Summer Institute in Statistics for Clinical Research

Obtaining insights

to recognize and effectively address scientifically challenging issues in

- Design
- Conduct
- Analysis/Reporting

of clinical trials

Summer Institute in Statistics for Clinical Research

Exploratory Analyses: Why Do We Need Particular Caution?

July 13, 2023

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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

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Illustrations and Motivation:

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Illustrations and Motivation:

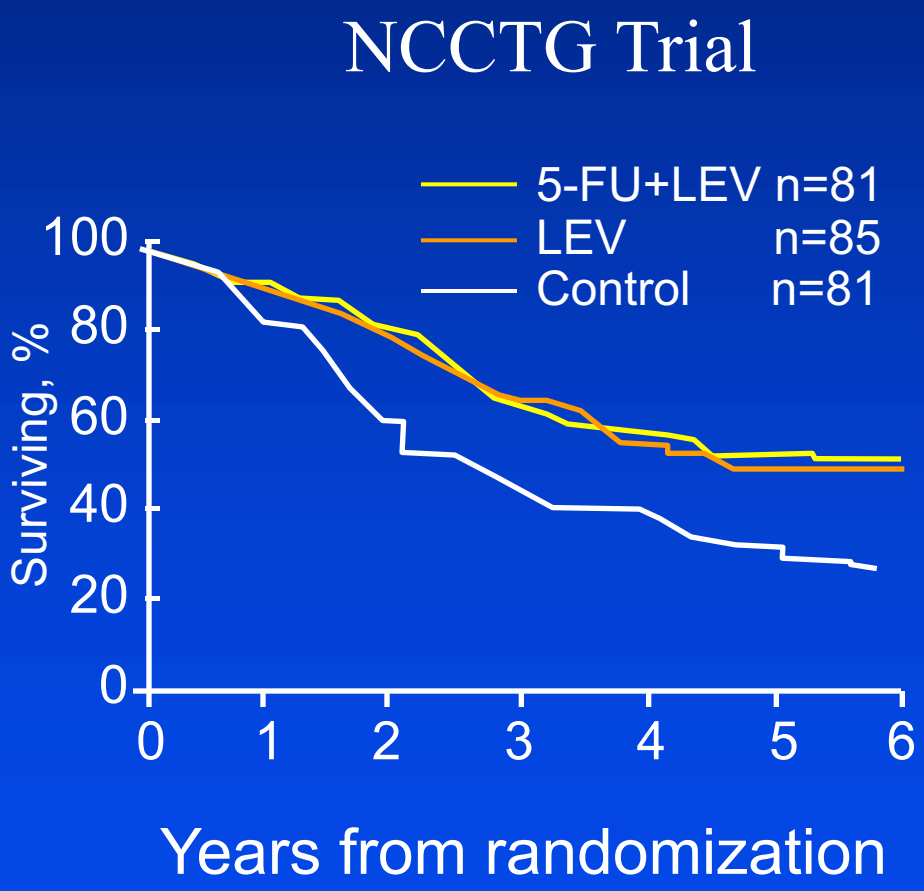
Maternity Wards, Baseball & Clinical Research

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



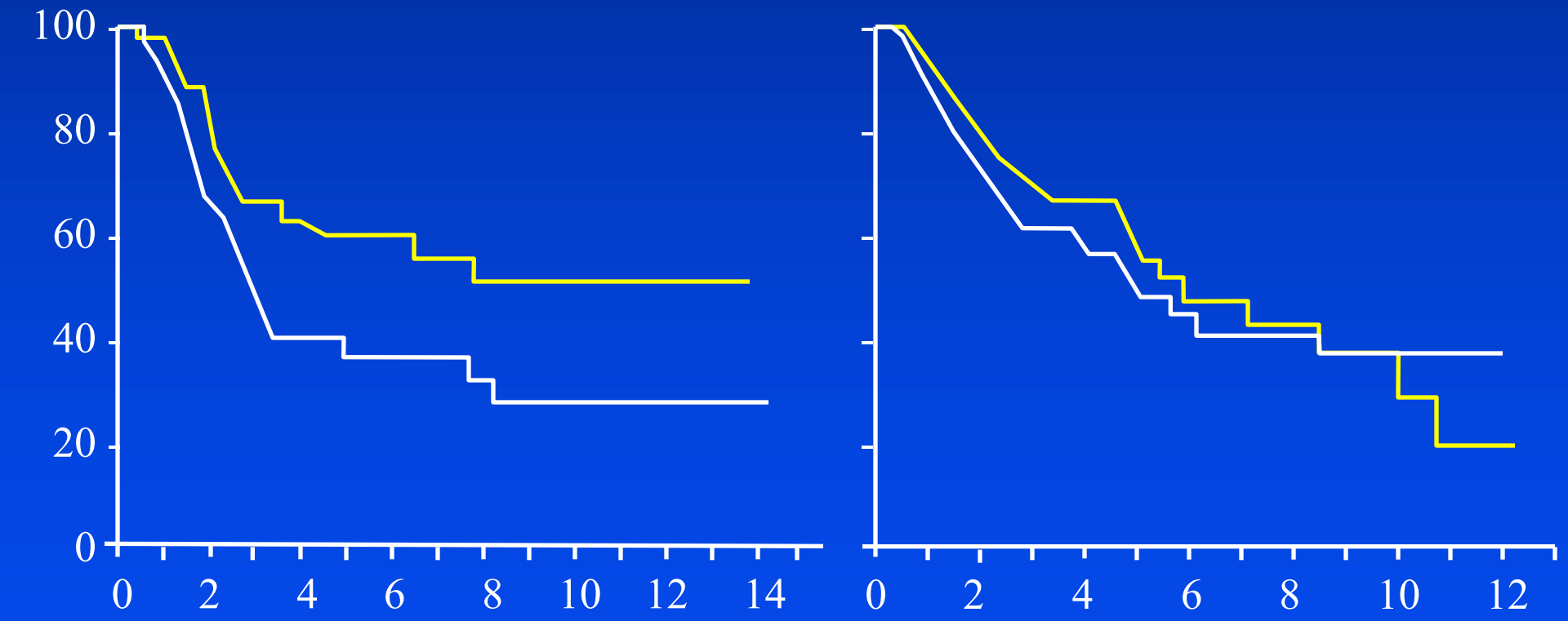
NORTH CENTRAL TREATMENT GROUP STUDY
Looking at Treatment Effect on Overall Survival

Females Only

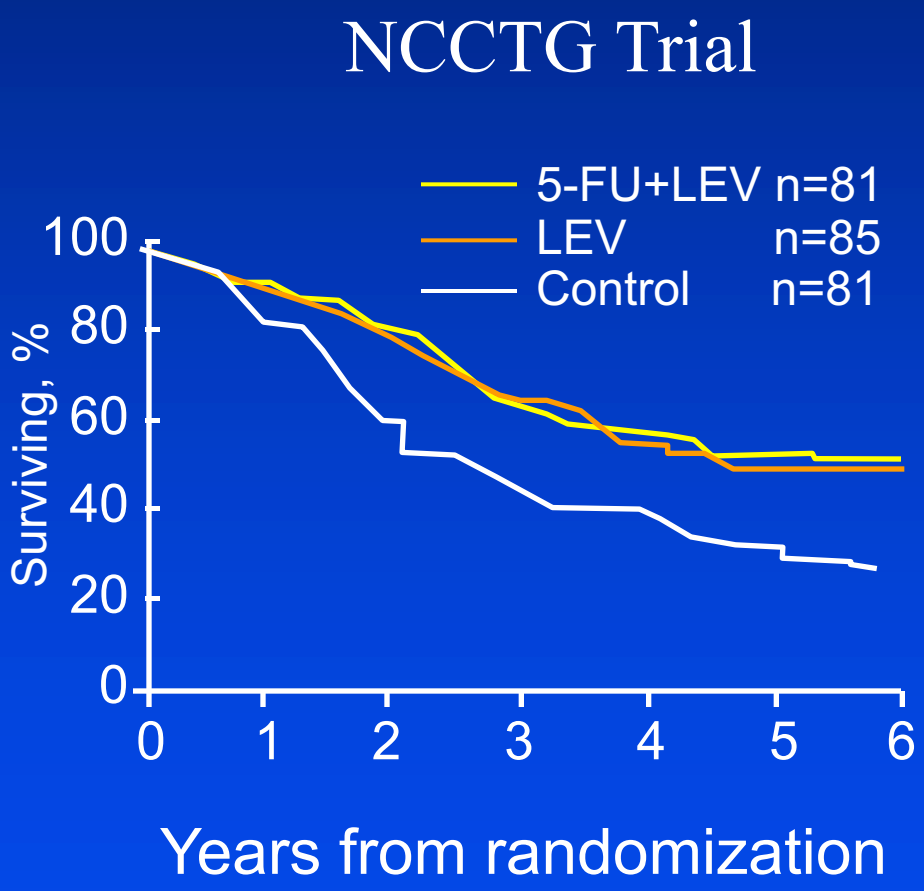
	At Risk	Death	5-Yr Estimate
5-FU+Levamisole	44	21	57%
Follow-Up Only	43	29	40%

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



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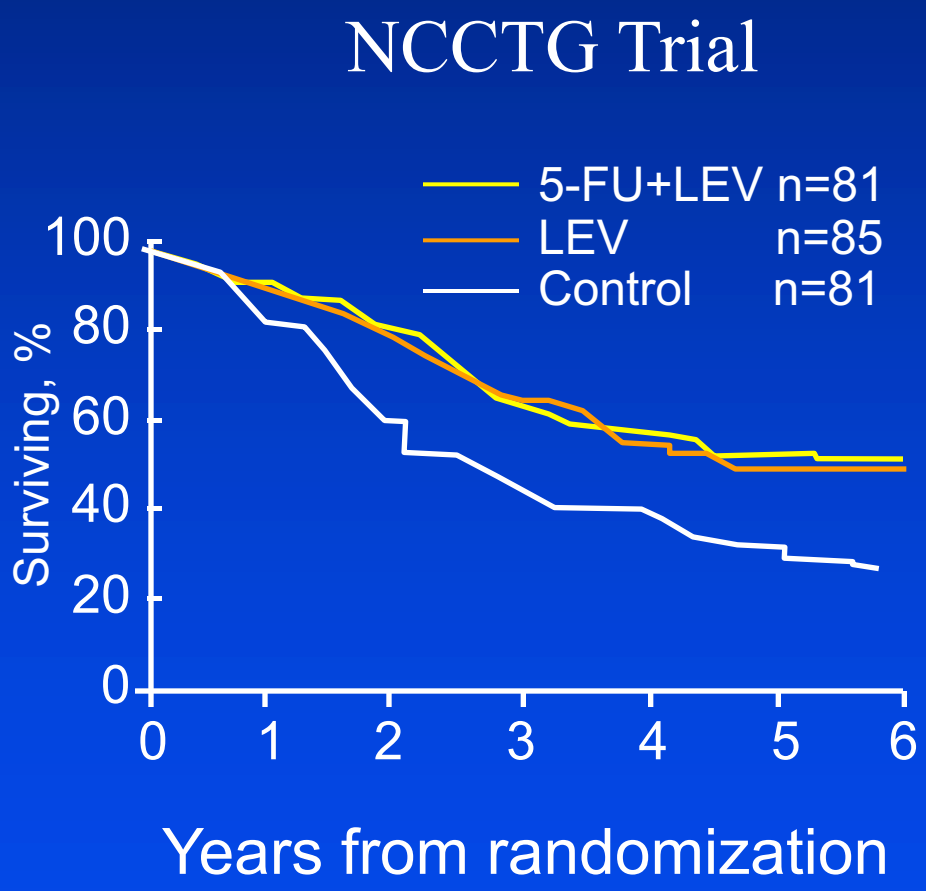
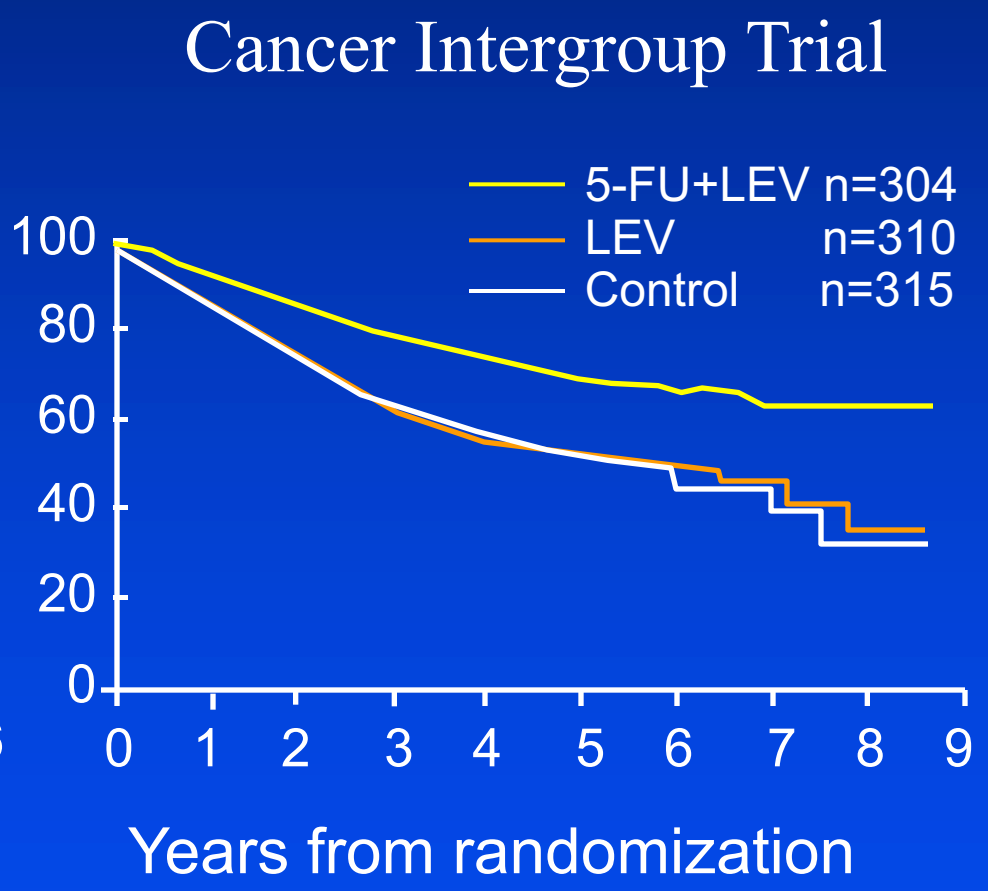




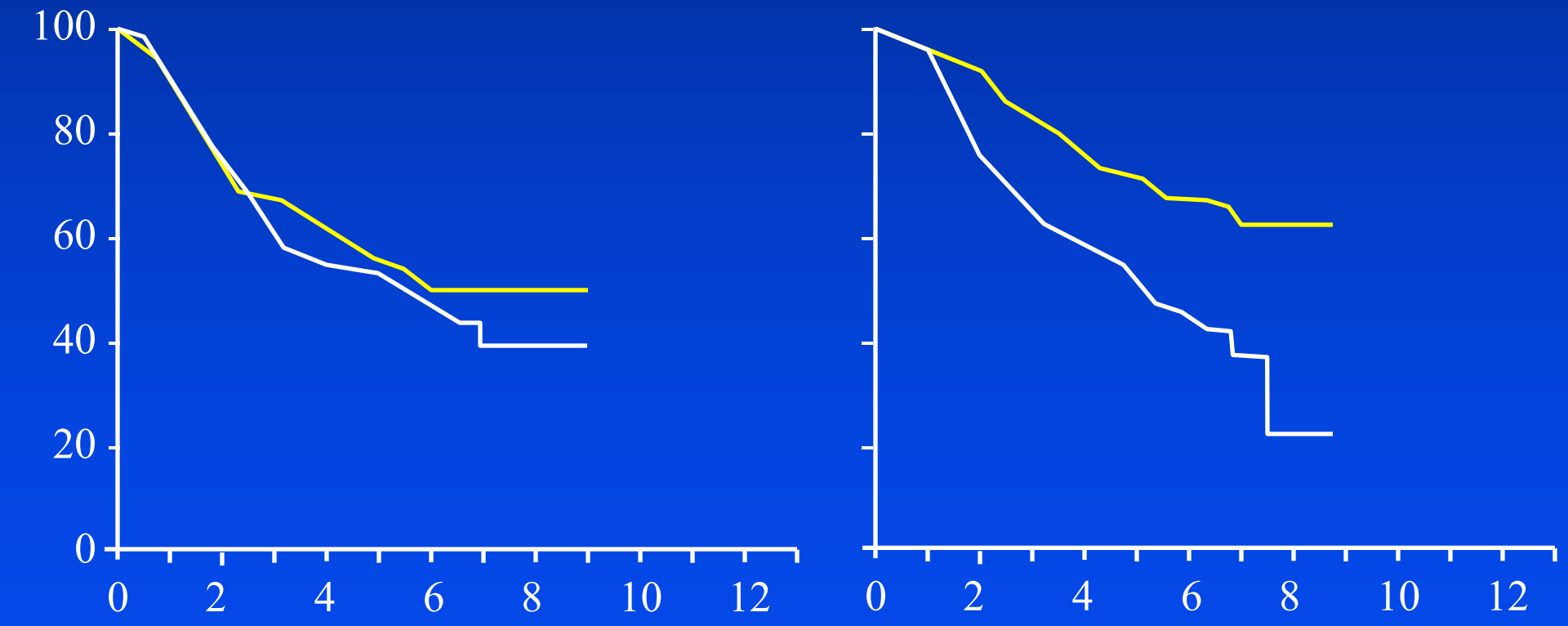
INTERGROUP STUDY 0035
Looking at Treatment Effect on Overall Survival

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

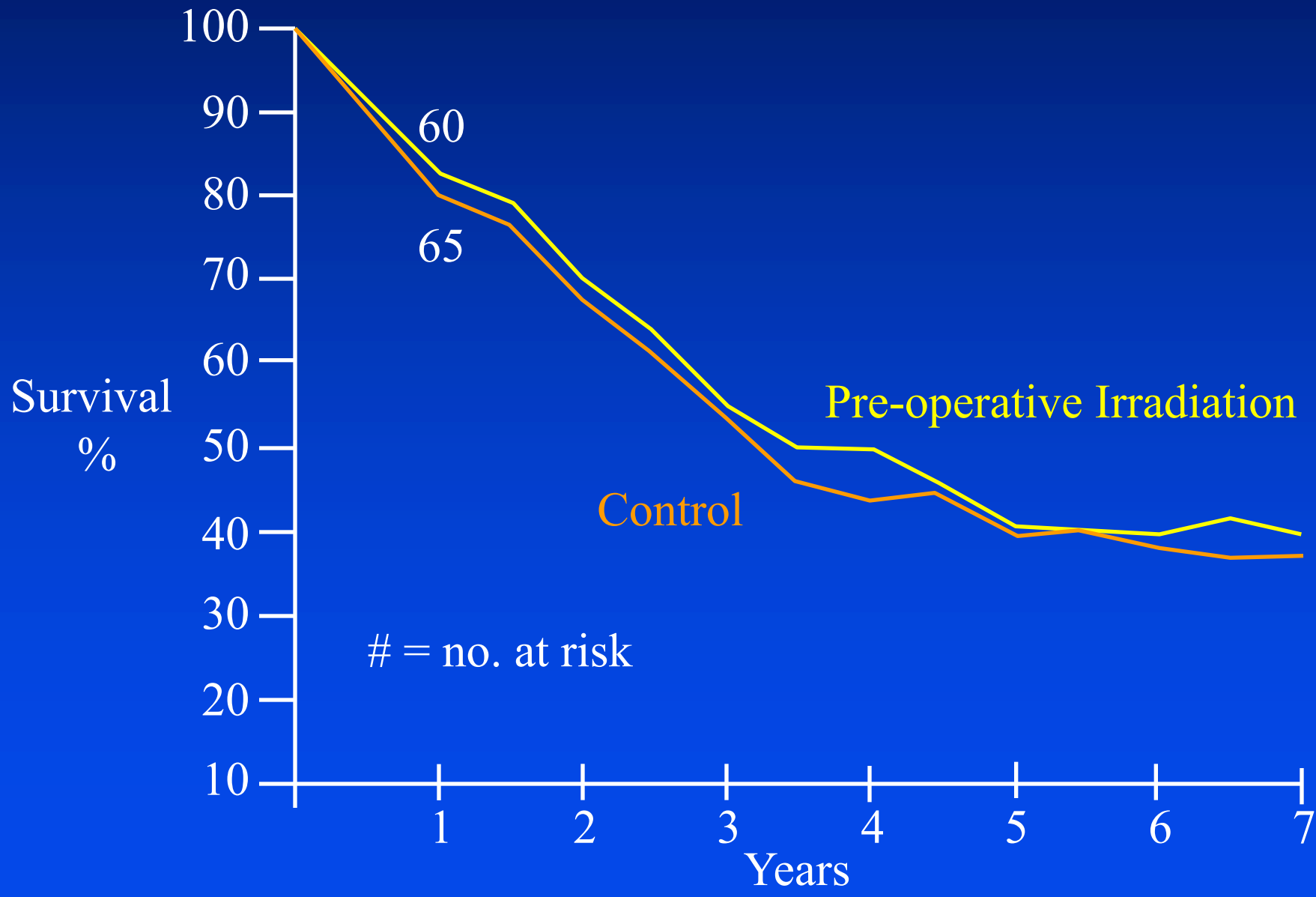
Percent ↓ in Death Rate: $\frac{\text{5-FU + Levamisole}}{\text{Control}}$

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%**

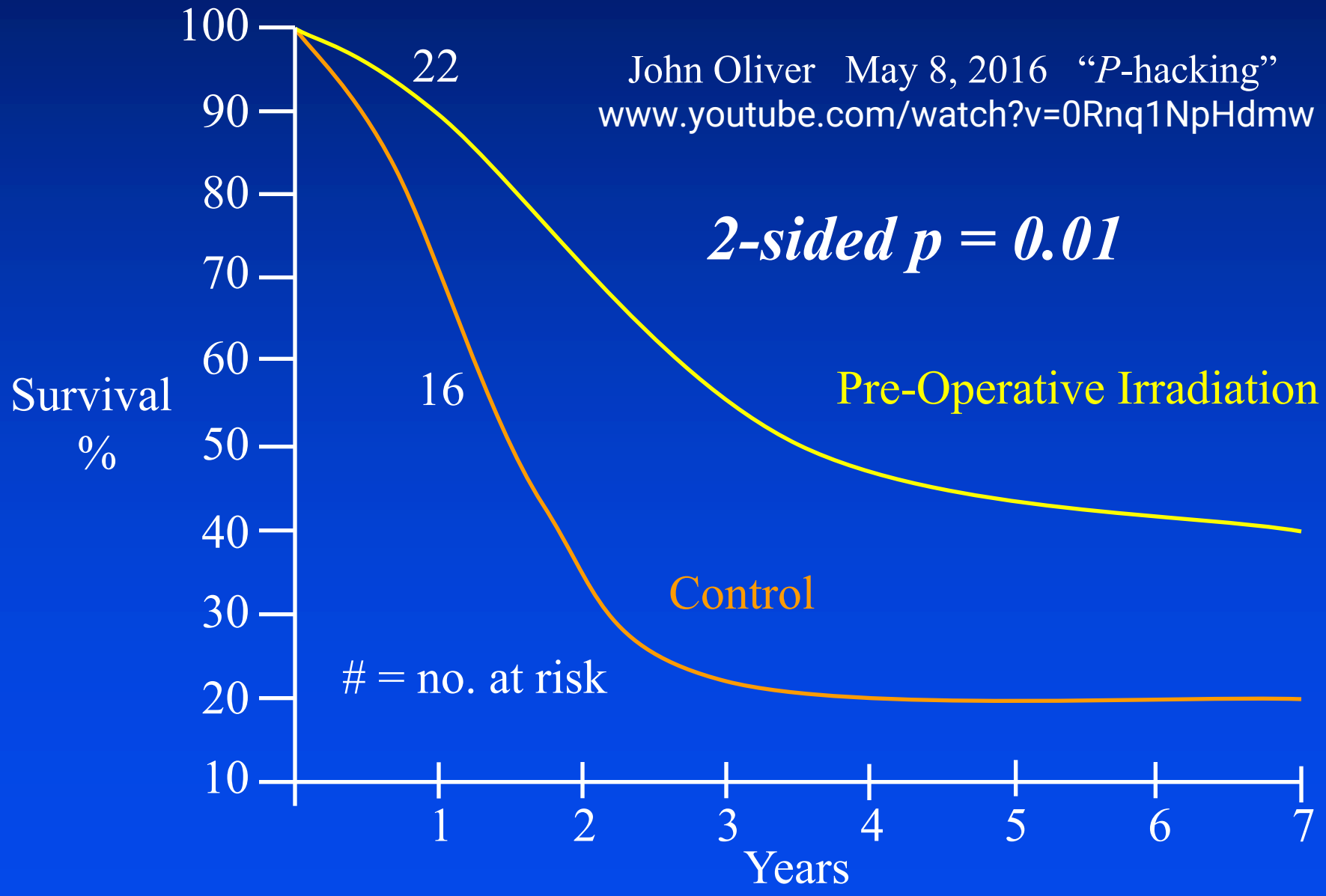
An Illustration of Exploratory Analyses: Post-hoc Subgroup Analyses

Radiation Treatment in Rectal Cancer
Princess Margaret Hospital

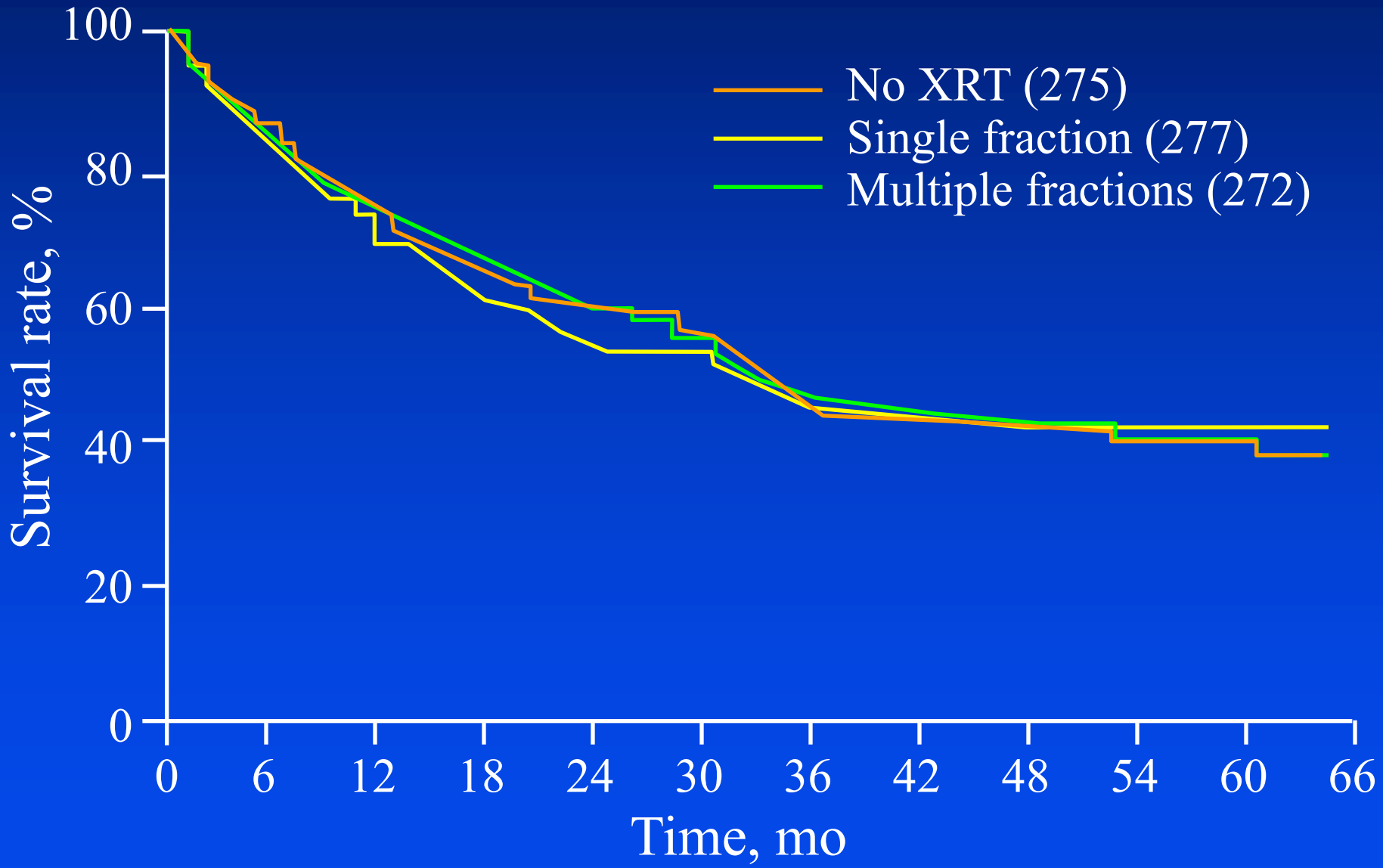
Survival of Patients with Rectal Carcinoma
Princess Margaret Hospital, Toronto (1977)



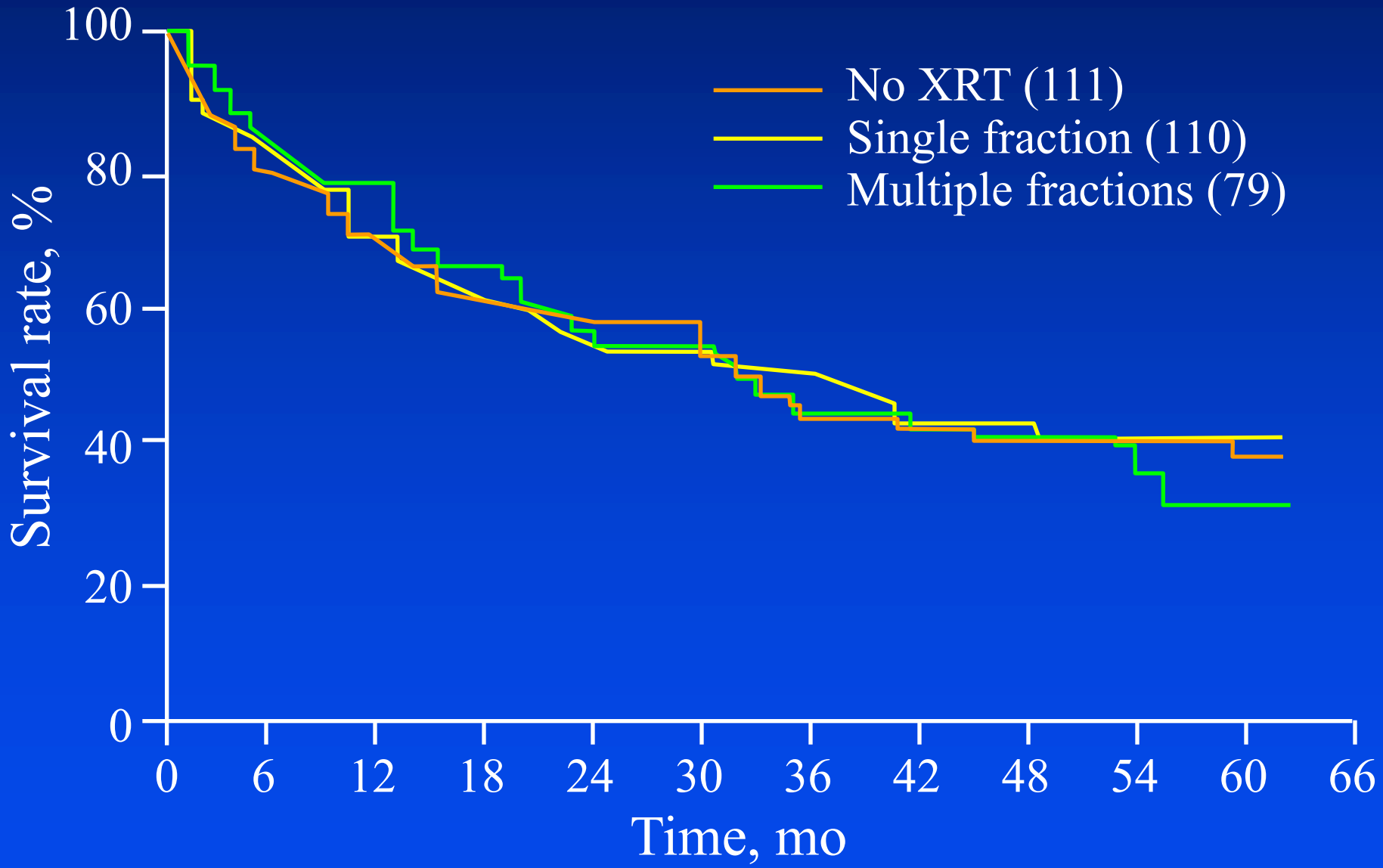
Survival of Patients with Rectal Carcinoma
Exploratory Subgroup: **Dukes' Stage C Disease**



Medical Research Council (MRC) Confirmatory Trial



MRC Subgroup Analysis: **Dukes' C Cases**



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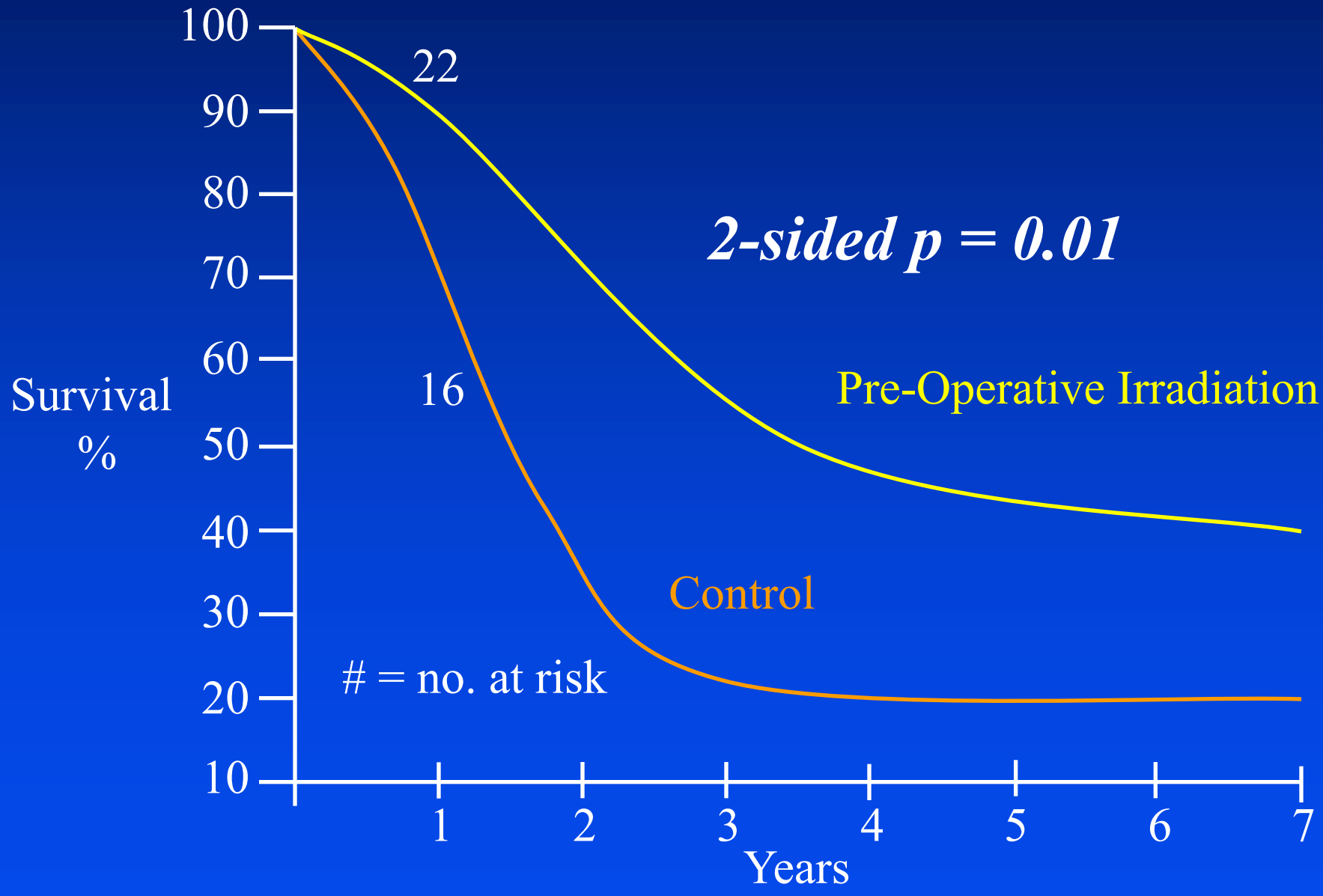

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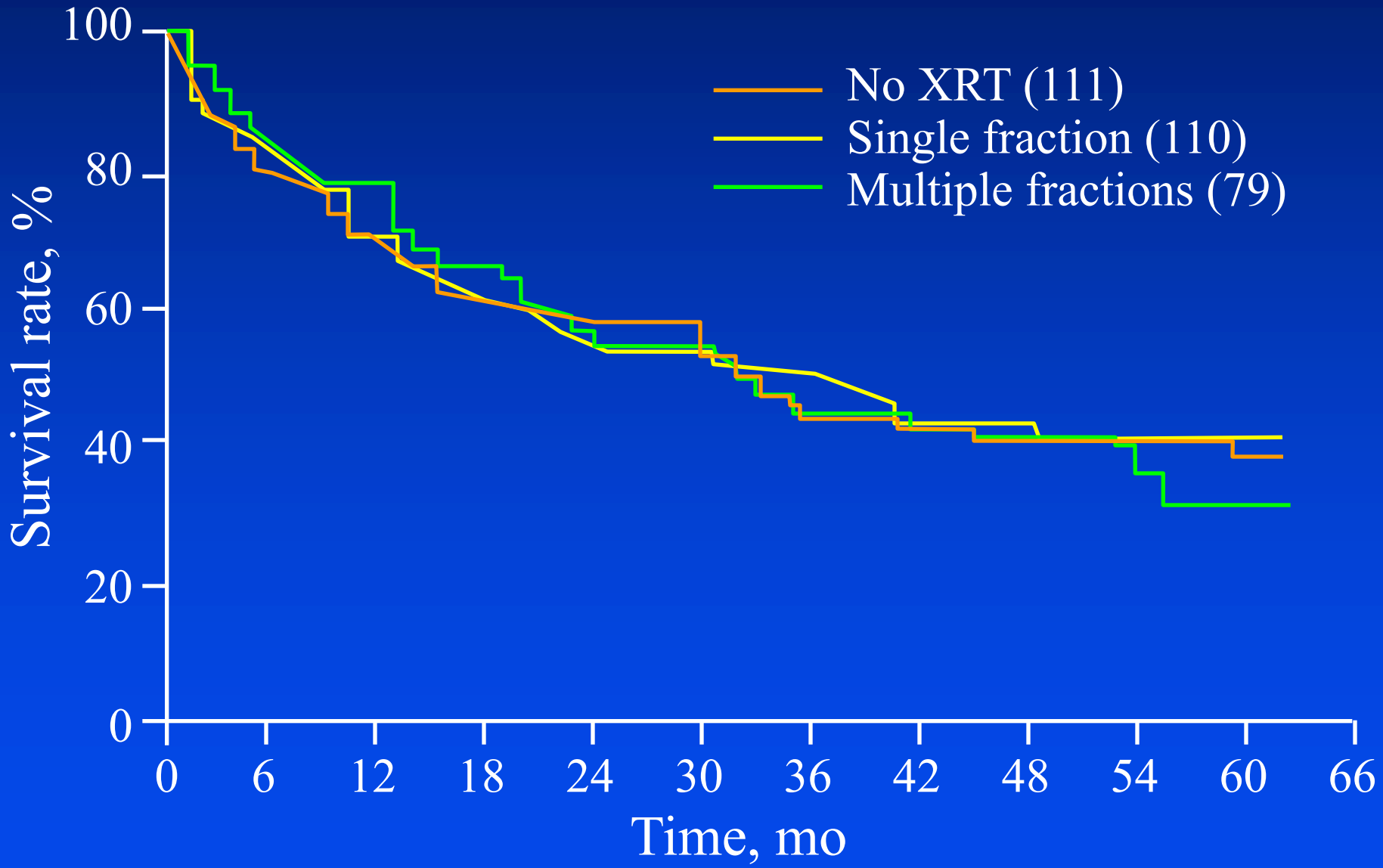

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  - Subset restriction not confirmed by ISIS-2, ASSET, AIMS
  - While in ISIS-2:
    Aspirin beneficial overall…
    … yet **harmful to** patients with
      astrological signs **Libra** and **Gemini**

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

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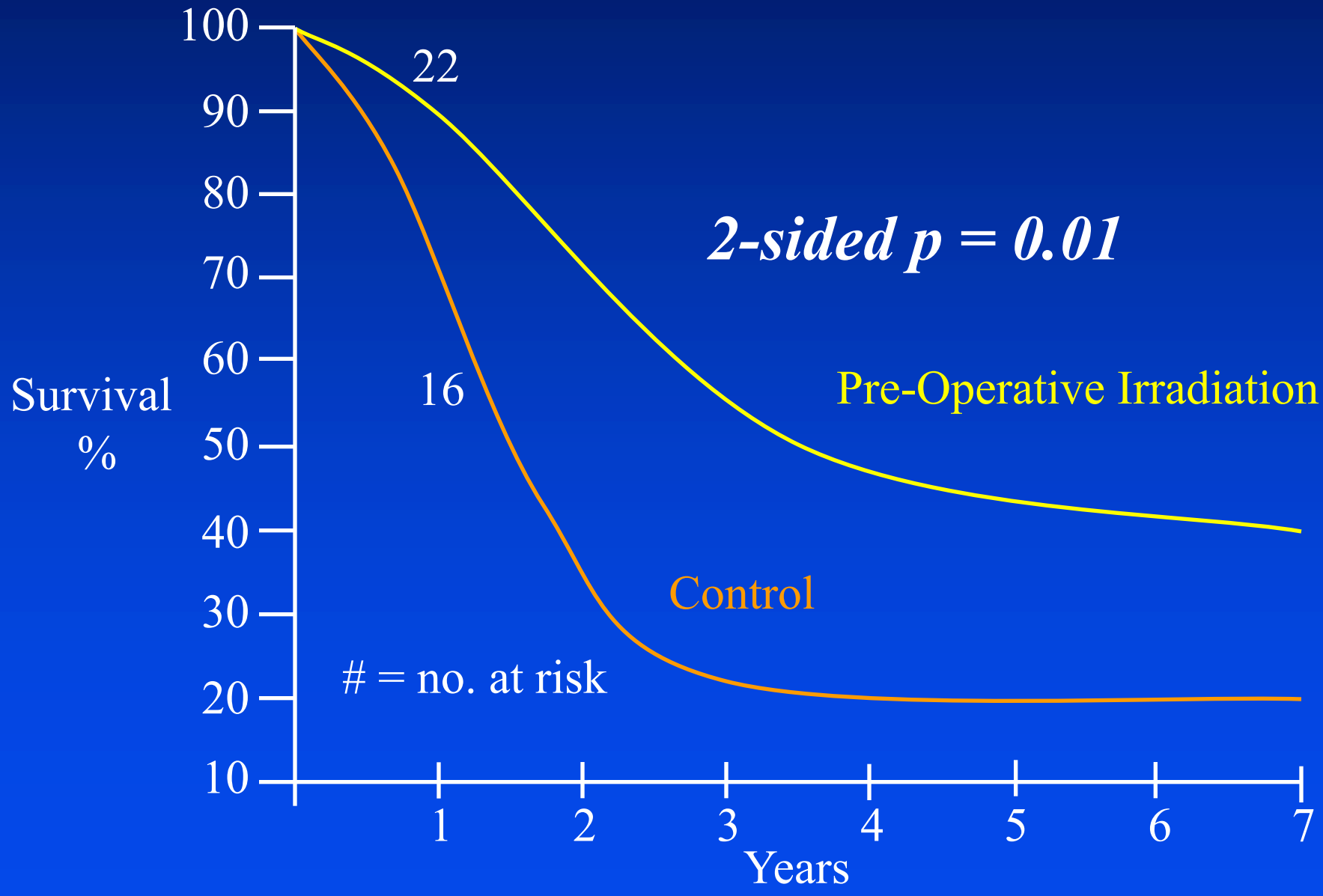

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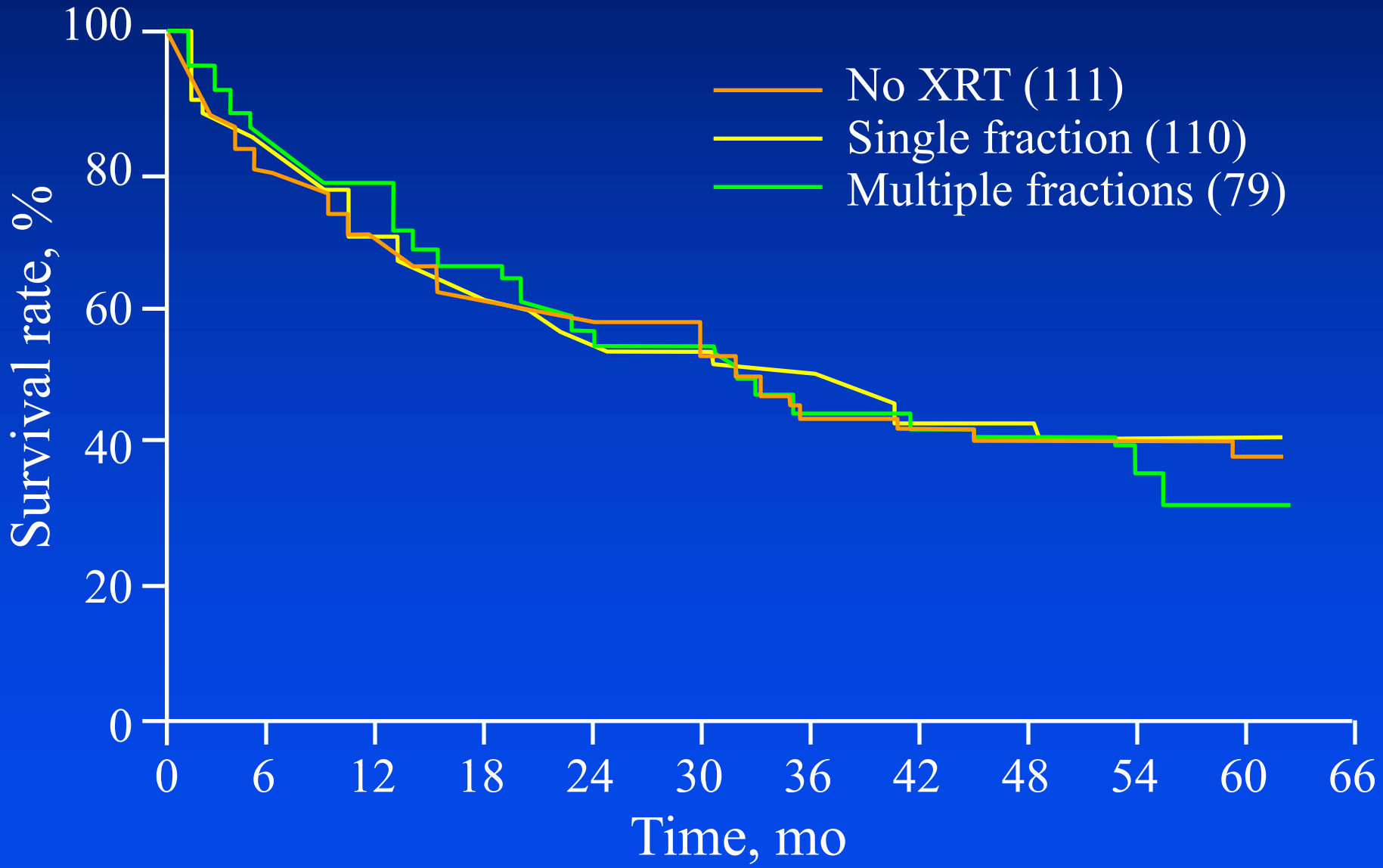

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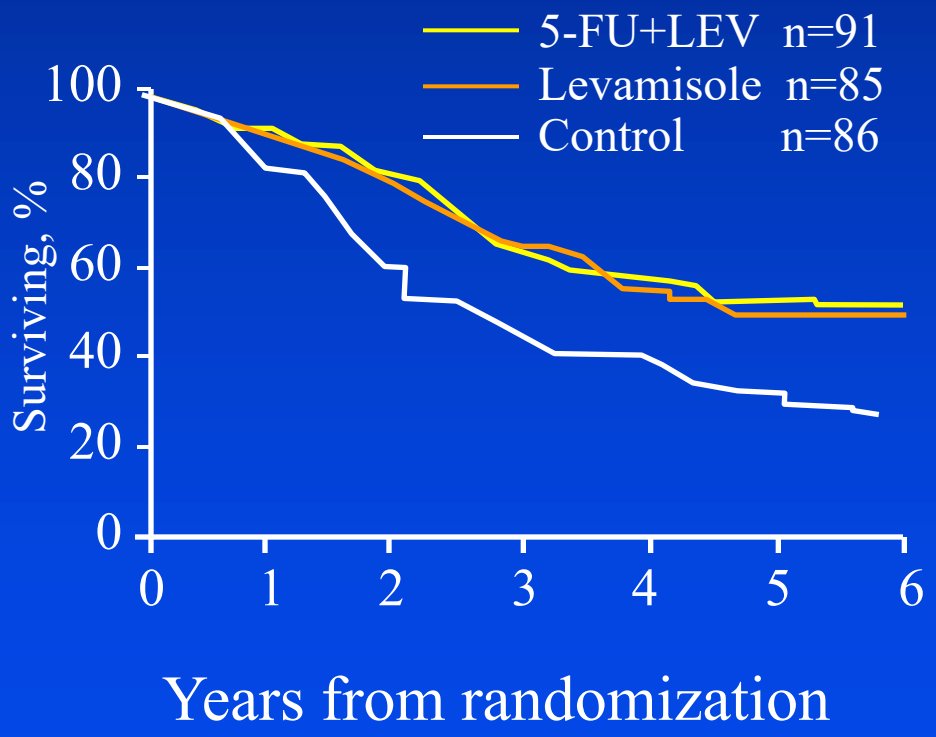

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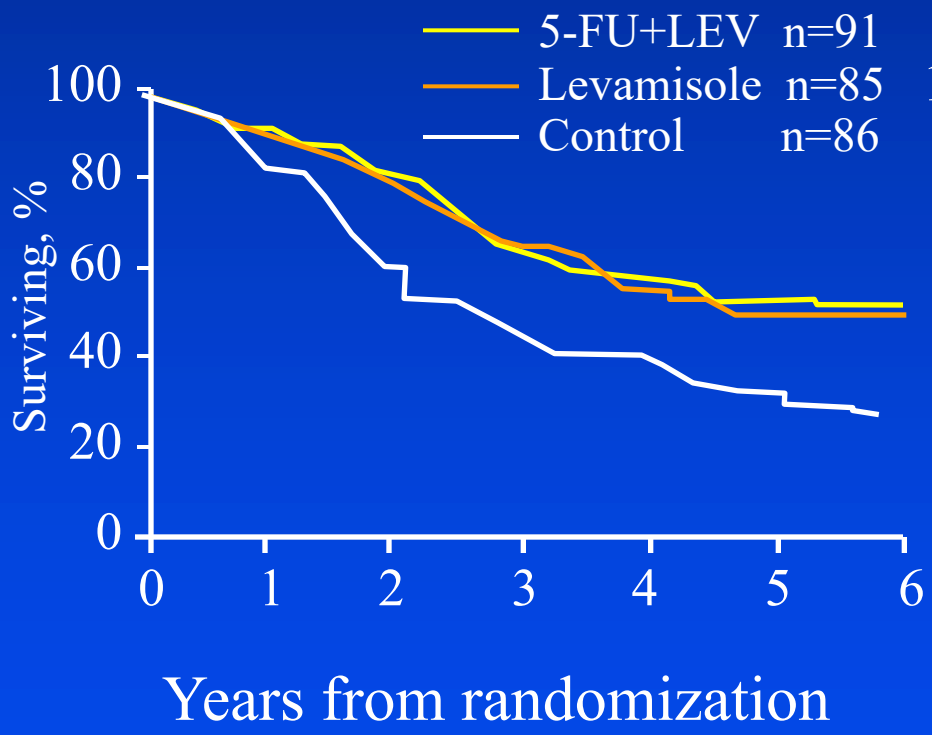
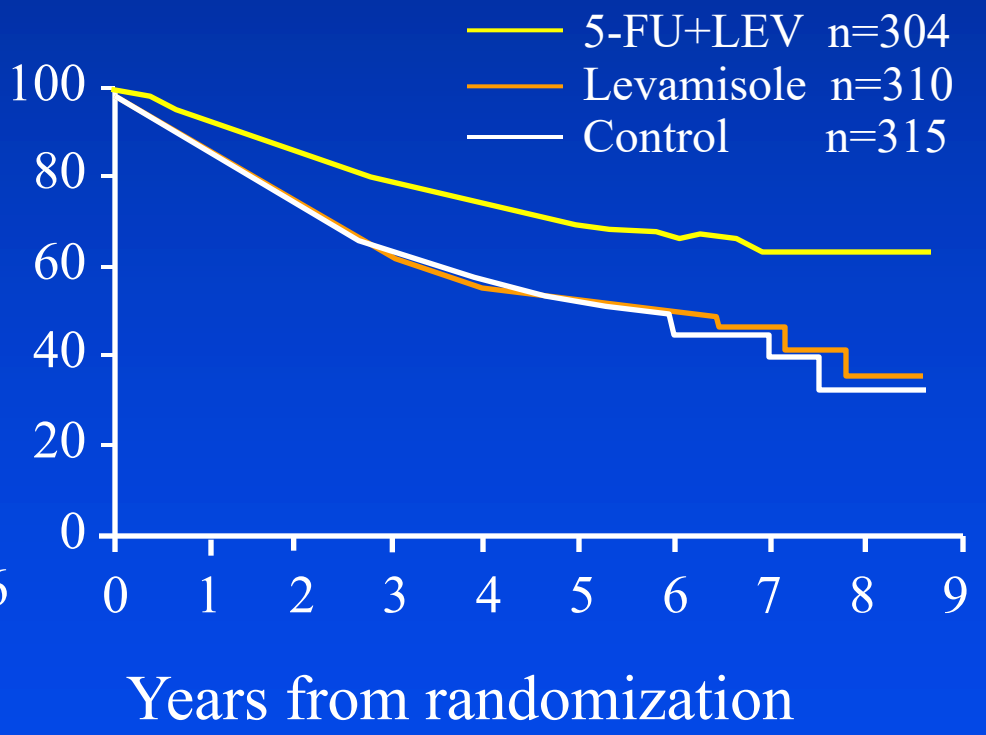


Cancer Intergroup Trial



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
	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

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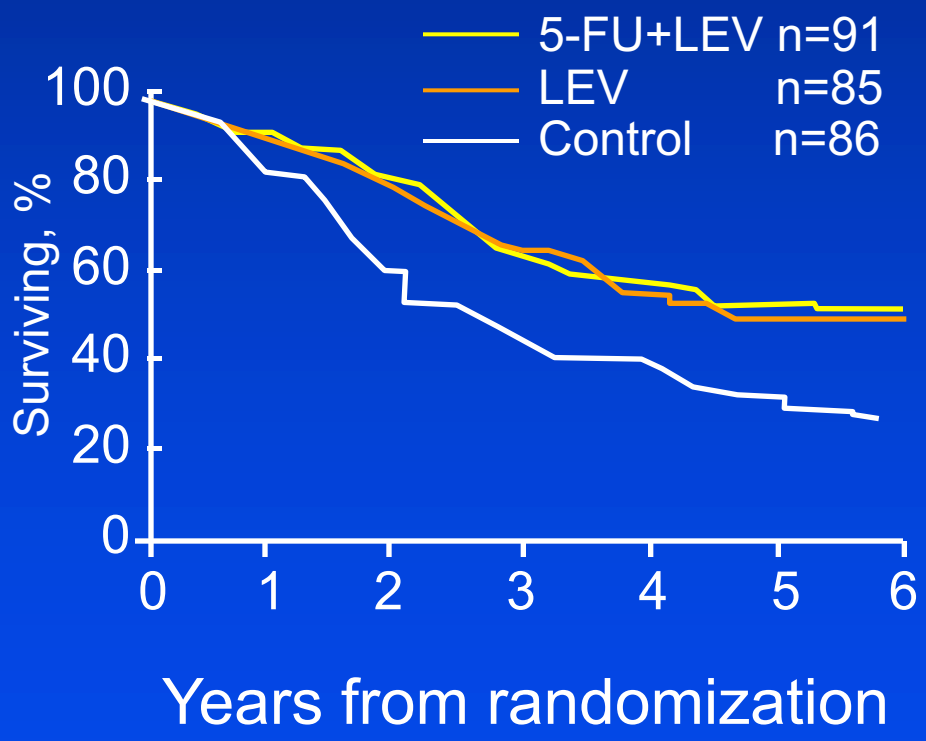

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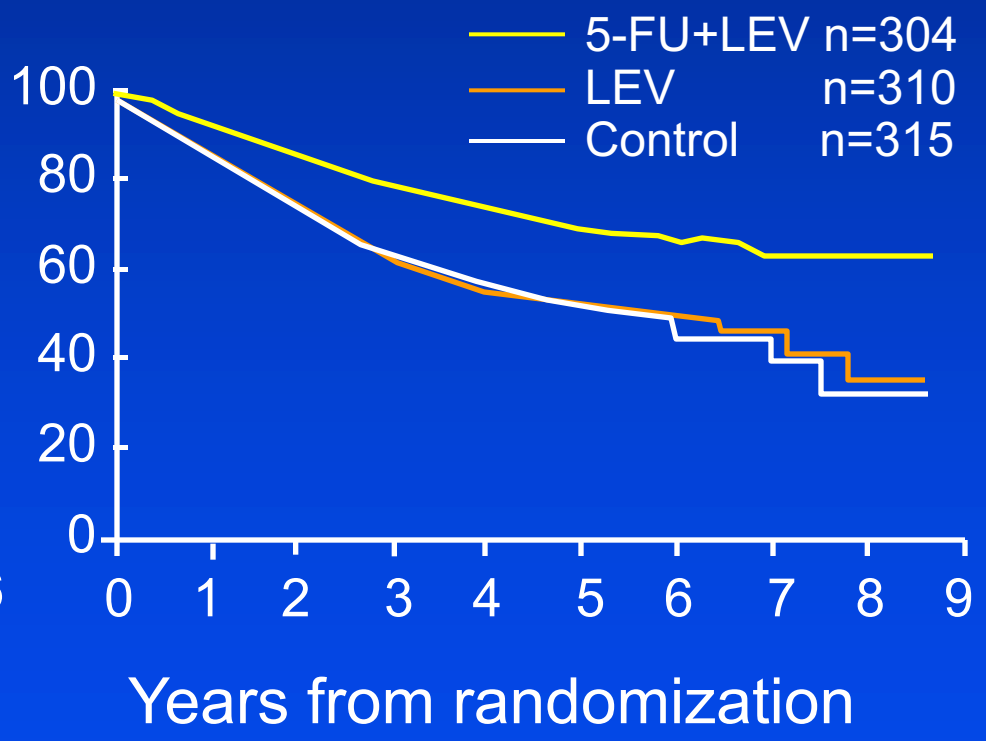

"It isn't so much the things we *don't know* that get us in trouble.

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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- 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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  …early termination by DMC for futility.

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

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Some Conclusions

- Recognize bias resulting from
  strong interest to achieve "positive" results
- When refereeing journal publications, request:
  - *the clinical trial protocol*
  - *the statistical analysis plan (SAP)*
  - *the clinical study report (CSR)*
- The only *P*-values presented in CSRs & publications should be for α-spending analyses pre-specified in the SAP
- Recognize unreliability of Exploratory Analyses…
  …generating hypotheses, but with "random high" bias

Principles & Insights

"The Goal of Clinical Research:

Principles & Insights

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To *Determine Whether*,
Not to *Establish*,
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