

THIRD ANNUAL

*Update on the Management
of Gastrointestinal
Malignancies*

*October
20-22, 2006*

**Estancia La Jolla Hotel & Spa
LA JOLLA, CALIFORNIA**

Chairman:

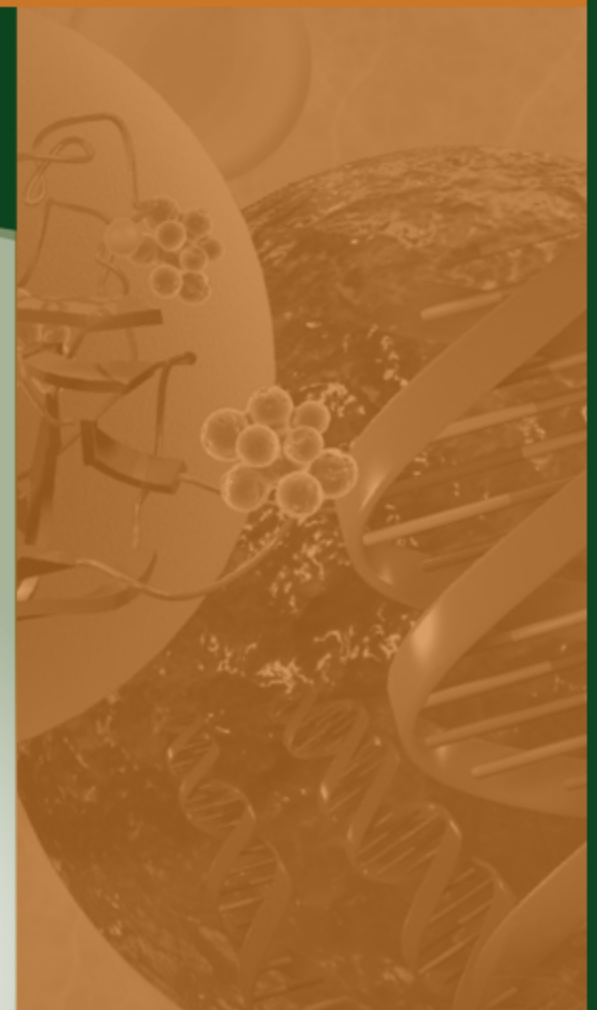
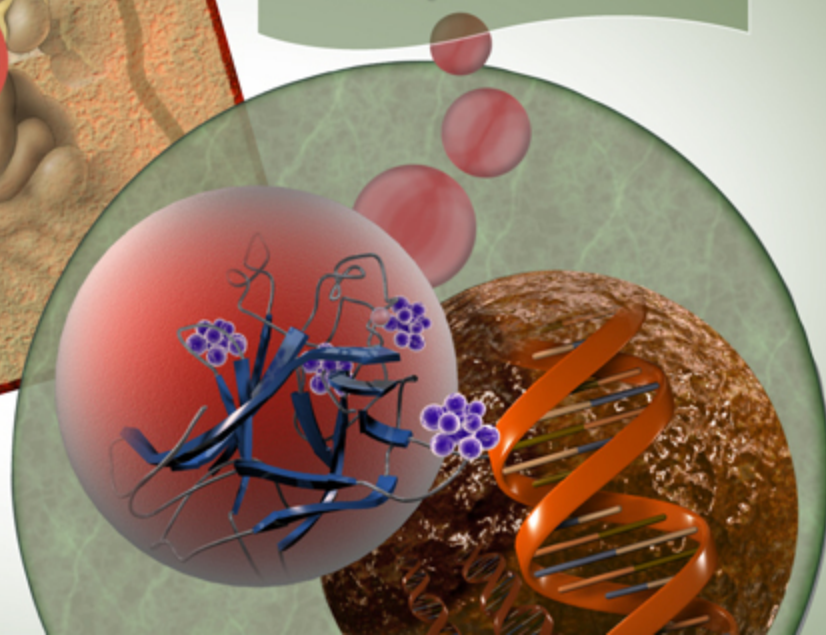
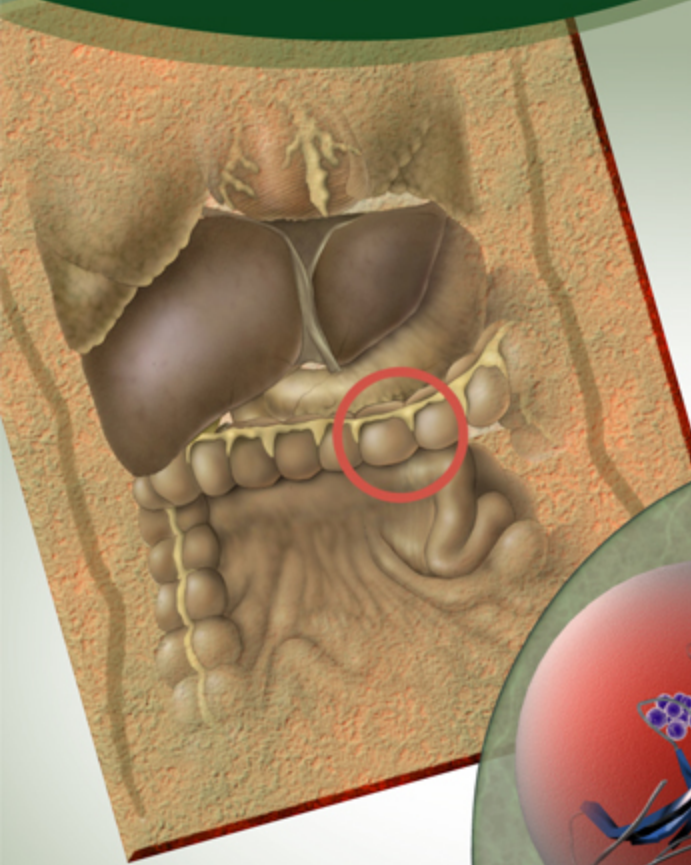
Mace L. Rothenberg, MD

Ingram Professor of Cancer Research

Professor of Medicine

Director, Phase I Drug Development Program

Vanderbilt Ingram Cancer Center



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Chemoradiation in the Management of Locally Advanced Rectal Cancer

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Comprehensive Cancer Center

Disclosure Statement

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The NCI Consensus Conference concluded in 1990 that combined modality therapy was the standard post-operative adjuvant treatment for patients with pathological T3 and/or N1/2 disease

National Institutes of Health Consensus Conference
Adjuvant Therapy for Patients with Colon and Rectal Cancer

Chemoradiation for Locally Advanced Rectal Cancer

Prolongation of the disease-free interval in surgically treated rectal carcinoma.

Gastrointestinal Tumor Study Group

NEJM Volume 312:1465-1472 June 6, 1985 Number 23

Chemoradiation for Locally Advanced Rectal Cancer

Postoperative Adjuvant Chemotherapy or Radiation Therapy for Rectal Cancer: Results From NSABP Protocol R-01.

Fisher B, Wolmark N, Rockette H, Redmond C, Deutsch M, Wickerman DL, Fisher ER, Caplan R, Jones J, Lerner H, Gordon P, Feldman M, Cruz A, Legault-Poisson S, Wexler M, Lawrence W, Robidoux A.

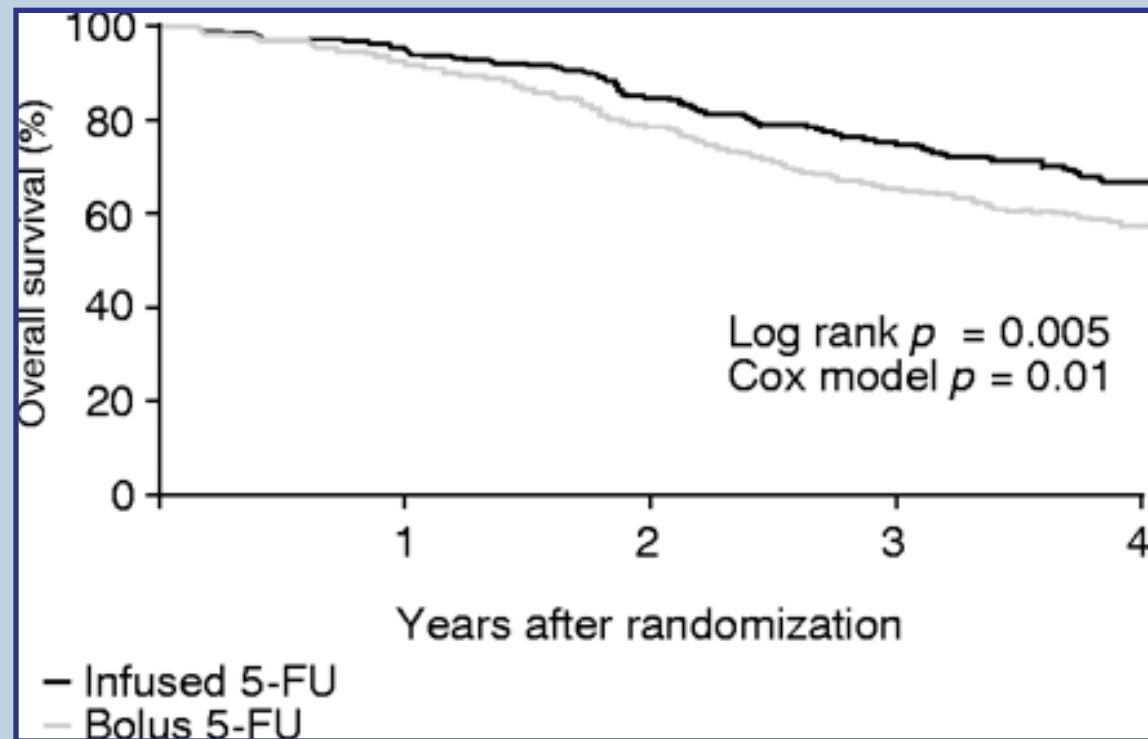
JNCI Volume 80:21-29 March, 1988 Number 1

Chemoradiation for Locally Advanced Rectal Cancer

- O'Connell MJ, Martensen JA, Wieand HS et al.
 - 660 patients TNM stage II or III rectal cancer
 - Randomized to:
 - Continuous infusion 5-FU (225 mg/m²/d) 5-week during the radiotherapy (45 Gy + 5.4 Gy boost)
 - versus*
 - Bolus 5-FU (500 mg/m²/d) days 1-3 weeks 1 and 4 during the radiotherapy

Chemoradiation for Locally Advanced Rectal Cancer

Adjuvant XRT/PVI 5-FU resulted in a significantly improved overall survival ($P = 0.005$) and disease-free survival ($P = 0.01$)

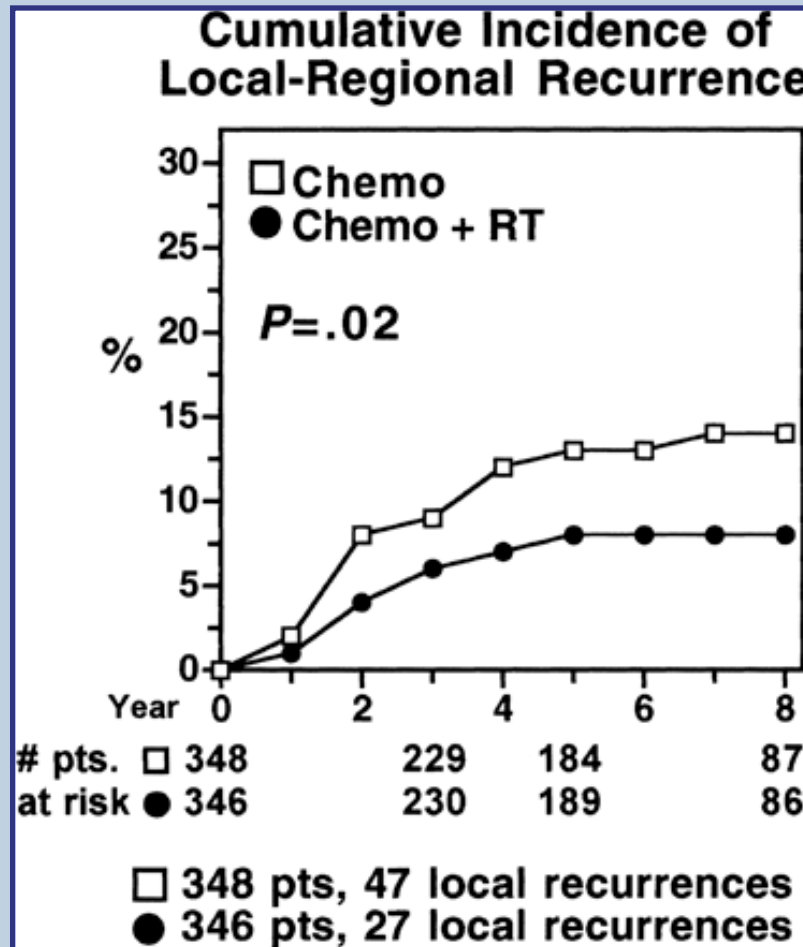


Chemoradiation for Locally Advanced Rectal Cancer

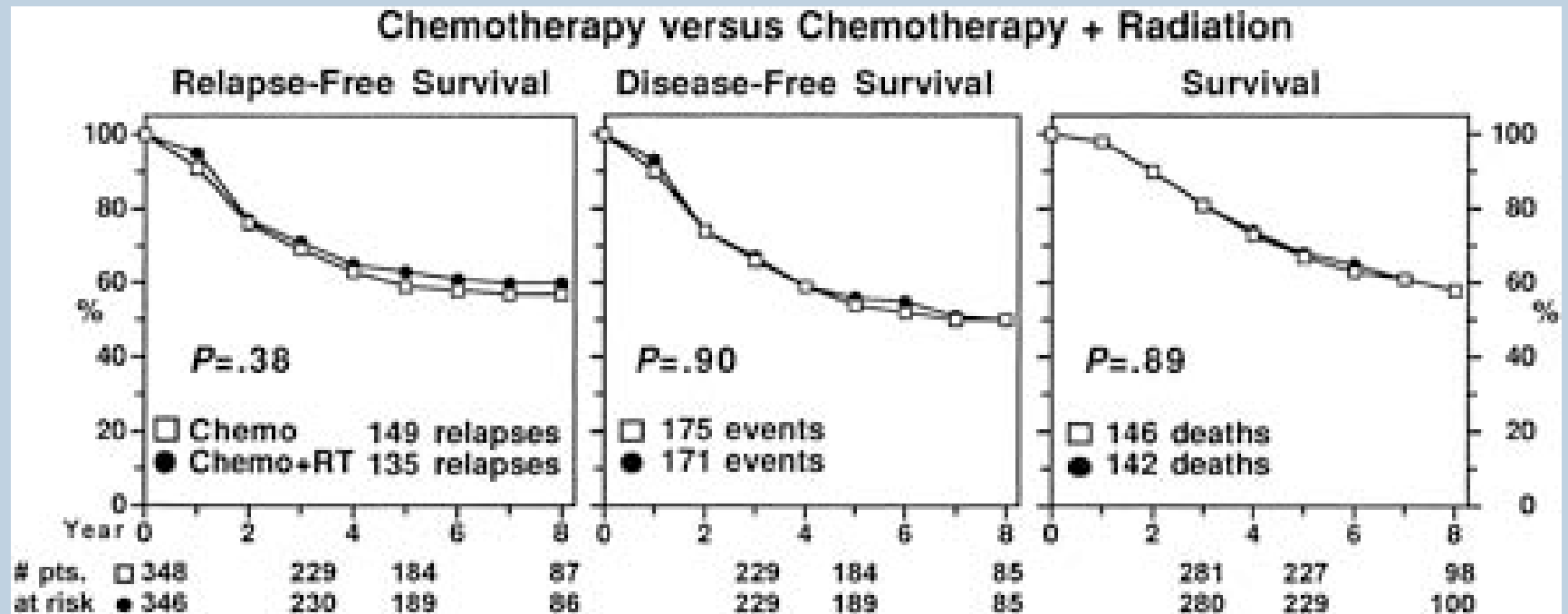
Randomized Trial of Postoperative Adjuvant Chemotherapy With or Without Radiotherapy for Carcinoma of the Rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02

Norman Wolmark, H. Samuel Wieand, David M. Hyams, Linda Colangelo, Nikolay V. Dimitrov, Edward H. Romond, Marvin Wexler, David Prager, Anatolio B. Cruz, Jr., Philip H. Gordon, Nicholas J. Petrelli, Melvin Deutsch, Eleftherios Mamounas, D. Lawrence Wickerham, Edwin R. Fisher, Howard Rockette, Bernard Fisher

Randomized Trial of Postoperative Adjuvant Chemotherapy With or Without Radiotherapy for Carcinoma of the Rectum: NSABP Protocol R-02



Chemoradiation for Locally Advanced Rectal Cancer



JNCI - 92: (5) 388-396, March 1, 2000

Chemoradiation for Locally Advanced Rectal Cancer

“Whether the 5% absolute decrease in the cumulative incidence of locoregional relapse is sufficient to justify the routine use of postoperative radiotherapy is a decision that must be made by the clinician.”

JNCI - 92: (5) 388-396, March 1, 2000

Adjuvant Therapy in Rectal Cancer: Analysis of Stage, Sex, and Local Control – Final Report of Intergroup 0114

Tepper JE, O'Connell M, Niedzwiecki D, Hollis DR, Benson AB
3rd, Cummings B, Gunderson LL, Macdonald JS, Martenson
JA, Mayer RJ.

Impact of T and N Stage and Treatment on Survival and Relapse in Adjuvant Rectal Cancer: A Pooled Analysis

Gunderson LL, Sargent DJ, Tepper JE, Wolmark N, O'Connell MJ, Begovic M, Allmer C, Colangelo L, Smalley SR, Haller DG, Martenson JA, Mayer RJ, Rich TA, Ajani JA, MacDonald JS, Willett CG, Goldberg RM

Chemoradiation for Locally Advanced Rectal Cancer

- Who may not benefit from adjuvant chemoradiation?
 - High Rectal Lesion
 - TME Resection
 - T3 disease (microscope only)
 - Node negative (with adequate dissection)
 - No adverse pathologic findings (LVI, poorly differentiated)



Other potential
Strategies . . .

Pre-Operative Chemoradiation for Locally Advanced Rectal Cancer

- Rationale
 - Less Morbidity . . .
 - Tumor Downstaging . . .
 - Drug delivery improved . . .
 - Less Tumor Hypoxia . . .

Radiation for Locally Advanced Rectal Cancer

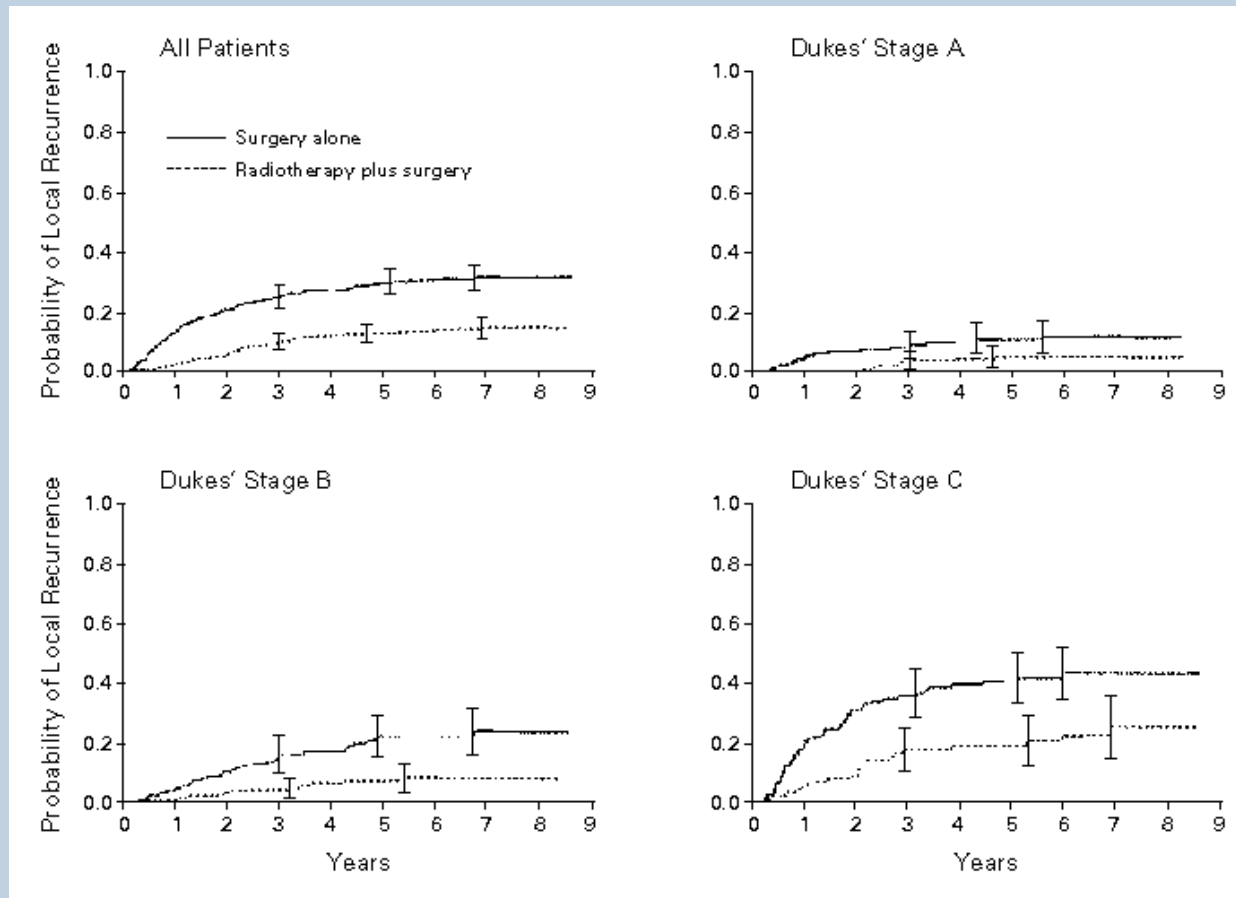
- Swedish Rectal Cancer Trial
- Clinically resectable (T1-3) rectal cancer randomized to 25 Gy (500 cGy X 5) followed by surgery one week later vs. surgery alone

TABLE 1. SELECTION OF THE STUDY COHORT.

PATIENT CATEGORY	RADIOTHERAPY- PLUS-SURGERY GROUP	SURGERY-ALONE GROUP
	no. of patients	
Randomized	583	585
Ineligible	10	11
Eligible	573	574
Refused surgery	1	0
No resection performed	19	17
Local resection performed	553	557
Distant metastases found	42	41
Locally noncurative surgery	14	19
Local cure uncertain	43	43
Curatively treated	454	454

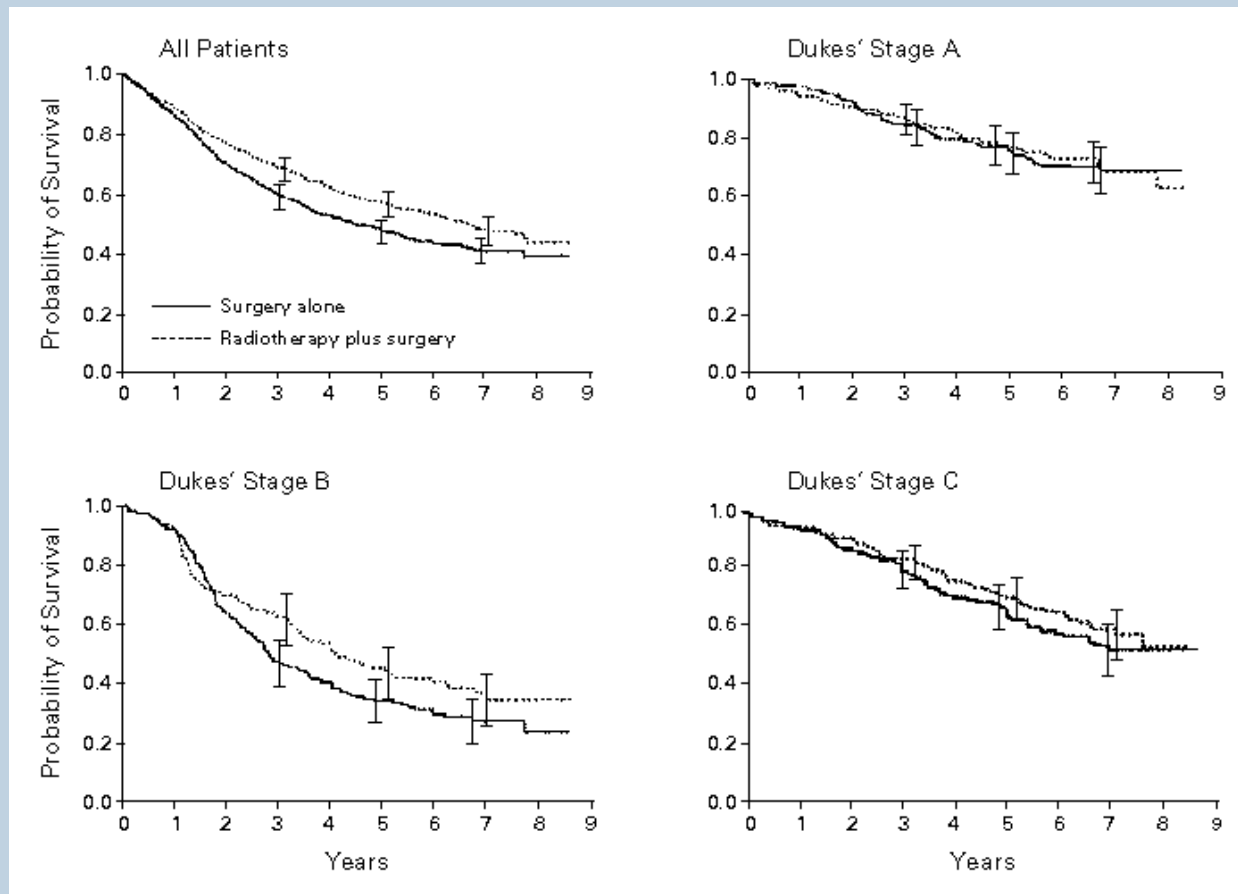
Radiation for Locally Advanced Rectal Cancer

Significant decrease in local recurrence (12% vs. 27%)



Radiation for Locally Advanced Rectal Cancer

5-year survival 58% for XRT-surgery vs 48% for surgery-alone ($P = 0.004$)

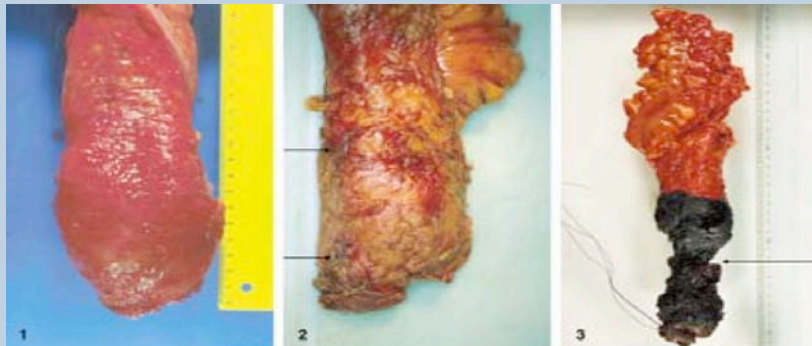


Dutch CKVO 95-04 Trial

- 1805 patients
- Clinically resectable (T1-3) disease
- Randomized to:
 - Surgery alone with a Total Mesorectal Excision (TME)

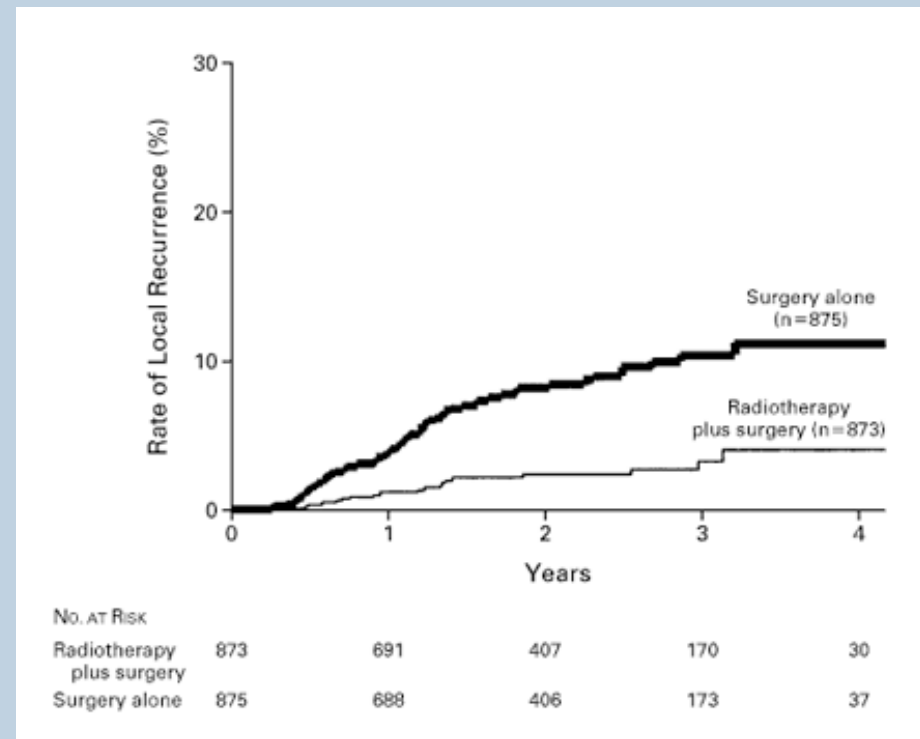
versus

 - Intensive short course pre-operative radiation followed by TME



Dutch CKVO 95-04 Trial

- Radiation significantly decreased local recurrence (8% vs. 2%).
- No difference in 2-year survival.
- 5-year local recurrence was 12% with TME versus 6% with pre-operative radiation.



Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer

Intergroup 0147 – 53 patients accrued and closed.

Clinical trial to evaluate the worth of preoperative multimodality therapy in patients with operable carcinoma of the rectum: a progress report of NSABP Protocol R-03

Hyams DM, Mamounas EP, Petrelli N, Rockette H, Jones J, Wieand HS, Deutsch M, Wickerham L, Fisher B, Wolmark N.

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., Rudolf Raab, M.D., for the German
Rectal Cancer Study Group

CAO/ARO/AIO-94

Preoperative versus Postoperative Chemoradiotherapy

- 50.4 Gy Radiation
- 5-FU 1000 mg/m² weeks 1 and 5 of the Radiation
- Surgery at 4-6 weeks
- 5-FU 500 mg/m² (bolus) q 4 weeks

CAO/ARO/AIO-94

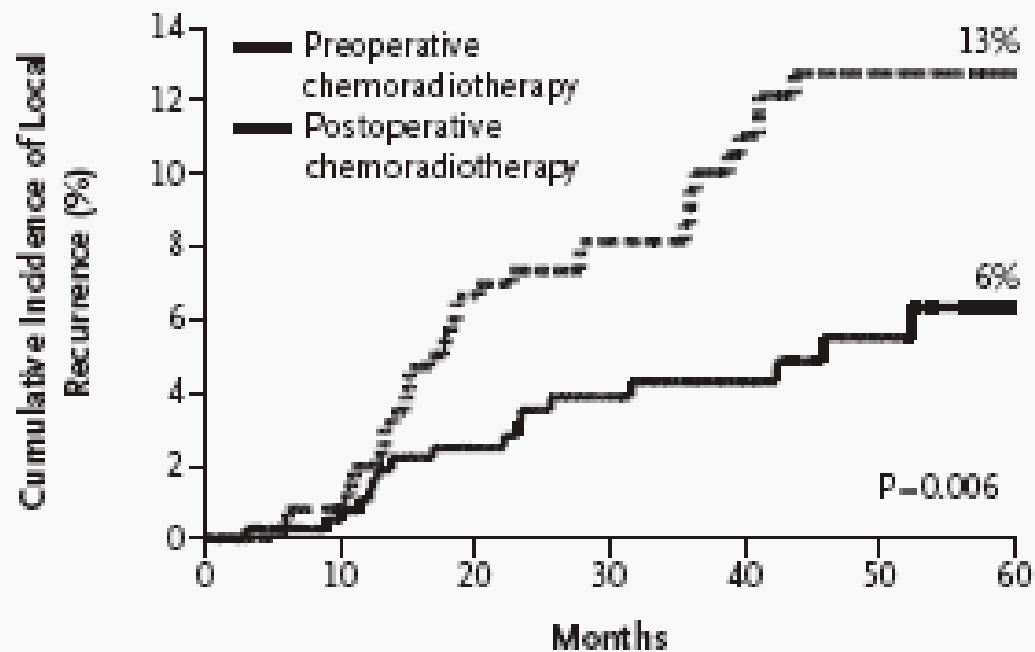
Preoperative versus Postoperative Chemoradiotherapy

Table 4. Rates of Sphincter-Sparing Surgery in 194 Patients Determined by the Surgeon before Randomization to Require Abdominoperineal Resection, According to Actual Treatment Given.

Variable	Preoperative Chemoradiotherapy (N= 415)	Postoperative Chemoradiotherapy (N= 384)	P Value
Abdominoperineal resection deemed necessary — no. (%)	116 (28)	78 (20)	
Sphincter-preserving surgery performed — no./total no. (%)	45/116 (39)	15/78 (19)	0.004

CAO/ARO/AIO-94

Preoperative versus Postoperative Chemoradiotherapy



No. at Risk

Preoperative chemo-radiotherapy	397	368	312	250	190	133	97
Postoperative chemo-radiotherapy	384	351	299	240	184	135	85

CAO/ARO/AIO-94

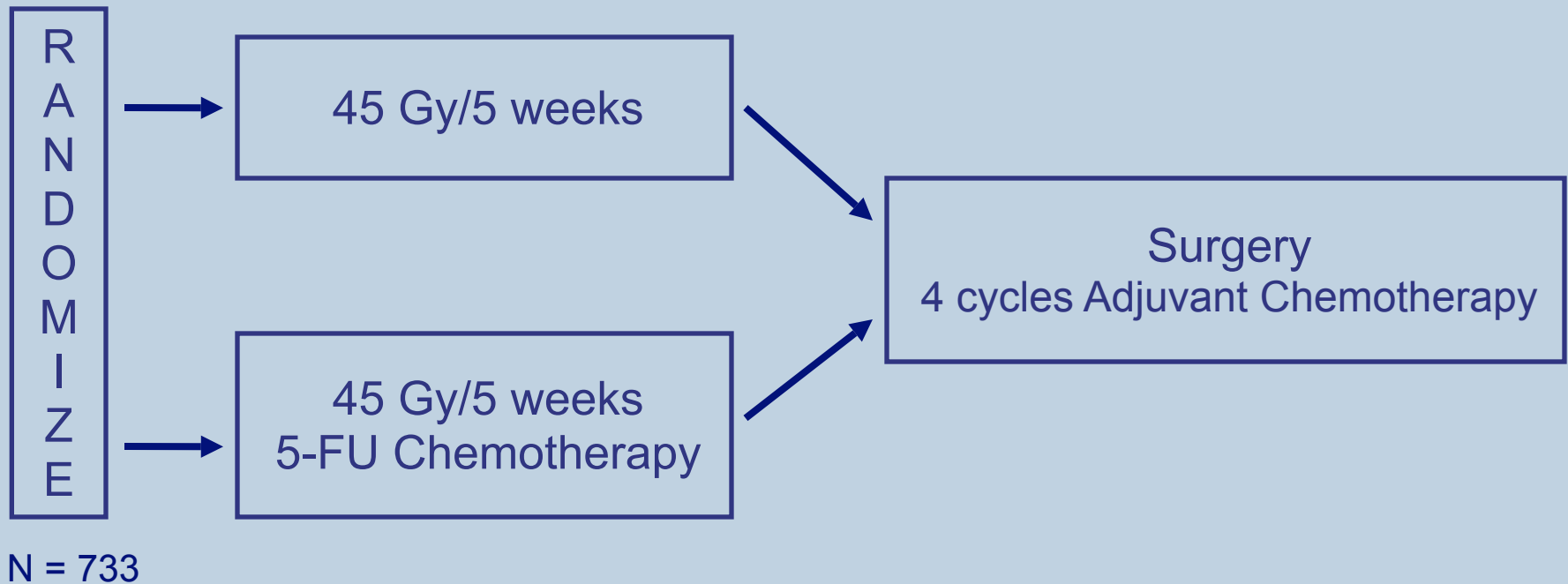
Preoperative versus Postoperative Chemoradiotherapy

- Conclusions
 - Sphincter preservation is improved. . .
 - Survival is similar . . .
 - Toxicity may be improved . . .
 - Differences in local failure . . .

Pre-operative Radiotherapy \pm 5-FU/Folinic Acid in T3-T4 Rectal Cancers: Results of the FFCD 9203 Randomized Trial

J Gerard, F. Bonnetain, T Conroy, O Chapet, O Bouche, M Closon-Dejardin, M Untereiner, B Leduc, E Francois and L Bedenne

FFCD 9203 Schema



FFCD 9203

Results

	XRT	Chemo-XRT	
Local Failure	16.5%	8.1%	<i>P</i> = .004
PFS (5-year)	55.5%	59.4%	HR = 0.96
OS (5-year)	67.9%	67.4%	<i>P</i> = .684

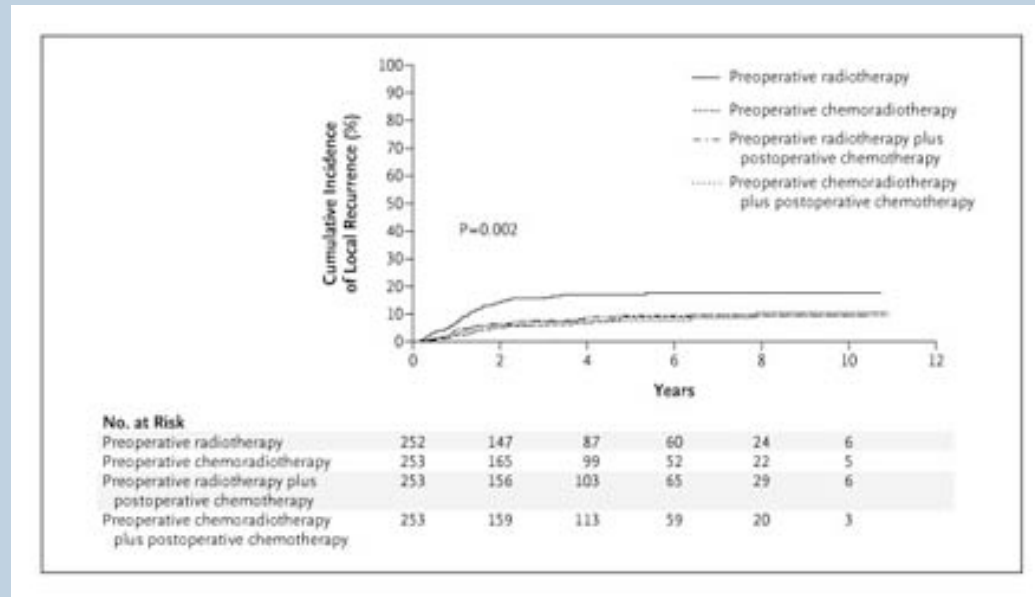
Chemotherapy with Preoperative Radiotherapy in Rectal Cancer

Jean-François Bosset, M.D., Laurence Collette, Ph.D., Gilles Calais, M.D., Laurent Mineur, M.D., Philippe Maingon, M.D., Ljiljana Radosevic-Jelic, M.D., Alain Daban, M.D., Etienne Bardet, M.D., Alexander Beny, M.D., Jean-Claude Ollier, M.D., for

EORTC Radiotherapy Group Trial 22921

N Engl J Med. 2006 Sep 14;355(11):1114-23

Chemotherapy with Preoperative Radiotherapy in Rectal Cancer



Cumulative Incidence of Local Recurrence as a First Event.

17.1% - preoperative-radiotherapy

8.7% - preoperative-chemoradiotherapy

9.6% - preoperative radiotherapy / postoperative chemotherapy

7.6% - preoperative chemoradiotherapy / postoperative chemotherapy.

RTOG-0247 Schema

Randomized Phase II Trial

Arm 1

Capecitabine 600 mg/m² x 5 days
Irinotecan 50 mg/m² d 1, 8, 22, 29
EBRT 45 Gy + 5 Gy Boost



Surgery



mFOLFOX6 x 9 Cycles

Arm 2

Capecitabine 825 mg/m² x 5 days
Oxaliplatin 50 mg/m² d 1, 8, 15, 22, 29
EBRT 45 Gy + 5 Gy Boost



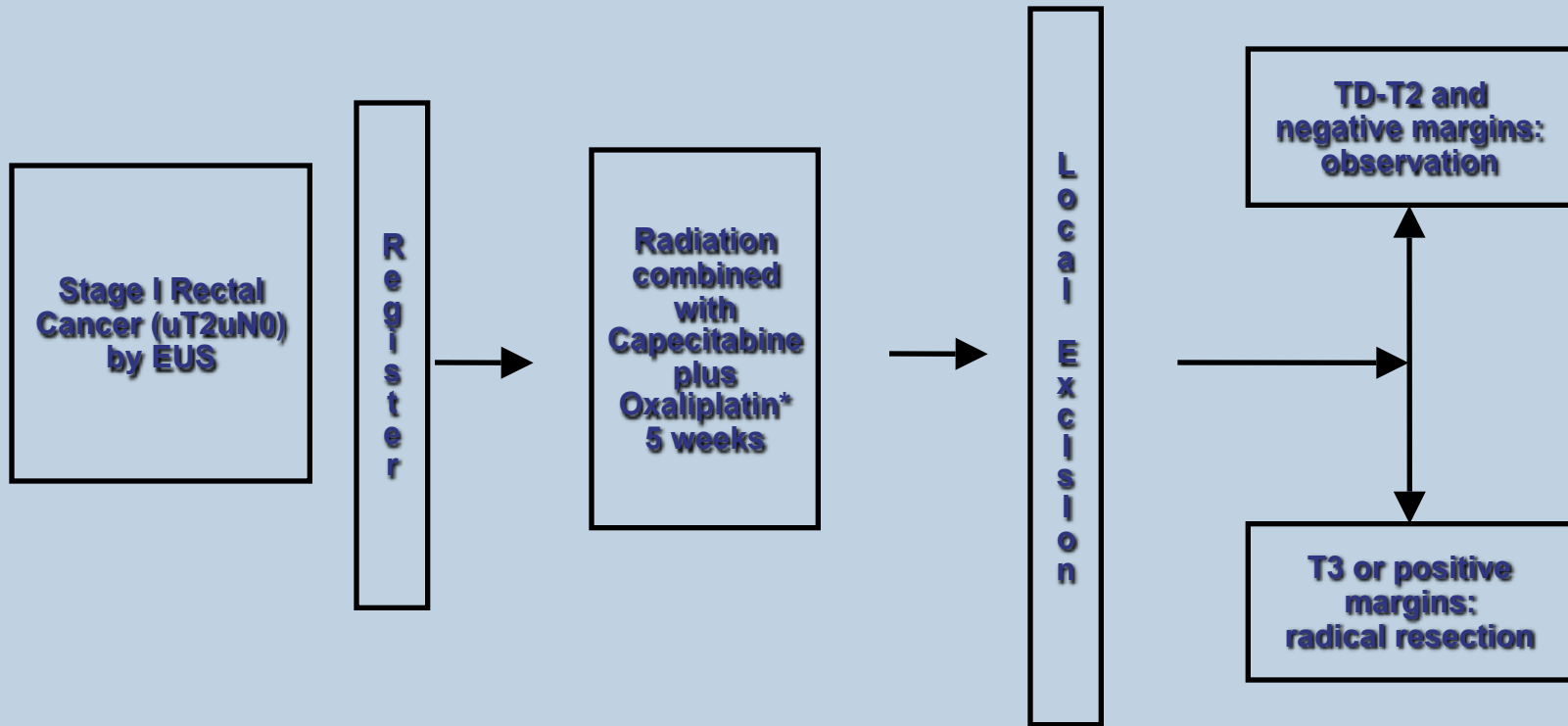
Surgery



mFOLFOX6 x 9 Cycles

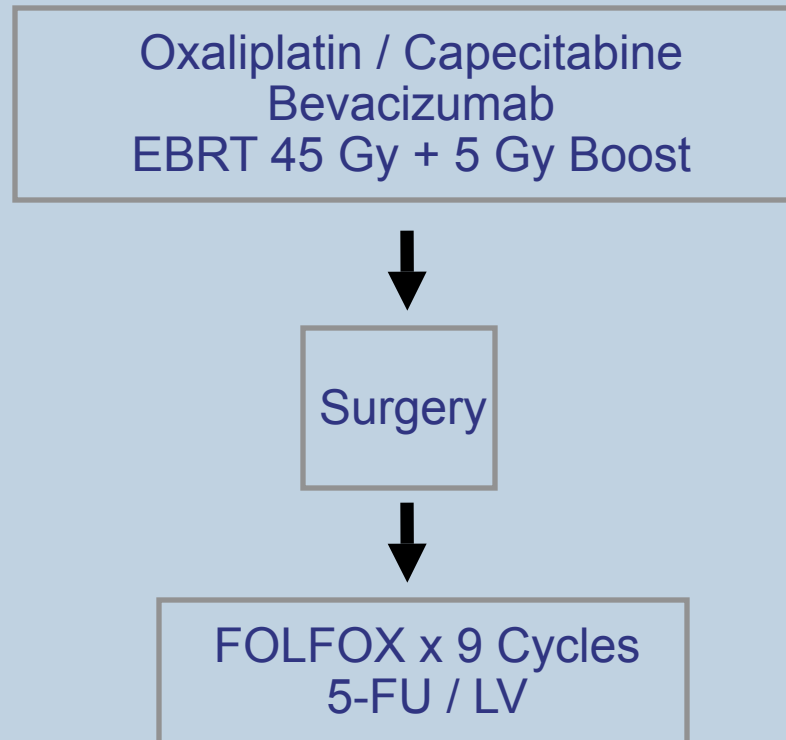
ACOSOG Z6041 Schema

Neoadjuvant Chemoradiation and Local Excision for uT2uN0 Rectal Cancer



ECOG-3204 Schema

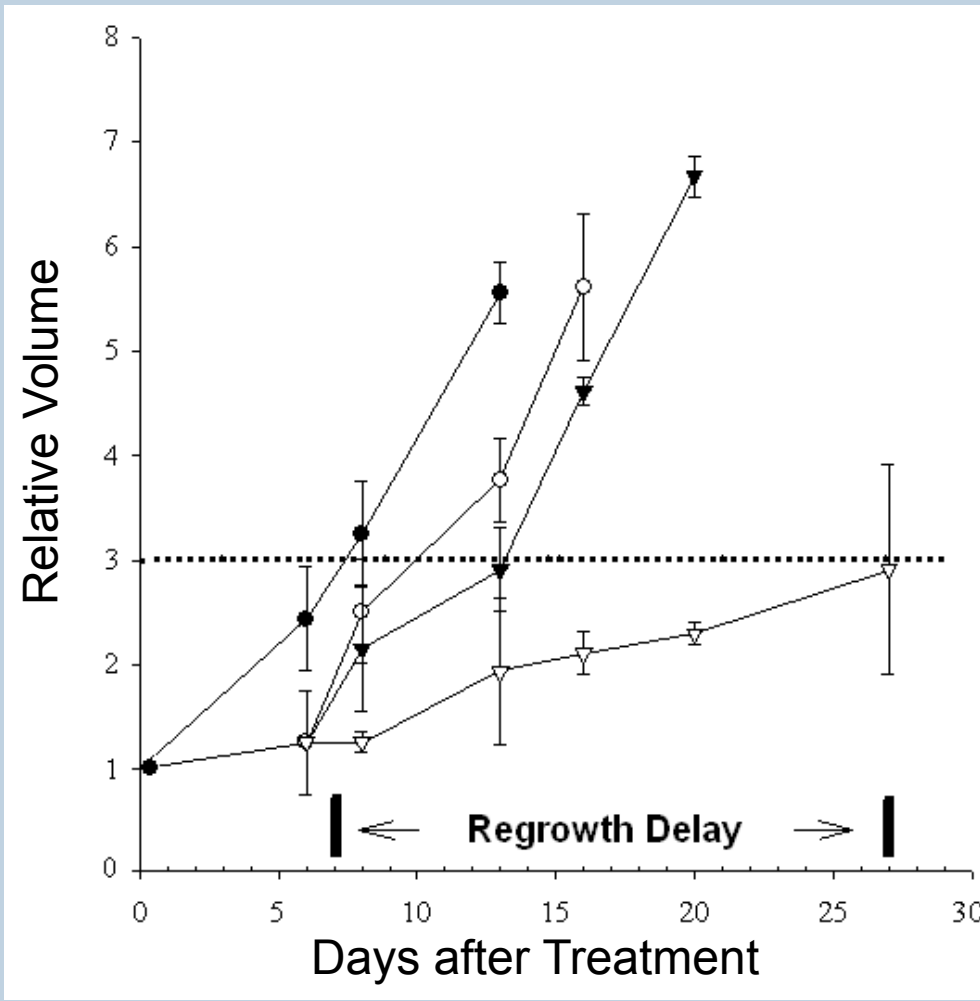
Phase II Trial



Phase I/II Study of Preoperative Oxaliplatin,
Fluorouracil, and External-Beam Radiation Therapy in
Patients With Locally Advanced Rectal Cancer:
Cancer and Leukemia Group B 89901

David P. Ryan, Donna Niedzwiecki, Donna Hollis, Brent E.
Mediema, Scott Wadler, Joel E. Tepper, Richard M. Goldberg,
Robert J. Mayer

Effect of Treatment with Oxaliplatin and Radiation on HT-29 Human Colon Tumor Xenografts Grown in Nude Mice



- The mice received either:
- No treatment
 - Radiation alone
 - ▼ Oxaliplatin 5 mg/kg alone
 - ▽ Radiation 8 h after treatment with oxaliplatin 5 mg/kg

CALGB 89901

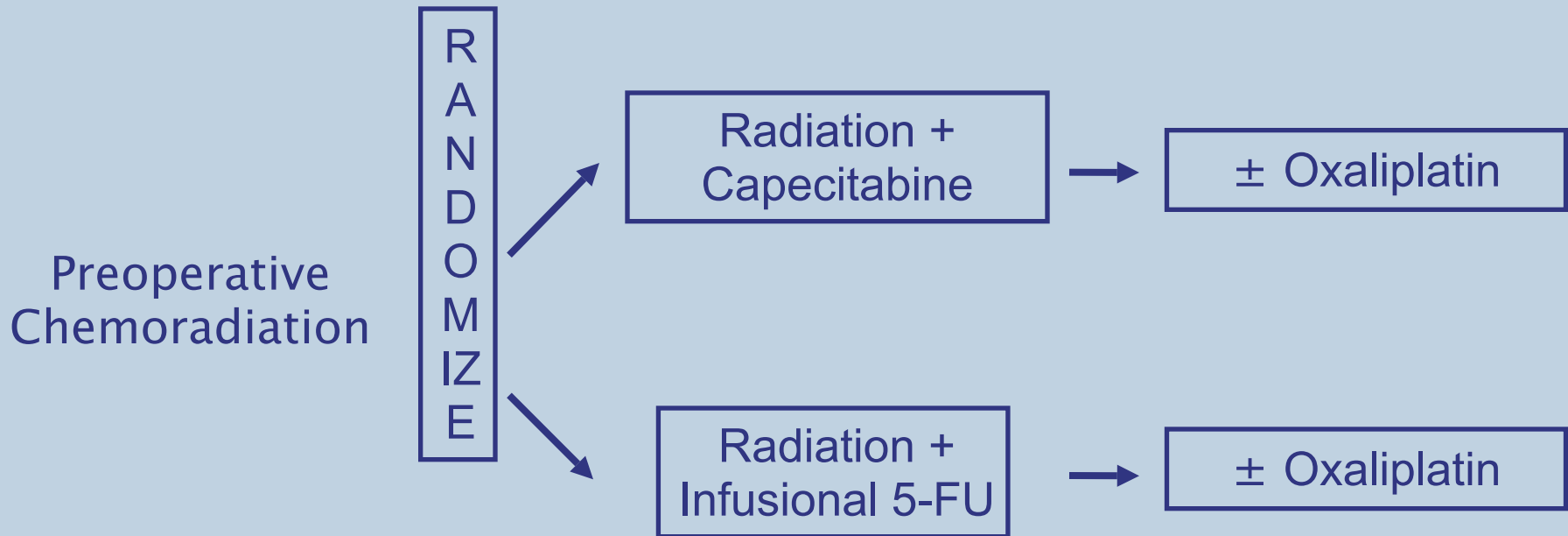
Results

Response	No. of Patients	%
Pathologic response	32*	
Complete response	8	25
ypT1	0	0
ypT2	6	19
ypT3	18	56
Node negative	23	72
R0 resection	30	94

* At Phase II dose

NSABP R-04: Preoperative Chemoradiation in Locally Advanced Rectal Cancer

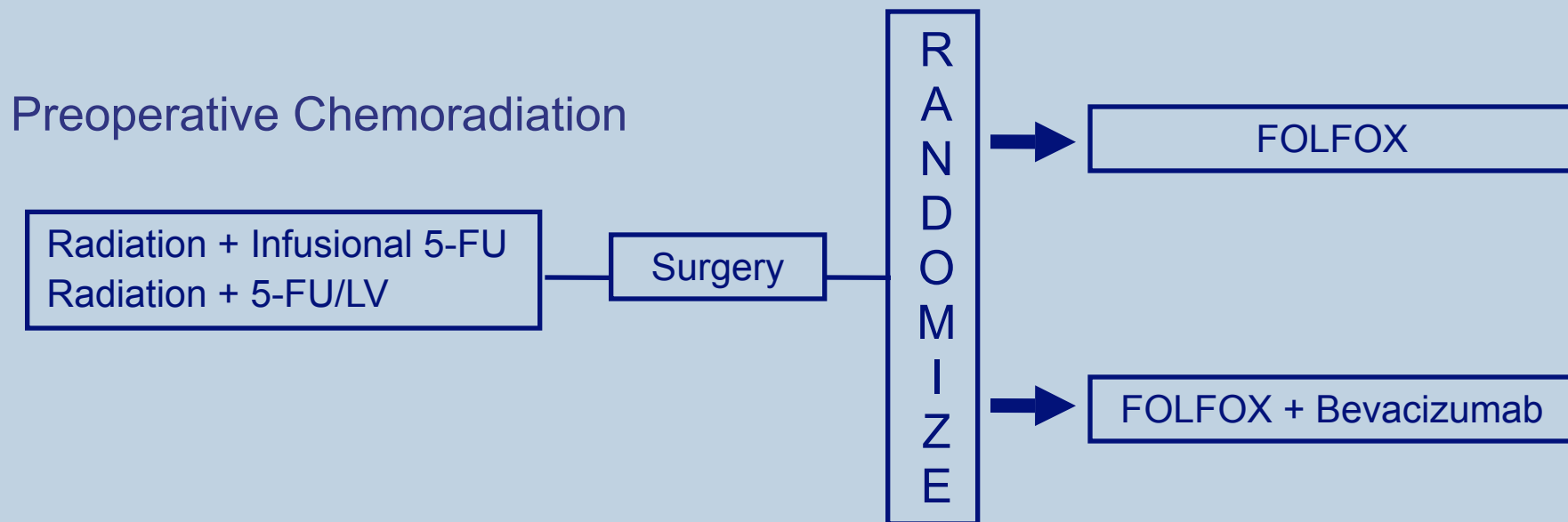
2 X 2 Design



Meropol: RTOG 0247 Trial

- Oxaliplatin 50 mg/m² weekly x 5 (concurrently w/RT)
- Capecitabine 825 mg/m² BID 5 days out of 7 (weekends off)
- 5-FU 225 mg/m² CI, 5 days/wk
- RT 4500 cGy in 25 fx over 5 wks + 540 cGy boost for non-fixed tumors (3 fx)
or 1,080 cGy boost for fixed tumors (6 fx)

ECOG 5204: Randomized Phase III Study of Postoperative Oxaliplatin, 5-Fluorouracil and Leucovorin vs Oxaliplatin, 5-Fluorouracil, Leucovorin and Bevacizumab for Patients with Stage II or III Rectal Cancer Receiving Preoperative Chemoradiation



Next Generation . . .

- Chemoradiation + VEGf Inhibitor
 - Bevacizumab Phase I/II (MD Anderson)
 - Bevacizumab Phase I/II (Duke)

- Chemoradiation + EGFR Inhibitor
 - Cetuximab Phase I/II (Citzo)
 - Erlotinib Phase I/II (MSKCC)
 - Panitumumab Phase I/II



- It's important to know when to quit . . .

The Chair would like to thank the following companies for their generous support of this CME activity.



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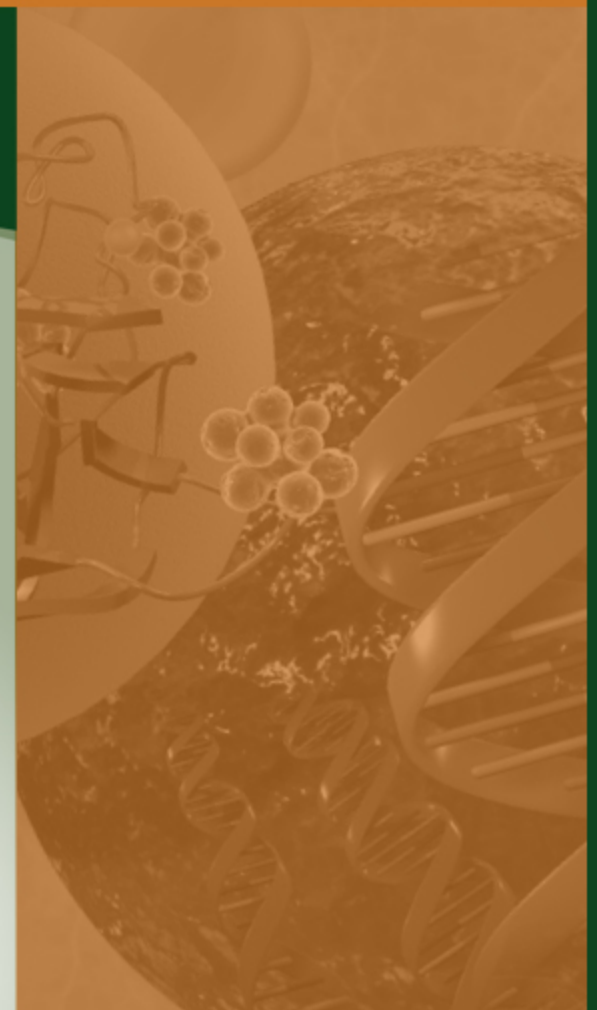
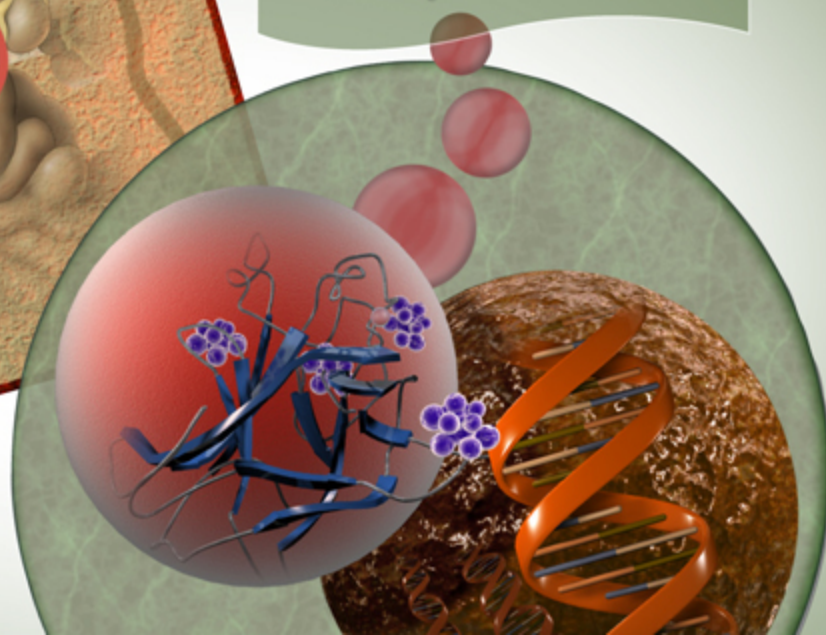
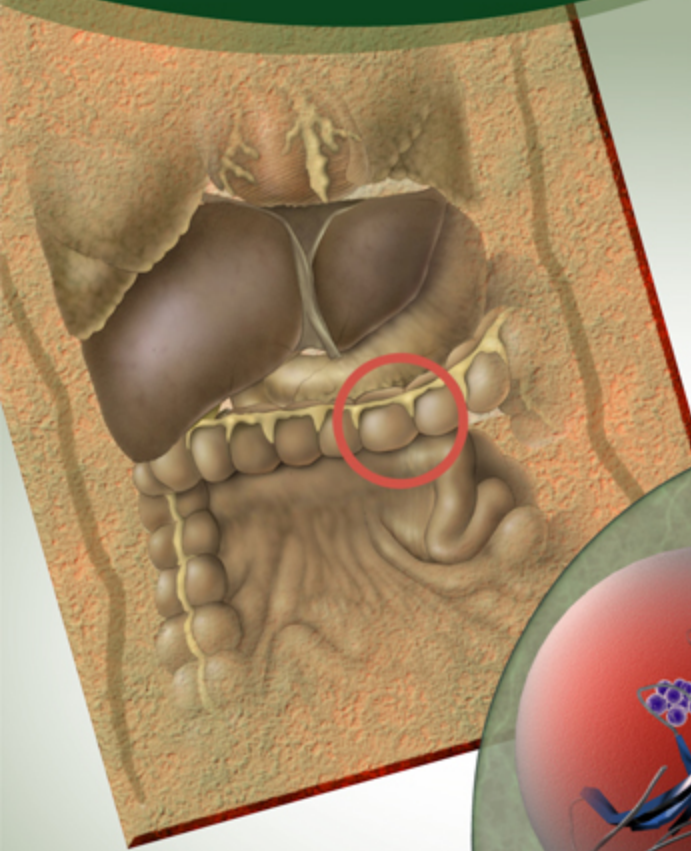
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