Statistics in Cancer Trials

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Cancer clinical trials

Phase II studies - Therapeutic exploratory trials

- Small studies early in the development of a regimen.
- Typically focus on toxicity and response data.
- Require precise definition of response & toxicity criteria.

Phase III studies - Therapeutic confirmatory trials

- Larger comparative studies.
- Also assess survival and disease-free survival.
- Require survival analysis.

Phase IV - Postmarketing surveillance / trials

- May or may not be comparative studies.
- May be done to assess benefit, harm, QOL, economics.

Medical statistics

"... statisticians apply, to problems in which we are interested, a technique which we do not understand. It is exasperating, when we have studied a problem by methods that we have spent laborious years in mastering, to find our conclusions questioned, and perhaps refuted, by someone who could not have made the observations himself."

- Sir Austin Bradford Hill

Father of the Randomized Controlled Trial

Medical statistics

Statistics is the science of data analysis.

Can data be analyzed without statistics?

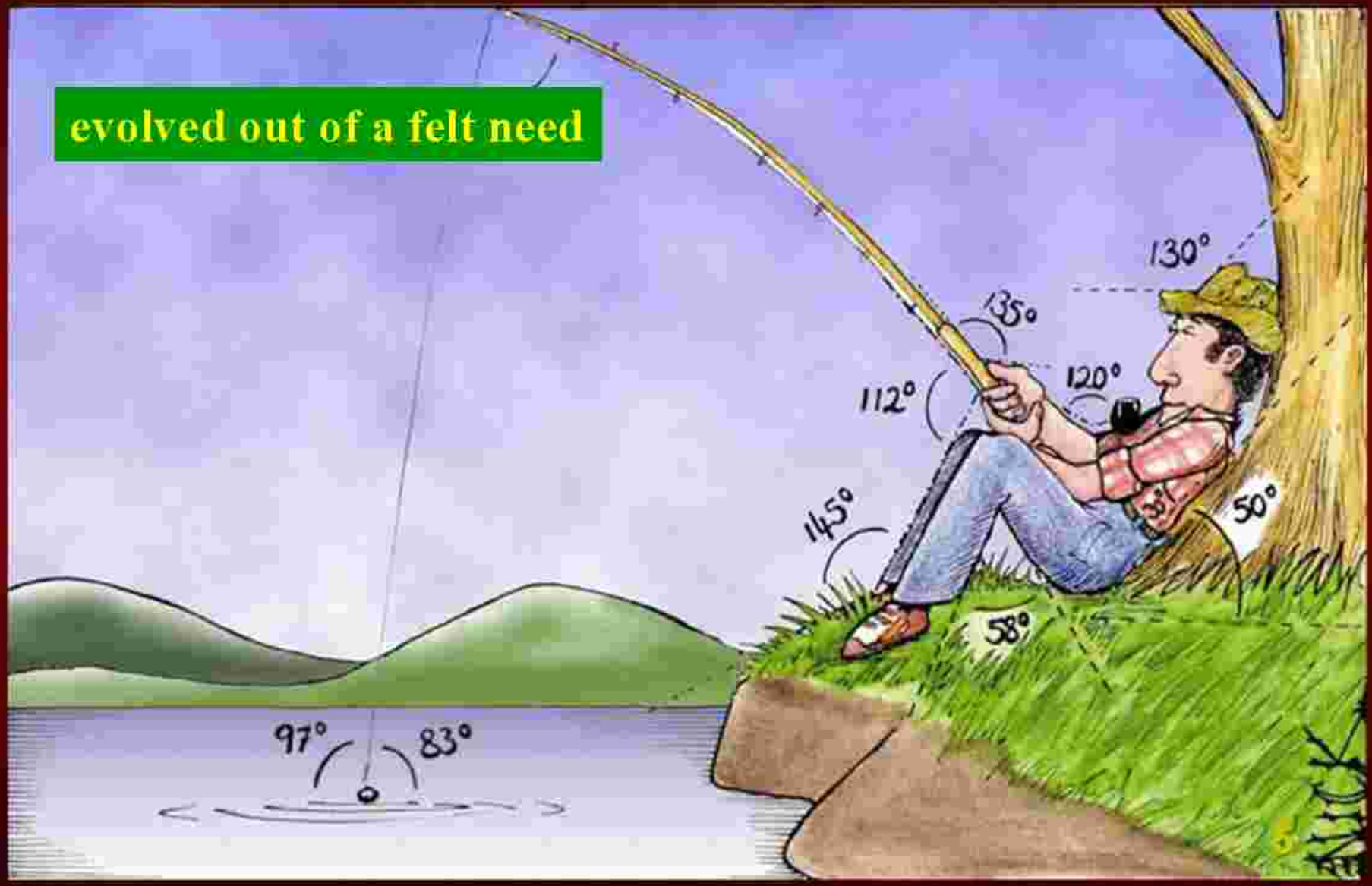
"If your experiment needs statistics, then you ought to have done a better experiment."

- Ernst Rutherford

Most biological researchers are not so lucky

- **Enormous biological variability**
- **Inability to control all relevant variables**
- **Interest in small effects**

Medical statistics



Clinical trial designs

- Single treatment

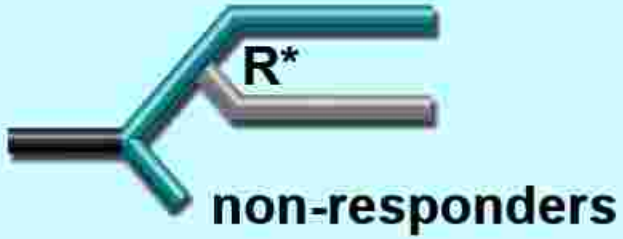
- Parallel groups

- Crossover

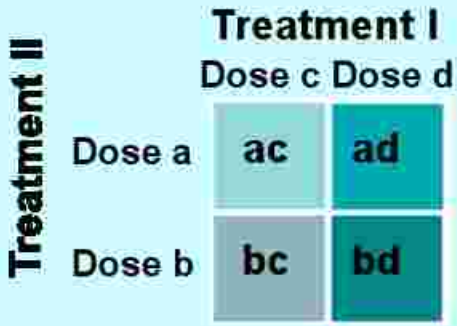
* R = Randomization Point

Clinical trial designs

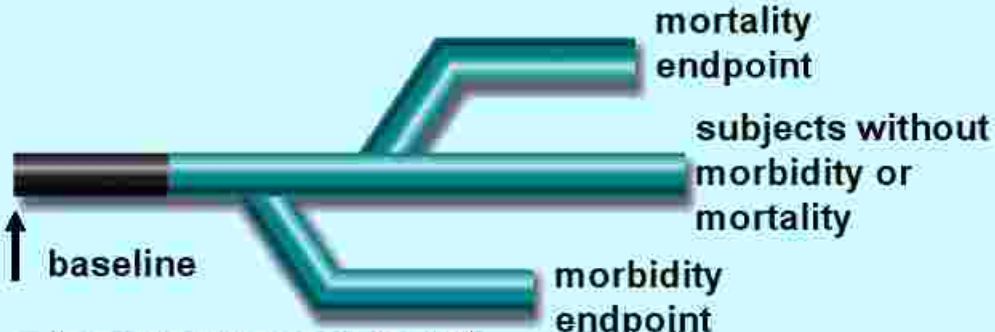
- **Withdrawal**



- **Factorial**



- **Survival**

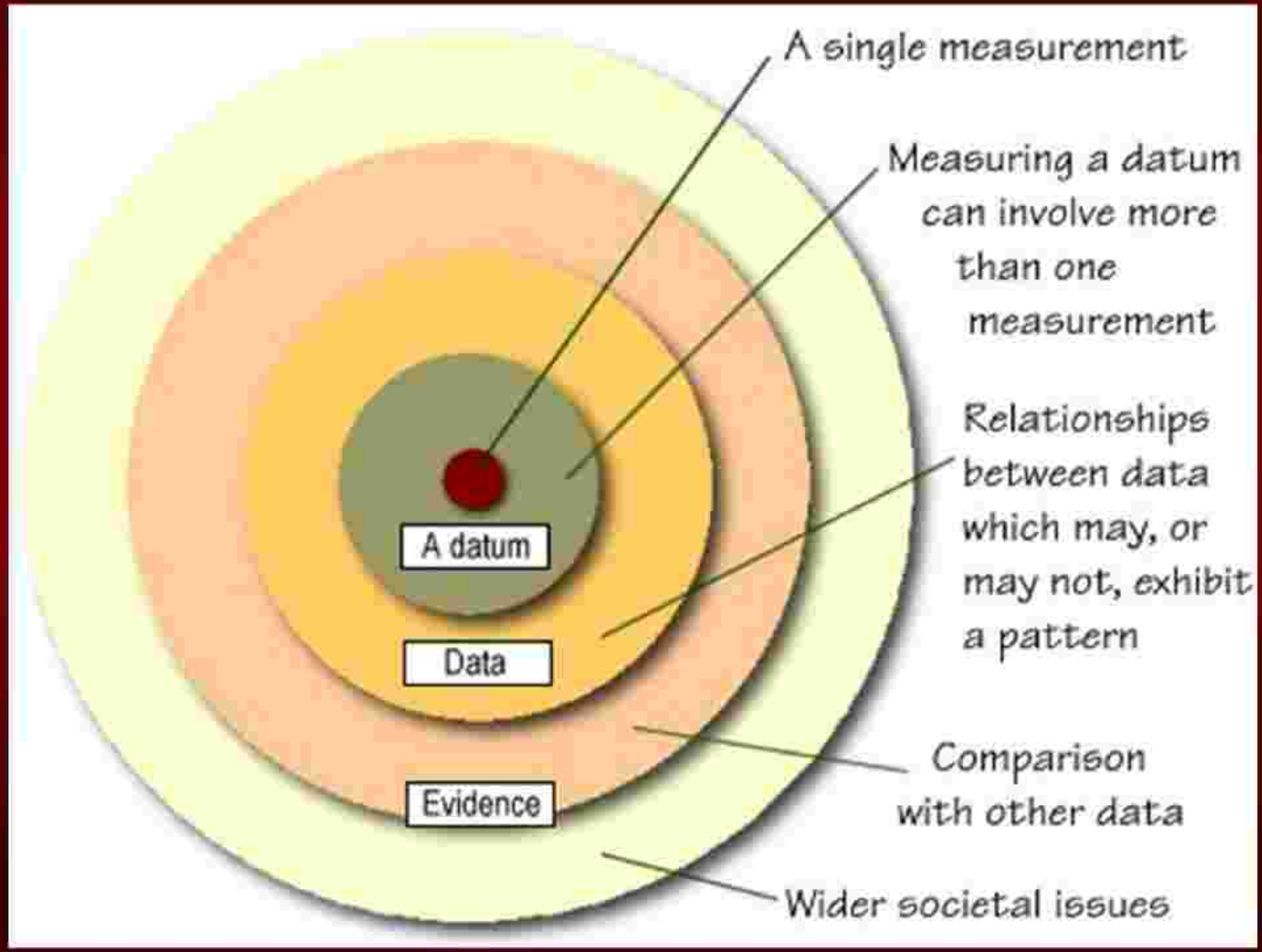


* R = Randomization Point

Controls in clinical trials

- **No treatment**  *vs.* Nil
- **Placebo**  *vs.* 
- **Dose-response**  *vs.* 
- **Active**  *vs.* 
- **External**
  (including Historical)  *vs.* 

The goal of medical statistics



Data types

Categorical / (Ordinal) / Qualitative data

That which can be classified into mutually exclusive categories based on a predetermined set of criteria.

e.g. Tumor response - Complete response, Partial response, Stable disease, Increasing

Numerical / Measurement / Quantitative data

That which comes from measurement.

e.g. CA-125 level in ovarian cancer.

Time-to-event data is a special case of quantitative data.

Inferential statistics

- Process by which we acquire information about populations from samples.
- Three procedures for making inferences.

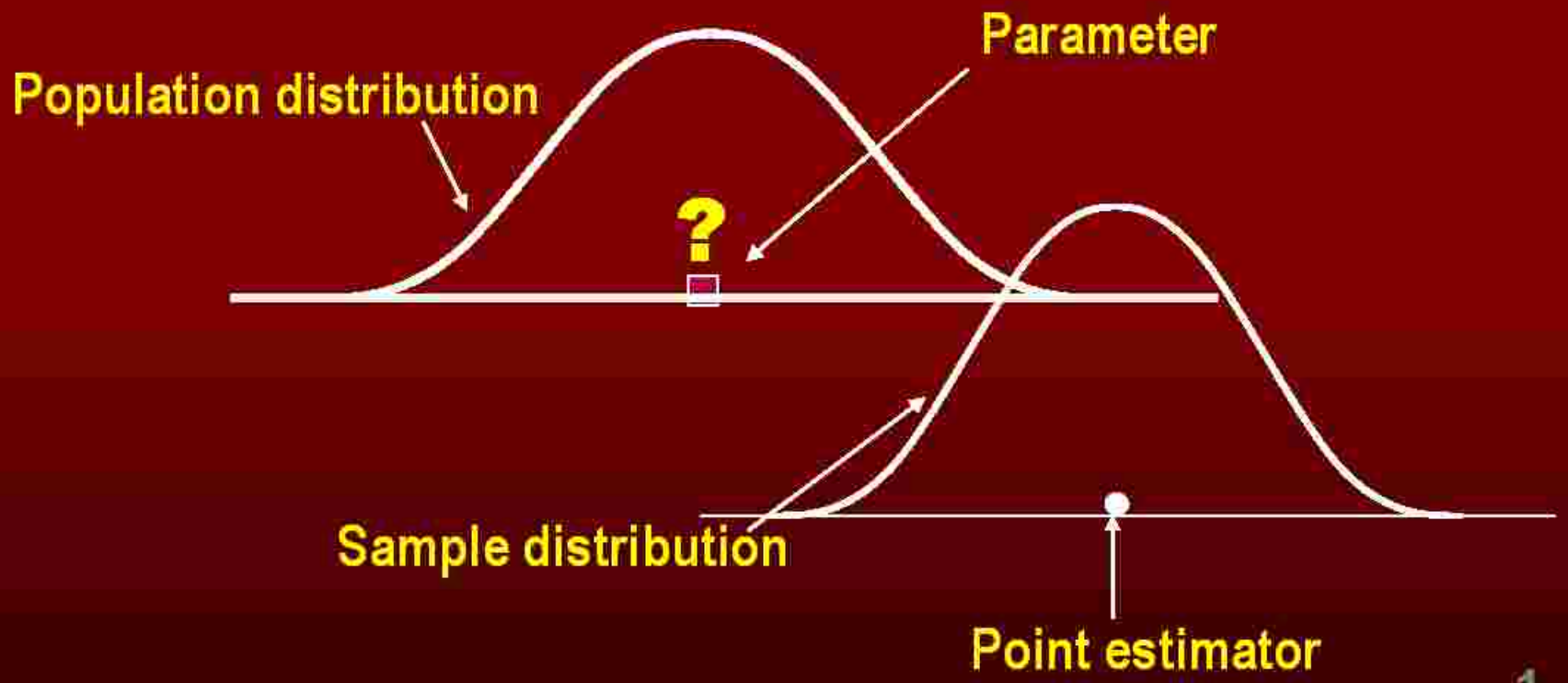
Point estimates

Interval estimates

Hypothesis testing

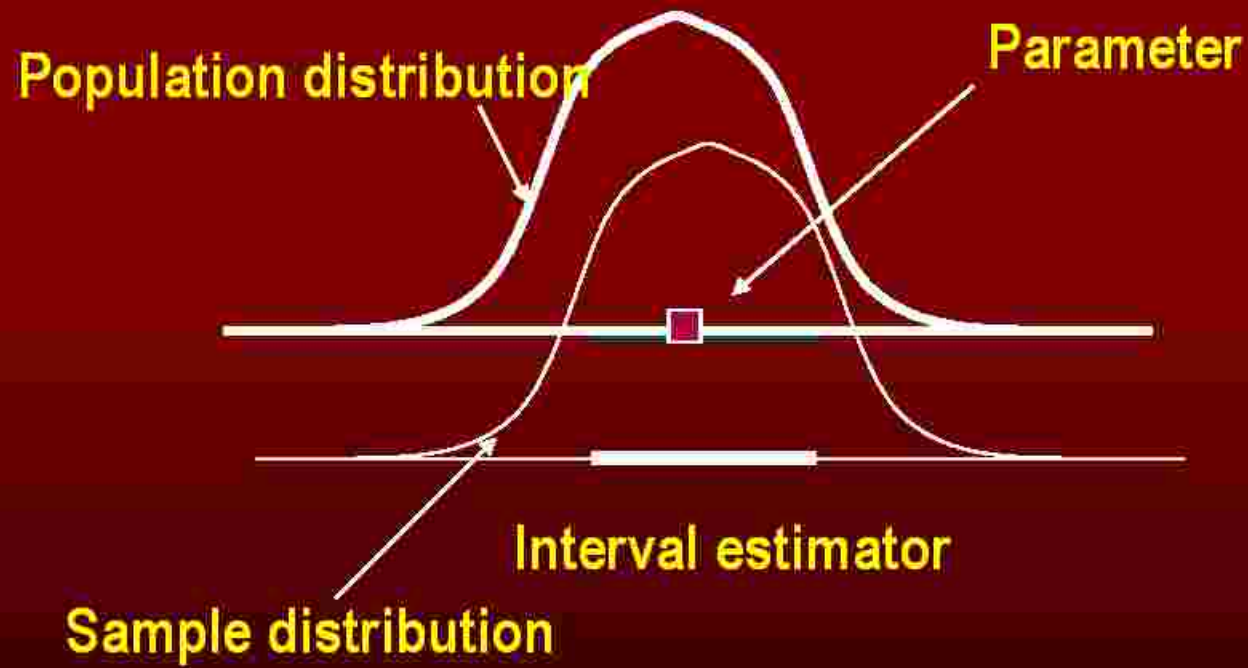
Point estimation

A point estimator draws inference about a population by estimating the value of an unknown parameter using a single value.



Interval estimation

An interval estimator draws inferences about a population by estimating the value of an unknown parameter using an interval.



Confidence interval 1

- A confidence interval has the form:

  point estimate ± margin of error

- The point estimate is our guess for the value of the unknown parameter.
- The margin of error shows how accurate we believe our guess is, based on the sampling distribution of the estimate.

Confidence interval 2

- A confidence interval has the form:

  point estimate ± margin of error

- The confidence interval is therefore likely to include the true population parameter with the given confidence level.
- The given confidence level (e.g. 95% or 99%) shows how confident we are that the procedure will catch the true population parameter.
- Sample size influences the confidence interval.

Confidence interval 3

Consider Hazard ratio:

Ratio of death rates in two study arms.

Estimated Hazard Ratio of **2.1** in favor of a new Rx seems appealing.

However if 95% CI is **0.4 to 3.8** , the Hazard Ratio is no longer so appealing.

Importance of a large sample 1

		Response +	Response –
Rx arm	A	25	25
	B	30	20

n = 100

Chi-square *p* value 0.3149 ⇒ Non-significant

Importance of a large sample 2

		Response +	Response –
Rx arm	A	250	250
	B	300	200

n = 1000

Chi-square *p* value 0.0015 ⇒ Significant

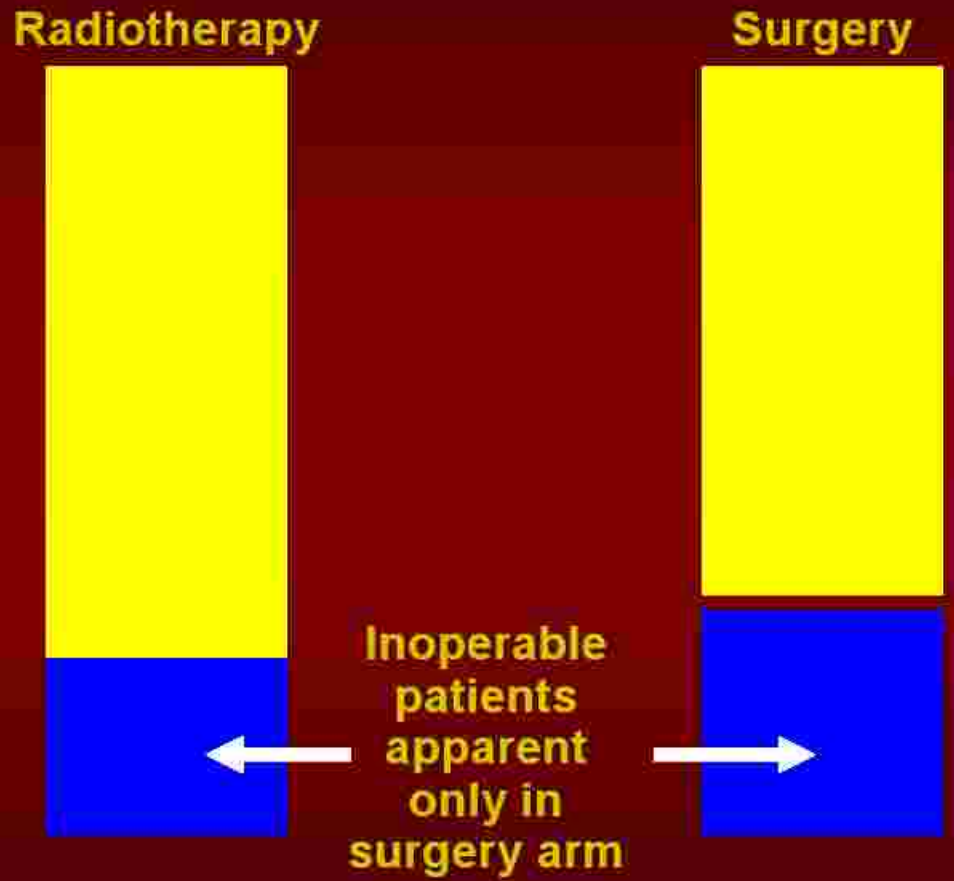
Analysis strategy 1

An RCT is planned to compare surgery and radiotherapy in the Rx of operable lung cancer. However, during conduct of the trial it was found that some patients randomized for surgery were inoperable and had to be Rx by radiotherapy.

What is to be done for analysis in this situation?

Continued ...

Analysis strategy 2



There are likely to be inoperable patients in both groups but they cannot be identified in the radiotherapy group.

Patients with inoperable tumors are likely to have more advanced disease.

Intention-to-treat analysis is the best approach.

Survival analysis

The outcome of interest is time to an event - this does not necessarily have to be death.
Studying time to an event poses two problems:

- Time interval can vary from one subject to another. Also at the end of the study the event may not have occurred for many subjects.
  So time to event is not **Normally distributed**.
- In a long period of follow-up many subjects drop out. The information we have about them is only till last follow-up. So data is **Censored**.

Survival analysis

- Model time to death or time to event.
  - Unlike linear regression, survival analysis has a dichotomous (binary) outcome.
  - Unlike logistic regression, survival analysis analyzes the time to an event.
- Able to account for censoring.
- Can compare survival between 2+ groups.
- Can assess relationship between covariates and survival time.

Regression vs. survival analysis

Technique	Predictor Variables	Outcome Variable	Censoring permitted?
Linear Regression	Categorical or continuous	Normally distributed	No
Logistic Regression	Categorical or continuous	Binary (except in polytomous logistic regression)	No
Survival Analyses	Time and categorical or continuous	Binary	Yes

Regression vs. survival analysis

Technique	Mathematical model	Yields
Linear Regression	Y=B1X + Bo (linear)	Linear changes
Logistic Regression	Ln(P/1-P) = B1X+Bo (sigmoidal prob.)	Odds ratios
Survival Analyses	h(t) = ho(t)exp(B1X+Bo)	Hazard rates

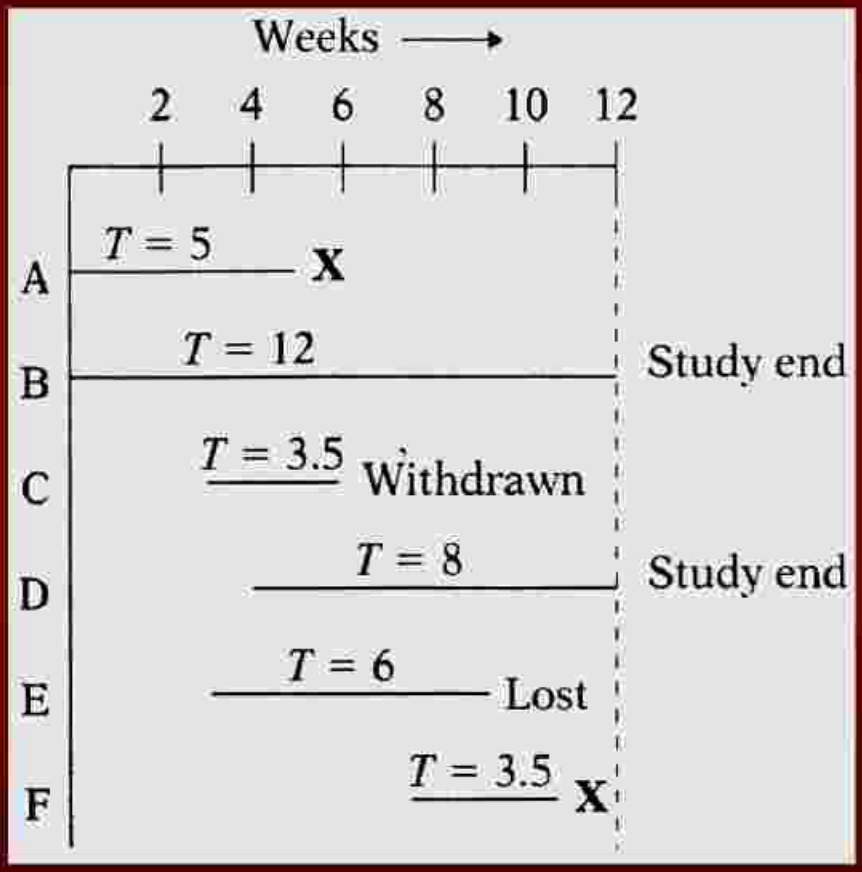
When to use survival analysis

- Examples
  - Time to death or clinical endpoint
  - Time in remission after Rx of disease
  - Time to wean from ventilator support
  - Time to relapse in alcoholism Rx
- When one believes that 1+ explanatory variable(s) explains the differences in time to an event
- Especially when follow-up is incomplete or variable

Assumptions in survival analysis

- Survival prospects are assumed to stay the same throughout the study.
- Subjects lost to follow-up have the same prognosis as those who continue with the study.
- The probability that an individual is censored is unrelated to the probability that the individual suffers an event.
- Anything which affects the hazard does so by the same proportion at all time.

Censored data in survival analysis



- Subject does not experience event of interest
- Incomplete follow-up
  - Lost to follow-up
  - Withdraws from study
  - Dies (if death not a study outcome)
- Left or right censored

Approaches to survival analysis

Like other statistical analysis, survival type data can be dealt with by:

- Descriptive statistics
- Univariate statistics
- Multivariate statistics

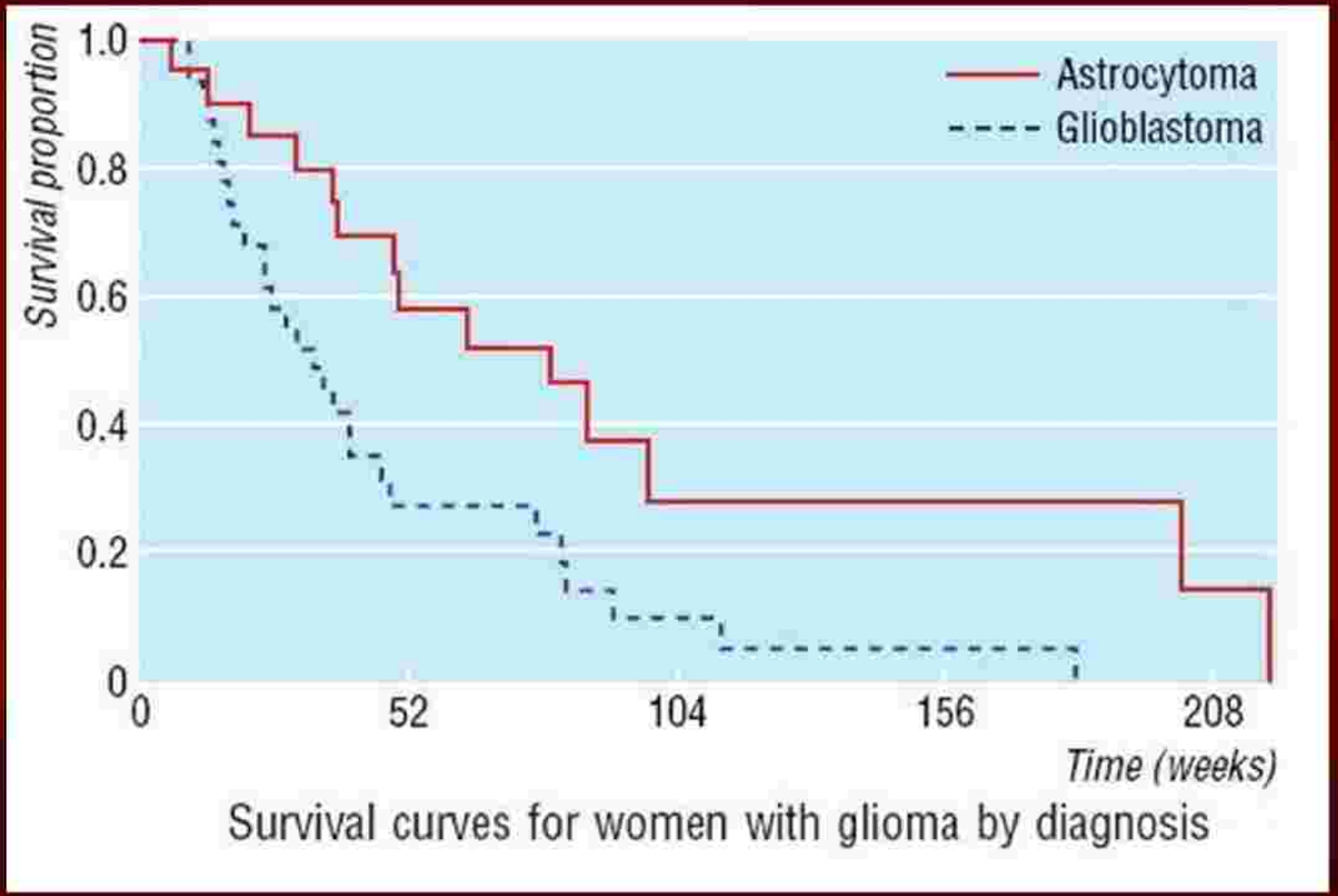
Descriptive statistics in survival analysis

- **Average survival**
  - When can this be calculated?
  - What test should be used to compare average survival between 2 groups?
- **Average hazard rate**
  - Total number of failures divided by observed survival time (units are therefore 1/t or 1/pt-yrs)
  - An incidence rate, with a higher value indicating more events per time

Univariate methods: Kaplan-Meier survival plots

- Also known as product-limit method
- Accounts for censoring
- Generates the characteristic 'crazy stairs' survival curves
- Does not account for confounding or effect modification by other covariates

Typical Kaplan-Meier survival plots



Survival curves for women with glioma by diagnosis

Relationship between Survivor Function and Hazard Function

- **Survivor function, S(t) defines the probability of surviving longer than time *t***
  - This is what the Kaplan-Meier curves show.
  - Hazard function is the derivative of the survivor function over time h(t)=dS(t)/dt
    - instantaneous risk of event at time *t*
- **Survivor and hazard functions can be converted into each other**

Comparing Kaplan-Meier plots 1

- Log-rank test can be used to compare survival curves
- Compares 'observed' and 'expected' number of deaths in the two samples
- 'Expected' calculated by sharing the next death between the groups in proportion to numbers at risk in each group
- Assumption is no difference in risk factors between groups
- Test statistic is compared to χ^2 distribution

Comparing Kaplan-Meier plots 2

- **Hypothesis test (test of significance)**
  - H_0: the curves are statistically the same
  - H_1: the curves are statistically different
- **Can be generalized to more than two groups**
- **Then use judicious pair-wise testing**
- **Other non-parametric tests available**
  - Mantel-Cox, Mantel-Haenszel, Peto & Peto, Gehan, etc.

Comparing multiple Kaplan-Meier plots

- **Multiple pair-wise comparisons produce cumulative Type I error – multiple comparison problem**
- **Instead, compare all curves at once**
  - Analogous to using ANOVA to compare more than two groups
  - Then use judicious pair-wise testing

Limit of Kaplan-Meier plots

- What happens when you have several covariates that you believe contribute to survival?
  - e.g. Tumor grade at presentation, nodal metastasis, histological type, family history, time to start of Rx
- Can use stratified K-M curves – for 2 or maybe 3 covariates
- A multivariate approach needed for many covariates
  - Think multivariate regression or logistic regression rather than a Student's t-test or the Odds ratio from a 2 x 2 table

Multivariate methods: Cox proportional hazards model

- **Used to assess effect of multiple covariates on survival**
- **The the most commonly used multivariate survival method**
  - Relatively easy to implement in standard statistical software
  - Parametric approaches are an alternative, but they require stronger assumptions about h(t).

Cox proportional hazards model 1

- **Conveniently separates baseline hazard function from covariates**
  - Baseline hazard function over time
    - $h(t) = h_o(t)\exp(B_1X+B_o)$
  - Covariates are time independent
  - B_1 is used to calculate the hazard ratio, which is similar to the relative risk
- **Nonparametric**
- **Quasi-likelihood function**

Cox proportional hazards model 2

- Can handle both continuous and categorical predictor variables
- Without knowing baseline hazard $h_o(t)$, can still calculate coefficients for each covariate, and therefore hazard ratio
- Assumes multiplicative risk — this is the proportional hazard assumption

Limitations of the Cox proportional hazards model

- **Does not accommodate variables that change over time**
  - Luckily most variables (e.g. gender, ethnicity, congenital condition) are constant.
- **Baseline hazard function, $h_o(t)$, is never specified**
  - You can estimate $h_o(t)$ accurately if you need to estimate S(t).

Summing up survival analysis

- Survival analyses quantifies time to a single, dichotomous event.
- Handles censored data well.
- Survival and hazard can be mathematically converted to each other.
- Kaplan-Meier survival curves can be compared mathematically and graphically.
- Cox proportional hazards models help distinguish individual contributions of covariates on survival, provided certain assumptions are met.

And finally ...

- Cancer is a heterogenous disease - even within a given site, stage and histological type. Little understood disease trends, large response variability, and unquantifiable physician & patient biases are all indications for carefully controlled RCTs.
- Careful attention to design is needed for success of such RCTs. Population, intervention, endpoints all need to be carefully defined and potential benefits and harms carefully quantified with defined limits of precision.

Statistics in Cancer Trials

Statistical principles, and thus statisticians, have a large role - but certainly not the sole role - in the design, analysis and conduct of cancer trials.

"... it is an error to argue in front of your data. You find yourself insensibly twisting them round to fit your theories."

- Sherlock Holmes