

Exploratory Analyses: Why Do We Need Particular Caution?

July 25, 2018

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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**

	<u>N</u>	<u>CA. Incidence</u>	<u>CA. Deaths</u>
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**

	<u>N</u>	<u>CA. Incidence</u>	<u>CA. Deaths</u>
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 χ^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 Epoprostenol +/- Sildenafil
 - ~ Age: By decade
 - ~ Ethnicity: White v Black v Asian v Other
 - ~ mean PAP: < 50 v > 50

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Illustrations and Motivation:

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Illustrations and Motivation:

Maternity Wards, Baseball & Clinical Research

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

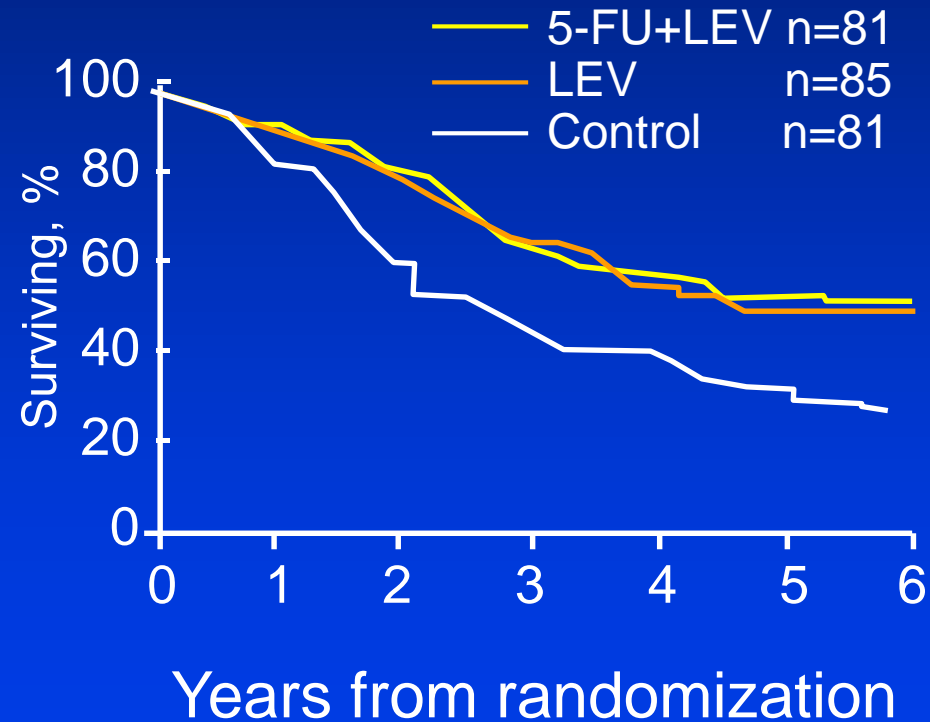
An Illustration of Exploratory Analyses: Post-hoc Subgroup Analyses

Surgical Adjuvant Therapy
of Colorectal Cancer



Surgical Adjuvant Therapy: Colorectal Cancer

NCCTG Trial



NORTH CENTRAL TREATMENT GROUP STUDY

Looking at Treatment Effect on Overall Survival

Females Only

Males Only

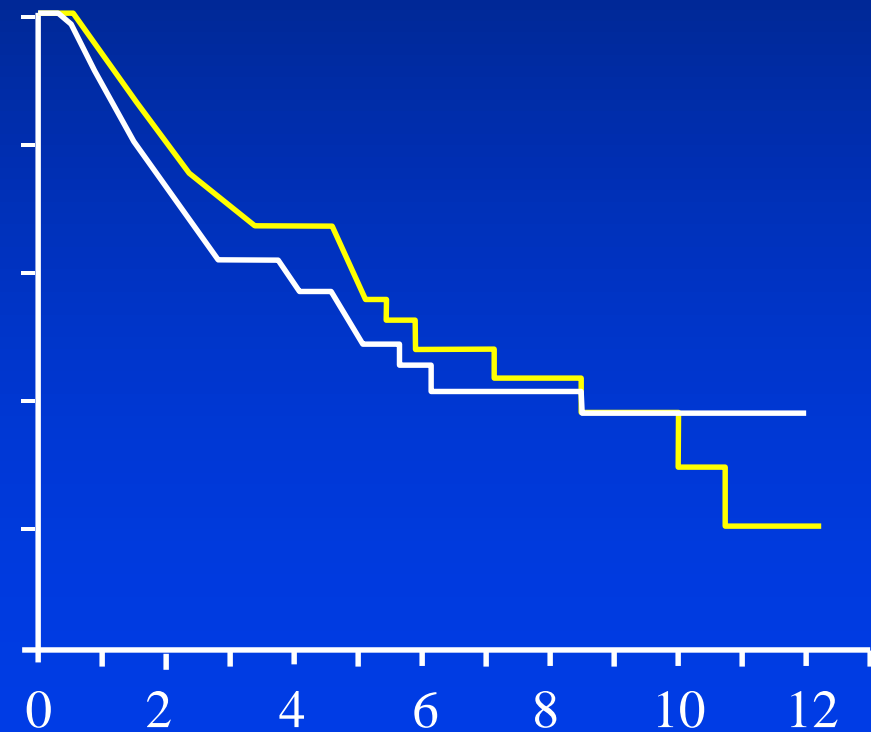
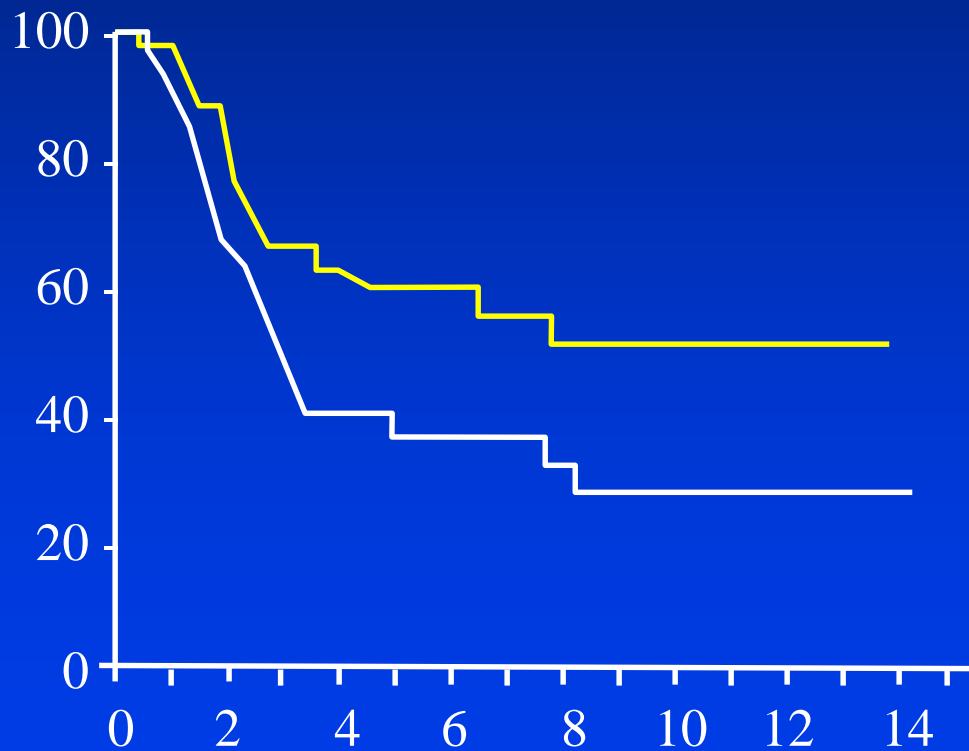
At Risk Death 5-Yr Estimate

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— 5-FU+Levamisole
— Follow-Up Only

5-FU+Levamisole	44	21	57%
Follow-Up Only	43	29	40%

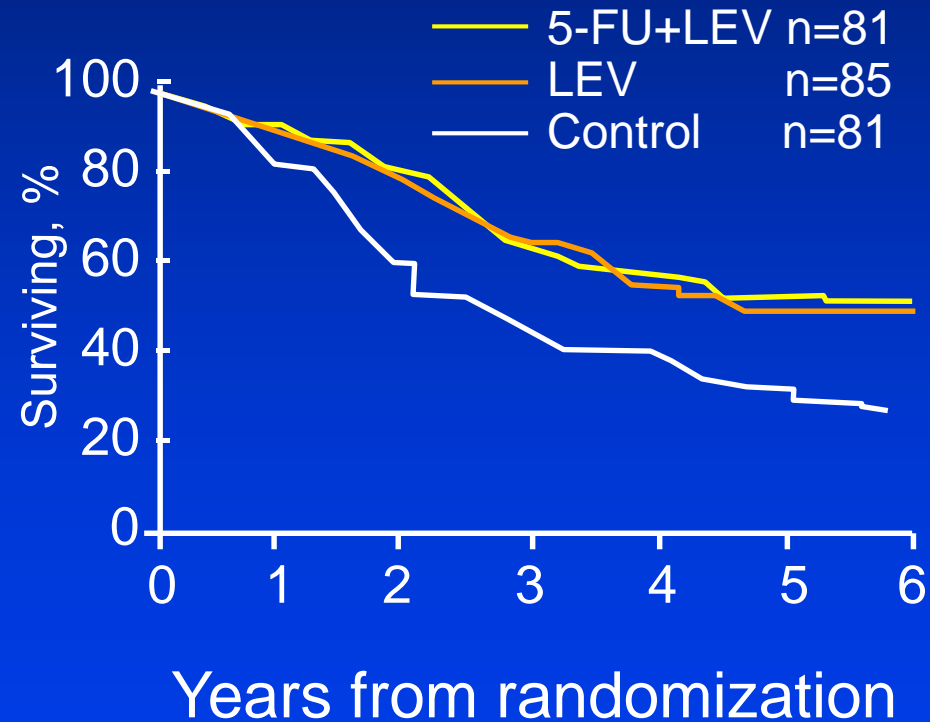
5-FU+Levamisole	37	25	51%
Follow-Up Only	38	24	47%



Years from Registration

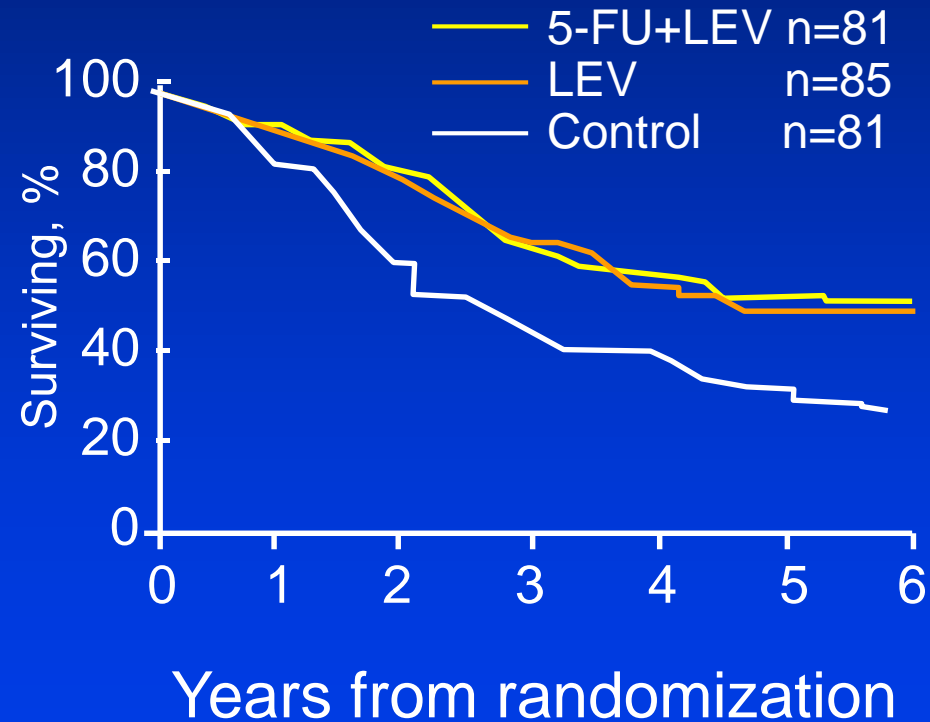
Surgical Adjuvant Therapy: Colorectal Cancer

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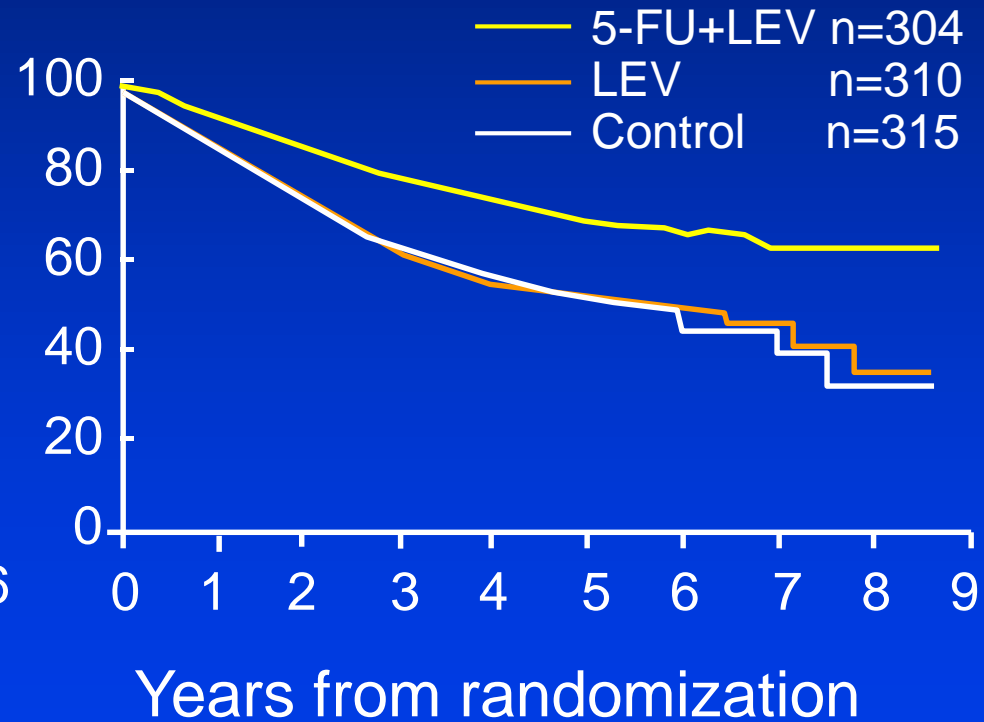


Surgical Adjuvant Therapy: Colorectal Cancer

NCCTG Trial



Cancer Intergroup Trial



INTERGROUP STUDY 0035

Looking at Treatment Effect on Overall Survival

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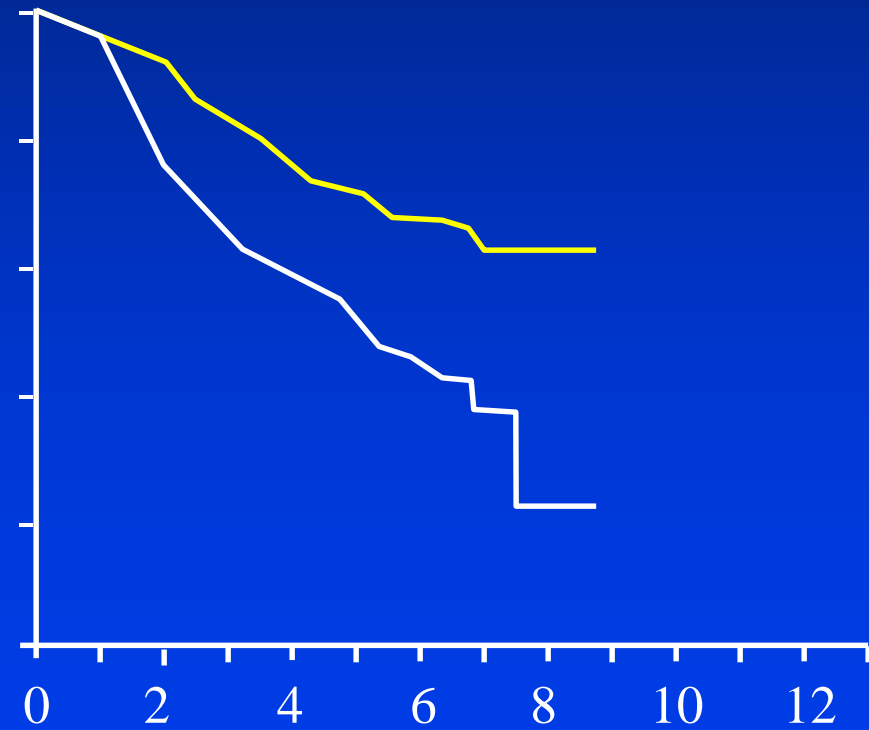
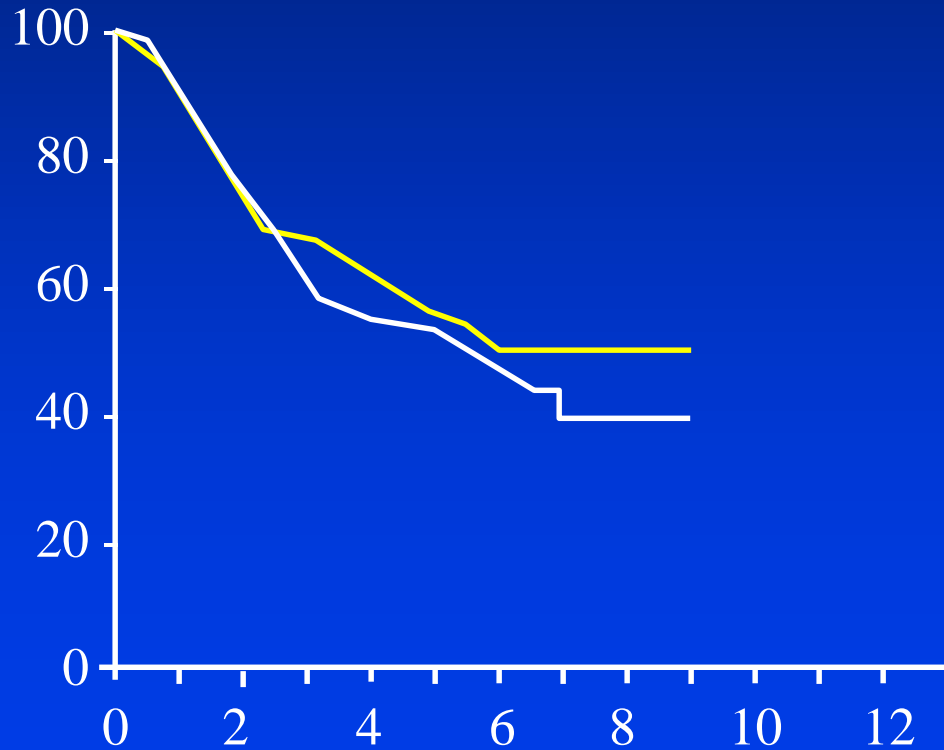
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163	74	58%
149	77	54%

141	47	70%
166	91	51%



Years from Registration

Duke's C Colon Cancer Adjuvant

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

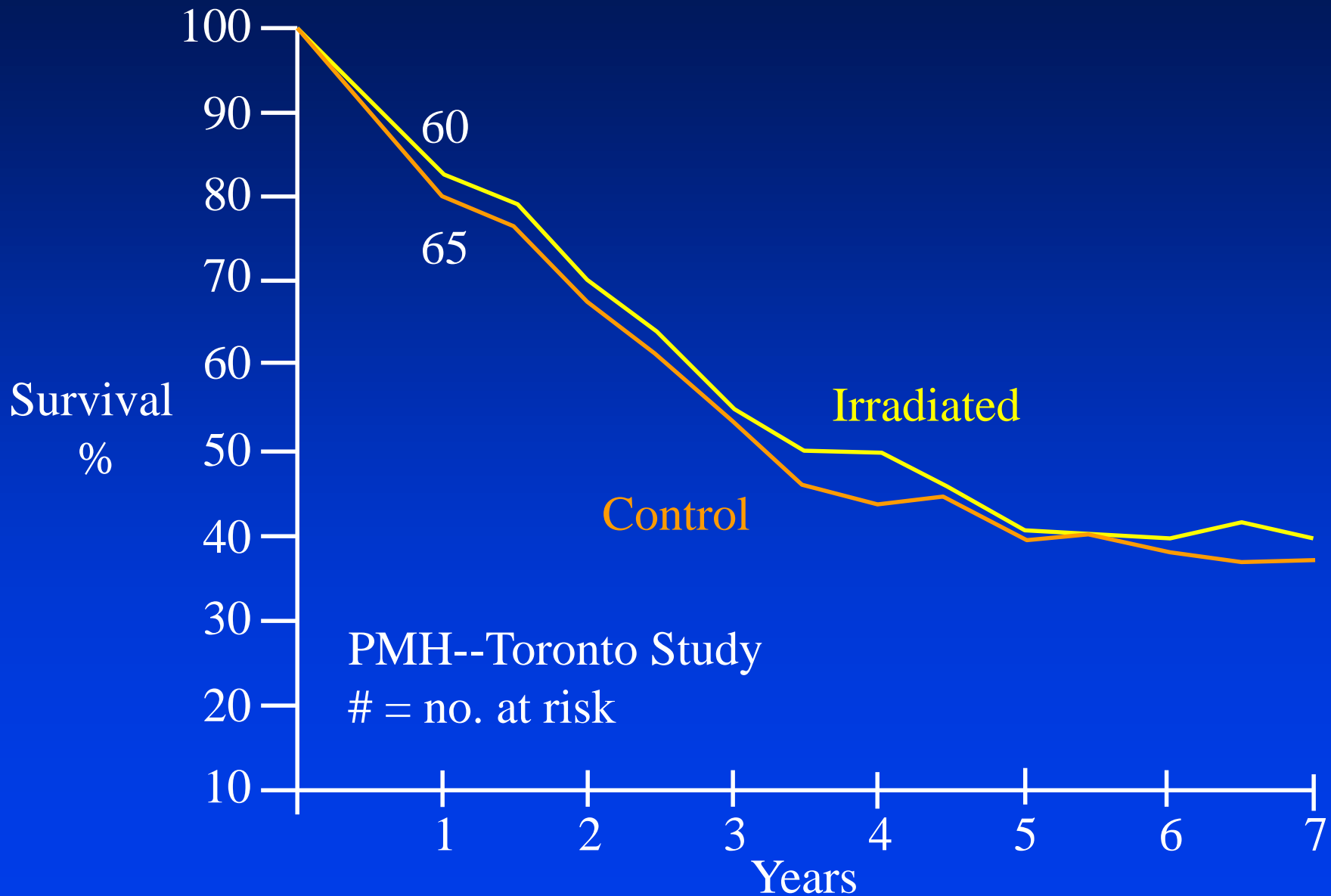
Analysis Group	North Central Treatment Group Study (n = 162)	Intergroup Study # 0035 (n = 619)
All patients	28%	33%
Female	43%	15%
Male	9%	50%
Young	40%	23%
Old	13%	41%

An Illustration of Exploratory Analyses: Post-hoc Subgroup Analyses

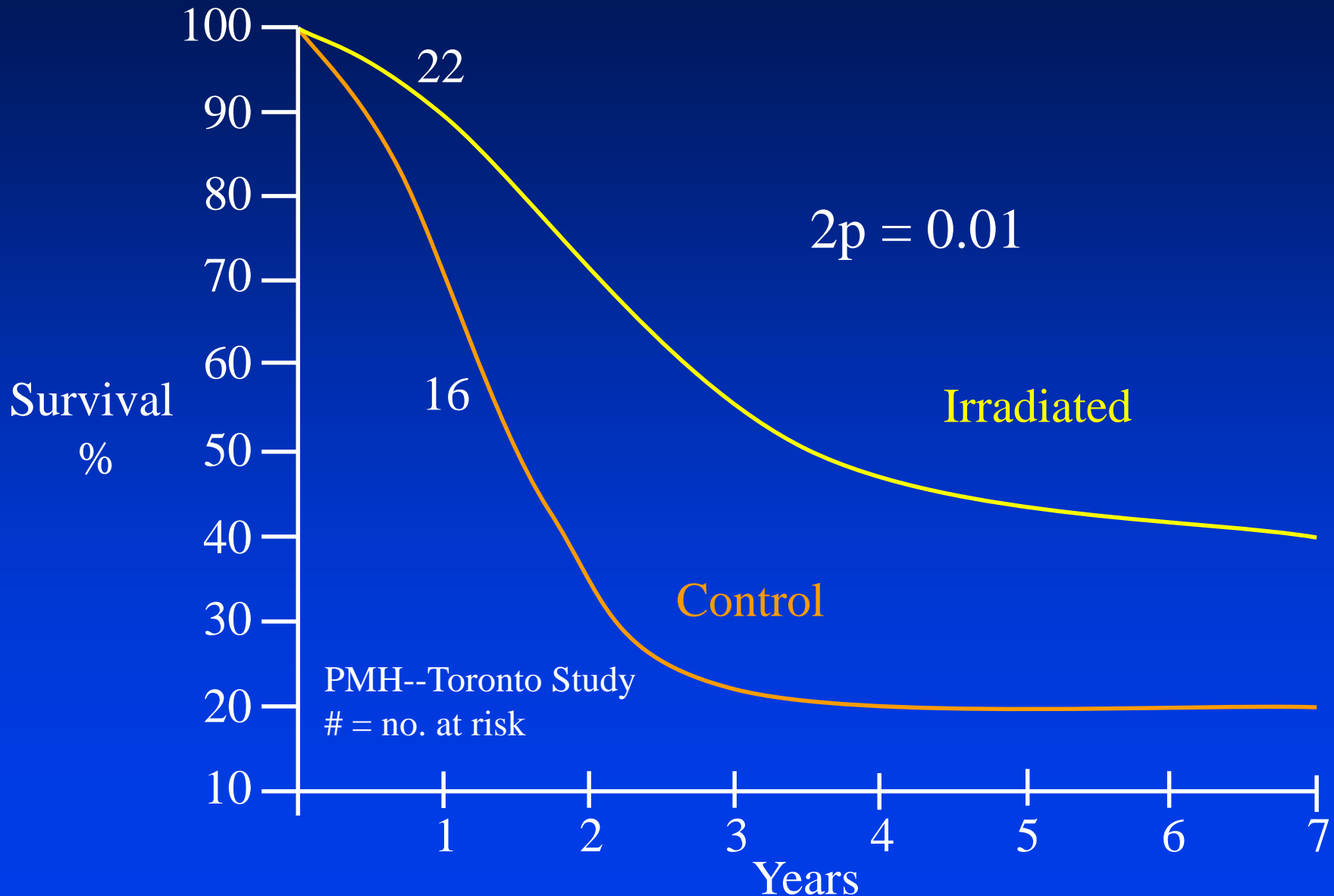
Radiation Treatment in Rectal Cancer
Princess Margaret Hospital



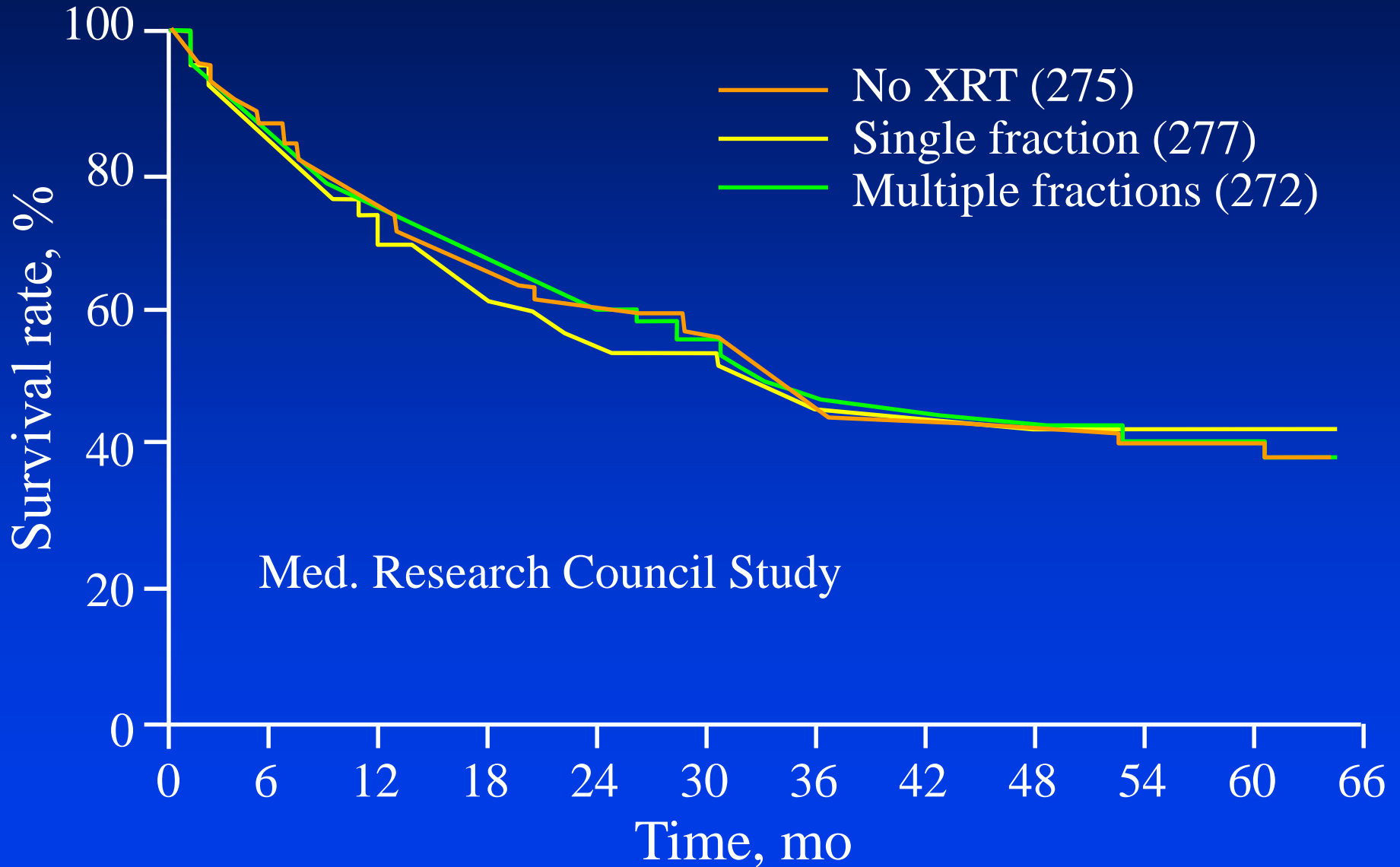
Survival of Patients with Rectal Carcinoma in Control and Irradiated Groups



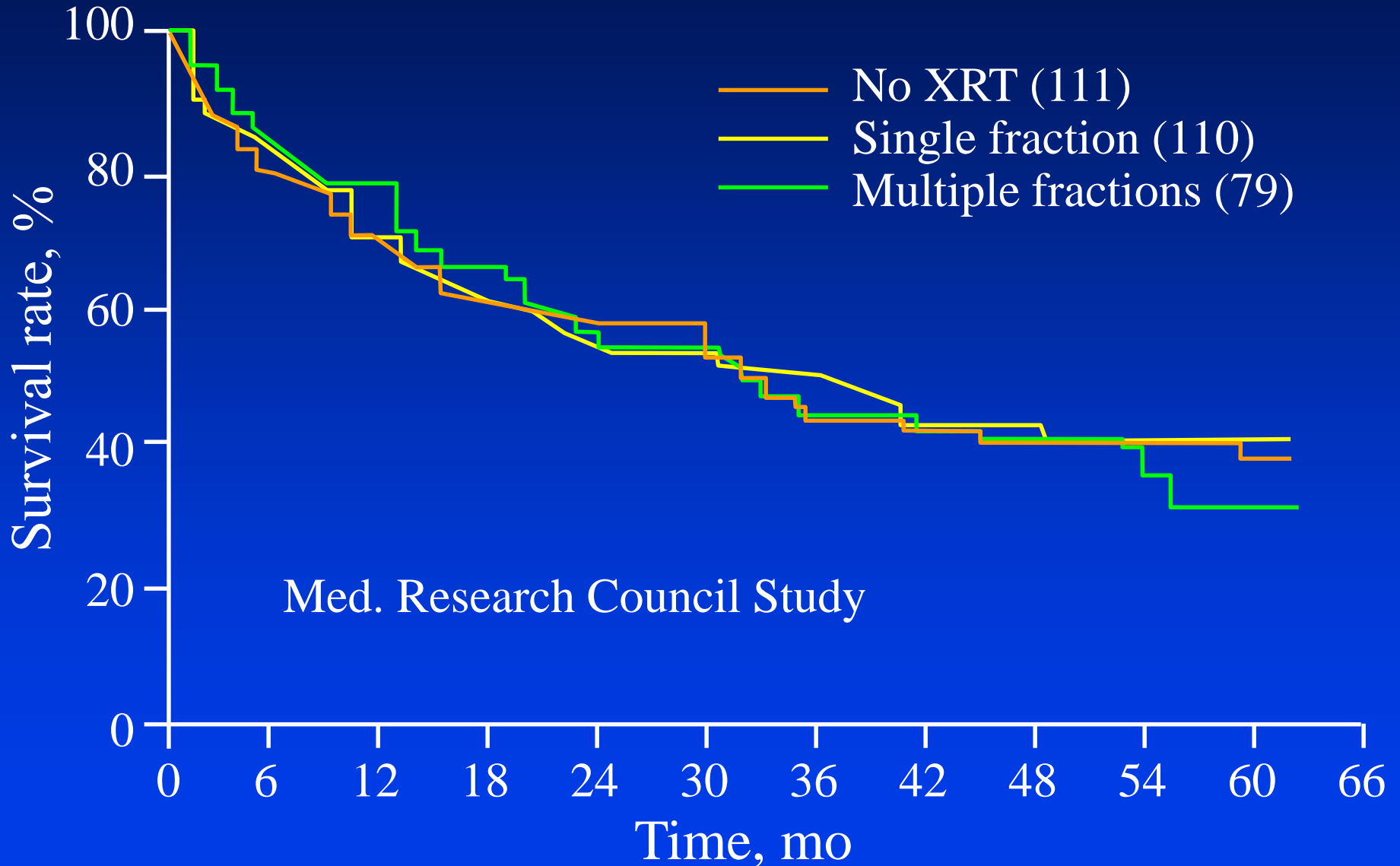
Survival of Patients with Dukes' Stage C Rectal Carcinoma in Control and Irradiated Groups



Survival by Treatment Allocated



Survival by Treatment for Dukes' C Cases



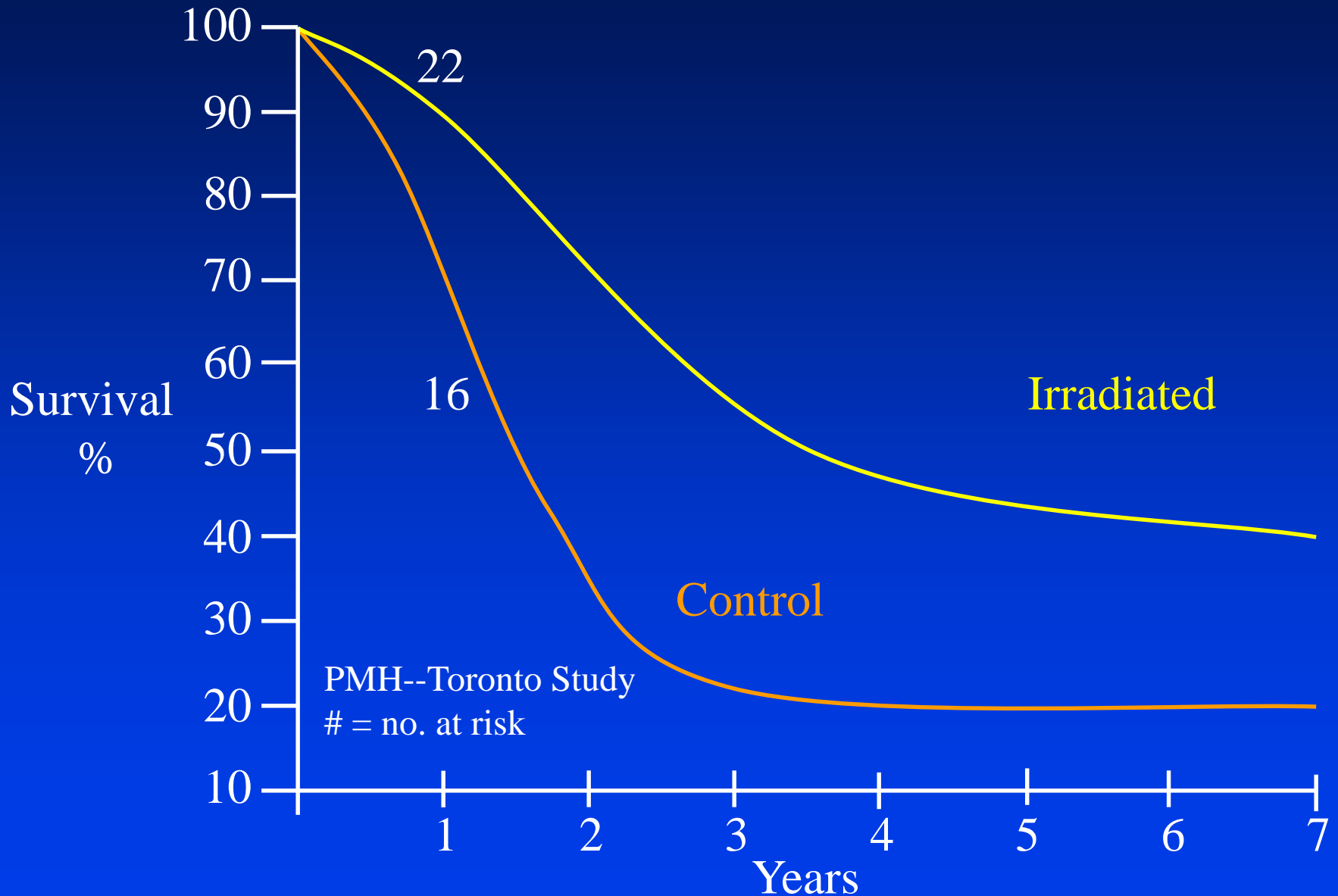
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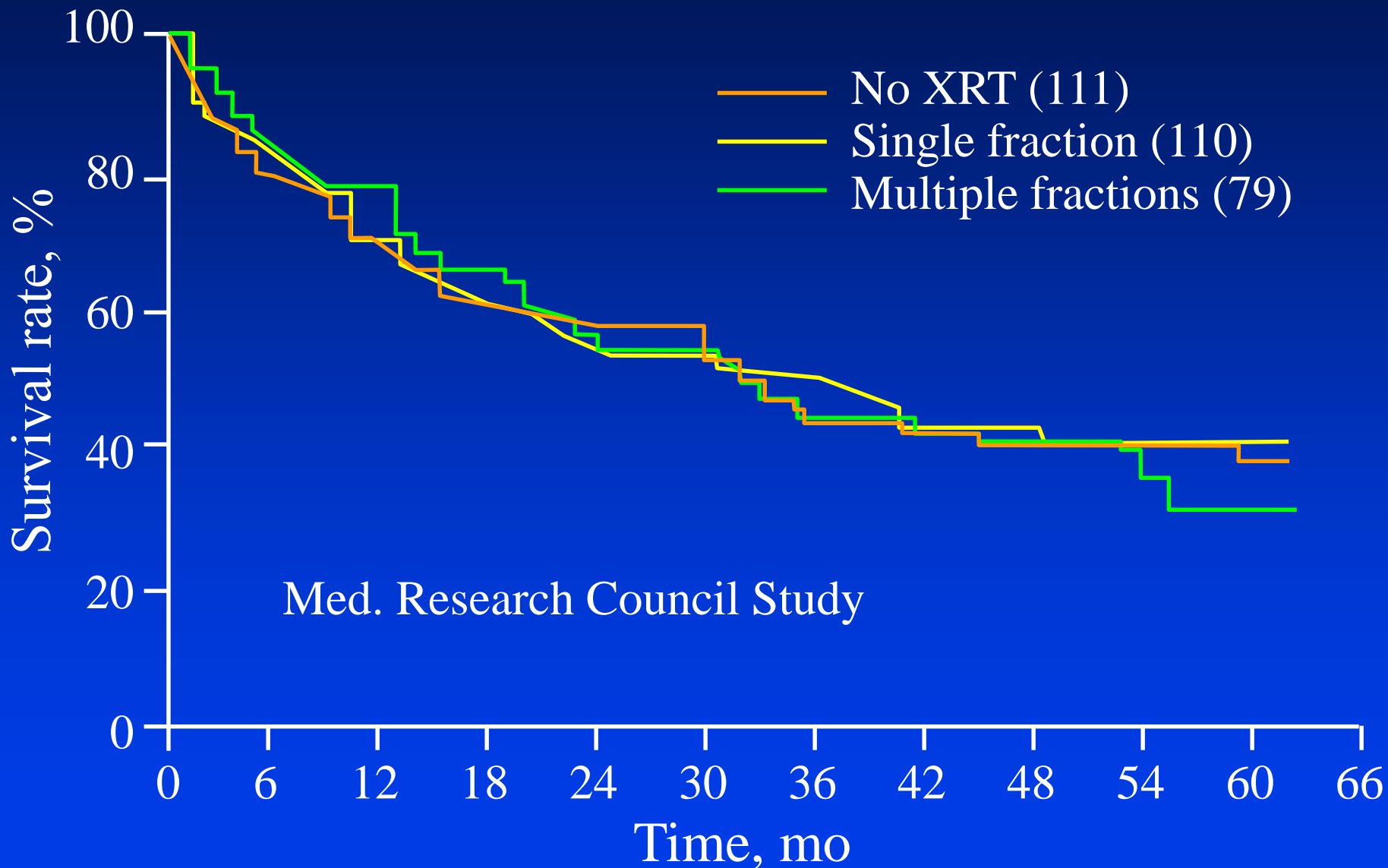
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Maternity Wards, *Baseball* & Clinical Research

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

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 - While in ISIS-2:
 - Aspirin beneficial overall...**

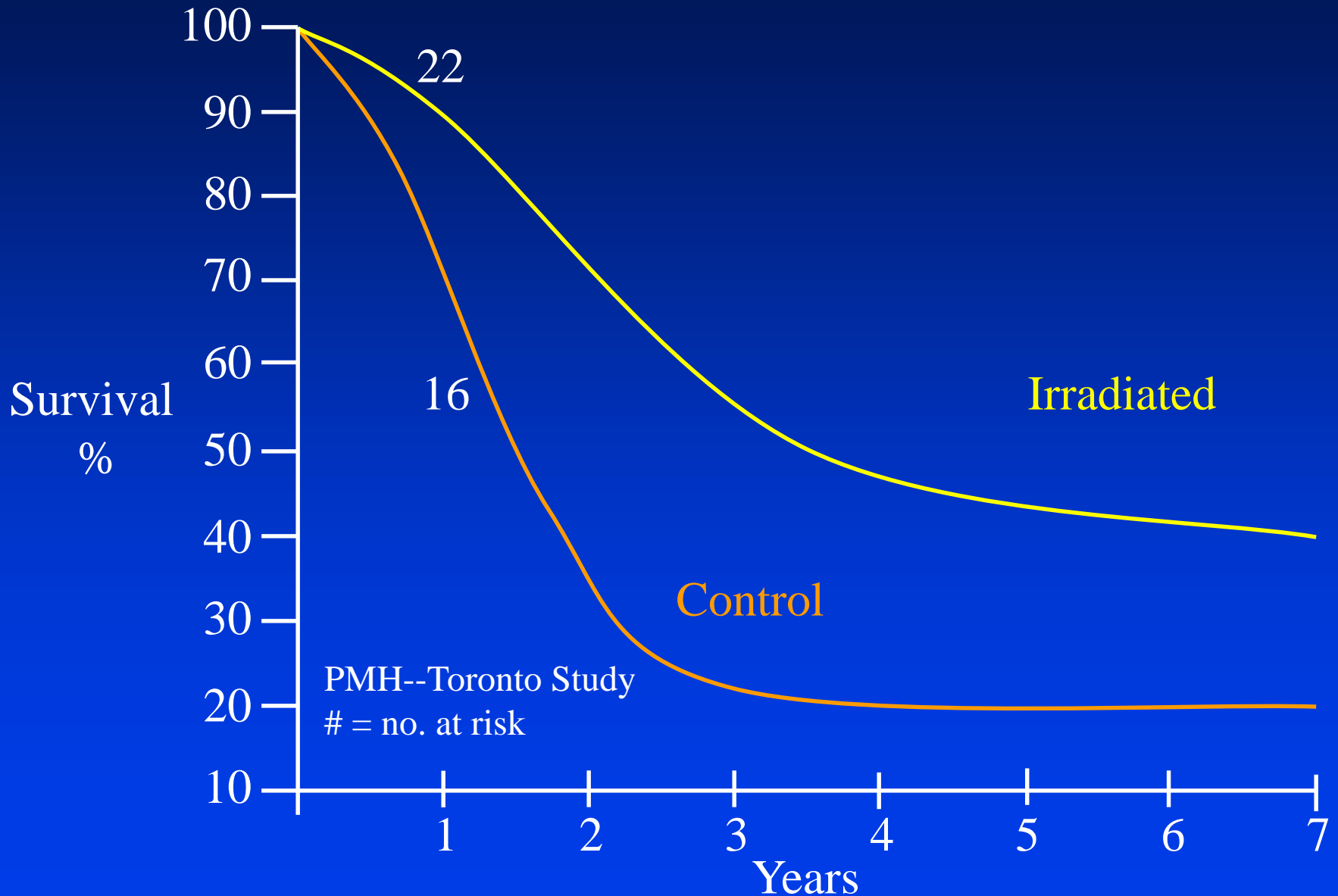
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 - While in ISIS-2:
 - Aspirin** beneficial overall...
 - ... yet **harmful** to patients with
astrological signs **Libra** and **Gemini**

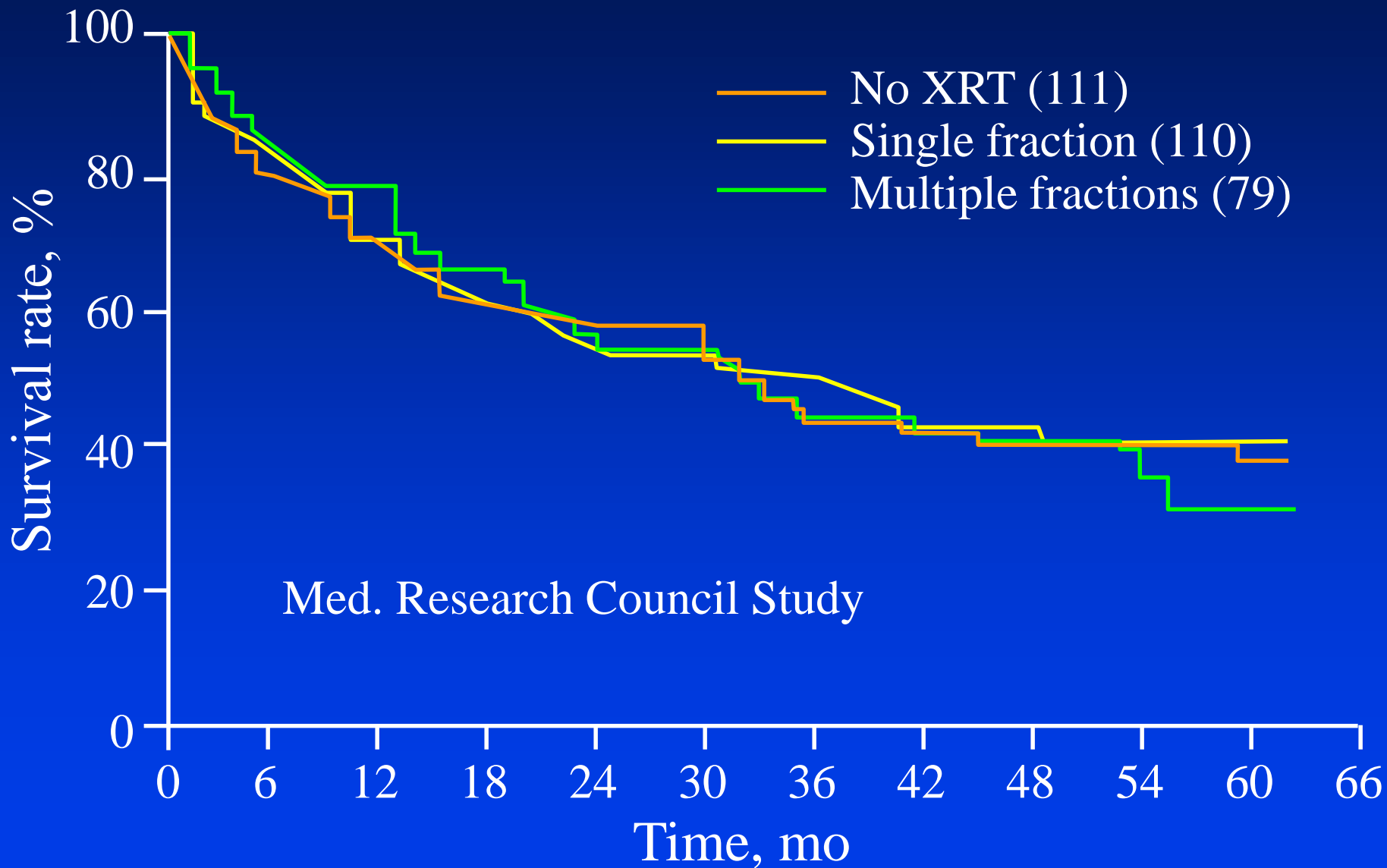
Can Efficacy or Safety Signals Discovered in Exploratory Analyses Be Viewed to be Reliable Results?

- 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

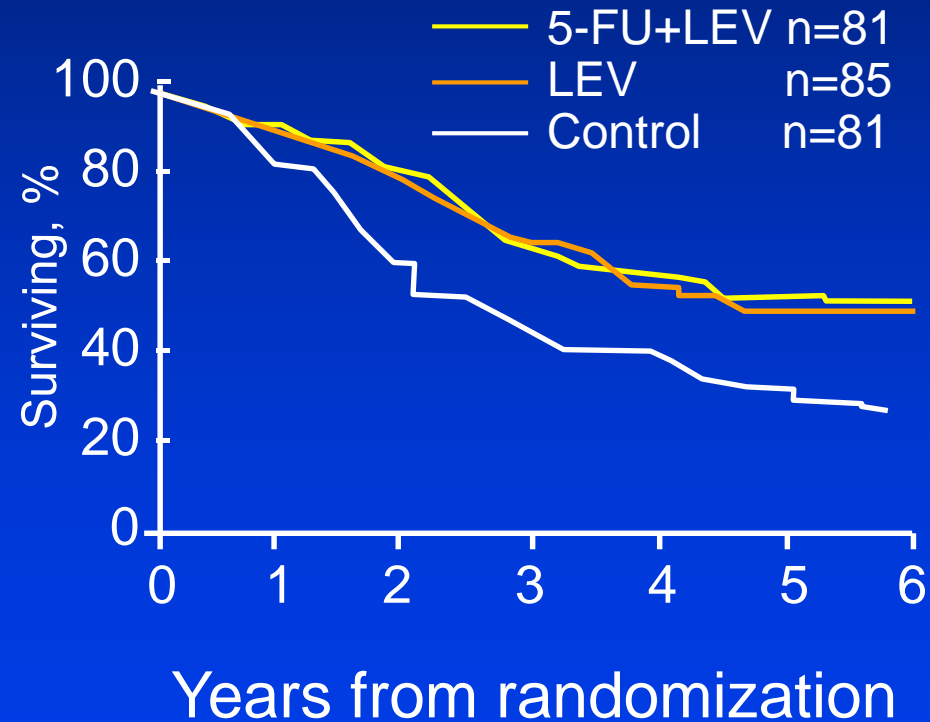


Survival by Treatment for Dukes' C Cases



Surgical Adjuvant Therapy: Colorectal Cancer

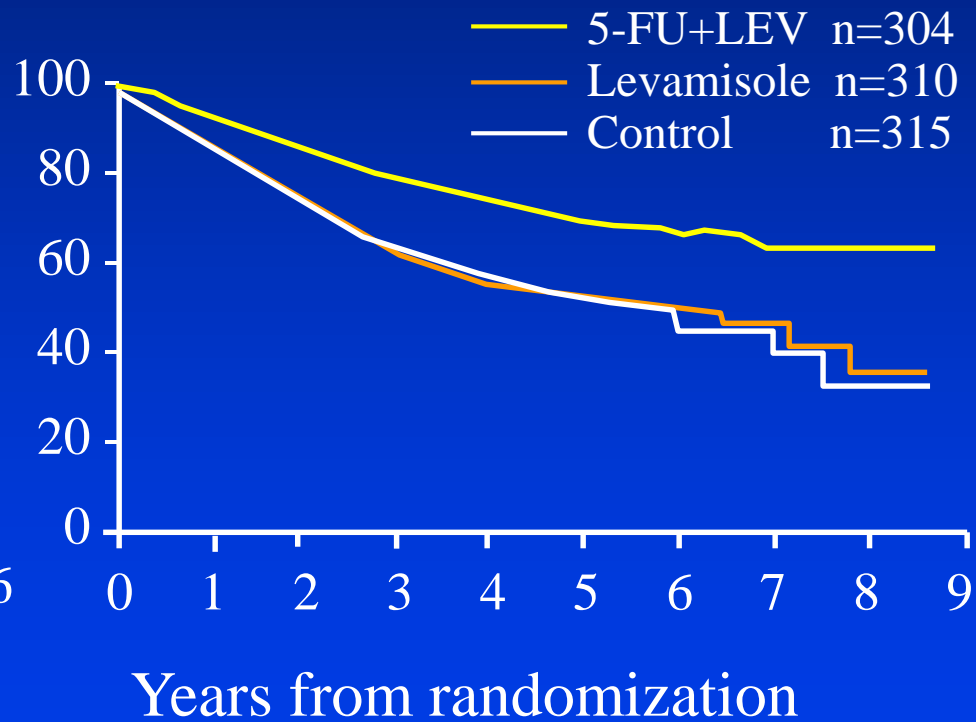
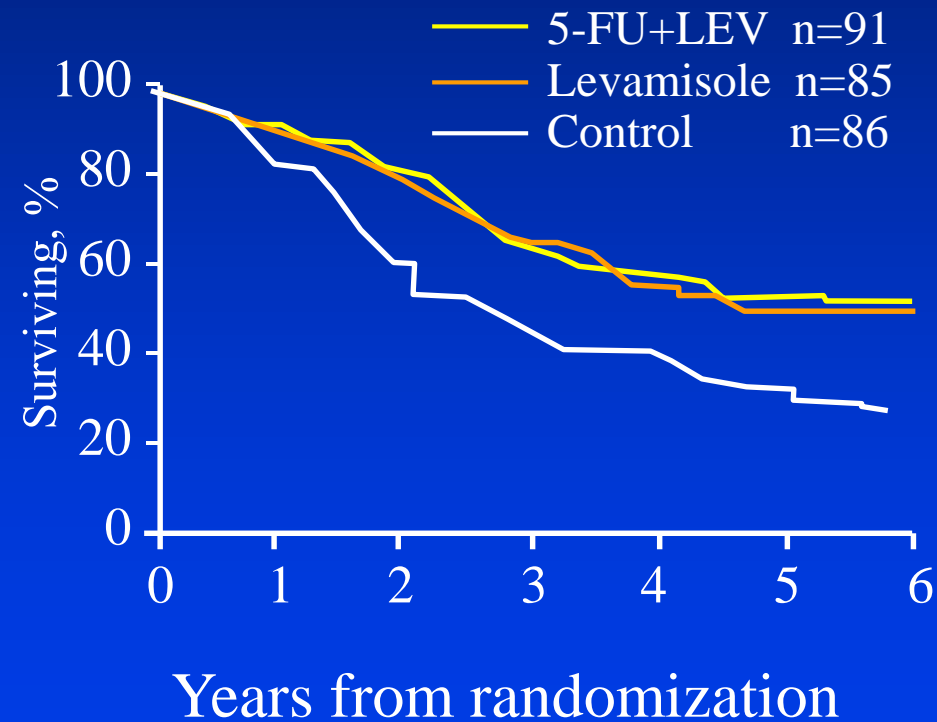
NCCTG Trial



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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
<hr/>			
	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 $\alpha = 0.025$

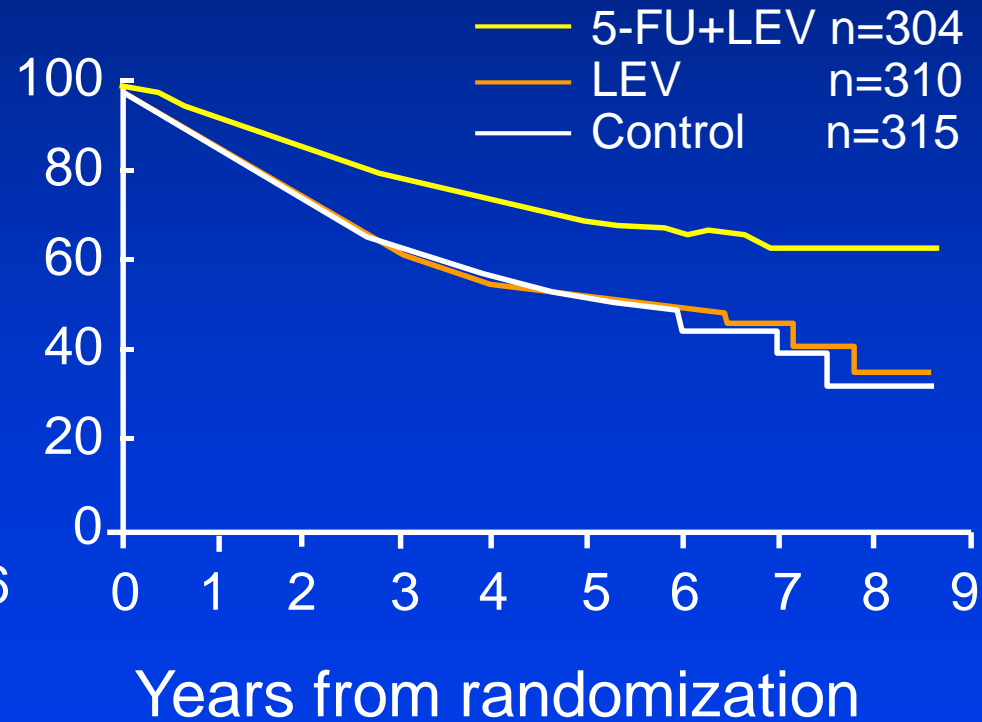
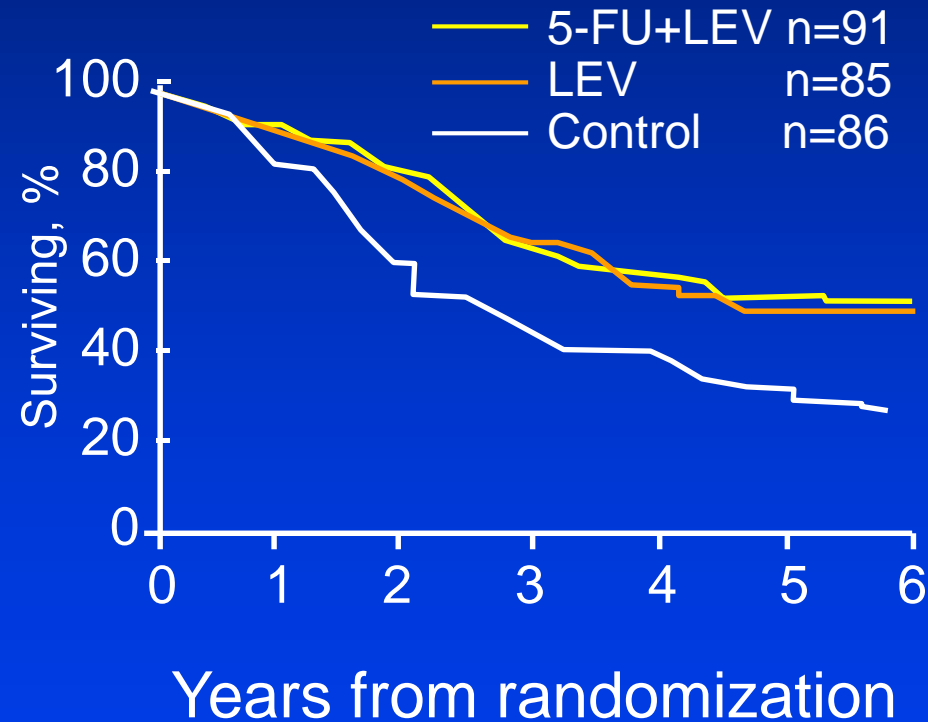
Then, the probability a trial positive will be
a true positive is $540 / 550 = 0.98$

RESULT OF EXPERIMENT	TRUTH		
	Positive	Negative	
Positive	540	10	550
Negative	60	390	450
<hr/>			
	600	400	1000

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“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

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Illustrations and Motivation:

Maternity Wards, Baseball & Clinical Research

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

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

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- Protocol Specified Primary Objective
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- Very frequent wording:
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 - 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...

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

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- Trial #2 conducted in high affinity subgroup:
Time to renal flare:

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- Trial #3 conducted in high affinity subgroup
with prespecified truncation at 12 months follow-up:

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with prespecified truncation at 12 months follow-up:
...early termination by DMC for futility.

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

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Principles & Insights

"The Goal of Clinical Research:

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