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Exposure-response modeling in oncology: technical challenges and proposed solutions

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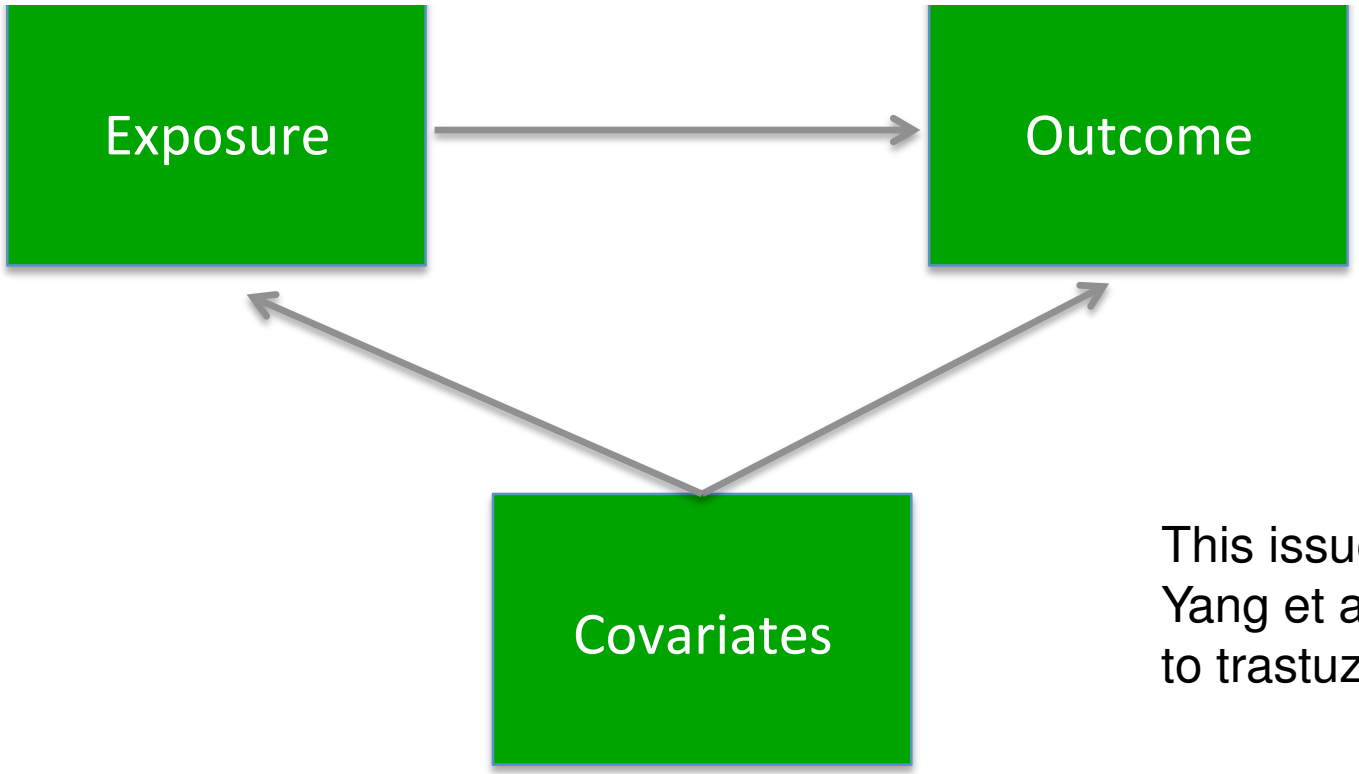
Why is exposure-response analysis hard in oncology?

- Studies not designed to understand exposure-response
  - Phase 2/3 studies often limited to one dose/regimen of the experimental treatment
  - Sparse PK sampling
  - Endpoint collection (e.g., timing of scans)
- Substantially more patient heterogeneity than in other disease areas
- Multi-treatment regimens used more frequently than in other disease areas
- Key endpoints may occur after the end of treatment

There are many challenges . . .

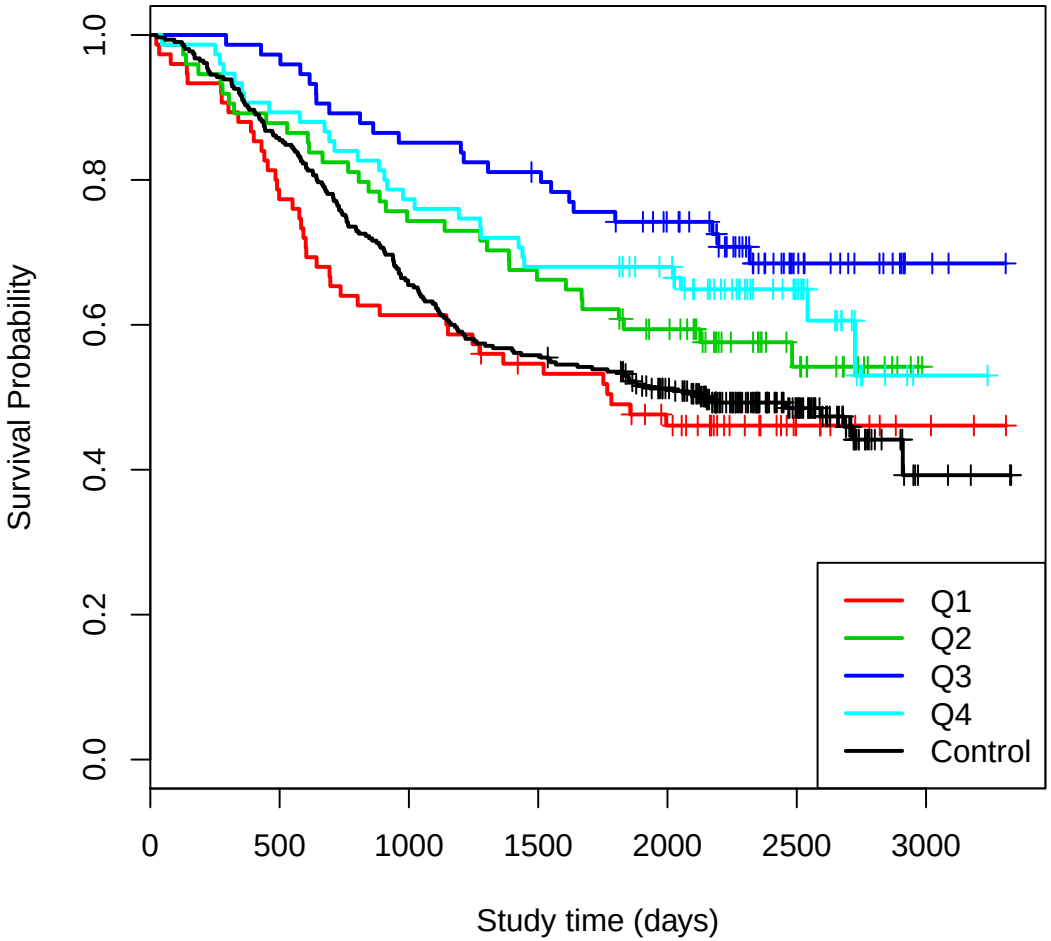
- Confounding of exposure-response relationship
- Challenges in selecting appropriate exposure measure
- Exposure-response for events after the end of treatment
- . . .

What is confounding?



This issue was highlighted by Yang et al. [2012] with regard to trastuzumab in mGC.

An apparent exposure-response relationship. . .

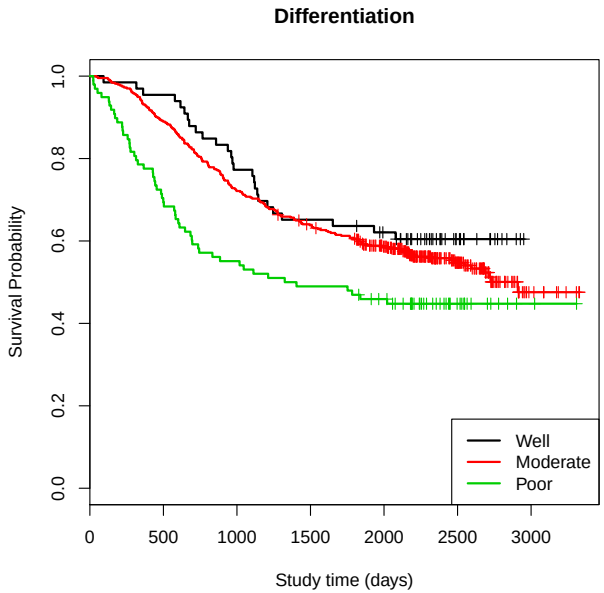


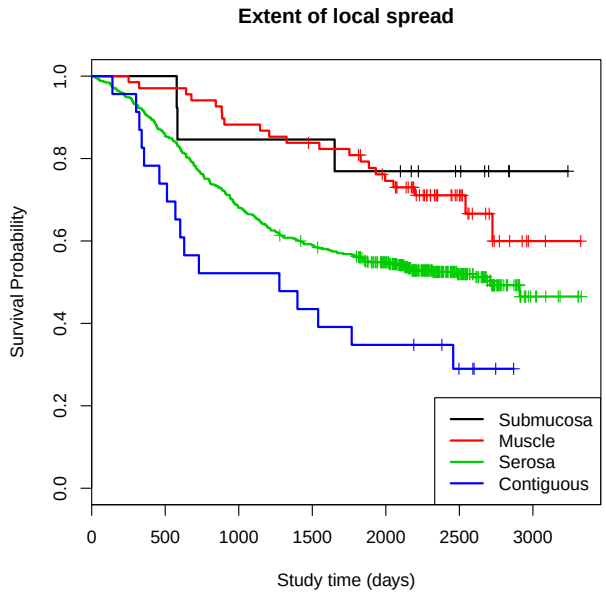
Suppose we want to . . .

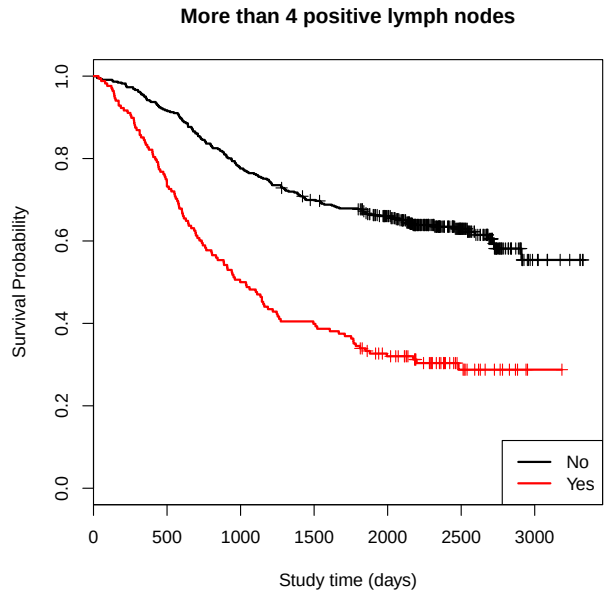
- *Estimate* E-R relationship
- *Estimate* the hazard ratio for Q1 relative to control
- *Predict* the effects of a higher dose in patients with lower exposure

. . . in an unbiased (causal) manner.

What if there are covariates associated with the outcome and exposure?







Group	Q1	Q2-4	Control
N	75	223	310
% Poorly differentiated	37	12	15
Extent of local spread	95	83	87
% $>$ 4 lymph nodes	64	13	29

Defining the problem

- We no longer have a fully randomized experiment - there is imbalance in prognostic factors across the range of exposures.
- Not accounting for this imbalance will lead to biased estimates of E-R relationship
- Primarily an issue when studying E-R based on only one dose

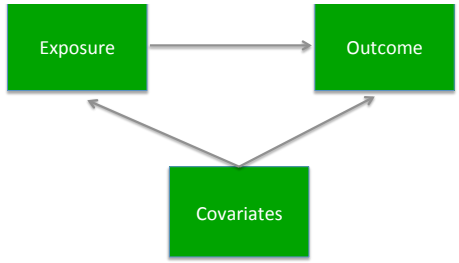
How might we solve the confounding issue?

- Design
  - Multiple doses/regimens in Phase 2/3
- Analysis
  - Adjust for the covariate effects in a regression model
  - Perform a matched analysis (case-matching) - e.g., Yang et al. [2012]
  - Generalizations of propensity score methods

Case-matching

- Find patients in the control group that have a similar covariate distribution as the patients in the treated (low exposure) group.
- In a sense, we are trying to create a pseudo-randomized comparison.
  - Goal: obtain samples that are comparable with respect to covariate distributions (not 1:1 matches)
- The resulting difference in outcome using the matched data should then be due to treatment and not covariate effects.
- Good for description but not prediction

Implementing the matching



- Defining 'similar'
  - Which variables should you match on?
    - Those (likely to be) associated with the outcome.
  - What is a good metric for similarity?
    - Mahalanobis distance, propensity score, combination

- What if not all treated patients can be matched to a control patient?

Challenges in selecting an appropriate exposure measures

- Studies not typically designed for E-R analysis
  - Inadequate collection of dosing info
  - PK sampling design and early discontinuation
  - PK sampling design not sufficient to capture true concentration at specific event times, or fluctuation in exposure due to dose adjustments
- Apparent design mis-match between TTE endpoints and continuous PK
  - Typically a single TTE outcome per individual
  - Event observation time is not determined by study design; results in a distribution of event times across individuals
  - PK data are continuous repeated-measures, with sampling times usually driven by study design
- Dose reductions/holidays in response to tolerability

Use summary measure of exposure?

- Observed summary measure [AUC(interval), Cmax, or Cmin]
  - No model needed
  - Does not capture all dose reductions/holidays
  - Potentially biased sample of patients
- Model-predicted summary measure [AUC(interval), Cmax, Cmin]
  - Utilizes entire dosing history
  - Requires accurate dosing history and PK model at the individual level
  - Differential shrinkage?
- All of these measures will be correlated unless design specifically includes different regimens
- When to capture exposure measure relative to event?

Could use continuous PK as driver of event

- The underlying pharmacologic/toxicologic mechanisms are continuous with respect to exposure and time
- Link continuous PK to event through time-varying hazard function
  - Could be direct link or indirect (e.g. indirect PD response, latent variable)
  - Increased complexity in model building and model checking, due to integration of time-varying hazard
  - Requires accurate dosing history and PK model at the individual level
- May be closer to ”true” system, but trade-off of assumptions and complexity when compared to other approaches

Practical considerations

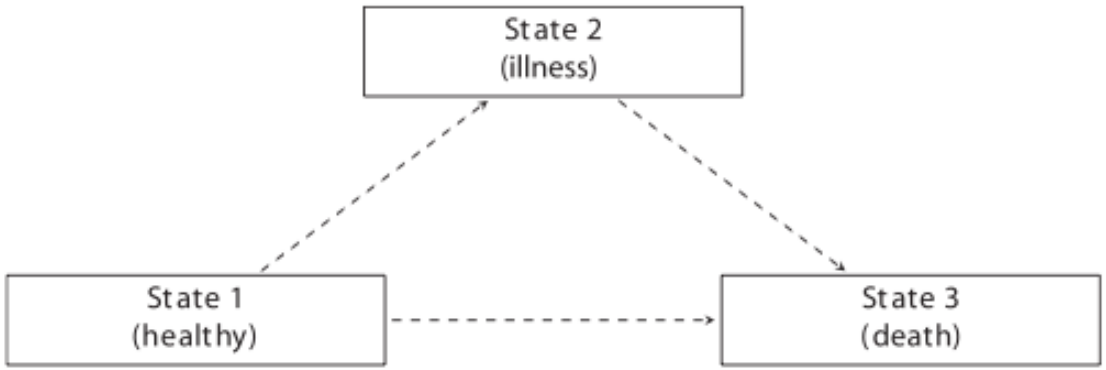
- Generally prefer model-based exposure measures over observed
- Must consider PK sampling at the design stage for use in E-R analysis
- Selection of exposure measure is dependent upon clinical setting, dosing patterns, event type, and specific data analysis questions
- Studies are not typically designed to compare different exposure measures...
  - Be careful when making conclusions about which exposure measure is the ”true” driver, based on GOF-based criteria alone.
- Requires model checking to assess performance of exposure-response model for intended purpose

Conclusions

- Improved study design is the most effective solution to these challenges and something we can influence
  - More than one dose/regimen
  - Thoughtful PK sampling design
  - Multiple scans before and after treatment
- Addressing these challenges through analysis methods is less effective but something we can control
  - Matched analyses
  - Regression models
- Other things are important but generally out of our influence (e.g., tumor genetic heterogeneity)

Back-up Slides

Exposure-response for events after the end of treatment



From Putter et al. [2007]

Extension of work illness-death model to exposure-response setting.

See, for example, Putter et al. [2006] and Broglio and Berry [2009]

References

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