

## **Study of Cure Rate of Colorectal Cancer Considering A New Quantile Parametric Regression Model for Bounded Response**

Vicente G. Cancho<sup>1</sup>, Jorge L. Bazán<sup>\*1,2</sup>, and Dipak K. Dey<sup>2</sup>  
<sup>1</sup>University of São Paulo

<sup>2</sup>Department of Statistics, University of Connecticut

The main purpose of research is to identify if some characteristics of the population e.g., sex and race can explain the cure rate of colorectal cancer cases in the United States considering the data from Siegel, R., DeSantis, C. & Jemal, A. (2014). In this paper, we propose a new class of regression models for bounded response by considering a new distribution in the open unit interval introducing a new parameter to make a more flexible distribution which controls the shape and skewness of the distribution. The new distribution generalizes the general class of distributions introduced by Lemonte, A. J. & Bazán, J. L. (2016). We also present inferential procedures based on the Bayesian methodology, specifically a Metropolis-Hastings algorithm is used to obtain the Bayesian estimates of parameters. The results of the application to real data to illustrate the use of the new model to show differences in the prediction of the distribution of cure rates for the profiles obtained by combining Sex and Race. It shows clearly as these populations present different behavior of cure rates. For example, to the profile where the gender female and race Hispanic group is considered, we predict a cure rate of 0.904 (mortality rate of 0.096) and to the profile where we take the group of gender male and race Non-Hispanic, we obtain a cure rate of 0.718 (mortality rate of 0.282). By considering this model, new extensions can be considered in future developments.

## **Tumor-growth Modeling for Informed Go/No-go Decisions**

Wei Wei<sup>\*1</sup>, Denise Esserman<sup>1</sup>, Michael Kane<sup>1</sup>, Sarah B Goldberg<sup>2</sup>, Daniel Zelterman<sup>1</sup>

<sup>1</sup>Yale School of Public Health, New Haven, CT

<sup>2</sup>Yale School of Medicine and Yale Cancer Center, New Haven, CT

Tumor burden is regularly assessed in cancer clinical trials. However, the dynamics of tumor growth are often ignored in evaluation of treatment efficacy and a binary indicator of tumor shrinkage is commonly used as the primary efficacy endpoint in early phase cancer clinical trials. To provide more accurate measures of efficacy, we develop a Bayesian mixed-effects mixture model to estimate tumor growth trajectory in response to treatment. This model characterizes tumor growth through a mixture of three functions. The tumor trajectory of patients with progressive disease is described with the use of a log linear function with an intercept and a growth rate (Model 1), whereas a function with log linear and quadratic terms is used to estimate the tumor

trajectory of patients who progressed after initial response to treatment (Model 2). The tumor trajectory of patients with durable response is described by a log linear function with a tumor regression rate (Model 3). The resulting tumor growth curve is the weighted average of these three functions. The probability of assigning a patient to Model 1 or 2 provides a patient specific estimate for the risk of progression. Based on simulation studies, we demonstrate that the model estimated progression risk predicts overall survival and leads to more efficient and informative designs for early phase cancer clinical trials. We also illustrate our approach using data from a phase II trial of non-small cell lung cancer.

## The i3+3 Design for Phase I Clinical Trials

Meizi Liu\* and Yuan Ji

The University of Chicago

**Purpose** The 3+3 design has been shown to be less likely to achieve the objectives of phase I dose-finding trials when compared with more advanced model-based designs. One major criticism of the 3+3 design is that it is based on simple rules, does not depend on statistical models for inference, and leads to unsafe and unreliable operating characteristics. On the other hand, being rule-based allows 3+3 to be easily understood and implemented in practice, making it the first choice among clinicians. Is it possible to have a rule-based design with great performance?

**Methods** We propose a new rule-based design called i3+3, where the letter “i” represents the word “interval”. The i3+3 design is based on simple but more advanced rules that account for the variabilities in the observed data. We compare the operating characteristics for the proposed i3+3 design with other popular phase I designs by simulation.

**Results** The i3+3 design is far superior than the 3+3 design in trial safety and the ability to identify the true MTD. Compared with model-based phase I designs, i3+3 also demonstrates comparable performances. In other words, the i3+3 design possesses both the simplicity and transparency of the rule-based approaches, and the superior operating characteristics seen in model-based approaches. An online R Shiny tool (<https://i3design.shinyapps.io/i3plus3/>) is provided to illustrate the i3+3 design, although in practice it requires no software to design or conduct a dose-finding trial.

**Conclusion** The i3+3 design could be a practice-altering method for the clinical community.

## **To Randomize or not to Randomize: Using Data from Prior Clinical Trials to Inform Future Designs**

Alyssa M. Vanderbee <sup>\*1,7§</sup>, Steffen Ventz <sup>1,2§</sup>, Rifaquat Rahman MD<sup>4</sup>, Geoffrey Fell<sup>1,2</sup>, Timothy F. Cloughesy<sup>6</sup>, Patrick Y. Wen<sup>4</sup>, Lorenzo Trippa<sup>1,2§§</sup>, Brian M. Alexander MD<sup>1,3,4§§</sup>

<sup>1</sup>Program in Regulatory Science, <sup>2</sup>Department of Biostatistics and Computational Biology, <sup>3</sup>Department of Radiation Oncology, <sup>4</sup>Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA

<sup>5</sup>Harvard Radiation Oncology Program, Boston, MA

<sup>6</sup>UCLA Neuro-Oncology Program and Department of Neurology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California,

<sup>7</sup>Department of Biostatistics, Columbia University Mailman School of Public Health, New York, NY

<sup>§</sup>Co-first authors, <sup>§§</sup>Co-senior authors

Non-randomized single arm designs with historical benchmark comparison are common in early stage drug development, especially in neuro-oncology. In a recent study, we found that over 70% of phase II trials in newly diagnosed glioblastoma (ndGBM) over the last decade were non-randomized and historically controlled. This phenomenon has been proposed as contributing to poor go/no-go decisions that lead to a high phase III failure rate. But it is unclear under what circumstances randomization to a comparison arm – or the lack thereof – ought to be favored for a given disease. We propose a simple and interpretable quantitative framework for assessing the indication-specific value of randomization for a fixed sample size. Three factors are included in our model: (i) the variability of the primary endpoint distributions across past studies, (ii) potential for incorrectly specifying the single arm trial’s benchmark comparison, and (iii) the hypothesized effect size. Using outcomes from prior trials in ndGBM that compare experimental outcomes to the standard of care (temozolomide and radiation), we compare randomized controlled and single arm trial designs. Design merit is assessed on its ability to distinguish between effective and ineffective agents (using AUC), deviations from pre-specified type I error and power, and ability to precisely estimate the treatment effect (using MSE of the estimate). In our chosen application, we find that the value of randomization is sensitive to the model parameter estimates. Compared to randomized controlled trials, single arm trials are prone to inflated type I error and biased treatment effect, and use benchmark comparison values that tend towards underestimation. For phase II trials in ndGBM using an overall survival endpoint, randomization should be preferred over single arm designs.

# **A Bayesian Analysis of Small n Sequential Multiple Assignment Randomized Trials (snSMARTs)**

Boxian Wei

Department of Biostatistics, University of Michigan, Ann Arbor, MI

Designing clinical trials to study treatments for rare diseases is challenging because of the limited number of available patients. A suggested design is known as the small-n Sequential Multiple Assignment Randomized Trial (snSMART), in which patients are first randomized to one of multiple treatments (stage 1). Patients who respond to their initial treatment continue the same treatment for another stage, while those who fail to respond are re-randomized to one of the remaining treatments (stage 2). Analysis approaches for snSMARTs are limited, and we propose a Bayesian approach that allows for borrowing of information across both stages to compare the efficacy between treatments. Through simulation, we compare the bias, root mean-square error (rMSE), width and coverage rate of 96% confidence/credible interval (CI) of estimators from our approach to estimators produced from (a) standard approaches that only use the data from stage 1, and (b) a log-Poisson model using data from both stages whose parameters are estimated via generalized estimating equations. We demonstrate the rMSE and width of 95% CIs of our estimators are smaller than the other approaches in realistic settings.

## **Gene Expression Alterations Associated with Histologic Aggressiveness in Stage I Lung Adenocarcinomas**

Jiarui Zhang<sup>\*1</sup>, Eric Burks<sup>2</sup>, Jennifer Beane<sup>1</sup>, Travis Sullivan<sup>2</sup>, Gang Liu<sup>2</sup>, Steven Dubinett<sup>3</sup>, Avrum Spira<sup>1</sup>, Kimberly Rieger-Christ<sup>2</sup>, and Marc E Lenburg<sup>1</sup>

<sup>1</sup>Section of Computational Biomedicine, Boston University School of Medicine, Boston MA

<sup>2</sup>Lahey Hospital & Medical Center 3. David Geffen School of Medicine at UCLA

### **RATIONALE:**

The National Lung Screening and Nelson Trials demonstrated a 20% and 26% (for men) reduction, respectively in lung cancer mortality for patients screened using low-dose CT. However, lung cancer screening has the potential for over-diagnosis of indolent tumors. Therefore, we sought to identify molecular features that could distinguish indolent from aggressive early stage lung tumors based on histologic aggressiveness profiling, with the ultimate goal being to translate these findings into biomarkers that could inform post-biopsy/surgery management.

### **METHODS:**

63 FFPE samples of stage I lung adenocarcinomas were included for pathologic annotation and Whole Exome sequencing. An average of  $48.2 \pm 15.6$  million total reads per sample were generated with  $78.4\% \pm 4.8\%$  reads uniquely mapped. Tumors were categorized into 3 groups based on

histologic features previously associated with tumor aggressiveness: Minimally-Aggressive (n=18): containing zero aggressive components (e.g. zero solid/cribriform); Medium-Aggressive (n=19): not yet dominated by aggressive components; Highly-Aggressive (n=26): solid/cribriform predominant. Tumor histology was characterized for percentage of lepidic, acinar, papillary, micro-papillary, solid and cribriform components. Negative binomial models were used to identify genes whose expression was associated with tumor histology. Estimate Algorithm was used to estimate immune cell type infiltration of these tumors.

### **RESULTS:**

430 genes (FDR  $q < 0.05$ ) were differentially expressed between the three histologic groups. Genes with elevated expression in the Medium- and Highly-Aggressive subgroups were enriched for genes with roles in cell-cycle regulation and the EMT transition. The genes elevated in the Minimally-Aggressive subgroup were enriched for genes with roles in inflammatory pathways and cytokine production. This gene signature was also associated with tumor invasiveness and mitotic grades ( $p < 0.05$ ). Using the Estimate Algorithm, we compared whether the three histologic groups had differential immune cell infiltrations using hallmark gene sets of lymphocytes and myeloid cells. We identified that Minimally-Aggressive subgroups had significantly higher Th-1, Tfh, Th17 and NK cell infiltration than Medium- and Highly-Aggressive subgroups (adjusted  $p$  value  $< 0.05$ ).

### **CONCLUSION:**

We identified gene expression alterations among stage I adenocarcinomas associated with histologic features of tumor aggressiveness. This gene signature may help identify more indolent tumors and potentially impact their post biopsy/surgery clinical management.

## **Non-inferiority Clinical Trials with Binary Outcome: Statistical Methods Used in Practice.**

Yulia Sidi\* and Ofer Harel

Department of Statistics, University of Connecticut

It is common to compare results from different clinical trials in order, for example, to assess a benefit risk of a new treatment. One of the factors that needs to be taken into consideration while performing such comparison is differences in statistical methods used across the trials. Thus, a thorough reporting of statistical methodology is essential in published research papers. In this systematic review, we focus on non-inferiority clinical trials that use binomial proportions as the primary endpoint analysis. We believe that non-inferiority clinical trials deserve a special attention due to their complex study design features, and due to a growing use of this design in recent years. Moreover, we anticipated that binomial proportions is the most common primary endpoint outcome for non-inferiority trials.

We reviewed 71 non-inferiority randomized clinical studies that were published between Jun-2017 and May-2018. We found that the specification of a statistical method used to calculate sample size is omitted for 63 (89%) of the articles we reviewed. Moreover, among the study analysis

attributes, the statistical method used to construct the confidence intervals is omitted in 25 (35%) of the articles. Sixty four (90%) encountered some incomplete data in primary endpoint, however only 18 (28%) studies specified how the incomplete data were handled for primary analysis.

Since there are different statistical methods that could be used to calculate sample sizes and construct confidence intervals for binomial proportions, these findings are concerning as it has a major impact on reproducibility and replicability. We believe that these gaps in reporting of statistical methods could be easily minimized by journal editors, reviewers and manuscript authors. Clearly stated statistical methodology used in design and analysis of a clinical trials will be beneficial for the research community.

## **Depth Importance in Precision Medicine (DIPM): A Tree and Forest Based Method for Right-Censored Survival Outcomes**

Victoria Chen\* and Heping Zhang

Department of Biostatistics, Yale School of Public Health, New Haven, CT

Improving the field of medicine using personalized health data has become a primary focus for researchers. Instead of the traditional focus on average responses to interventions, precision medicine recognizes the heterogeneity that exists between individuals and aims to find the optimal treatment for each person. We propose the novel implementation of a depth variable importance score in a classification tree method designed for the precision medicine setting. The goal of the analysis is to identify clinically meaningful subgroups to better inform treatment decisions. The proposed Depth Importance in Precision Medicine (DIPM) method is designed for the analysis of clinical datasets with continuous or right-censored survival outcomes and binary treatments. Here, we focus on data with right-censored survival outcomes. The approach first modifies the split criteria of the traditional classification tree to fit the precision medicine setting. Then, a random forest of trees is constructed at each node and used to identify the best split variable. The variable with the highest depth variable importance score is the best split variable, and this measure is adapted to the analysis of time-to-event outcomes accordingly. The depth variable importance score is a flexible and simply constructed measure that makes use of the observation that more important variables tend to be selected closer to the root node of a tree. We present the results of an application to a breast cancer dataset. The DIPM method yields promising results that demonstrate its capacity to guide personalized treatment decisions in the field of oncology and beyond.

# **A Flexible Non-Parametric Procedure for Testing Known-Form Hazards with Applications to Oncology Studies**

Yiming Zhang\*<sup>1</sup>, Abidemi K. Adeniji<sup>2</sup>, and Ming-Hui Chen<sup>1</sup>

<sup>1</sup>Department of Statistics, University of Connecticut, Storrs, CT

<sup>2</sup>ResTORbio, Inc, Boston, MA

Hazard function plays an important role in the survival analysis because physicians are interested in how the hazard of a disease changes over time. In an oncology study, it is of great interest to know if the hazard is constant over certain period of time. In this research, we develop a non-parametric hypothesis testing procedure to test if time-to-event data have a known-form cumulative hazard function given a continuous scope of time. This testing procedure is based on the Kaplan Meier estimators and their asymptotic covariance matrix. Our testing approach is very flexible since it allows us to choose the time period and to specify any partially known-form distribution. In addition, the approximate asymptotic distributions of the test statistic are derived under either the null hypothesis or the alternative hypothesis. Subsequently, the computational algorithms for power analysis and sample size calculation are developed using the proposed testing procedure. Extensive simulation studies show that the proposed procedure enjoys a reasonable Type-I error control and a good power. The proposed methodology is further applied to examine the hazard rates for various types of cancer over different time-periods under different treatments for various subgroups of patients.

## **The Biodynamics of Cancer Progression in Cohort Studies and Clinical Trials Automatically Yield Non-proportional Hazards: Proportional Hazards are Biodynamically Impossible**

Sidney Klawansky

Harvard Chan School of Public Health

Analysts of cancer clinical trials routinely assume proportional hazards. The relatively small number of endpoints such as death, give rise to fuzzy hazards often making it difficult to decide proportional or non-proportional. To decisively discern the shapes of the hazards requires tens of thousands of cases and deaths. For this purpose, we compare the time dependent hazards of 22,968 women diagnosed with regional breast to 22,488 women diagnosed with local disease using data taken from the NCI Registry. There were more than 25,000 deaths over 20 yrs.

A central feature of cancer is the wide variability in rates of progression. Progression can lead to a critical event like death from tumor burden. It will take a shorter time period, on average, for the typically larger tumor burden in women with regional disease to reach lethal size as compared

to the longer time required for the smaller local disease burden to grow to lethal size. For the same growth rate, the time that the local disease burden arrives at death is postponed compared to the regional burden's arrival. A structural feature, such as a peak, in the local hazard will therefore occur at a later time as compared to the peak in the regional hazard. For this basic reason, the observed local hazard cannot be proportional to the observed regional hazard.

The distribution of progression rates for a diagnosed group results, biodynamically, in a distribution of arrival times at death, producing the time dependent hazard. The mathematical formulation of the distribution of tumor progression rates producing the time dependent hazard yields the following equations for the hazards,  $h$ , the cumulative hazards,  $H$ , and the survival functions,  $S$ . In (1), Regional = 1, Local = 2

$$h_2(tK_t)/h_1(t) = K_h \quad H_2(tK_t)/H_1(t) = K_h K_t \quad S_2(tK_t) = [S_1(t)]^{K_h K_t} \quad (1)$$

The time scaling parameter,  $K_t > 1$ , scales, or stretches, the observed regional hazard in the time dimension so that the observed local hazard will be proportional to the time scaled regional hazard.  $K_t$  is a conservative estimate of the ratio of life expectancies of local to regional patients.  $K_h < 1$ , is the constant proportional hazard ratio between the observed local hazard and the time scaled regional hazard, also called the time scaled hazard ratio. For early and mid-stage disease, two invariant and highly conservative outcome metrics are: (a)  $(1 - K_h K_t)$  is the conservative percent reduction in long-term deaths of local to regional patients. (b)  $(K_t - 1)$  is the conservative percent increase in average life expectancy of local to regional patients. Note, importantly, that two outcome metrics, not just one, must be reported in a cohort study or clinical trial. In the present context,  $K_t=1$ , corresponding to PH, makes no sense. In the NCI data,  $K_t = 1.77$ ,  $K_h = 0.263$  and  $K_h K_t = 0.466$ .  $(1 - K_h K_t) = 53.4\%$ ,  $(K_t - 1) = 77\%$ .

In a successful clinical trial, the treated tumors will shrink more than the control tumors. Then, the control hazard takes the role of the regional hazard and the treated hazard takes the role of the local hazard. In (1), Control = 1, Treated = 2. The relationship of the hazards, cumulative hazards and survival functions in (1) all carry over into the clinical trial situation.