Summer Institute in Statistics for Clinical Research

Exploratory Analyses: Why Do We Need Particular Caution?

July 26, 2019

Thomas R. Fleming, Ph.D.
Professor, Dept. of Biostatistics
University of Washington

* Fleming TR "Clinical Trials: Discerning Hype from Substance"
- *Annals of Internal Medicine* 2010; 153:400-406

Data Driven Hypothesis for the Cancer Risk with Vytorin in Aortic-Valve Stenosis

- **SEAS Trial**

	N	CA. Incidence	CA. Deaths
Vytorin	944	101	37
Placebo	929	65	20
Relative Risk:		**1.55**	**1.78**
95% C.I.:		(1.13, 2.12)	(1.03. 3.11)

- **IMPROVE-IT & SHARP Trials**

	N	CA. Incidence	CA. Deaths
Vytorin	10,391	313	97
Control	10,298	326	72
Relative Risk:		**0.96**	**1.34**
95% C.I.:		(0.82, 1.12)	(0.98, 1.84)

Interest in "Positive" Results in Clinical Trials

- Industry Sponsors
  - ~ Company profits, ↑ value of stock options, promotion
- Government Sponsors
  - ~ Claims of success in advancing health care
  - ~ Leverage for ↑ in federal funding
- Journal Editors (Publication bias)
- Academic Investigators / Caregivers
  - ~ Increased ability to publish results
    - ↑ professional stature, earlier promotion, ↑ salary
  - ~ Desire to offer more therapeutic options to patients

….Result: *Wide Spread & Significant Conflicts of Interest*

Bias for "Positive" Results in Clinical Trials

~ What is the definition of a

successful clinical trial?

➢ A very common response:

"A clinical trial that achieves a *positive* result"

Bias for "Positive" Results in Clinical Trials

~ What is the definition of a

successful clinical trial?

- A very common response:

  "A clinical trial that achieves a *positive* result"

- The proper scientific response:

  "A clinical trial that

  addresses a clinically important issue,

  and that *reliably answers* the questions

  it was designed to address"

Confirmatory vs. *Exploratory* Analyses

- Hyp. Confirmation vs. Hyp. Generation
  - ~ Post-hoc analyses & Random High Bias
    (new endpoints, new analyses, interim analyses
    subgroup analyses, covariate adjustments)

Confirmatory vs. *Exploratory* Analyses

- Clinical Endpoints in Pulmonary Arterial Hypertension
  - ~ Overall survival
  - ~ Quality of Life: SF-36 (8 domains), Borg Dyspnea Score
- ~ NYHA Functional Class
  - ~ **6MWT**: @18 wk, **24 wk**, 48 wk, etc.
  - ~ Time to Clinical Worsening
    - ✓ Death, PAH Hosp, L.T., (NYHA↑ & 6MWT↓)
- Analysis Methods
  - ~ Normally distributed: **T-test**, ANCOVA, Wilcoxon
  - ~ Time to event: Log-rank, Cox Regression
  - ~ Dichotomous: Fisher's Exact Test, Pearson χ^2

Confirmatory vs. *Exploratory* Analyses

- Biomarker Endpoints (Hemodynamic parameters)
  - ~ Pulmonary Arterial Pressure
  - ~ Systolic & Diastolic Systemic Arterial Pressure
  - ~ Systemic & Pulmonary Vascular Resistance
  - ~ Heart Rate & Cardiac Output
- Analyses over Calendar Time
- ~ Normally distributed: T-test, ANOVA, Wilcoxon
- ~ Time to event: Log-rank, Cox Regression
  ~ Dichotomous: Fisher's Exact Test, Pearson $\chi 2$

Confirmatory vs. *Exploratory* Analyses

- Subgroup Analysis & Prognostic Covariate Adjustment

  ~ WHO PAH Functional Class: I v II v III v IV

  ~ Etiology: Idiopathic PAH, Assoc w CTD, SLE, Other

  ~ Baseline Walking Distance: < 325 v > **325 meters**

  ~ Gender: male v female

  ~ Age: By decade

  ~ Ethnicity: White v Black v Asian v Other

  ~ mean PAP: < 50 v > 50

Epoprostenol +/– Sildenafil

Confirmatory vs. *Exploratory* Analyses

- Hyp. Confirmation vs. Hyp. Generation
  - ~ Post-hoc analyses & Random High Bias
    (new endpoints, new analyses, interim analyses
    subgroup analyses, covariate adjustments)

Illustrations and Motivation:

Confirmatory vs. *Exploratory* Analyses

- Hyp. Confirmation vs. Hyp. Generation
  - ~ Post-hoc analyses & Random High Bias
    (new endpoints, new analyses, interim analyses
    subgroup analyses, covariate adjustments)

Illustrations and Motivation:

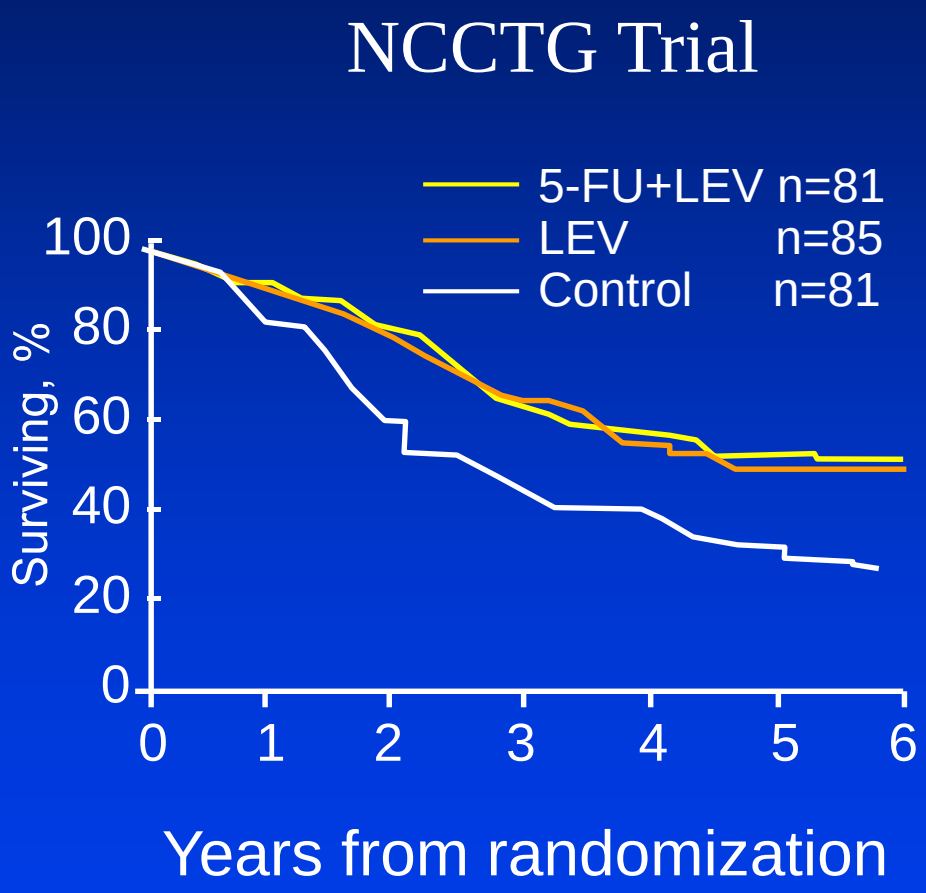
Maternity Wards, Baseball & Clinical Research

20 vs 2: (.71, .99), 2p = 0.0001

An Illustration of Exploratory Analyses: Post-hoc Subgroup Analyses

Surgical Adjuvant Therapy of Colorectal Cancer

Surgical Adjuvant Therapy: Colorectal Cancer



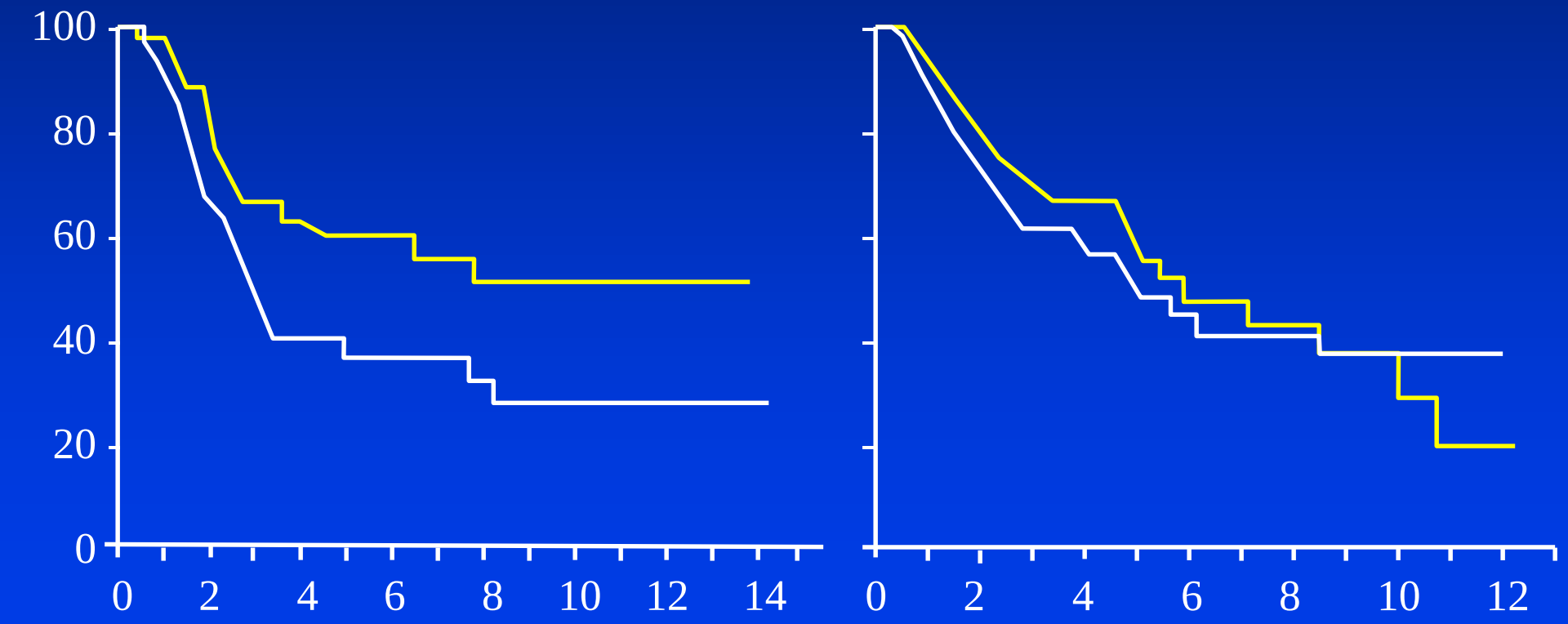
NORTH CENTRAL TREATMENT GROUP STUDY
Looking at Treatment Effect on Overall Survival

Females Only

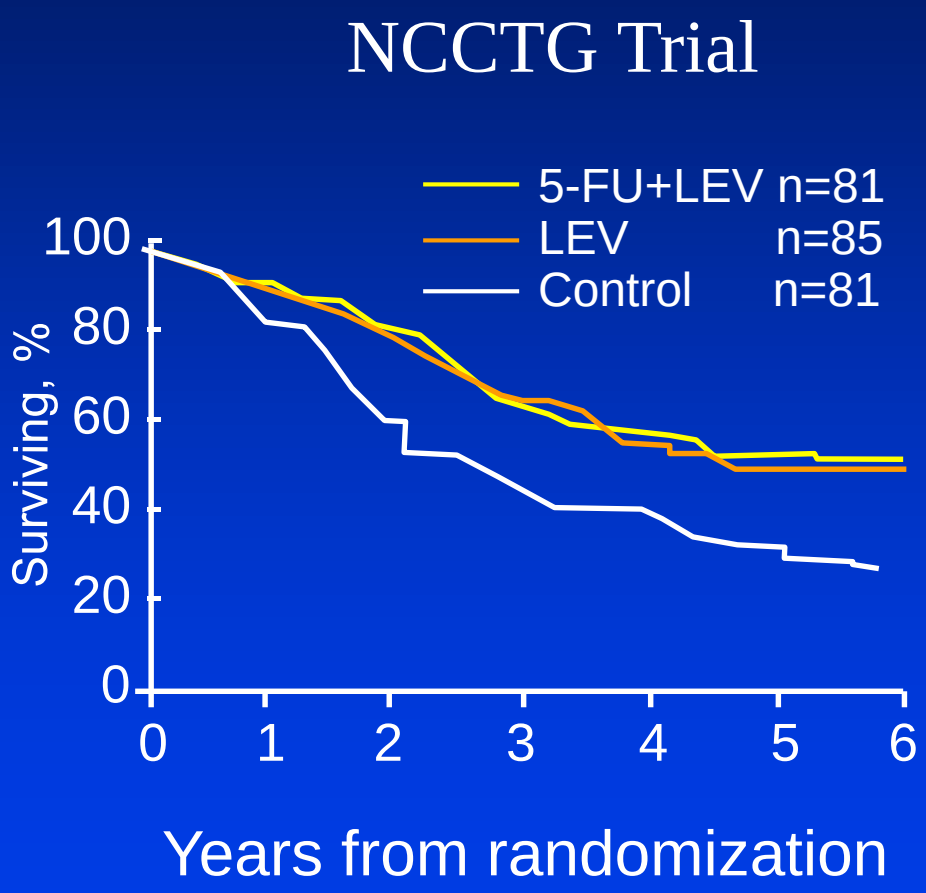
	At Risk	Death	5-Yr Estimate
5-FU+Levamisole	44	21	57%
Follow-Up Only	43	29	40%

Males Only

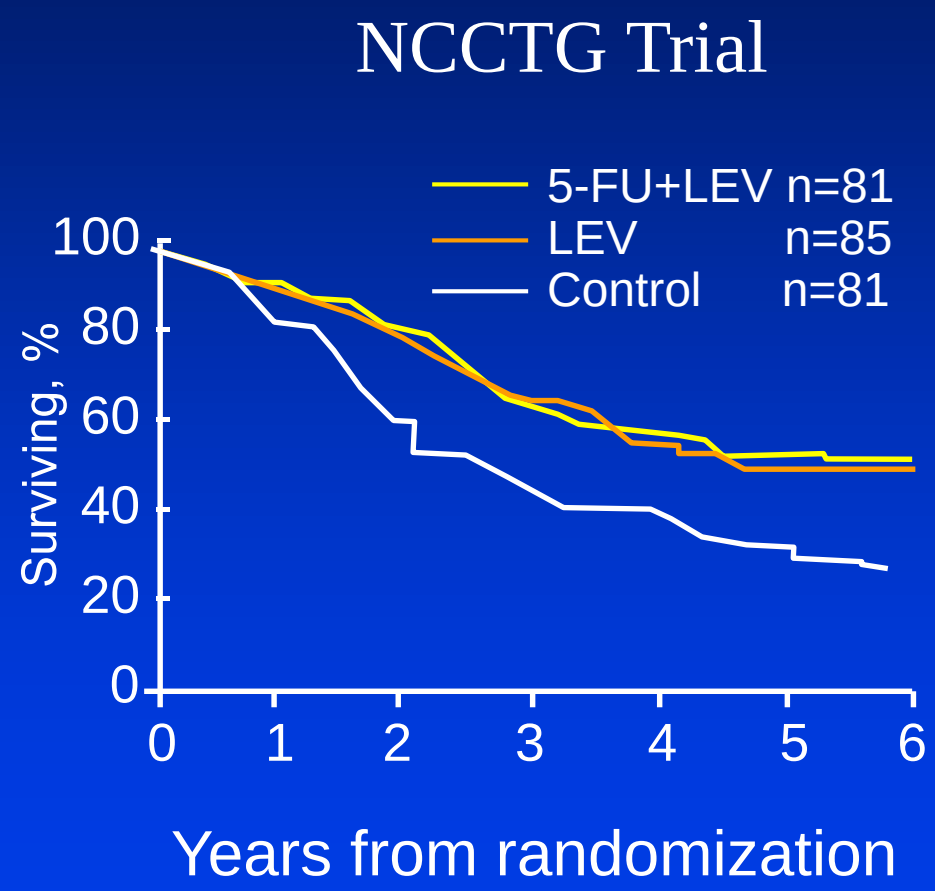
	At Risk	Death	5-Yr Estimate
5-FU+Levamisole	37	25	51%
Follow-Up Only	38	24	47%

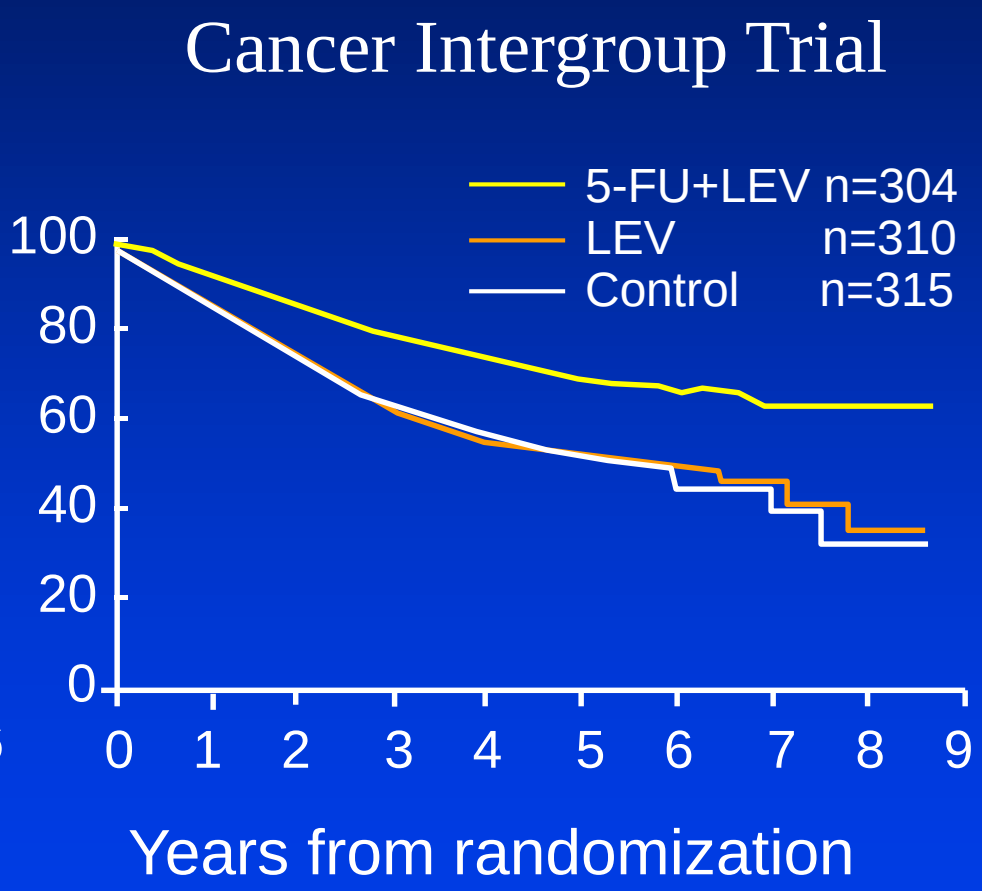


Surgical Adjuvant Therapy: Colorectal Cancer



Surgical Adjuvant Therapy: Colorectal Cancer





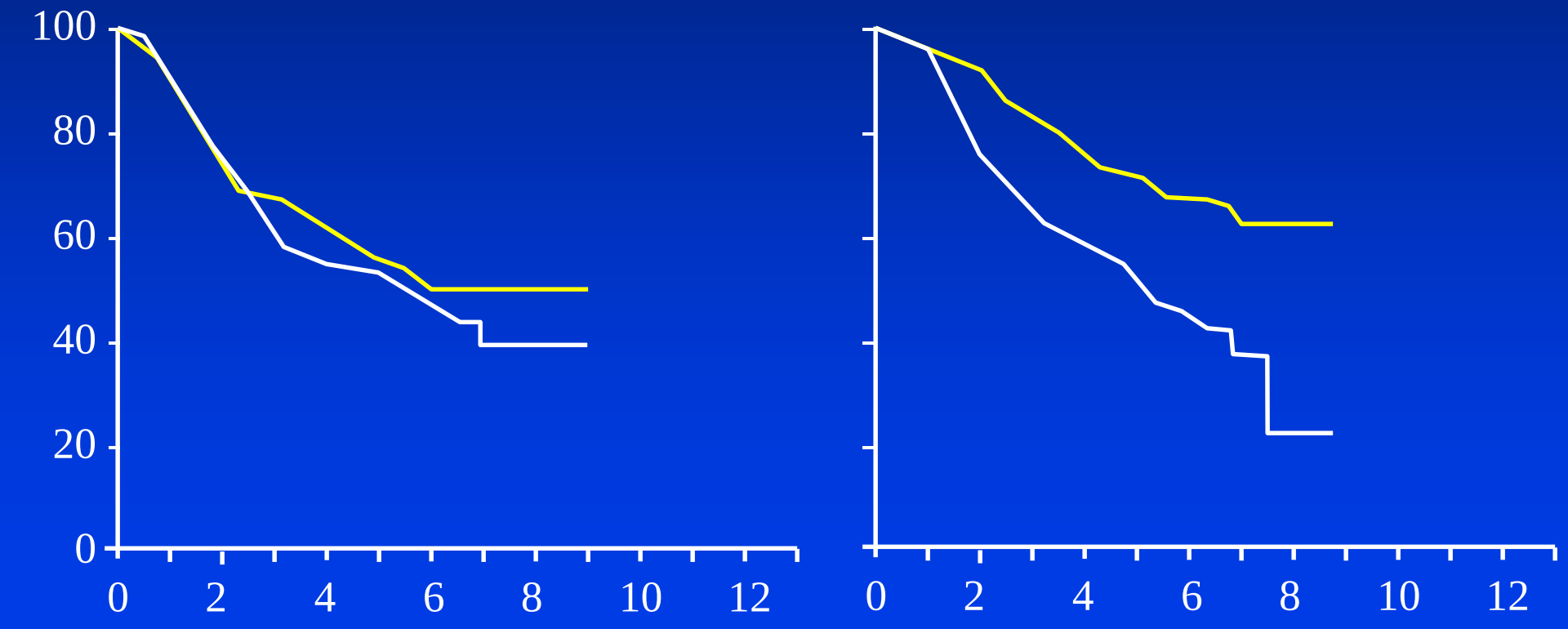
INTERGROUP STUDY 0035
Looking at Treatment Effect on Overall Survival

Females Only

	At Risk	Death	5-Yr Estimate
5-FU+Levamisole	163	74	58%
Follow-Up Only	149	77	54%

Males Only

	At Risk	Death	5-Yr Estimate
5-FU+Levamisole	141	47	70%
Follow-Up Only	166	91	51%



Duke's C Colon Cancer Adjuvant

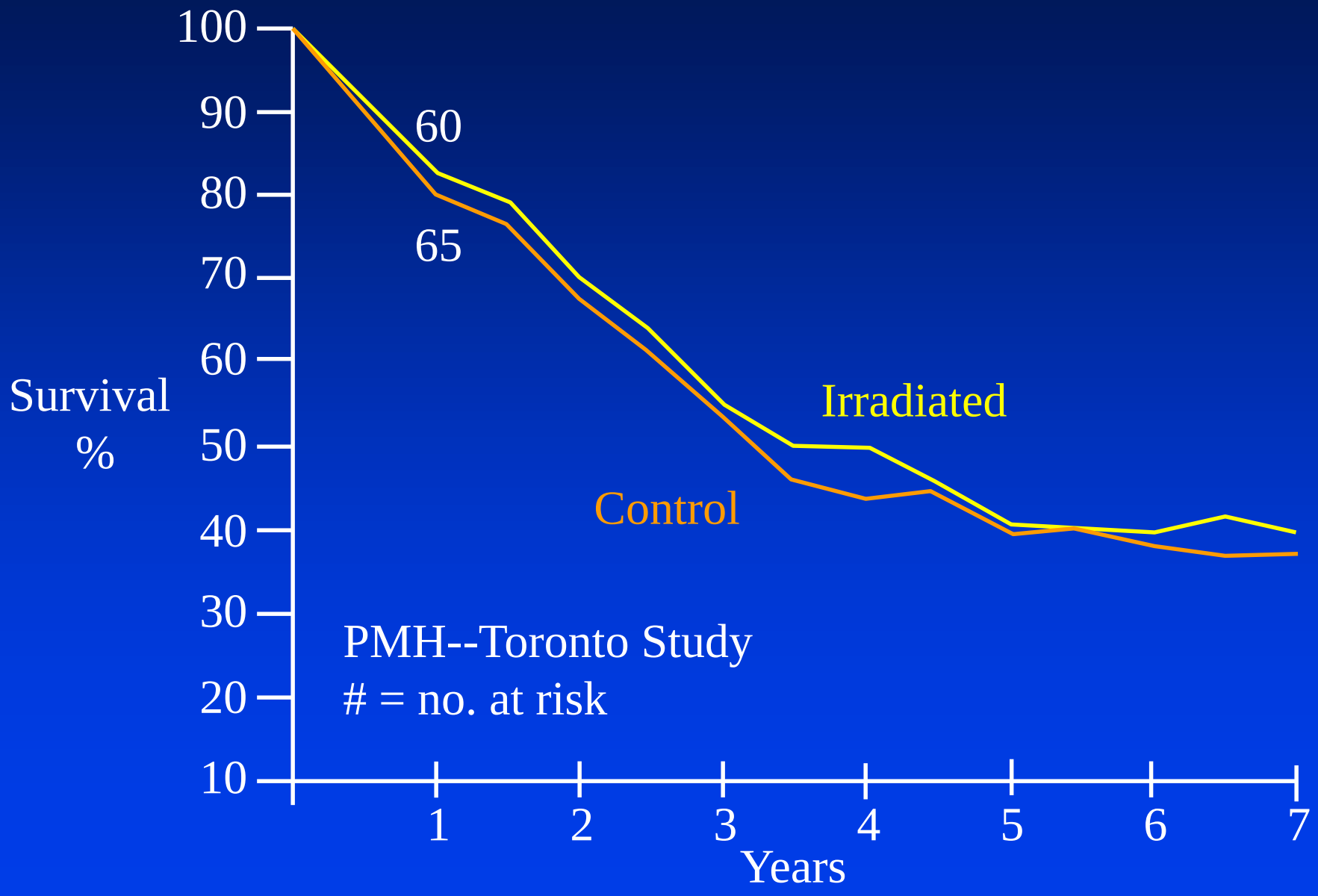
Percent ↓ in Death Rate: 5-FU + Levamisole / Control

Analysis Group	North Central Treatment Group Study (n = 162)	Intergroup Study # 0035 (n = 619)
All patients	**28%**	**33%**
Female	**43%**	**15%**
Male	**9%**	**50%**
Young	**40%**	**23%**
Old	**13%**	**41%**

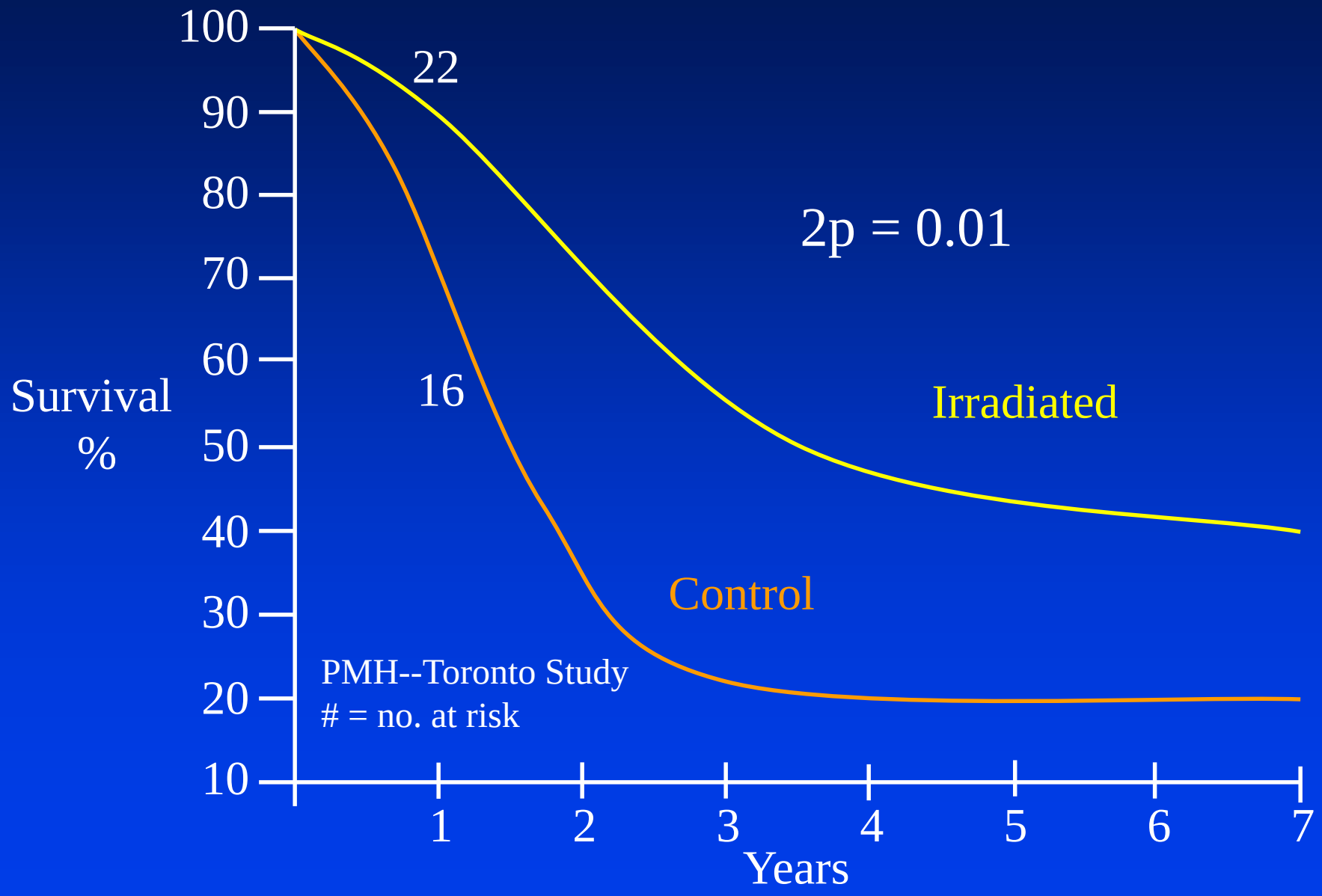
An Illustration of Exploratory Analyses: Post-hoc Subgroup Analyses

Radiation Treatment in Rectal Cancer
Princess Margaret Hospital

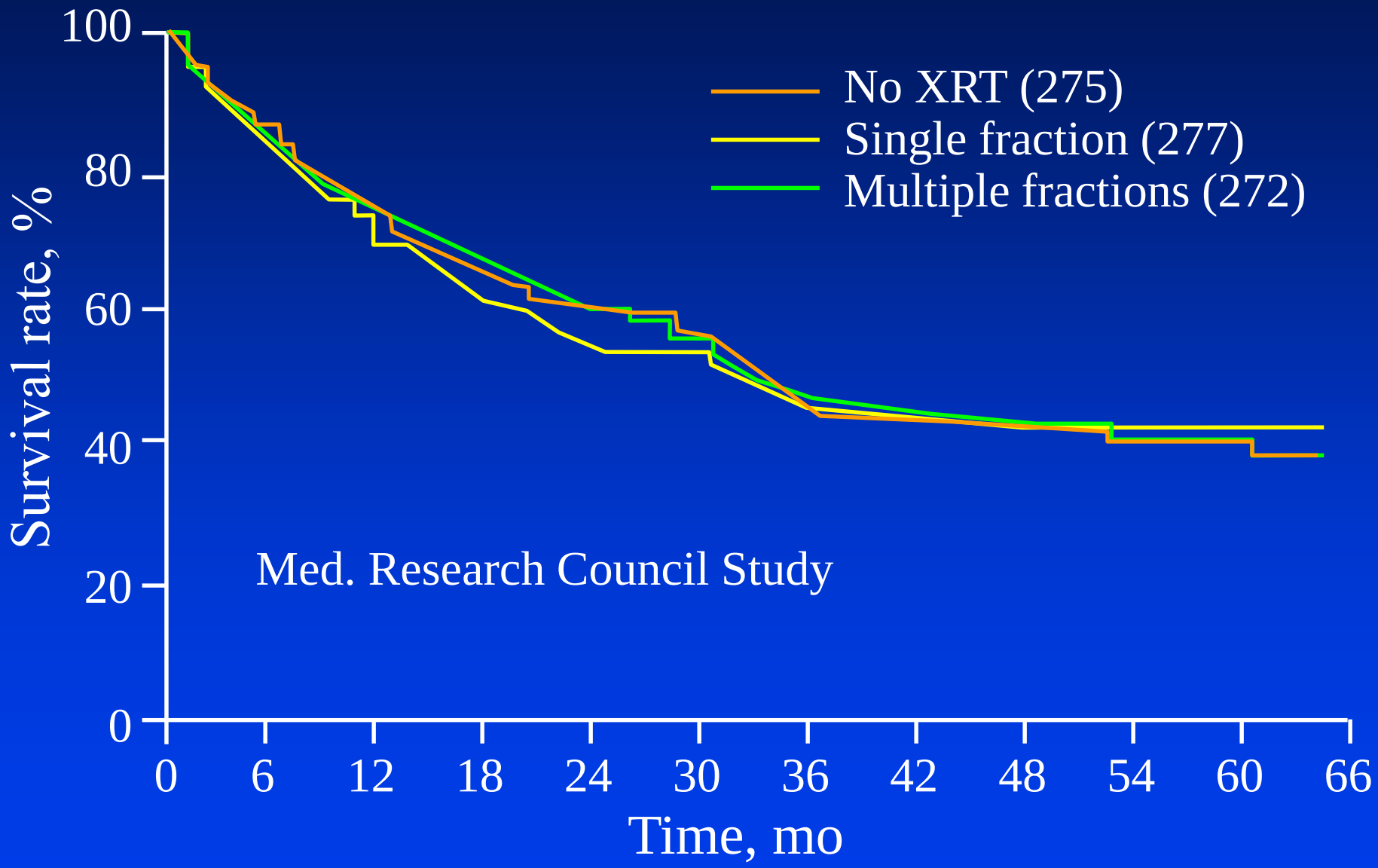
Survival of Patients with Rectal Carcinoma in Control and Irradiated Groups



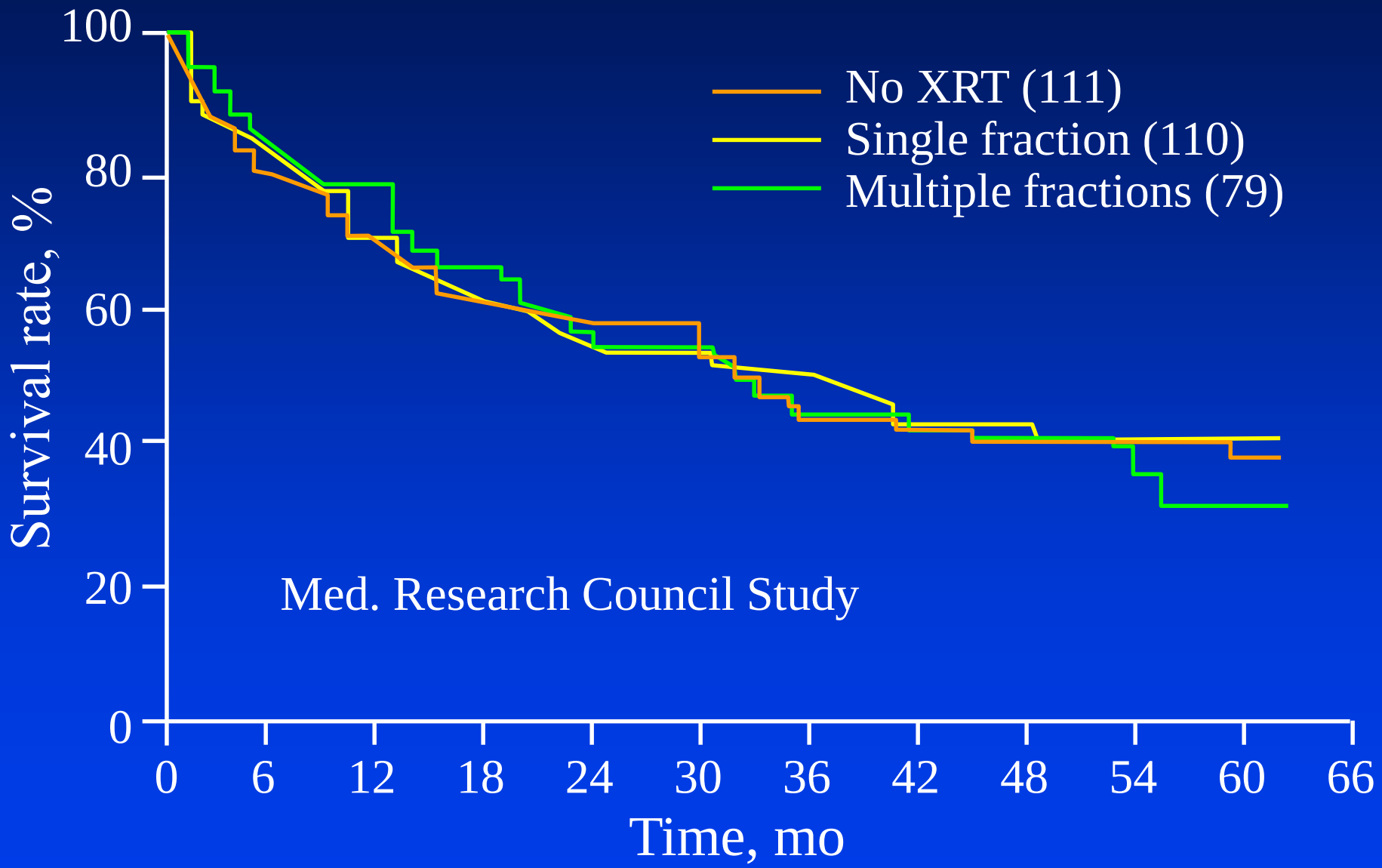
Survival of Patients with Dukes' Stage C Rectal Carcinoma in Control and Irradiated Groups



Survival by Treatment Allocated



Survival by Treatment for Dukes' C Cases



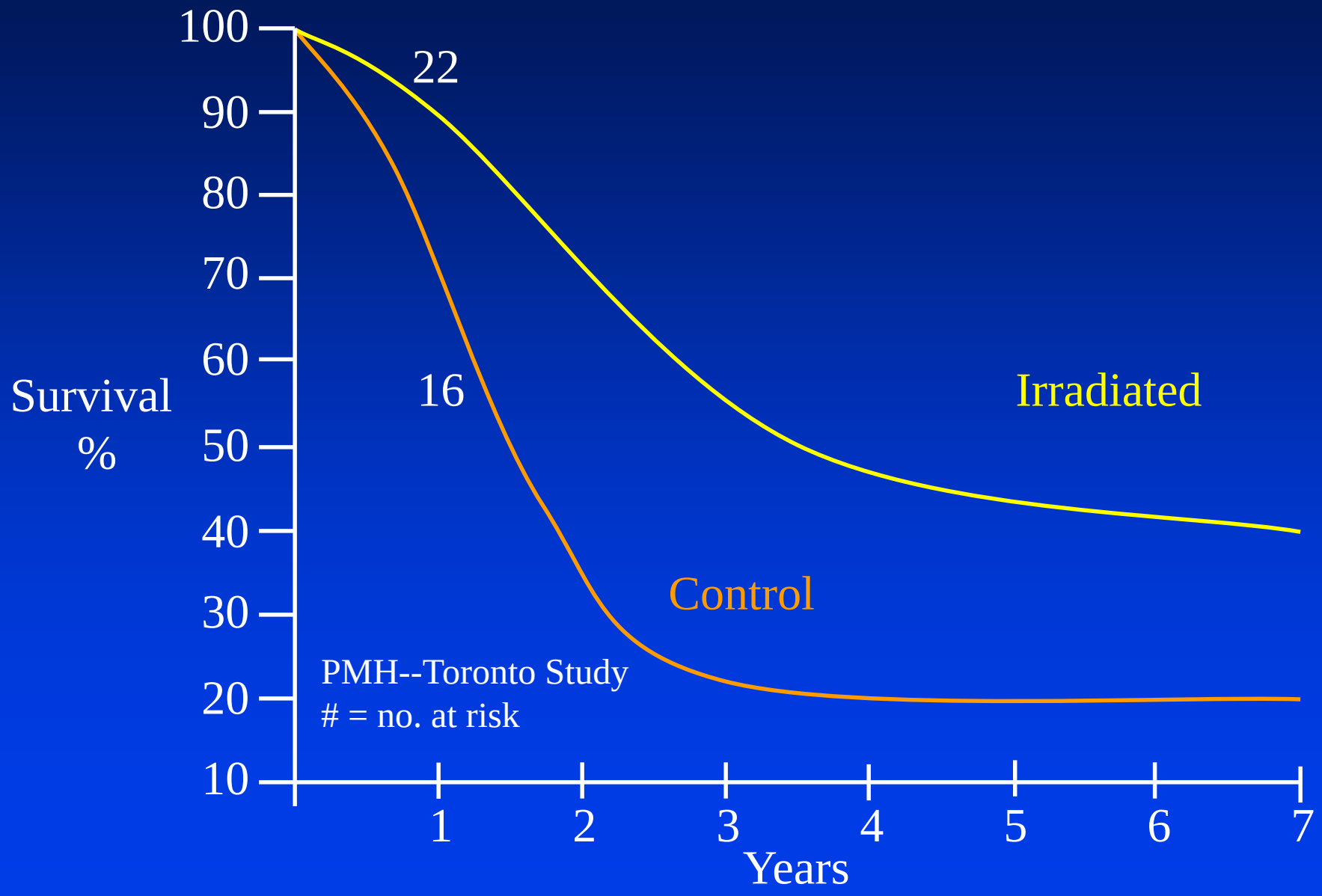
Confirmatory vs. *Exploratory* Analyses

- Hyp. Confirmation vs. Hyp. Generation
  - ~ Post-hoc analyses & ***Random High Bias***
    (new endpoints, new analyses, interim analyses
    subgroup analyses, covariate adjustments)

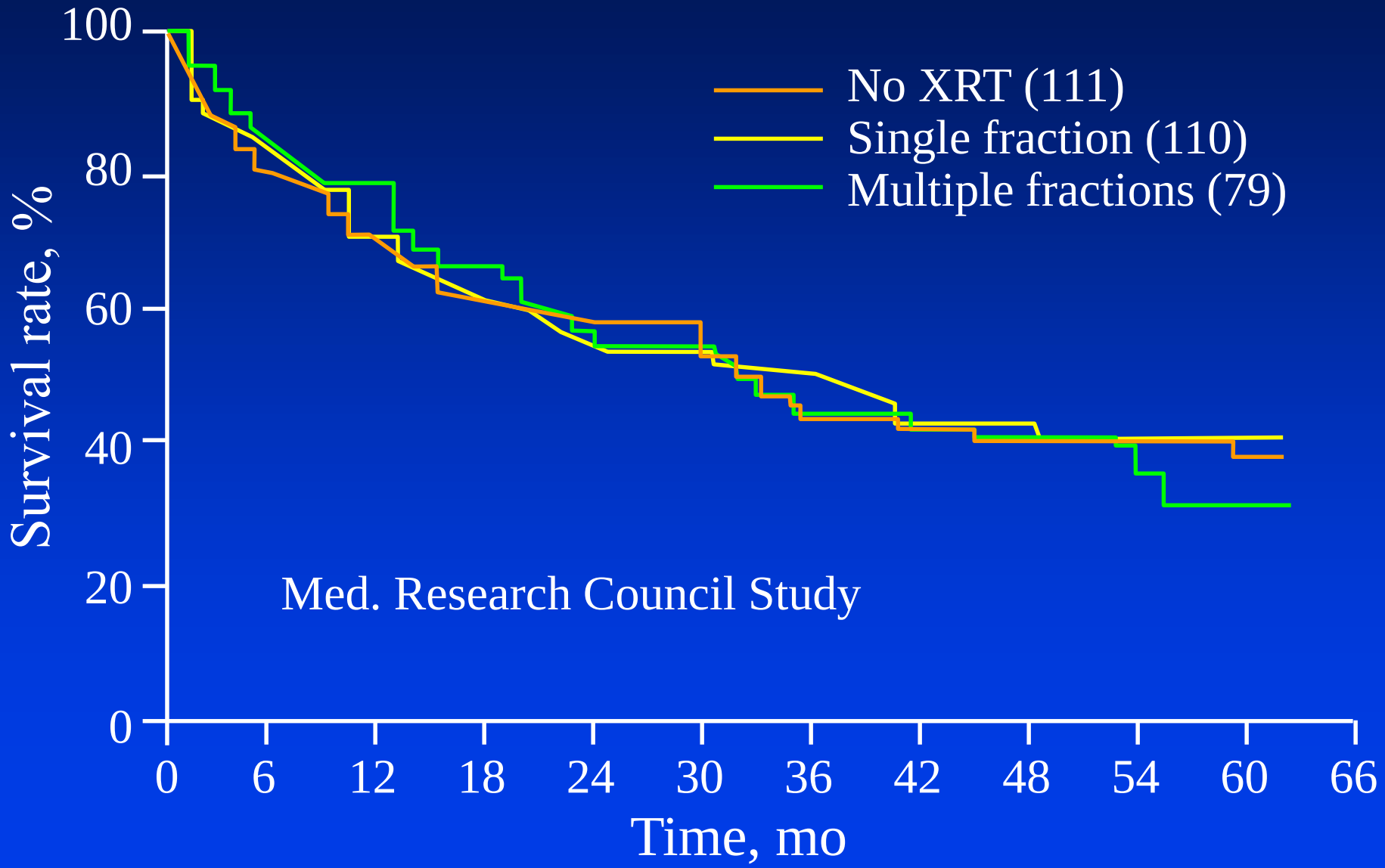
Illustrations and Motivation:

Maternity Wards, ***Baseball*** & Clinical Research

Survival of Patients with Dukes' Stage C Rectal Carcinoma in Control and Irradiated Groups



Survival by Treatment for Dukes' C Cases



Thrombolytics in Acute Myocardial Infarction

- GISSI (Lancet ’86)
  - **SK reduces mortality by 20%**

Thrombolytics in Acute Myocardial Infarction

- GISSI (Lancet ’86)
  - SK reduces mortality by 20%
    confined to:
    anterior MI
    < 65 years
    < 6 hours from symptom onset

Thrombolytics in Acute Myocardial Infarction

- GISSI (Lancet ’86)
  - SK reduces mortality by 20%
    confined to:
    anterior MI
    < 65 years
    < 6 hours from symptom onset
  - Subset restriction not confirmed by ISIS-2, ASSET, AIMS

Thrombolytics in Acute Myocardial Infarction

- GISSI (Lancet ’86)
  - SK reduces mortality by 20%
    confined to:
      anterior MI
      < 65 years
      < 6 hours from symptom onset
  - Subset restriction not confirmed by ISIS-2, ASSET, AIMS
  - While in ISIS-2:
    Aspirin beneficial overall…

Thrombolytics in Acute Myocardial Infarction

- GISSI (Lancet ’86)
  - SK reduces mortality by 20%
    confined to:
      anterior MI
      < 65 years
      < 6 hours from symptom onset
  - Subset restriction not confirmed by ISIS-2, ASSET, AIMS
  - While in ISIS-2:
    Aspirin beneficial overall…
    … yet **harmful to** patients with
    astrological signs **Libra** and **Gemini**

Can Efficacy or Safety Signals Discovered in Exploratory Analyses Be Viewed to be Reliable Results?

- Criteria to be simultaneously satisfied:

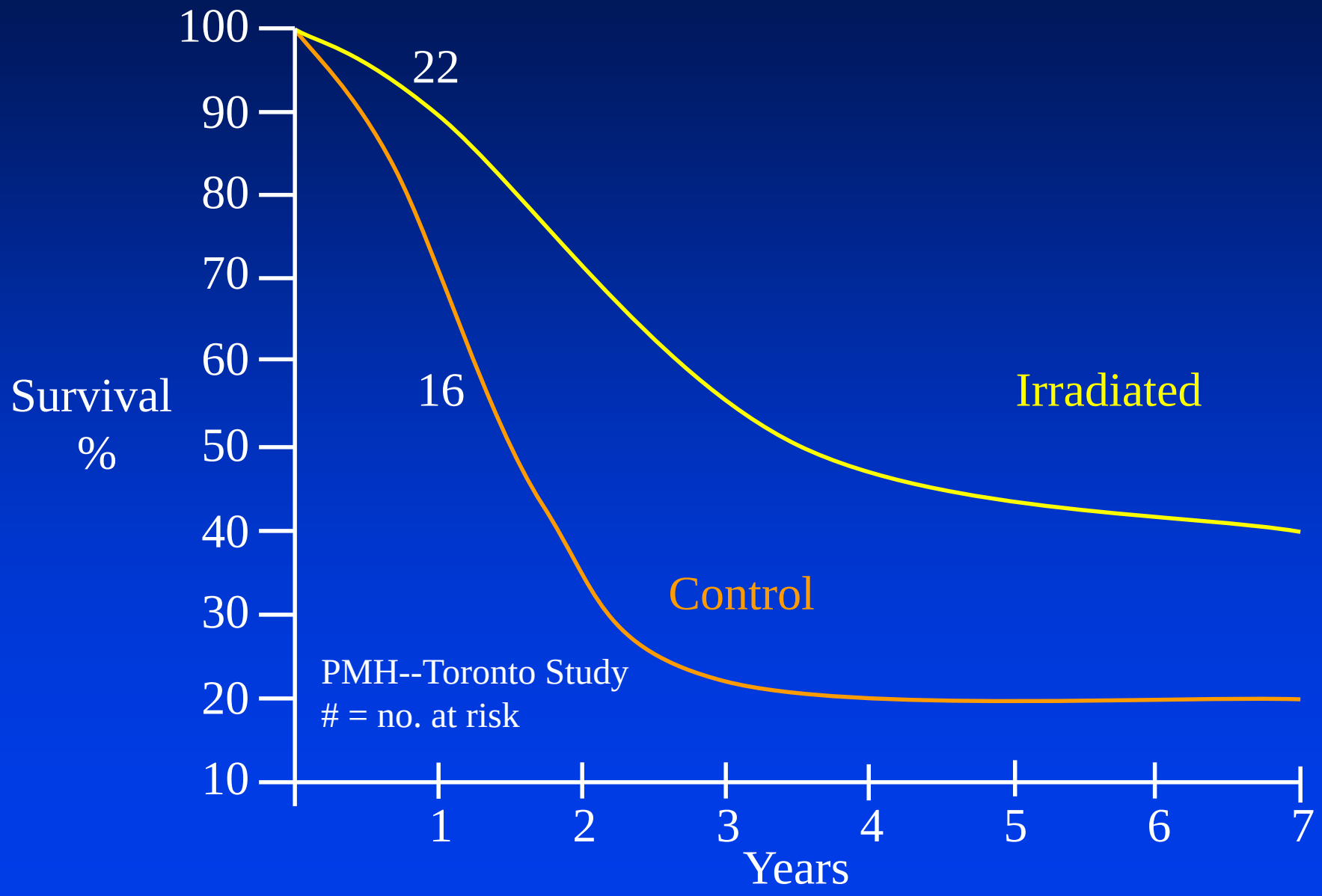
✓ < < P-values *(e.g., Natalizumab & PML & Carvedilol in Heart Failure)*

✓ Biologically plausible effect

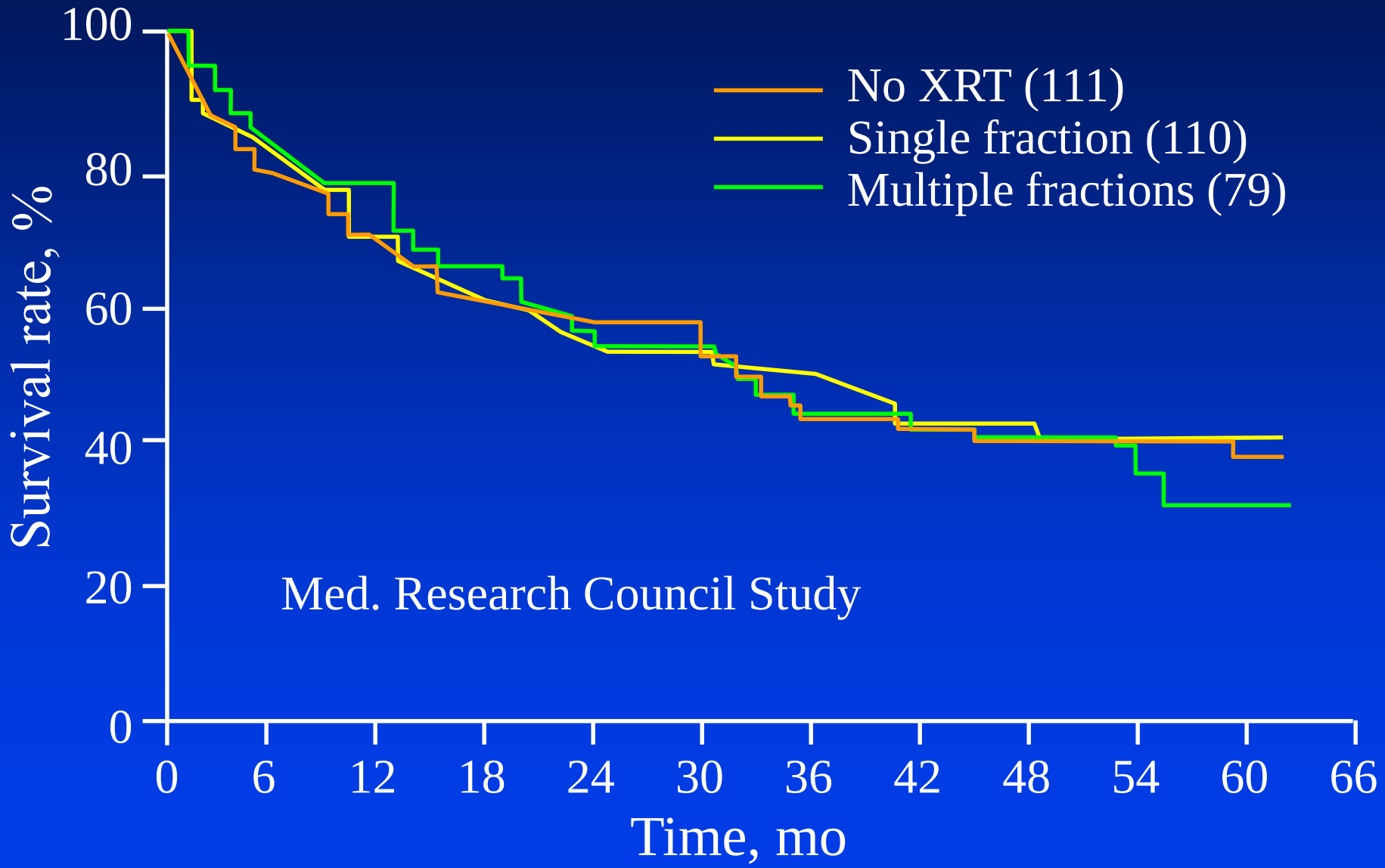
- *White Paper Illustration*

✓ Confirmed by external results

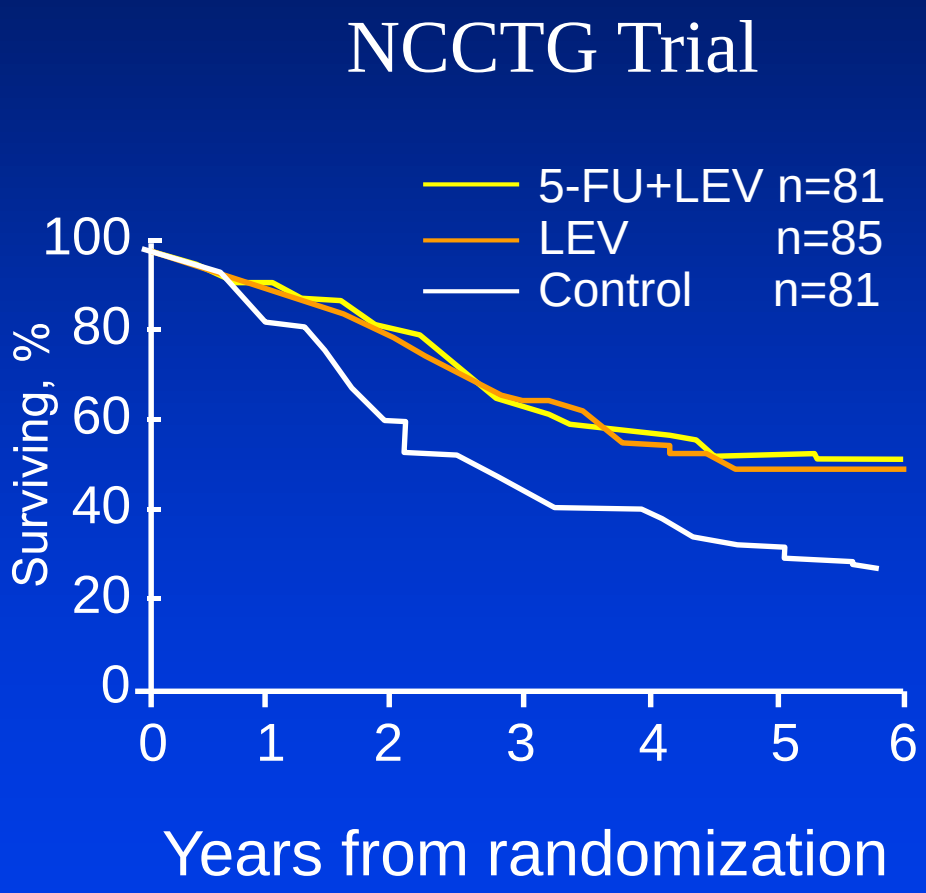
Survival of Patients with Dukes' Stage C Rectal Carcinoma in Control and Irradiated Groups



Survival by Treatment for Dukes' C Cases

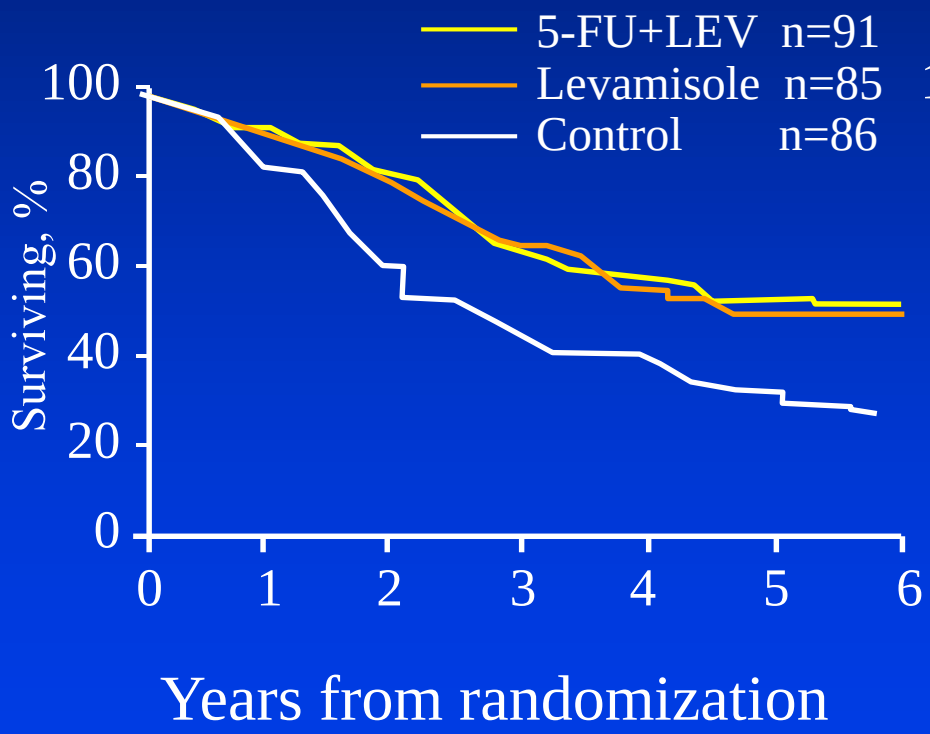


Surgical Adjuvant Therapy: Colorectal Cancer

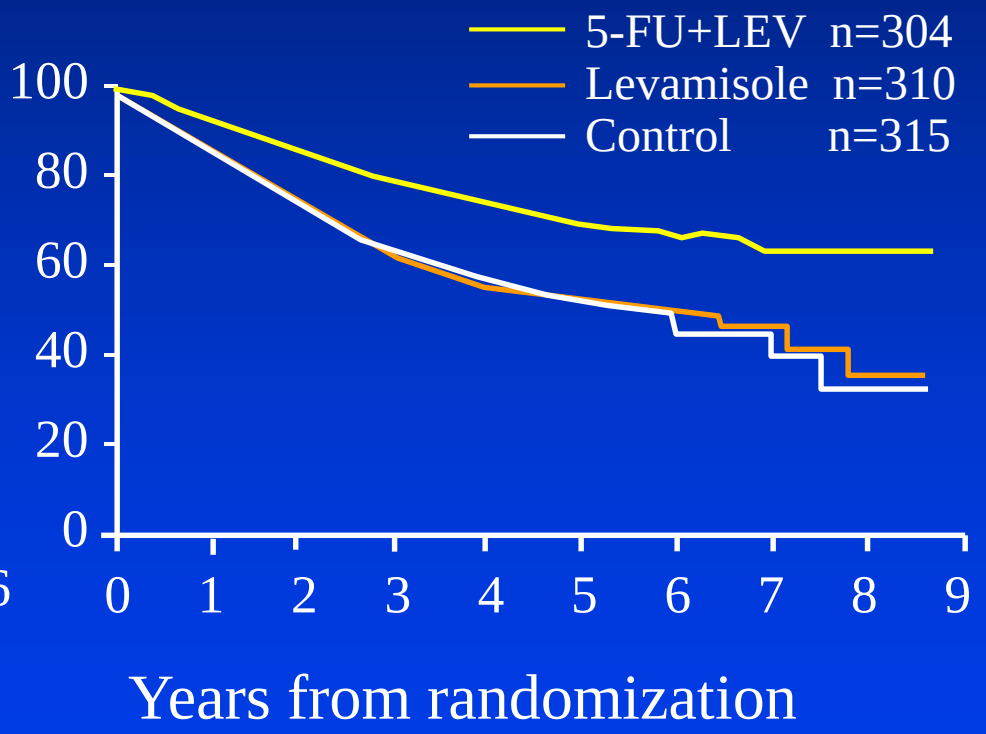


Surgical Adjuvant Therapy Of Colorectal Cancer

NCCTG Trial



Cancer Intergroup Trial



Of all experimental interventions studied in colon adjuvant, suppose only 4% are truly positive & 96% are truly negative.

Suppose the "*false negative error rate*" is $\beta = 0.10$
(so the "*statistical power*" is $1-\beta = 0.90$)
& Suppose the "*false positive error rate*" is $\alpha = 0.025$

Then, the probability a trial positive will be a true positive is $36 / 60 = 0.60$

RESULT OF EXPERIMENT	TRUTH Positive	Negative	
Positive	36	24	60
Negative	4	936	940
	40	960	1000

Of all experimental interventions studied,
suppose 60% are truly positive & 40% are truly negative

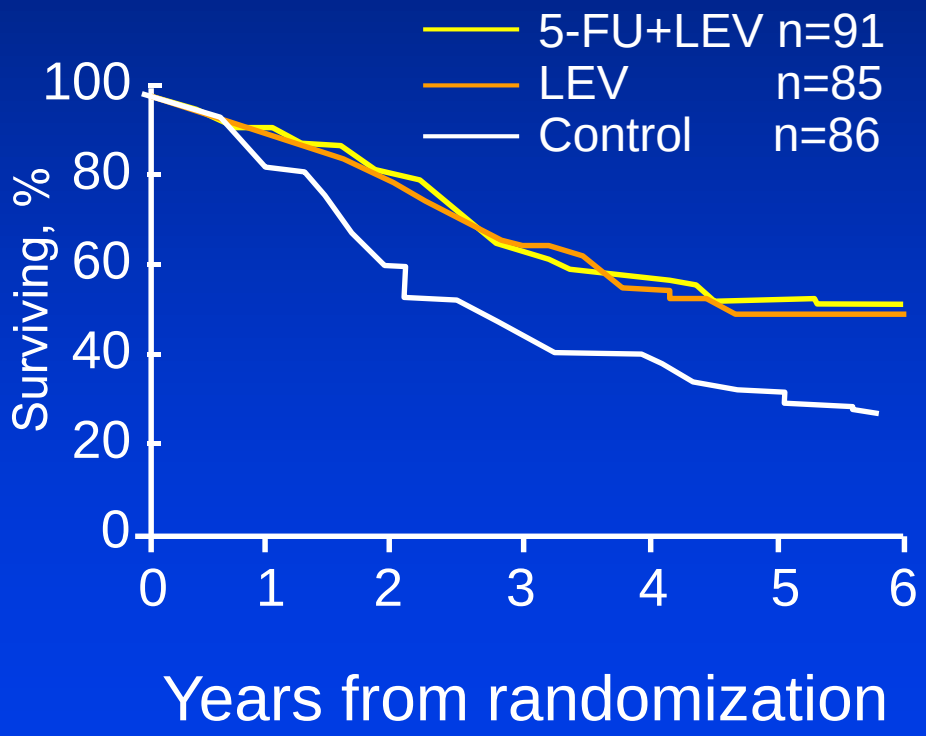
Suppose the "*false negative error rate*" is $\beta = 0.10$
(so the "*statistical power*" is $1-\beta = 0.90$)
& Suppose the "*false positive error rate*" is $\alpha = 0.025$

Then, the probability a trial positive will be
a true positive is $540 / 550 = 0.98$

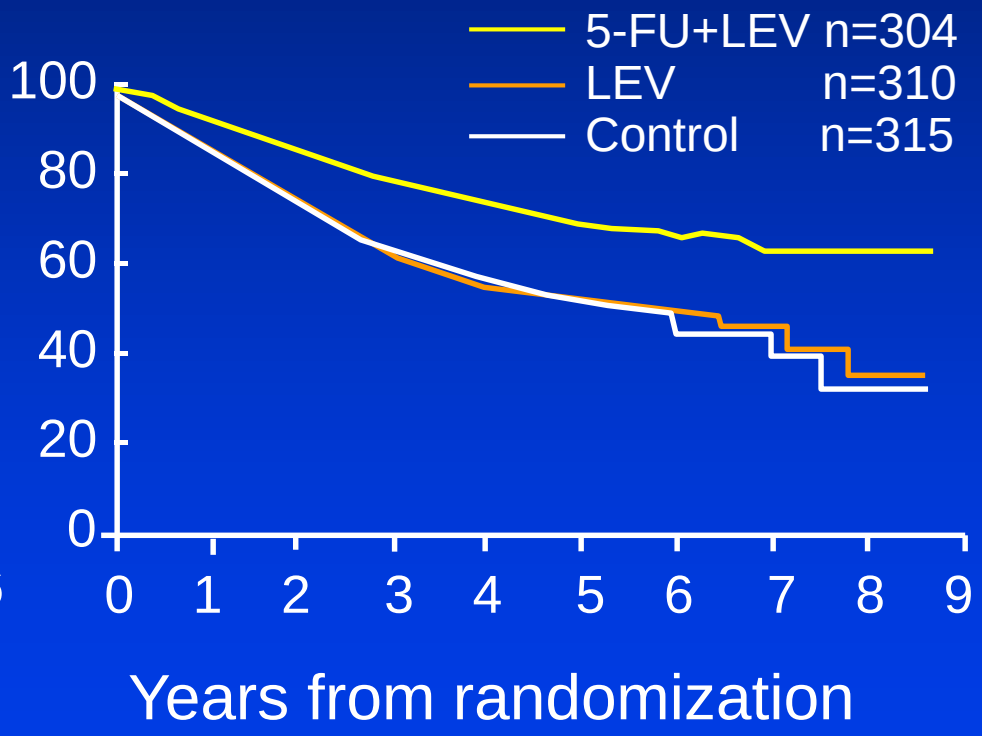
RESULT OF EXPERIMENT	TRUTH Positive	Negative	
Positive	540	10	550
Negative	60	390	450
	600	400	1000

Surgical Adjuvant Therapy Of Colorectal Cancer

NCCTG Trial



Cancer Intergroup Trial



"It isn't so much the things we *don't know* that get us in trouble.

It's the things we *know* that aren't so".

—Artemus Ward (1834-1867)

Some Conclusions

- P-values are only interpretable when you understand
  the sampling context from which they were derived
- Random High bias is real
- Exploratory Analyses usually should be viewed
  to be "Hypothesis Generating"
- Confirmatory Trials
  greatly enhance the reliability of conclusions

Confirmatory vs. *Exploratory* Analyses

- Hyp. Confirmation vs. Hyp. Generation
  - ~ Post-hoc analyses & Random High Bias
    (new endpoints, new analyses, interim analyses
    subgroup analyses, covariate adjustments)

Illustrations and Motivation:

Maternity Wards, Baseball & Clinical Research

20 vs 2: (.71, .99), 2p = 0.0001

Meta-Analysis: 31 vs 13: (.55, .83), 2p = 0.0096

Bias for "Positive" Results in Clinical Trials

- Protocol Specified Primary Objective of the Clinical trial:

- Very frequent wording:
  - ~ " To *establish* that the experimental regimen is safe and effective"

Bias for "Positive" Results in Clinical Trials

- Protocol Specified Primary Objective of the Clinical trial:

- Very frequent wording:
  - ~ " To *establish* that the experimental regimen is safe and effective"

- Scientifically unbiased wording:
  - ~ " To *determine whether* the experimental regimen is safe and effective"

…building a story with supportive analyses…

Bias for "Positive" Results in Clinical Trials

…Andrew Fleming's insight from Psychology…

"*Cognitive Dissonance*"

…The Harvard Professor's Course…

…The Apparent Lack of Benefit in Males…

Interest in “Positive” Results in Clinical Trials

- Abetimus Sodium: Reducing Renal Flare Rate in Lupus
- Trial #1: Time to renal flare: Minimal effect, ($2p = 0.51$)

Interest in "Positive" Results in Clinical Trials

- Abetimus Sodium: Reducing Renal Flare Rate in Lupus
- Trial #1: Time to renal flare: Minimal effect, ($2p = 0.51$)
  …exploratory high affinity subgroup: $2p = 0.007$
- Trial #2 conducted in high affinity subgroup:
  Time to renal flare:

Interest in "Positive" Results in Clinical Trials

- Abetimus Sodium: Reducing Renal Flare Rate in Lupus
- Trial #1: Time to renal flare: Minimal effect, ($2p = 0.51$)
  …exploratory high affinity subgroup: $2p = 0.007$
- Trial #2 conducted in high affinity subgroup:
  Time to renal flare: Minimal non-significant effect

Interest in "Positive" Results in Clinical Trials

- Abetimus Sodium: Reducing Renal Flare Rate in Lupus
- Trial #1: Time to renal flare: Minimal effect, ($2p = 0.51$)
  …exploratory high affinity subgroup: $2p = 0.007$
- Trial #2 conducted in high affinity subgroup:
  Time to renal flare: Minimal non-significant effect
  …exploratory truncation at 12 months is favorable

Interest in "Positive" Results in Clinical Trials

- Abetimus Sodium: Reducing Renal Flare Rate in Lupus
- Trial #1: Time to renal flare: Minimal effect, ($2p = 0.51$)
  …exploratory high affinity subgroup: $2p = 0.007$
- Trial #2 conducted in high affinity subgroup:
  Time to renal flare: Minimal non-significant effect
  …exploratory truncation at 12 months is favorable
- Trial #3 conducted in high affinity subgroup
  with prespecified truncation at 12 months follow-up:

Interest in "Positive" Results in Clinical Trials

- Abetimus Sodium: Reducing Renal Flare Rate in Lupus
- Trial #1: Time to renal flare: Minimal effect, ($2p = 0.51$)
  …exploratory high affinity subgroup: $2p = 0.007$
- Trial #2 conducted in high affinity subgroup:
  Time to renal flare: Minimal non-significant effect
  …exploratory truncation at 12 months is favorable
- Trial #3 conducted in high affinity subgroup
  with prespecified truncation at 12 months follow-up:
  …early termination by DMC for futility.

"If you Torture Data Long Enough, They will Confess"

* Fleming TR "Clinical Trials: Discerning Hype from Substance" *Annals of Internal Medicine* 2010; 153:400-406

Principles & Insights

"The Goal of Clinical Research:

Principles & Insights

"The Goal of Clinical Research:
To *Determine Whether*,
Not to *Establish*,
the Experimental Regimen
Is Safe and Effective"

Fleming TR "Clinical Trials: Discerning Hype from Substance"
Annals of Internal Medicine 2010; 153:400-406