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

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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 introduce 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 shows 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

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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

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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

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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)**

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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

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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±15.6 million total reads per sample were generated with 78.4%±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.