Minimum statistical knowledge required for clinical trials on cancer

~Key points for interpreting the results of phase III randomized controlled trials~

Part 1 of 2

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The 23rd JCOG Clinical Trial Seminar

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*** Japan Clinical Oncology Group** (https://jcog.jp/en/)

JCOG Japan Clinical Oncology Group

ATLAS ASIAN CLINICAL TRIALS NETWORK FOR CANCERS PROJECT

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

I want to interpret the results of a randomized controlled trial!

Lung Cancer Study Group, JCOG
JCOG0301

Unresectable stage III non-small cell lung cancer in patients aged ≥71 years

Randomization

(standard treatment) — 100 cases — Radiotherapy (RT)

RT cases: 98
RT completion: 93
RT non-completion: 5

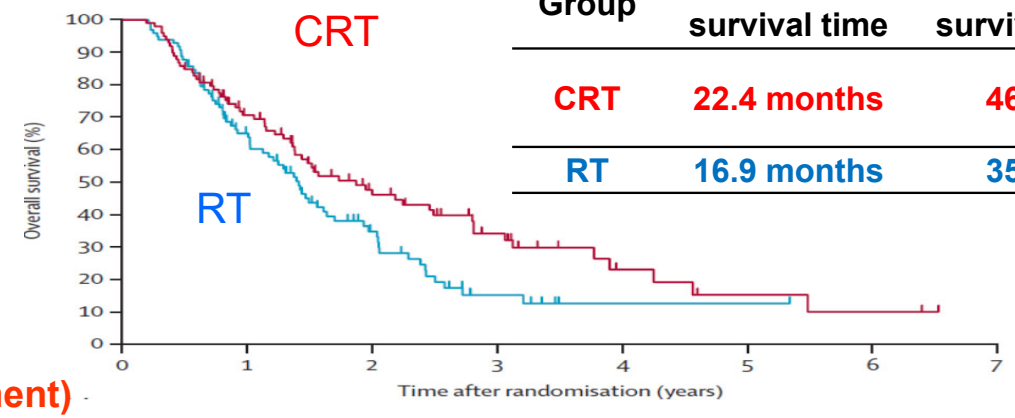
Untreated cases: 2

(new treatment) — 100 cases — Radiotherapy + chemotherapy (CRT)

CRT cases: 96
CRT completion: 88
CRT non-completion: 8

Untreated cases: 4

One-sided p=0·0179
Hazard ratio 0·68 (95·4% CI 0·47–0·98)



Group	Median survival time	Two-year survival rate
CRT	22.4 months	46.3%
RT	16.9 months	35.1%

Conclusion: CRT has clinically meaningful benefits compared with RT, and CRT should be considered as the standard therapy for this population.

Why was this conclusion reached?

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

Outline ~What to know for interpreting a randomized trial~

- Interpretation of results of a **survival curve**
  - Annual survival rate, median survival time
- Why is **randomization** necessary?
  - **Confounding and randomization**
- Result verification method
  - Concept of **hypothesis testing** and meaning of **p-value**
  - Comprehension of **α error, β error, and statistical power**
- Views on magnitude of treatment effects
  - Meaning of **hazard ratio**
- What is an analysis set?
  - **Intention-to-treat analysis** (ITT analysis)

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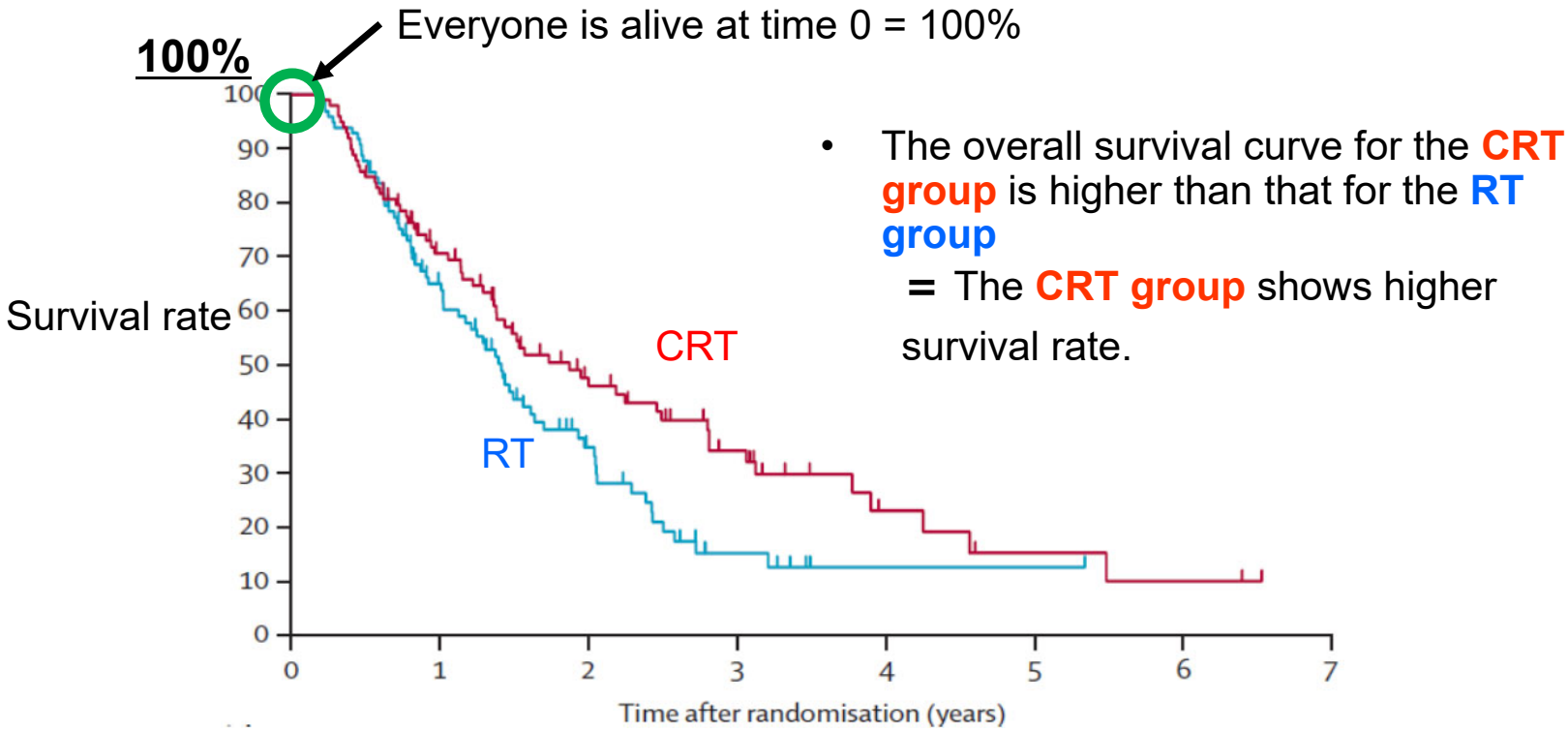
What is a survival curve?

- Time on horizontal axis, survival rate on vertical axis, and survival rate at each timepoint in population is connected.
- When death occurs, survival rate at that point decreases.



- The overall survival curve for the **CRT group** is higher than that for the **RT group**
  = The **CRT group** shows higher survival rate.

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

What is a survival curve?

JCOG 0301

FOLLOW-UP

OUTCOME

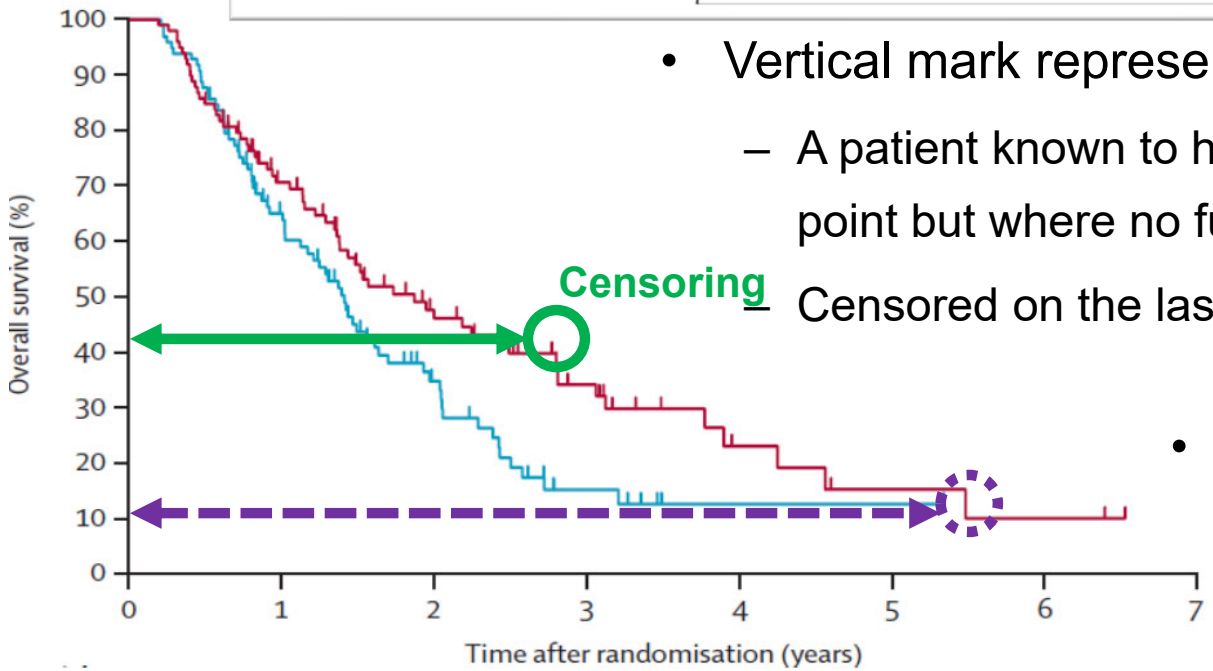
0 Alive — Latest date of survival confirmation: Y M D

1 Dead — Date of death: Y M D

Previous outcome:

Cause of death: 1 Primary disease 2 Other disease 3 Treatment-related 4 Others 9 Unknown

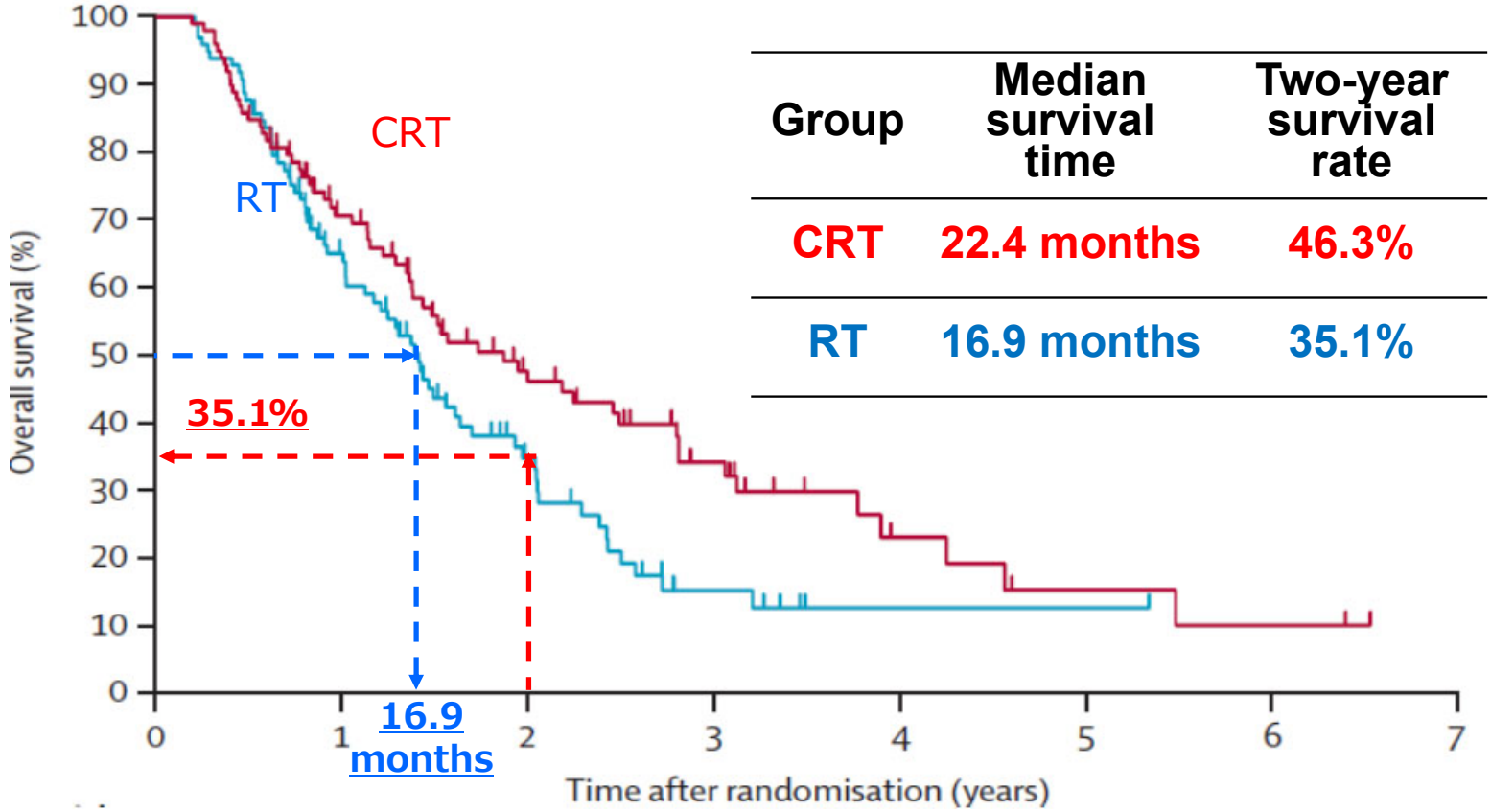
Details:



- Vertical mark represents **censored cases**
  - A patient known to have had no events up to that point but where no further information is available
  - Censored on the last day that the patient was alive
- Steps represent **fatal cases**
  - Event on the date of death

Summary values obtained from survival curves

- Median survival time, annual survival rate
  - The median survival time in the RT group was **16.9 months**, and the two-year survival rate was **35.1%**



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Randomization??

Lung Cancer Medical Group
JCOG0301

Unresectable stage III non-small cell lung cancer in patients aged ≥71 years

Randomization

100 cases → **Radiotherapy (RT)** **(standard treatment)**

100 cases → **Radiotherapy + chemotherapy (CRT)** **(new treatment)**

What is randomization used for?
Why don't physicians and patients use their preferred treatments?

Group	Median survival time	Two-year survival rate
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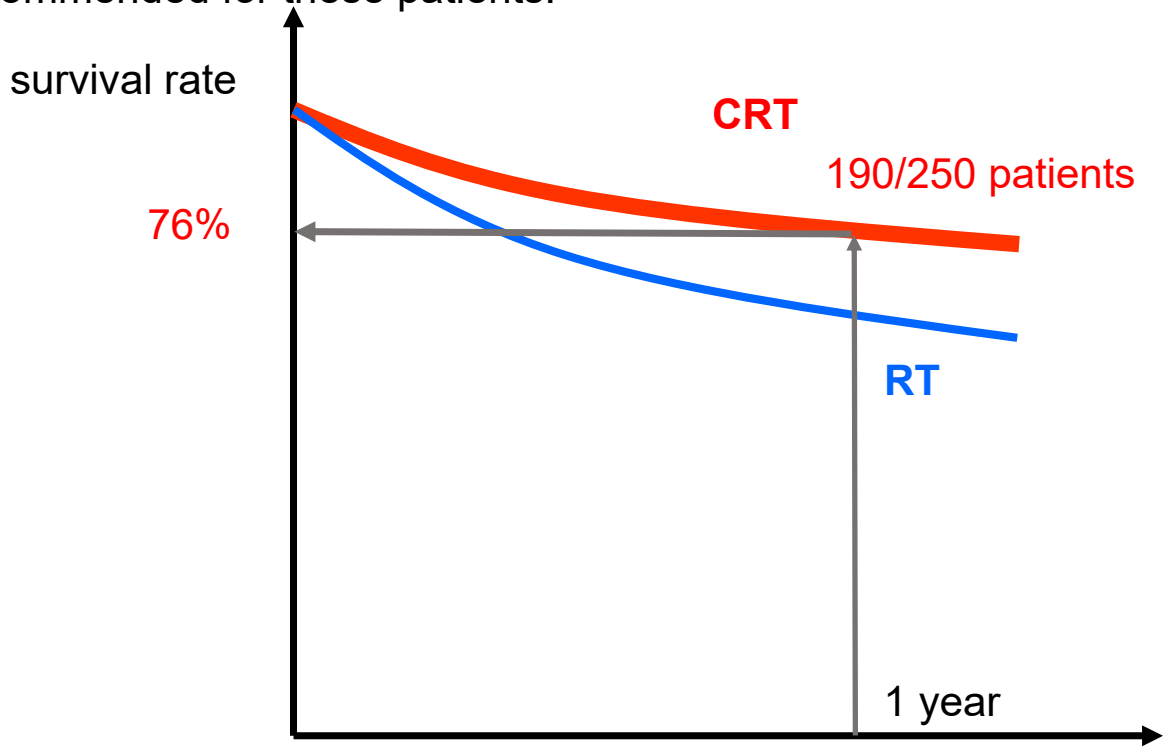
Presentation at an academic conference

Note: hypothetical example

- Patients who met the eligibility criteria XX at their hospital were divided into a **CRT group** (250 cases) and an **RT group** (60 cases) and were retrospectively examined.
- The **CRT group** had a better prognosis than the **RT group**.
- **CRT** is recommended for these patients.



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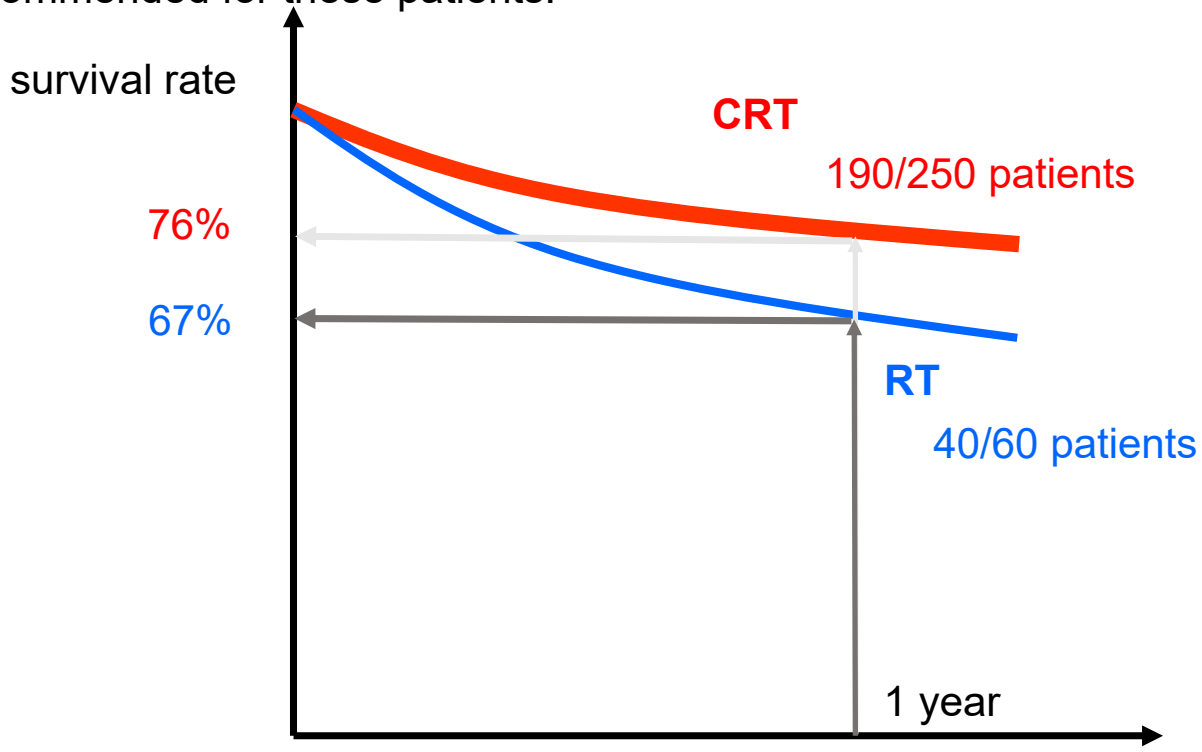
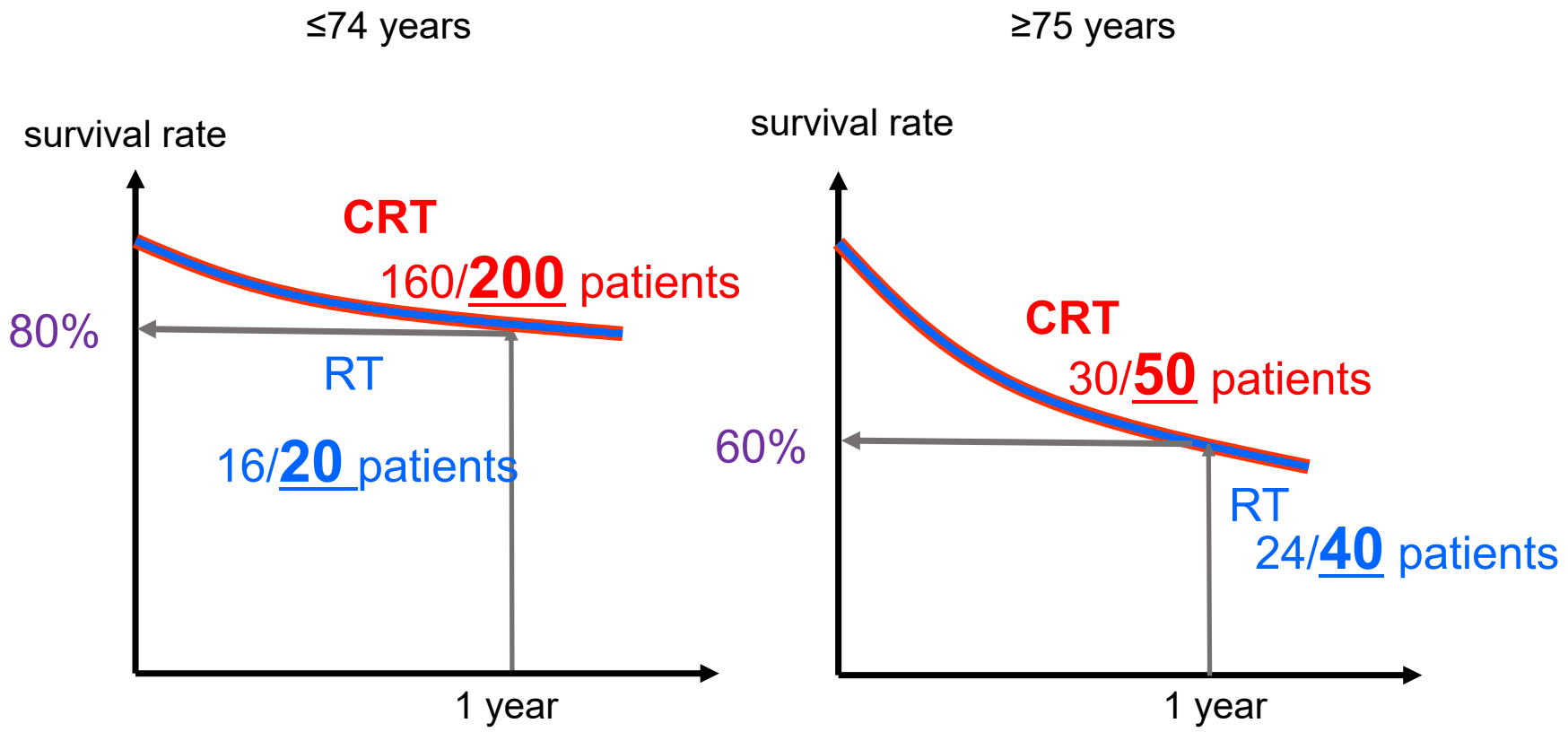


Prognosis according to age

Note: hypothetical example



Prognosis did not differ between the **CRT** and **RT** groups when divided by age.

Question 1: What is the correct interpretation?

Select one of the following.

① Overall results are correct (there is a difference between the effect of CRT and RT)

② Age-specific results are correct (there is no difference between the effect of CRT and RT)

③ Both overall and age-specific results are correct (there is a difference in the overall effect, but there is no age-specific difference)

④ Both overall and age-specific results are incorrect

What we want to compare is CRT and RT

Note: hypothetical example

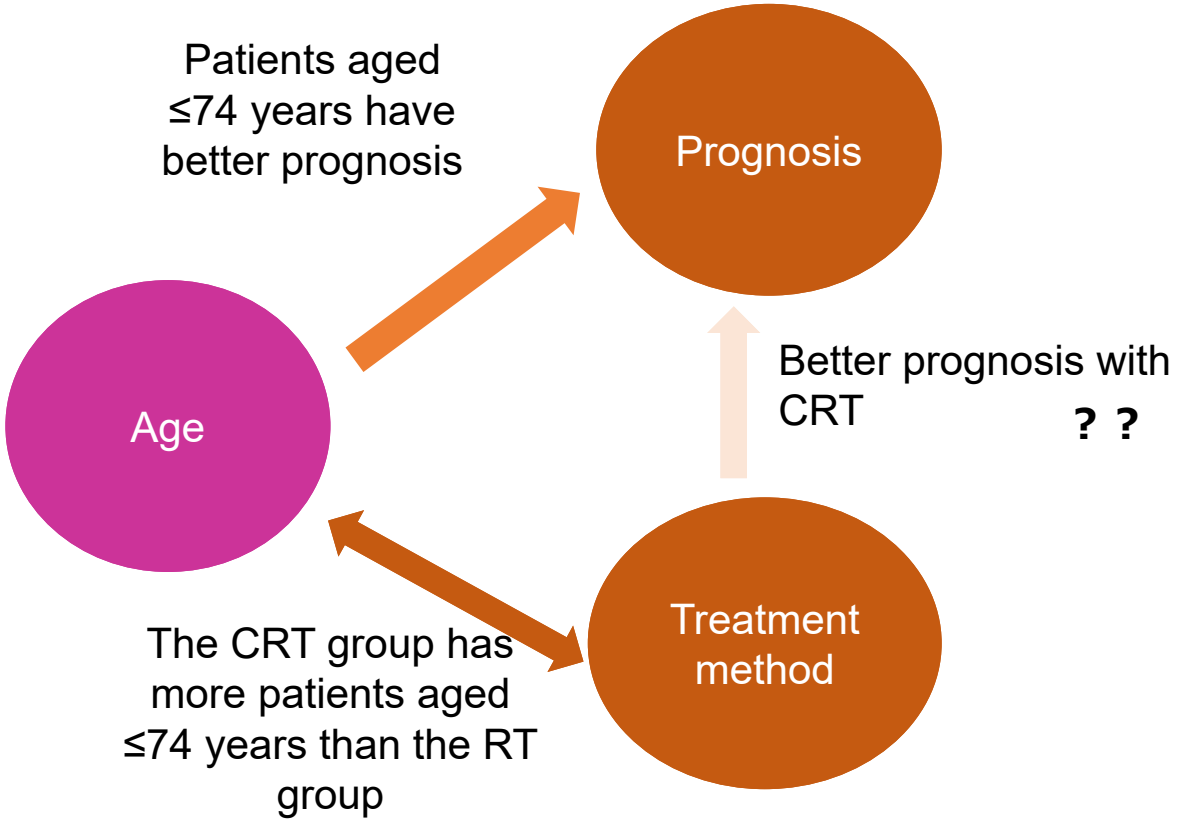
- If the conditions of factors that influence prognosis other than treatment methods are not the same, it is not a "comparison"!!

Treatment method	≤74 years		≥75 years	Total
CRT	**200 patients** (80%)	＞＞	50 patients	250 patients
RT	20 patients (33.3%)	＜＜	**40 patients**	60 patients

- CRT has a higher proportion of patients aged "**≤74 years**" than RT
- Prognosis varies depending on age (patients aged ≤74 years has good prognosis)

Summary on confounding effect

- Phenomenon in which a third factor (age) related to treatment and prognosis causes an apparent association
  - Factors that cause confounding effect (= age) are called **confounding factors**



Question 1: What is the correct interpretation? (which factor has no confounding?

Select one of the following.

① Overall results are correct (there is a difference between the effect of CRT and RT)
- Incorrect because there is confounding due to age

② Age-specific results are correct (there is no difference between the effects of CRT and RT effects)
- Correct because the confounding factor (age) is the same between the groups

③ Both overall and age-specific results are correct (there is a difference in the overall effect, but there is no age-specific difference)

④ Both overall and age-specific results are incorrect

To ensure no confounding effects

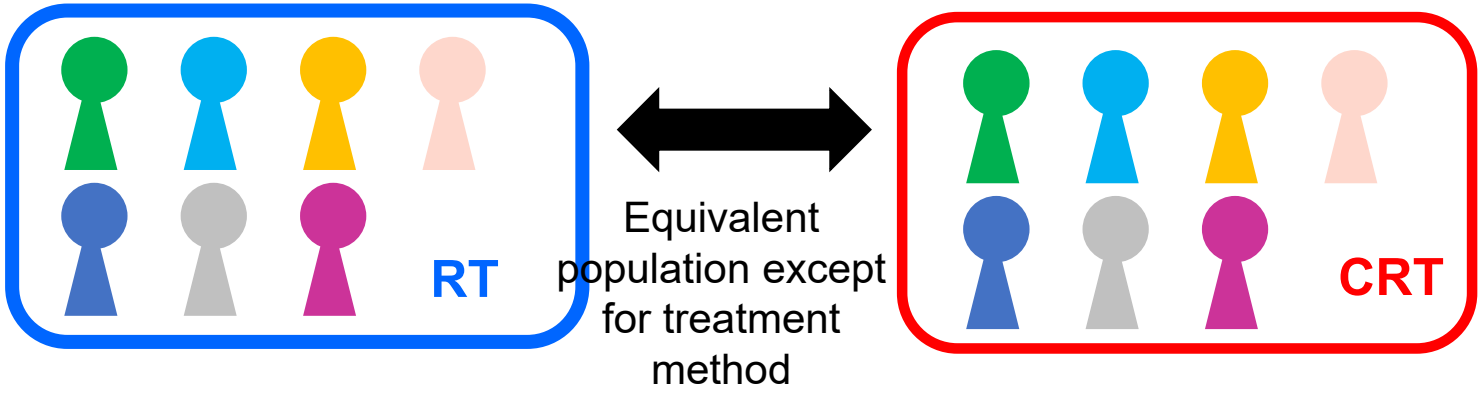
- Make background factors related to prognosis consistent across treatment groups
  - Age
  - Stage (progress of cancer)
  - Performance status (general condition)
  - Others (including unknown factors)

Many factors / unknown factors; therefore, not all of them can be considered

Randomly determine the treatment method

Randomization

- Allocate patients to treatment groups based on probability, regardless of physician or patient preference
- Prevention of patient selection bias due to prognosis
  - Prevent cases wherein patients with good health condition are more likely to be assigned to the CRT group
- **Comparability (internal validity) is guaranteed**
  - Equivalent population except for treatment method → difference in treatment method if there is difference in effect



JCOG0301 case

- **Randomization** in order to compare **RT** and **CRT**
  - Background factors other than treatment method were equivalent on average between the treatment groups
  - Differences in survival curves can be expected to be due to treatment method differences

Unresectable stage III non-small cell lung cancer in patients aged ≥71 years

Randomization

100 cases

Radiotherapy (RT)

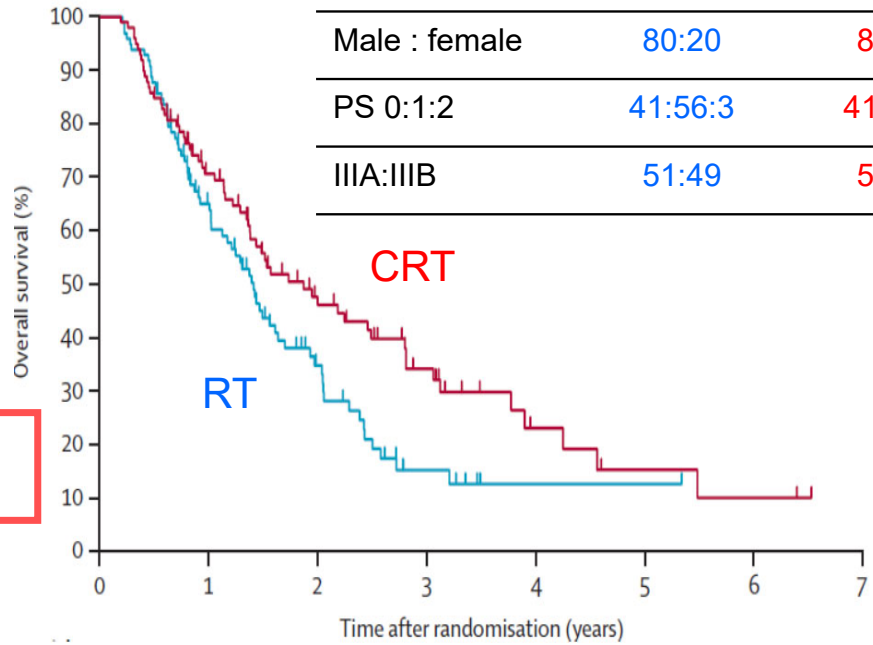
(standard treatment)

100 cases

Radiotherapy + chemotherapy (CRT)

(new treatment)

	RT	CRT
Median age	77 years	77 years
Male : female	80:20	84:16
PS 0:1:2	41:56:3	41:55:4
IIIA:IIIB	51:49	54:46



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