Understanding Hazard Ratios

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What are Hazard Ratios?

• Hazard ratios reflect the analysis of time survived by a patient and may have nothing to do with prolongation of survival
  – A hazard is the rate at which events happen, so that the probability of an event happening in a short time interval is the length of time multiplied by the hazard
  – Hazards (or probability of hazards) may vary with time, while the assumption in proportional hazard models for survival is that the hazard is a constant proportion
  – This lack of constancy may result in erroneous conclusions from the clinical data
• The weighted risk (Hazard Ratio) is the ratio of the probability of an event (death or progression) in the experimental arm to the probability in the comparator arm
  – When expressing the results of clinical trials, it is best to consider the hazard ratio alongside a measure of time, such as median survival

The forest plot quickly summarizes the hazard ratio data across multiple variables.

- If the line crosses the 1.0 value, the hazard ratio is not significant and there is no clear advantage for either arm.
Misinterpretation of Hazard Ratios

• A hazard ratio is often reported as a “reduction in risk of death or progression”
  – This reduction is calculated as 1 minus the Hazard Ratio
    • e.g., HR of 0.84 is equal to a 16% reduction in risk
  – The hazard ratio can only be applied to patients during a specific timeframe and the outcomes should not be broadly inferred
    • An HR of 0.5 for a specific therapy could be misinterpreted that treated patients progressed at half the rate as those in the control group or that the median TTP was twice as fast in the control arm
    • The correct interpretation is that treatment will cause the patient to progress more slowly, and that a treated patient who has not yet progressed by a certain time has half the chance of having progressed at the next point in time compared with someone in the control group

• It is important to combine the hazard ratio for death or progression with another measure of the same outcome (overall survival, median survival, and/or time to progression)
Changes in Outcome Reporting

- The increase in the number of cancer clinical trials has required greater physician reliance on statistical analyses to define the value of new agents
  - Assessing the clinical relevance of the difference between similar survival curves can pose significant challenges for those without formal training in statistical interpretation
  - As a result, there has been increasing reliance on the use of hazard ratios, often to the exclusion of more traditional survival data
    - Because hazard ratios lack time-based characteristics, they can only inform physicians about the reliability and uniformity of the trial data
    - They also provide no quantitative data to help define relative value between therapies or information they can discuss with patients
    - The following graphics present the increasing trend in the use of hazard ratios and the almost 50:50 split in providing hazard ratios without any survival or other time-based outcomes
Increasing Use of Hazard Ratios

a. Increase in the use of hazard ratios in journal articles reporting cancer clinical trial data (2001-2010)
b. 57% of clinical trial abstracts in Q1 2011 included both the hazard ratio and the relevant outcome times (survival, TTP, etc.; blue bar) compared to 43% of abstracts that only reported a hazard ratio

Interpreting Clinical Data

• Hazard ratios provide clear insight into the relative reduction of risk for death or progression and can provide confidence in the reliability of the trial data.

• However, overall survival statistics are the most clinically relevant data in that they provide physicians with clear benefits that they can discuss with patients.
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