Published in final edited form as:

Stat Methods Med Res. 2017 February ; 26(1): 88–107. doi:10.1177/0962280214539655.

Surrogacy Assessment Using Principal Stratification and a Gaussian Copula Model

A.S.C. Conlon¹, J.M.G. Taylor¹, and M.R. Elliott^{1,2}

¹Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, U.S.A

²Survey Methodology Program, Institute for Social Research, Ann Arbor, Michigan, U.S.A

Abstract

In clinical trials, a surrogate outcome (S) can be measured before the outcome of interest (T) and may provide early information regarding the treatment (Z) effect on T . Many methods of surrogacy validation rely on models for the conditional distribution of T given Z and S . However, S is a post-randomization variable, and unobserved, simultaneous predictors of S and T may exist, resulting in a non-causal interpretation. Frangakis and Rubin¹ developed the concept of principal surrogacy, stratifying on the joint distribution of the surrogate marker under treatment and control to assess the association between the causal effects of treatment on the marker and the causal effects of treatment on the clinical outcome. Working within the principal surrogacy framework, we address the scenario of an ordinal categorical variable as a surrogate for a censored failure time true endpoint. A Gaussian copula model is used to model the joint distribution of the potential outcomes of T , given the potential outcomes of S . Because the proposed model cannot be fully identified from the data, we use a Bayesian estimation approach with prior distributions consistent with reasonable assumptions in the surrogacy assessment setting. The method is applied to data from a colorectal cancer clinical trial, previously analyzed by Burzykowski *et al.*²

Keywords

Causal inference; Gaussian copula; Potential outcomes; Surrogate endpoint

1 Introduction

A surrogate endpoint (S) is an intermediate outcome variable occurring in between the treatment (Z) and the outcome of interest (T). The surrogate is usually known to be involved in the disease process and associated in some way with the final outcome of interest and can be measured at an earlier time than the desired outcome. There is considerable interest in the use of surrogate markers in clinical trials, as they offer the potential to run trials more cheaply and quickly by extracting information regarding the treatment effect on T through the earlier measured S . However, demonstrating the validity of a given surrogate for the outcome of interest can be difficult. Prentice³ proposed a formal definition of surrogacy

Correspondence to: A.S.C. Conlon.

Supplementary Materials

Web Appendices are available online with this paper.

along with a validation strategy, requiring that S and T be correlated and the treatment effect on T be fully captured by S . Other methods for surrogacy evaluation include the proportion of treatment effect explained by S ,⁴ and individual-level and trial-level surrogacy association measures in meta-analyses.⁵ As these methods rely on estimating treatment effects by adjusting for a variable measured after randomization, and there may be unmeasured confounders in the pathway between the surrogate and final outcome, the resulting estimates may not have a causal interpretation.⁶ Therefore, much recent work has been done on the evaluation of surrogate endpoints using the “principal surrogacy” (PS) framework introduced by Frangakis and Rubin¹ (henceforth FR). In this framework, each subject has two potential outcomes for each of the surrogate and final endpoints corresponding to each treatment, denoted by $S(Z)$ and $T(Z)$, for $Z = \{0, 1\}$. The principal surrogacy approach looks at the distribution of the potential outcomes of T conditional on principal strata based on the values of $S(0)$ and $S(1)$. The principal strata are unaffected by treatment, and are thus pre-randomization variables. Treatment effect estimates that condition on these principal strata are therefore causal estimates when treatments are randomly assigned.

There is a growing literature on methods for surrogacy assessment using the principal stratification approach. As working within the principal surrogacy framework involves the estimation of quantities based on unobserved potential outcomes, some assumptions about unidentified parameters must be made in order to aid in their estimation. The assumptions that are typically made vary based on the setting being explored and on the estimated quantities of interest. Li, Taylor, and Elliott⁷ used a Bayesian estimation strategy to examine the setting in which both S and T are binary and used prior distributions and a monotonicity assumption to reduce the problem of non-identifiability. Gilbert and Hudgens⁸ and Zigler and Belin⁹ have proposed surrogacy validation measures in the setting of continuous S and binary T . In this case, progress was made in the estimation of the unidentified parameters through the use of baseline covariates used to predict missing surrogate values as well as through reasonable conditional independence assumptions on certain unidentified correlations. Qin et al.¹⁰ considered the setting of a continuous surrogate marker and time-to-event final outcome and explored novel trial designs to predict missing surrogate values. Work in the PS framework when both S and T are continuous has been discussed in the application to partial compliance,^{11,12} where the joint counterfactual distribution of partial compliances is modeled either parametrically or non-parametrically, and then separate models are proposed for the counterfactual outcomes, conditional on compliance, thus reducing the number of unidentified parameters that must be estimated. The correlation between the counterfactual values of S is treated as a sensitivity parameter with a sensitivity analysis performed to determine the impact of different values of this parameter on the estimation of the quantities of interest, and prior distributions are placed on the remaining two unidentified model parameters. Conlon, Taylor, and Elliott¹³ explored the scenario where the joint distribution of the counterfactual observations of S and T is multivariate normal and explored the use of different prior assumptions that could be placed on the unidentified correlation parameters to aid in estimation.

Here, we consider the scenario in which S is a discrete ordinal random variable and T is a continuous time-to-event random variable. The values of $S(0)$ and $S(1)$ are assumed to arise from separate underlying latent normal random variables, denoted $\tilde{S}(0)$ and $\tilde{S}(1)$. A Gaussian

copula model is used to obtain the joint distribution of the four counterfactual outcomes, $S(1)$, $S(0)$, $T(1)$, and $T(0)$, given their marginal distributions. In this setting, there is no baseline covariate information available that can be used to aid in predicting unobserved outcomes of S . Additionally, we make no conditional independence or monotonicity assumptions. We model the full joint distribution of the four potential outcomes and use a Bayesian estimation strategy to estimate the parameters of this distribution. Bayesian estimation is used as it allows for prior distributions that are reasonable in the surrogate marker setting to be placed on unidentified parameters to reduce the non-identifiability problem of modeling counterfactual observations and to aid in estimation of the quantities of interest. We explore the use of different plausible prior distributions and some reasonable constraints on model parameters. Once parameter estimates are obtained, quantities are derived from the joint distribution to determine the value of S as a surrogate marker for T . These principal surrogacy measures are not analytically estimable, but using a Bayesian estimation strategy, they can be obtained from the posterior predictive distributions of the potential markers and outcomes under the Gaussian copula model.

In our data example, we consider the use of the ordinal variable “tumor response” as a surrogate for overall survival in advanced colorectal cancer. Tumor response and overall survival are common endpoints of interest in cancer clinical trials, and there is a large literature on the use of tumor response as a surrogate marker for overall survival.^{14–16} In this setting of mixed discrete and continuous outcomes, surrogacy validation methods have been explored by Molenberghs, Geys, and Buyse,¹⁷ where a joint model for the underlying continuous latent variable of the observed discrete surrogate marker and the observed continuous final outcome was developed. The use of copula models in this setting has been explored by Burzykowski, Molenberghs, and Buyse,² who proposed a bivariate Plackett copula to jointly model tumor response and survival in advanced colorectal cancer, and assessed surrogacy using a meta-analytic approach. The application of a Gaussian copula model to jointly model bivariate discrete and continuous outcomes was examined by de Leon and Wu.¹⁸ Here, we extend the use of this Gaussian copula model to a four dimensional model, two for the potential surrogate marker values under each treatment arm and two for the potential outcomes under each treatment arm. The Gaussian copula model was chosen as opposed to another type of copula because it allows for a multivariate correlation structure with separate coefficients for the six pairwise correlations. This is particularly useful because the correlation matrix has interpretable correlation coefficients, which greatly facilitate the use of meaningful prior distributions. Other classes of copulas, such as the Archimedian class, typically use a single parameter to accommodate correlation. Since this correlation is a nuisance parameter, it is convenient in many settings. However, it does not work well in our setting, where we want to impose some structure on the correlation through the use of prior distributions.

The remainder of the paper is organized as follows. In Section 2, we describe the model. Section 3 outlines the proposed surrogacy measures and Section 4 outlines the estimation strategy. Simulation results are presented in Section 5, and in Section 6 the estimation procedure is applied to data from a meta-analysis in advanced colorectal cancer. Section 7 concludes with a discussion.

2 The Model

2.1 Potential Outcomes

For a randomized trial with treatment assignment Z ($Z = 1$ or 0), surrogate marker S and true endpoint T , each subject i , $i = 1, \dots, n$, has two potential outcomes for each of S_i and T_i , denoted by $S_i(z)$ and $T_i(z)$. Only one outcome, corresponding to the received treatment for subject i in each of the pairs $(S_i(0), S_i(1))$ and $(T_i(0), T_i(1))$ can be observed. The joint distribution of $(S_i(0), S_i(1), T_i(0), T_i(1))$ describes the causal associations between Z , S and T . We denote the marginal cumulative distributions of $S_i(0)$, $S_i(1)$, $T_i(0)$ and $T_i(1)$ by $F_{S_i(0)}$, $F_{S_i(1)}$, $F_{T_i(0)}$ and $F_{T_i(1)}$, respectively. We make the standard assumptions of ignorable treatment assignments¹⁹ and the stable unit treatment value assumption (SUTVA). Ignorable treatment assignment implies that Z is independent of $(S_i(0), S_i(1), T_i(0), T_i(1))$ and holds for blinded, randomized trials. SUTVA implies that the potential outcomes $(S_i(0), S_i(1), T_i(0), T_i(1))$ are independent of the treatment assignments of other subjects, allowing us to write the potential outcomes for subject i as a function of Z_i rather than of the entire vector of subject treatment assignments. Additionally, we assume equal drop-out and risk of death in the control group and treatment group up to the time at which S is measured,¹⁰ and that S is measured in everyone before T occurs.

We consider the setting where S is an ordinal categorical variable and T is a failure-time random variable. Let $V_i(Z) = \min(T_i(Z), W_i(Z))$ be the minimum of the observed failure time, $T_i(Z)$, and censoring time, $W_i(Z)$, and let $C_i(Z) = \mathbb{I}(W_i(Z) > T_i(Z))$ be the censoring indicator. Then, for each subject we have the observed data $S_i(Z)$, $V_i(Z)$, and $C_i(Z)$. We make the ignorable censoring assumption, $T_i(Z) \perp W_i(Z)$, reasonable in cases where censoring is administrative and enrollment times are simultaneous or otherwise unrelated to the outcome. In our estimation procedure, we iteratively impute survival times for censored subjects so that each subject has the vector of outcomes $\mathbf{y}_i = (S_i(0), S_i(1), T_i(0), T_i(1))$. Let $\tilde{S}_i(Z)$ be a latent, Gaussian continuous random variable underlying the surrogate endpoint $S_i(Z)$ such that

$$S_i(Z) = \begin{cases} 1_Z, & \text{if } \tilde{S}_i(Z) \in (-\infty, \alpha_{1_Z}) \\ 2_Z, & \text{if } \tilde{S}_i(Z) \in (\alpha_{1_Z}, \alpha_{2_Z}) \\ \vdots & \\ M_Z, & \text{if } \tilde{S}_i(Z) \in (\alpha_{(M-1)_Z}, \infty) \end{cases}$$

where $\alpha_{1_Z} < \alpha_{2_Z} < \dots < \alpha_{(M-1)_Z}$ are unknown cutpoints with $\alpha_{0_Z} = -\infty$ and $\alpha_{M_Z} = \infty$. We assume a cumulative probit model for the cutpoints of the underlying continuous random variables of $S(0)$ and $S(1)$ and a proportional hazards model with a Weibull baseline hazard function for the marginal distributions of $T(0)$ and $T(1)$. These models are given by

$\Phi^{-1}\{P(S(Z) = k_Z)\} = \alpha_{k_Z}$ and $\lambda(T(Z)) = \left(\frac{\gamma_{T_Z}}{\nu_{T_Z}}\right) \left(\frac{T(Z)}{\nu_{T_Z}}\right)^{\gamma_{T_Z}-1}$, respectively, where $\lambda(T(Z))$ is a hazard function for a Weibull distribution with scale parameter ν_{T_Z} and shape parameter γ_{T_Z} . Let $\tilde{\mathbf{y}}_i = (\tilde{S}_i(0), \tilde{S}_i(1), T_i(0), T_i(1))$ represent the set of counterfactual latent surrogate and final outcomes for subject i .

2.2 Copulas

Sklar²⁰ provided the basis for multivariate modeling using copulas. A multivariate function $C = C(u_1, \dots, u_k)$ is a copula if it is a continuous distribution function and each marginal is a uniform distribution function. That is, C is a mapping of $(0, 1)^k \rightarrow (0, 1)$, with $C(u) = P(U_1 \leq u_1, \dots, U_k \leq u_k)$, where each $U_i \sim \text{Unif}(0, 1)$. Using known marginal distributions $F_1(y_1), \dots, F_k(y_k)$, the function $C(F_1(y_1), \dots, F_k(y_k)) = G(y)$ defines a joint distribution for $y_1, \dots, y_k$.²¹

In this paper, we focus on the Gaussian copula denoted as $C_\Phi(u|\Gamma) = \Phi_k\{\Phi^{-1}(u_1), \dots, \Phi^{-1}(u_k)|\Gamma\}$, where Φ is the standard normal cumulative distribution function and $\Phi_k(x|\Gamma)$ is a k -variate normal cumulative distribution function with covariance matrix Γ . The density of the Gaussian copula is given by $c_k(\mathbf{q}|\Gamma) = |\Gamma|^{-\frac{1}{2}} \exp\{-\frac{1}{2}\mathbf{q}^T(\mathbf{I}_k - \Gamma^{-1})\mathbf{q}\}$ where $\mathbf{q} = (q_1, \dots, q_k)^T$ with $q_j = \Phi^{-1}(u_j)$, $\mathbf{q} \sim N_k(0, \Gamma)$ and Γ is a correlation matrix.²² The copula framework can then be used to obtain a multivariate distribution with specified marginals.

2.3 Gaussian Copula Regression Model

Assuming the data were complete, in the setting of a single surrogate and single outcome each measured at separate time points, we would have n observations each of dimension four, corresponding to the four potential outcomes for each subject. Let $\mathbf{y}_i = (S_i(0), S_i(1), T_i(0), T_i(1))$ represent the set of observations from subject i . For continuous S and T , the Gaussian copula regression model can be obtained by taking $q_{ij} = \Phi^{-1}\{F_j(y_{ij}, \theta_j)\}$ where θ_j is the parameter vector for marginal distribution j , where $j = 1, \dots, 4$ corresponds to the four marginal distributions for $S_i(0)$, $S_i(1)$, $T_i(0)$, and $T_i(1)$, respectively. By this construction, we have:

$$\mathbf{q}_i = [\Phi^{-1}\{F_1(S_i(0))\}, \Phi^{-1}\{F_2(S_i(1))\}, \Phi^{-1}\{F_3(T_i(0))\}, \Phi^{-1}\{F_4(T_i(1))\}] \sim N_4(\mathbf{0}, \Gamma)$$

and the density of y_{ij} is given by:

$$f(y_{ij}|\theta, \Gamma) = \prod_{i=1}^n \left[|\Gamma|^{-\frac{1}{2}} \exp\left\{-\frac{1}{2}\mathbf{q}_i^T(\mathbf{I}_4 - \Gamma^{-1})\mathbf{q}_i\right\} f_1(S_i(0); \theta_1) f_2(S_i(1); \theta_2) f_3(T_i(0); \theta_3) f_4(T_i(1); \theta_4) \right]$$

We assume that the joint cumulative distribution of $\tilde{S}_i(0)$, $\tilde{S}_i(1)$, $T_i(0)$, $T_i(1)$ is generated by the Gaussian copula function:

$$F_{\tilde{\mathbf{y}}_i}(\tilde{\mathbf{y}}_i) = \Phi_4\{\Phi^{-1}(F_1(\tilde{S}_i(0))), \Phi^{-1}(F_2(\tilde{S}_i(1))), \Phi^{-1}(F_3(T_i(0))), \Phi^{-1}(F_4(T_i(1)))|\Gamma\},$$

where the subscripts $\tilde{1}$ and $\tilde{2}$ correspond to the CDF of the underlying latent variables of $S(0)$ and $S(1)$, respectively, Φ is the standard normal distribution and Φ_4 is the standard four-variate normal distribution with correlation matrix:

$$\Gamma = \begin{pmatrix} 1 & \rho_s & \rho_{00} & \rho_{01} \\ & 1 & \rho_{10} & \rho_{11} \\ & & 1 & \rho_t \\ & & & 1 \end{pmatrix}.$$

As $\tilde{S}_\lambda(Z)$ is assumed to be Gaussian, the terms $\Phi^{-1}(F_1(\tilde{S}_\lambda(0)))$ and $\Phi^{-1}(F_2(\tilde{S}_\lambda(1)))$ are simply $\tilde{S}_\lambda(0)$ and $\tilde{S}_\lambda(1)$, respectively. The joint distribution of $S_\lambda(0)$, $S_\lambda(1)$, $T_\lambda(0)$, and $T_\lambda(1)$ under these distributional assumptions is then given by:

$$P(S_i(0)=k_0, S_i(1)=k_1, T_i(0) \leq t_0, T_i(1) \leq t_1) = [F_{\tilde{\mathbf{y}}_i}(\alpha_{k_0}, \alpha_{k_1}, t_0, t_1) - F_{\tilde{\mathbf{y}}_i}(\alpha_{(k_0-1)}, \alpha_{k_1}, t_0, t_1) - F_{\tilde{\mathbf{y}}_i}(\alpha_{k_0}, \alpha_{(k_1-1)}, t_0, t_1) + F_{\tilde{\mathbf{y}}_i}(\alpha_{(k_0-1)}, \alpha_{(k_1-1)}, t_0, t_1)].$$

When both $T_\lambda(0)$ and $T_\lambda(1)$ are uncensored observations, the joint density of $S_\lambda(0)$, $S_\lambda(1)$, $T_\lambda(0)$, and $T_\lambda(1)$ is given by:

$f_{\mathbf{y}_i}(k_0, k_1, t_0, t_1) = \frac{\partial^2}{\partial t_0 \partial t_1} P(S_i(0)=k_0, S_i(1)=k_1, T_i(0) \leq t_0, T_i(1) \leq t_1)$, where the derivative of $F_{\tilde{\mathbf{y}}_i}(\alpha_{k_0}, \alpha_{k_1}, t_0, t_1)$ with respect to t_1 and t_0 is given by:¹⁸

$$\begin{aligned} \frac{\partial^2 F_{\tilde{\mathbf{y}}_i}(\alpha_{k_0}, \alpha_{k_1}, t_0, t_1)}{\partial t_0 \partial t_1} &= \frac{\phi\left(\frac{\Phi^{-1}(F_3(t_0)) - \rho_t \Phi^{-1}(F_4(t_1))}{\sqrt{1-\rho_t^2}}\right)}{\sqrt{1-\rho_t^2}} \Phi_2[S_{0|0:1}, S_{1|0:1} | \Gamma_{|0:1}] \frac{f_4(t_1)f_3(t_0)}{\phi(\Phi^{-1}(F_3(t_0)))} \text{ for} \\ S_{0|0:1} &= \frac{\left(\frac{\alpha_{k_0} - \rho_{01} \Phi^{-1}(F_4(t_1))}{\sqrt{1-\rho_{01}^2}}\right) - \left(\frac{\rho_{00} - \rho_{01} \rho_t}{\sqrt{1-\rho_{01}^2} \sqrt{1-\rho_t^2}}\right) \left(\frac{\Phi^{-1}(F_3(t_0)) - \rho_t \Phi^{-1}(F_4(t_1))}{\sqrt{1-\rho_t^2}}\right)}{\sqrt{1 - \left(\frac{\rho_{00} - \rho_{01} \rho_t}{\sqrt{1-\rho_{01}^2} \sqrt{1-\rho_t^2}}\right)^2}} \text{ and} \\ S_{1|0:1} &= \frac{\left(\frac{\alpha_{k_1} - \rho_{11} \Phi^{-1}(F_4(t_1))}{\sqrt{1-\rho_{11}^2}}\right) - \left(\frac{\rho_{10} - \rho_{11} \rho_t}{\sqrt{1-\rho_{11}^2} \sqrt{1-\rho_t^2}}\right) \left(\frac{\Phi^{-1}(F_3(t_0)) - \rho_t \Phi^{-1}(F_4(t_1))}{\sqrt{1-\rho_t^2}}\right)}{\sqrt{1 - \left(\frac{\rho_{10} - \rho_{11} \rho_t}{\sqrt{1-\rho_{11}^2} \sqrt{1-\rho_t^2}}\right)^2}}, \end{aligned}$$

where:

$$\begin{aligned}
f_3(t_0) &= \left(\frac{\gamma_{T_0}}{\nu_{T_0}} \right) \left(\frac{t_0}{\nu_{T_0}} \right)^{\gamma_{T_0}-1} \exp \left(- \left(\frac{t_0}{\nu_{T_0}} \right)^{\gamma_{T_0}} \right), \\
f_4(t_1) &= \left(\frac{\gamma_{T_1}}{\nu_{T_1}} \right) \left(\frac{t_1}{\nu_{T_1}} \right)^{\gamma_{T_1}-1} \exp \left(- \left(\frac{t_1}{\nu_{T_1}} \right)^{\gamma_{T_1}} \right), \\
F_3(t_0) &= 1 - \exp \left(- \left(\frac{t_0}{\nu_{T_0}} \right)^{\gamma_{T_0}} \right), \\
F_4(t_1) &= 1 - \exp \left(- \left(\frac{t_1}{\nu_{T_1}} \right)^{\gamma_{T_1}} \right) \text{ and} \\
\Gamma_{|0:1} &= \begin{pmatrix} 1 & \frac{\left(\frac{\rho_{S0}-\rho_{11}}{\sqrt{1-\rho_{11}^2}} \frac{\rho_{01}}{\sqrt{1-\rho_{01}^2}} \right) - \left(\frac{\rho_{00}-\rho_{01}}{\sqrt{1-\rho_{01}^2}} \frac{\rho_t}{\sqrt{1-\rho_t^2}} \right) \left(\frac{\rho_{10}-\rho_{11}}{\sqrt{1-\rho_{11}^2}} \frac{\rho_{11}}{\sqrt{1-\rho_t^2}} \right)}{\sqrt{1-\left(\frac{\rho_{00}-\rho_{01}}{\sqrt{1-\rho_{01}^2}} \frac{\rho_t}{\sqrt{1-\rho_t^2}} \right)^2} \sqrt{1-\left(\frac{\rho_{10}-\rho_{11}}{\sqrt{1-\rho_{11}^2}} \frac{\rho_t}{\sqrt{1-\rho_t^2}} \right)^2}} \\ \frac{\left(\frac{\rho_{S0}-\rho_{11}}{\sqrt{1-\rho_{11}^2}} \frac{\rho_{01}}{\sqrt{1-\rho_{01}^2}} \right) - \left(\frac{\rho_{00}-\rho_{01}}{\sqrt{1-\rho_{01}^2}} \frac{\rho_t}{\sqrt{1-\rho_t^2}} \right) \left(\frac{\rho_{10}-\rho_{11}}{\sqrt{1-\rho_{11}^2}} \frac{\rho_{11}}{\sqrt{1-\rho_t^2}} \right)}{\sqrt{1-\left(\frac{\rho_{00}-\rho_{01}}{\sqrt{1-\rho_{01}^2}} \frac{\rho_t}{\sqrt{1-\rho_t^2}} \right)^2} \sqrt{1-\left(\frac{\rho_{10}-\rho_{11}}{\sqrt{1-\rho_{11}^2}} \frac{\rho_t}{\sqrt{1-\rho_t^2}} \right)^2}} & 1 \end{pmatrix}.
\end{aligned}$$

The scale parameters, ν_{T_Z} and shape parameters, γ_{T_Z} from the Weibull models as well as the cutpoints of the latent distributions for $S(0)$ and $S(1)$ are identifiable from the data. The correlation coefficients ρ_{00} and ρ_{11} are the Pearson correlation coefficients between $\tilde{S}(0)$ and the normally transformed $T(0)$ and between $\tilde{S}(1)$ and the normally transformed $T(1)$, respectively, and can be seen as a proxy for the polyserial correlations between $T(0)$ and $S(0)$ and between $T(1)$ and $S(1)$.¹⁸ These polyserial correlations are estimable from the data.²³ Because only one of the counterfactual pairs of outcomes is observed for each subject, ρ_s , ρ_b , ρ_{01} , and ρ_{10} are not identifiable. However, the identifiable correlation parameters together with the requirement that the correlation matrix be positive definite place boundary constraints on these non-identified parameters, which, along with other plausible assumptions that we can make, aids in their estimation.

2.4 Prior Distributional Assumptions

We place weakly informative priors on the fully identified parameters ν_{T_Z} , γ_{T_Z} and α_{k_Z} 's. Specifically, the priors for $\log(\nu_{T_Z})$ and the α_{k_Z} 's are $N(0, 10^2)$ and the priors for γ_{T_Z} are gamma distributions with mean 1 and standard deviation 3. We place marginal priors on each of the correlation parameters in Γ and following Conlon et al.,¹³ we consider four different sets of prior assumptions. For each of these there is the additional assumption that Γ must be positive definite. The four priors are

- a. Jointly uniform prior such that for each of the six correlations $p(\rho) \sim \text{Unif}(-1, 1)$
- b. Jointly uniform prior such that for each of the six correlations $p(\rho) \sim \text{Unif}(0, 1)$
- c. All ρ 's > 0 , $\rho_{01} < \min(\rho_{00}, \rho_{11}, \rho_s, \rho_b)$, and $\rho_{10} < \min(\rho_{00}, \rho_{11}, \rho_s, \rho_b)$
- d. Beta priors such that:
 - $p(\rho_{11}) \sim \text{Unif}(-1, 1)$

- $p(\rho_{00}) \sim \text{Unif}(-1, 1)$
- $p(\rho_{10})$ and $p(\rho_{01}) \sim \text{Beta}(3a_0, 3 - 3a_0)$ such that $P(\rho_{01}, \rho_{10} \mid \min(\tilde{\rho}_{00}, \tilde{\rho}_{11})) = 0.80$
- $p(\rho_s)$ and $p(\rho_t) \sim \text{Beta}(3a_1, 3 - 3a_1)$ such that $P(\rho_s, \rho_t \mid E(\rho_{10})) = 0.80$

where $\tilde{\rho}_{00}$ and $\tilde{\rho}_{11}$ are the identifiable polyserial correlation coefficients for $T(0)$, $S(0)$ and $T(1)$, $S(1)$, respectively, estimated from the observed data using the “polyserial” function in R and $E(\rho_{10}) = E(\rho_{01})$ is the mean under the $\text{Beta}(3a_0, 3 - 3a_0)$ distribution. Prior assumption (a) is a non-informative prior on all of the correlations. Under scenario (b), all correlations are constrained to be positive, a plausible assumption especially when $\tilde{\rho}_{00}$ and $\tilde{\rho}_{11}$ are positive. In scenario (c), in addition to the positivity assumption, we restrict ρ_{01} and ρ_{10} to be smaller than the other four correlation parameters. This seems reasonable as ρ_{01} and ρ_{10} are measures of the correlation between the surrogate response and final outcome response in opposite treatment arms, which is unlikely to be larger than the correlation between the surrogate response and final outcome response within the same treatment arm, or the correlation between the surrogate responses or final treatment responses across treatment arms. Finally, prior assumption (d) places similar restrictions on the correlations as assumption (c), but is a little bit more exible.

3 Measures of Surrogacy from the Gaussian Copula Model

To determine the validity of S as a surrogate marker for T , we work within the principal surrogacy (PS) framework proposed by FR which uses a principal stratification approach to assess the validity of a surrogate marker. This framework focuses on the distribution of $p(T(0), T(1) \mid S(0), S(1))$. Since $S(1)$ and $S(0)$ are unaffected by treatment assignment, they can be treated as baseline covariates and quantities estimated by conditioning on them will always have a causal interpretation. This framework therefore avoids the potentially noncausal estimates that can result from surrogacy measures that condition on the observed post-randomization variable S . FR proposed two measures of surrogacy, the “associative effect” and the “dissociative effect”. The dissociative effect quantifies the causal treatment effect on T when there is no treatment effect on S , and the associative effect quantifies the causal treatment effect on T within principal strata where there is a causal treatment effect on S . In the setting where the joint distribution of $S(0)$, $S(1)$, $T(0)$, and $T(1)$ is multivariate normal, the associative and dissociative effects can be estimated through $E(T(1) - T(0) \mid S(1) - S(0) = s)$. This conditional expectation provides an estimate of the dissociative effect when $s = 0$ and a measure of the associative effect when $s \neq 0$. In this setting, the conditional distribution of $(T(1) - T(0) \mid S(1) - S(0))$ is also Gaussian. In our setting of a time to event outcome, we estimate the dissociative effect by $E(\log(T(1)/T(0)) \mid S(1) = S(0))$ and the associative effect is by $E(\log(T(1)/T(0)) \mid S(1) \neq S(0))$. Values of the dissociative effect near zero indicate that the causal effect of treatment on the final outcome is near zero when the causal effect of treatment on the surrogate is near zero, a characteristic that a good principal surrogate should possess. When the dissociative effect is large, there can be a causal effect of the treatment on the final outcome even if there is no causal effect of the treatment on the surrogate. The value of the associative effect provides information on how the causal

treatment effect on the outcome changes as the causal effect of the treatment on the surrogate changes. A good principal surrogate should result in a large associative effect, which would occur if as the treatment effect on the surrogate increases, the treatment effect on the final outcome increases as well. Also of interest is the “causal effect predictiveness” (CEP) surface proposed by Gilbert and Hudgens⁸ and defined as $CEP(s_1, s_0) = h(r_1(s_1, s_0), r_0(s_1, s_0))$ where $h(x, y)$ is a function that satisfies $h(x, y) = 0$ for $x = y$. This surface considers the entire surface defined by all principal strata and provides a measure of the treatment effect on T within subgroups defined by the treatment effect on the surrogate. Here, we take $r_X(S(1) = s_1, S(0) = s_0) = E[\log(T(Z)) | s_1 - s_0]$ and $h(x, y) = x - y$.

An additional useful measure to assess surrogacy is the correlation between the difference in the normal variables, $\Phi^{-1}(F_4(T(1))) - \Phi^{-1}(F_3(T(0)))$ and $\tilde{S}(1) - \tilde{S}(0)$. Measures of the associative effect, dissociative effect and correlation are functions of the parameters, both the identifiable and non-identifiable ones and are not analytically estimable as in the multivariate normal case, but can be obtained from the posterior predictive distributions.

4 Estimation Procedure

A Bayesian approach is used to estimate parameters, using the prior assumptions detailed in Section 2.4. Unobserved potential outcomes are treated as missing data and imputed from the appropriate posterior distribution at each iteration of the Markov chain. Posterior estimates of the unobserved potential outcomes and parameter values are obtained using a Metropolis Hastings algorithm. When drawing each element of Γ , the range of possible 13 values must first be determined in order to satisfy the positive definite requirement, given that the other correlations are held fixed. The range of values corresponding to a positive definite matrix are those in the interval determined by the roots of the quadratic equation that result from solving $|\Gamma| = 0$. Each iteration of the Markov chain is done as follows:

- Let $\alpha = (\alpha_{10}, \alpha_{20}, \alpha_{30}, \alpha_{11}, \alpha_{21}, \alpha_{31}), \theta = (\nu_{T0}, \nu_{T1}, \gamma_{T0}, \gamma_{T1})$,

$$\mathbf{q} = [\Phi^{-1}(F_1(\tilde{S}(0))), \Phi^{-1}(F_2(\tilde{S}(1))), \Phi^{-1}(F_3(T(0))), \Phi^{-1}(F_4(T(1)))]$$

$$= [\tilde{S}(0), \tilde{S}(1), \Phi^{-1}(F_3(T(0))), \Phi^{-1}(F_4(T(1)))]$$

$$= [\tilde{S}(0), \tilde{S}(1), q(T(0)), q(T(1))]$$
- Impute death times for subjects censored at time $V(Z)$ by drawing from

$$\frac{P(q(T(Z)) > q(V(Z)) + v | q(T(1-Z)) > q(V(Z)), q(T(1-Z)), \tilde{S}(0), \tilde{S}(1), \alpha, \theta)}{P(q(T(Z)) > q(V(Z)) + v, q(T(1-Z)), \tilde{S}(0), \tilde{S}(1), \alpha, \theta)} = \frac{P(q(T(Z)) > q(V(Z)) + v | q(T(1-Z)), \tilde{S}(0), \tilde{S}(1), \alpha, \theta)}{P(q(T(Z)) > q(V(Z)) | q(T(1-Z)), \tilde{S}(0), \tilde{S}(1), \alpha, \theta)}.$$

For each censored subject, we draw a uniform random variable $u \sim \text{Unif}(0, 1)$ and solve

$g^{-1}(u) = v$, where $g(v) = \frac{P(q(T(Z)) > q(V(Z)) + v | q(T(1-Z)), \tilde{S}(0), \tilde{S}(1), \alpha, \theta)}{P(q(T(Z)) > q(V(Z)) | q(T(1-Z)), \tilde{S}(0), \tilde{S}(1), \alpha, \theta)}$. This can be solved analytically for v by $v = F^{-1}[1 - u(1 - F(q(V(Z))))] - q(V(Z))$ where F is the CDF of the conditional distribution with mean given by:

$$\begin{pmatrix} \rho_{0Z} & \rho_{1Z} & \rho_t \end{pmatrix} \begin{pmatrix} 1 & \rho_s & \rho_{0(1-Z)} \\ \rho_s & 1 & \rho_{1(1-Z)} \\ \rho_{0(1-Z)} & \rho_{1(1-Z)} & 1 \end{pmatrix}^{-1} \begin{pmatrix} \tilde{S}(0) \\ \tilde{S}(1) \\ q(T(1-Z)) \end{pmatrix}, \text{ and variance given}$$

$$\text{by: } 1 - \begin{pmatrix} \rho_{0Z} & \rho_{1Z} & \rho_t \end{pmatrix} \begin{pmatrix} 1 & \rho_s & \rho_{0(1-Z)} \\ \rho_s & 1 & \rho_{1(1-Z)} \\ \rho_{0(1-Z)} & \rho_{1(1-Z)} & 1 \end{pmatrix}^{-1} \begin{pmatrix} \rho_{0Z} \\ \rho_{1Z} \\ \rho_t \end{pmatrix}.$$

- Draw missing counterfactual observations of $\tilde{S}(Z)$ and $q(T(Z))$ from their conditional distributions:

$$\begin{aligned} & \begin{pmatrix} \tilde{S}(1) \\ q(T(1)) \end{pmatrix} | \tilde{S}(0), q(T(0)), \Gamma \sim \\ N & \left(\begin{pmatrix} \rho_s & \rho_{10} \\ \rho_{01} & \rho_t \end{pmatrix} \begin{pmatrix} 1 & \rho_{00} \\ \rho_{00} & 1 \end{pmatrix}^{-1} \begin{pmatrix} \tilde{S}(0) \\ q(T(0)) \end{pmatrix}, \begin{pmatrix} 1 & \rho_{11} \\ \rho_{11} & 1 \end{pmatrix} - \begin{pmatrix} \rho_s & \rho_{10} \\ \rho_{01} & \rho_t \end{pmatrix} \begin{pmatrix} 1 & \rho_{00} \\ \rho_{00} & 1 \end{pmatrix}^{-1} \begin{pmatrix} \rho_s & \rho_{10} \\ \rho_{10} & \rho_t \end{pmatrix} \right) \\ & \begin{pmatrix} \tilde{S}(0) \\ q(T(0)) \end{pmatrix} | \tilde{S}(1), q(T(1)), \Gamma \sim \\ N & \left(\begin{pmatrix} \rho_s & \rho_{01} \\ \rho_{10} & \rho_t \end{pmatrix} \begin{pmatrix} 1 & \rho_{11} \\ \rho_{11} & 1 \end{pmatrix}^{-1} \begin{pmatrix} \tilde{S}(1) \\ q(T(1)) \end{pmatrix}, \begin{pmatrix} 1 & \rho_{00} \\ \rho_{00} & 1 \end{pmatrix} - \begin{pmatrix} \rho_s & \rho_{01} \\ \rho_{10} & \rho_t \end{pmatrix} \begin{pmatrix} 1 & \rho_{11} \\ \rho_{11} & 1 \end{pmatrix}^{-1} \begin{pmatrix} \rho_s & \rho_{10} \\ \rho_{01} & \rho_t \end{pmatrix} \right) \end{aligned}$$

- For unobserved counterfactuals, transform draws to $S(Z)$, and $T(Z)$:

$$\begin{aligned} [\tilde{S}(Z) \leq \alpha_{1_Z}] &\rightarrow S(Z)=1 \\ [\alpha_{1_Z} < \tilde{S}(Z) \leq \alpha_{2_Z}] &\rightarrow S(Z)=2 \\ [\alpha_{2_Z} < \tilde{S}(Z) \leq \alpha_{3_Z}] &\rightarrow S(Z)=3 \\ [\tilde{S}(Z) > \alpha_{3_Z}] &\rightarrow S(Z)=4 \\ T(Z) &= \lambda_{T_Z} [-\log(1 - \Phi\{q(T(Z))\})]^{1/\gamma_{T_Z}} \end{aligned}$$

- Draw α 's from posterior distribution using a Metropolis Hastings algorithm.
- For observed $S(Z)$'s, draw $\tilde{S}(Z)$'s from a truncated normal distribution, where:

$$\begin{aligned} & [\tilde{S}(0) | \tilde{S}(1), q(T(0)), q(T(1)), \Gamma, \alpha, Z=0] \sim \\ N & \left(\begin{pmatrix} \rho_s & \rho_{00} & \rho_{01} \end{pmatrix} \begin{pmatrix} 1 & \rho_{10} & \rho_{11} \\ \rho_{10} & 1 & \rho_t \\ \rho_{11} & \rho_t & 1 \end{pmatrix}^{-1} \begin{pmatrix} \tilde{S}(1) \\ q(T(0)) \\ q(T(1)) \end{pmatrix}, 1 - \begin{pmatrix} \rho_s & \rho_{00} & \rho_{01} \end{pmatrix} \begin{pmatrix} 1 & \rho_{10} & \rho_{11} \\ \rho_{10} & 1 & \rho_t \\ \rho_{11} & \rho_t & 1 \end{pmatrix}^{-1} \begin{pmatrix} \rho_s \\ \rho_{00} \\ \rho_{01} \end{pmatrix} \right) I(\alpha_{(Z)}) \\ & [\tilde{S}(1) | \tilde{S}(0), q(T(0)), q(T(1)), \Gamma, \alpha, Z=1] \sim \\ N & \left(\begin{pmatrix} \rho_s & \rho_{10} & \rho_{11} \end{pmatrix} \begin{pmatrix} 1 & \rho_{00} & \rho_{01} \\ \rho_{00} & 1 & \rho_t \\ \rho_{01} & \rho_t & 1 \end{pmatrix}^{-1} \begin{pmatrix} \tilde{S}(0) \\ q(T(0)) \\ q(T(1)) \end{pmatrix}, 1 - \begin{pmatrix} \rho_s & \rho_{10} & \rho_{11} \end{pmatrix} \begin{pmatrix} 1 & \rho_{00} & \rho_{01} \\ \rho_{00} & 1 & \rho_t \\ \rho_{01} & \rho_t & 1 \end{pmatrix}^{-1} \begin{pmatrix} \rho_s \\ \rho_{10} \\ \rho_{11} \end{pmatrix} \right) I(\alpha_{(Z)}) \end{aligned}$$

- Use the Metropolis Hastings algorithm to draw ν_{T_Z} , γ_{T_Z} , ρ_s , ρ_{00} , ρ_{01} , ρ_{10} , ρ_{11} , ρ_t from their posterior distributions. The posterior distributions for all of the parameters can be obtained from the product of the observed data

likelihood, detailed in Section 2.3 and the prior distributions, described in Section 2.4. The chain is run for a 8,000 iteration burn-in period, and then 2,000 draws from the posterior distribution of each parameter are saved. All of the proposal distributions are normal and centered at the most recent parameter draw. As the shape parameter of the Weibull distribution must be positive, the proposal distribution for γ_{TZ} is truncated at 0 and the proposal distribution for each α_{kZ} is truncated by $\alpha_{(k-1)Z}$ and $\alpha_{(k+1)Z}$. The proposal distribution for each of the correlation parameters is truncated by the bounds which results in a positive definite matrix. These bounds are determined by solving for the roots of the quadratic equation $|\Gamma| = 0$. For each parameter, the variance of the proposal distribution is adjusted so that the resulting acceptance rates are close to 40%.

5 Simulations

We conduct simulations to evaluate the performance of the above methods of surrogacy assessment. We consider three scenarios: one where S is a good principal surrogate for T , one where it is a moderately good principal surrogate, and one where it is a poor principal surrogate. In each scenario, a sample size of 300 is used with 150 subjects in each treatment arm and approximately 30% of the survival outcomes are censored. Figure 1 provides plots of the true relationship between $E[\log(T(1)/T(0)) | S(1) - S(0) = s]$ for the three surrogacy scenarios considered. In the case of a poor principal surrogate, the plot shows that $E[\log(T(1)/T(0)) | S(1) - S(0) = 0]$, the dissociative effect is greater than 0, indicative of a poor surrogate. In the moderate principal surrogate case, the dissociative effect is close to 0 and there is a moderate increasing trend in $E[\log(T(1)/T(0)) | S(1) - S(0) = s]$ as $S(1) - S(0)$ increases. For the strong principal surrogate case, the dissociative effect is very close to 0 and there is a strong increasing trend in the associative effect, $E[\log(T(1)/T(0)) | S(1) - S(0) = s]$, as $S(1) - S(0)$ increases. We first explore the sensitivity of the estimation to the plausible prior restrictions on β that are made. For each of the three different surrogacy scenarios we perform four simulations, with the estimation procedure done using each of the priors outlined in Section 2.4. This results in a total of 12 simulations, each with 200 simulated data sets. Table 1 provides the posterior means and standard deviations of the Bayesian estimates and means of the posterior standard deviations ($P\bar{SD}$). The identified parameters are not sensitive to changes in the prior specifications, while the unidentified parameters are quite sensitive to prior assumptions. The standard deviation of the Bayesian estimates is generally smaller than $P\bar{SD}$ for the unidentified parameters. Table 2 provides the means and mean squared errors (MSE) of the Bayesian estimates and the coverage rates for the causal quantities of interest, $E[\log(T(1)/T(0)) | S(1) - S(0) = s]$ and $\text{cor}(\Phi^{-1}(F_4(T(1))) - \Phi^{-1}(F_3(T(0))), \tilde{S}(1) - \tilde{S}(0))$. There is some bias in estimating these quantities, as these depend on the unidentified parameters. Prior scenarios 3 and 4 appear to perform better than scenarios 1 and 2 in terms of MSE and coverage rates, generally maintaining conservative coverage and small to moderate biases across all surrogate scenarios. Under both of these priors, the estimation procedure does reasonably well at distinguishing the validity of S as a principal surrogate. The estimates of $E[\log(T(1)/T(0)) | S(1) - S(0) = 0]$ are near 0 in the case of a moderate or strong PS, and larger when S is a poor principal surrogate. The

estimated correlation of the causal treatment effects on S and T is largest when S is a strong principal surrogate and smallest when it is a poor principal surrogate.

As an investigation of sensitivity to assumptions, two additional simulations, shown below the dashed lines, are also shown in Table 2. In the first, the estimation procedure is carried out using the beta priors of scenario four, along with the conditional independence assumption for $T(0)$ and $T(1)$ given $S(0)$ and $S(1)$, used in Gilbert and Hudgens⁸ and Zigler and Belin.⁹ This reduces the number of unidentified parameters that must be estimated from 4 to 3, as ρ_t can be written as a function of the other correlation parameters,

$\rho_t = \frac{\rho_{11}\rho_{10} + \rho_{01}\rho_{00} - \rho_s(\rho_{01}\rho_{10} + \rho_{11}\rho_{00})}{(1 - \rho_s^2)}$. In the 3 simulations considered, the true value of this conditional correlation is 0.25, 0.30, and 0.34 for the moderate, poor and strong principal surrogacy scenarios, respectively. We use the Beta priors of prior scenario 4 on the other five correlation parameters. The second additional simulation considered uses the approach proposed by Conlon et al.¹³ for multivariate normal $S(0)$, $S(1)$, $T(0)$, and $T(1)$ with beta priors on the unidentified correlation parameters. For this approach, we approximately normalize the survival outcomes by taking their log. The S values are left as integers. To obtain parameter estimates from this distribution, a Bayesian estimation approach is used, with unobserved potential outcomes imputed from the appropriate posterior distribution at each iteration of the Markov chain. Additionally, at the beginning of each iteration of the chain, death times are imputed for censored subjects. We draw a death time from the residual survival distribution, $P(\log(T(Z)) > \log(t_Z) + b \mid \log(T(Z)) > \log(t_Z), \log(T(1 - Z)), S(0), S(1), \mu, \Sigma)$, for observed censoring time $\log(t_Z)$. Non informative priors are placed on the observed parameters. Specifically, the prior for each μ is $N(0, 10^6)$, the prior for each σ is $\propto 1$, and the priors for ρ_{00} and ρ_{11} are $Unif(-1, 1)$. We place mildly informative Beta priors on the remaining partially identified parameters, ρ_s , ρ_{10} , ρ_{01} , and ρ_t . In the four scenarios considered, the simulation results under the conditional independence assumption and under the multivariate normality assumption tend to have slightly larger MSE s than those obtained using the Gaussian copula model under priors 3 and 4, indicating that when the assumptions of conditional independence or multivariate normality are not met, estimation of the principal surrogacy quantities of interest will be less efficient than under the Gaussian copula model. Web Appendix A provides plots of $E(\log(T(1) - T(0)) \mid S(1) - S(0))$ vs. $S(1) - S(0)$ for each of the simulation scenarios considered under each set of assumptions.

6 Application

We apply our estimation method to data from six clinical trials in advanced colorectal cancer²⁴ to determine whether cancer progression is a valid surrogate for overall survival. These data, along with 21 additional trials comprising four separate meta-analyses, were previously analyzed by Burzykowski et al.² where a meta-analytic surrogacy validation method was used. All six of the trials considered compared the administration of fluorouracil (5-FU) by continuous intravenous infusion (CI) to bolus administration of 5-FU. As these trials all compared the same two treatments and there were no notable differences in patient characteristics among the trials, we pool the data from these six trials in the application of our method. All together, there were 1,216 patients with 607 randomized to the 5-FU by CI arm and 609 randomized to the bolus 5-FU arm. Patients were followed with

tumor response and survival time recorded. Tumor response was defined by one of four categories: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). In our analysis, the true endpoint T is survival time, defined as the time from randomization to death from any cause and the surrogate end point S is tumor response, defined as a categorical variable with $S = 1, 2, 3, 4$ for PD, SD, PR, and CR, respectively. The binary treatment indicator for treatment Z is set to 0 for 5-FU by CI and 1 for bolus 5-FU. Tumor response was measured after approximately 3 to six months of follow-up in advance of the recorded survival time. In all six of the trials, a higher tumor response rate (combined percentage of CR and PR) was observed for the bolus 5-FU arm, with three of these attaining statistical significance. In five of the six trials the hazard ratio for overall survival between the treatment arms was less than one, but no statistically significant difference in the hazard of overall survival was found for any of the trials considered separately.

The combined observed tumor response frequencies were 52% for PD, 32% for SD, 14% for PR and 3% for CR. The response rate was higher in the treatment arm, with 20.8% responding compared to 12.8% responding in the control arm. The odds ratio for response in the treatment vs. control arm was 1.84 (95% CI: 1.35, 2.51). The median survival time was longer for those in the treatment group (12.1 months) than for those in the control group (11.3 months), with an estimated hazard ratio of 0.89 (95% CI: 0.79, 1.00) for the treatment vs. control group. Table 3 provides the means and standard deviations of $E[\log(T(1)/T(0)) | S(1) - S(0) = s]$ and of the correlation between $\Phi^{-1}(F_4(T(1))) - \Phi^{-1}(F_3(T(0)))$ and $\tilde{S}(1) - \tilde{S}(0)$ for each of the four prior scenarios described in the simulation section. We focus on the estimation done using priors 3 and 4, as these priors performed better in the simulation settings. Under these two priors, $E[\log(T(1)/T(0)) | S(1) - S(0) = 0]$ is approximately 0, indicative of a good principal surrogate, with a fairly large correlation between the causal standardized treatment effects. We would therefore conclude that tumor response appears to be a moderately good principal surrogate for overall survival. Web Appendix B provides the four by four table of $E[\log(T(1)/T(0)) | S(0), S(1)]$ for every pair of values for $S(0)$ and $S(1)$ from the estimation done using Beta priors, as well as the average fraction of the population within each of the cells across all of the iterations of the Markov chain. The assessment of principal surrogacy done here is for a single trial, but if S is a good principal surrogate, then $E[\log(T(1)/T(0)) | S(0), S(1)]$ in the 16 cells of this table should be similar in trials that consider the same S and T , but the estimated proportion of data in each cell may differ. Web Appendix C provides plots of the Kaplan-Meier survival curves for the observed data and the mean and 95% credible interval of the posterior predictive distribution from the model for each of the tumor response categories and for each treatment group. The plots suggest that the model appears to provide an appropriate fit to the data.

We compare the results obtained under the Gaussian copula model to those that would have been obtained had the data been analyzed as multivariate normal using the methods of Conlon et al.,¹³ and under the conditional independence of $T(1)$ and $T(0)$ given $S(1)$ and $S(0)$ assumption. For the multivariate normal model, to approximately normalize T , we take the log and S is kept as an ordinal variable. For this model, we use the same estimation procedure as the one carried out in the simulations under the multivariate normal model. Web Appendix D provides histograms and normal QQ plots of this data. The plots show that

the distribution of $\log(T)$ is slightly skewed and the distribution of S is clearly non-normal, indicating that the multivariate normal model is not the appropriate model to use for these data. For the conditional independence model, we use the Beta priors of prior scenario 4 for ρ_s , ρ_{00} , ρ_{11} , ρ_{01} , and ρ_{10} and calculate ρ_t as a function of these five parameters. Table 4 provides the results from analyzing the data as multivariate normal and under the conditional independence assumption. These methods of analysis would identify S as a slightly weaker principal surrogate than under the copula model, as the estimates of $E[\log(T(1)/T(0)) | S(1) - S(0) = 0]$ are a little bit larger, and the correlation between treatment effects smaller. The results also show larger standard deviations as compared to the estimates obtained from the copula model. The copula model, therefore provides more efficient estimation of the principal surrogacy quantities in this setting.

7 Discussion

In this paper, we develop a method for surrogacy assessment under the principal stratification framework for an ordinal surrogate marker and time to event final outcome. We use a Gaussian copula model to jointly model the potential surrogate outcomes and potential final outcomes, and propose quantities from this model that can be used to determine the validity of S as a surrogate marker for T . A Bayesian estimation strategy is used, allowing the use of context specific prior assumptions on the unidentified parameters to be explored in order to aid in estimation. Our simulation results suggest that the estimation procedure is able to distinguish valid principal surrogates from invalid ones.

Working within the principal stratification framework for surrogacy validation requires assumptions to be made in order to aid in the estimation of unidentified quantities. Here, we have chosen to place assumptions on the parameters of the correlation matrix of the Gaussian copula model. The assumptions placed on these parameters through the use of prior distributions seem reasonable in the principal surrogacy setting that we are considering. In the simulations, the priors that put ordering constraints on the correlations (priors 3 and 4) appeared to perform the best. In prior 3, ρ_{01} and ρ_{10} are constrained to be less than the other four correlations with probability 1. Under the Beta priors, ρ_{01} and ρ_{10} are less than the other four correlations with probability 0.8. The Beta priors could be adjusted to allow ρ_{01} and ρ_{10} to be less than the other four with a different probability. We explored this in the data application, and the results were similar to those for the Beta prior shown. Different assumptions about these parameters or about conditional relationships between the potential outcomes could be made to accommodate the context of the trial of interest and specifics of the trial setting.

We use measures of $E[\log(T(1)/T(0)) | S(1) - S(0) = s]$ and the correlation between $\Phi^{-1}(F_4(T(1))) - \Phi^{-1}(F_3(T(0)))$ and $\tilde{S}(1) - \tilde{S}(0)$ to quantify the validity of S as a principal surrogate for T . A valid principal surrogate would have $E[\log(T(1)/T(0)) | S(1) - S(0) = 0]$ near 0, indicating that there is no expected treatment effect on T when there is no treatment effect on S , $E[\log(T(1)/T(0)) | S(1) - S(0) = s]$ non 0 and increasing as the value of s increases, indicating that a treatment effect on S corresponds to a treatment effect on T , and a large correlation of $\Phi^{-1}(F_4(T(1))) - \Phi^{-1}(F_3(T(0)))$ and $\tilde{S}(1) - \tilde{S}(0)$, indicating a positive correlation of the causal treatment effects on the surrogate and on the outcome. As all three

of these measures are attributes that a valid surrogate marker should possess, they should be used in combination to provide evidence of the surrogate validity of S . The validity of S as a surrogate marker may be less certain if only one or two of the above criteria are met.

However, if the above conditions on all three measures are met, suggesting that S is a good principal surrogate, we can be more confident in claiming S to be a valid principal surrogate for T .

In our data example, we compare the results obtained using the proposed Gaussian copula model to those obtained using a multivariate normal model. While the difference is modest, the Gaussian copula model is a more appropriate model to use for data arising from a non-normal distribution, and the results show that there is some efficiency gained by fitting the more appropriate marginal distributions to the data and using the Gaussian copula than by assuming multivariate normality when it may not hold.

In our model formulation, we assume a cumulative probit model for S and a proportional hazards model with a Weibull baseline hazard function for T . The use of different parametric models for these marginal distributions could be explored. Semi-parametric or non-parametric alternatives for the marginal distributions could also be used to model the marginal distributions of S and T .

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors are grateful to Marc Buyse for providing the data. This research was supported by NIH grants CA 129102 and T32 CA 083654

References

1. Frangakis CE, Rubin DB. Principal stratification in causal inference. *Biometrics*. 2002; 58:21–29. [PubMed: 11890317]
2. Burzykowski T, Molenberghs G, Buyse M. The validation of surrogate end points by using data from randomized clinical trials: a case-study in advanced colorectal cancer. *Journal of the Royal Statistical Association, Series A*. 2004; 167:103–124.
3. Prentice RL. Surrogate endpoints in clinical trials: Definition and operational criteria. *Statistics in Medicine*. 1989; 8:431–440. [PubMed: 2727467]
4. Freedman L, Graubard B, Schatzkin A. Statistical evaluation of intermediate end-points for chronic diseases. *Statistics in Medicine*. 1992; 11:167–178. [PubMed: 1579756]
5. Buyse M, Molenberghs G, Burzykowski D, et al. The validation of surrogate endpoints in meta-analyses of randomized experiments. *Biostatistics*. 2000; 1:49–67. [PubMed: 12933525]
6. Rosenbaum P. The consequences of adjustment for a concomitant variable that has been affected by treatment. *Journal of the Royal Statistical Society, Ser B*. 1984; 147:656–666.
7. Li Y, Taylor JMG, Elliott MR. A Bayesian approach to surrogacy assessment using principal stratification in clinical trials. *Biometrics*. 2010; 66:523–531. [PubMed: 19673864]
8. Gilbert PB, Hudgens MG. Evaluating candidate principal surrogate endpoints. *Biometrics*. 2008; 64:1146–1154. [PubMed: 18363776]
9. Zigler CM, Belin TR. A Bayesian approach to improved estimation of causal effect predictiveness for a principal surrogate endpoint. *Biometrics*. 2012; 68:922–932. [PubMed: 22348277]

10. Qin L, Gilbert PB, Follmann D, et al. Assessing surrogate endpoints in vaccine trials with case-cohort sampling and the Cox model. *The Annals of Applied Statistics*. 2008; 2(1):386–407. [PubMed: 19079758]
11. Schwartz SL, Li F, Mealli F. A Bayesian semiparametric approach to intermediate variables in causal inference. *Journal of the American Statistical Association*. 2011; 106:1331–1344.
12. Bartolucci F, Grilli L. Modeling partial compliance through copulas in a principal stratification framework. *Journal of the American Statistical Association*. 2011; 106:469–479.
13. Conlon ASC, Taylor JMG, Elliott MR. Surrogacy assessment using principal stratification when surrogate and outcome measures are multivariate normal. *Biostatistics*. 2013; doi: 10.1093/biostatistics/kxt051
14. Ellenberg SS, Hamilton JM. Surrogate endpoints in clinical trials: cancer. *Statistics in Medicine*. 1989; 8:405–413. [PubMed: 2727464]
15. Torri V, Simon R, Russek-Cohen E, et al. Statistical model to determine the relationship of response and survival in patients with advanced ovarian cancer treated with chemotherapy. *Journal of the National Cancer Institute*. 1992; 84:407–414. [PubMed: 1531682]
16. Buyse M, Piedbois P. On the relationship between response to treatment and survival. *Statistics in Medicine*. 1996; 15:2797–2812. [PubMed: 8981687]
17. Molenberghs G, Geys H, Buyse M. Evaluation of surrogate end-points in randomized experiments with mixed discrete and continuous outcomes. *Statistics in Medicine*. 2011; 20:3023–3038.
18. de Leon AR, Wu B. Copula-based regression models for a bivariate mixed discrete and continuous outcome. *Statistics in Medicine*. 2011; 30:175–185. [PubMed: 20963753]
19. Rubin DB. Bayesian-inference for causal effects-role of randomization. *The Annals of Statistics*. 1978; 6:34–58.
20. Sklar A. Fonctions de répartition à n dimensions et leurs marges. *Publications de l'Institut de Statistique de L'Université de Paris*. 1959; 8:229–231.
21. Nelsen, RB. *An Introduction to Copulas*. 2. New York: Springer-Verlag; 2006.
22. Song PX. Multivariate dispersion models generated from Gaussian copula. *Scandinavian Journal of Statistics*. 2000; 27:305–320.
23. Olsson U, Drasgow F, Dorans NJ. The polyserial correlation coefficient. *Psychometrika*. 1982; 47:337–347.
24. Meta-Analysis Group in Cancer. Efficacy of intravenous continuous infusion of 5-fluorouracil compared with bolus administration in patients with advanced colorectal cancer. *Journal of Clinical Oncology*. 1998; 16:301–308. [PubMed: 9440757]

Figure 1.
Plots of $E[\log(\mathcal{T}(1))/\log(\mathcal{T}(0)) \mid \mathcal{S}(1) - \mathcal{S}(0) = s]$ for the three simulation scenarios

Table 1

Simulation Results Under Different Prior Specifications

Parameter	Prior Scenario	Poor PS			Moderate PS			Strong PS		
		True Value	Mean (SD)	PSD	True Value	Mean (SD)	PSD	True Value	Mean (SD)	PSD
$\log(\lambda_{\eta_0})$	1 ¹	2	2.01 (0.08)	0.08	2	2.01 (0.08)	0.08	2	2.00 (0.08)	0.08
	2 ²		2.01 (0.09)	0.08		2.00 (0.08)	0.08		2.01 (0.09)	0.08
	3 ³		2.01 (0.08)	0.08		2.00 (0.09)	0.08		2.01 (0.08)	0.08
	4 ⁴		2.01 (0.08)	0.08		2.02 (0.08)	0.08		2.00 (0.08)	0.08
γ_0	1	1.2	1.21 (0.10)	0.10	1.2	1.19 (0.09)	0.10	1.2	1.22 (0.11)	0.11
	2		1.18 (0.10)	0.10		1.21 (0.10)	0.10		1.20 (0.11)	0.10
	3		1.20 (0.09)	0.10		1.20 (0.11)	0.10		1.21 (0.10)	0.10
	4		1.20 (0.10)	0.10		1.22 (0.10)	0.10		1.21 (0.11)	0.10
$\log(\lambda_{\eta_1})$	1	2.5	2.51 (0.11)	0.11	2.3	2.32 (0.10)	0.10	2.3	2.31 (0.09)	0.09
	2		2.51 (0.11)	0.11		2.32 (0.10)	0.10		2.31 (0.09)	0.09
	3		2.52 (0.11)	0.11		2.31 (0.10)	0.09		2.31 (0.09)	0.10
	4		2.52 (0.12)	0.11		2.31 (0.09)	0.09		2.31 (0.09)	0.10
γ_{η}	1	1.2	1.20 (0.14)	0.13	1.2	1.21 (0.12)	0.12	1.2	1.23 (0.13)	0.12
	2		1.20 (0.13)	0.13		1.20 (0.12)	0.12		1.23 (0.12)	0.12
	3		1.20 (0.12)	0.13		1.22 (0.12)	0.12		1.22 (0.11)	0.12
	4		1.20 (0.13)	0.13		1.21 (0.11)	0.12		1.21 (0.11)	0.12
a_{01}	1	-0.67	-0.68 (0.12)	0.11	-0.67	-0.70 (0.11)	0.11	-0.67	-0.69 (0.10)	0.11
	2		-0.68 (0.11)	0.11		-0.70 (0.12)	0.11		-0.69 (0.11)	0.11
	3		-0.69 (0.11)	0.11		-0.68 (0.10)	0.11		-0.70 (0.11)	0.11
	4		-0.68 (0.11)	0.11		-0.70 (0.11)	0.11		-0.69 (0.12)	0.11
a_{02}	1	0	0.004 (0.10)	0.10	0	-0.008 (0.10)	0.10	0	0.003 (0.09)	0.10
	2		-0.002 (0.10)	0.10		0.001 (0.10)	0.10		-0.0008 (0.10)	0.10
	3		-0.01 (0.10)	0.10		0.009 (0.11)	0.10		-0.009 (0.10)	0.10
	4		0.007 (0.10)	0.10		-0.006 (0.10)	0.10		0.009 (0.11)	0.10

Parameter	Prior Scenario	Poor PS			Moderate PS			Strong PS		
		True Value	Mean (SD)	PSD	True Value	Mean (SD)	PSD	True Value	Mean (SD)	PSD
α_{03}	1	0.67	0.69 (0.11)	0.11	0.67	0.69 (0.11)	0.11	0.67	0.69 (0.11)	0.11
	2		0.68 (0.12)	0.11		0.69 (0.13)	0.11		0.69 (0.12)	0.11
	3		0.69 (0.11)	0.11		0.70 (0.11)	0.11		0.68 (0.12)	0.11
	4		0.68 (0.12)	0.11		0.68 (0.11)	0.11		0.69 (0.12)	0.11
α_{11}	1	-0.67	-0.69 (0.11)	0.11	-1.28	-1.32 (0.13)	0.14	-1.28	-1.34 (0.16)	0.14
	2		-0.69 (0.11)	0.11		-1.32 (0.14)	0.14		-1.32 (0.13)	0.14
	3		-0.69 (0.10)	0.11		-1.33 (0.15)	0.14		-1.34 (0.14)	0.14
	4		-0.68 (0.10)	0.11		-1.31 (0.14)	0.14		-1.31 (0.15)	0.14
α_{12}	1	0	0.003 (0.10)	0.10	-0.52	-0.53 (0.11)	0.11	-0.52	-0.53 (0.10)	0.10
	2		0.006 (0.10)	0.10		-0.53 (0.10)	0.11		-0.54 (0.11)	0.10
	3		-0.02 (0.10)	0.10		-0.54 (0.11)	0.11		-0.54 (0.11)	0.10
	4		-0.003 (0.10)	0.10		-0.53 (0.11)	0.11		-0.54 (0.11)	0.11
α_{13}	1	0.67	0.69 (0.11)	0.11	0.25	0.26 (0.10)	0.10	0.25	0.26 (0.10)	0.10
	2		0.68 (0.11)	0.11		0.27 (0.10)	0.10		0.26 (0.10)	0.10
	3		0.67 (0.12)	0.11		0.25 (0.10)	0.10		0.26 (0.10)	0.10
	4		0.67 (0.11)	0.11		0.26 (0.11)	0.10		0.25 (0.10)	0.10
ρ_{00}	1	0.2	0.18 (0.09)	0.08	0.6	0.58 (0.06)	0.06	0.8	0.78 (0.04)	0.04
	2		0.20 (0.08)	0.08		0.58 (0.07)	0.06		0.78 (0.04)	0.04
	3		0.20 (0.08)	0.09		0.57 (0.07)	0.06		0.78 (0.04)	0.04
	4		0.21 (0.08)	0.09		0.58 (0.06)	0.06		0.79 (0.04)	0.04
ρ_{11}	1	0.2	0.18 (0.09)	0.09	0.6	0.57 (0.07)	0.07	0.8	0.78 (0.04)	0.04
	2		0.20 (0.09)	0.09		0.58 (0.06)	0.06		0.78 (0.04)	0.04
	3		0.20 (0.09)	0.09		0.57 (0.07)	0.06		0.78 (0.04)	0.04
	4		0.20 (0.09)	0.09		0.58 (0.06)	0.06		0.78 (0.04)	0.04
ρ_s	1	0.2	0.004 (0.24)	0.35	0.4	0.0006 (0.35)	0.28	0.4	0.08 (0.37)	0.19
	2		0.41 (0.12)	0.23		0.48 (0.12)	0.21		0.47 (0.16)	0.17
	3		0.48 (0.09)	0.22		0.51 (0.08)	0.15		0.49 (0.14)	0.12

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Parameter	Prior Scenario	Poor PS			Moderate PS			Strong PS		
		True Value	Mean (SD)	PSD	True Value	Mean (SD)	PSD	True Value	Mean (SD)	PSD
ρ_{01}	4		0.22 (0.07)	0.22		0.48 (0.09)	0.20		0.57 (0.13)	0.15
	1	0.04	−0.04 (0.30)	0.33	0.3	0.005 (0.34)	0.27	0.32	0.09 (0.37)	0.18
	2		0.41 (0.15)	0.21		0.46 (0.15)	0.20		0.47 (0.18)	0.16
	3		0.05 (0.03)	0.06		0.23 (0.06)	0.12		0.33 (0.14)	0.11
ρ_{10}	4		0.12 (0.06)	0.14		0.35 (0.12)	0.19		0.53 (0.14)	0.15
	1	0.04	0.03 (0.31)	0.32	0.3	−0.003 (0.34)	0.26	0.32	0.07 (0.37)	0.18
	2		0.39 (0.13)	0.21		0.47 (0.14)	0.20		0.49 (0.17)	0.16
	3		0.05 (0.03)	0.06		0.24 (0.06)	0.12		0.33 (0.14)	0.11
ρ_t	4		0.12 (0.05)	0.14		0.35 (0.11)	0.19		0.54 (0.15)	0.15
	1	0.3	−0.01 (0.34)	0.30	0.4	−0.002 (0.36)	0.26	0.4	0.08 (0.39)	0.17
	2		0.41 (0.16)	0.20		0.46 (0.14)	0.19		0.48 (0.18)	0.15
	3		0.49 (0.11)	0.21		0.52 (0.09)	0.15		0.48 (0.15)	0.11
	4		0.34 (0.09)	0.21		0.47 (0.12)	0.18		0.57 (0.15)	0.13

1 No restrictions on ρ

2 $\rho = 0$

3 $\rho = 0$ and $\rho_{10}, \rho_{01} < \rho_s, \rho_t, \rho_{00}, \rho_{11}$

4 Beta priors

Table 2

Simulation results: Bias, variability and coverage rate of surrogacy parameters

Quantity	Prior Scenario	Poor PS				Moderate PS				Strong PS			
		True Value	Mean	MSE	95% Coverage	True Value	Mean	MSE	95% Coverage	True Value	Mean	MSE	95% Coverage
$E[\log(T(1)/T(0)) S(1) - S(0) = -3]$	1	-0.02	-0.02	0.55	0.92	-1.18	-1.60	0.85	0.86	-2.10	-2.18	0.60	0.91
	2		1.32	2.00	0.65		-0.37	1.02	0.94		-1.40	0.97	0.87
	3		-0.17	0.08	1		-1.66	0.35	1		-2.28	0.19	0.995
	4		0.18	0.12	1		-0.99	0.20	0.99		-1.33	0.98	0.88
$T(0) \perp T(1) S(0), S(1)$													
	Normal		0.38	0.24	1		-1.09	0.20	1		-1.79	0.35	1
$E[\log(T(1)/T(0)) S(1) - S(0) = -2]$	1	0.19	0.19	0.23	0.94	-0.73	-0.98	0.35	0.89	-1.39	-1.33	0.26	0.92
	2		1.04	0.82	0.64		-0.17	0.53	0.94		-0.91	0.48	0.88
	3		-0.02	0.09	0.99		-1.16	0.25	0.99		-1.47	0.07	0.995
	4		0.27	0.06	0.995		-0.68	0.10	0.995		-0.88	0.45	0.90
$T(0) \perp T(1) S(0), S(1)$													
	Normal		0.44	0.11	1		-0.77	0.11	1		-1.15	0.16	1
$E[\log(T(1)/T(0)) S(1) - S(0) = -1]$	1	0.33	0.34	0.08	0.96	-0.35	-0.47	0.14	0.93	-0.73	-0.68	0.10	0.91
	2		0.80	0.27	0.73		0.006	0.23	0.91		-0.44	0.19	0.87
	3		0.22	0.04	0.98		-0.63	0.11	0.98		-0.79	0.03	0.98
	4		0.37	0.03	0.995		-0.33	0.05	0.995		-0.43	0.17	0.88
$T(0) \perp T(1) S(0), S(1)$													
	Normal		0.52	0.07	0.98		-0.31	0.05	1		-0.55	0.07	0.995
$E[\log(T(1)/T(0)) S(1) - S(0) = 0]$	1	0.49	0.49	0.02	0.99	0.11	0.07	0.02	0.97	0.01	-0.001	0.02	0.96
	2		0.51	0.03	0.94		0.23	0.03	0.95		0.10	0.03	0.88
	3		0.51	0.02	0.98		0.06	0.01	0.98		0.004	0.01	0.96
	4		0.50	0.02	0.98		0.13	0.01	0.995		0.11	0.02	0.90

Quantity	Prior Scenario	Poor PS			Moderate PS			Strong PS		
		True Value	Mean	MSE	95% Coverage	True Value	Mean	MSE	95% Coverage	True Value
$E[\log(T(1)/T(0)) S(1) - S(0) = 1]$	$T(0) \perp T(1) S(0), S(1)$		0.53	0.02	0.98		0.13	0.02	0.99	0.04
	Normal		0.61	0.04	0.98		0.20	0.03	0.98	0.10
	1	0.69	0.65	0.08	0.95	0.52	0.55	0.02	0.99	0.64
	2		0.22	0.27	0.73		0.41	0.04	0.94	0.55
	3		0.79	0.04	0.995		0.60	0.02	0.96	0.66
$E[\log(T(1)/T(0)) S(1) - S(0) = 2]$	4		0.62	0.03	0.995		0.49	0.02	0.99	0.53
	$T(0) \perp T(1) S(0), S(1)$		0.40	0.12	0.94		0.51	0.01	1	0.61
	Normal		0.68	0.03	1		0.59	0.02	0.98	0.63
	1	0.83	0.80	0.23	0.94	0.89	1.03	0.11	0.96	1.24
	2		-0.03	0.85	0.66		0.58	0.19	0.90	0.99
$E[\log(T(1)/T(0)) S(1) - S(0) = 3]$	3		1.03	0.08	0.995		1.13	0.09	0.96	1.30
	4		0.73	0.06	1		0.85	0.05	0.99	0.95
	$T(0) \perp T(1) S(0), S(1)$		0.33	0.31	0.97		0.85	0.06	0.99	1.16
	Normal		0.75	0.06	1		0.95	0.04	1	1.11
	1	1.01	0.97	0.55	0.94	1.31	1.69	0.47	0.81	1.95
$\text{cor}(q(T(1)) - q(T(0)), q(S(1)) - q(S(0)))$	2		-0.30	1.91	0.66		0.78	0.51	0.95	1.49
	3		1.18	0.08	1		1.72	0.23	0.98	2.03
	4		0.83	0.11	1		1.25	0.11	0.99	1.42
	$T(0) \perp T(1) S(0), S(1)$		0.24	0.70	0.96		1.20	0.17	0.99	1.77
	Normal		0.83	0.12	1		1.46	0.12	1	1.77
$\text{cor}(q(T(1)) - q(T(0)), q(S(1)) - q(S(0)))$	1	0.22	0.18	0.07	0.91	0.50	0.55	0.04	0.81	0.80
	2		-0.35	0.35	0.50		0.22	0.12	0.90	0.57
	3		0.35	0.03	0.99		0.72	0.05	0.92	0.86
	4		0.14	0.02	1		0.47	0.02	1	0.57
	$T(0) \perp T(1) S(0), S(1)$		0.24	0.70	0.96		1.20	0.17	0.99	1.77
	Normal		0.83	0.12	1		1.46	0.12	1	1.77

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Quantity	Prior Scenario	Poor PS			Moderate PS			Strong PS		
		True Value	Mean	MSE	95% Coverage	True Value	Mean	MSE	95% Coverage	True Value
I	$T(0) \perp T(1) \mid S(0), S(1)$		-0.11	0.12	0.74		0.34	0.04	0.98	
	Normal		0.07	0.03	0.93		0.35	0.03	1	

¹No restrictions on ρ

² $\rho = 0$

³ $\rho = 0$ and $\rho|0, \rho01 < \rho_s, \rho_t, \rho00, \rho11$

⁴Beta priors

Table 3

Application of Method to Colorectal Cancer Data

	ρ 's unrestricted	$\rho = 0$	$\rho = 0$ and $\rho_{10}, \rho_{01} < \rho_s, \rho_t, \rho_{00}, \rho_{11}$	Beta priors
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
$E[\log(T(1)/T(0)) \mid S(1) - S(0) = -3]$	-1.09 (0.49)	-0.47 (0.74)	-1.02 (0.53)	-1.08 (0.46)
$E[\log(T(1)/T(0)) \mid S(1) - S(0) = -2]$	-0.91 (0.30)	-0.42 (0.39)	-0.79 (0.26)	-0.79 (0.20)
$E[\log(T(1)/T(0)) \mid S(1) - S(0) = -1]$	-0.67 (0.16)	-0.21 (0.21)	-0.46 (0.13)	-0.49 (0.12)
$E[\log(T(1)/T(0)) \mid S(1) - S(0) = 0]$	-0.28 (0.08)	0.01 (0.10)	-0.005 (0.06)	-0.03 (0.07)
$E[\log(T(1)/T(0)) \mid S(1) - S(0) = 1]$	0.84 (0.12)	0.43 (0.14)	0.54 (0.12)	0.66 (0.09)
$E[\log(T(1)/T(0)) \mid S(1) - S(0) = 2]$	1.74 (0.22)	0.72 (0.26)	0.96 (0.23)	1.22 (0.19)
$E[\log(T(1)/T(0)) \mid S(1) - S(0) = 3]$	2.82 (0.38)	1.08 (0.50)	1.35 (0.50)	1.75 (0.44)
$\text{cor}(q(T(1)) - q(T(0)), q(S(1)) - q(S(0)))$	0.78 (0.10)	0.31 (0.15)	0.63 (0.14)	0.84 (0.10)

Table 4

Application of Method to Colorectal Cancer Data, for $T(0) \perp T(1) \mid S(0), S(1)$ and analyzed as normal

Parameter	Normal	$T(0) \perp T(1) \mid S(0), S(1)$
	Posterior Mean (SD)	Posterior Mean (SD)
$E[\log(T(1)/T(0)) \mid S(1) - S(0) = -3]$	-0.92 (0.77)	-1.32 (1.17)
$E[\log(T(1)/T(0)) \mid S(1) - S(0) = -2]$	-0.52 (0.29)	-1.09 (0.58)
$E[\log(T(1)/T(0)) \mid S(1) - S(0) = -1]$	-0.20 (0.14)	-0.53 (0.30)
$E[\log(T(1)/T(0)) \mid S(1) - S(0) = 0]$	0.09 (0.08)	0.05 (0.08)
$E[\log(T(1)/T(0)) \mid S(1) - S(0) = 1]$	0.37 (0.11)	0.58 (0.22)
$E[\log(T(1)/T(0)) \mid S(1) - S(0) = 2]$	0.69 (0.27)	1.03 (0.44)
$E[\log(T(1)/T(0)) \mid S(1) - S(0) = 3]$	1.05 (0.56)	1.54 (0.90)
$\text{cor}(q(T(1)) - q(T(0)), q(S(1)) - q(S(0)))$	0.28 (0.12)	0.42 (0.16)