How to summarise the treatment effect when survival curves have unusual shapes

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Hazard

- The instantaneous risk of event (e.g. mortality) in next time interval
- Hazard changes with time
- Sometimes referred to as “force of mortality”
Hazards vs. survival

- Behind every survival curve, there is a hazard function that is the force that “provokes” the events.
Proportional hazards (PH)

- When hazards are proportional, the hazard ratio is constant.

Hazard rate

Hazard for treatment A

Hazard for treatment B

Survival curve

Survival for treatment A

Survival for treatment B

Hazard ratio (HR)

hazard A divided by hazard B

constant

- When hazards are proportional, the hazard ratio is constant.
Reporting of time-to-event outcomes with PH

Survival curves

- Difference in medians = 1 month (4.5 minus 3.5)
- Absolute effect
- HR = 0.64
  (95% CI: 0.56-0.73)
- Relative effect

- HR calculated with Cox regression, which assumes PH
- In this example, hazards are proportional, and so HR is constant
Example of non-proportional hazards

IPASS trial: Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

Survival curves cross over; 2 distinct periods

Example of non-proportional hazards

- The single HR value of 0.74 clearly does not apply throughout
- HR is inappropriate
Example of non-proportional hazards

- Multiple forms of non-proportional hazards (NPH)
- NPH have been seen in many disciplines, including cancer, infectious diseases, cardiovascular disease

Lancet Oncology 2015; 16: 908-918
When survival curves cross over (or have other unusual shapes), the HR and difference in medians are inappropriate

=> What can we do in these situations?
RMST* as a measure of life expectancy

- The area under a survival curve is a measure of the life expectancy during the study period.
- The area is called the restricted mean survival time.

* Concept introduced by P. Royston and M. Parmer.
LED and LER

- **LED (life expectancy difference):** difference between RMSTs
  - Absolute effect

- **LER (life expectancy ratio):** ratio of RMSTs
  - Relative effect
LED and LER in practice

ADAM trial: drug called ADI-PEG20 in 68 patients with pleural mesothelioma

<table>
<thead>
<tr>
<th></th>
<th>LED (95% CI), months</th>
<th>LER (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 10 months</td>
<td>-0.5 (-1.7, 0.6)</td>
<td>0.94 (0.78, 1.09)</td>
</tr>
<tr>
<td>After 10 months</td>
<td>3.8 (0.3, 7.3)</td>
<td>2.07 (0.64, 3.51)</td>
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</tbody>
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Difference in median = 0.6 months (11.3 vs 10.7) (??)

HR = 0.68 (95% CI: 0.39, 1.16) (??)

- Unique HR of 0.68 does not reflect accurately the trial
- LER + LED in *multiple periods* provide a more exhaustive picture

JAMA Oncology 2017; 3: 58-66
Conclusion

• HR and difference in medians are not appropriate for survival curves with NPH

• RMST is measure of life expectancy, that is intuitive and calculable for any shape of curves

• LED: life expectancy difference; LER: life expectancy ratio

• LER + LED in *multiple periods* provide a more exhaustive picture than any single measure (HR) for situations with NPH

• Practical recommendation: important to mention in protocol and SAPs what method of analysis to use if curves show NPH
“Life expectancy difference and life expectancy ratio: two measures of treatment effects in randomised trials with non-proportional hazards”

Dehbi H-M, Royston P, Hackshaw A
Thank you! Any questions?
Back-up slides
LED and LER in practice

Simulated trial with crossing over curves

<table>
<thead>
<tr>
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<th>LED (95% CI) months</th>
<th>LER (95% CI)</th>
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<tbody>
<tr>
<td>All time periods</td>
<td>0.4 (-0.5, 1.3)</td>
<td>1.06 (0.91, 1.21)</td>
</tr>
<tr>
<td>Before 10 months</td>
<td>-0.8 (-1.3, -0.3)</td>
<td>0.85 (0.77, 0.93)</td>
</tr>
<tr>
<td>After 10 months</td>
<td>1.2 (0.7, 1.8)</td>
<td>3.01 (1.78, 4.25)</td>
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<tr>
<td>Difference in median</td>
<td>-0.9 month (5.7 vs 6.6)</td>
<td></td>
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<tr>
<td>HR</td>
<td>0.70 (95% CI: 0.53, 0.92)</td>
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In this particular example, the ‘crossing over’ can be explained by a biomarker.

But in the absence of this, HR is difficult to interpret (and can be nonsense).

So you will need to examine the curves yourself, unless the authors have provided alternative effect sizes.
Time-to-event outcomes

• In RCTs the effect of an intervention on survival is often of interest, in particular in phase 3

Example of survival data