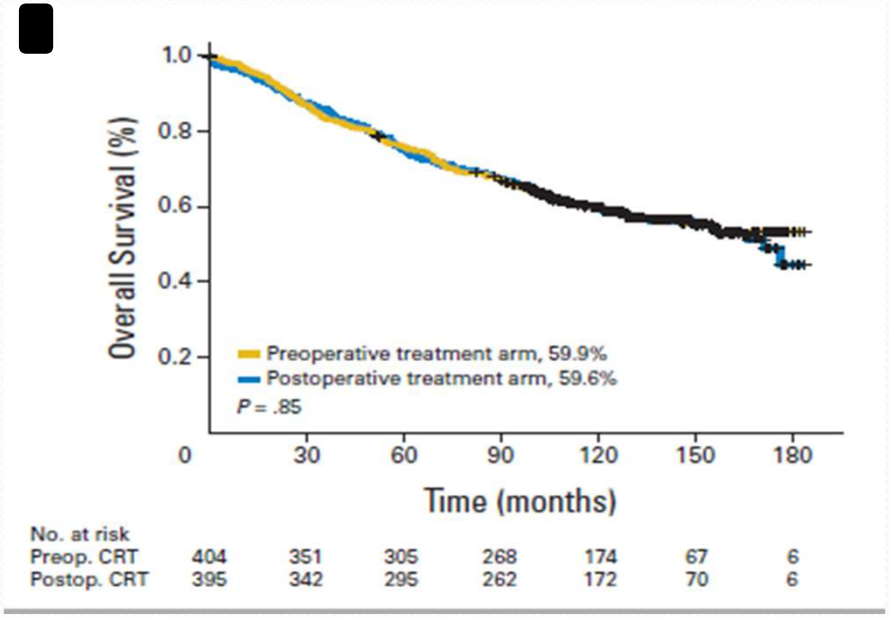
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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





Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial

Lancet Oncol 2012; 13: 579–88

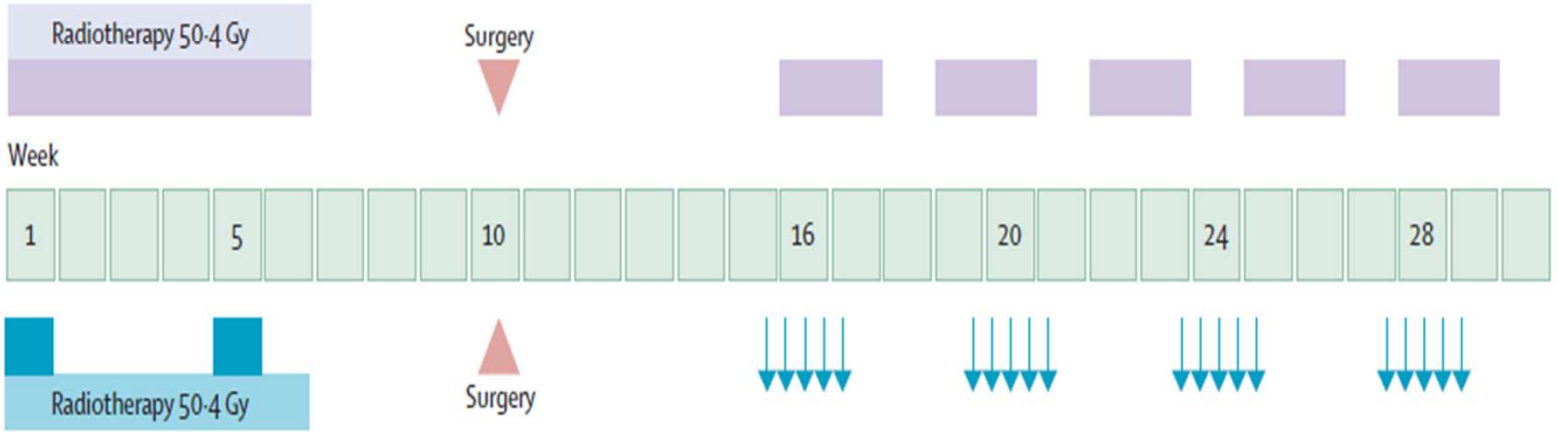
Ralf-Dieter Hofheinz, Frederik Wenz, Stefan Post, Axel Matzdorff, Stephan Laechelt, Jörg T Hartmann, Lothar Müller, Hartmut Link, Markus Moehler, Erika Kettner, Elisabeth Fritz, Udo Hieber, Hans Walter Lindemann, Martina Grunewald, Stephan Kremers, Christian Constantin, Matthias Hipp, Gernot Hartung, Deniz Gencer, Peter Kienle, Iris Burkholder, Andreas Hochhaus

Comment

Capecitabine in the treatment of rectal cancer

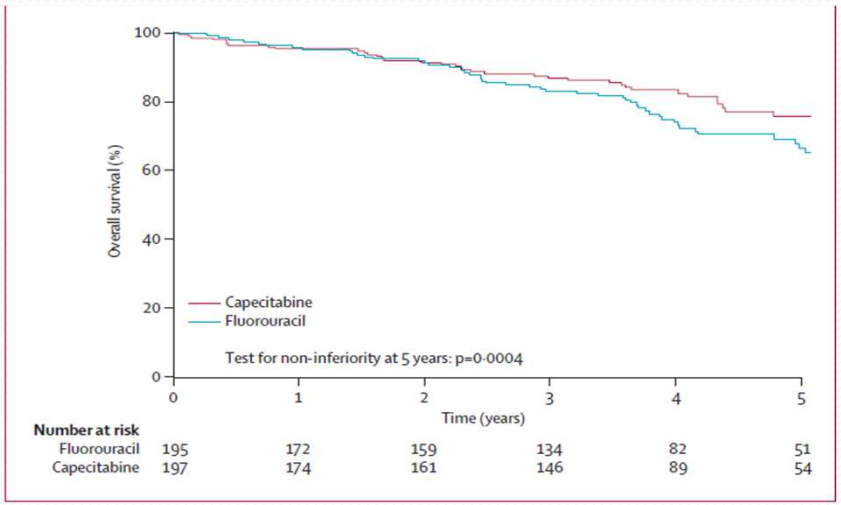
Capecitabine group

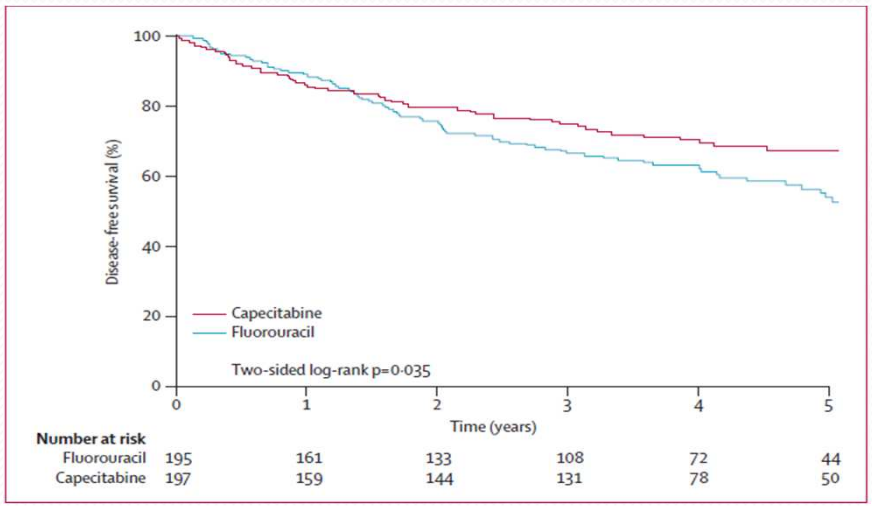
Capecitabine 1650 mg/m² per day during radiotherapy, then 2500 mg/m² per day



Fluorouracil group

Fluorouracil 1000 mg/m² days 1–5, days 29–33 during radiotherapy, then 500 mg/m² days 1–5





Lancet Oncol 2012; 13: 579–88

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The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2012.42.9597

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Trial of Short-Course Radiotherapy Versus Long-Course Chemoradiation Comparing Rates of Local Recurrence in Patients With T3 Rectal Cancer: Trans-Tasman Radiation Oncology Group Trial 01.04

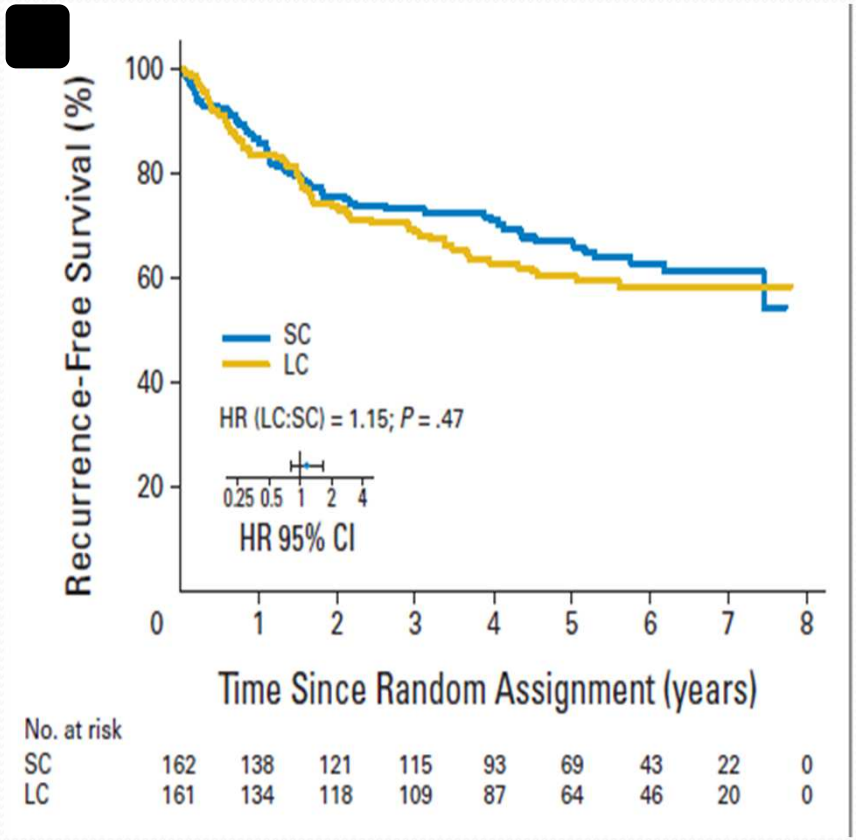
VOLUME 30 · NUMBER 31 · NOVEMBER 1 2012

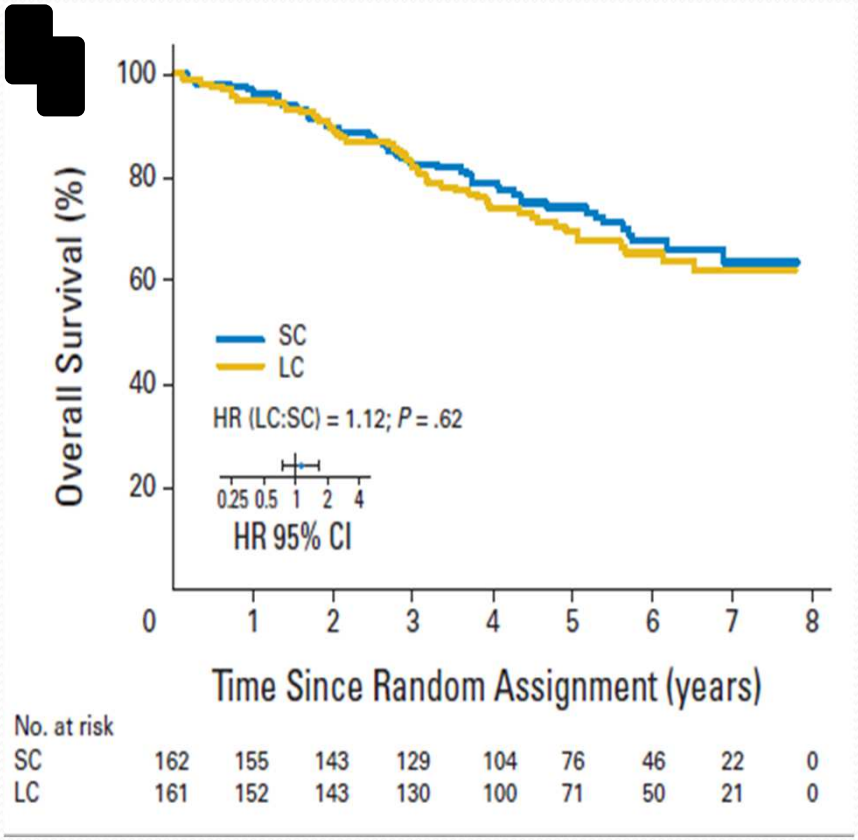
JOURNAL OF CLINICAL ONCOLOGY EDITORIAL

Short-Course Radiation Versus Long-Course Chemoradiation for Rectal Cancer: Making Progress

Bruce D. Minsky, *MD Anderson Cancer Center, Houston, TX*

Median follow up 5.9 yrs





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Challenging Cases

Short-Course Versus Standard Chemoradiation in T3 Rectal Cancer

Section Editor's note: Locally advanced rectal cancer, in contrast to colon cancer, has a substantial risk for local recurrence. Two approaches of neoadjuvant therapy have been formally tested in multiple randomized trials. Short-course radiation therapy uses 1 week of radiation without chemotherapy (5 Gy × 5) followed by surgery the next week. In contrast, standard chemoradiation uses 45–50.4 Gy in 25–28 fractions with concurrent 5-FU chemotherapy followed by 4–8 weeks of rest before surgery. Short-course radiation therapy is not frequently used in the U.S. The pros and cons of short-course radiation therapy and standard chemoradiation are presented herein.

The Oncologist 2011;16:717–721 www.TheOncologist.com

Articles

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

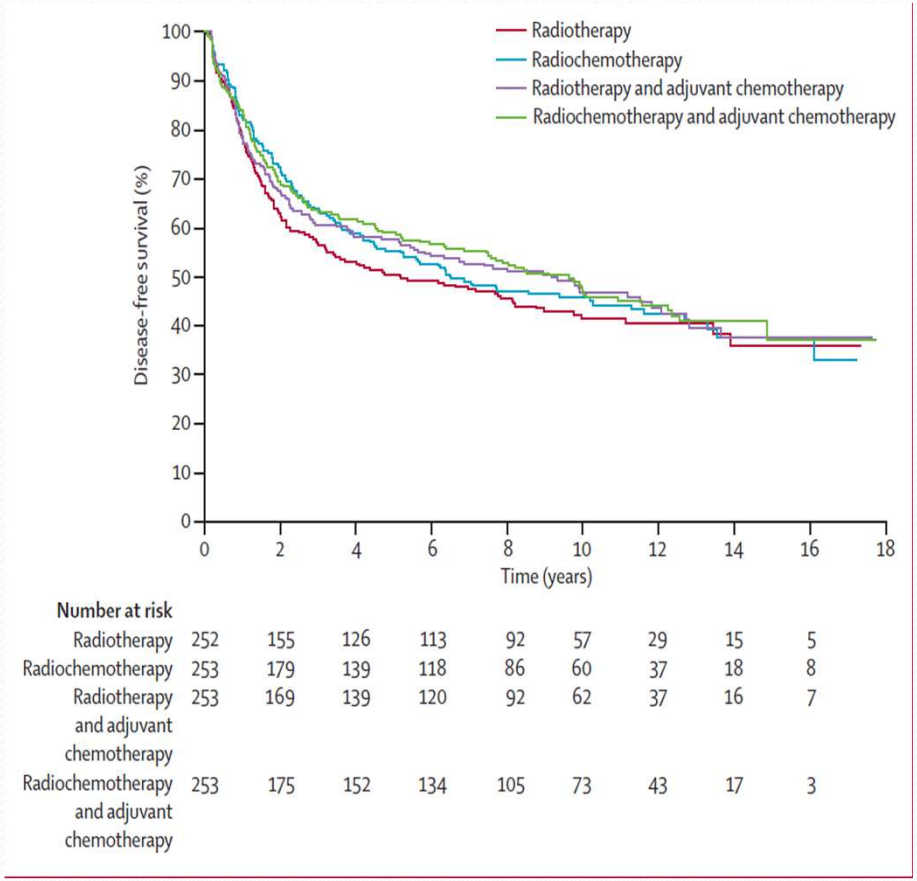
Jean-François Bosset, Gilles Calais, Laurent Mineur, Philippe Maingon, Suzana Stojanovic-Rundic, René-Jean Bensadoun, Etienne Bardet, Alexander Beny, Jean-Claude Ollier, Michel Bolla, Dominique Marchal, Jean-Luc Van Laethem, Vincent Klein, Jordi Giralt, Pierre Clavère, Christoph Glanzmann, Patrice Cellier,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

Comment

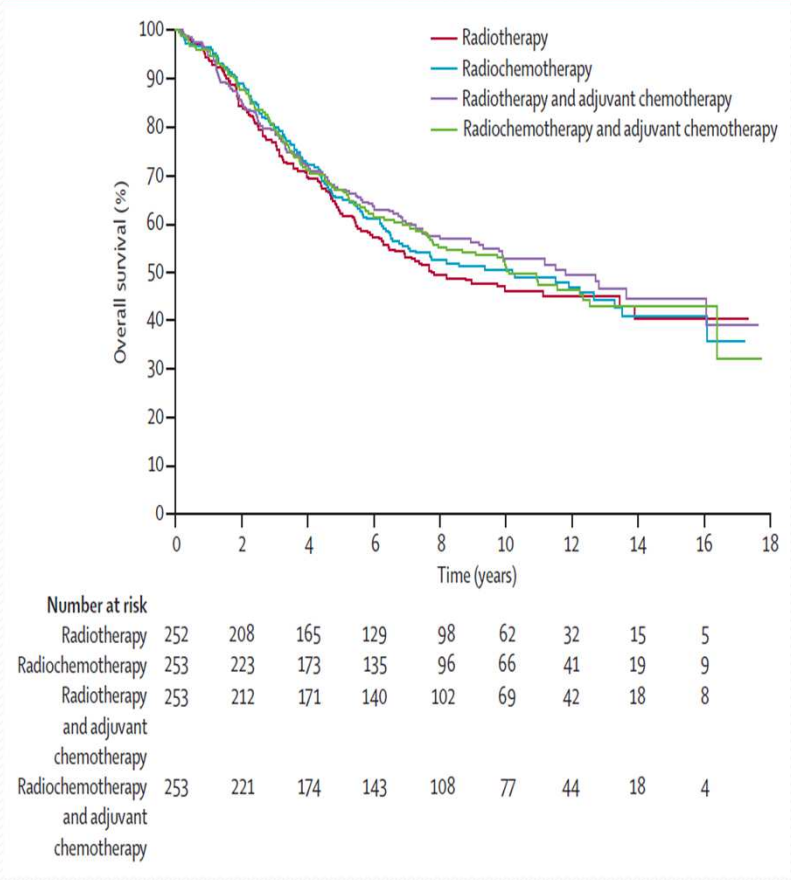
Lancet Oncol 2014; 15: 184–90

Adjuvant chemotherapy for rectal cancer still controversial

Median follow up 10.4 yrs



Number at risk									
Radiotherapy	252	155	126	113	92	57	29	15	5
Radiochemotherapy	253	179	139	118	86	60	37	18	8
Radiotherapy and adjuvant chemotherapy	253	169	139	120	92	62	37	16	7
Radiochemotherapy and adjuvant chemotherapy	253	175	152	134	105	73	43	17	3



Number at risk									
Radiotherapy	252	208	165	129	98	62	32	15	5
Radiochemotherapy	253	223	173	135	96	66	41	19	9
Radiotherapy and adjuvant chemotherapy	253	212	171	140	102	69	42	18	8
Radiochemotherapy and adjuvant chemotherapy	253	221	174	143	108	77	44	18	4

Lancet Oncol 2014; 15: 184-90

Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine + oxaliplatin vs. capecitabine alone in locally advanced rectal cancer: Early results of the PETACC 6 trial

H-J. Schmoll[1], K. Haustermans[2] T. Price[3], B. Nordlinger[4], R.D. Hofheinz[5], J-F. Daisne[6], J. Janssens[7], B. Brenner[8], P. Schmidt[9], H. Reinel[10], S. Hollerbach[11], K. Caca[12], F. Fauth[13], C.V. Hannig[14], J. Zalcberg[15], N. Tebbutt[16], M.E. Mauer[17], C. Messina[17], M. Lutz[18], E. Van Cutsem[2].

For the EORTC GITCG, AIO, AGITG, EORTC ROG, BGDO, FFCD and PETACC

Conclusions I

1. The addition of oxaliplatin to preoperative capecitabine-based chemo-radiation led to
   - decreased treatment compliance due to toxicity,
   - but did not improve R0 resection, pathological CR or sphincter preservation
   - in accordance with STAR, ACCORD/PRODIGE 2, NSABP R04, except CAO/ARO/AIO-04 favouring 5FU+oxaliplatin.

2. Interim results at a median follow up of 2.6 years indicate no DFS-benefit for the addition of oxaliplatin to pre-and post-op Capecitabine.

Conclusions

Patterns of relapse -different for rectal & colonic cancer

LR 5-50%

Adjuvant chemo RT improves survival

Post OP -5040 Gy/28 fr for along with Chemo 5 FU

No additional benefit with another agent

TME - LR is 10%

Short Course XRT increases survival (Swedish Trial)

Conclusions….

Better LCR ?OS

Proper counseling before long course RT

Addition of chemo increased pCR

German trial

- Decreased LR
- Decreased toxicity
- Increased sphincter preservation
- No diff in OS

Capecitabine is equivalent to 5 FU

No benefit by adding oxaliplatin and toxicity increased

Short course VS Long course- early results promising

Adjuvant Chemo- controversial

Chemotherapy forms an integral part in management of carcinoma rectum which has definite advantage in the concurrent setting.