Statistical measures for time-to event endpoint ～Choices other than HR～

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  - Survival probabilities
  - Median survival time
  - Restricted mean survival time (RMST)

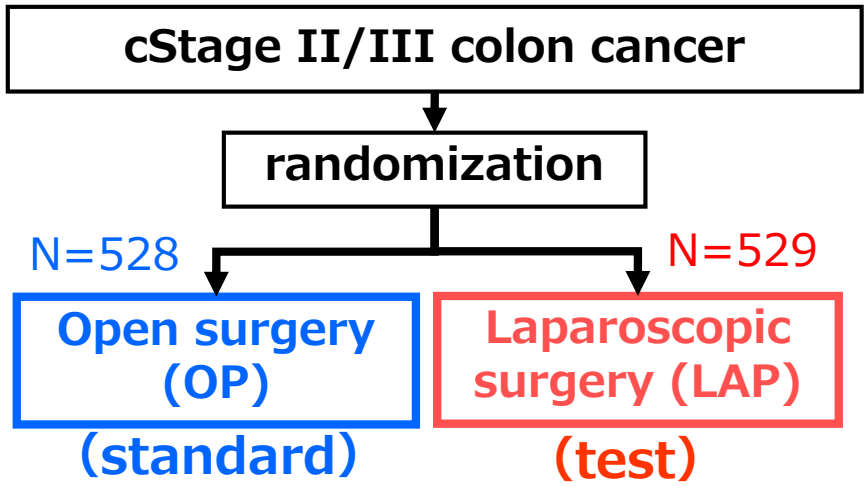
- Summary & conclusion

Trends in JCOG surgical trials

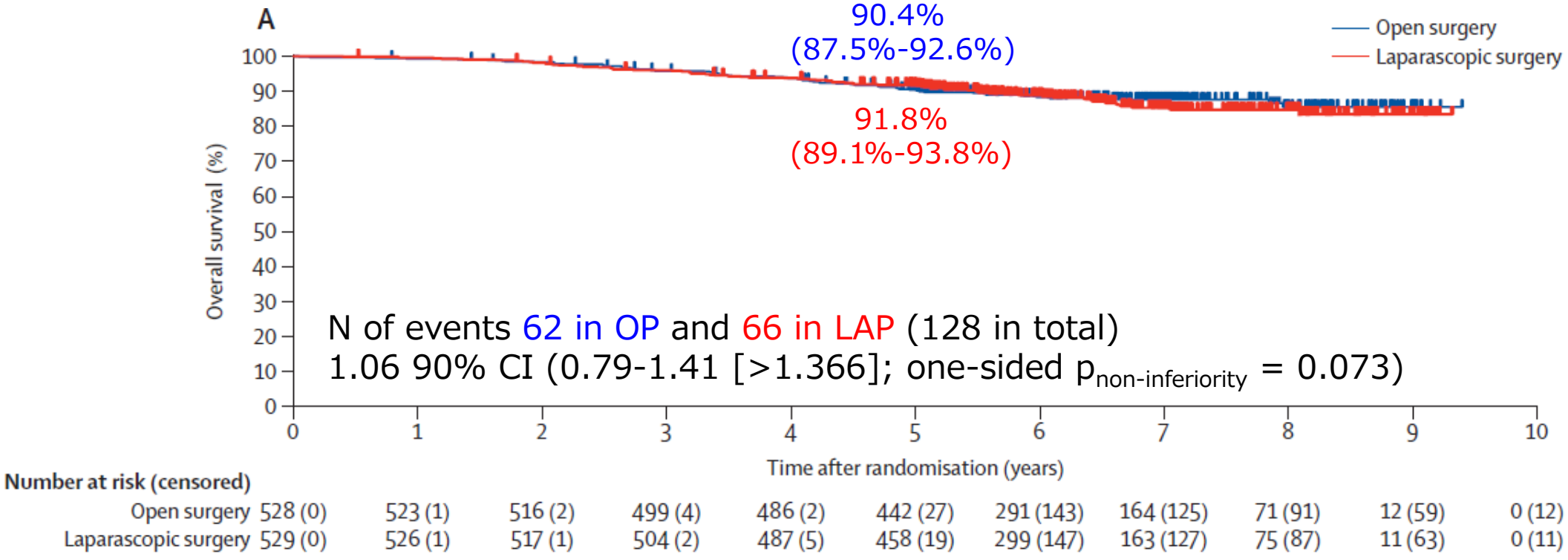
- Few accurate historical control data for surgical trials
  - Usually, survival in standard treatment is based on retrospective studies
  - Challenging to collect detailed information to check whether a patient meet the eligibility criteria of the planned study
- Actual trials tend to show better survival than expected
  - Strict eligibility criteria
  - Performed by expert surgeon
- Test treatment is gradually performed in practice during the trial
  - Considering feasibility to complete the trial in a realistic time frame is required

Kitano S, et al., Lancet Gastroenterol Hepatol. 2017;2(4):261-8.

JCOG0404

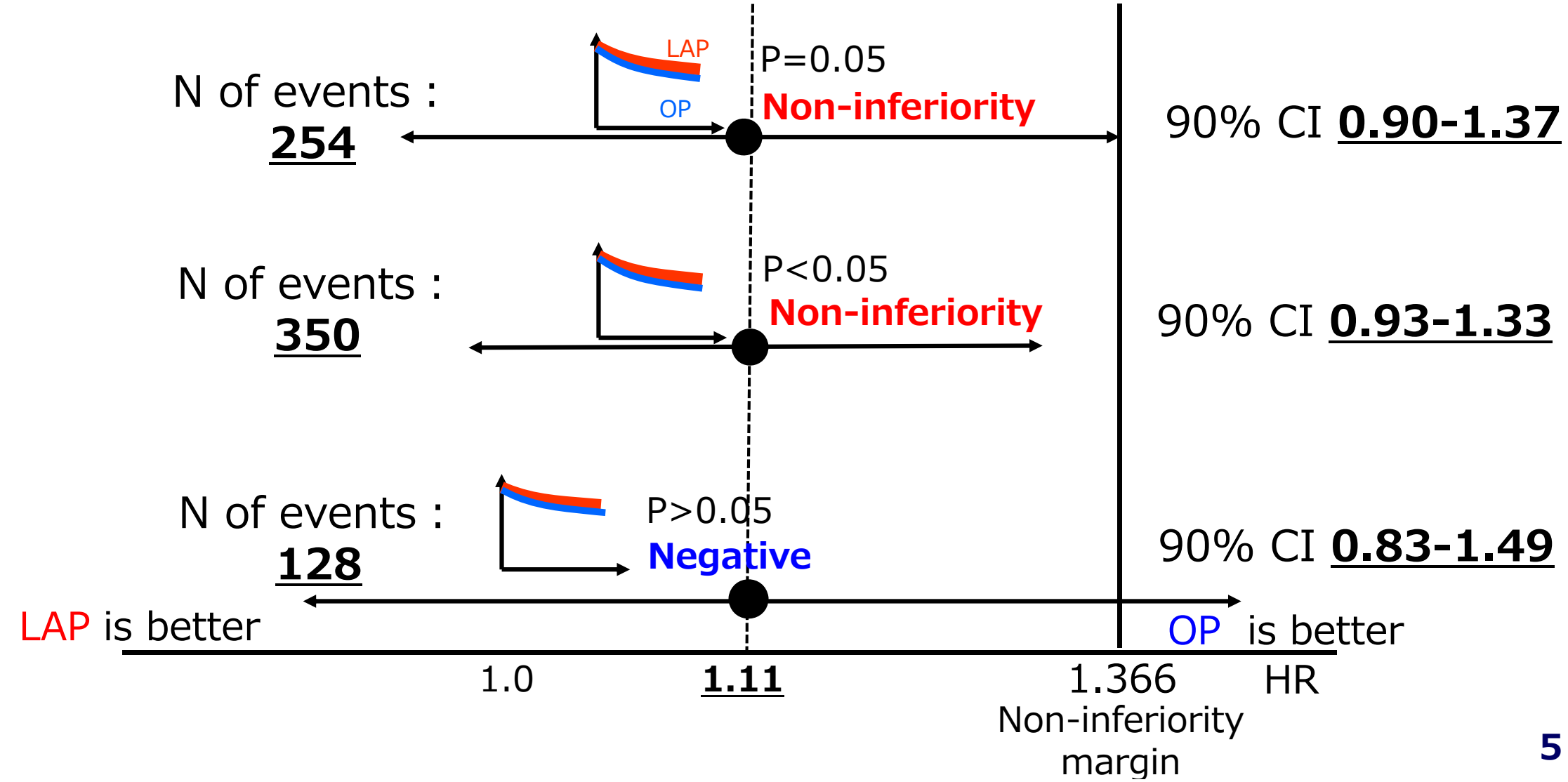


- Primary endpoint: Overall survival (OS)
- Sample size (planned events):1050 (254)
  - Non-inferiority setting
  - One-sided α=5%, power=80%
  - 5yOS = 82% in both arms
  - non-inferiority margin of hazard ratio (HR)=1.366



Why was JCOG0404 statistically negative trial?

Margin of error of CI for HR depends on N of events



Examples of non-inferiority setting surgical RCT in JCOG

- JCOG0802 : cStage I small peripheral NSCLC (**5yOS=90%**)
  - Lobectomy vs limited resection (segmentectomy), N=1100
- JCOG0912 : cStage I gastric cancer (**5yOS=90%**)
  - Open surgery vs Laparoscopic surgery, N=920
- JCOG1413 : cStage I/II NSCLC (**5yOS=70%**)
  - Systematic LND vs lobe-specific LND, N=1450
- JCOG1601 cStage I/II tongue cancer (**5yOS=85%**)
  - Prophylactic neck dissection vs partial glossectomy alone, N=440

Summaries thus far

- In non-inferiority setting for surgical trials, sample size tends to be large
- The N of observed events in JCOG studies was often much lower than expected
  - Challenging to increase sample size and/or prolong follow-up time due to excellent survival when it is revealed during the trial
- "Clinical judgement" and "statistical judgement based on HR and its confidence interval" can be inconsistent
  - Interpretation of the result is challenging

Are there any alternatives to HR?

Several measures were proposed as an alternative of HR

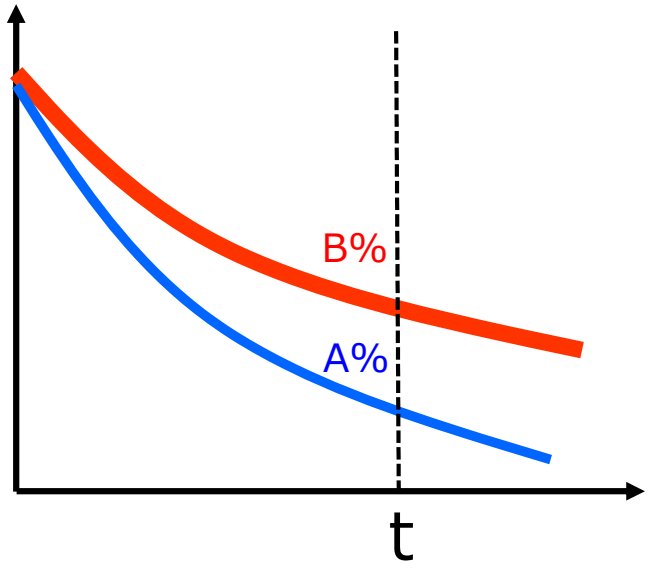
Uno H, Wittes J, Fu H, et al. Annals of Internal Medicine. 2015;163(2):127-34.

1. Difference or ratio between survival probabilities at time points (t)

2. Difference or ratio between medians (or specific percentile)

3. Difference or ratio between restricted mean survival time (RMST)

Difference or ratio between survival probabilities at time points (t)



- **Difference** : B% – A%
  - **Superiority**: if CI for the difference excluded an absolute difference of 0%.
  - **Non-inferiority**: if CI for the difference excluded an absolute difference of X% (non-inferiority margin).
- **Ratio** : B% ÷ A%
  - **Superiority**: if CI for the ratio excluded an ratio of 1.
  - **Non-inferiority**: if CI for the ratio excluded an ratio of X (non-inferiority margin).

Example case : COLOR II

Adeno with rectum within 15 cm from the anal verge with M0

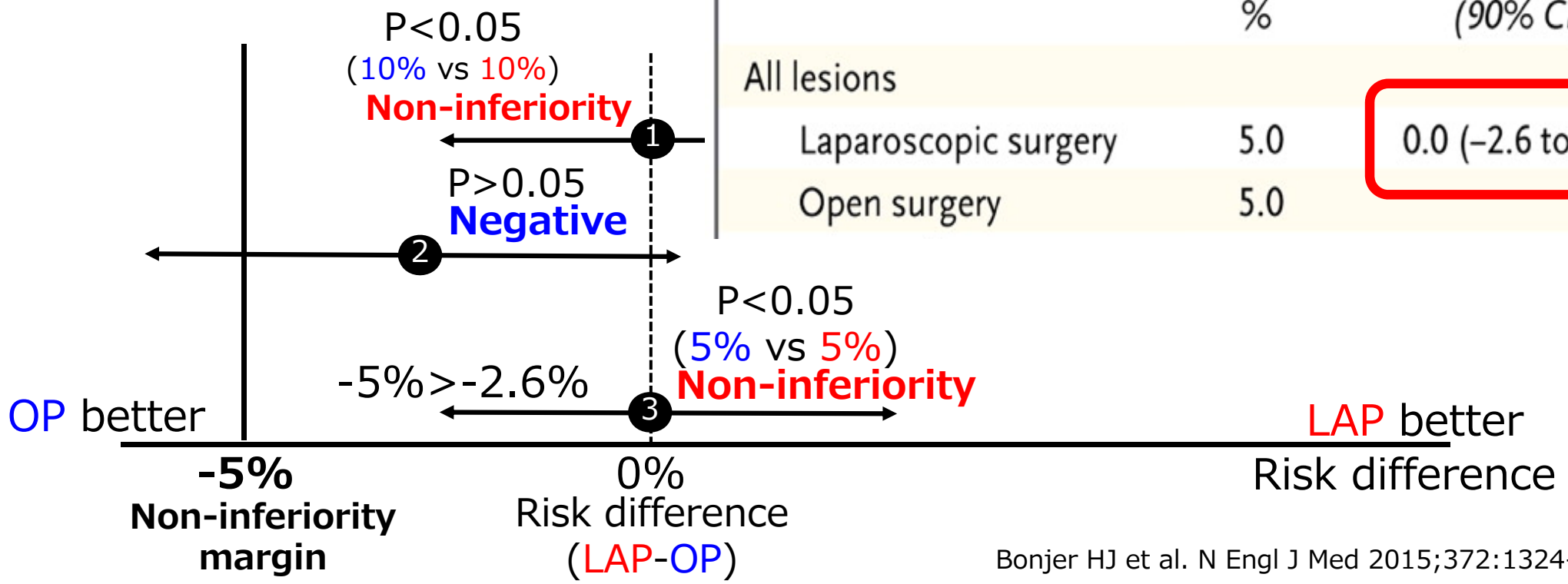
randomization

N=345 → **Open surgery (OP)** **(standard)**

N=699 → **Laparoscopic surgery (LAP)** **(test)**

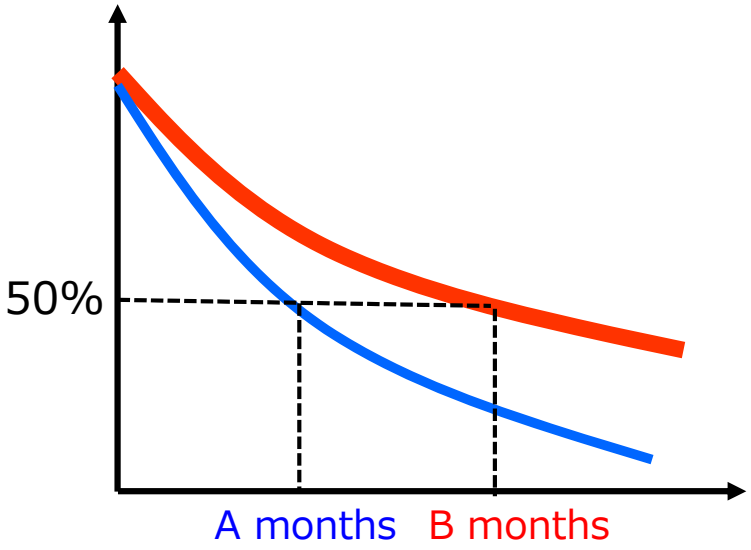
- Primary endpoint: locoregional recurrence 3 yrs after the index surgery (LR)

Type of Lesion and Surgery	Locoregional Recurrence in Intention-to-Treat Population	
	Rate	Between-Group Difference‡
	%	*percentage points (90% CI)*
All lesions		
Laparoscopic surgery	5.0	0.0 (–2.6 to 2.6)
Open surgery	5.0	



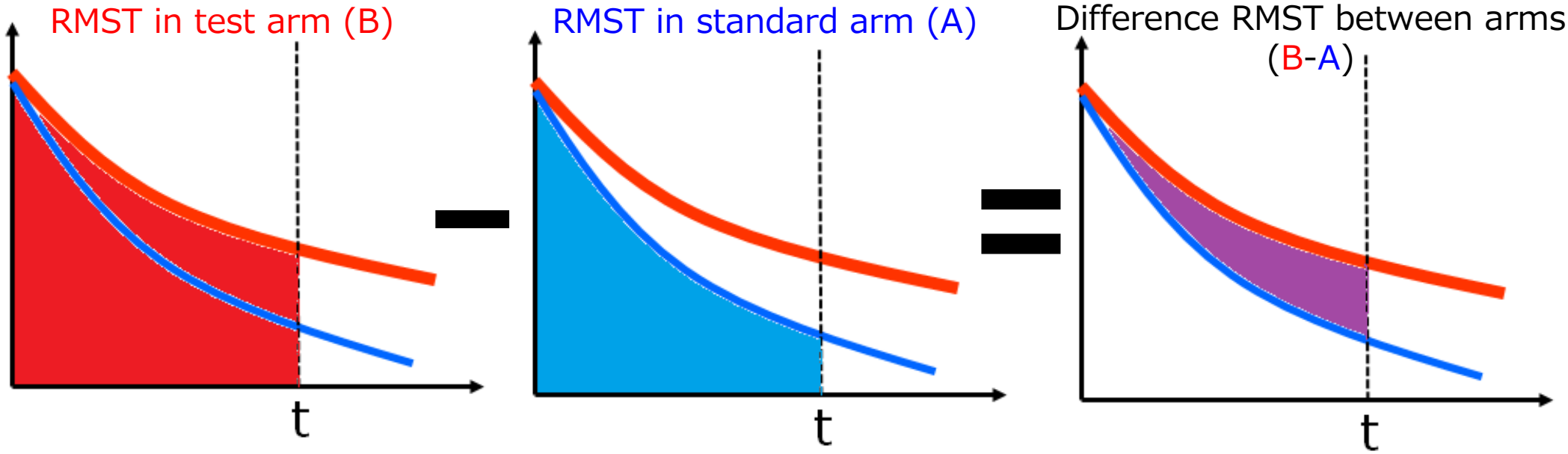
Bonjer HJ et al. N Engl J Med 2015;372:1324-1332.

Difference or ratio between medians (or specific percentile)



- **Difference** : B months – A months
  - **Superiority**: if CI for the difference excluded an absolute difference of 0%.
  - **Non-inferiority**: if CI for the difference excluded an absolute difference of X% (non-inferiority margin).
- **Ratio** : B months ÷ A months
  - **Superiority**: if CI for the ratio excluded an ratio of 1.
  - **Non-inferiority**: if CI for the ratio excluded an ratio of X (non-inferiority margin).

Difference or ratio between restricted mean survival time (RMST)



- **Difference** : B − A
  - **Superiority**: if CI for the difference excluded an absolute difference of 0.
  - **Non-inferiority**: if CI for the difference excluded an absolute difference of X (non-inferiority margin).
- **Ratio** : B ÷ A
  - **Superiority**: if CI for the ratio excluded an ratio of 1.
  - **Non-inferiority**: if CI for the ratio excluded an ratio of X (non-inferiority margin).

In JCOG0404 case,

- Sample size setting
  - 5yOS = 82% in both arms
  - non-inferiority margin of hazard ratio (HR)=1.366
    - Which corresponded to about -5.74% in 5yOS and -0.16 in 5yrs RMST under exponential distribution
- Hazard ratio

  Negative
  - 1.06 90% CI (0.79-1.41 [>1.366]; one-sided $p_{non\text{-}inferiority}$ = 0.073)
- Difference between survival probabilities at 5 years

  Positive?
  - 91.8% in LAP and 90.4% in OP, 1.4% 90% CI ([-5.74%<]-1.5% – 4.3%)
- Difference between medians
  - Not reached
- Difference between RMST in 5 years

  Positive?
  - 4.826 in LAP and 4.824 in OP, 0.002 90% CI ([-0.16 <] -0.066 – 0.070)

	Advantages	Disadvantages
• Hazard ratio	• Valid if proportionality of hazards is satisfied • Takes entire survival curve into account • Standard measures in oncology	• Difficult to interpret especially when proportionality of hazards is not satisfied • Depends on N of events (sample size can be impractical)
• Difference or ratio between survival probabilities at time points (t)	• Does not depend on model assumption • Does not depend on N of events • Easy to interpret • Can be surrogate of cure	• Not take entire survival curve into account • Loss of information • t must be prespecified and chosen arbitrarily
• Difference or ratio between medians (or specific percentile)	• Does not depend on model assumption • Easy to interpret	• Affected by schedule of assessment other than OS • Not take entire survival curve into account • Not always reached
• Difference or ratio between restricted mean survival time (RMST)	• Does not depend on model • Easy to interpret • Takes almost entire survival curve into account • Does not depend on N of events	• t must be prespecified and chosen arbitrarily • Chosen especially when low event rate and/or to claim non-inferiority • Very seldom reported

Concluding remarks

- Alternative measures of HR for time-to event endpoint have been proposed and discussed
  - Model-free measures
  - Margin of error of CI is independent from N of events
- HR is not a perfect measure to interpret study result
- Using and reporting other measures like RMST in addition to HR may well and should be considered in future studies

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Thank you for your kind attention !