Clinical Trials Statistics for Non-Statisticians

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Components of Research

1. Formulate hypotheses
2. Define sample
3. Design the study
4. Analyze the data
5. Report the results
   – Aim of our research is to evaluate cancer treatment

Planning a Study: How It Starts

Investigator → Idea !

New treatment = Rx E(xperimental)

Standard treatment = Rx S(tandard)

Planning a Study: Quantifying the Idea

- Aim of the study
  - Compare Rx E with Rx S
  - Rx S is basis of comparison for Rx E
- Study hypothesis
  - Rx E will be better than Rx S
- Define study endpoint
  - How will 'better' be measured?

Planning a Study: Defining Endpoints

What do we mean ‘is better’ ?

Efficacy = effective = it works !

- How long patient lives (survival)
- How tumor responds (tumor response)
- If/when disease returns (disease recurrence)

Planning a Study: Identifying a Target Population

Want to make conclusions about population

- Usually cannot assess population
- Take sample of population
  - Random or at least representative
- Generalize to population
- Probability of being correct/incorrect

Planning a Study: Identifying a Target Population

- Cannot randomly select patients
- Can randomize treatment
- Can stratify

Designing the Study

Target pop: Patients with metastatic breast cancer

Endpoint: Tumor response [TR] (Response/non-response)

Given: TR of Rx S is 20%

Want to test: TR of Rx E is 40%

Number of patients

Error probabilities

Designing the Study

- Hypotheses
- Error probabilities – margin of error
- Power probability
- Number of patients (N)

- All components are interrelated

Designing the Study: Setting Error Probabilities

Decision	Truth	
	No difference	**Difference**
Difference	**alpha**	**power (1-beta)**
No difference	**confidence (1-alpha)**	**Beta**

Designing the Study

- Probability of being incorrect
  - Decide there IS a difference when there really IS NOT
  - Alpha → small
- Probability of being correct
  - Decide there IS a difference when there really IS
  - Power → large

Designing the Study: Example 1

- Testing new drug *in vitro*
- If ‘significant’, continue development
- If not, abandon drug

Designing the Study: Example 1

Decision	Truth	
	Drug not effective	**Drug is effective**
Is effective	**alpha = do more experiments**	**power (1-beta)**
Not effective	**confidence (1-alpha)**	**Beta = abandon effective drug**

Strategy = Set larger alpha, smaller beta
(→ larger power)

Designing the Study: Example 2

- Testing new drug in patients
- Several existing alternative Rxs
- If ‘significant’, market drug
- If not, abandon drug

Designing the Study: Example 2

Decision	Truth	
	Drug not effective	**Drug is effective**
Is effective	**alpha = use useless drug, deprive good standard**	**power (1-beta)**
Not effective	**confidence (1-alpha)**	**Beta = abandon effective drug (but others available)**
Strategy = Set smaller alpha		

Designing the Study

Aim is to make a definitive decision
Therefore, set cutoff that will define significance'

Set
- Alpha small (incorrect)
- Power large (correct)

Convention
- Alpha 0.05 – 0.10
- Power 0.80 +

Designing the Study

Given 20%

To test 40%
with alpha = 0.05
and power = 0.80

How many patients do we need?

Designing the Study

Given 20%

To test 40%
with alpha = 0.05
and power = 0.80

How many patients do we need?
Requires 80 pts/Rx

Designing the Study: Power & N

Given 20%

To test	40%	40%
alpha =	0.05	0.05
power =	0.80	0.90
Pts/Rx	80	107

Designing the Study: Power & N

Given 20%

To test	40%	40%	40%
alpha =	0.05	0.05	0.05
power =	0.80	0.90	0.95
Pts/Rx	80	107	133

Designing the Study: Alpha & N

Given 20%

To test	40%	40%
alpha =	0.05	0.10
power =	0.80	0.80
Pts/Rx	80	63

Designing the Study: Alpha & N

Given 20%

To test	40%	40%	40%
alpha =	0.05	0.10	0.15
power =	0.80	0.80	0.80
Pts/Rx	80	63	53

Designing the Study: Effect Size & N

Given 20%

To test	40%	50%
alpha =	0.05	0.05
power =	0.80	0.80
Pts/Rx	80	38

Designing the Study: Effect Size & N

Given 20%

To test	40%	50%	60%
alpha =	0.05	0.05	0.05
power =	0.80	0.80	0.80
Pts/Rx	80	38	22

Analyzing the Data: P-value

- Calculated from data
- Probability of getting a result as big or bigger than what we've gotten *if truly no difference*
- Convention for 'significance'

    0.05 or smaller

Analyzing the Data: P-value

We found: TR of Rx S = 21% P=0.02

TR of Rx E = 39%

- *If truly no difference,* repeating the trial many times would give a result as or more extreme than our trial (<21% vs >39%) 2% of the times.
- There is a 2% probability that results are caused by random chance.

Analyzing the Data: Confidence Interval (CI)

- Calculated from data
- Measure of precision
- Convention is 95% CI
- If we were to repeat the trial many times, then the true value would be included in the interval 95% of times.

Analyzing the Data: Confidence Interval

- We found:

  TR of Rx E was 39%

  with 95% CI = 28% – 50%

- If we were to repeat the same trial many times, 95% of times the true TR would lie somewhere between 28% and 50%.
- The true TR would be <28% or >50%.

Analyzing the Data: Confidence Interval

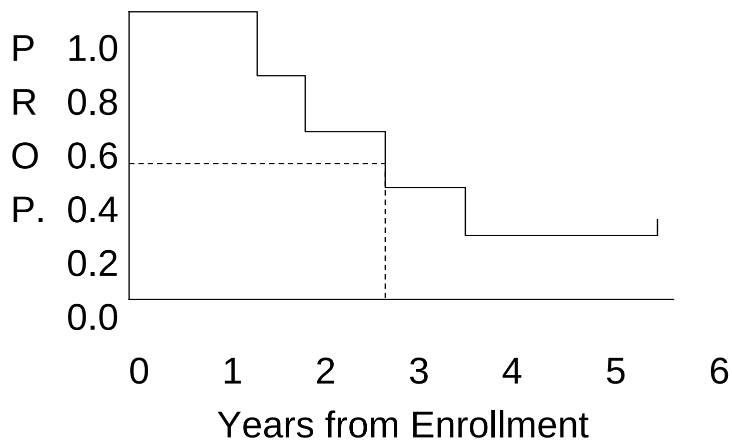
- Role of sample size
- Study reports TR of 65%

# Pts	95% CI
60	52 – 77%
250	59 – 71%
500	61 – 69%
3000	63 – 67%

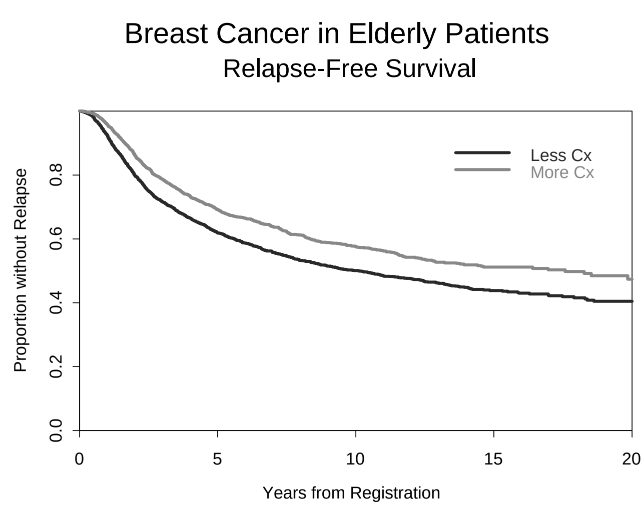
Analyzing the Data: Confidence Interval

- All things remaining equal [eg, hypotheses, alpha] increasing the sample size will result in a narrower interval.

Analyzing the Data: Time to Clinical Event Survival



Analyzing the Data



Analyzing the Data: Subset Analyses

- Examples of subset analyses
  - Patients with ER-positive tumors
  - Patients < 50 years
- Advantages
  - Explore patterns
  - Use results as basis for future studies
- Concerns
  - Study often not powered for subset analyses

Designing the Study

Given 20%

To test 40%
with alpha = 0.05
and power = 0.80

How many patients do we need?
Requires 80 pts/Rx = 160

Analyzing the Data

Given 20%

To test 40%
with alpha = 0.05
and power = 0.80

Requires 80 pts/Rx = 160

Subset analysis on age < 50
40 pts/Rx = 80

Designing the Study

Given 20%

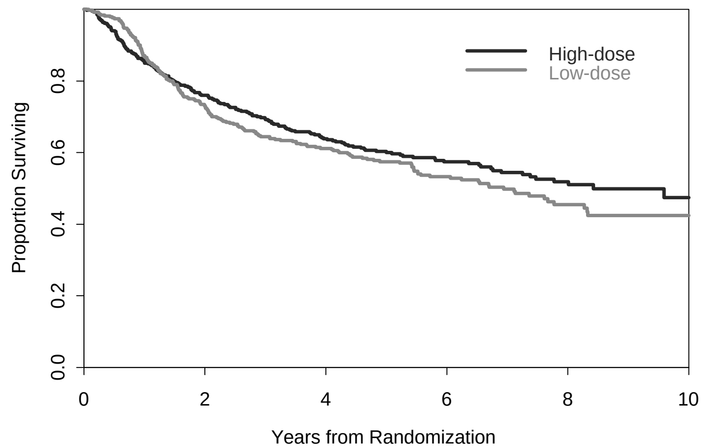
To test 40%
with alpha = 0.05
and power = 0.80 → 0.51

Subset analysis
40 pts/Rx = 80

Just as good as flipping a coin !

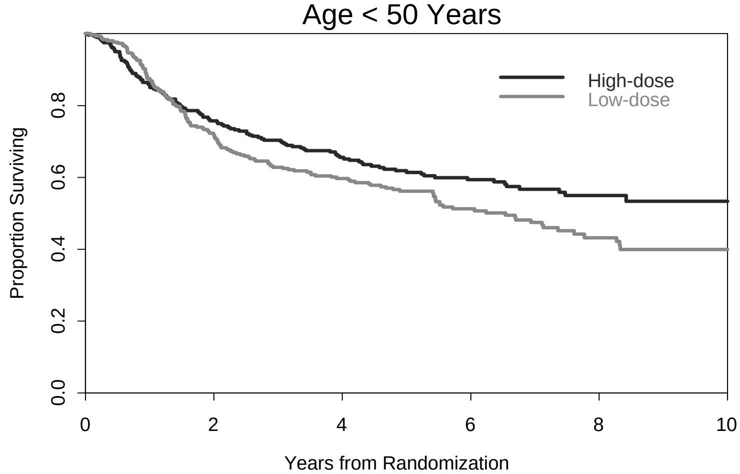
Reporting the Results

Chemotherapy in Breast Cancer
Overall Survival

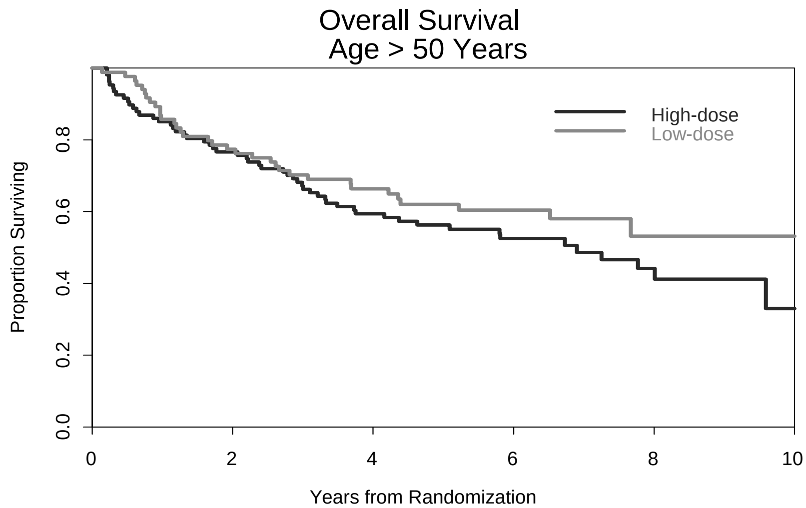


Reporting the Results

Overall Survival
Age < 50 Years



Reporting the Results



Reporting the Results

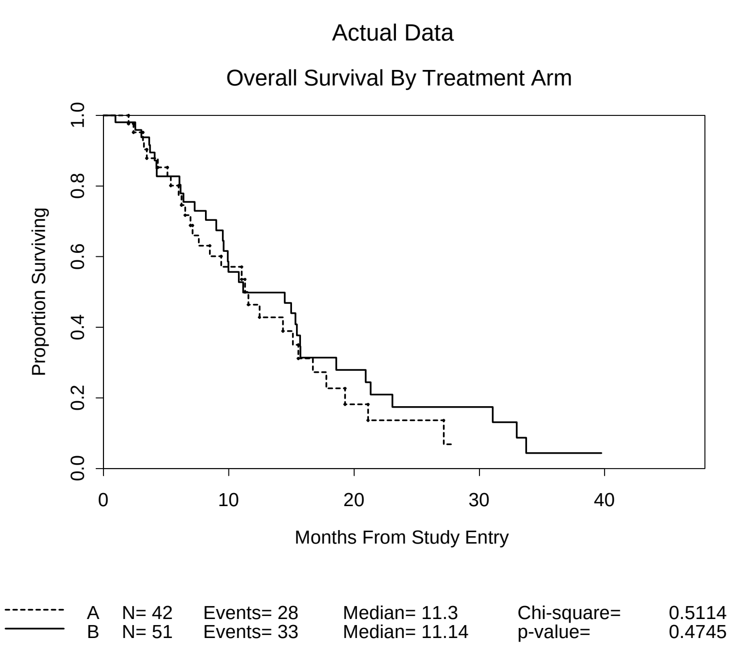
Results: Overall survival was not significantly different between the two treatment groups (P=0.24).

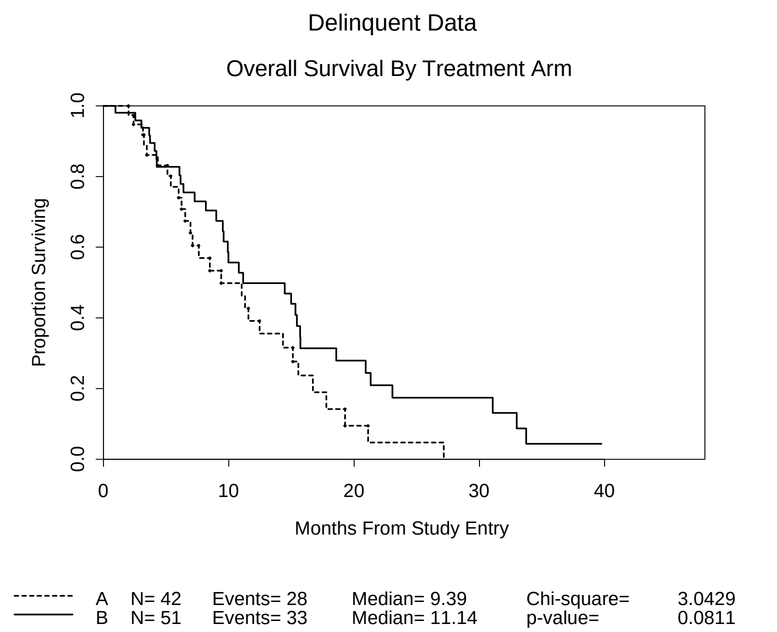
There appears to be a significant interaction on survival between treatment and age. Women younger than 50 randomized to high-dose experienced a longer time to disease recurrence compared to women in the same age category randomized to low-dose (P=0.02).

Summary: High-dose was not superior to std low-dose for overall survival in women with high-risk breast cancer. However, among women under 50 years of age, high-dose had improved survival.

Data Maturity/Currency: Tumor Response

	Rx A N=40	Rx B N=40
RESPONSE	50%	50% ?
		63% ?
		38% ?





Reference

Motulsky, H. (1995). *Intuitive Biostatistics*, Oxford University Press, New York, NY.