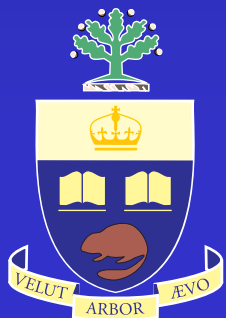


Chemoradiation for Anal Canal Cancer

Early Luck but Slow Progress

B.J. Cummings



Outline

- Background to current standard of RT, 5FU, Mitomycin.
- Randomized clinical trials.
- Unresolved questions.
- Current and future studies.

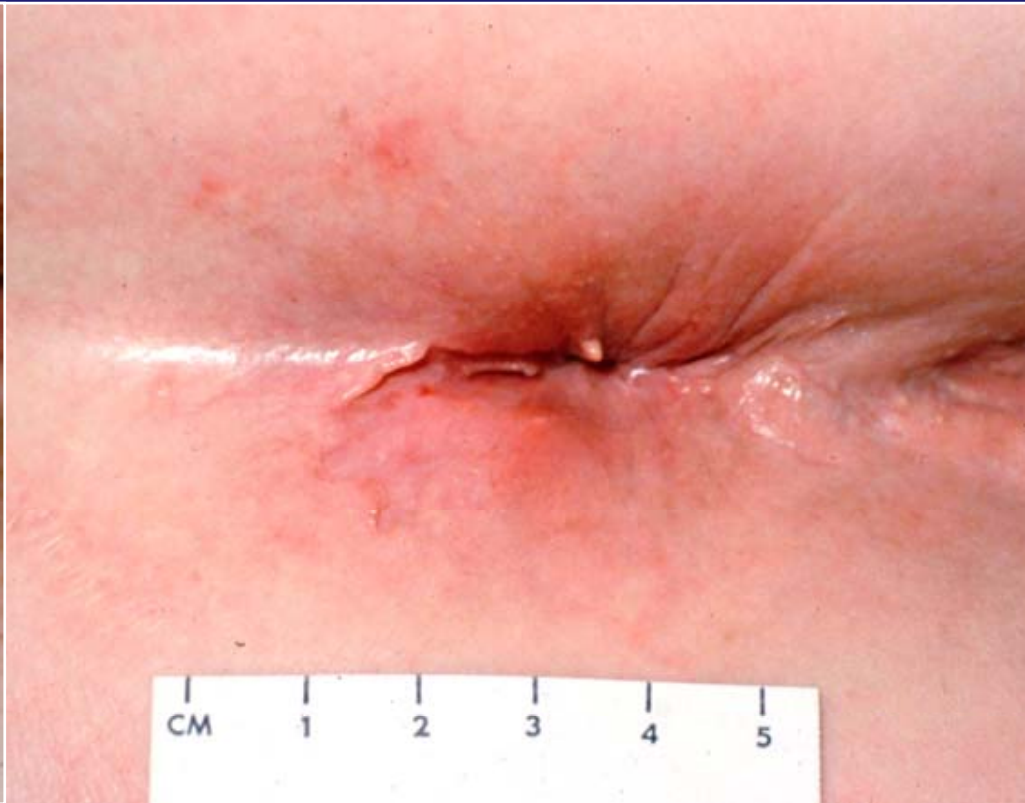
Combined Therapy for Cancer of the Anal Canal: A Preliminary Report*

NORMAN D. NIGRO, M.D.,† V. K. VAITKEVICIUS, M.D.,‡ BASIL CONSIDINE, JR., M.D.§

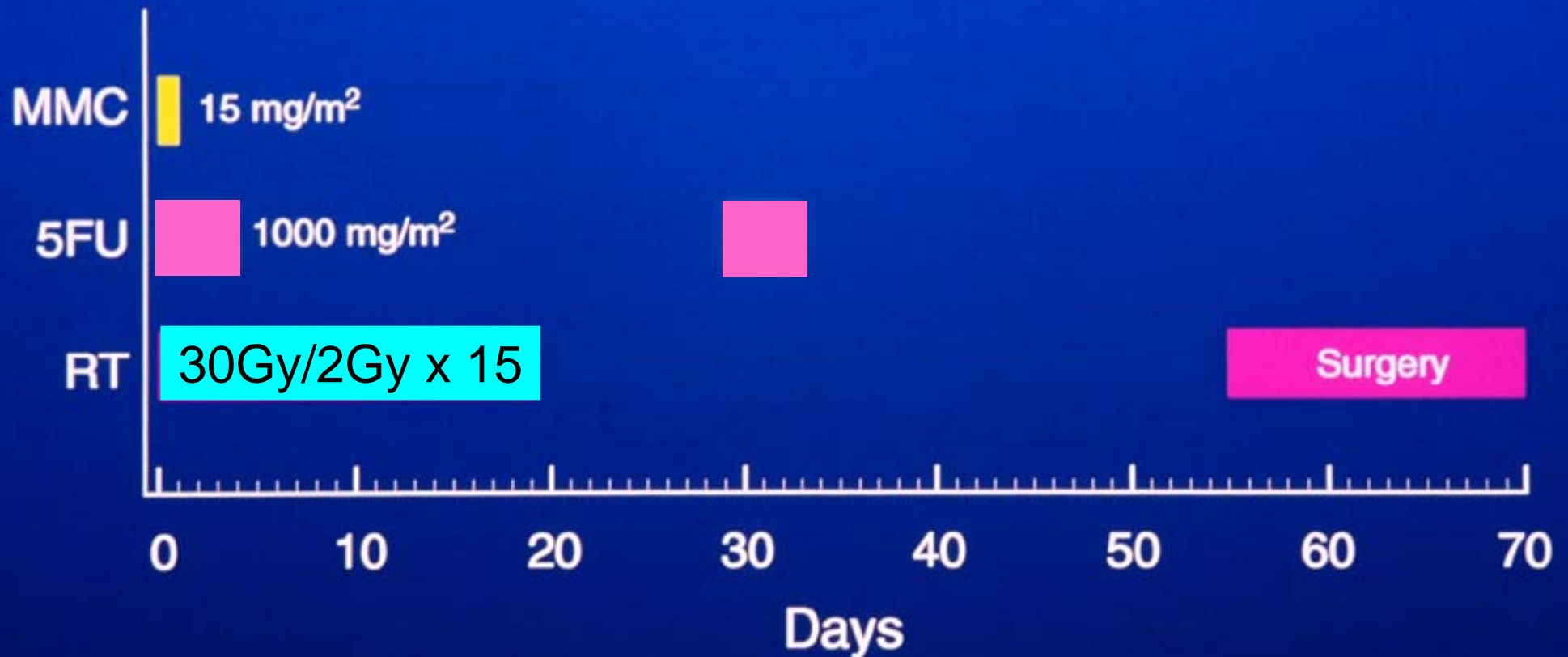
From Wayne State University, School of Medicine, Detroit, Michigan

IN COMPARISON with adenocarcinoma of the rectum, anal cancer is uncommon.² According to Morson,³ one squamous-cell can-

There are causes for the low cure rates even beyond the biologic characteristics of the neoplasm itself. The anatomic features



Anal Canal Cancer—Nigro et al 1974



Background to Nigro Protocol

Laboratory

1. Increased cytotoxicity 5FU plus concurrent RT.

Vietti

2. Effects of bioreductive alkylating agents
(eg Mitomycin) on hypoxic cells.

Liu

Background to Nigro Protocol

Clinical

1. Responses to 5FU and MMC in advanced anal cancer.
Nigro (unpublished)
2. Improved outcome RT and 5FU in GI adenoca.
Moertel
3. Infusional 5FU less marrow toxic than bolus. Seifert

Background to Nigro Protocol

Clinical

4. Nigro et al had designed an identical protocol for preoperative treatment of adenoca rectum.

Radical Radiation with 5FU and Mitomycin

Treatment: 50Gy in 20 fractions in 4 weeks,
5FU 1000mg/m²/24hr continuous
infusion for 96hr Day 1-4
Mitomycin 10mg/m² IV Day 1

Local control: 6/6

Acute toxicity \geq Gd 3: 6/6 Late toxicity \geq Gd 3: 0/6

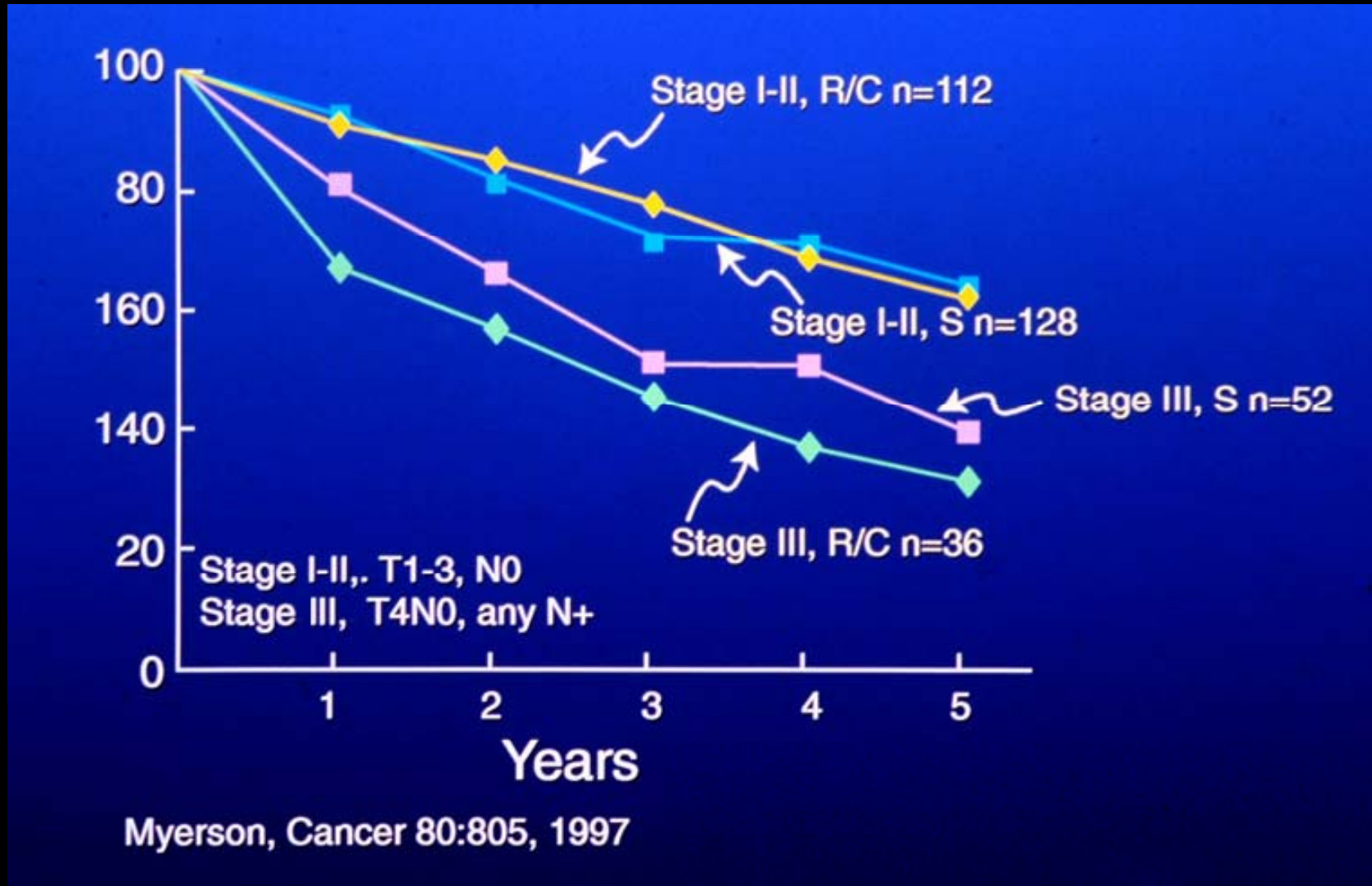
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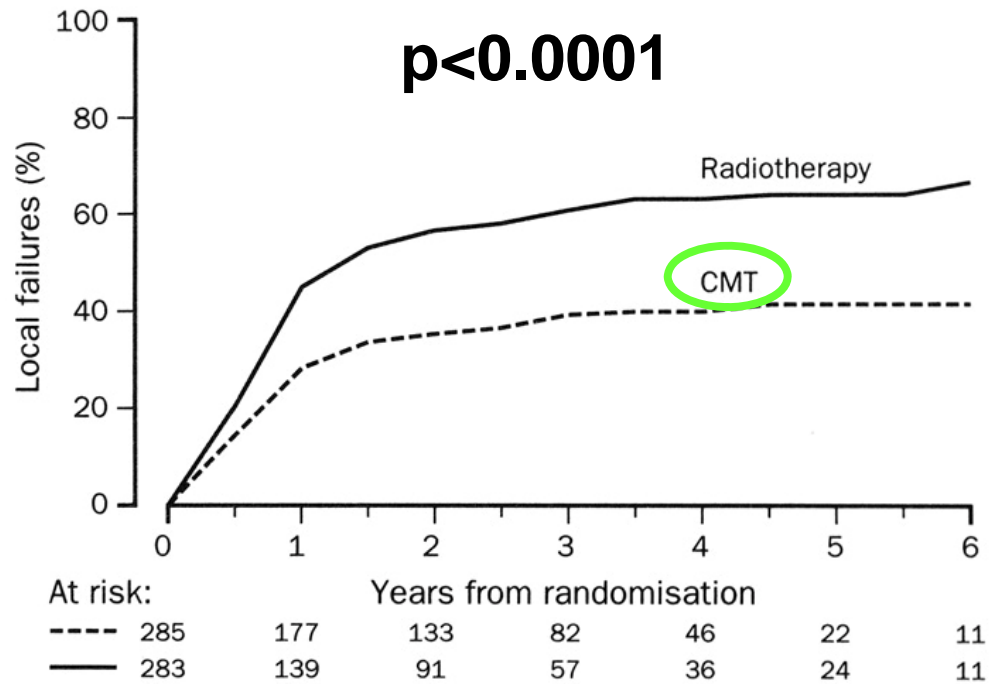
Acute toxicity \geq Gd 3: 6/6 Late toxicity \geq Gd 3: (5/6)

USA National Cancer Data Base Epidermoid Anal Cancer Cases Registered 1988 – Survival Comparable

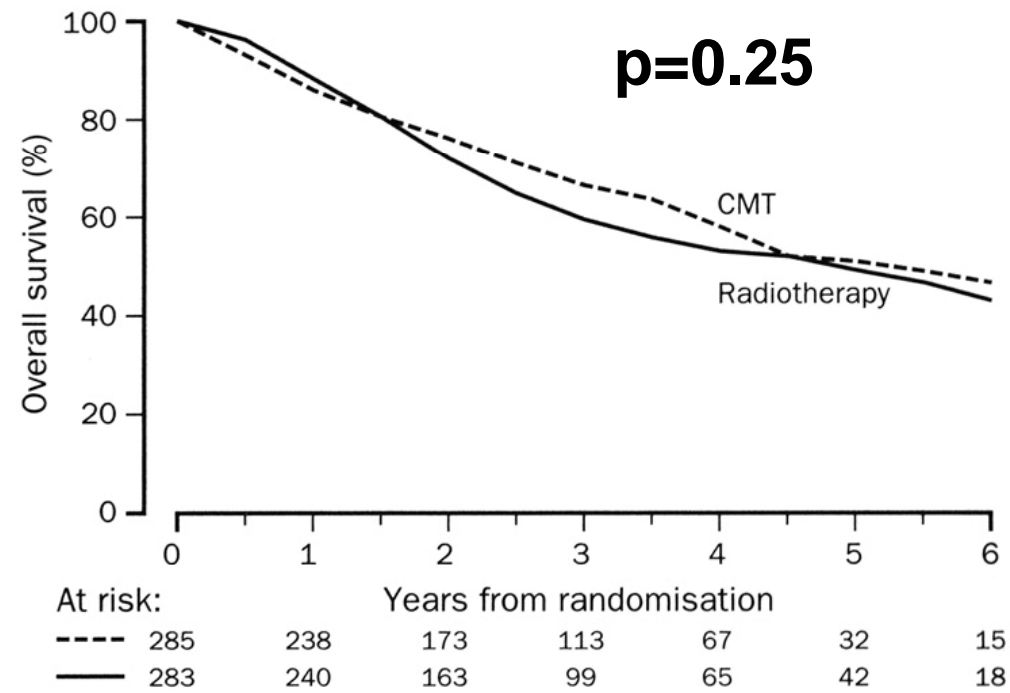


RT + 5FU/Mito vs. RT

Local Failure

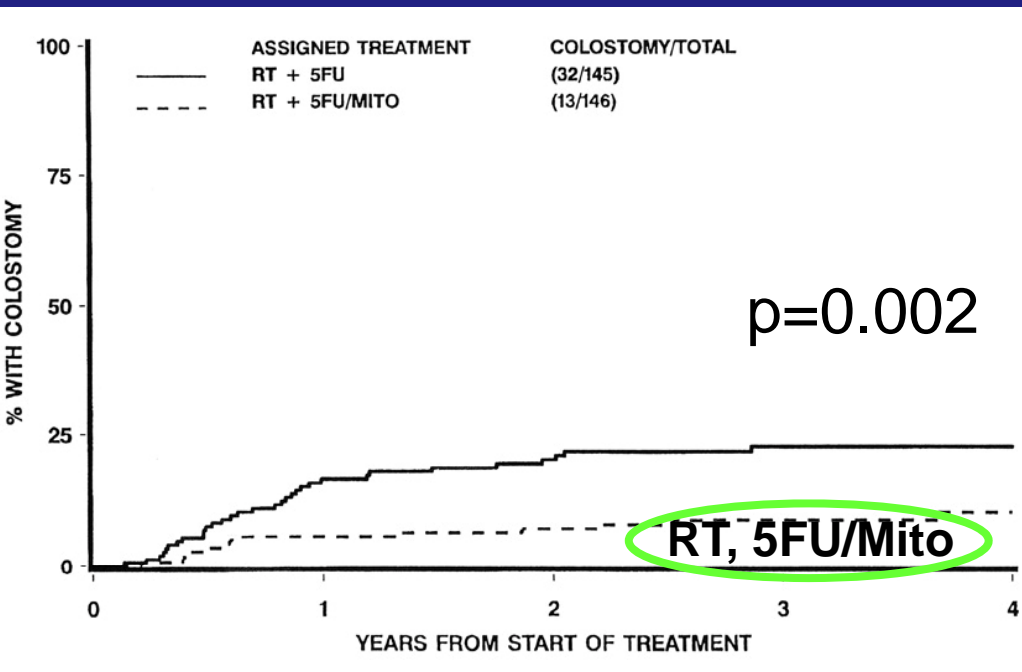


Overall Survival

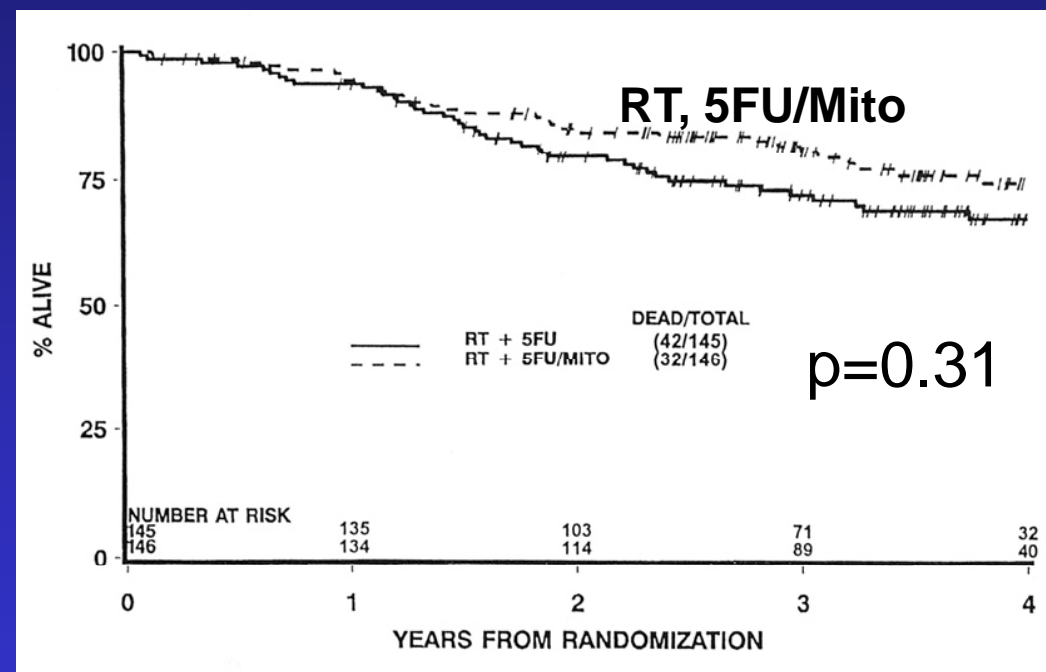


RT + 5FU/Mito vs. RT + 5FU

Time to Colostomy



Overall Survival

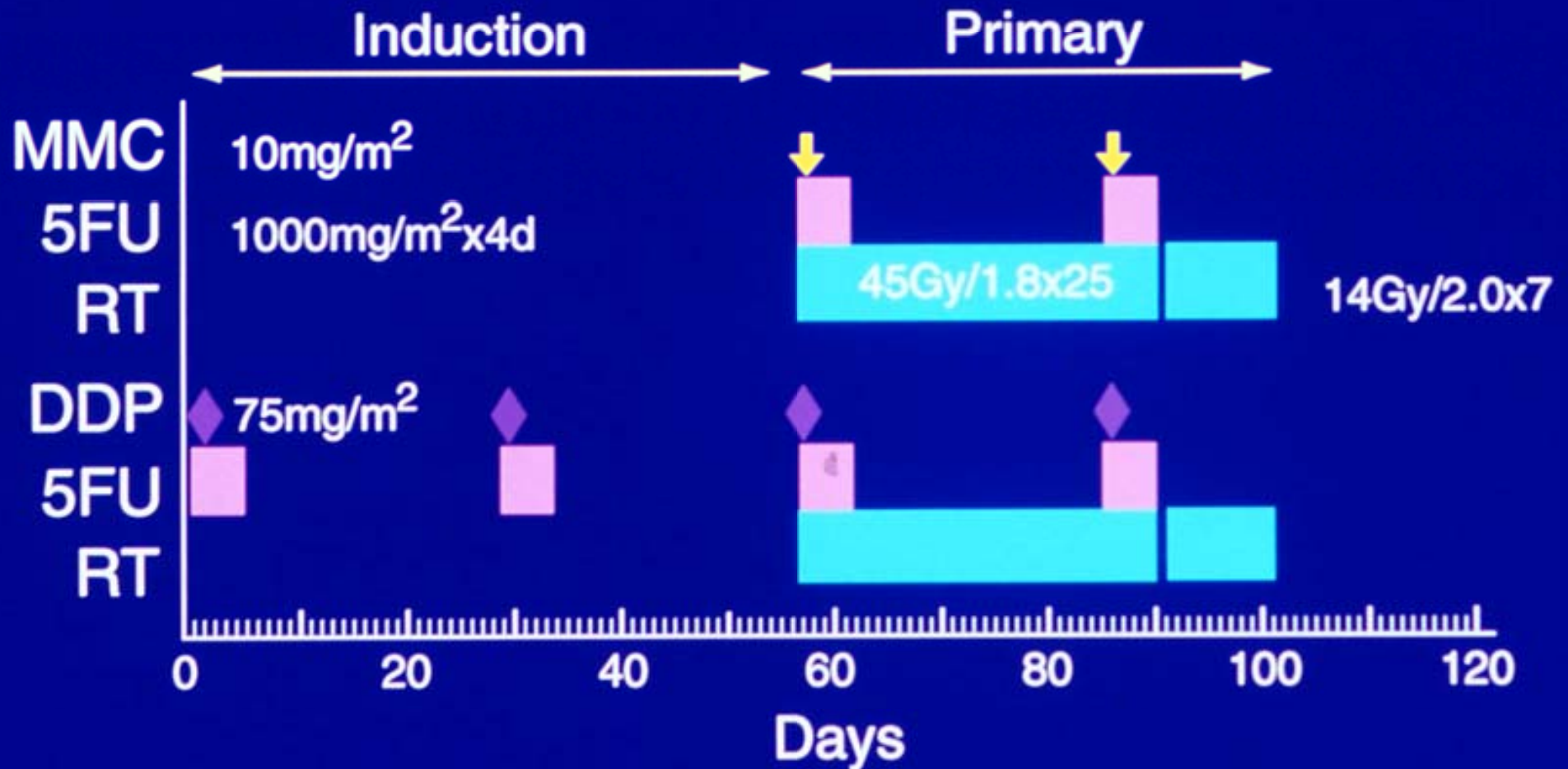


Induction Chemotherapy with 5FU, Cisplatin

Response after Chemo
(percent)

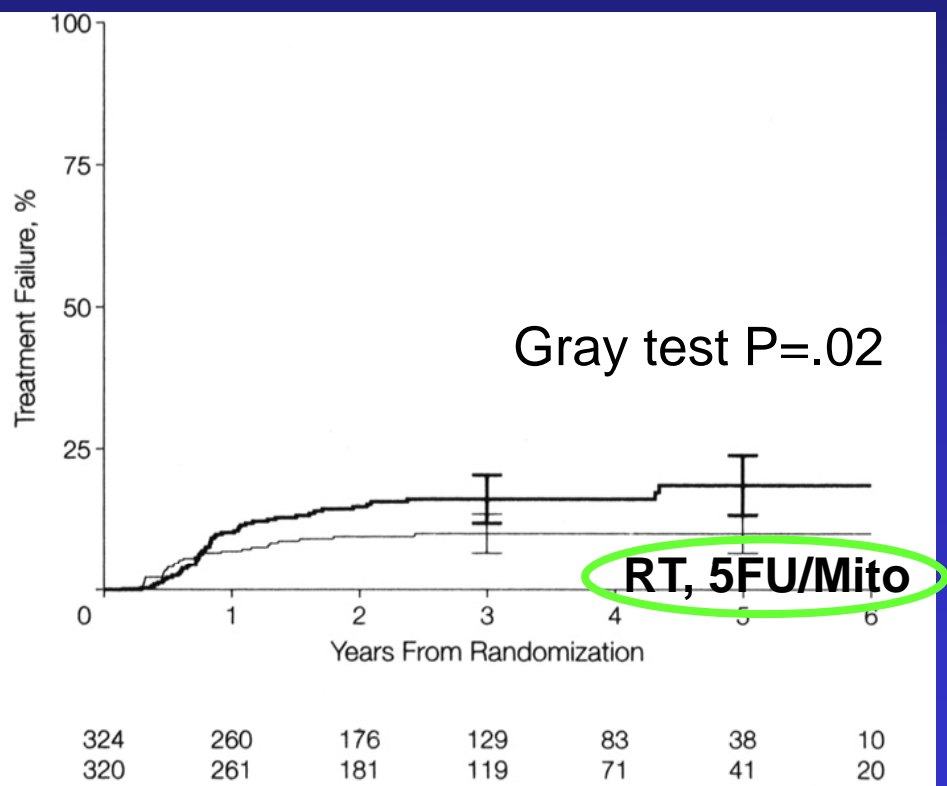
Author	N	CR	PR	Stable	Prog
Brunet 1990	22	27	59	14	0
Meropol 1999	45	18	47	29	2
Peiffert 2001	79	10	49	35	2

RTOG 98II Anal Cancer

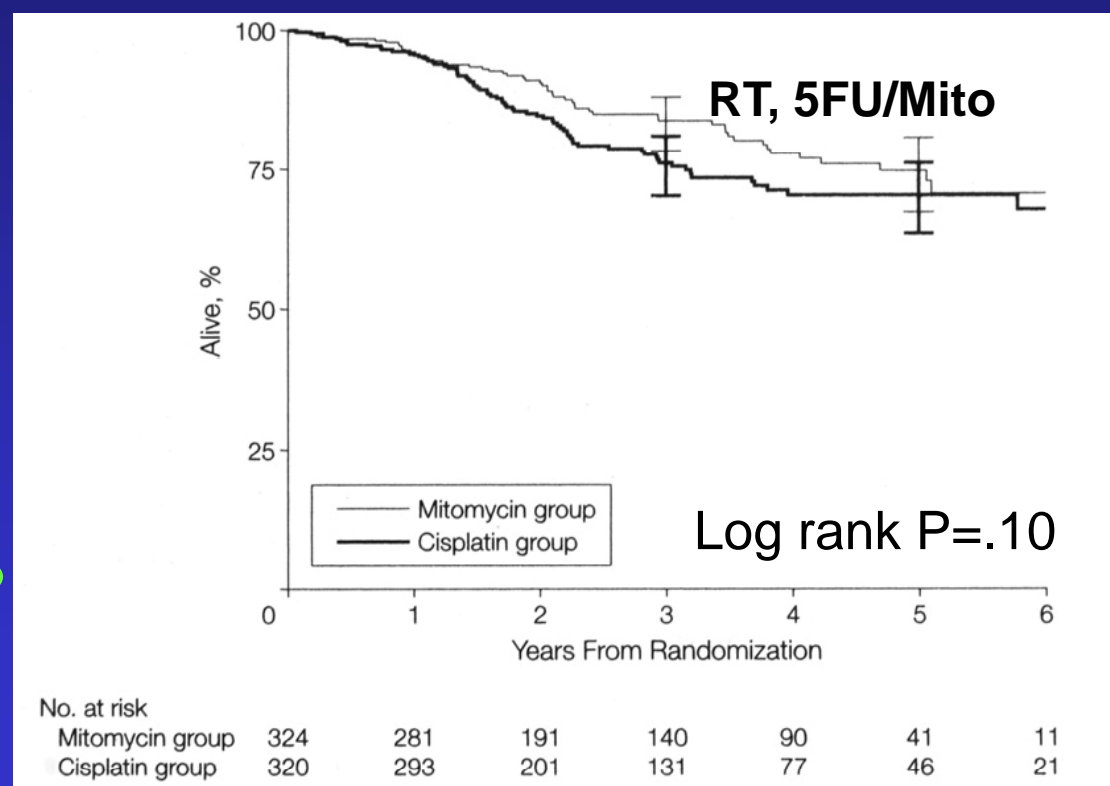


RT + 5FU/Mito vs. RT + 5FU/Cisplat

Time to Colostomy



Overall Survival



Trials in Progress

Phase III

UKCCCR ACT II

1. RT, 5FU, Mitomycin vs RT, 5FU, Cisplatin
2. Adjuvant 5FU, Cisplatin vs No adjuvant

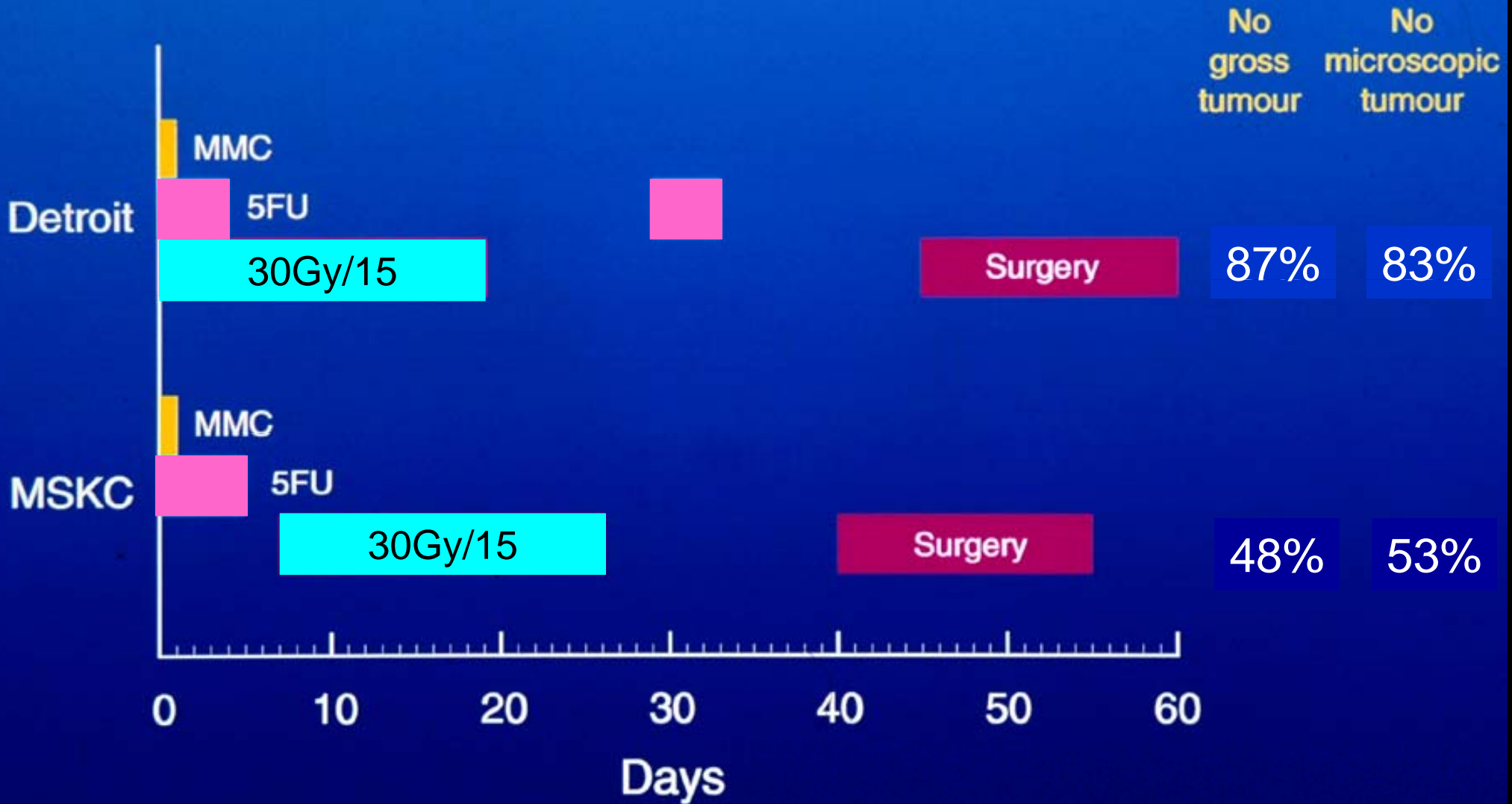
France – FNCLCC

1. Induction 5FU, Cisplatin vs No induction
(5FU, Cisplatin concurrent with RT)
2. Low dose RT (60Gy split) vs High dose RT (70Gy split)

Concurrent Radiation and 5FU Additive or Interactive?

- Byfield et al 1982 In vitro Hela and HT-29 cells
10 day colony formation.
–Time dependent enhancement
(synergism) with post-RT 5FU
- Weinberg and Rauth 1987 Murine scc VII/To
Regrowth delay assay.
–Additive, independent of time

Concurrent vs Sequential Treatment



Radiation Therapy

Dose and Technique Studies

1. Reduce acute and late toxicity (dose, conformal RT, IMRT etc).
2. Establish effective dose by T stage.
3. Shorten overall treatment time (no breaks in radiation).

PMH Sequential Studies

Radiation – 5FU – Mitomycin

Protocol	RT dose per fraction (Gy)	Local Control Number (%)	Late Toxicity ≥ Grade 3 Number (%)
Uninterrupted 50Gy	2.5	14/16 (88)	10 (63)
Split 25Gy x 2	2.5	13/14 (93)	5 (36)
Split 24Gy x 2	2.0	28/33 (85)	1 (4)
Split 27Gy x 2	1.8	42/50 (84)*	3 (6)*
Split 45-63Gy by T size	1.8	65/75 (87)*	4 (6)*
Uninterrupted IMRT	1.8	ongoing	ongoing

Cummings, Int J Radiat Oncol Biol Phys 21:1115, 1991

*analysis in progress

Post Radiation Telangiectasia



Rectum



Skin

Intermediate Grade Late Toxicity Radiation – 5 FU – Mitomycin

	<u>Gr 2</u>	<u>Gr 3</u>	<u>Overall (125)</u>
Skin – atrophy/telangiectasia/fibrosis	65%	15%	80%
Rectum – bleeding/urgency/frequency/ incontinence	57%	8%	65%
Dyspareunia (45/70)	46%	44%	90%

IMRT Technique

3,Phase 3

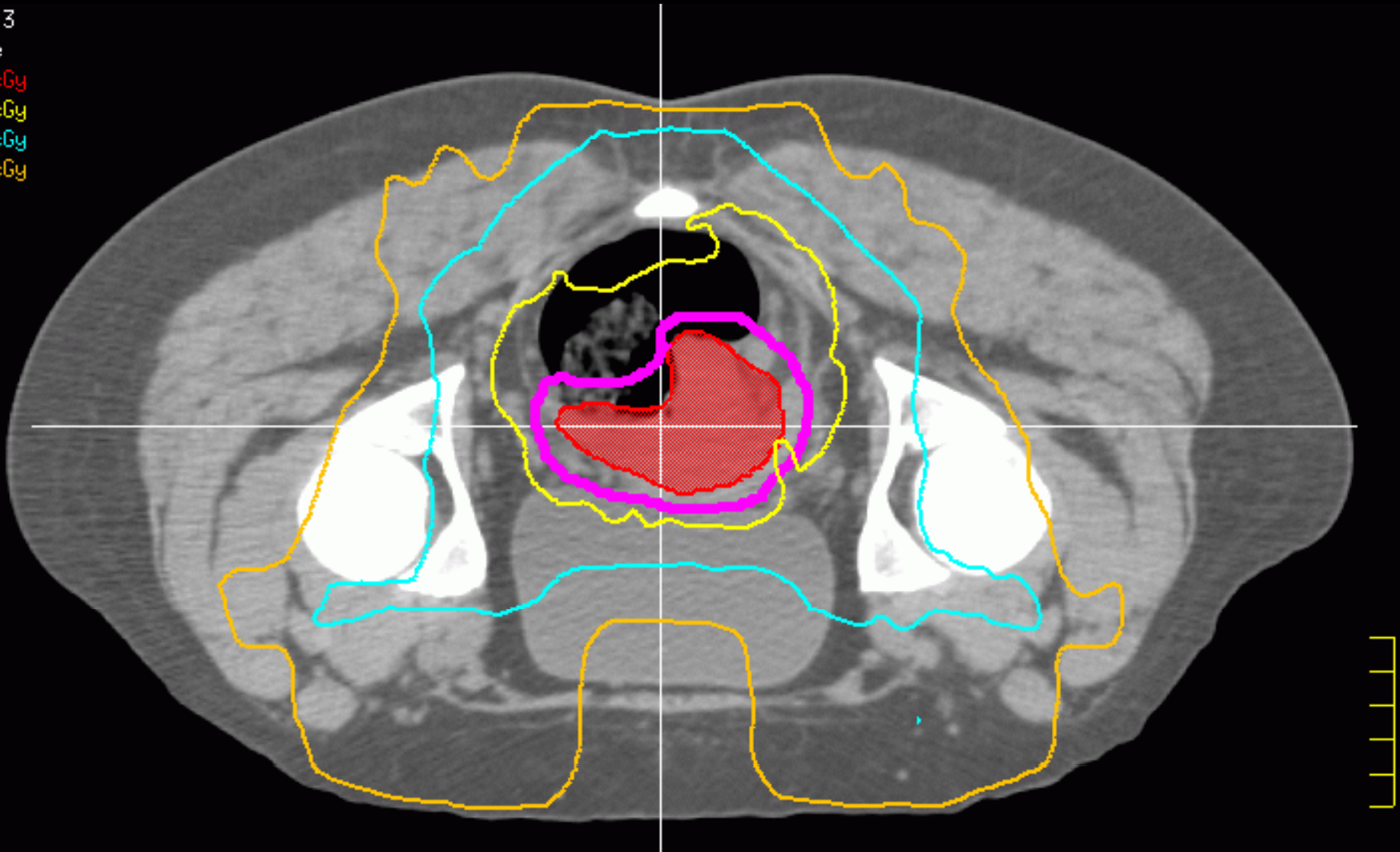
Absolute

6600,0 cGy

6300,0 cGy

5400,0 cGy

4500,0 cGy



Proliferation Parameters of Anal Cancers

Median (Range)

	Anal (n=26)	Cervical (n=101)
Labelling Index (%)	6.8 (0.9 – 35.7)	6.7 (1.4 – 36.1)
T _{pot} (days)	4.1 (0.9 – 30.0)	5.5 (1.2 – 42.1)
S-phase fraction (%)	8.2 (1.0 – 54.2)	15.1 (0.6 – 64.7)
T _s (hours)	7.7 (5.8 – 22.1)	9.9 (5.6 -29.2)

Trials in Progress

Phase III

EORTC

RT, 5FU, Mitomycin vs RT, Mitomycin, Cisplatin

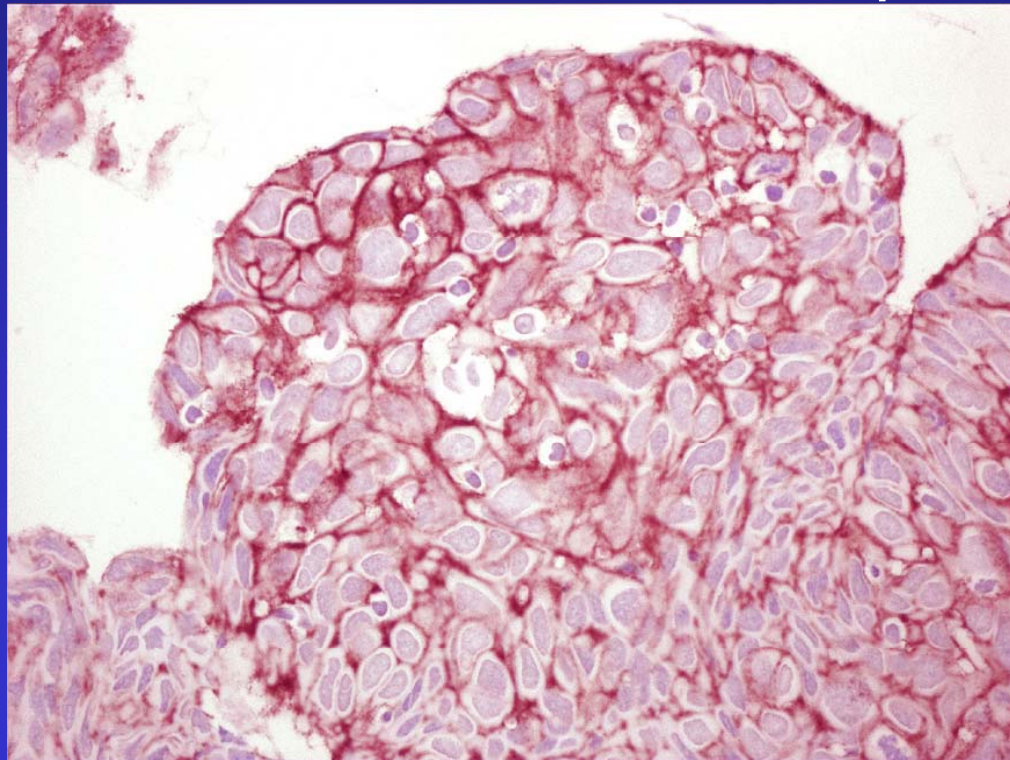
EGFR Receptor Expression in Anal Cancer

EGFR Expression

21/21 (100%)

Degree of Expression

4+ (>75% cells stain positive)



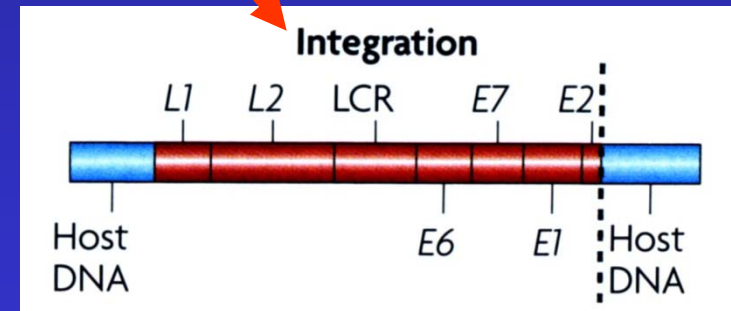
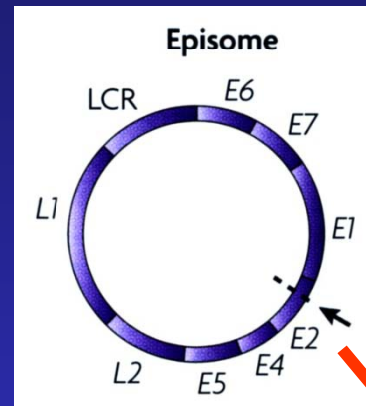
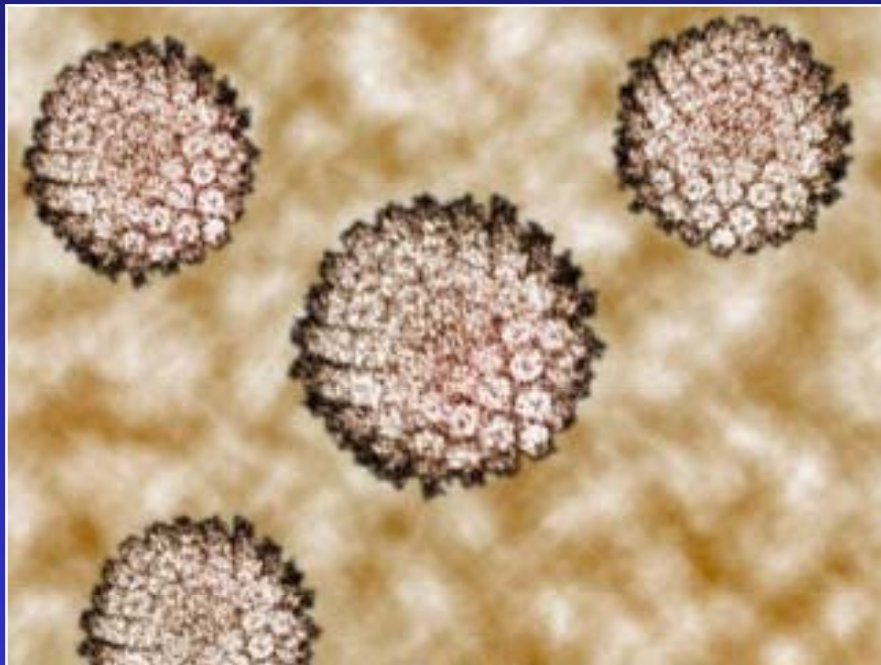
Trials in Progress

Phase II

Country	Treatment
USA	5FU, Cisplatin, Cetuximab, RT
USA	Capecitabine, Oxaliplatin, RT

Human Papilloma Virus

High risk HPV. Anal canal ca 80%; Perianal ca 60%
HPV 16 – 70%; HPV 18 – 10%; HPV 31, 33 etc <10%



Potential for prophylactic and/or therapeutic vaccines?

5 Year Relative Survival Rates SEER Program, USA

	Men	Women	(Approx. Colostomy Rate)
1973-1979	0.60	0.59	(0.95)
1994-2000	0.61	0.73	(0.25)

Johnson, Cancer 2004; 101:281

The current standard treatment
is Radiation Therapy with
concurrent 5FU and Mitomycin.

