Bayesian and hierarchical Bayesian analysis of response - time data with concomitant variables

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ABSTRACT

This paper considers the Bayes and hierarchical Bayes approaches for analyzing clinical data on response times with available values for one or more concomitant variables. Response times are assumed to follow simple exponential distributions, with a different parameter for each patient. The analyses are carried out in case of progressive censoring assuming squared error loss function and gamma distribution as priors and hyperpriors. The possibilities of using the methodology in more general situations like dose-response modeling have also been explored. Bayesian estimators derived in this paper are applied to lung cancer data set with concomitant variables.

Keywords: Bayes Estimator; Bayesian Posterior Density; Gamma Prior Density (GPD); Hierarchical Bayes Estimator; Hyperprior; Noninformative Prior Quasi-Density (NPQD); Progressive Censoring; Squared Error Loss Function (SELF); Whittaker Function W s1, s2 (.).

1. INTRODUCTION

In biomedical studies, a considerable interest is laid upon developing statistical techniques for analyzing survival data which utilize information available on concomitant variables. In classical analysis of survival data, several models [1-7] are used for such situations. The usual proportional hazards (PH) regression model proposed by Cox [8] has been extensively discussed in the literature. Byar *et al.* [9] and Greenberg *et al.* [10] presented analysis of survival data assuming linear hazard model in classical set-up.

Bhattacharya *et al.* [11] discussed for the first time the problem on estimation of survival probabilities adjusting the effect of a single concomitant variable in the Bayesian framework. The present paper presents the Bayesian and hierarchical Bayesian analysis of response-time data in more general situations of more than one concomitant variables available for their effects to be adjusted. The exponential survival model

$$f(y \mid \lambda) = \lambda e^{-\lambda y} \left(0 \leq \infty; \ \lambda > 0\right), \tag{1}$$

representing the death density function (DDF) corresponding to the survival time Y is assumed. We also assume that the hazard λ for a patient under clinical investigation is linearly related to measurements on 'p' concomitant variables $x_1, x_2, \ldots, x_p$ as follows

$$\lambda = \lambda\left(t; \underset{\sim}{x}\right) = \beta_0 + \sum_{r=1}^{p} \beta_r x_r = \sum_{r=1}^{p} \beta_r x_r \left(0 < \beta_0, \beta_1, \ldots, \beta_p < \infty\right) \tag{2}$$

where $\beta_0, \beta_1, \ldots, \beta_p$ are $(p + 1)$ unknown parameters and $x_0 = 1$ is a dummy variable which is set equal to 1 for all individuals for notational symmetry. In (2) β_0 can be interpreted as the underlying hazard rate or the intercept. Of course, it is necessary that the right hand side of (2) be positive. The above hazard model can also be written as

$$\lambda\left(t; \underset{\sim}{x}\right) = \underset{\sim}{x} \ \underset{\sim}{\beta} \tag{3}$$

where $\underset{\sim}{x} = (x_0, x_1, \ldots, x_p)$ is a $1 \times (p + 1)$ vector of concomitant variables measured on the individual under clinical investigation and $\underset{\sim}{\beta} = (\beta_0, \beta_1, \ldots, \beta_p)'$ is a $(p + 1) \times 1$ vector of unknown parameters.

A natural extension of the model (2) is a dose-response model with hazard as a polynomial function of concomitant variables covering the situations wherein some concomitant variables are functions of others. In dose-response studies, Y represents the time to occurrence of a toxic response and x represents the dose metameter, the hazard can be expressed in the form (2) with $\underset{\sim}{x} = (x^0, x^1, \ldots, x^q)$ and $\underset{\sim}{\beta} = (\beta_0, \beta_1, \beta_2, \ldots, \beta_q)'$, where q is the number of stages in the dose-response phenomena.

Prentice *et al.* [12] gave specific applications of the Cox model to the analysis of dose-response experiments. The detailed account of dose-response models is available in an expository paper by Kalbfleisch *et al.* [13].

Bayesian and hierarchical Bayesian estimation of the parameters $\beta_0, \beta_1, \ldots, \beta_p$, the hazard rate, and the survival function are presented here under the assumptions of the squared error loss function (SELF) and suitable joint prior density of $(\beta_0, \beta_1, \ldots, \beta_p)$. A numerical illustration based on the model (2) is presented for survival data set on advanced lung cancer patients.

2. TOOLS AND TECHNIQUES

2.1. Model Parameters

Under the model assumptions (1) and (2), the hazard rate (HR) and the survival function (SF) are respectively given by

$$h\left(t; \underset{\sim}{x}\right) = \sum_{r=0}^{p} \beta_r x_r \qquad (4)$$

$$S \equiv S\left(t; \underset{\sim}{x}\right) = \exp\left[-\left(\sum_{r=0}^{p} \beta_r x_r\right) t\right] \qquad (t > 0) \quad (5)$$

The SF (5) gives the probability of survival of an individual with a given vector x of concomitant variables, up to time t measured from the chosen origin, which may be the start of the clinical study or the point at diagnosis.

2.2. Data Set

It is assumed that 'n' individuals enter the clinical study at different points of time and the clinical study lasts a predetermined follow-up period $t = T_0$. Let 'd' be the number of individuals responding prior to the follow-up period T_0, then the rest of individuals, say $s = (n - d)$ consist of those who are lost to follow-up at different time points during the study and those who did not respond till the end of the clinical study. This type of censoring is also known as "progressive censoring" in the literature. It is also assumed that measurements on $(p + 1)$ concomitant variables for all the patients are also available. For this situation the sample data will consist of the observation vectors $(t_j, x_{j0}, x_{j1}, \ldots, x_{jp})$, $j = 1, 2, \ldots, d$ and $(t'_k, x'_{k0}, x'_{k1}, \ldots x'_{kp})$, $k = 1, 2, \ldots, s$, where t_j denotes the time-to-response of the jth individual measured from his entry point, t'_k denotes the censored response-time of the kth individual and x_{jr} and x'_{kr}, $r = 0, 1, 2, \ldots, p$ denote r^{th} concomitant variable on the said j^{th} and k^{th} individuals respectively.

2.3. Likelihood Function

For the hazard model (2) and the Type III censored sample data set described earlier LF works out as

$$\ell\left(\underset{\sim}{\beta}\right) = \left[\prod_{j=1}^{d}\left(\beta_0 x_{j0} + \beta_1 x_{j1} + \ldots + \beta_p x_{jp}\right)\right] e^{-\sum_{r=0}^{p} \beta_r Q_r} \qquad (6)$$
$$\left(0 < \beta_0, \beta_1, \ldots, \beta_p < \infty\right)$$

where

$$Q_r = \left[\sum_{j=1}^{d} t_j x_{jr}\right] + \left[\sum_{k=1}^{s} t^{s/k} x'^{kr}\right], \qquad r = 0, 1, 2, \ldots, p \quad (7)$$

The product term in (6) can be written as a sum as

$$\prod_{j=1}^{d}\left(\beta_0 x_{j0} + \beta_1 x_{j1} + \ldots + \beta_p x_{jp}\right) = \sum {}^* S_{\underset{\sim}{m},d}\, \beta_0{}^{m_0} \beta_1{}^{m_1} \ldots \beta_p{}^{m_p} \qquad (8)$$

where $\sum^*$ is the sum over all possible combinations of $m_0, m_1, \ldots, m_p$, such that

$$\sum_{r=0}^{p} m_r = d \qquad m_r \in \left(0, 1, 2, \ldots, d\right) \qquad (9)$$

and for given $(m_0, m_1, \ldots, m_p)$, $S_{\underset{\sim}{m}}$, d has been defined in the appendix. Hence, the LF can be written as

$$\ell\left(\underset{\sim}{\beta}\right) = \sum {}^* S_{\underset{\sim}{m},d}\left\{\prod_{r=0}^{p} \beta_r{}^{m_r} e^{-\beta_r Q_r}\right\} \qquad \left(0 < \beta_0, \beta_1, \ldots, \beta_p < \infty\right) \qquad (10)$$

Throughout this paper, g and g* will be used as the generic notations for the prior and the posterior densities respectively and the loss structure will be characterized by the usual squared error loss function (SELF). We shall also use the generic notation K for the normalization constant.

3. BAYESIAN ESTIMATION OF THE MODEL PARAMETERS

Here it is assumed that prior densities of $\beta_0, \beta_1, \ldots, \beta_p$ mentioned earlier are *a priori* independent and that β_r, $r = 0, 1, 2, \ldots, p$, follows the gamma prior density with known scale and shape hyperparameters b_r and a_r respectively. For this situation, the joint prior density of $(\beta_0, \beta_1, \ldots, \beta_p)$ is given by

$$g\left(\beta_0, \beta_1, \ldots, \beta_p\right) \propto \prod_{r=0}^{p} \beta_r{}^{a_r-1} e^{-b_r \beta_r} \qquad \left(0 < \beta_0, \beta_1, \ldots, \beta_p < \infty\right) \qquad (11)$$

The Bayesian results for the non-informative prior quasi-density (NPQD) specified by

$$g\left(\beta_0, \beta_1, \ldots, \beta_p\right) = 1 \qquad \left(0 < \beta_0, \beta_1, \ldots, \beta_p < \infty\right) \quad (12)$$

are also obtained. The role of NPQD in Bayesian analysis is elucidated in a basic paper of Bhattacharya [14]. The raison d'être for priors mentioned above and details

of their use are available in Raiffa and Schlaifer [15].

On the basis of sample data set described earlier, the Bayesian posterior density of $(\beta_0, \beta_1, \ldots, \beta_p < \infty)$ is obtained by combining the LF (10) and joint prior density (11) with the help of the Bayes theorem. This works out to be

$$g*(\beta_0, \beta_1, ..., \beta_p) = K^{-1} \sum *S_{m,d} \left\{ \prod_{r=0}^{p} \beta_r^{a_r+m_r-1} e^{-\beta_r(b_r+Q_r)} \right\}$$
$$\left(0 < \beta_0, \beta_1, ..., \beta_p < \infty \right)$$
(13)

where

$$K = \sum *S_{m,d} \left\{ \prod_{r=0}^{p} \frac{\Gamma(a_r + m_r)}{(b_r + Q_r)^{a_r+m_r}} \right\}$$
(14)

From (13), the marginal posterior density of β_r $(r = 0, 1, \ldots, p)$ is given by

$$g*(\beta_r) =$$
$$K^{-1} \sum *S_{m,d} \beta_r^{a_r+m_r-1} e^{-\beta_r(b_r+Q_r)} \left\{ \prod_{r \neq u=0}^{p} \frac{\Gamma(a_u + m_u)}{(b_u + Q_u)^{a_u+m_u}} \right\}$$
(15)
$$\left(0 < \beta_r < \infty; r=0, 1, 2, ..., p \right)$$

Under the assumption of the SELF, the Bayes estimator of β_r $(r = 0, 1, 2, \ldots, p)$ and its posterior variance respectively are obtainable from the following expressions

$$\hat{\beta}_r = K^{-1} \sum *S_{m,d} \frac{(a_r + m_r)}{(b_r + Q_r)} \left\{ \prod_{u=0}^{p} \frac{\Gamma(a_u + m_u)}{(b_u + Q_u)^{a_u+m_u}} \right\}$$
(16)

$$V(\beta_r) = K^{-1} \sum *S_{m,d} \frac{(a_r + m_r)(a_r + m_r + 1)}{(b_r + Q_r)^2}$$
$$\left\{ \prod_{u=0}^{p} \frac{\Gamma(a_u + m_u)}{(b_u + Q_u)^{a_u+m_u}} \right\} - \left(\hat{\beta}_r \right)^2$$
(17)

The Bayes estimator of the SF is given by the expression:

$$\hat{S}(t;\underset{\sim}{x}) = \int_0^\infty \int_0^\infty ..\int_0^\infty \exp\left[-(\beta_0 x_0 + \beta_1 x_1 + ... + \beta_p x_p)t \right]$$
$$g*(\beta_0, \beta_1, ..., \beta_p) d\beta_0 d\beta_1..d\beta_p$$
(18)

Evaluating the above multiple integral we obtain

$$\hat{S}(t;\underset{\sim}{x}) = K^{-1} \sum *S_{m,d} \left\{ \prod_{u=0}^{p} \frac{\Gamma(a_r + m_r)}{(b_r + Q_r + x_r t)^{a_r+m_r}} \right\}$$
(19)

Similarly, the posterior variance of $\hat{S}(t;x)$ is obtained as

$$V\hat{S}(t;\underset{\sim}{x}) =$$
$$K^{-1} \sum *S_{m,d} \left\{ \prod_{u=0}^{p} \frac{\Gamma(a_r + m_r)}{(b_r + Q_r + 2x_r t)^{a_r+m_r}} \right\} - \left(\hat{S}(t;\underset{\sim}{x}) \right)^2$$
(20)

The Bayes estimator of the HR of the patient having concomitant variable vector $x = x_0, x_1, \ldots, x_p)$ is obtained as

$$\hat{h} = \sum_{r=0}^{p} x_r \hat{\beta}_r$$
(21)

where $\hat{\beta}_r$ $(r = 0, 1, 2, \ldots, p)$ is to be substituted from (16). The Bayesian results for the NPQD (12) can be obtained from those corresponding to the prior density (11) given above, by replacing $b_r = 0$, and $a_r = 1$, $r = 0, 1, 2, \ldots p$.

4. HIERARCHICAL BAYESIAN ESTIMATION OF THE MODEL PARAMETERS

In hierachical Bayes approach [16-20] a second stage prior is assumed for the unknown hyperparameter of the prior distribution assumed at the first stage. Here the hirachical Bayes (HB) estimators of the parameters: β_r $(r = 0, 1, 2, \ldots, p)$, the HR and the SF have been derived under the assumptions of the SELF and the gamma distributions as prior and hyperprior densities. At the first stage β_r $(r = 0, 1, 2, \ldots, p)$ is assumed to follow the gamma prior density.

$$g(\beta_r) = g(\beta_r | b_r) = \frac{b_r^{a_r}}{\Gamma a_r} \beta_r^{a_r-1} e^{-b_r \beta_r}$$
$$\left(0 < \beta_r < \infty; b_r, a_r > 0; a_r \text{ known} \right)$$
(22)

For the unknown scale hyperparameter b_r in (22) the following GPD as hyperprior is assumed at the second stage

$$g(b_r) = g(b_r | \rho_r, v_r) = \frac{\rho_r^{v_r}}{\Gamma v_r} b_r^{v_r-1} e^{-\rho_r b_r}$$
$$\left(0 < b_r < \infty; \rho_r, v_r > 0; \rho_r, v_r \text{ known} \right)$$
(23)

From (22) and (23) the prior pdf of β_r is obtained as

$$g(\beta_r) = \int_0^\infty g(\beta_r, b_r) db_r = \int_0^\infty g(\beta_r | b_r) g(b_r) db_r$$
(24)

Assuming *a priori* independence, the joint prior density of $(\beta_0, \beta_1, \ldots, \beta_p)$ in this case comes out to be

$$g(\beta_0, \beta_1, ..., \beta_p) \propto \left\{ \prod_{r=0}^{p} \frac{\beta_r^{a_r-1}}{(\rho_r + \beta_r)^{\rho_r}} \right\}$$
(25)

On the basis of sample data set described earlier obtained by combining the LF (10) joint prior density (25)

with the help of the Bayes theorem. This works out to be

$$g*\left(\beta_0, \beta_1, \ldots, \beta_p\right) = K^{-1}\sum *S_{m,d} \left\{ \prod_{r=0}^{p} \frac{\beta_r^{m_r+a_r-1}e^{-\beta_r Q_r}}{\left(\rho_r+\beta_r\right)^{v_r}} \right\} \quad (26)$$

where K can be computed by using the result (A.2) of the appendix as

$$K = \sum *S_{m,d} \left\{ \prod_{r=0}^{p} \frac{\Gamma\left(m_r+a_r\right)e^{\rho_r Q_r/2}\rho_r^{(\delta_1-1)/2}}{Q_r^{(\delta_1+1)/2}} \quad \frac{\delta_2^{W}}{2}, \frac{-\delta_1^{(\rho_r Q_r)}}{2} \right\}$$
$$(27)$$

where

$$\delta_1 = m_r + a_r - v_r \quad (28)$$

and

$$\delta_2 = 1 - v_r - m_r - a_r \quad (29)$$

From (26) the marginal posterior density of β_r (r = 0, 1, . . . , p) is obtained as

$$g*\left(\beta_r\right) = K^{-1}\sum *S_{m,d} A(\underset{\sim}{m}) \left\{ \frac{\beta_r^{m_r+a_r-1}e^{-\beta_r Q_r}}{\left(\rho_r+\beta_r\right)^{v_r}} \right\} \quad (30)$$

where

$$A(\underset{\sim}{m}) =$$
$$\prod_{r \neq u=0}^{d} \frac{\Gamma\left(m_u+a_u\right)e^{\rho_u Q_u/2}\rho_u^{(\delta*_1-1)/2}}{Q_u^{(\delta_1+1)/2}} \quad \frac{W_{\delta*_2}}{2}, \frac{-\delta*_1^{(\rho_u Q_u)}}{2}$$
$$(31)$$

where

$$\delta*_1 = m_u + a_u - v_u \quad (32)$$

and

$$\delta*_2 = 1 - v_u - m_u - a_u \quad (33)$$

Using the BPD (30) and the result (A.3) of the appendix, the HB estimator of β_r (r = 0, 1, 2, . . . , p) is given by

$$\tilde{\beta}_r = K^{-1}\sum *S_{m,d} B(\underset{\sim}{m})\left(m_r+a_r\right)$$
$$\left[\frac{\rho_r}{Q_r}\right]^{1/2} \frac{W_{\delta_{2-1}}}{2}, \frac{-\left(\delta_1+1\right)^{(\rho_r Q_r)}}{2} \quad (34)$$

where

$$B(\underset{\sim}{m}) = \frac{\Gamma\left(m_r+a_r\right)e^{\rho_r Q_r/2}\rho_r^{(\delta_1-1)/2}}{Q_r^{(\delta_1+1)/2}} A(\underset{\sim}{m}) \quad (35)$$

Similarly, the posterior variance of $\tilde{\beta}_r$ (r = 0, 1, 2, . . . , p) is computed as

$$V\left(\tilde{\beta}_r\right) = K^{-1}\sum *S_{m,d} B(\underset{\sim}{m})\left(m_r+a_r\right)\left(m_r+a_r+1\right)$$
$$\left\{\frac{\rho_r}{Q_r}\right\}^{1/2} \frac{W_{(\delta_2-2)}}{2}, \frac{-\left(\delta_1+2\right)^{(\rho_r Q_r)}}{2} \quad (36)$$

The HB estimator of S and its posterior variance respectively are evaluated as

$$\tilde{S}(t;\underset{\sim}{x}) =$$
$$\sum *S_{m,d} \left\{ \prod_{r=0}^{p} \frac{\Gamma\left(m_r+a_r\right)e^{\rho_r(Q_r+x_r t)}\rho_r^{(\delta_1-1)/2}}{\left(Q_r+x_r t\right)^{(\delta_1+1)/2}} \quad \frac{W_{\delta_2}}{2}, \frac{-\delta_1^{(\rho_r[Q_r+x_r t])}}{2} \right\}$$
$$(37)$$

and

$$V(\tilde{S}t;\underset{\sim}{x}) = \sum *S_{m,d}$$
$$\left\{ \prod_{r=0}^{p} \frac{\Gamma\left(m_r+a_r\right)e^{\rho_r(Q_r+2x_r t)}\rho_r^{(\delta_1-1)/2}}{\left(Q_r+2x_r t\right)^{(\delta_1+1)/2}} \quad \frac{W_{\delta_2}}{2}, \frac{-\delta_1^{(\rho_r[Q_r+2x_r t])}}{2} \right\}$$
$$-\left(\tilde{S}(t;\underset{\sim}{x})\right)^2$$
$$(38)$$

The HB estimator of the HR for the patient having concomitant variable vector $x = (x_0, x_1, \ldots, x_p)$ is given by

$$\tilde{h} = \sum_{r=0}^{p} x_r\tilde{\beta}_r \quad (39)$$

where $\tilde{\beta}_r$ (r=0, 1, 2, . . . , p) is to be substituted from (34).

5. NUMERICAL ILLUSTRATION ON LUNG CANCER PATIENTS

To illustrate the use of the model characterized by the **Eq.4**, the survival data set on 137 advanced lung cancer patients previously studied by Prentice [21] is used. Patients were randomized according to one of two chemotherapeutic agents: standard and test. To study the possible differential effects of therapy on tumor cell type, tumors were classified into four broad groups termed as squamous, small, adeno and large. The author used four covariates: performance status, time from diagnosis to study, age, and previous therapy to be denoted by x_1, x_2, x_3 and x_4 respectively. Assuming the intercept to be zero and taking noninformative prior quasi-density (NPQD) at (12) for (β_1, β_2, β_3, β_4) the Bayes estimates of the model parameters are obtained for different tumor types and the results for the standard and the test therapies are compared.

The Bayes estimates of β_1, β_2, β_3, and β_4 for different

Table 1. Estimates of model parameters for different tumor types.

| Type of therapy | i | Estimates of β_i | | | |
| | | Type of Tumor | | | |
		Squamous	Small	Adeno	Large
	1	2.331×10^{-5}	1.841×10^{-5}	3.707×10^{-5}	1.027×10^{-5}
	2	4.274×10^{-5}	6.649×10^{-5}	6.690×10^{-5}	1.010×10^{-4}
Standard	3	2.206×10^{-5}	1.484×10^{-5}	6.316×10^{-5}	1.520×10^{-5}
	4	2.091×10^{-4}	2.364×10^{-4}	8.790×10^{-3}	1.802×10^{-4}
	1	5.753×10^{-6}	3.352×10^{-5}	3.539×10^{-5}	1.739×10^{-5}
	2	5.041×10^{-5}	1.445×10^{-4}	2.934×10^{-4}	1.561×10^{-4}
Test	3	7.354×10^{-6}	6.449×10^{-5}	3.584×10^{-5}	2.116×10^{-5}
	4	6.563×10^{-5}	8.231×10^{-4}	7.890×10^{-4}	2.201×10^{-4}

Table 2. Estimates of the survival function for different tumor types.

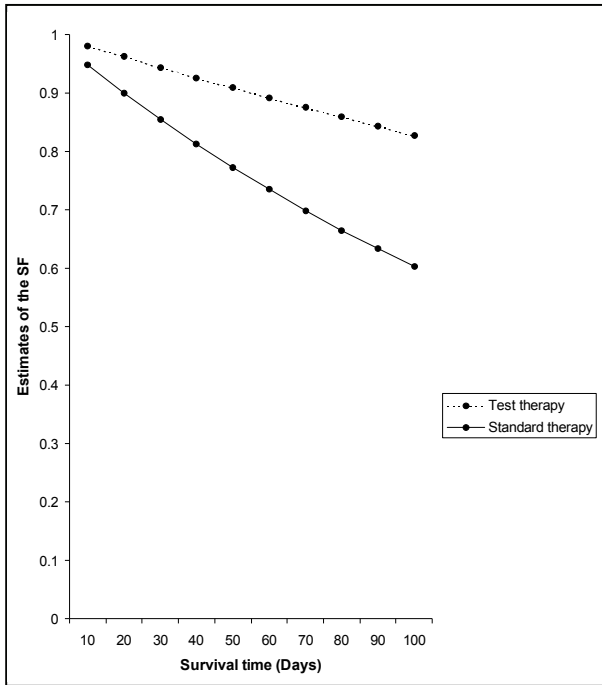| Therapy | Survival time in days | Estimates of the SF | | | |
| | | Type of Tumor | | | |
		Squamous	Small	Adeno	Large
Standard	10	0.9488	0.9515	0.4405	0.9583
	20	0.9007	0.9057	0.2426	0.9186
	30	0.8554	0.8627	0.1506	0.8810
	40	0.8128	0.8221	0.1008	0.8451
	50	0.7726	0.7837	0.0709	0.8109
	60	0.7347	0.7475	0.0518	0.7784
	70	0.6990	0.7133	0.0389	0.7475
	80	0.6653	0.6810	0.0298	0.7179
	90	0.6335	0.6504	0.0234	0.6898
	100	0.6034	0.6215	0.0185	0.6630
Test	10	0.9810	0.8580	0.8637	0.9422
	20	0.9625	0.7402	0.7497	0.8881
	30	0.9443	0.6417	0.6536	0.8376
	40	0.9265	0.5589	0.5722	0.7904
	50	0.9091	0.4887	0.5028	0.7462
	60	0.8921	0.4290	0.4434	0.7048
	70	0.8755	0.3779	0.3923	0.6660
	80	0.8592	0.3339	0.3482	0.6297
	90	0.8432	0.2960	0.3099	0.5956
	100	0.8276	0.2631	0.2765	0.5636

Figure 1. Estimates of the survival functions of standard and test therapies for 'squamous' tumor cell.

Figure 2. Estimates of the survival functions of standard and test therapies for 'small' tumor cell type.
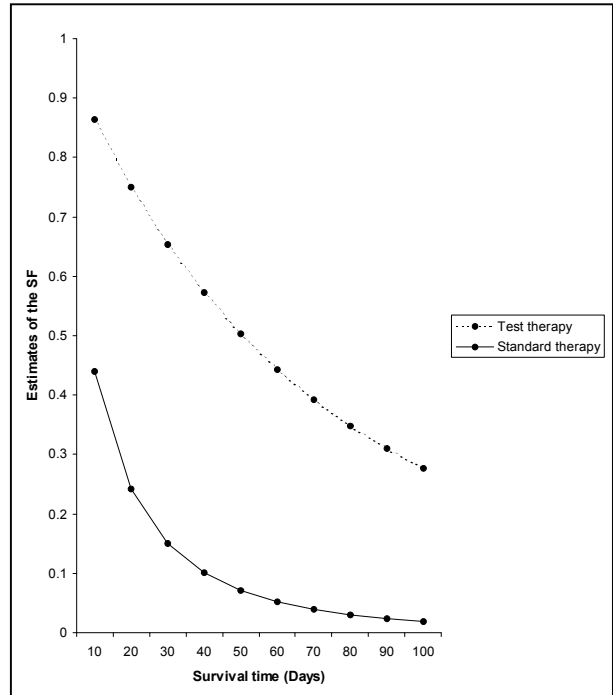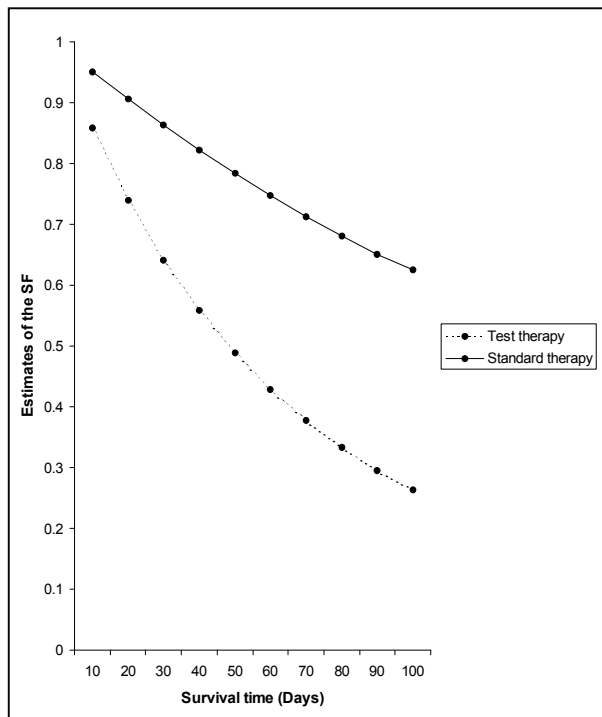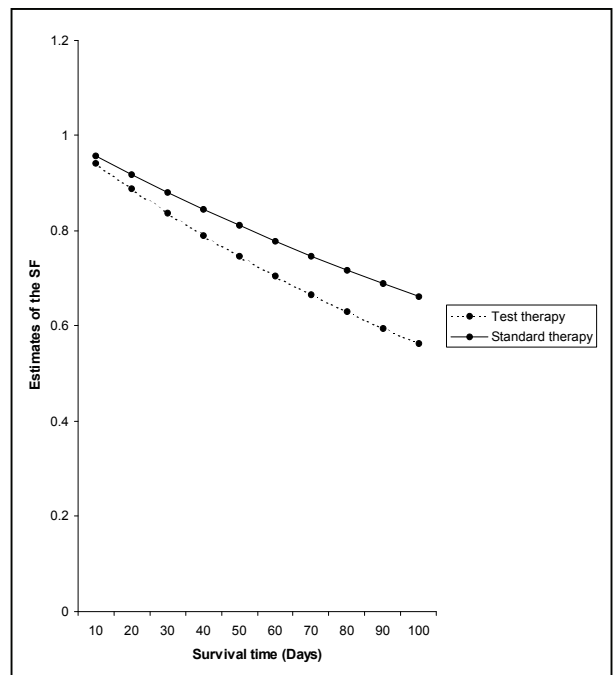

Figure 3. Estimates of the survival functions of standard and test therapies for 'adeno' tumor cell type.

Figure 4. Estimates of the survival functions of standard and test therapies for 'large' tumor cell type.

tumor types for the standard and test therapies are shown in **Table 1**. The estimates of the survival function S = S (t; x) for given vector $\underset{\sim}{x}$ = (60, 9, 63, 10) (say) of con-

comitant variables are presented in **Table 2**. **Figures 1** to **4** provide the plots of estimates of the survival function of standard and test therapies for different tumor cell types.

From the comparison of estimates for the two therapies, for given arbitrary concomitant vector $\underset{\sim}{x}$ for squamous and adeno tumor cell types, the test therapy prolong the survival of patients. The test therapy comes out to be the most effective for adeno tumor cell type for this particular case.

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APPENDIX

The definition of $S_{m,d}$ notation and a mathematical result on a special function used in the present work are presented here.

1) The $S_{m,d}$ Notation

Let X denotes a d x (p + 1) matrix of concomitant variables given below

$$X = \begin{pmatrix} x_{10} & x_{11} & ... & x_{1p} \\ x_{20} & x_{21} & ... & x_{2p} \\ & & & \\ x_{d0} & x_{d1} & ... & x_{dp} \end{pmatrix} \quad (A.1)$$

and $m = (m_0, m_1, \ldots, m_p)$. For given combinations of $m_0, m_1, \ldots, m_p$, satisfying the condition:

$$m_0 + m_1 + \ldots + m_p = d \quad (A.2)$$

$S_{m,d}$ is given by the sum of all products of m_r elements from r^{th} column (r = 0, 1, 2, . . . , p) of the matrix X, such that no two elements in the product term lie in same row of the matrix.

2) Integral for the Whittaker Function

The following variant of the integral representation ([22] p.319, Sec. 3. 383, Formula 4) has been used in the present work:

$$\int_0^\infty \frac{w^{A-1}e^{-Bw}}{(v+w)^q} \, dw = \Gamma A \, e^{Bv/2} B^{(q-A-1)/2} v^{(A-q-1)/2} W_{\frac{(1-q-A)}{2}, \frac{(q-A)}{2}} (Bv)$$

$$(A.3)$$

This results holds good provided that ReA > 0, ReBv > 0, where $W_{s_1, s_2}(.)$ is the well known Whittaker function.