Comparisons of Multiple Exposure-Response Methodologies in Oncology

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OBJECTIVES

Exposure-Response assessment in oncology is complicated by many factors, e.g. dose delay/reduction. In addition, for monoclonal antibodies (mAbs) exposure is usually confounded by key prognostic factors for the disease. There are multiple exposure-response (ER) methodologies, such as direct or indirect (e.g., via tumor growth inhibition (TGI)) ER for progression free survival (PFS) and overall survival (OS). Here, we compare different aspects of multiple direct ER methods, with a case example in oncology.

METHODS

Comparison of Direct ER methods using an oncology Phase 3 study

1. **Stratified Kaplan-Meier (KM) estimates by exposure quartiles (AUC_{ss}, Cmin)**
   - This method is naive to covariates which means that confounding factors e.g. patient disease may impact the interpretation of the ER.
   - Makes no assumptions about the hazard function between groups.

2. **Cox proportional hazards (CPH) analysis with covariate adjustment by exposure quartiles or as a continuous function.**
   - Adjust for confounding covariates but makes a strong assumption about the effect across exposure range.
   - Using conventional tools, exposure as continuous function assumes linear or log-linear ER relationship but allows simulation of other doses at the same regimen (e.g. 3-weekly).
   - Covariate screening is stepwise backward (at α = 0.05) from the set identified from a univariate screen at α = 0.1.
   - Residuals of exposure vs Martingale residuals are used to assess fit of continuous forms of the ER response.

3. **Case matching (CM) using Propensity scores by exposure quartiles**
   - Adjust for confounding covariates [1].
   - Optimal matching based on Propensity scores [2,3] due to their ability to easily deal with mixed variable types [4].
   - Balance between comparator groups was assessed by standardized differences.
   - Correlation structure was preserved by testing pairwise interaction of covariates between comparator groups.

4. **Parametric survival modeling (PS) with covariate adjustment**
   - Longitudinal exposure (plasma compartment or effect compartment) drives the Hazard function
   - Allows for flexible forms of the ER function
   - Account for dosing history (e.g. dose reduction/delay)
   - Adjust for confounding covariates but makes an assumption about the effect across exposure range.
   - Allows simulation including extrapolation to other dosing regimens.

Time and concentration varying hazard

$$h(t) = exp\left(\theta_0 + \sum_j \theta_j x_j + \mathrm{DEFF}(t)\right) \text{ (exponential)}$$

$$\mathrm{DEFF} = \begin{cases} \theta^{\mathrm{Eff}} \mathrm{AUC}_{SS} & \text{linear function of exposure} \\ \dfrac{\theta_1^{\mathrm{Eff}} \mathrm{AUC}_{SS}}{\theta_2^{\mathrm{Eff}} + \mathrm{AUC}_{SS}} & \text{Emax function of exposure} \\ \dfrac{\theta_1^{\mathrm{Eff}} \mathrm{C}(t)}{\theta_2^{\mathrm{Eff}} + \mathrm{C}(t)} & \text{Emax function of concentration} \end{cases}$$

CONCLUSION

- ER in oncology is complicated by many factors, including limitations in estimation arising from the need to evaluate integrated hazard functions and with large molecule treatments, exposure confounding with key prognostic covariates.
- Models should be developed with both the goal of effect assessment and simulation for dose optimization
- Non-parametric representations of exposure help to assess the true shape with and without the presence of covariates but are limited with respect to simulation
- Causal inference approaches can greatly reduce dependence upon modeling assumptions for assessing exposure response
- We propose a M&S strategy that is fit for purpose and provides a clear strategy for dose optimization if indicated, and addresses regulatory review questions

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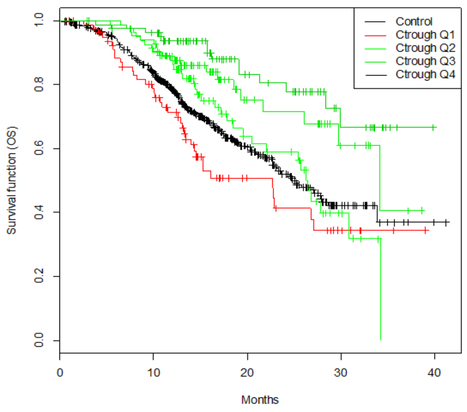
RESULTS

ER assessment using standard methods by exposure quartiles

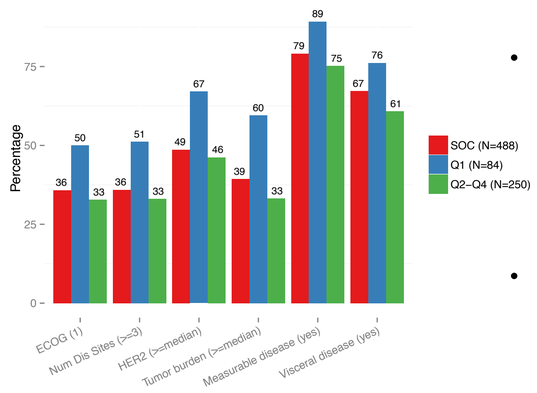


Covariate	HR	P-value	95% CI
Ctrough Q1	0.87	0.47	(0.6, 1.26)
Ctrough Q2	0.79	0.22	(0.54, 1.15)
Ctrough Q3	0.55	0.01	(0.34, 0.88)
Ctrough Q4	0.38	< 0.005	(0.22, 0.67)
Indicators for Measurable Disease (yes)	1.07	0.72	(0.73, 1.58)
Tumor burden	1.35	< 0.005	(1.21, 1.5)
Number of disease sites ($>= 3$)	1.53	< 0.005	(1.16, 2.02)
SGOT/AST	1.01	< 0.005	(1.01, 1.02)
Brain metastasis	1.74	< 0.005	(1.21, 2.51)
Region (W Europe)	0.85	0.33	(0.62, 1.18)
Region (Other)	1.32	0.06	(0.99, 1.77)

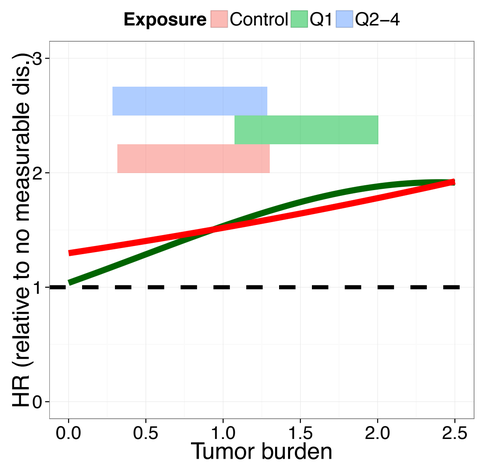
- KM indicates a positive ER for overall survival
- Low exposure appears to underperform compared to the control in absence of covariate correction
- A similar trend was seen in PFS

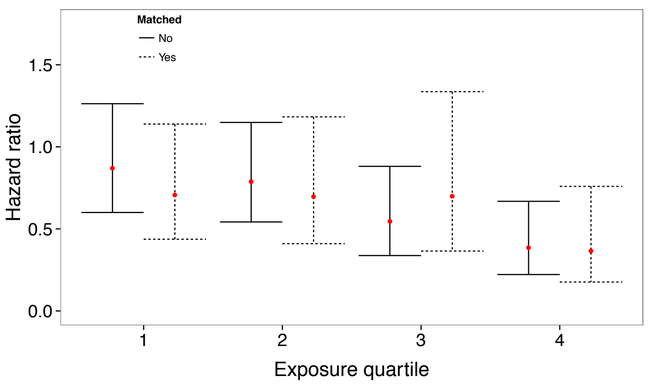
- Cox-proportional Hazard model with covariate adjustment
- Similar fits using linear and log-linear functions of exposure show residuals trends (over/under prediction)
- Low exposure is no worse than control after adjusting for covariates, but are these adjustments made correctly over the range of exposures?

Addressing confounding covariates with exposure



- Several key prognostic covariates are confounded with exposure
- Matching was performed on a large set of covariates determined by ER and clinical input. Three tiers were identified:
  1. Likely confounders, stratification variables, and significant variables per the full model
  2. Suspected confounders not identified in tier 1
  3. Not likely to be confounders.
- Match criteria were set with the requirement that Tier 1 covariates must be balanced to accept the match, but matching on Tier 2 covariates was also prioritized. The final match balanced (all standardized differences < 0.2 on both Tier 1 and Tier 2 covariates.

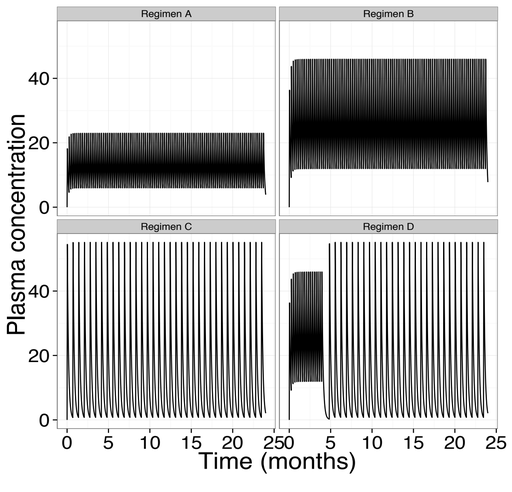


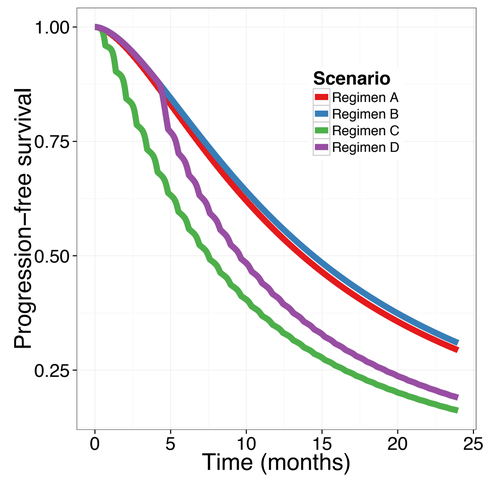


- Covariate correction makes strong assumptions about the covariate effect across the exposure range
- The red line is our covariate effect (linear in tumor burden) while the green line is the true effect (based on a smoothing spline)
- Lack of overlap between Q1 and the control, Q1 and Q2-4 is exaggerated here for demonstrative purposes

- To investigate the degree to which covariate adjustment addressed confounding, we can compare the hazard ratios from before and after matching to like control patients
- Each quartile is independently matched to the control, and the final CoxPH model is used to assess HR (i.e., the HR estimate is "doubly robust").

Simulating expected survival at different doses





- To investigate the effect on PFS of modifying the dose for the low exposure patients, four different dosing regimens were simulated

- A log-logistic baseline hazard with an Emax function of plasma drug concentration was chosen to describe the exposure response relationship
- Both the baseline hazard and the EC50 were covariate driven using a similar process as outlined for the CoxPH modeling