Standardization of imaging endpoints in clinical trials: some statistical considerations

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Uses of imaging in a Phase III trial

- As the primary endpoint
  - Treatment effect is measured by this endpoint.
  - When patient achieves endpoint (e.g., disease progression), he/she may be taken "off trial."
- As an entry criterion for trial
  - Patients may need measurable disease of a specified severity
- As a management strategy
  - Imaging biomarker may indicate initiation of new treatment

Potential of quantitative imaging

- Minimize between- and within-reader variability, providing more reproducible measurements
- Eliminate potential reader bias
  - Reduces the concern that evaluation might be influenced by knowledge of a patient's treatment assignment in an unblinded randomized trial.
  - Any means of mitigating this potential bias is key for a valid trial result.
- Auditing trial endpoints (e.g., a central review) may be easier.

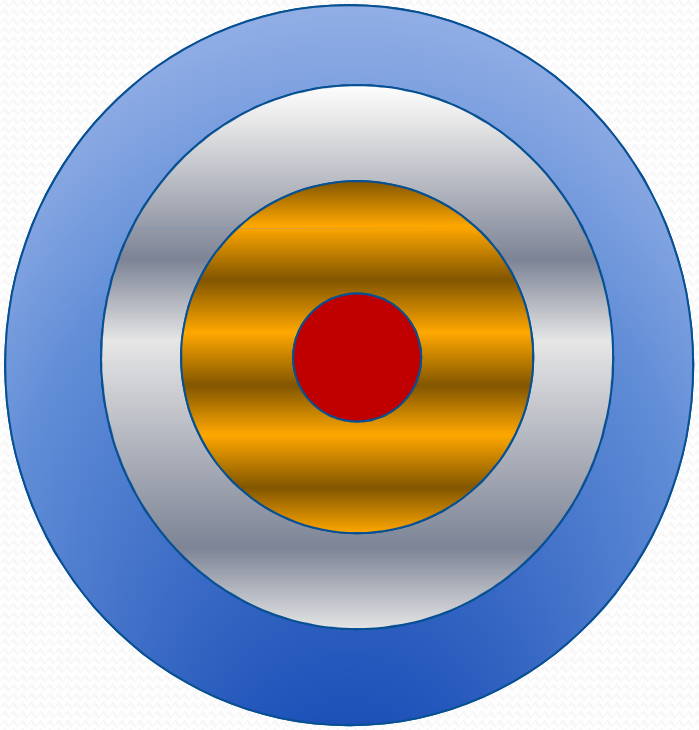
Important Considerations:

- Endpoint need not be 100% quantitative.
  - Methods to improving consistency are needed:
    - Track the same lesions
      - Initial selection should be unbiased and pre-specified.
    - Archiving should facilitate tracking lesions selected at local sites for central reads.
- Define endpoints so that patient management decisions are made contemporaneous to the primary trial endpoint:
  - If imaging endpoint is not attained before a patient is taken off therapy, patient should be followed by imaging until endpoint is met.
  - Otherwise, may bias estimate of treatment effect.

Important Considerations:

- Ensuring high-quality, independent (i.e., masked) evaluations at the local site, is ideal.
- If this is not possible:
  - Facilitate real-time central reads or
  - Detect reader-evaluation bias early for corrective actions.

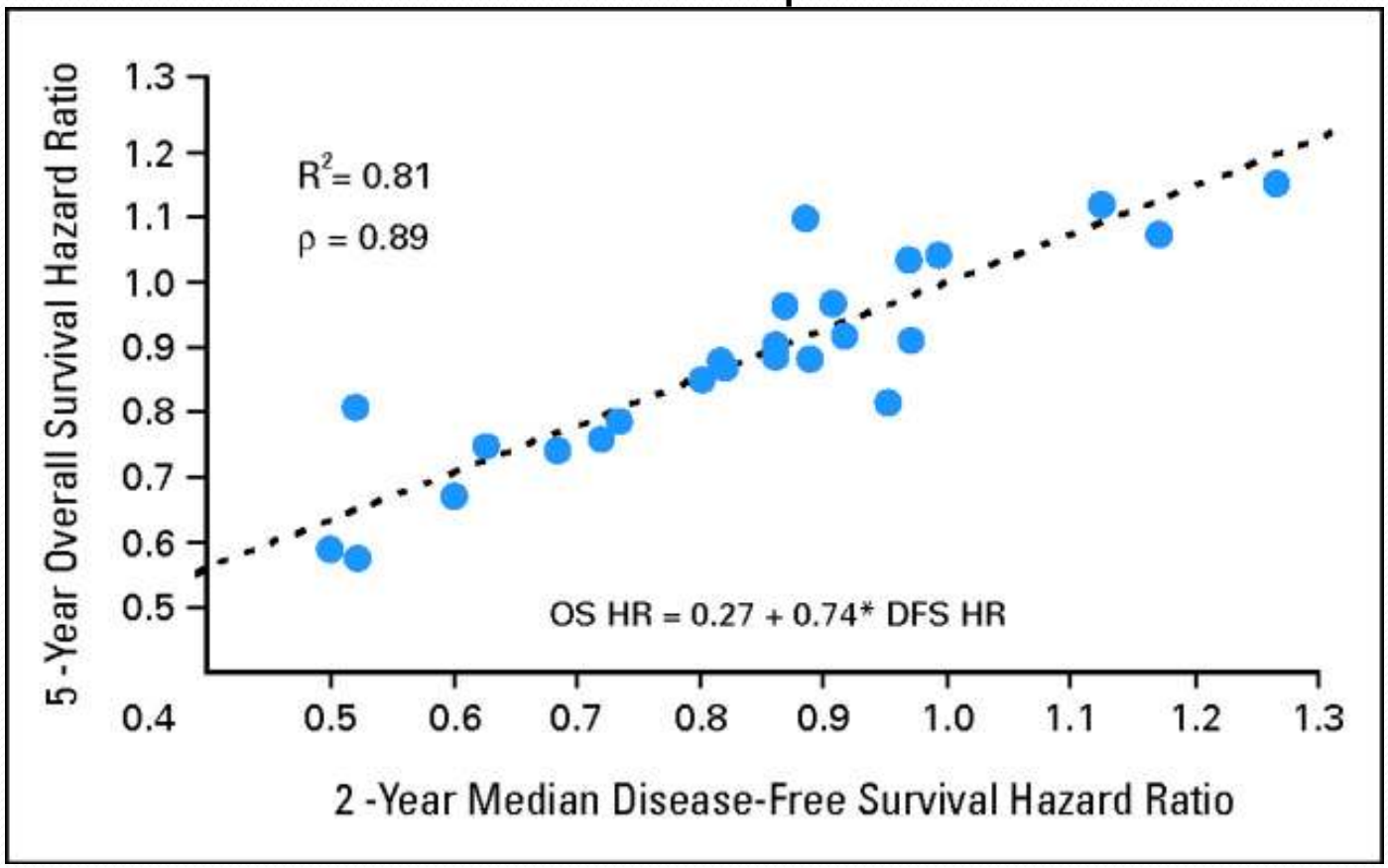
Reproducibility alone not sufficient



- Need an imaging biomarker that is both reproducible *and* is a good measure of clinical benefit.
  - To be of clinical benefit, a treatment must improve how a patient functions, feels or survives.
- An imaging endpoint for a primary endpoint in a Phase III clinical trial:
  - Should directly measure clinical benefit, or
  - Be a surrogate for a clinical benefit endpoint.

Establishing surrogacy is difficult and rare

Fig 3. Hazard ratios (HRs) for 2-year median disease-free survival (DFS) v 5-year overall survival (OS) for 25 within-trial comparisons



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