ATLAS
ASIAN CLINICAL TRIALS NETWORK FOR CANCERS PROJECT

National Cancer Center Japan

Survival Analysis

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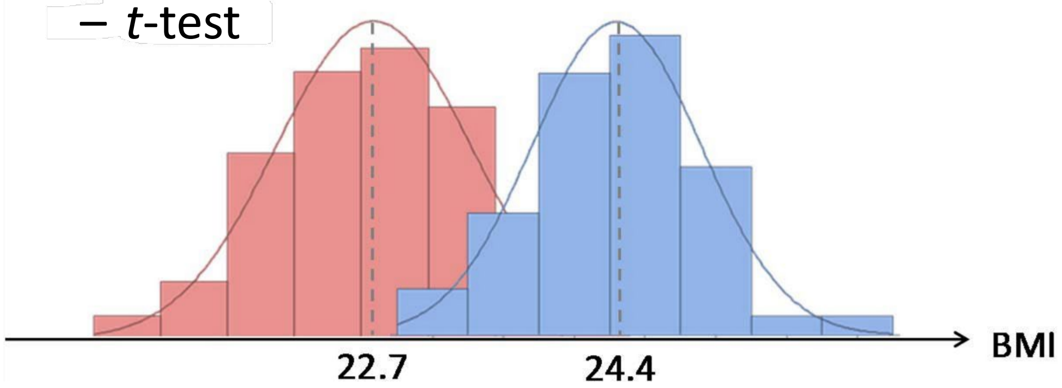
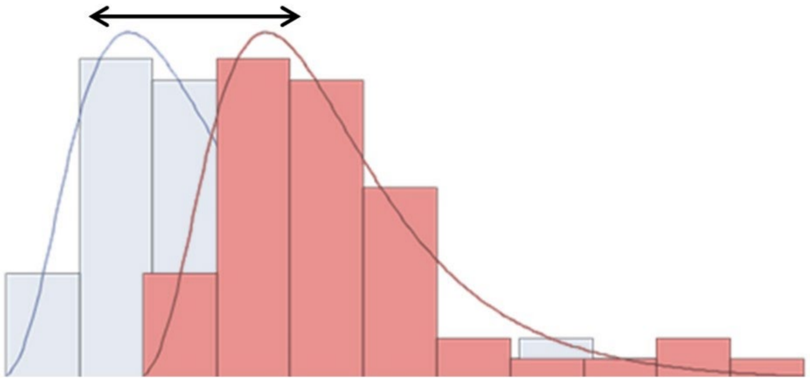
Review of the Previous Lecture: Analysis of Continuous Data

- Step 1: Confirm distribution with histogram
- Step 2: Group comparison
  - *t*-test



$$t = \frac{\bar{X}_A - \bar{X}_B}{\sqrt{V\left(\frac{1}{n_A} + \frac{1}{n_B}\right)}}$$

  - Wilcoxon rank sum test



	BMI (kg/m^2)				Mean
Group A	22.0 [2]	28.3 [8]	19.4 [1]	22.3 [3]	23.0
Group B	23.3 [4]	25.1 [7]	24.6 [6]	23.5 [5]	24.1

Review of the Previous Lecture: Analysis of Binary Data

- Step 1: Create a (2 × 2) contingency table and tabulate frequencies

		Onset of colorectal cancer		
		Yes	No	Total
Aspirin	Yes	129	4932	5061
	No	87	2440	2527
	Total	216	7372	7588

- Step 2: Group comparison
  - Fisher's exact test
  - One-sided P value = 0.0053 + … + 1.2 × 10−106 = 0.0174

216	4845	5061
0	2527	2527
216	7372	7588

$Pr = 2.4 \times 10^{-37}$

215	4846	5061
1	2526	2527
216	7372	7588

$Pr = 1.3 \times 10^{-35}$

214	4847	5061
2	2525	2527
216	7372	7588

$Pr = 5.0 \times 10^{-34}$

・・・

129	4932	5061
87	2440	2527
216	7372	7588

Pr = 0.0053

・・・

0	5061	5061
216	2311	2527
216	7372	7588

$Pr = 1.2 \times 10^{-106}$

The same contingency table as the observed data

Review of the Previous Lecture: Analysis of Binary Data

- Step 1: Create a (2 × 2) contingency table and tabulate frequencies

		Onset of colorectal cancer		
		Yes	No	Total
Aspirin	Yes	129	4932	5061
	No	87	2440	2527
	Total	216	7372	7588

- Step 2: Group comparison
  - Chi-square test

Observed values	
129 (2.5%)	4932 (97.5%)
87 (3.4%)	2440 (96.6%)

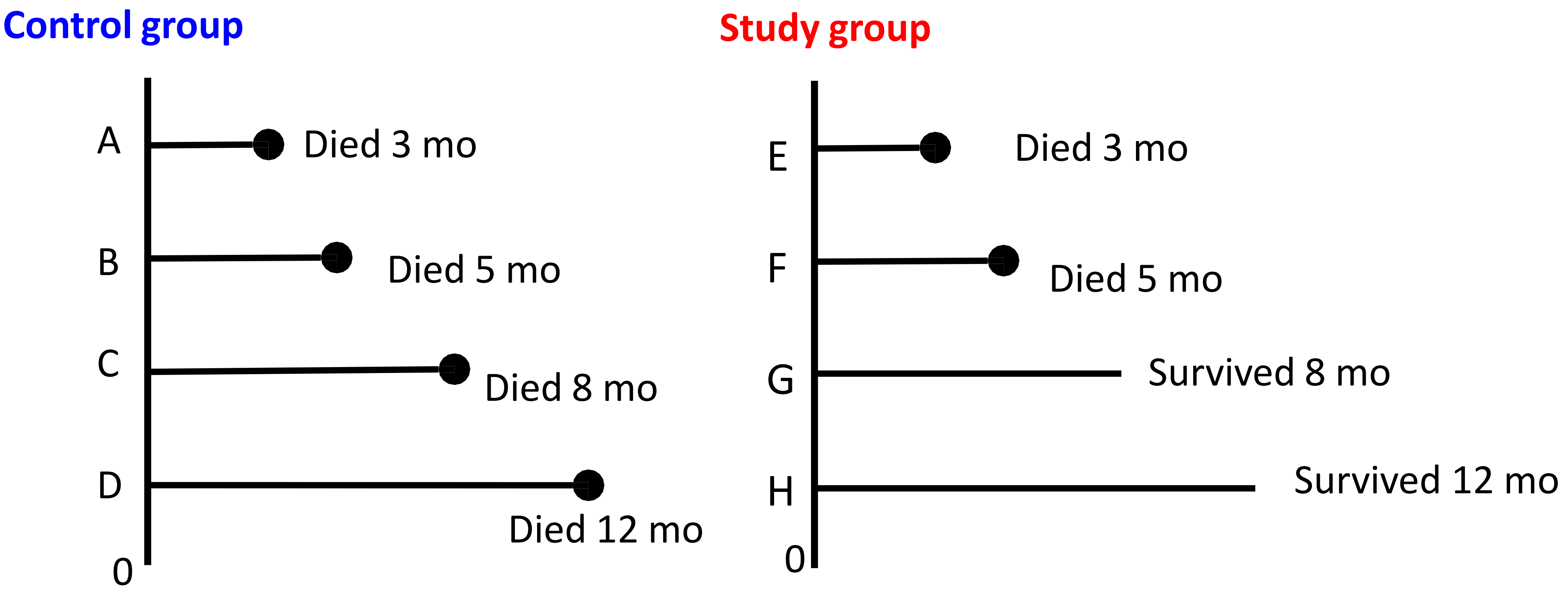
Expected values	
144 (2.8%)	4917 (97.2%)
72 (2.8%)	2455 (97.2%)

- Test based on the difference between observed and expected frequencies
  - The greater the difference between the observed and expected frequencies, the rarer the result observed under the null hypothesis.
- Statistic $\frac{(1239-144)^2}{144}+\frac{(4932-4917)^2}{4917}+\frac{(87-72)^2}{72}+\frac{(2440-2455)^2}{2455}$
- Approximates a chi-square distribution with one degree of freedom
  - The higher the expected frequency, the better the approximation.
- P = 0.0273 (Significant at the two-sided 5% level!)

Outcome Types and Statistical Methods

	Continuous Variable	Binary (0/1)	Survival Time
Outcome examples	BMI, blood pressure, laboratory values	Response rate	Overall survival, progression-free survival
Data summary	Histogram	Contingency table	?
Group comparison (test)	*t*-test, Wilcoxon test	Chi-square test, Fisher's exact test	?
Model fitting	Multiple regression analysis	Logistic regression	?

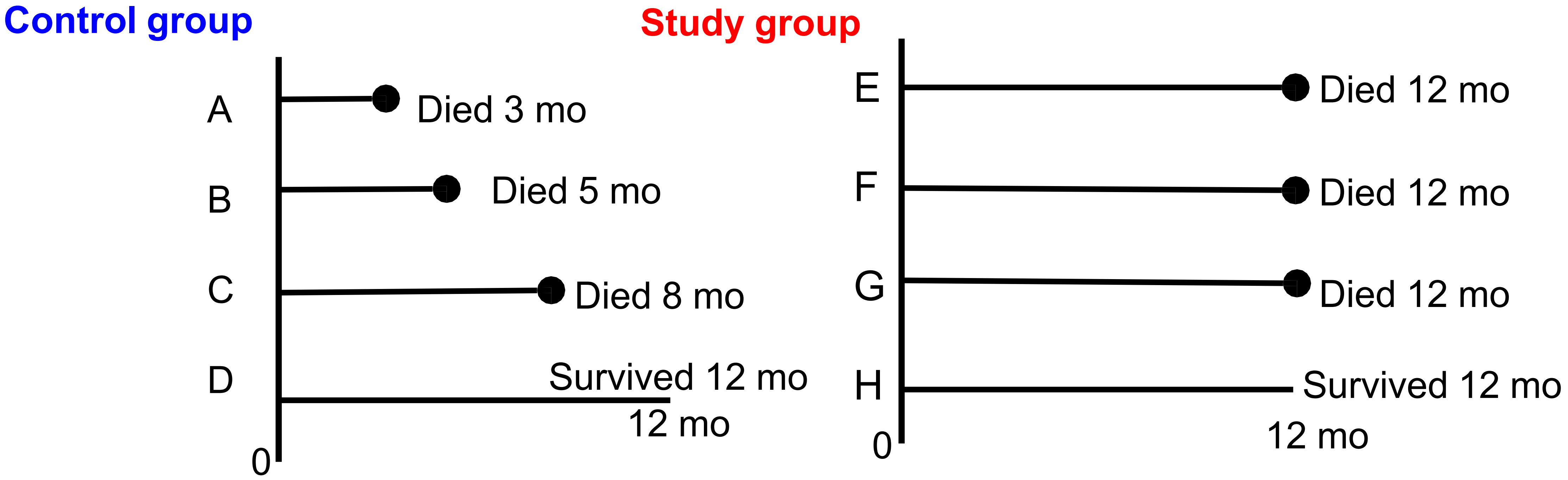
Question 1: Are Mean and *t*-test Sufficient?



- Mean of control group: (3 + 5 + 8 + 12)/4 = 7 mo
- Mean of study group: (3 + 5 + 8 + 12)/4 = 7 mo??

The survival in the study group is expected to be longer

Question 2: Is It Correct to Compare (Chi-square Test and Fisher's Exact Test) the Survival Rates at the 12-Month Time Point?

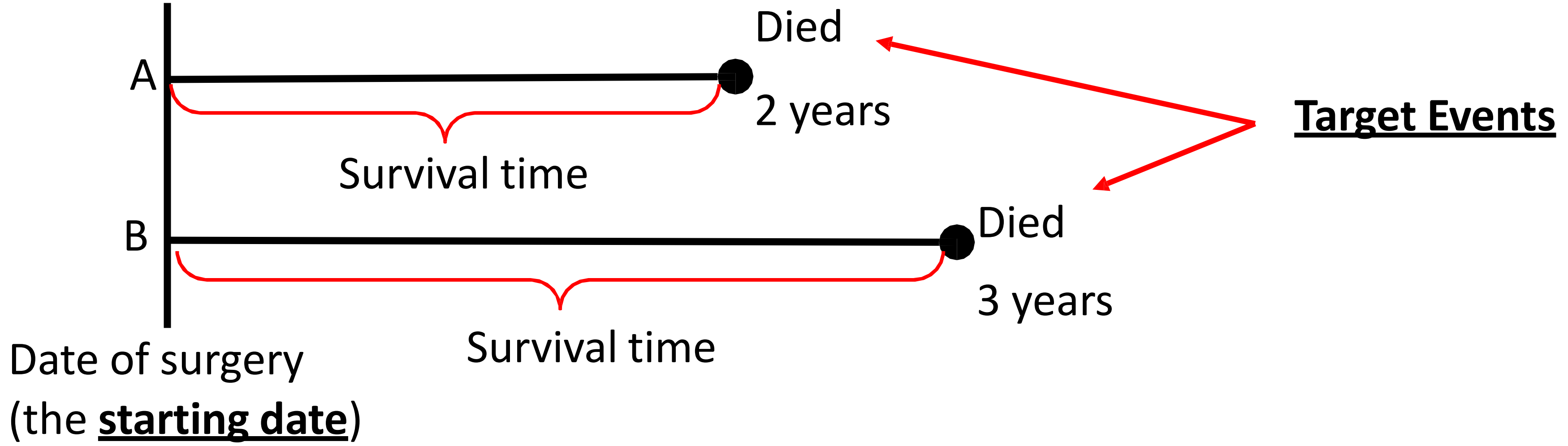


- Survival rate of control group: 1/4 = 25%
- Survival rate of study group: 1/4 = 25% ??

The survival in the study group is expected to be longer

What is Survival Analysis?

- What is survival time?
  - The **time** from a specific time point (the **starting date**) until the target **event** occurs.
    - From the date of enrollment in the clinical study to the date of death
    - From the date of surgery to the date of recurrence



- The analytical method used when interested in survival time is called **survival analysis**.

Survival Analysis for Clinical Study

Lung cancer internal medicine group JCOG0301

Unresectable stage III NSCLC
≥71 years

↓

Random assignment

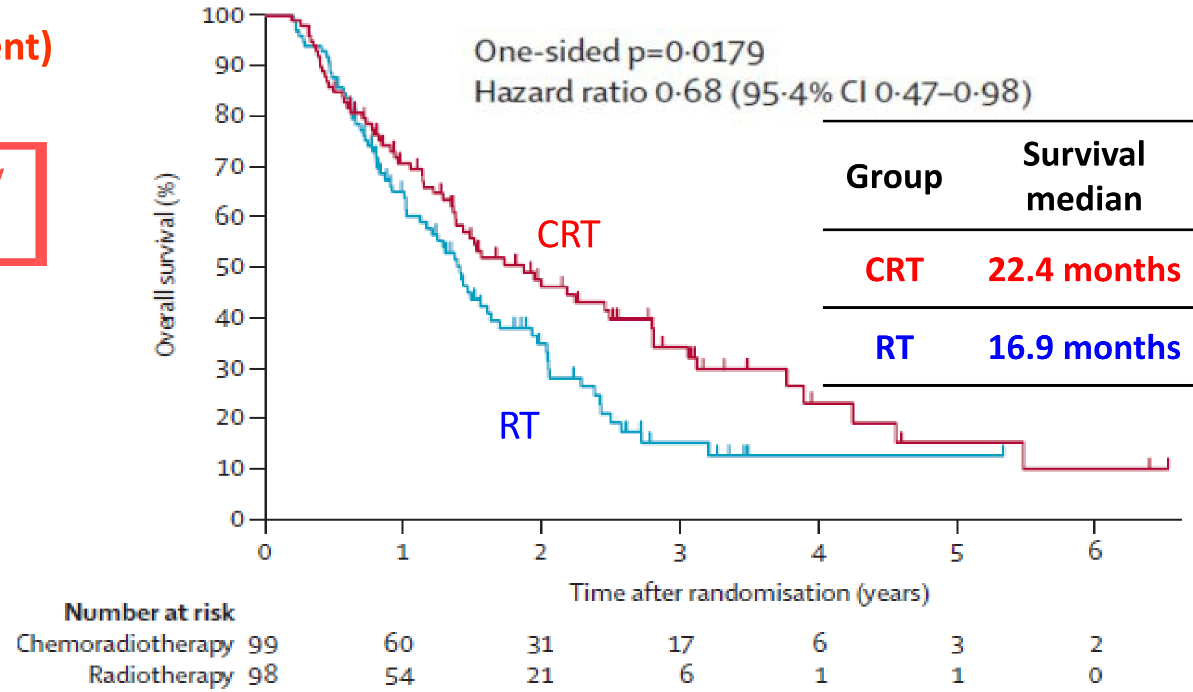
(Standard of care) 100 cases → Radiation alone (RT)

(New treatment) 100 cases → Radiation + chemotherapy (CRT)

Atagi *et al.* (2012) Lancet Oncol. 13(7): 671-8.

Statistical analysis

The primary endpoint of overall survival was analysed by the stratified log-rank test for eligible patients with performance status (0 *vs* 1–2 [because of the small number of patients with performance status of 2]) and stage (IIIA *vs* IIIB) as stratification factors. Overall survival and PFS were estimated using the Kaplan-Meier method; hazard ratios (HRs) were calculated by Cox regression, and response rates were compared by the



Group	Survival median	2 years survival rate
CRT	22.4 months	46.3%
RT	16.9 months	35.1%

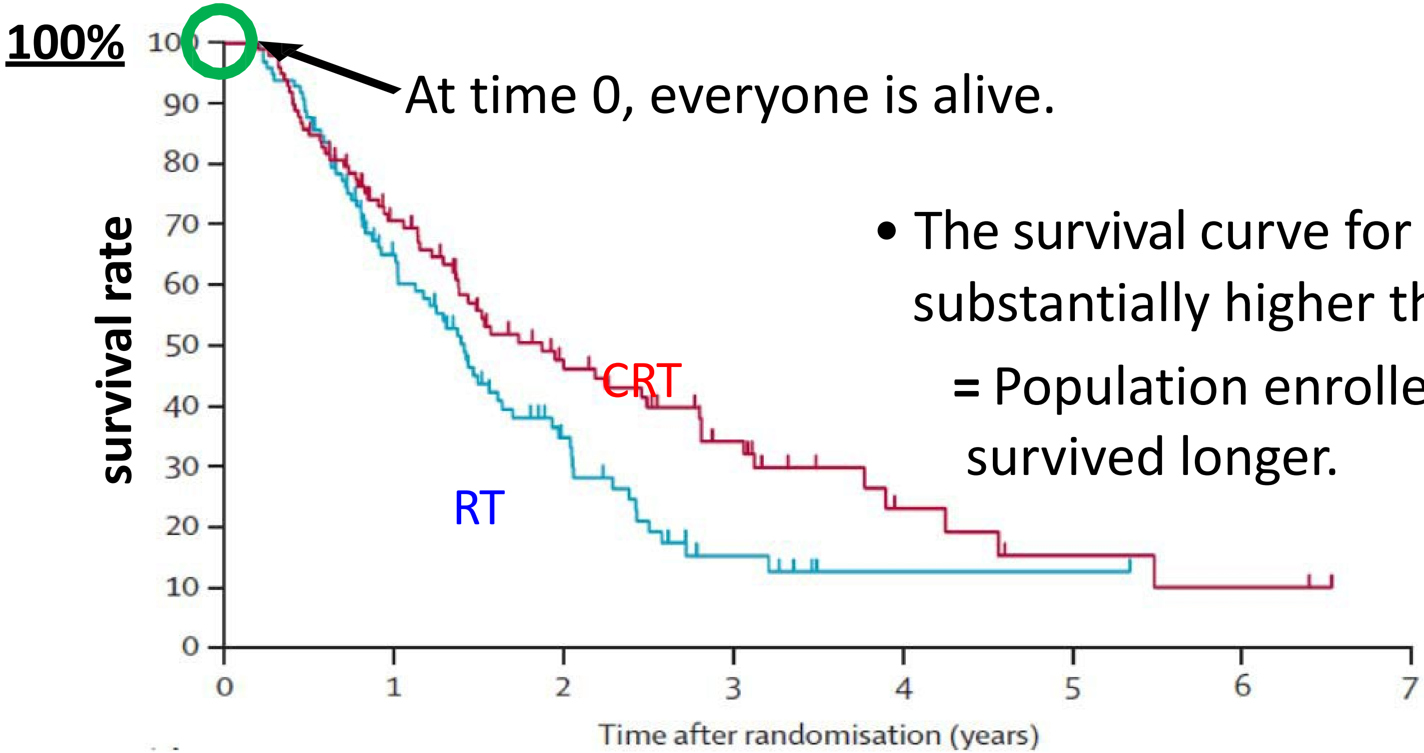
Learn the Three Essentials of Survival Analysis

- How to estimate and interpret the survival curve
  - **Kaplan–Meier method**
  - Number at risk
- Comparison of survival curves between groups
  - **Log-rank test**
- Estimation of treatment effect between groups of survival curves
  - **Cox regression** and proportional hazards
- Differences between rate, ratio, and proportion

Survival Curve

What Is a Survival Curve?

- The vertical axis represents the survival rate at each time point, the horizontal axis represents time, and the survival rate at each time point in the population is connected.
- When there is a death, the survival rate is reduced at that time.

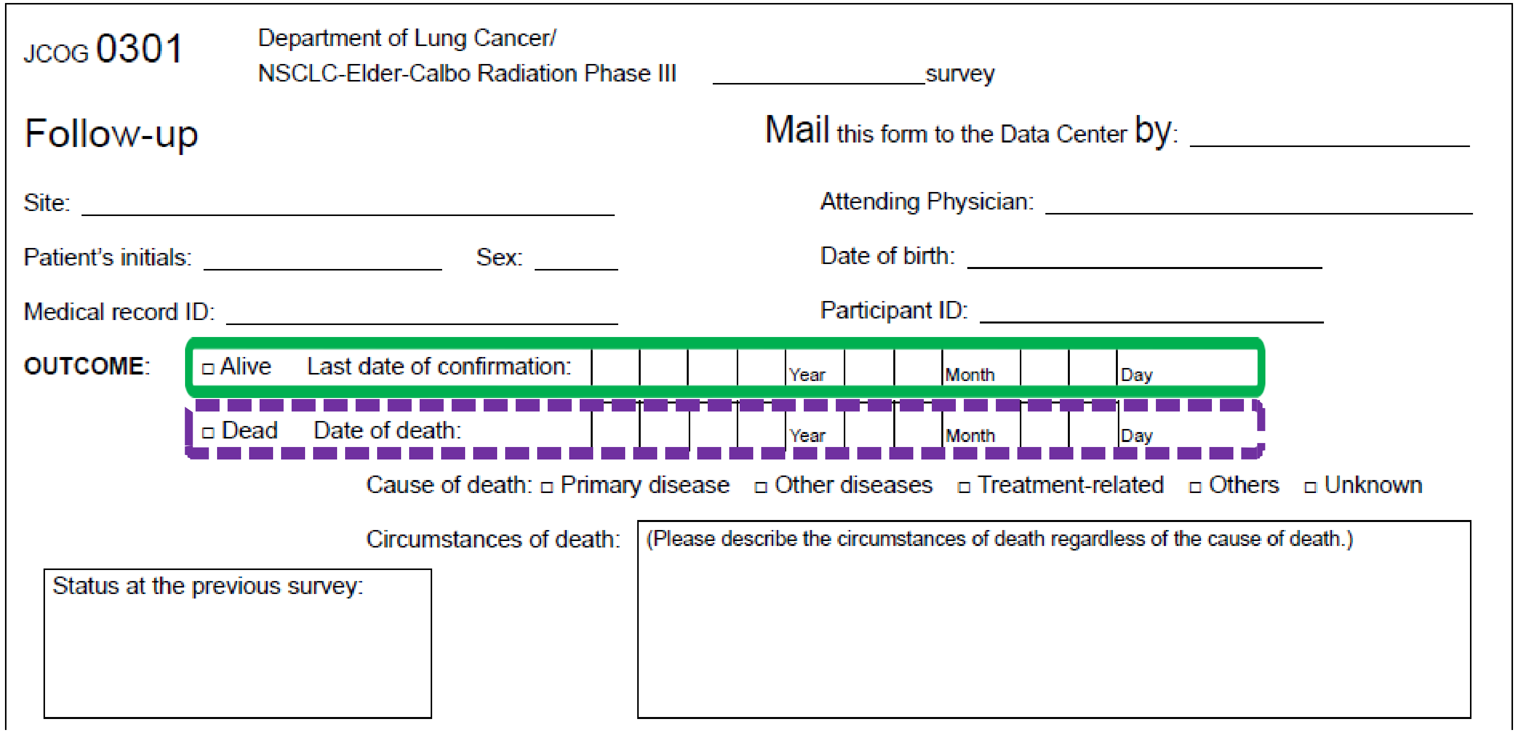


- The survival curve for the **CRT group** is substantially higher than that for the **RT group**.

  = Population enrolled in the **CRT group** survived longer.

Atagi *et al.* (2012) Lancet Oncol. 13(7): 671-8.

What Is a Survival Curve?



JCOG 0301 Department of Lung Cancer/ NSCLC-Elder-Calbo Radiation Phase III ______________survey

Follow-up

Mail this form to the Data Center by: ______________

Site: ______________ Attending Physician: ______________

Patient's initials: ______________ Sex: ______ Date of birth: ______________

Medical record ID: ______________ Participant ID: ______________

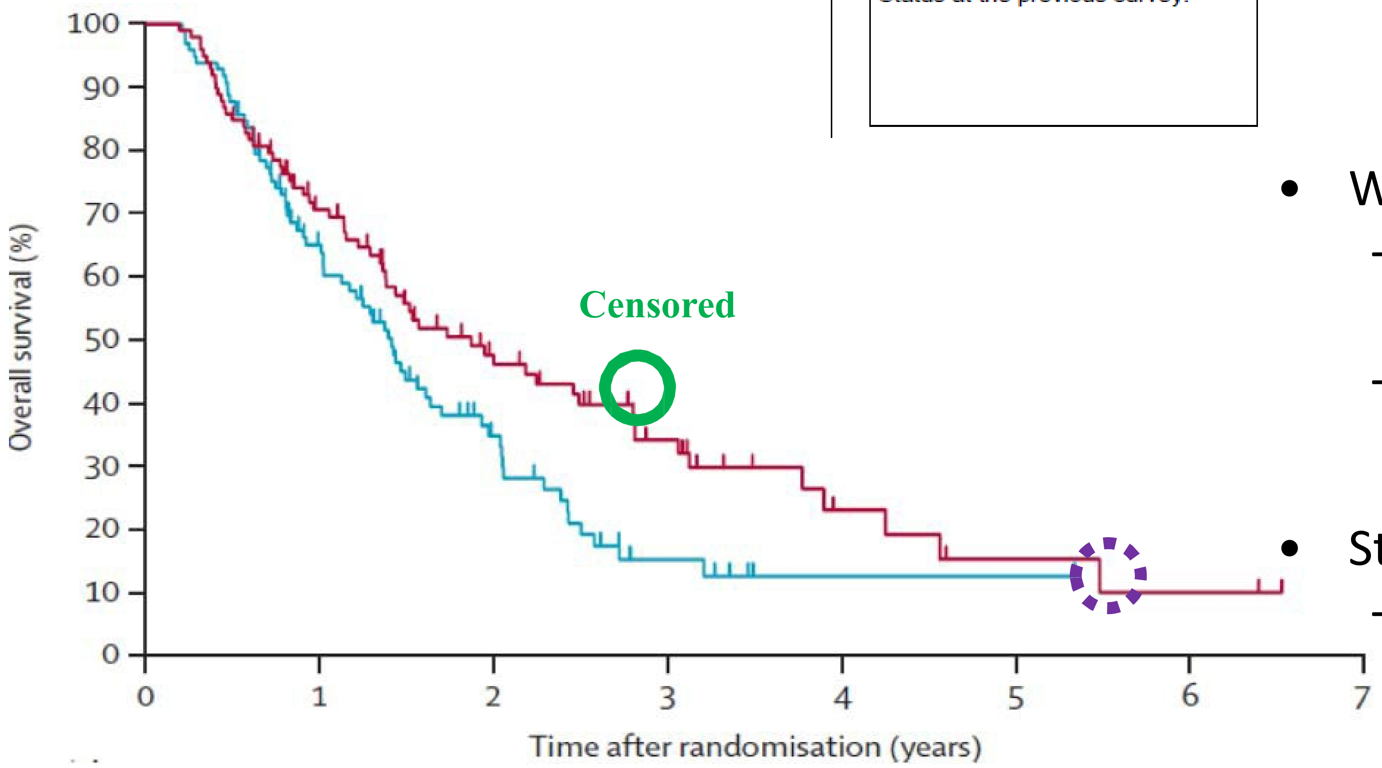
OUTCOME: ◻ Alive Last date of confirmation: Year Month Day

◻ Dead Date of death: Year Month Day

Cause of death: ◻ Primary disease ◻ Other diseases ◻ Treatment-related ◻ Others ◻ Unknown

Circumstances of death: (Please describe the circumstances of death regardless of the cause of death.)

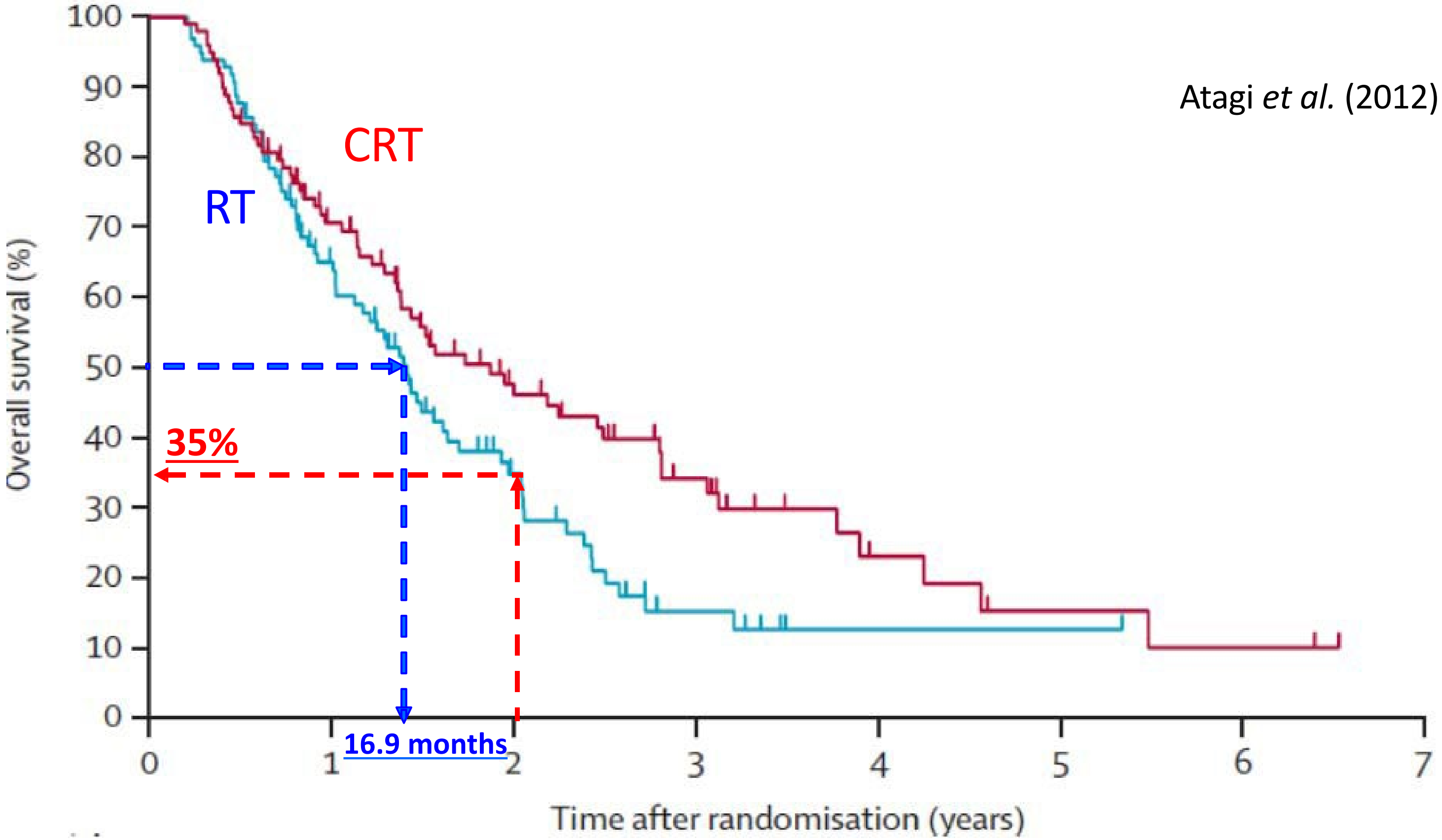
Status at the previous survey:



- Whiskers indicate censored cases
  - A patient who had no events up to that point but no further information is available.
  - Censored at the date of the last confirmation of survival
- Steps represent deaths.
  - Events at the date of death

Summary Values Obtained from Survival Curves

- Median survival time (MST), annual survival rate
  - The MST of the RT group was **16.9 months** and the 2-year survival rate was **35%**.

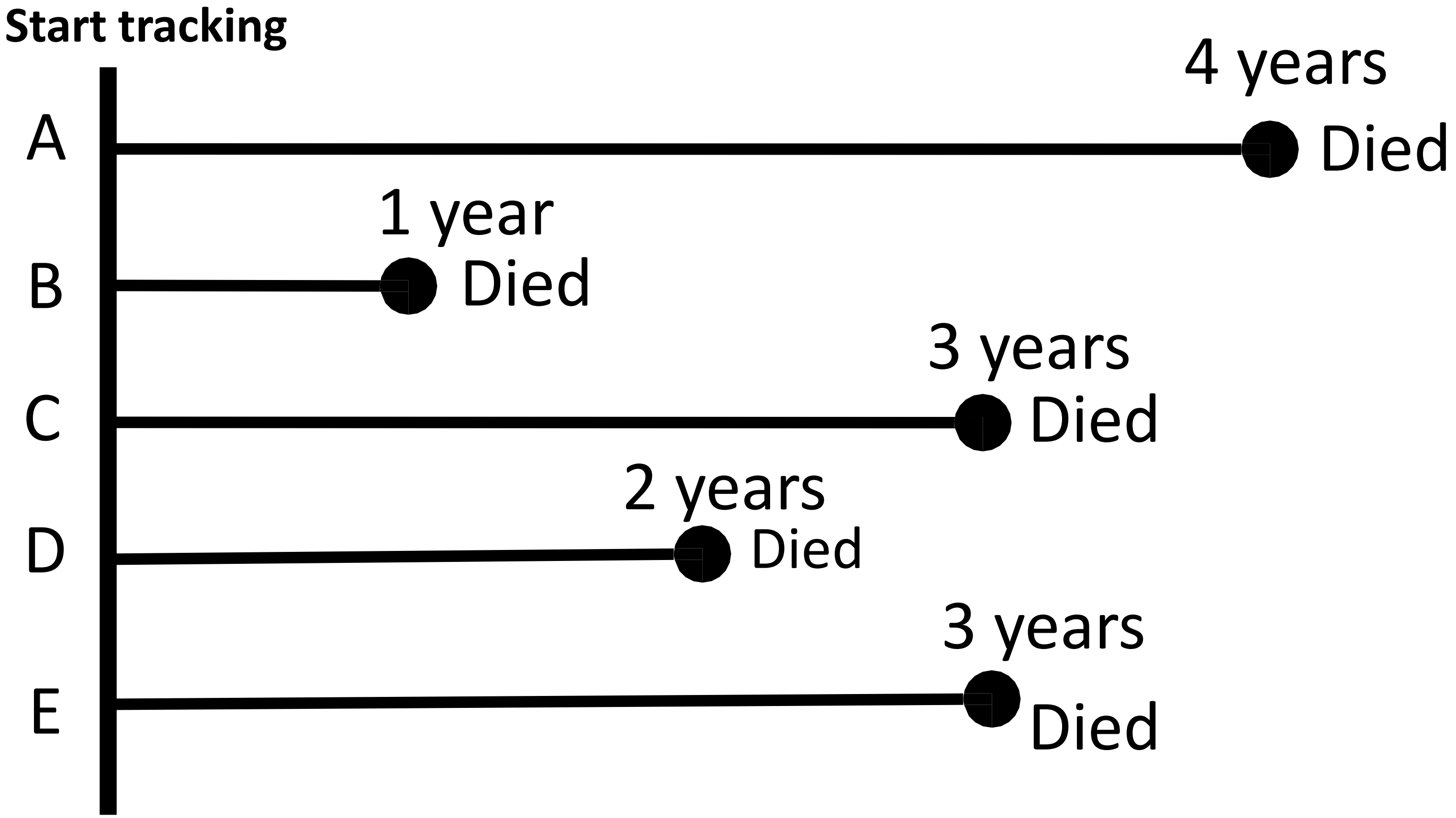


Atagi *et al.* (2012) Lancet Oncol. 13(7): 671-8.

Kaplan-Meier Method

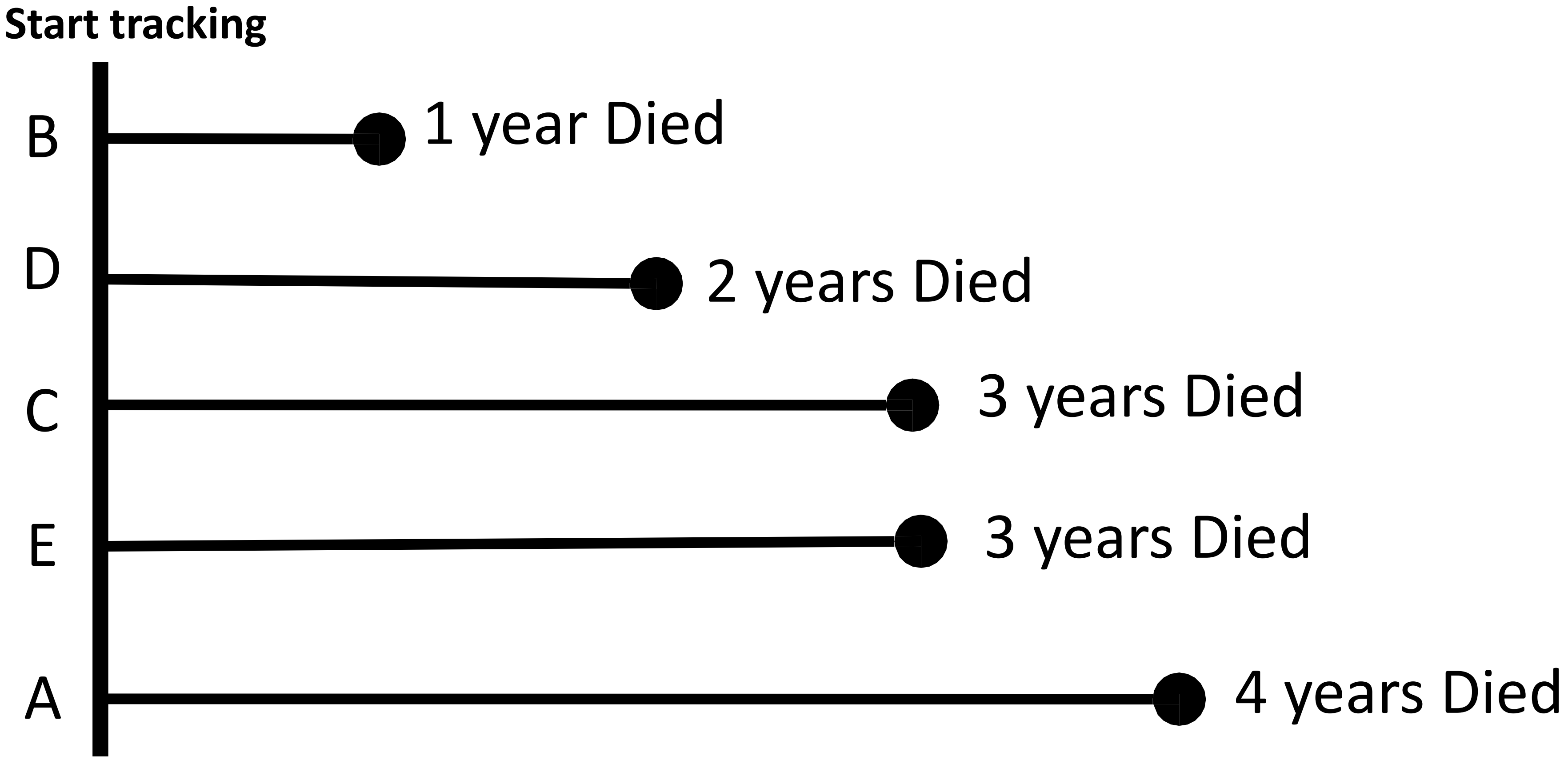
Example 1: When There Is No Censoring

- Estimation of the survival curve by the Kaplan–Meier method



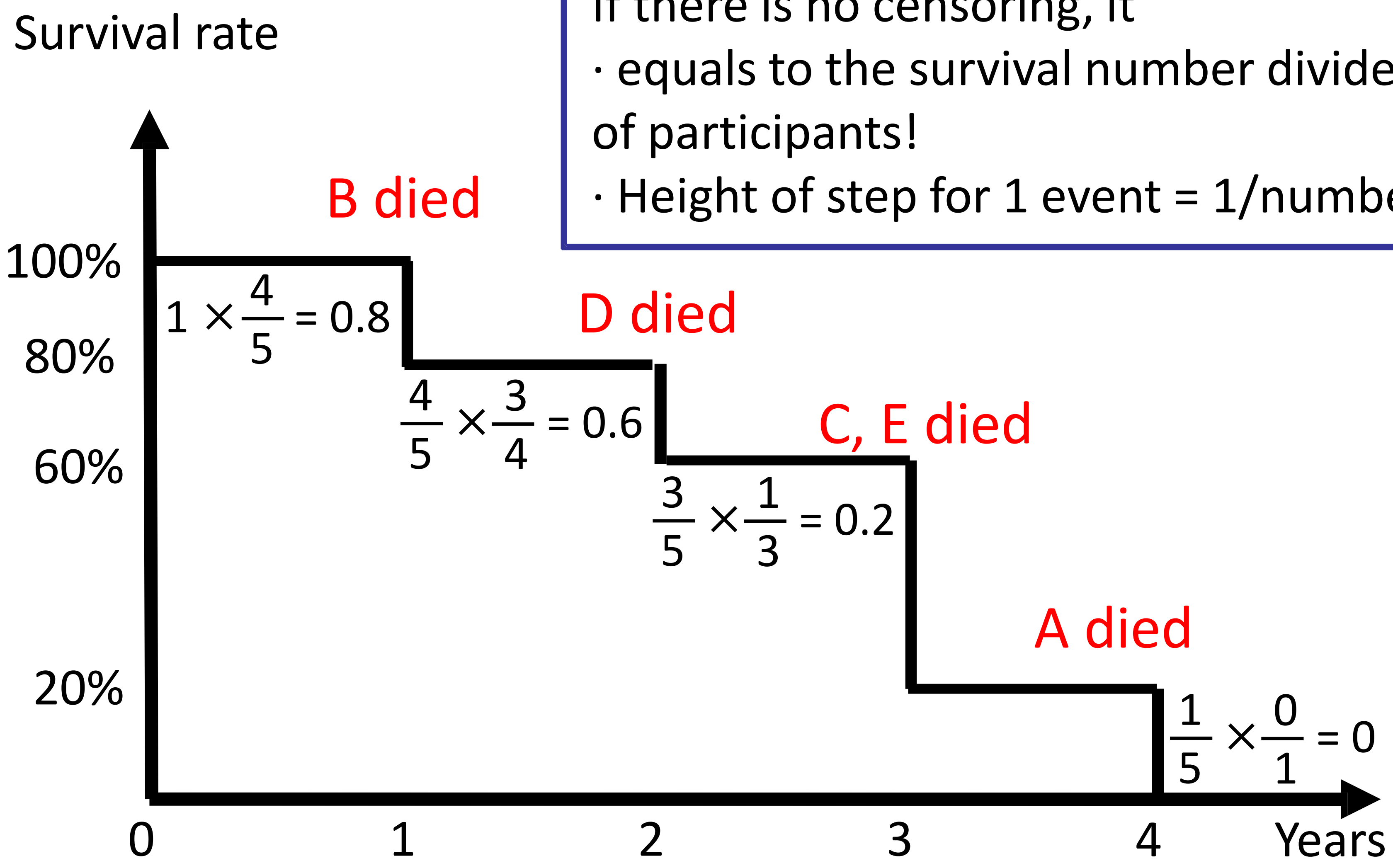
Rearrange in the Order of the Shortest Survival to Longest

- In short order, B → D → C , E → A



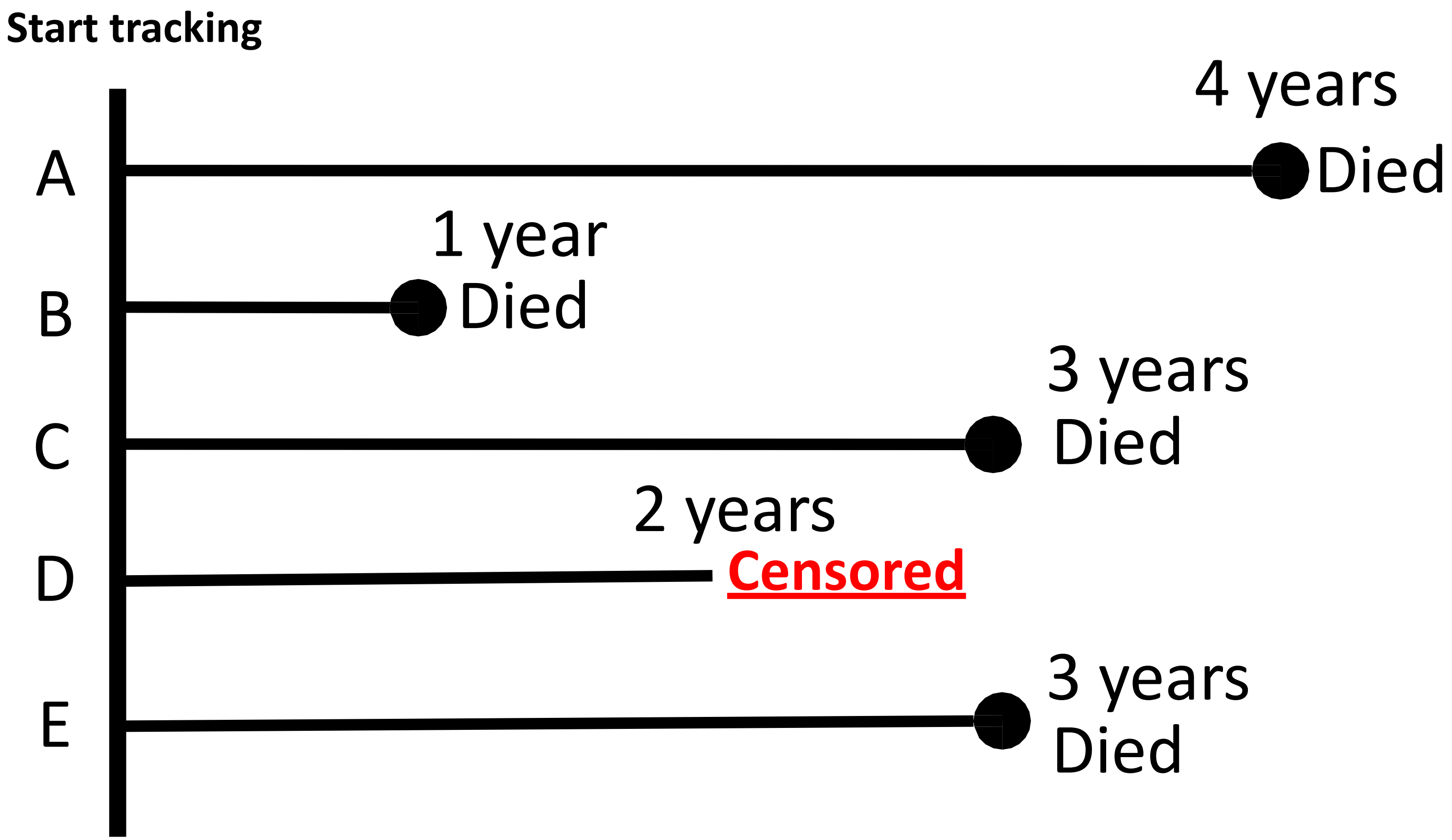
Kaplan–Meier Curve (KM Curve)

If there is no censoring, it
· equals to the survival number divided by the number of participants!
· Height of step for 1 event = 1/number of participants



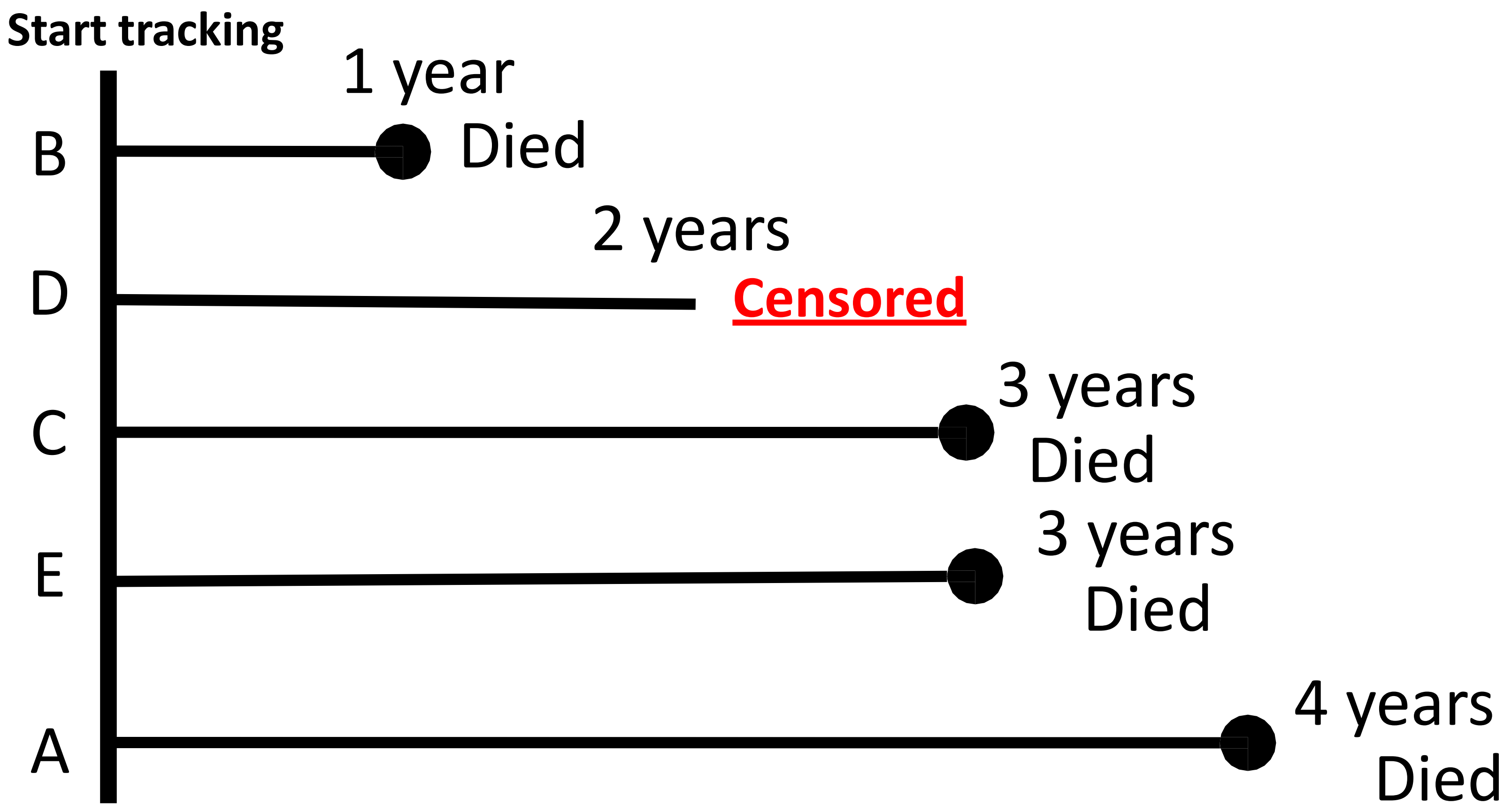
Example 2: When There is Censoring

- Estimation of the survival curve using the Kaplan–Meier method



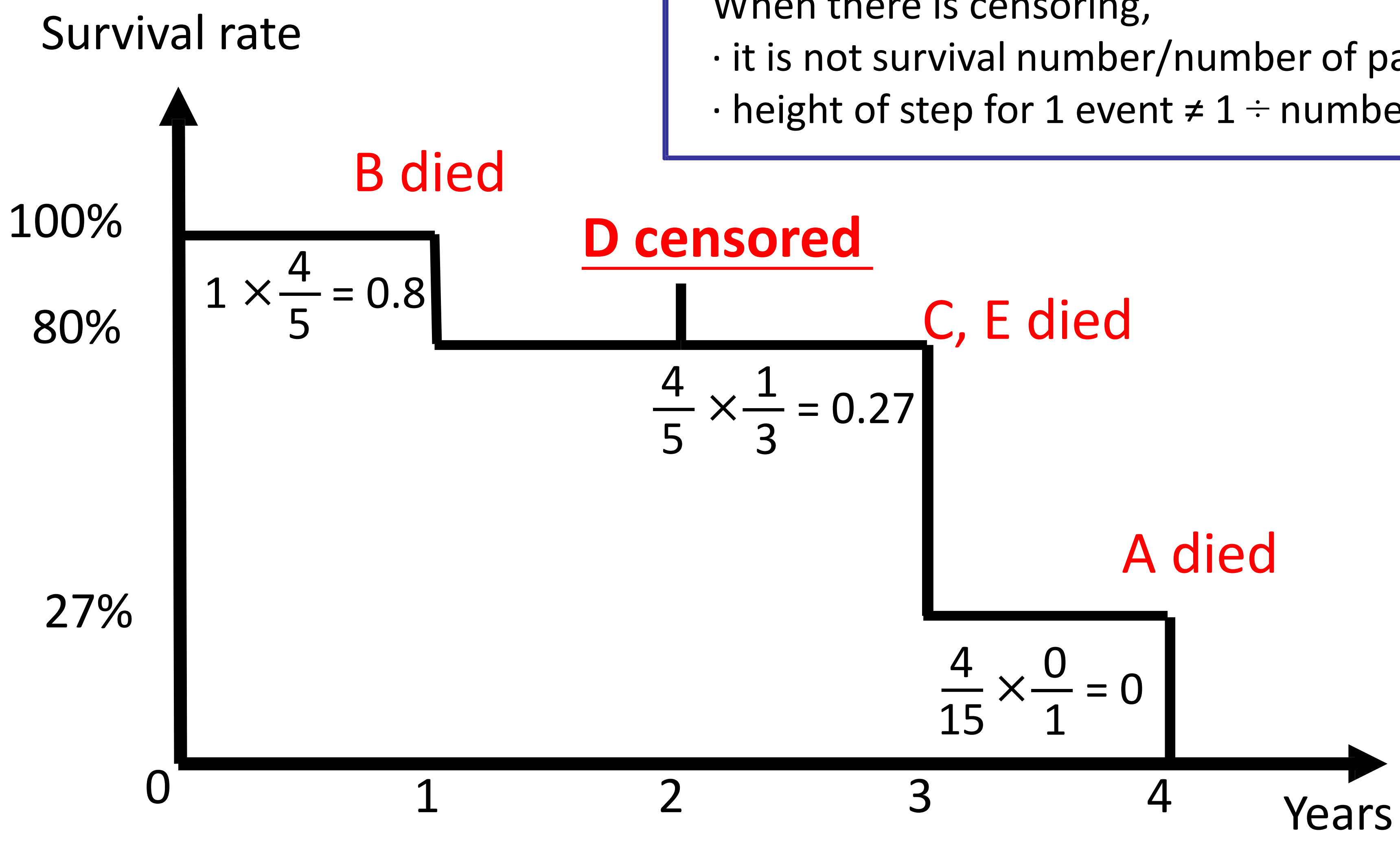
Rearrange in the Order of the Shortest to Longest Survival

- In short order, B → D → C, E → A

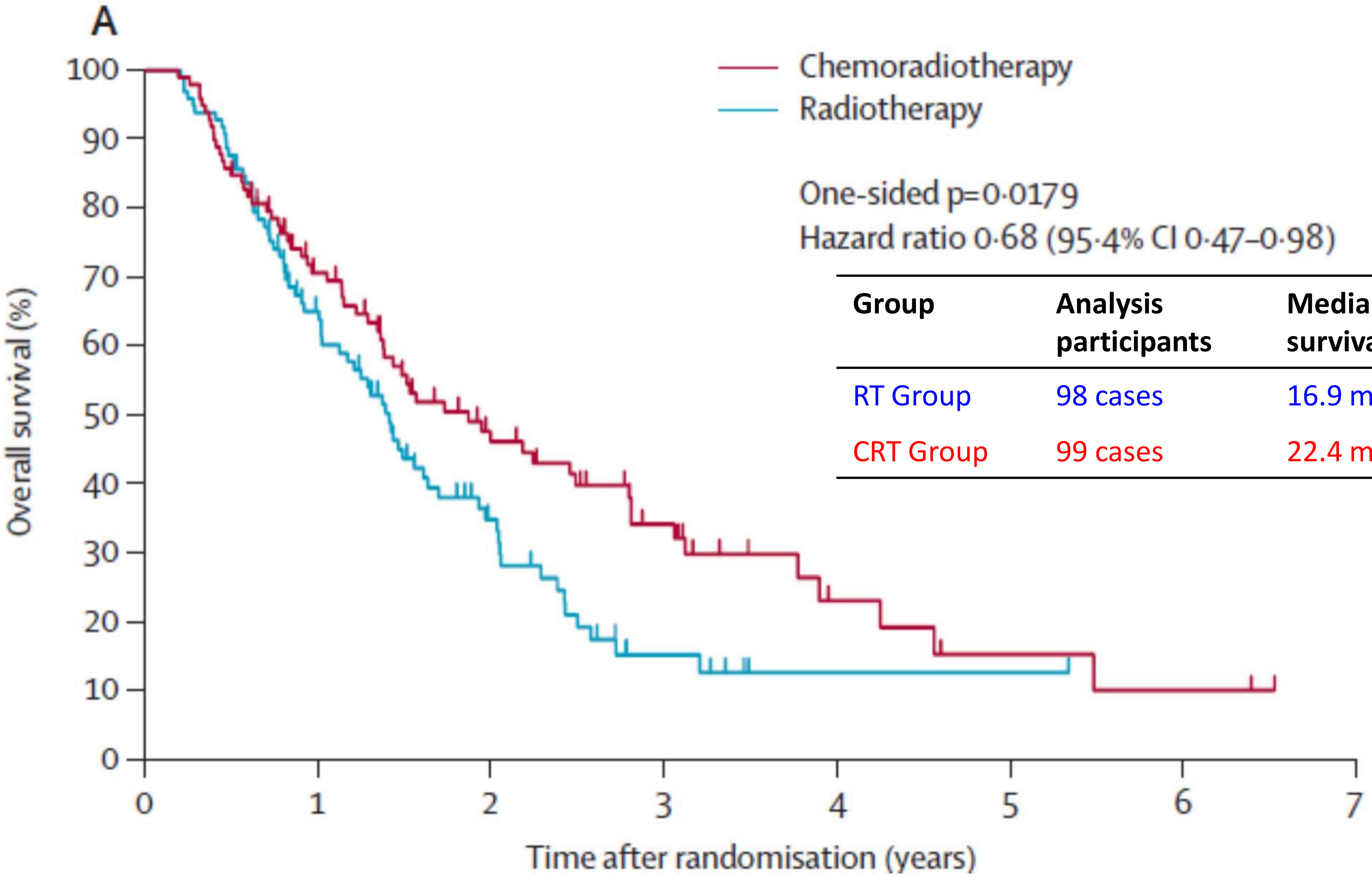


Kaplan–Meier Curve (KM Curve)

When there is censoring,
· it is not survival number/number of participants
· height of step for 1 event ≠ 1 ÷ number of participants



Determine the Values in the Table and the Survival Curves Using the Kaplan–Meier Method



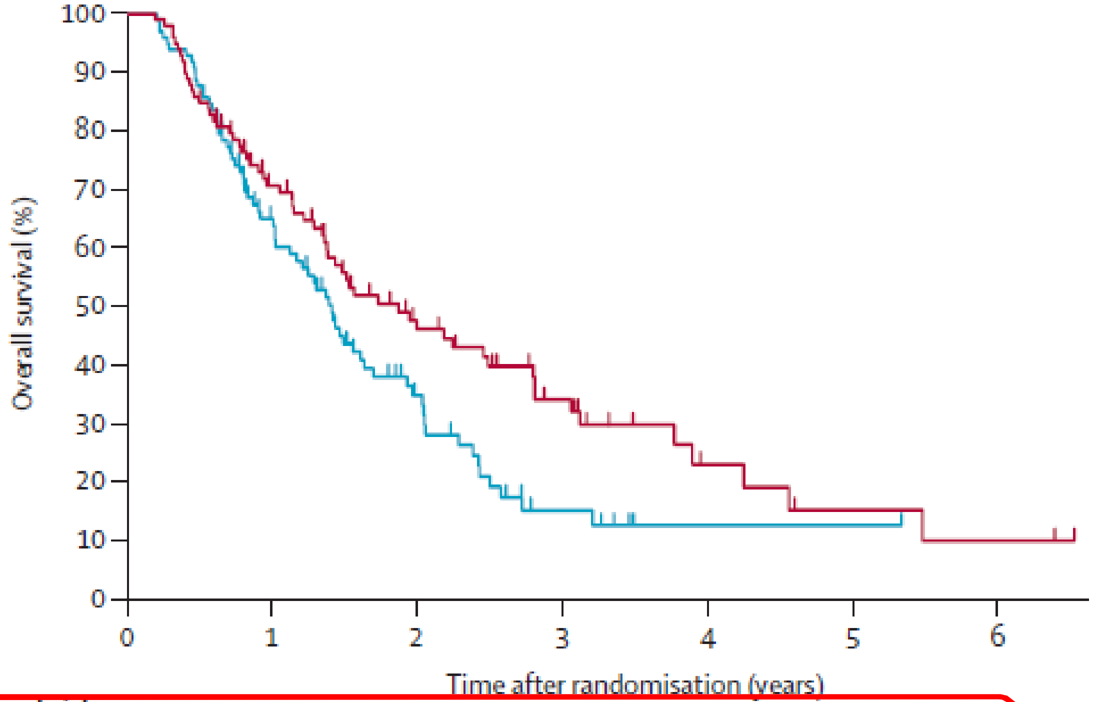
Group	Analysis participants	Median survival	2-year survival rate
RT Group	98 cases	16.9 months	35.1%
CRT Group	99 cases	22.4 months	46.3%

Number at Risk

Number [Patients] at Risk

- The number of cases that have been followed up to a certain time point (without receiving an event or censored)
- Recently, we are often asked by journals to describe "if the tracking is sufficient"

Number at risk

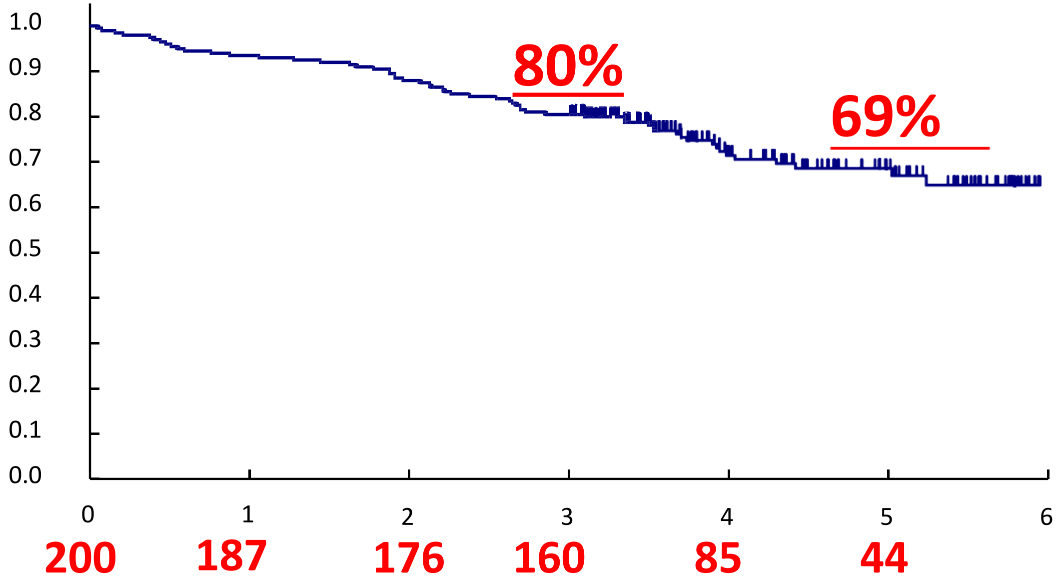


Number at risk							
Chemoradiotherapy	99	60	31	17	6	3	2
Radiotherapy	98	54	21	6	1	1	0

Atagi *et al.* (2012) Lancet Oncol. 13(7): 671-8.

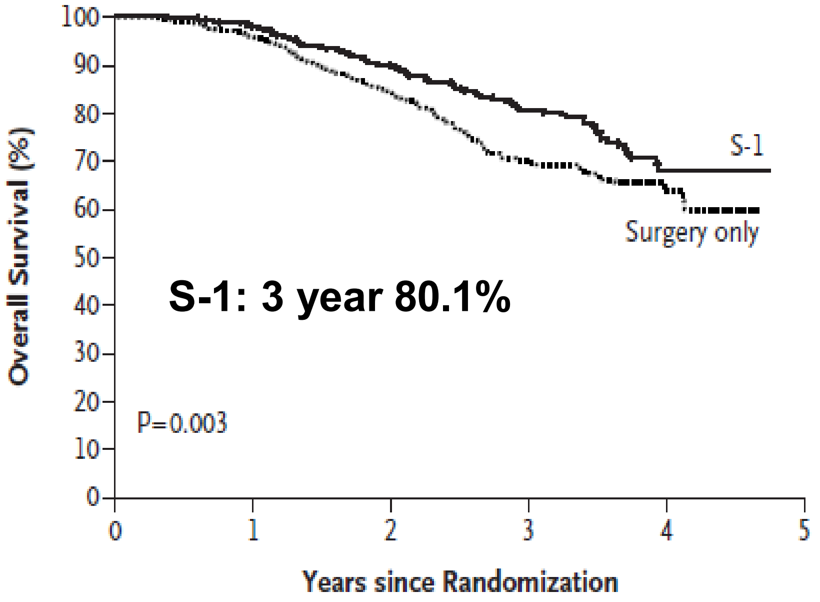
Predictable Distribution of Censoring from Number at Risk

- If there is no censoring, the survival rate of KM curve
  = survival number/number of participants
- At 3 year
  - 160/200 = **80%**
  - Match with KM curve
- At 5 year
  - 44/200 = **22%**
  - Different from KM curve
  - Many censorings between 3 and 5 years



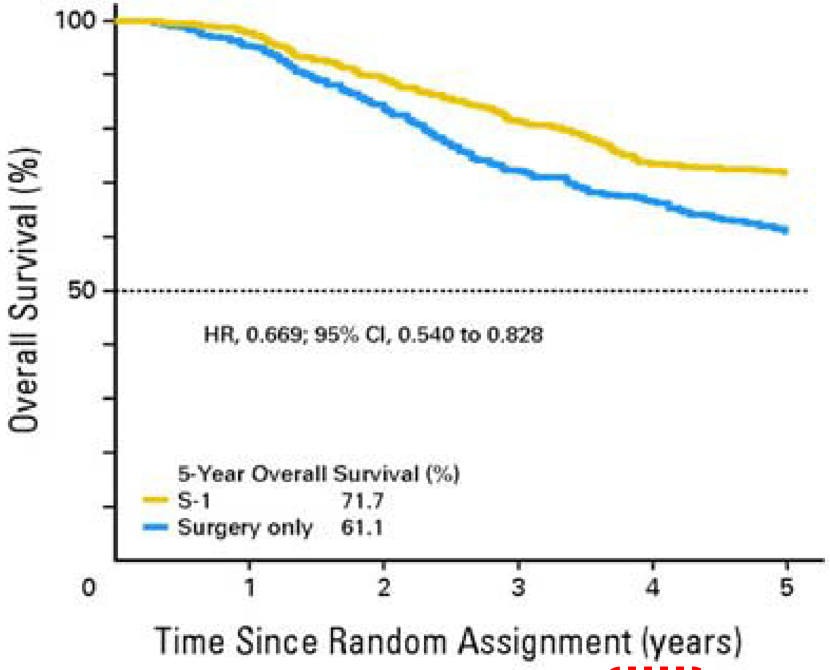
The Study Accuracy Can be Judged Without a Censoring Sign

- Compare numbers at risk to see how well they have been tracked.
  - S-1 group at 4 years at risk 46 ⇒ 363



No. at Risk					
S-1	529	515	370	196	46
Surgery only	530	504	352	163	40

Sakuramoto S et al. NEJM **2007**; 357: 1810-20



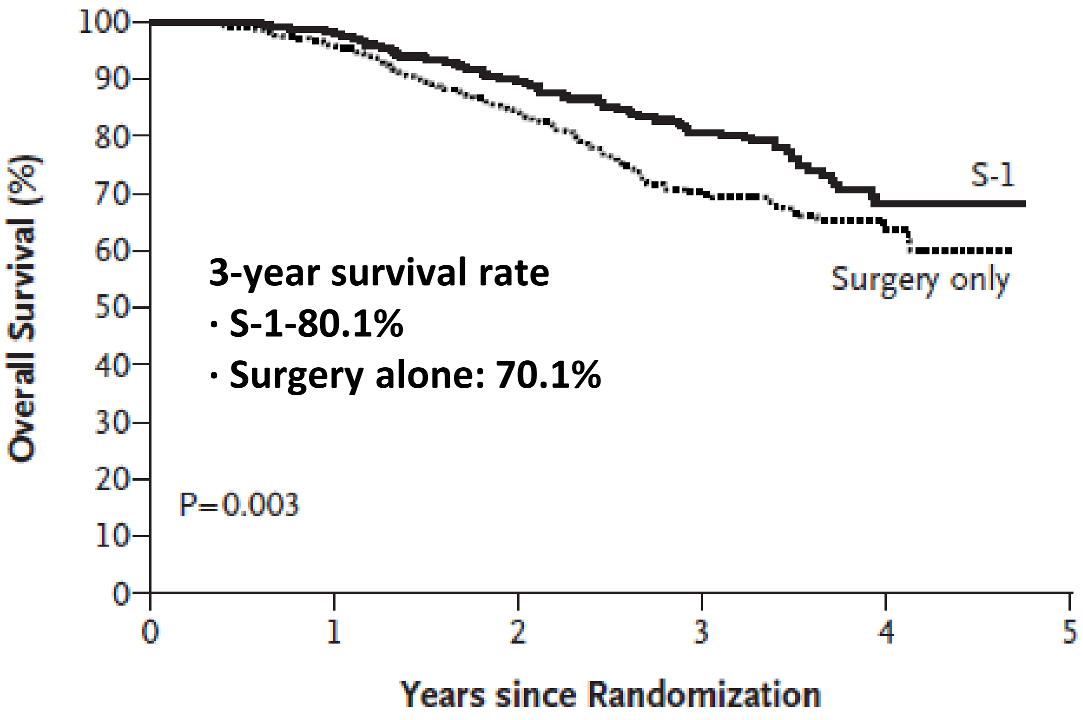
No. at risk						
S-1	529	515	465	416	363	316
Surgery only	530	504	438	365	327	268

Sasako M et al. JCO **2011**; 29: 4387-4393

Log-Rank Test

At What Time Point Is the P value of the Log-rank Test Compared?

- Protocol Setup
  - **5-year** survival rate 80% vs. 70% (HR = 0.70)
  - Enrollment 3 years, follow-up **5 years**
- Results at 1 year and 6 months after the end of registration
  - Log-rank P = 0.003
  - **3-year survival rate**
    - 80.1% vs. 70.1%



Sakuramoto S et al. NEJM 2007; 357: 1810-20

Which Understanding Is Correct?

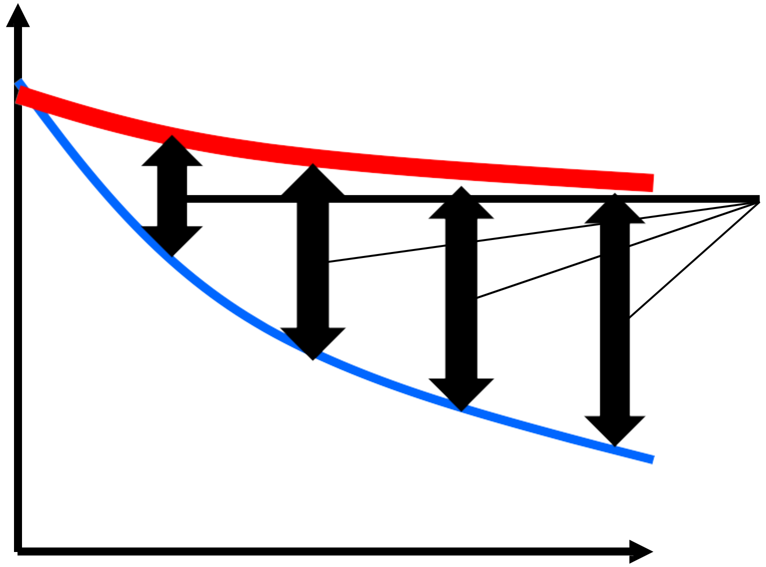
Because the protocol states that the follow-up period is 5 years, I think this is a comparison of the **5-year survival rate**.
But why does it show the 3-year survival rate?

In advanced cancer, we usually compare MSTs; thus, I think this is also a comparison of **MSTs**.
However, this has not reached MST.
How was it calculated?

I think this is a comparison of the **3-year survival rate**, as 3-year survival rate is written. The curve is the widest around 3 years, and I think that area was intentionally chosen, wasn't it?

The Key Idea of the Log-Rank Test (1)

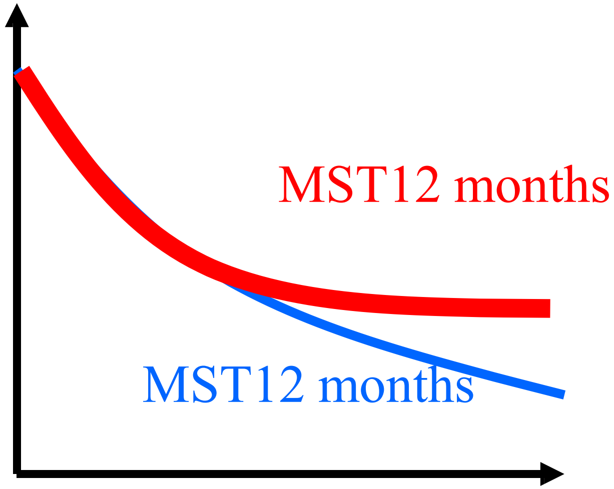
- The entire survival curves are compared
  - It does not compare the differences at a particular time point!



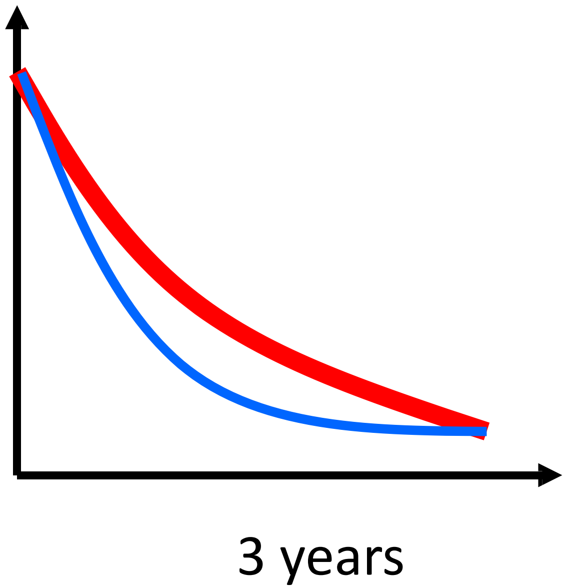
- The differences across the entire curve are assessed by summing the gaps in the survival curve at each time point when events occur.
- In other words, the further apart the two survival curves are, the larger is the gap (= lower *P* value).

Because It Is Not the Difference at One Time Point ...

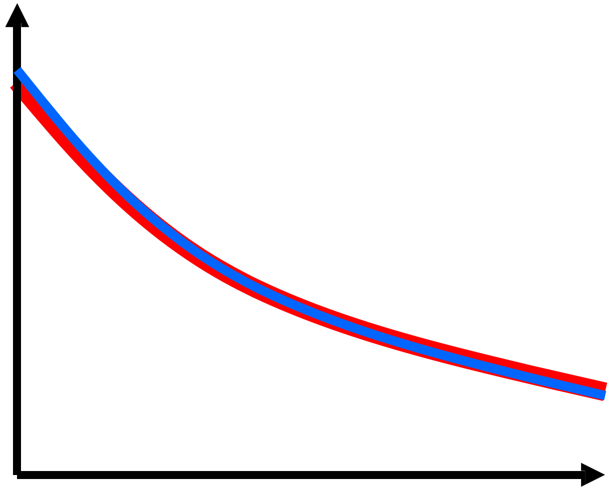
Even MST is the same,
two-sided p ≠ 1.00



Even if the curves
overlap at 3 years,
two-sided p ≠ 1.00

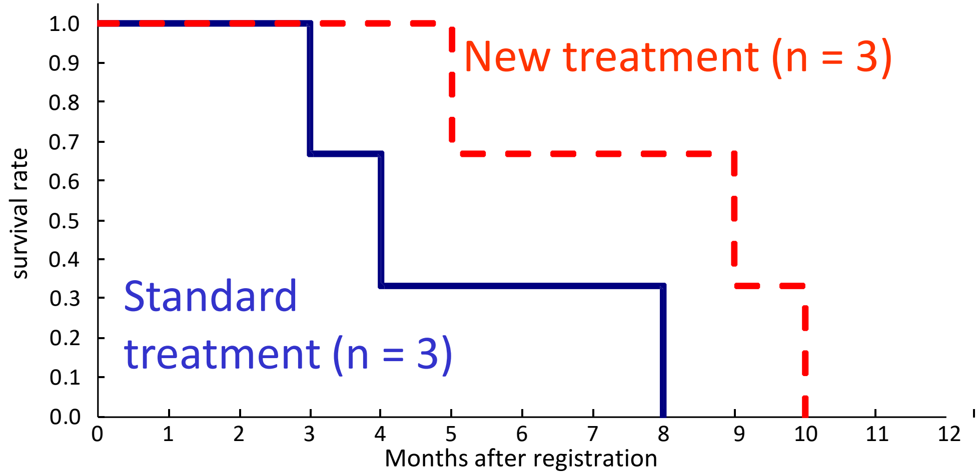


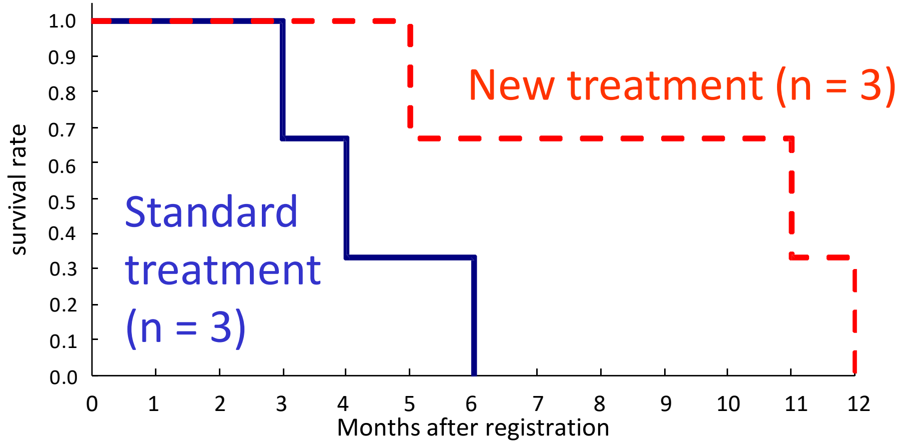
If they overlap all the way,
two-sided p = 1.00



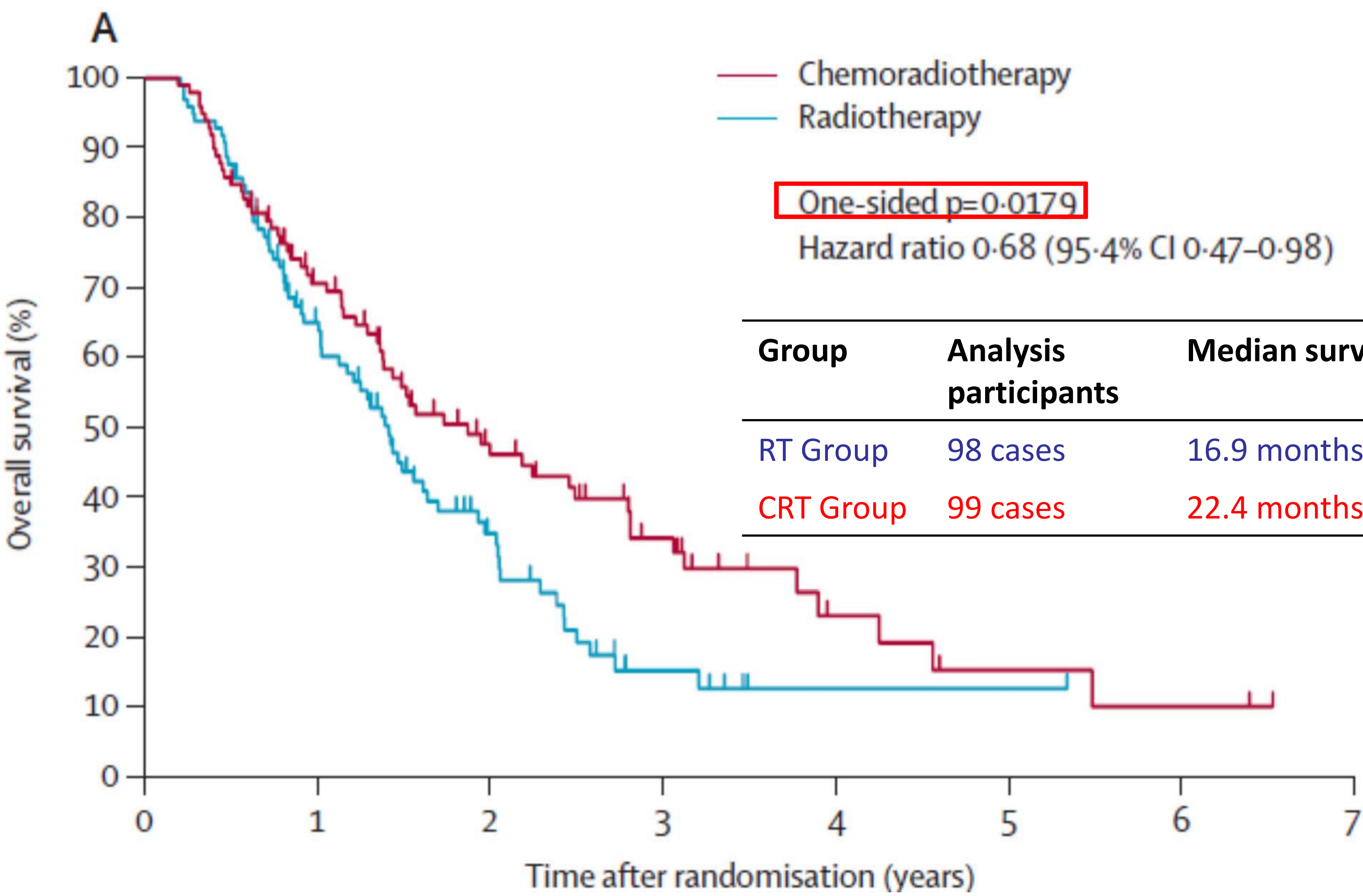
The Key Idea of the Log-Rank Test (2)

- **Only the order** in which **events** occurred is used in the calculation of the test
  - No calculation for no event
  - **Time** when the event occurred is not used.
- The following comparisons of the curves have the same log-rank test *P* value
  - The same idea applies to the Cox regression described later. Both have the same hazard ratio (HR) and 95% confidence interval (CI)
  - Two-sided log-rank: p = 0.108, HR 0.19, 95% CI [0.02–1.84]





The *P* Value is Obtained Using the Log-Rank Test



Group	Analysis participants	Median survival	2-year survival rate
RT Group	98 cases	16.9 months	35.1%
CRT Group	99 cases	22.4 months	46.3%

Cox Regression

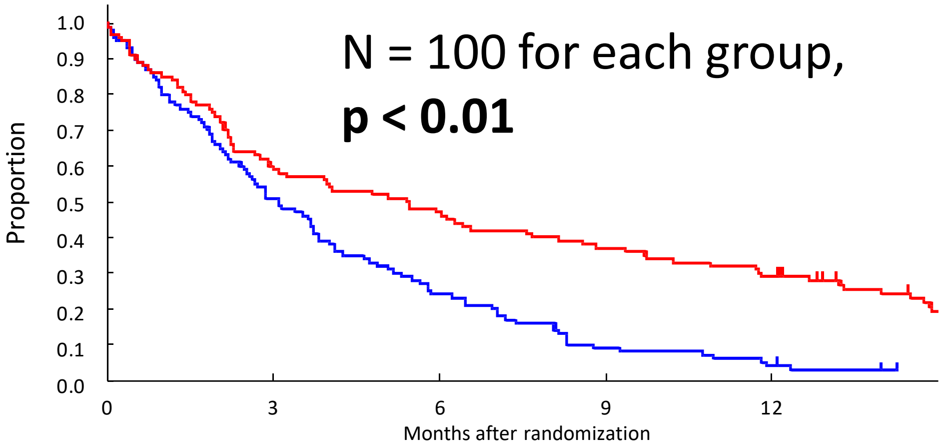
(Cox Proportional Hazards Model)

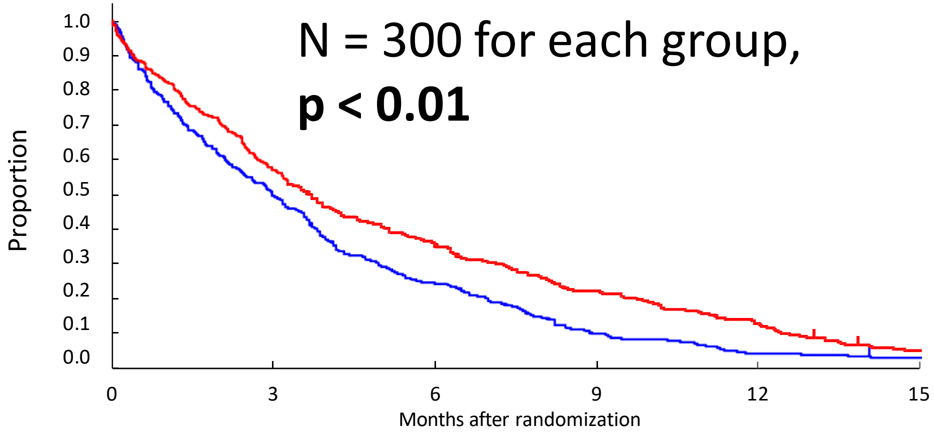
Statistical Significance ≠ Clinical Significance

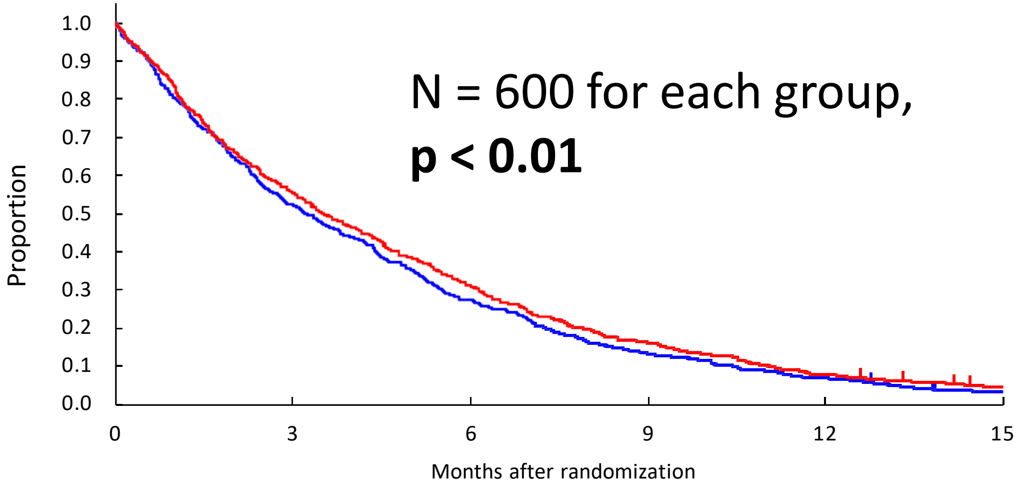
The same $p < 0.01$ could have different clinical meanings

P **value is not an indicator of the magnitude of treatment effect**

Note: Hypothetical example





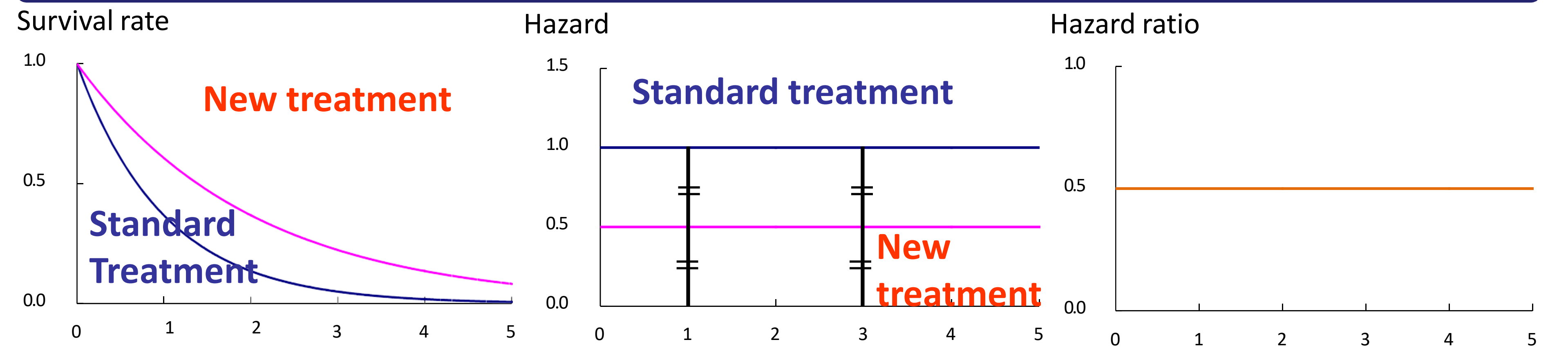


Indicator of the Magnitude of Treatment Effect

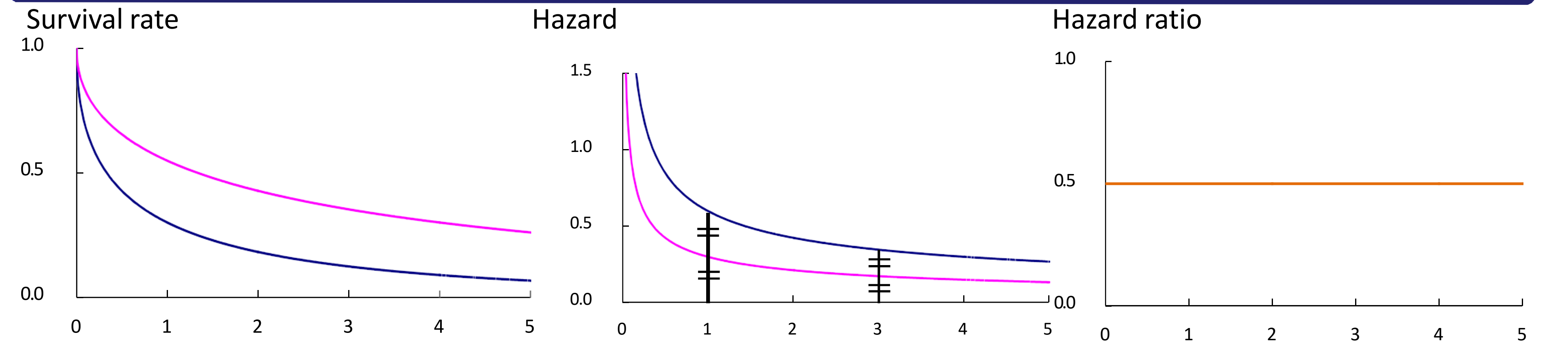
- Indicator focused on one point on the curve
  - Annual survival rate
    - 2-year survival rate CRT: 46.3% vs. RT: 35.1%
  - Median Survival Time (MST)
    - CRT: 22.4 months vs. RT: 16.9 months
- Indicator that combines the entire curve into one effect
  - **Hazard Ratio (HR)**
    - **Hazard (instantaneous mortality)** ratio between groups

Relationship between “Survival Curve,” “Hazard,” and “Hazard Ratio”

Exponential distribution: Hazard is constant through time if both groups have exponential distribution, HR is constant

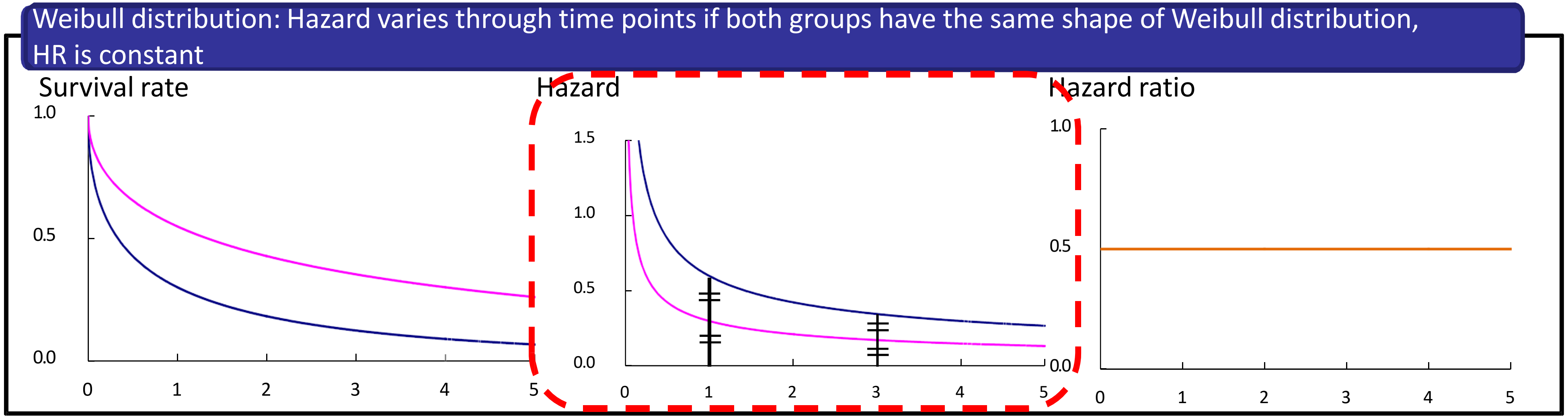


Weibull distribution: Hazard varies through time points if both groups have the same shape of Weibull distribution, HR is constant



When the HR is constant regardless of the time point, “**proportional hazard** is established.”

Cox's Proportional Hazards Model (Cox Regression)

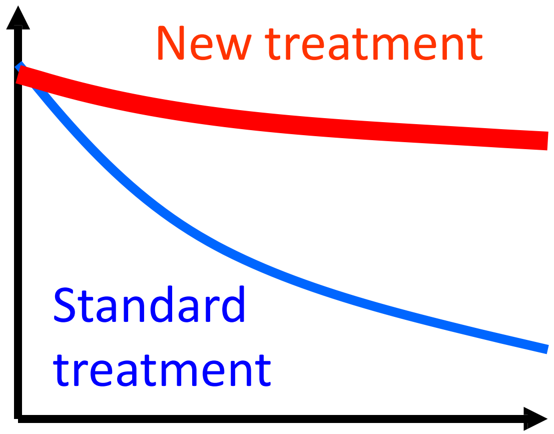


- The model represented by an equation as shown below
  - models the relationship between time and the hazard at that time point

Hazard for the new treatment group at time point t
= Hazard for standard treatment group at time point t × exp(β)

- For multivariate analysis, multiple variables are added in exp

What You Can Do with Cox Regression



- The magnitude of the treatment effect can be estimated
  - Summary Indicator: **Hazard ratio (HR)**
- When determining the HR of the new treatment group relative to the standard treatment group,
  - hazard of standard treatment cases
    = (hazard for standard treatment group at time point t) × 1
  - hazard of new treatment cases
    = (hazard for standard treatment group at time point t) × exp(β)

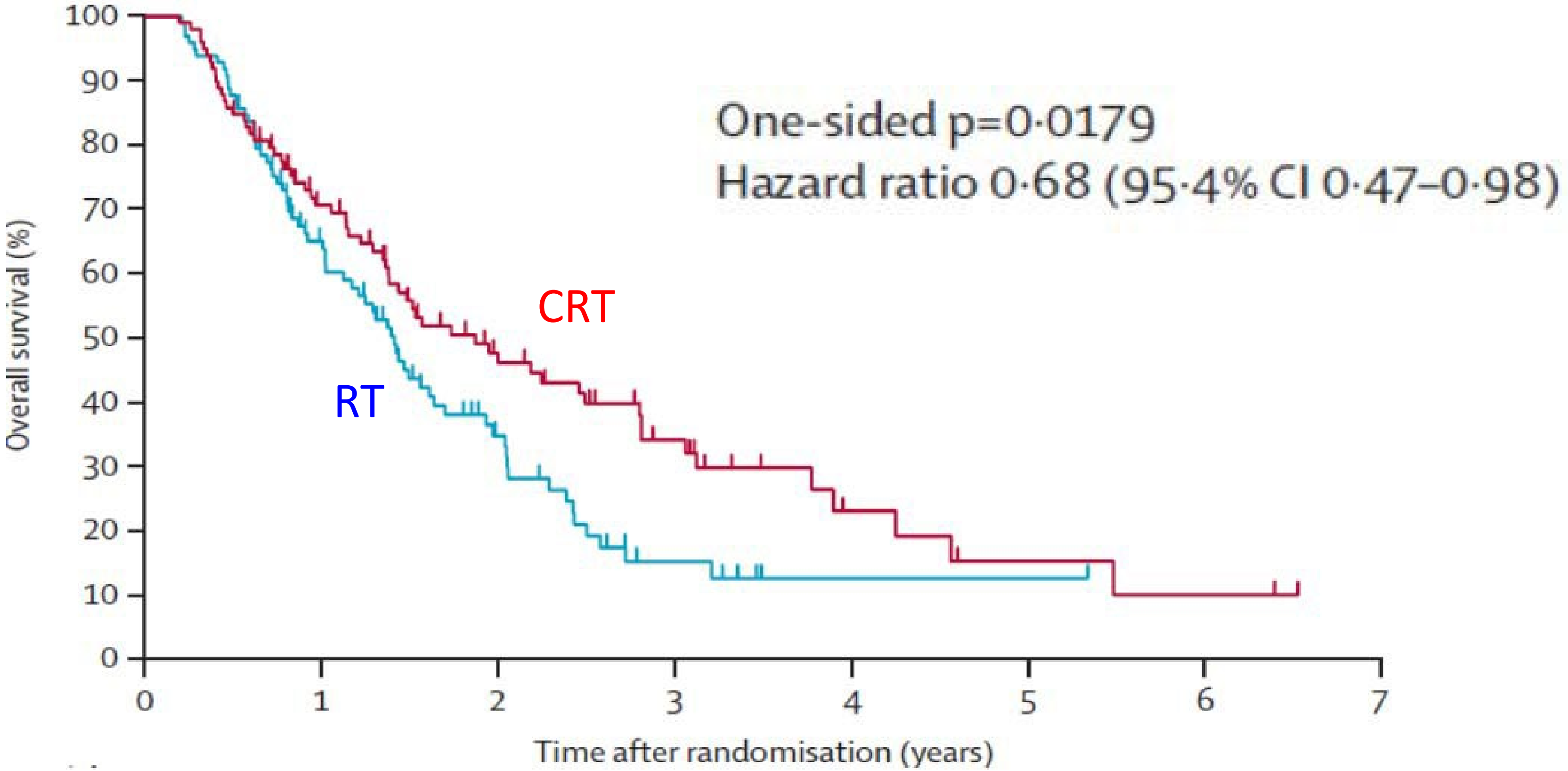
$$\text{HR} = \frac{\text{Hazard for new treatment group}}{\text{Hazard for standard treatment group}} = \frac{\cancel{\text{Hazard for standard treatment group}}}{\cancel{\text{Hazard for standard treatment group}}} \cdots \frac{\exp(\beta)}{1} = \exp\boxed{(\beta)}$$

Estimation from data

Interpretation of Hazard Ratio (HR)

- HR of CRT for RT = 0.68
  - CRT reduces risk of death by 32% over RT.
  - CRT is 0.68 times more riskier than RT.

Atagi *et al.* (2012) Lancet Oncol. 13(7): 671-8.

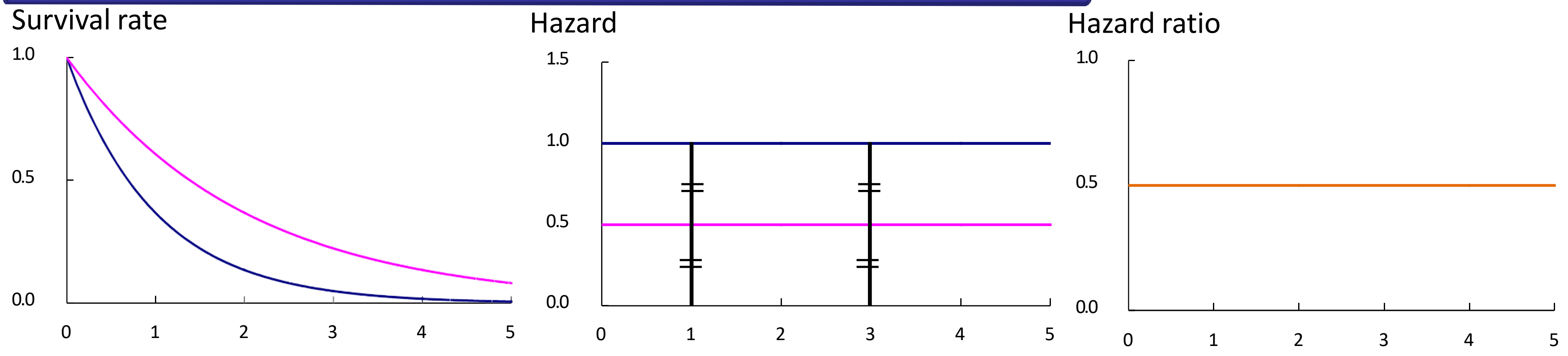


Assumptions of Cox Regression

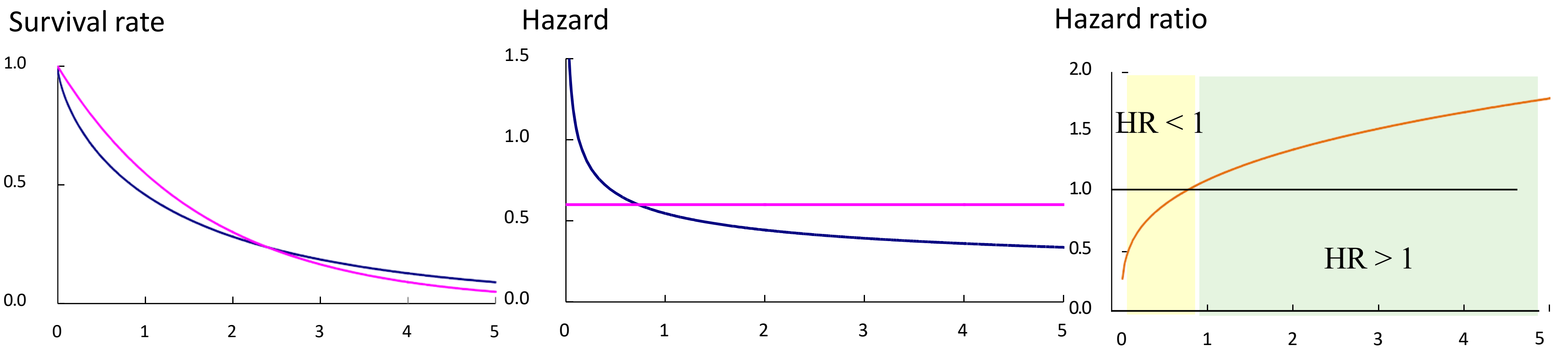
- There is one HR that can be obtained by Cox regression
  - Averages the effects of the entire curve and summarizes them into one
- The “proportional hazard property” holds true
  - “Hazard proportionality is almost constant at all time points”
- If the proportional hazard does not hold true,
  - it is not appropriate to use a single HR to summarize the effect
  - interpretation becomes more difficult

Validity of HR as determined by Cox regression

Proportional hazard holds true. HR = 0.5 obtained by Cox regression.



Proportional Hazard does not hold true. HR = 1.2 obtained by Cox regression ⇐ Interpretable?



HR is not appropriate when **proportional hazard** does not hold true.

IPASS study

Mok, Tony S., et al. *NEJM* 361.10 (2009): 947-957.

Stage IV/recurrent Non-small cell lung cancer 1st line

Random assignment

608 Examples

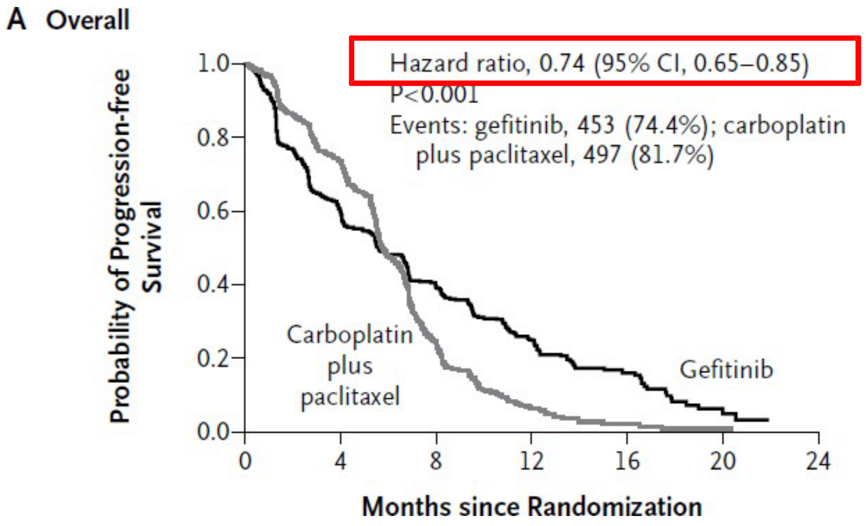
Carboplatin+ Paclitaxel

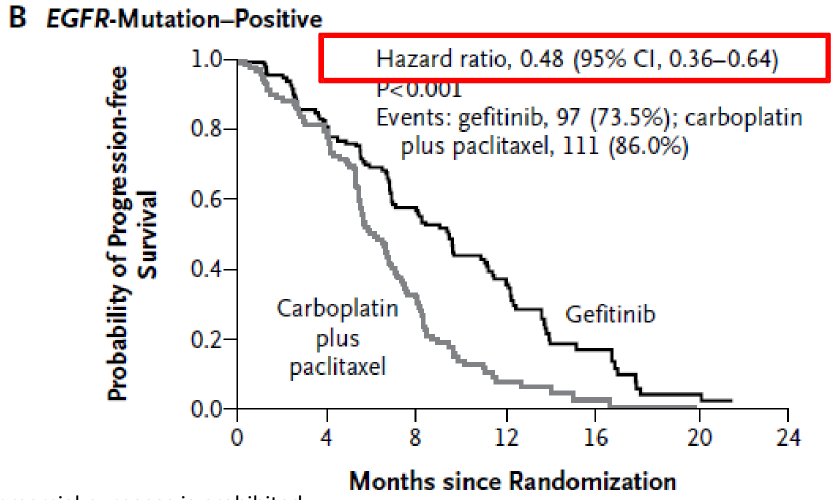
(Standard treatment)

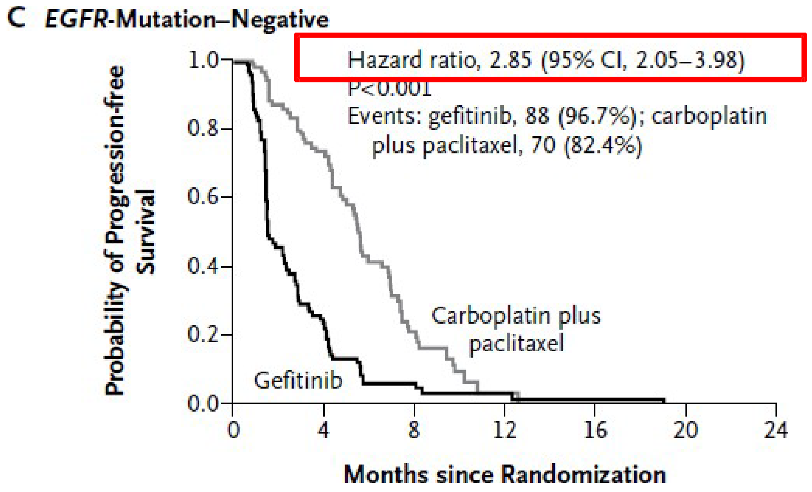
609 Examples

Gefitinib

(New treatment)







Dutch D1D2 trial

Songun, Ilfet, et al. *Lancet Oncol.* 11.5 (2010): 439-449.

Resectable stomach cancer

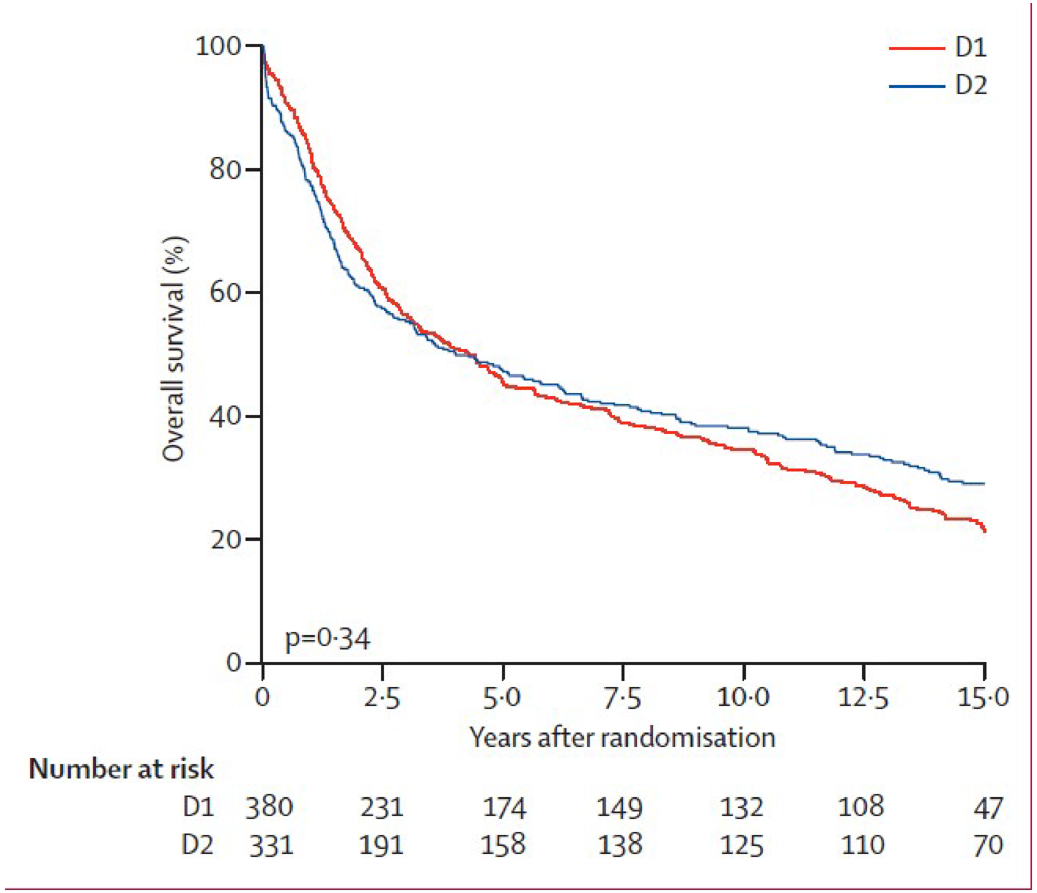
↓

Random assignment

↓

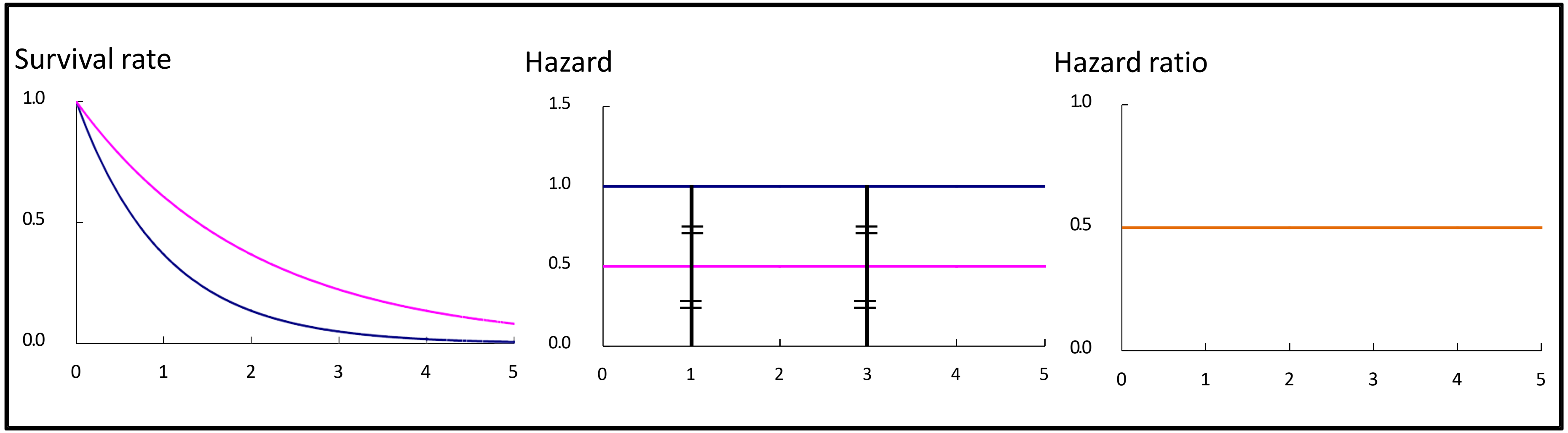
D1 dissection (Standard treatment) | **D2 dissection** (New treatment)

	D1	D2
Postoperative death	15 (4%)	32 (10%)
Complications (in an illness)	94 (25%)	142 (43%)
Repeat surgery	30 (8%)	59 (18%)



Difference between Rate, Ratio, and Proportion

Definition of Usage Terms



- Survival rate <u>sometimes referred to as "survival proportion"</u>
- Can mortality <u>**be**</u> calculated as "1 - survival rate"?
- To which concept does "hazard" apply?

Proportion, Rate, and Ratio: From Kojien (Japanese Dictionary)

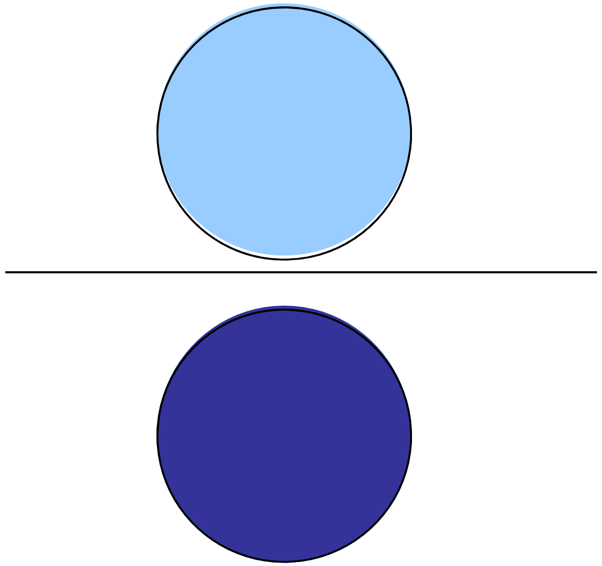
- Rate: proportion, percentage
- Proportion: ratio between quantities, percentage, ratio.
- Ratio: two quantities A and B of the same kind exist, and when B is not zero, the relation of how many times A is equal to B is called the proportionality of A to B. This is written as A:B.

Everything becomes “comparison”

Ratio

- It has the broadest meaning among the three. It is a quantity divided by another quantity (in general, it has a dimension).

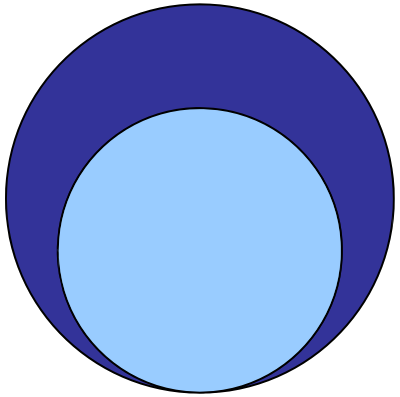
- The denominator and numerator are separate and do not contain each other's counterparts.
- Example
  - Sex ratio = number of men/number of women
  - BMI = weight (kg)/height 2 (m)



Proportion

- Form of ratio in which numerator is contained in denominator (no dimension, between 0 and 1)

- Example
  - Proportion of men = number of men/size of a population
  - Batting average = hits/at bat
  - Response rate = (CR + PR)/all eligible counts



Rate

- Relates to the rate of change of a phenomenon under certain conditions (has dimension, may exceed 1)

- Example
  - Divorce rate = number of divorces **per year** per 1,000 people
  - Mortality (Hazard by person-year method)
    - Number of deaths/Total observation time

      = 2 deaths per 3 person-years

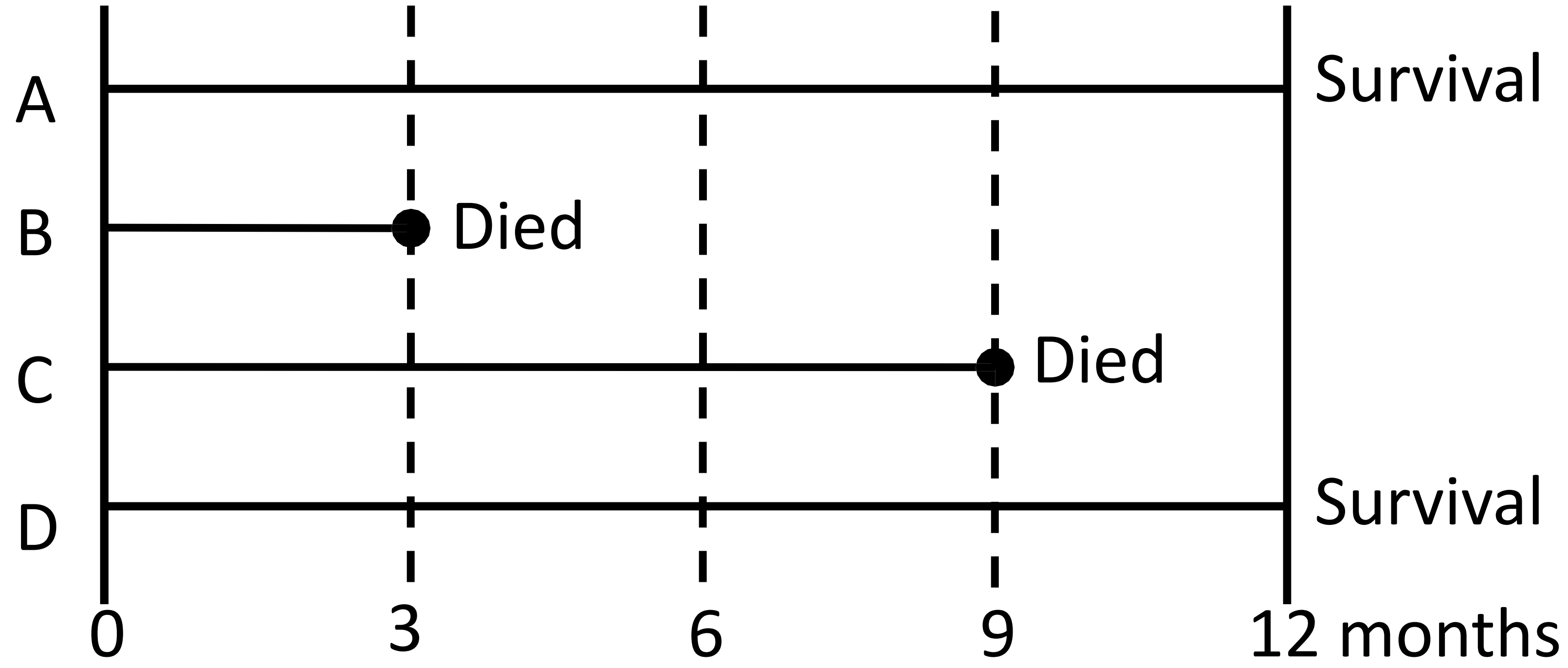
      = 66.7 deaths per 100 person-years

  ⇔ Interpretation: If 100 people are observed for 1 year, 66.7 will die.

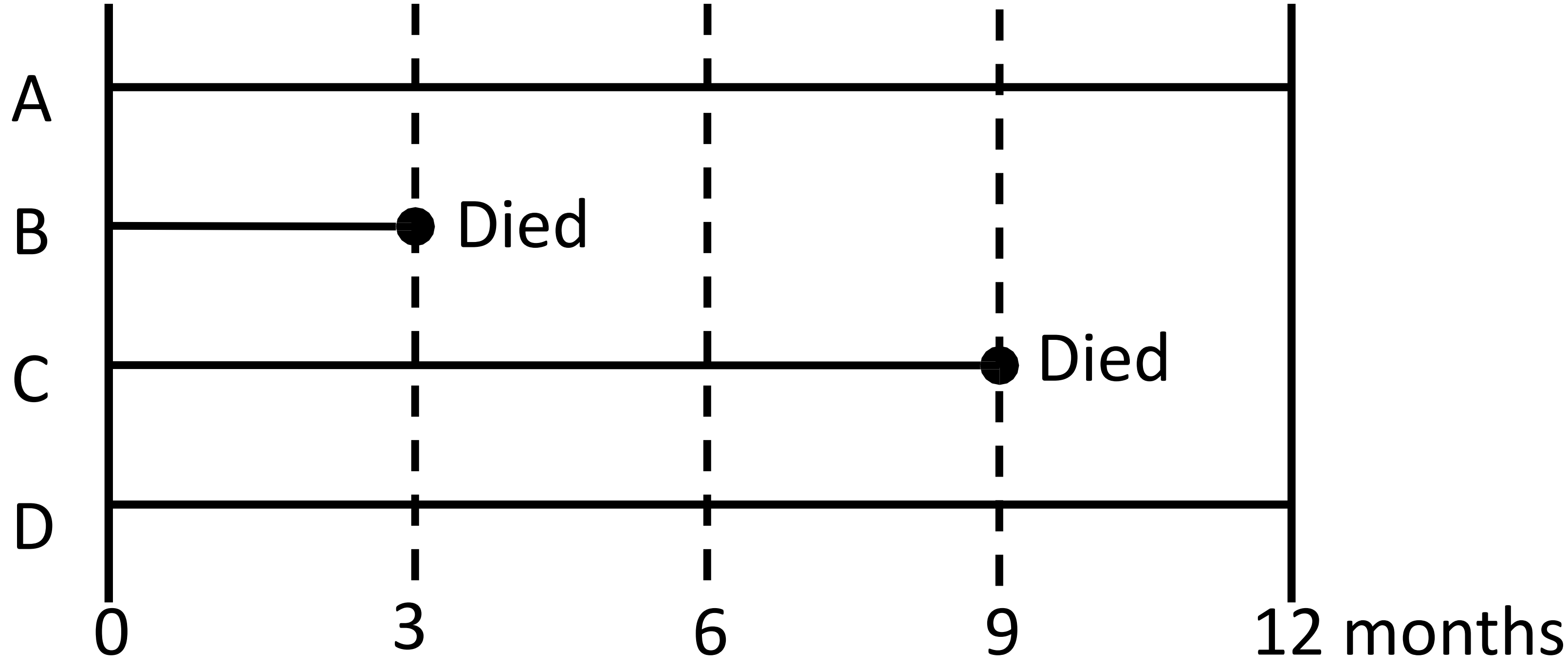
Question 1: Which One Is It among Rate, Ratio, and Proportion?

1. Batting average: **proportion**
2. Mortality: **rate (Mortality ≠ 1 − survival proportion!)**
3. Response **rate**: **proportion**
4. Survival **rate**: **proportion**
5. Hazard: **rate**

Question 2. What Is the Proportion of Deaths and Mortality for These Four Individuals?



Answer to Question 2



Proportion of deaths: 2 people/4 people = 0.5

Mortality: 2 people/3 years = 0.67 people/year

2 people/36 months = 0.056 people/month

Outcome Types and Statistical Methods

	Continuous Variable	Binary (0/1)	Survival Time
Outcome examples	BMI, blood pressure, laboratory values	Response rate	Overall survival, progression-free survival
Data summary	Histogram	Contingency table	**Kaplan-Meier method**
Group comparison (test)	*t*-test, Wilcoxon test	Chi-square test, Fisher’s exact test	**Log-rank test**
Model fitting	Multiple regression analysis	Logistic regression	**Cox regression**

Summary

- To estimate the survival curve, use the **Kaplan–Meier method**.
- The survival rate determined using the Kaplan–Meier curve is the same as the number of survivors divided by the number of participants, if there is no censoring.
- **Use log-rank test** to perform an intergroup comparison of the survival curve.
- The log-rank test compares the entire curve, not just one time point
- **Use Cox regression** to obtain the treatment effect
- The treatment effect can be summarized by hazard ratio based on the Cox regression.
- When the proportional hazard does not hold true, hazard ratio determined by Cox regression is not appropriate.
- In research, be aware of the difference between rates, ratios, and proportions.