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Assessing Cure Rates via Piecewise Gompertz model with Covariates

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Abstract

We modify the Gompertz regression model for estimation of cure rates from pediatric clinical trials by assuming different hazard rates on the different periods. A treatment period may be divided by the stages of treatments under the different treatment arms. The piecewise Gompertz models provide an efficient method for estimation of the cure rates and a method for testing the difference of the treatment effects in the given interval.

Key Words and Phrases: Cure rate, Piecewise Gompertz Model, Maximum likelihood Estimate(MLE)

1. Introduction

In recent years, considerable research has been conducted in censored survival analysis, where the data include the observed survival time, which may be terminated either by a failure or by a censoring, and a vector of covariates. See Kaplan and Meier(1958), Feigl and Zelen(1965), Cox(1972, 1975), Kalbfleisch(1974), Kalbfleisch and McIntosh(1977), Gray and Tsiatis(1989) and Laska and Meisner(1992).

The problem of estimating the fraction of subjects who will never do experience a particular life event such as like death or recurrence of diseases, has been discussed by several authors. For example Geiser et al.(1998) developed the method of estimating the cure rate using the maximum likelihood for the Gompertz model and compared it with using the Farewell(1982) model and the plateaus of the Kaplan-Meier curves in the presence of covariates.

Cantor and Shuster(1992) suggested a modified Gompertz approach with the hazard function

$$\lambda(t) = \alpha \exp(\beta t), \quad \alpha > 0, \quad \beta < 0,$$

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to analyze the survival data from pediatric clinical trials, since the hazard function for competing risks is virtually zero. The corresponding survival function and cure rate are respectively

$$S(t) = \exp\{\beta^{-1}\alpha(1 - \exp(\beta t)\}$$

and $\pi = \exp(\beta^{-1}\alpha)$. Because of the convexity of the log likelihood function, the parameters and the cure rate are guaranteed to be estimated by the method of maximum likelihood (Garg, Rao and Redmond(1970) and Cantor and Shuster (1992)).

In most situations the assumption of a smooth relative hazard rate is reasonable. But there are applications in survival analysis for which the smooth functions are not applicable. In pediatric cancer, we may find the hazard rates of individuals changes whenever patients receive treatment. The hazard rates might decrease after an appropriate treatment. Hence, it is reasonable to assume different hazard rates in periods between treatments. An interpretable model for this situation can be represented by a piecewise hazard rate. A partitioning of the period is automatic tool. The partitions are usually taken to be equal length(for example, six months, one year or two years), but that is not necessary because the periods when patients are under different treatments are varied. This allows easier analytic study and more flexible survival model building.

With estimating the cure rate, we are also interested in comparing the effects of treatment. In this article, we propose a piecewise parametric model that allows us to estimate the cure rates, assuming different regression coefficients in the stages between treatments under different treatment arms. We describe the model and the method of deriving the maximum likelihood estimates of regression parameters and the cure rates. Section 3 contains the aspects of the properties of the proposed model. An example illustrating the possible types of inference is presented in Section 4.

2. The piecewise Gompertz model: basic properties and maximum likelihood estimation

Suppose there are I periods and $p-1$ covariates. The hazard function of the individual in the gth treatment arm with covariate $z' = (1, z_1, \cdots, z_{p-1})$ is modeled as

$$\lambda(t : z, g) = \exp(\lambda_i{}^g t + \beta' z), \quad t \in [\tau_{i-1}, \tau_i), \quad i = 1, \cdots, I, \quad g = 1, 2 \tag{1}$$

where $t \in [\tau_{i-1}, \tau_i)$, $i = 1, \cdots, I$, is a disjoint partition of $[0, \infty)$ with $\tau_0 = 0$ and $\tau_I = \infty$.

The likelihood function for the model involves $(2I + p)$ parameters: λ_i^gs are associated with treatment arm g and the ith period. β is associated with covariates. Let R_{ig} denote the set of individuals entering interval i from treatment arm g and

let D_{ig} denote the set of individuals dying in interval i from treatment arm g. If t_l is the observed survival time of the lth individual, let t_{l_i} be the portion of interval i in which the l individual is observed as surviving,

$$t_{l_i} = \begin{cases} t_l - \tau_{i-1}, & \text{the } i\text{th individual dies or is censored in interval } i, \\ \Delta_i, & \text{the } i\text{th individual survives through interval } i \end{cases}$$

where Δ_i is the length of interval i, $\Delta_i = \tau_i - \tau_{i-1}, i = 1, \cdots, I$.

The likelihood function is then

$$\mathcal{L}(\lambda, \beta) = \prod_{i=1}^{I} \prod_{g=1}^{2} [\prod_{l \in R_{ig}} \exp\{e^{\beta' z_l} e^{\lambda_i{}^g \tau_{i-1}} (1 - e^{\lambda_i{}^g t_{l_i}}) \frac{1}{\lambda_i{}^g}\} \prod_{l \in D_{ig}} e^{\lambda_i{}^g t_l + \beta' z_l}]$$

The log-likelihood can , therefore, be written as

$$l(\lambda, \beta) = \sum_{i=1}^{I} \sum_{g=1}^{2} \{\sum_{l \in R_{ig}} e^{\beta' z_l} e^{\lambda_i{}^g \tau_{i-1}} (1 - e^{\lambda_i{}^g t_{l_i}}) \frac{1}{\lambda_i{}^g} + \sum_{l \in D_{ig}} (\lambda_i{}^g t_l + \beta' z_l)\} \tag{2}$$

The maximum likelihood estimates(MLE's) could be obtained by setting the $(2I+p)$ derivatives of $l(\lambda, \beta)$ equal to 0 and solving the resulting system of equations.

To obtain the MLE's for (λ, β), we compute the following derivatives of (2)

$$\begin{aligned} \frac{\partial l(\lambda, \beta)}{\partial \lambda_i{}^g} &= \sum_{l \in R_{ig}} \exp(\beta' z_l) \{-e^{\lambda_i{}^g \tau_{i-1}} - \frac{e^{\lambda_i{}^g (\tau_{i-1} + t_{l_i})}}{(\lambda_i{}^g)^2} \\ &\quad \times \frac{\tau_{i-1} e^{\lambda_i{}^g \tau_{i-1}} - (\tau_{i-1} + t_{l_i}) e^{\lambda_i{}^g (\tau_{i-1} + t_{l_i})}}{\lambda_i{}^g}\} + \sum_{l \in D_{ig}} t_l \end{aligned}$$

$$\frac{\partial l(\lambda, \beta)}{\partial \beta_k} = \sum_{i=1}^{I} \sum_{g=1}^{2} \{\sum_{l \in R_{ig}} z_{lk} \exp(\beta' z_l) \frac{e^{\lambda_i{}^g \tau_{i-1}} - e^{\lambda_i{}^g (\tau_{i-1} + t_{l_i})}}{\lambda_i{}^g} + \sum_{l \in D_{ig}} z_{lk}\}$$

$$\frac{\partial^2 l(\lambda, \beta)}{\partial \beta_k \partial \beta_{k'}} = \sum_{i=1}^{I} \sum_{g=1}^{2} \sum_{l \in R_{ig}} z_{lk} z_{lk'} \exp(\beta' z_l) \frac{e^{\lambda_i{}^g \tau_{i-1}} - e^{\lambda_i{}^g (\tau_{i-1} + t_{l_i})}}{\lambda_i{}^g} \tag{3}$$

From the structure (3), it is seen that (2) is a convex function of $\beta_0, \beta_1, \cdots, \beta_{p-1}$ for fixed $\lambda_i^{g'}$s.

Moreover

$$\frac{\partial^2 l(\lambda, \beta)}{\partial \lambda_i{}^g \partial \lambda_{i'}^{g'}} = 0 \quad for \quad g \neq g' \quad and \quad for \quad g = g', \quad i = i'.$$

$$\frac{\partial^2 l(\lambda,\beta)}{\partial(\lambda_i{}^g)^2} = \sum_{l\in R_{ig}} \frac{\exp(\beta' z_l)}{(\lambda_i{}^g)^3}[2(e^{\lambda_i{}^g\tau_{i-1}} - e^{\lambda_i{}^g(\tau_{i-1}+t_{l_i})}) - 2\lambda_i{}^g(\tau_{i-1}e^{\lambda_i{}^g\tau_{i-1}} - (\tau_{i-1}+t_{l_i})e^{\lambda_i{}^g(\tau_{i-1}+t_{l_i})}) + (\lambda_i{}^g)^2(\tau_{i-1}^2 e^{\lambda_i{}^g\tau_{i-1}} - (\tau_{i-1}+t_{l_i})^2 e^{\lambda_i{}^g(\tau_{i-1}+t_{l_i})})] \quad (4)$$

$$\frac{\partial l(\lambda,\beta)}{\partial\lambda_i{}^g\partial\beta_k} = \sum_{l\in R_{ig}} z_{lk}\exp(\beta' z_l)[-\frac{(e^{\lambda_i{}^g\tau_{i-1}} - e^{\lambda_i{}^g(\tau_{i-1}+t_{l_i})})}{(\lambda_i{}^g)^2}]$$

Notice that [ ] in the expression of (4) can be written as $G(x_1) - G(x_2)$ where $G(x) = 2e^x - 2xe^x + x^2e^x$, $x_1 = \lambda_i{}^g\tau_{i-1}$, $x_2 = \lambda_i{}^g(\tau_{i-1} + t_{l_i})$.

It can be shown that $G(x)$ is an increasing function. Therefore the right hand side of (4) is strictly negative. Consequently (2) is a convex function of the λ_i^g's for fixed β's.

The Newton-Raphson algorithm is one of the well-known methods to solve the system equations. However a simple and computationally preferable methods exists(Richards, 1961).

It is a 2-step procedure to compute the MLE's:

1. For fixed λ_i^g's, apply the Newton-Raphson method to find β such that Equation (2) is maximized.

2. At the value of β found in 1, apply the Newton-Raphson method to find λ_i^g's such that 1 is maximized.

Step 1 and 2 will be repeatedly applied until the desired accuracy is achieved. The advantage of this procedure is obvious. In each step, the convergence is guaranteed by the convexity of (2), which was discussed by Geiser et al.(1998). The value of the likelihood function is guaranteed to increase from one step to the next.

Note that it is possible to prove that, under mild conditions, the maximum likelihood estimates exist and are unique by the Fix Point Theorem(Friedman,1982).

To obtain asymptotic variances and covariances of the MLE's, evaluate the observed information matrix at $(\hat{\lambda},\hat{\beta})$:

$$I(\hat{\lambda},\hat{\beta}) = \begin{bmatrix} I_{11} & I_{12} \\ I_{21} & I_{22} \end{bmatrix},$$

where I_{11} is the $2I \times 2I$ diagonal matrix, whose diagonals are the negative of (4) and I_{21} is the $2I \times p$ matrix. I_{12} is the transpose matrix of I_{21} and I_{22} is the $p \times p$ matrix obtained from (3).

As usual the inverse of $I(\hat{\lambda},\hat{\beta})$ provides asymptotic variances and covarianves for the $\hat{\lambda}$'s and $\hat{\beta}$'s.

For the piecewise Gompertz model, we have

$$\lambda(t;z,g) = \exp(\lambda_i{}^g t + \beta' z), \quad t \in (\tau_{i-1}, \tau_i], \quad i = 1, \cdots, I, \quad g = 1, 2.$$

The corresponding survival function is

$$S(t;z,g) = \exp\{e^{\beta' z}(\sum_{i=1}^{k-1} \frac{e^{\lambda_i^g \tau_{i-1}} - e^{\lambda_i^g \tau_i}}{\lambda_i^g} + \frac{e^{\lambda_k^g \tau_k} - e^{\lambda_k^g t}}{\lambda_k^g})\},$$
$$for \quad \tau_{k-1} \le t < \tau_k, \quad k = 1, \cdots, I-1.$$

Assume $\lambda_I^g < 0$. By taking the limit $t \to \infty$, the cure rate corresponding to z in treatment arm g is expressed as

$$\pi(z,g) = \exp[\exp(\beta' z_l)\{\sum_{i=1}^{I-1} \frac{e^{\lambda_i{}^g \tau_{i-1}} - e^{\lambda_i{}^g \tau_i}}{\lambda_i{}^g} + \frac{e^{\lambda_I^g \tau_{I-1}}}{\lambda_I^g}\}]$$

By replacing λ_i^g's by $\hat{\lambda}_i^g$'s and β by $\hat{\beta}$, we obtain the estimator of $\pi(z,g)$. To compare the cure rates between treatment arm 1 and arm 2, we may propose comparing the averages $\hat{\pi}(z,g)$, $g = 1, 2$,

$$\hat{\pi}(z,g) = \frac{1}{N} \sum \hat{\pi}(z_l, g)$$

where the summation is over the observed covariates arising from both treatment arms. We use the difference $\hat{\pi}(z,1) - \hat{\pi}(z,2)$ as the test statistic. The delta method can be applied to obtain the standard error of $\hat{\pi}_1 - \hat{\pi}_2$ as usual.

Given the parameter estimates, the survival function is estimated as:

$$\hat{S}(t;z,g) = \exp\{e^{\hat{\beta}' z}(\sum_{i=1}^{k-1} \frac{e^{\hat{\lambda}_i^g \tau_{i-1}} - e^{\hat{\lambda}_i^g \tau_i}}{\hat{\lambda}_i^g} + \frac{e^{\hat{\lambda}_k^g \tau_k} - e^{\hat{\lambda}_k^g t}}{\hat{\lambda}_k^g})\}, \tag{5}$$
$$for \quad \tau_{k-1} \le t < \tau_k, \quad k = 1, \cdots, I-1.$$

This gives the estimated survival function at a fixed value z of the covariate vector and treatment arm g. The asymptotic variance of $\hat{S}(t;z,g)$ can be obtained by using the delta method. If we consider as a function of $(\hat{\lambda}, \hat{\beta})$, the relevant derivatives are

$$\frac{\partial \hat{S}(t;z,g)}{\partial \hat{\lambda}_i^g} = \hat{S}(t;z,g) \frac{e^{\hat{\beta}' z}}{(\hat{\lambda}_i^g)^2} \{(\tau_{i-1} e^{\hat{\lambda}_i^g \tau_{i-1}} - \tau_i e^{\hat{\lambda}_i^g \tau_i}) \hat{\lambda}_i^g - (e^{\hat{\lambda}_i^g \tau_{i-1}} - e^{\hat{\lambda}_i^g \tau_i})\}$$
$$for \quad i = 1, \cdots, k, \quad k = 1, \cdots, I-1.$$

$$\frac{\partial \hat{S}(t;z,g)}{\partial \hat{\lambda}_i^g} = \hat{S}(t;z,g)\frac{e^{\hat{\beta}'z}}{(\hat{\lambda}_{k+1}^g)^2}\{(\tau_k e^{\hat{\lambda}_{k+1}^g \tau_k} - te^{\hat{\lambda}_i^g t})\hat{\lambda}_{k+1}^g - (e^{\hat{\lambda}_{k+1}^g \tau_k} - e^{\hat{\lambda}_{k+1}^g t})\}$$
$$for \quad i = k+1 \quad \tau_k \le t < \tau_{k+1}, \quad k = 1, \cdots, I-1.$$

$$\frac{\partial \hat{S}(t;z,g)}{\partial \hat{\beta}_k} = \hat{S}(t;z,g)\log \hat{S}(t;z,g)z_k \quad for \quad \tau_k \le t < \tau_{k+1}, \quad k = 1, \cdots, I-1.$$

To compare the survival functions of patients under two different treatment arms, we propose the averages of $\hat{S}(t;z,g)$ over the observed marginal covariates arising from both treatment arms. Pooling of the two treatments provides a fairer comparison that averaging by treatment. From $\hat{\lambda}(t : z,g) = \exp(\hat{\lambda}_i^g t + \hat{\beta}'z)$, we measure the difference in hazard rates over the ith period between treatment arm 1 and 2 by $\theta_{ii} = \frac{\hat{\lambda}(t:z,1)}{\hat{\lambda}(t:z,2)}$. For testing the null hypothesis $H_0 : \log\theta_{ii} = 0$ (no difference in the effects between two treatment arms). We can use the test statistic

$$Z = \frac{\hat{\lambda}_i^1 - \hat{\lambda}_i^2}{s.e.},$$

where the denominator is the standard error of the numerator. We apply the delta method to compute this standard error. Since Z approximately follows a standard normal distribution for large sample, we conclude that the hazard rates are significantly different for large values of $|z|$.

3. Conclusions and Remarks

One of the advantages of the model (1) is to consider the different regression coefficients in the different periods. The hazard rates would be changed during the periods when patients received treatments as scheduled. This allows easier analytic study and more flexible survival model building. For a nonpiecewise model, we assume the regression coefficients are constant respective of what treatment arms patients are under and no matter what phases patients belong to.

It is important to notice that a desirable property of the model (1) is that it has log-linear hazard. As shown by Geiser et al.(1998) its log-linear property yielding the convex loglikelihood function leads to existence, uniqueness and asymptotic normality for the MLE.

In general the advantages and disadvantages of the proposed model are summarized as follows:
Advantages:

1. The proposed model is easy to implement. The maximum likelihood estimates exist and are unique. The consequence of the iterative computational procedure is guaranteed.

2. Interpretation is simple.

3. This model may fit the data better than nonpiecewise one because of its flexible nature.

4. There is considerable work on piecewise exponential models with covariates in the literature. For example, our approach is similar to Karrison(1987) and Friedman(1982).

5. Because of the stability of the computational procedure, simulation studies are feasible. For example, assuming that the underlying model is a mixed model as proposed by Farewell(1977,1982), we are able to perform simulation studies to see how well our model can asses the cure rates.

Disadvantages:

1. The cure rate is in a somewhat complicated form.

2. Similar to piecewise exponential model, the selection of intervals $[\tau_{i-1}, \tau_i)$ is arbitrary.

3. The number of parameters is larger than in other methods.

One can generalize the model by entering covariates into regressors associated with the ith period under treatment arm g via $\lambda(t; i, g) = exp[(\lambda_i^{g\prime} t + \beta')z]$ where λ and β are regression coefficients and z consists of covariates. The generalization is important, in practice when the model does not fit the data within each covariate but fits the data well within each of several strata defined as appropriate combinations of periods and covariates.

4. Example

In May of 1981, the Pediatric Oncology Group(POG) began a multi-center, prospective study of standard risk non-infant acute lymphocytic leukemia in children(ALinC). In this section, we use these data to illustrate practical uses of the proposed model, the piecewise Gompertz regression model. In this analysis that follows we include the covariates age and treatment, because there is previous evidence they are prognostic factors of survival in this patient population. Since we are interested in comparing the cure rates of male and female, we define gender as

treatment arm in the text. To dichotomize ages we use the cut point of 10 of age as this is what National Center Institute uses to define its consensus risk groups.

The variables initially included in the model are defined as follows:

$g = 1$ if male and 2 if female,

$$z_1 = \begin{cases} 1 & \text{if treatment S(standard)} \\ 0 & \text{if treatment SAM(standard plus high dose methotrexate pulses)} \end{cases}$$

$z_2 = 1$ if age $\geq$ 10.0 years and 0 if age $0.0 - 10.0$ years.

A Gompertz regression model with covariate vector $Z = (z_1, z_2)$ and treatment arm variable g is expressed as

$$\lambda(t_l; z, g) = \exp(\lambda_i{}^g t_l + \beta_0 + \beta_1 z_{1l} + \beta_2 z_{2l})$$

where t_l, z_{1l} , and z_{2l} are the observed survival time, treatment, age for the lth subject. λ_i^g is regression coefficient associated with ith interval and β's are related to sex and treatment. Since some patients had follow-up as long as 12 years, we partitioned the whole period into three sub-intervals subdivided 4 and 8 years.

There are 1125 patients with complete data included in model. Three hundred ninety patients experienced events, while the remaining 727 have censored event-free survival time, as the time from study registration until progressive disease, relapse, second malignancy, death or last contact. When we fit the data using the model, our program based on the Newton-Raphson method yields maximum likelihood estimates with convergency after only 8 iterations.

A summary of the resulting maximum likelihood estimates(MLE) and their estimated asymptotic standard errors(ASE) appears in Table 1.

The test of the null hypothesis of no treatment difference as described in (1) yields a significance level of 0.896. Thus the data does not show a significance difference between standard and standard plus high dose methotrexate pulses. So treatment has been omitted from the reduced model. But age yields a significant p-value of less than 0.0001. Table 3 shows the maximum likelihood estimates and their asymptotic standard errors resulting from the fitting the reduced model. All of estimates of yields significance levels of less than 0.0001. Age is also significantly related to survival time in the reduced model.

To compare the cure rates of male and female, we will consider the part of group who have the common covariates, since they should be compared under the same conditions. For the purpose of illustrations, consider 490 out of 1125 patients who are younger than 10 years and received by Standard . Out of 490, 246 are male and 226 are female. Table 4 shows the estimated cure rates and their asymptotic standard errors for the two gender groups. For comparison purposes we also estimated cure rates using the survival estimates and standard errors at 8 years when the plateaus of the Kaplan-Meier curves fitted to he two gender groups starts. Table 4 shows the estimated cure rates and their asymptotic standard errors of the two gender groups. The estimated cure rates are 53.65% and 68.86% for male and female respectively

using the Kaplan-Meier curves. The null hypothesis of no gender difference on cure rate under the conditions that they receive standard and are younger than 10 years yields a significance level less than 0.001. Thus we conclude that female's cure rate is considered significantly higher than male's cure rate if they are under 10 year old and treated with standard.

We note here that, the results of the piecewise Gompertz regression agree with corresponding Cox regression with the gender and the treatment. The advantage of the Gompertz approach is its provision of estimates of the cure rates.

Figure 1 shows the estimated survival curves using both Kalpan-Meier method and the piecewise Gompertz method. They show that the cure rate estimates obtained by both methods are similar. But the proposed model provides an estimate of cure rate, even though cure rate is considered after 10 years or later.

Table 1: Result of fitting Full Model

Parameter*	ML Estimate	Estimated ASE	p-value
λ_1^1	0.2809	0.0248	< 0.0001
λ_2^1	-0.1834	0.0305	< 0.0001
λ_3^1	-0.2744	0.0783	< 0.0001
λ_1^2	0.0410	0.0367	0.262
λ_2^2	-0.2923	0.0407	< 0.0001
λ_3^2	-0.3669	0.1100	< 0.0001
β_0	-2.5697	0.2213	< 0.0001
β_1	-0.0173	0.1385	0.896
β_2	0.4698	0.1657	< 0.0001

λ_i^1's are the Gompertz parameters associated with female and the i^{th} period ;
λ_i^2's are the Gompertz parameters associated with male and the i^{th} period ;
β_1 and β_2 are the parameters associated with treatment and age, respectively.

Table 2: Cox Regression

Parameter*	ML Estimate	Estimated ASE	p-value
Treatment	-0.0223	0.1003	0.8164
Age	0.5119	0.1051	< 0.0001
Gender	-0.4940	0.1009	< 0.0001

Table 3: Result of fitting Reduced Model

Parameter*	ML Estimate	Estimated ASE	p-value
λ_1^1	0.1595	0.0253	< 0.0001
λ_2^1	-0.2399	0.0307	< 0.0001
λ_3^1	-0.3109	0.0784	< 0.0001
λ_1^2	-0.0875	0.0376	< 0.0001
λ_2^2	-0.3500	0.0409	< 0.0001
λ_3^2	-0.4035	0.1101	< 0.0001
β_0	-2.2671	0.1551	< 0.0001
β_1	0.4701	0.2313	< 0.0001

λ_i^1's are the Gompertz parameters associated with female and the i^{th} period;
λ_i^2's are the Gompertz parameters associated with male and the i^{th} period ;
β_1 are the parameters associated with age.

Table 4: Estimated Cure Rates

	Estimate(Standard error) %	
Gender	Piecewise Gompertz Regression	Kaplan-Meier
Male	53.26(0.30)	53.65(3.02)
Female	65.34(0.28)	68.86(3.03)

References

1. Cantor, A. B. and Shuster, J, J. (1992). Parametric versus non-parametric methods for estimating cure rates based on censored survival data, *Statistics in Medicine,* 11, 931-937

2. Cox, D. R. (1972). Regression models and life tables(with discussion),*Journal of Royal Statistical Society,* B, 34, 187-220

3. Cox, D. R. (1975). Partial likelihood, *Biometrika,* 62, 269-276.

4. Farewell, V. T. (1977). A model for a binary variable with time-censored observations, *Biometrika,* 64,1, 43-46

5. Farewell, V. T. (1982). The use of mixture models for the analysis of survival data with long-term survivors, *Biometrics,* 38, 1041-1046

6. Figel, P. and Zelen M. (1965). Estimation of exponential survival probabilities with concomitant information, *Biometrics*, 21, 826-838

7. Friedman, M. (1982). Piecewise exponential models for survival data with covariates, *Annals of Statistics*, 10, No. 1, 101-113

8. Garg, M. L., Rao, B. R. , and Redmond, C. K. (1970). Maximum likelihood estimation of the parameters of the Gompertz survival function, *Applied Statistics*, 19, 152-159

9. Geiser, P. W., Chang, M. , P. V. Rao, Shuster, J. J. and Pullen, J. (1998). Modelling cure rates using the Gompertz model with covariate information. *Statistics in Medicine*, 17, 831-839

10. Gray, R. J. and Tsiatis, A. A. (1989). A linear rank test for use when the main interests is in cure rates, *Biometrics*, 45, 899-904.

11. Kalbfleisch, J. D. (1974). Some efficiency calculations for survival distributions, *Biometrika*, 61, 31-38.

12. Kalbfleisch, J. D. and McIntosh, A. A. (1977). Efficiency in survival distributions with time dependent covariables, *Biometrika*, 64, 47-50.

13. Kaplan, E. L. and Meier, P. (1958). Nonparmetric estimation from incomplete observations, *Journal of the American Statistical Association*, 53, 457-481

14. Karrison, T. (1987). Restricted mean life with adjustment for covariates, *Journal of American Statistical Association*, 82, 1169-1176

15. Laska, E. M. and Meisner, M. J. (1992). Nonparametric estimation and testing in a cure model, *Biometrics*, 48, 1223-1234.

16. Richards, F. S. G. (1961). A method of maximum-likelihood estimation, *Applied Statistics*, 10, 469-475