行政院國家科學委員會專題研究計畫 成果報告

以客觀貝氏參考分析卜瓦松程序於模式化復發性子宮頸癌研究成果報告(精簡版)

計 畫 類 別 ：個別型
計 畫 編 號 ：NSC 99-2628-E-040-001-
執 行 期 間 ：99 年 08 月 01 日至 100 年 07 月 31 日
執 行 單 位 ：中山醫學大學應用資訊科學學系（所）

計 畫 主 持 人：張啟昌
共 同 主 持 人：陳進典

報 告 附 件 ：出席國際會議研究心得報告及發表論文

處 理 方 式 ：本計畫涉及專利或其他智慧財產權，2 年後可公開查詢

中 華 民 國 100 年 10 月 21 日

行政院國家科學委員會補助專題研究計畫 ■成果報告 □期中進度報告

以客觀貝氏參考分析卜瓦松程序於模式化復發性子宮頸癌

Objective Bayesian Reference Analysis with the Poisson Process Model for Recurrent Cervical Carcinoma

計畫類別：■個別型計畫　□整合型計畫
計畫編號：NSC 99-2628-E-040-001-
執行期間：99 年 8 月 1 日 至 100 年 7 月 31 日

執行機構及系所：中山醫學大學應用資訊科學學系暨碩士班

計畫主持人：張啟昌
共同主持人：陳進典

成果報告類型(依經費核定清單規定繳交)：■精簡報告　□完整報告

本計畫除繳交成果報告外，另須繳交以下出國心得報告：
□赴國外出差或研習心得報告
□赴大陸地區出差或研習心得報告
■出席國際學術會議心得報告
□國際合作研究計畫國外研究報告

處理方式：除列管計畫及下列情形者外，得立即公開查詢
□涉及專利或其他智慧財產權，□一年■二年後可公開查詢

中　華　民　國　100 年　10　月　20　日

1. Introduction

The theory for survival data has been sufficiently developed to analyze the function of risk or survival of a patient. The methodology is designed to determine which variables affect the form of the risk function and to obtain estimates of these functions for each individual. This project involves the following individuals until the occurrence of some event of interest. Frequently, this event does occur for some units during the period of observation, thus producing censured data. Another characteristic of survival data is that some events of interest are not terminal, events which are able to occur more than once for the same individual, producing the recurrent events. In fact, recurrent events pervade many studies in variety of fields, and hence it is of paramount importance to have appropriate models and methods of statistical analyses.

Lifetime data where more than one event is observed on each subject arise in areas such as, manufacturing and industrial reliability, biomedical studies, criminology, demography, the event of primary interest is recurrent, so that for a given unit the event could be observed more than once during the study [13]. For example, several tumors may be observed for an individual; medical settings include outbreak of disease (e.g., encephalitis), repeated hospitalization of end-stage renal disease patients, recurrent pneumonia episodes arise in patients with human immunodeficiency syndrome; and angina pectoris in patients with chronic coronary disease. That is, the data on the *i*-th individual consists of the total number, m_i of the events observed over the time period $(0, T_i]$ and the ordered epoch of the m_i event, $0 \le t_{i1} \le t_{i2} \le t_{i3} \le \cdots \le t_{im_i} \le T_i$. Additionally, we may have covariate information on each subject defined by a vector of censoring indicators. In more studies, interest may lie in understanding and characterizing the event illustrate process for individual subject or may focus on treatment comparisons based on the time to each distinct event, the number of events, the type of events and interdependence between events. The development of statistical models based on counting process data were originally introduced by Aalen (1978) [1]. Several methodologies have been proposed to analyze the problem of recurrent events. Lawless (1982) [21] apply the Poisson process to develop models that focus on the expected number of events occurred in determined time interval. There is an extensive literature about point process models, (e.g., Cox and Isham 1980) [16]; this approach offers us tools powerful enough able to generalize several situations.

In this project the problem is treated under the focus of punctual counting process. Poisson process has been well studied many recent discussion about lifetime and stochastic process transition data have focused on modeling and analyzing the effects of so called unobserved heterogeneity. In addition, the model presented will be studied under a Bayesian perspective. It is well known that under a Bayesian perspective the posterior distribution for the quantity of interest represents the most complete inference that can be made the respect of this quantity. The posterior distribution combines the information contained in the data with the prior information about on the quantity of interest. The use of the prior function that represents lack of prior knowledge about the quantity of interest, has been a constant in the history of the Bayesian inference. Key pointers to the relevant literature include Bayes (1763) [2]. Reference analysis, introduced by Bernardo (1979) [11] and widely developed by Berger and Bernardo [5-8] is widely considered today the most successful algorithm to derive non-informative prior. In this paper, reference analysis is developed for a survival model based on proportional intensity Poisson process, where individuals may expected to experience repeated events and concomitant variables are observed. This project applied Bayesian reference analysis to an inferential problem of recurrent cervical cancer in survival analysis. A formulation is considered where individuals are expected to experience repeated events, along with concomitant variables. In addition, the sampling distribution of the observations is modeled through a proportional intensity homogeneous Poisson process. This direction will give us hopefully some additional therapy strategies for patients with recurrent cervical cancer.

2. Statement of the problem

Cervical cancer remains one of the leading causes of cancer-related death among women globally [19, 24]. Even though the morbidity and the mortality have been decreasing in recent years, the morbidity rates of cervical cancer are the second leading type in women and the mortality rates are the sixth of the top ten cancers in Taiwan. The cure rate of cervical cancer is quite high if detected early, but approximately 30% of International Federation of Gynecology and Obstetrics (FIGO) stage IB2 to stage IV disease will ultimately recur with modern multimodality treatment [20, 28]. Once the primary treatment has failed, the opportunity of secondary cure is slim. Probably several factors exist which indeed affect the ultimate prognosis of early stage cervical cancer other than clinical staging. In other words, early detection of recurrence may impact survival. Moreover, detection of asymptomatic recurrences is associated with prolonged overall survival and survival from the time of initial detection of recurrence [12]. Therefore, this project attempts to improve surveillance after treatment might lead to earlier detection of relapse, and precise assessment of recurrent status could improve outcome.

In Taiwan, cervical cancer is the second most common malignancy for women and contributing to a quarter of all female cancer cases. It remains one of the most pressing medical problems for women. The natural history of cervical cancer begins with a normal epithelium which progress through various stages of dysplasia - cervical intraepithelial neoplasia grade CIN 1, CIN 2, CIN 3 - and finally, to invasive cervical cancer (ICC). There is a long time interval for the progression to ICC, and consensus on the fact that regression occurs in CIN. The most important part of therapy is to detect and eradicate local CIN 3 lesions before the progression to ICC and metastasis can occur. In general, the Papanicolaou (Pap) smear has been used widely as the most effective screening tool for detecting precancerous cervical lesions. Though screening and treat in its early phase, cervical cancer will be decreased significantly to its rate of incidence as well as death. Because cervical cancer is a cancer which can be controlled and avoided, the studies related to the causes of and the treatment to the cervical cancer has been described sufficiently in lots of advanced researches. On the other hand, there are few researches on its relationship between recurrent events and the mortality and incidence rate. Indeed, recurrent cervical cancer is a devastating disease for those women unfortunate enough to suffer such an event. Patients with recurrent disease or pelvic metastases have a poor prognosis with a 1-year survival rate between 15 and 20% [4]. Since, the treatment of recurrent cervical cancer is still a clinical challenge. When the recurrence is not surgically resectable, and/or suitable for curative radiation, therapeutic options are limited. In some advanced countries, the combination of cisplatin and topotecan is preferred since this is the only regimen which was able to show a statistical significant improvement of overall survival (OS) (9.4 months) without impairing quality of life due to intolerable toxicity [22]. But one has to be careful, because due to a change in primary therapy since 1999, when concomitant chemotherapy and radiotherapy became standard [23, 25-27], and due to the current investigation of the role of neo-adjuvant chemotherapy (EORTC 55994 (Cochrane Database of Systematic Reviews, 2004)), most people with recurrent cervical cancer will have had some challenge with a chemotherapeutic agent. This will influence responses in secondary treatment lines and will limit comparison of new studies with older ones including more chemonaive patients. Therefore, in the absence of surgical/ radiotherapeutic indications, chemotherapy should be targeted to the prolongation of survival with minimum morbidity and to the improvement of subjective symptoms, thus preserving quality of life. Unfortunately, in these conditions, there is no evidence of a significant impact on survival or on quality of life. For these reasons, the role of chemotherapy in recurrent disease remains to be defined and the search for more active and less toxic agents must be continued.

3. Overview of Reference Analysis

The notion of a non-informative prior, that is, of a prior which describes lack of prior knowledge about the quantity of interest has been the object of many debates within the Bayesian community it is warranty that prior function which, by formal use of theorem Bayes produces a posterior distribution dominated by the information provided by the data [8, 11]. Objective reference priors do not depend on the data, but they

depend on the probabilistic model that is assumed to have generated the data, the idea basic is by allows the amount of information about an amount of interest θ, that we expect to learn how a clinical record to provide information regarding θ, is obviously a function of our prior knowledge regarding θ. Thus, if we already have a good prior knowledge of θ then we do not expect to learn much the clinical experience; on the other hand, if the prior knowledge regarding θ is scarce, then the data may be expected to provide a large amount of useful information. In other words, the bigger amount of available prior information, the lesser will be the quantity of information to be expected from the data. An infinitely larger clinical trial would eventually supply to all the information still regarding the amount of interest. Bernardo (2005) called this quantity missing information. Thus, it is natural to define a prior that determine no prior knowledge, or better, that becomes a posterior dominated for the data, as a prior that maximizes the missing information on the quantity of interest. However as missing information is defined as a limit that is not necessarily finite, the reference prior is defined as a type special of limit of a sequence of priors that maximize the expected information of successively having clinical trials. In this section we synthesize the formal construction reference priors as following [6].

3.1 One Parameter

Definition 1: Consider a clinical record ε which consists of one observation x from $p(x \mid \phi)$, $\phi \in \Phi \subset \Re$. Let $z_k = \{x_1, ..., x_k\}$ the result of k independent replications of ε.

Then, under suitable regularity conditions,

$$\pi_k(\phi) = \exp\left\{\int_{X^k} p(z_k|\phi) \log q(\phi|z_k) dz_k\right\} \tag{1}$$

where $q(\phi \mid z_k)$ is an asymptotic approximation to the posterior distribution $p(z_k \mid \phi)$.

The reference posterior distribution is a function $\pi(\phi \mid x)$ such that

$$\lim_{k\to\infty}[\int_\Phi \pi_k(\phi \mid x) \log\left\{\frac{\pi_k(\phi \mid x)}{\pi(\phi \mid x)}\right\} d\phi] = 0 \quad \text{, where } \pi_k(\phi \mid x) = \frac{p(x \mid \phi)\pi_k(\phi)}{\int_\Phi p(x\phi)\pi_k(\phi) d\phi}, \qquad k = 1,2,\ldots$$

A reference prior ϕ is a function which, for any data, provide the reference posterior $\pi(\phi \mid x)$ by formal use of Bayes theorem, i.e., a positive function $\pi(x)$ such that, for all $x \in \mathrm{X}$,

$$\pi(\phi \mid x) = \frac{p(x \mid \phi)\pi(\phi)}{\int_\Phi p(x \mid \phi)\pi(\phi) d\phi} \tag{2}$$

Thus the reference prior $\pi(\phi)$ is the limit of the sequence $\{\pi_k(\phi), k = 1,2,...\}$ defined by (1) in the precise sense that the information-type limit of the corresponding sequence of posterior distributions $\{\pi_k(\phi \mid x), k = 1,2,...\}$ is the posterior obtained from $\pi(\phi)$ by formal use of Bayes theorem.

■ Proposition 1: (Reference priors under asymptotic normality).

Let $p(x \mid \phi), x \in \mathrm{X}$, be a probability model with one real-valued parameter $\phi \in \Phi \subset \Re$. If the asymptotic posterior distribution of ϕ given k replications of the clinical record is normal, with standard deviation $S(\hat{\theta})$ such that $\hat{\phi}_k$ is an estimator consistent and asymptotically sufficient of the ϕ. In this case the reference prior is given by

$$\pi(\phi) \propto \left\{\frac{1}{S(\phi)}\right\}$$

where under regularity conditions $S(\phi) = h(\phi)^{1/2}$ and $h(\cdot)$ is the Fisher information (please refer to

Bernardo and Smith, 1994, p. 314). Notice, that in this case, the reference prior is Jeffrey's prior.

3.2 One Nuisance Parameter

Consider now the case where the statistical model $p(x|\phi,\omega)$, $(\phi,\omega)\in\Phi\times\Omega\subseteq\Re\times\Re$ contains one nuisance parameter, where the quantity of interest is ϕ, and the nuisance parameter is ω. We shall only consider here regular case where joint posterior asymptotic normality may be established.

■ Proposition 2: Let $p(x|\phi,\omega)$, $(\phi,\omega)\in\Phi\times\Omega\subseteq\Re\times\Re$ be a probability model with two real-valued parameters ϕ and ω, where ϕ is the quantity of interest, and suppose that the joint posterior distribution of (ϕ,ω) is asymptotically normal with covariance matrix $S(\hat{\phi},\hat{\omega})$, where $(\hat{\phi},\hat{\omega})$ is a consistent estimator of (ϕ,ω).Let $S(\phi,\omega)=H^{-1}(\phi,\omega)$ is information Fisher matrix.

(i). the conditional reference prior of ω is $\pi(\omega|\phi)\propto h_{22}(\phi,\omega)^{1/2}$, $\omega\in\Omega(\phi)$

(ii). if $\pi(\omega|\phi)$ is not proper, a compact approximation $\{\Omega_i(\phi),i=1,2...\}$ to $\Omega(\phi)$ is required, and the reference prior of ω given ϕ is given by $\pi_i(\omega|\phi)=\dfrac{h_{22}(\phi,\omega)^{1/2}}{\int_{\Omega_i(\phi)}h_{22}(\phi,\omega)^{1/2}d\omega}$, $\omega\in\Omega_i(\phi)$

(iii). within each $A_i(\phi)$ the marginal reference prior of ϕ is obtained as

$\pi_i(\phi)\propto\exp\{\int_{\Omega(\phi)}\pi_i(\omega|\phi)\log[s_{11}^{1/2}(\phi,\omega)]d\omega\}$ where $s_{11}^{1/2}(\phi,\omega)=h_\phi(\phi,\omega)=h_{11}-h_{12}h_{22}^{-1}h_{21}$

(iv). the reference posterior distribution of ϕ given data $\{x_1,...x_n\}$ is

$$\pi(\phi|x_1,...x_n)\propto\pi(\phi)\left\{\int_{\Omega(\phi)}[\prod_{l=1}^{n}p(x_1|\phi,\omega)]\pi(\omega|\phi)d\omega\right\}$$

■ Corollary: If the nuisance parameter space $\Omega(\phi)=\Omega$ is independent of ϕ, and the functions $s_{11}^{-1/2}(\phi,\omega)$ and $h_{22}^{1/2}(\phi,\omega)$ factorize in the form, $\{s_{11}(\phi,\omega)\}^{1/2}=f_1(\phi)g_1(\omega)$, $\{h_{22}(\phi,\omega)\}^{1/2}=f_2(\phi)g_2(\omega)$
Then $\pi(\phi)\propto f_1(\phi)$, $\pi(\omega|\phi)\propto g_2(\omega)$. The reference prior relative the parametric value ordered (ϕ,ω) is given by $\pi(\omega,\phi)=f_1(\phi)g_2(\omega)$, and in this case, there is no need for compact approximation, even if the conditional reference prior is not proper [6].

3.3 The Multiparameter Case

The approach to the nuisance parameter are considered above was based on the use of an ordered parametrization whose first and second components were (ϕ,ω), respectively, referred as the parameter of interest and the nuisance parameter. The reference prior for the ordered parametrization (ϕ,ω), was then successively constructed to obtain $\pi_\omega(\phi,\omega)=\pi(\omega|\phi)\pi(\phi)$. When the model parameter vector θ has more than two components, this sequential conditioning idea can obviously be extended by considering θ as an ordered parametrization, $\theta=(\theta_1,...,\theta_m)$, and generating, by successive conditioning, a reference prior, relative to this ordered parametrization, of the form

$$\pi(\theta)=\pi(\theta_m|\theta_1,...,\theta_{m-1})...\pi(\theta_2|\theta_1)\pi(\theta_1) \tag{3}$$

■ Proposition 3: Let $p(x|\theta)$, $\theta=(\theta_1,...,\theta_m)$ be a probability model with m real-valued parameters, let θ_1 be the quantity of interest, and suppose that the joint distribution of $(\theta_1,...,\theta_m)$ is asymptotically normal with

covariance matrix $S(\hat{\theta}_1,...,\hat{\theta}_m)$. Then, if S_j is the $j \times j$ upper matrix of S, $H_j = S_j^{-1}$ and $h_{jj}(\theta_1,...,\theta_m)$ is the (j,j) element of H_j.

(i). the conditional reference priors are $\pi(\theta_m \mid \theta_1,...,\theta_{m-1}) \propto h_{mm}(\theta_1,...,\theta_m)^{1/2}$ for $i = m-1, m-2, ...2$

$$\pi(\theta_i \mid \theta_1,...,\theta_{i-1}) \propto \exp\left[\int_{\Lambda_{i+1}} ... \int_{\Lambda_m} \log[h_{i+1,i+1}(\theta_1,...,\theta_m)^{1/2}][\prod_{j=1}^{m} \pi(\theta_j \mid \theta_1,...,\theta_{j-1})]d\theta_{i+1}\right], \text{ where } d\theta_j = d\theta_j \times ... \times d\theta_m$$

(ii). the marginal reference prior of θ_1 is $\pi(\theta_1) \propto \exp\left\{\int_{\Lambda_1} ... \int_{\Lambda_m} \log[s_{11}(\theta_1,...,\theta_m)^{-1/2}][\prod_{j=1}^{m} \pi(\theta_j \mid \theta_1,...,\theta_{j-1})]d\theta_1\right\}$

(iii). after data $\{x_1,...,x_n\}$ have been observed, the reference posterior distribution of the parameter of interest θ_1, is

$\pi(\theta_1 \mid x_1,...,x_n) \propto \pi(\theta_1) \propto \exp\left\{\int_{\Lambda_1} ... \int_{\Lambda_m} \prod_{j=1}^{m} p(x_1 \mid \theta_1,...,\theta_m)][\prod_{j=1}^{m} \pi(\theta_j \mid \theta_1,...,\theta_{j-1})]d\theta_1\right\}$, For proof and details see Berger and Bernardo (1992a, 1992b, 1992c).

4. Model Formulation

Suppose that n individuals may experience a single type of recurrent event. Let m_i denote the number of events occurring for the *i*-th individual. Assume that the *i*-th individual is observed over the interval $(0, T_i]$, where T_i is determined independently of m_i. Let $0 \le t_{i1} < t_{i2} < ... < t_{im_i} \le T_i$ where the variable of interest t_{ij} denote the continuous failure times for the i-th individual and the j-th occurrence events ($i = 1,...,n$ and $j = 1,...,m_i$). Besides that we are going to consider that individual carry a covariate vector represented by x, so data from i-th individual consist of the total number of events m_i observed about a time period $(0, T_i]$ in the ordered occurrence, $t_{i1},...,t_{im_i}$ and the covariate vector x. It is assumed that the repeated events of an individual with $k \times 1$ covariate vector x occur according to a nonhomogeneous Poisson process with intensity function given by

$$\lambda_{x_i}(t) = \lambda_0(t)\exp(x_i'\beta), t \ge 0, \text{ i = 1,2,…,n} \tag{4}$$

where $\lambda_0(t)$ is a baseline intensity function and $x_i = (x_{i1}, x_{i2},...,x_{ik})$ and $\beta = \beta_1,...,\beta_k$ is a vector of unknown parameters. The corresponding cumulative or integrated intensity function is

$$\Lambda_x(t) = \int_0^t \lambda_x(u)du = \Lambda_0(t)e^{x'\beta} \tag{5}$$

where $\Lambda_0(t) = \int_0^t \lambda_0(u)du$.

Methods of analysis will be considered semi parametric if $\lambda_0(t)$ is arbitrary, and completely parametric if $\lambda_0(t)$ is specified by a parameter vector θ. In the case of the function of baseline hazard to be constant, this is a homogeneous Poisson process (see Cox and Isham, 1980). The Poisson process model (4) is often known as Cox proportional risk model (see, Cox, 1972). Considers a parametric Poisson process where $\lambda_0(t) = \lambda_0(t;\theta)$. Then, the likelihood function for the model (4) for θ and β is given by (see, Cox and Lewis 1996),

$$L(\theta,\beta) = \prod_{i=1}^{n}\left\{\prod_{j=1}^{m_i} \lambda_{x_1}(t_{ij},\theta)\right\}\exp\left\{-\Lambda_{x_1}(T_i,\theta)\right\} \tag{6}$$

which can be decomposed as $L(\theta,\beta)=L_1(\theta)L_2(\theta,\beta)$, where $L_1(\theta)=\left\{\prod_{i=1}^{n}\prod_{j=1}^{m_i}\frac{\lambda_0(t_{ij};\theta)}{\Lambda_0(T_i;\theta)}\right\}$, and

$L_2(\theta,\beta)=\prod_{i=1}^{n}\exp\left[\Lambda_0(\theta,\beta)e^{x_i'\beta}\right]\left[\Lambda_0(T_i;\theta)e^{x_i'\beta}\right]^{m_i}$. The first likelihood kernel $L_1(\theta)$ arises from the conditional distribution of the event times, given the counts and the second the likelihood kernel $L_2(\theta,\beta)$ arises form the Poisson distribution of the counts $m_1,\ldots,m_n$.

4.1 Modeling the Baseline Hazard

The exponential distribution is one of the simplest and important probability distributions used in the modeling of data that represent the life time. It has been used intensively in the literature of survival and reliability, as for example in project areas on lifetime of items manufactured (Chang, 2008), in research involving survival or time of remission of chronic illnesses (see Feigl and Zelen, 1965). A characteristic of the exponential distribution say respect to the fact of the values next to one of the extremities of the random variable to present maximum probability and next to the other extremity to present probability zero. This characteristic is associated with a probabilistic mechanism that favors the events of higher intensity or lower. The exponential distribution has been extensively used to model the baseline hazard function due to its simplicity and flexibility. This is the particular case where

$$\lambda_0(t)=\lambda_0(t;\theta)=v \tag{7}$$

The corresponding intensity function and integrated intensity function are $\lambda_x(t)=ve^{x'\beta}$, and

$$\Lambda_x(T)=Tve^{x'\beta} \tag{8}$$

Considering the decomposition in (6) the likelihood function for v, β is given by

$$L(v,\beta)=\prod_{i=1}^{n}T_i^{-m_i}\exp[-vT_ie^{x_i'\beta}][vT_ie^{x_i'\beta}]^{m_i} \tag{9}$$

where $L_2(v,\beta)=\prod_{i=1}^{n}\exp[-vT_ie^{x_i'\beta}][vT_ie^{x_i'\beta}]^{m_i}$ is the nucleus of the regression model for which m_i has a Poisson distribution with average and variance $E(m_i\mid x_i)=Var(m_i\mid x_i)=vT_ie^{x_i'\beta}$. The log-likelihood function (9) is given by

$$l(v,\beta)\propto\sum_{i=1}^{n}m_i\log(v)+\sum_{i=1}^{n}m_ix_i'\beta-\sum_{i=1}^{n}vT_ie^{x'\beta} \tag{10}$$

Interval estimates and hypothesis tests for the parameters can be performed, in principle, by considering the asymptotic normal distribution of the maximum likelihood estimates and the asymptotic chi-squared distribution of the likelihood ratio statistics, respectively.

4.2 The Matrix of Information of Fisher Associated with the Model

The posterior distribution of the parameter is often asymptotically normal (see e.g., Bernardo and Smith, 1994, Sec.5.3). In this case, the reference prior is easily derived. If the posterior distribution is asymptotically normal, than reference prior only depends on Fisher information matrix. Considering the log of the likelihood function (10) we have the first and second derivatives given by

$$\frac{\partial l}{\partial v}=\sum_{i=1}^{n}\frac{m_i}{v}-\sum_{i=1}^{n}T_ie^{x_i'\beta}$$

$$\frac{\partial l}{\partial \beta_r} = \sum_{i=1}^{n} m_i x_{ir} - \sum v T_i x_{ir} e^{x_i'\beta} \quad , \quad \text{r} = 0,1,\ldots,\text{k}$$

$$\frac{\partial l}{\partial v^2} = -\sum_{i=1}^{n} \frac{m_i}{v^2}$$

$$\frac{\partial l}{\partial \beta_r \beta_s} = -\sum_{i=1}^{n} v T_i x_{ir} x_{is} e^{x_{1i}'\beta} \quad , \qquad \text{r , s} = 0,1,\ldots,\text{k}$$

$$\frac{\partial l}{\partial v \partial \beta_r} = -\sum_{i=1}^{n} T_i x_{ir} e^{x_i'\beta}$$

In this way, the elements of the Fisher information matrix are given by

$$I_{vv} = E[-\frac{\partial l(v,\beta)}{\partial v^2}] = \sum_{i=1}^{n} E[\sum_{i=1}^{n} \frac{m_i}{v^2}] = \frac{1}{v}\sum_{i=1}^{n} T_i e^{x_i'\beta} \quad I_{\beta_r\beta_s} = E[-\frac{\partial l(v,\beta)}{\partial \beta_r \beta_s}] = v\sum_{i=1}^{n} T_i x_{ir} x_{is} e^{x_i'\beta} \quad , \qquad \text{r , s} = 0 \text{ , } 1 \text{ , } \ldots \text{ , k}$$

$$I_{\beta_r v} = E[-\frac{\partial l(v,\beta)}{\partial \beta_r v}] = \sum_{i=1}^{n} T_i x_{ir} e^{x_i'\beta} \quad , \qquad \text{r , s} = 0 \text{ , } 1 \text{ , } \ldots \text{ , k}$$

Thus, Fisher information matrix associated with the model is given by

$$H(\theta) = H(v,\beta) = \begin{bmatrix} \frac{1}{v}\sum_{i=1}^{n} T_i e^{x_i'\beta} & \sum_{i=1}^{n} T_i x_{ir} e^{x_i'\beta} \\ \sum_{i=1}^{n} T_i x_{ir} e^{x_i'\beta} & v\sum_{i=1}^{n} T_i x_{ir} x_{is} e^{x_i'\beta} \end{bmatrix} \qquad (11)$$

5. Reference Analysis for Survival Model Parameters

Following the methodology described in section 3, now we derive the reference prior considering two potential groups (with surgically hysterectomy or not), which corresponds to the ordered partition $\{v,\beta\}$, where $\beta = \{\beta_1,\beta_2,...,\beta_k\}$ and v is considered to be the quantity of interest (to see Berger and Bernardo, 1992b). Hence the joint posterior distribution of the parameter is often asymptotically normal (see e.g., Bernardo and Smith, 1994. Sec.5.3). In this case, the reference prior is easily derived and reference prior only depends on Fisher information matrix found in (11). So the reference prior relative to this ordered parametrization is of the following form $\pi(v,\beta) = \pi(\beta \mid v)\pi(v)$. From Corollary of Proposition 3 where the nuisance parameter space $\Lambda(\beta) = \Lambda$ is independent of v, it is easy to see that

$$\pi(\beta \mid v) = |h_{22}|^{1/2} = v^{1/2}\left[\sum_{i=1}^{n} T_i x_{ir} x_{is} e^{x_i'\beta}\right]^{1/2} = f_1(v)g_1(\beta) \text{ and}$$

$$h_v(v,\beta) = h_{11} - h_{12}h_{22}^{-1}h_{21} = v^{-1/2}\left[\sum_{i=1}^{n} T_i e^{x_i'\beta} - \frac{[\sum_{i=1}^{n} T_i x_{ir} e^{x_i'\beta}]^2}{\sum_{i=1}^{n} T_i x_{ir} x_{is} e^{x_i'\beta}}\right]^{1/2} = f_2(v)g_2(\beta)$$

This implies that the conditional reference prior of the nuisance parameter β given the parameter of interest v is

$$\pi(\beta \mid v) \propto g_1(\beta) = [\sum_{i=1}^{n} T_i x_{ir} x_{is} e^{x_i'\beta}]^{1/2} \qquad (12)$$

The reference prior needed to obtain a reference posterior for the parameter of interest v is

$$\pi(v) \propto f_2(v) = v^{-1/2} \qquad (13)$$

It follows that the joint reference prior for parameters ν and β is given by

$$\pi(\nu,\beta)=\pi(\beta\,|\,\nu)\pi(\nu)\propto[\sum_{i=1}^{n}T_i x_{ir}x_{is}e^{x_i'\beta}]^{1/2}\nu^{-1/2} \tag{14}$$

The corresponding reference posterior for ν after data $T=\{t_1,...,t_n\}$ have been observed is

$$\pi(\nu|t_1,...,t_n)\propto\pi(\nu)\int_{\Lambda}L(\nu,\beta)\pi(\beta|\nu)d\beta\propto\nu^{-1/2}\int_{\Lambda}\prod_{i=1}^{n}T_i^{-m_i}\exp[-\nu T_i e^{X_i'\beta}][\nu T_i e^{X_i'\beta}]^{m_i}[\sum_{i=1}^{n}T_i x_{ir}x_{is}e^{X_i'\beta}]^{1/2}d\beta \tag{15}$$

The marginal reference posterior densities (15) cannot be obtained explicitly. We will overcome this difficulty by making use of the Markov Chain Monte Carlo (MCMC) methodology to obtain approximations for such densities. In order to make Bayesian inference for the parameters of interest ν we implement the MCMC methodology considering the Metropolis-Hastings (see, Hastings, 1970; Chib and Greenberg, 1995)

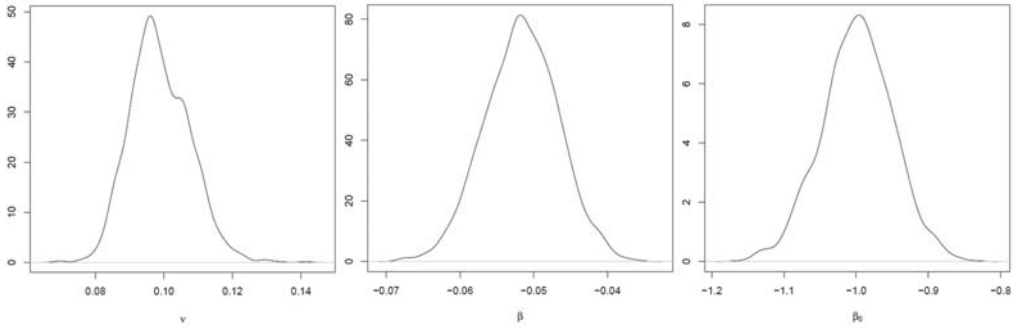
6. Example with the Cervical Cancer Data

The methodology is illustrated on cervical cancer data from the Chung Shan Medical University Hospital Tumor Registry. Each individual may experience different number of tumors. The objective of example was to compare effects of concomitant radiochemotherapy (RCTh) and radiotherapy (RTh) alone in patients with cervical cancer and with 48-months follow-up analysis. Suppose that the *i*th subject has intensity of tumors occurring according to (8). The covariate vector has just one covariate *x* indicating whether the individual *i* is in radiochemotherapy (RCTh) Group (x_i = 1) or in radiotherapy (RTh) Group (x_i = 0), for *i* = 1, … , 48. The sample for the reference posterior distributions (15) of the parameters and the regression parameters β and β_0, were obtained by the Metropolis-Hastings technique, i.e., through Markov chain Monte Carlo methods implemented in software R. The convergence of the chains were tested by using the Gelman and Rubin method (1995) implemented in CODA (Best et al., Graphical traces of those methods and kernel density estimation for each parameter showed that there were no convergence problems. We generated two chains of 30,000 iterations each for the model parameters. For each parameter we considered a sample size of 4,000 elements. In this simple two-sample problem, the results posterior for the current model are shown in the Table 1. It is important to note that there is some difference between RCTh Group and RTh Group regarding to the development of tumors indicated by the estimated β which is equal to (−0.0496). In the Fig 21, we show plots of the generated samples and the empirical marginal posteriors for model parameter ν.

Table 1 Estimated parameters of the posterior distribution

Parameters	Mean	D.P	IC(95%)
β	−0.0496	0.0050	[−0.0616 ; −0.0416]
β_0	−0.9991	0.0483	[−1.0945 ; −0.9012]
ν	0.0987	0.0081	[0.0842 ; 0.1157]

Fig 1 Density of ν, β and β_0 for the real data



7. Conclusion

In this project, we have summarized definition and derivation of reference posterior and illustrated the theory with an important example in survival analysis and we have mentioned some results which may be used to substantiate the claim that they constitute the more promissing avaliable method to derive non-subjective prior distributions. The same technique can be developed for other parameter of interest in the model. In simulation studies we know the true value of the parameter and so we can compare the approaches to see which one is more accurate in estimating the parameters of the model. In this problem, we observe that the obtained marginal reference posterior distribution showed to be adequate for estimating the parameter of interest. Response to therapy did not differ in both examined groups in this study. In our study we confirmed that the lack of response to initial therapy, whatever treatment scheme was used, depended on clinical stage of cervical cancer, which appeared to be the main prognostic factor.

[1] Aalen, O.O. Nonparametric inference for a family of counting processes, The Annals of Statistics, 1978, 6, 701–726.

[2] Bayes, T. 1763. An essay toward solving a problem in the doctrine of chances.Published posthumously in Phil. Trans. Roy. Soc. London 53, 370–418 and 54, 296–325. Reprinted in Biometrika 45 (1958), 293–315, with a biographical note by G. A. Barnard.

[3] Laplace, P. S. (1812). Th´eorie Analytique des Probabilit´ıes. Paris: Courcier. Reprinted as Oeuvres Compl´etes de Laplace 7, 1878–1912. Paris: Gauthier-Villars.

[4] Berek, J. S. and Hacker, N. F. Practical gynaecologic oncology. New York: Lippincott Williams & Wilkins 2005.

[5] Berger, J. O. and Bernardo, J. M. On the development of reference priors. Bayesian Statistics 1992c; 4 (J. M. Bernardo, J. O. Berger, A. P. Dawid and A. F. M. Smith, eds.) Oxford: University Press, 35-60 (with discussion).

[6] Berger, J. O. and Bernardo, J. M. Ordered group reference priors with applications to a multinomial problem. Biometrika. 1992a; 79:25-37.

[7] Berger, J. O. and Bernardo, J. M. Reference priors in a variance components problem. Bayesian Analysis in Statistics and Econometrics (P. K. Goel and N. S. Iyengar, eds.) Berlin: Springer, 1992b; 323–340.

[8] Berger, J. O., Bernardo, J. M., and Sun, D. Reference priors from first principles: A general definition. 2005 Tech. Rep., SAMSI, NC, USA.

[9] Bernardo, J. M. and Smith, A. F. M. Bayesian Theory. Chichester: Wiley 1994.

[10] Bernardo, J. M. Reference analysis. Handbook of Statistics 2005; 25 (D. K. Dey and C. R. Rao eds.). Amsterdam: Elsevier, 17-90

[11] Bernardo, J. M. Reference posterior distributions for Bayesian inference. J. Roy. Statist. Soc. 1979; B 41, 113-147 (with discussion).

[12] Bodurka-Bevers, D., Morris, M., Eifel, P. J., et al. Posttherapy surveillance of women with cervical cancer: an outcomes analysis. Gynecol Oncol. 2002; 78:187-193.

[13] Chang, C. C. and Cheng, C. S. A Structural Design of Clinical Decision Support System for Chronic Diseases Risk Management. CEJ Med. 2007; 2(2):129-139.

[14] Chang, C. C. Bayesian Value of Information Analysis with Linear, Exponential, Power law Failure Models for Aging Chronic Diseases JCSE. 2008; 2(2): 201-220.

[15] Cochrane Database of Systematic Reviews. Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration (NACCCMA) Collaboration. Neoadjuvant chemotherapy for locally advanced cervix cancer. John Wiley & Sons 2004.

[16] Cox, D. R. and Isham, V. Point Process, London: Chapman & Hall 1980.

[17] Cox, D. R. Regression models and life tables (with discussion), J. Roy. Statist. Soc. 1972; B 34: 187-220.

[18] Feigl, P. and Zelen, M. Estimation of exponential survival probabilities with concomitant Information. Biometrics 1965; 21:826-837.

[19] Goldie, S. J., Kuhn, L., Denny, L., Pollack, A. and Wright, T. Policy analysis of cervical cancer screening strategies in low-resource setting: clinical benefits and cost effectiveness. JAMA. 2001; 285:3107-3115.

[20] Lai, C. H., Hong, J. H., Hsueh S, et al. Preoperative prognostic variables and the impact of postoperative adjuvant therapy on the outcomes of stage IB or II cervical cancer patients with or without pelvic lymph node metastases. Cancer. 1999; 85:1537-1546.

[21] Lawless, J. F. Statisctical Models and Methods for Life Time Data. New York: Jonh Wiley 1982.

[22] Long III, H. J., Bundy, B. N., Grendys, E. C., Benda, J. A., McMeekin, D. S. and Sorosky, J., et al. Randomized phase III trial of cisplatin with or without topotecan in cancer of the uterine cervix: a Gynecologic Oncology Group Study. J Clin Oncol. 2005; 23(21):4626-33.
[23] Morris, M., Eifel, P. J., Lu, J., Grigsby, P. W., Levenback, C. and Stevens, R. E., et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med. 1999; 340(15):1137-43.
[24] Parkin, D. M., Bray, F. I. and Devesa, S. S. Cancer burden in the year 2000: the global picture. Eur J Cancer. 2001; 37 (suppl):S4-S66.
[25] Pearcey, R., Brundage, M., Drouin, P., Jeffrey, J., Johnston, D. and Lukka, H., et al. Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. J Clin Oncol. 2002; 20(4):966-72.
[26] Peters III, W. A., Liu, P. Y., Barrett, R. J., Stock, R. J., Monk, B. J. and Berek, J. S., et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol. 2000; 18(8):1606-13.
[27] Rose, P. G., Bundy, B. N.,Watkins, E. B., Thigpen, J. T., Deppe, G. and Maiman, M. A., et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med. 1999; 340(15):1144-53.
[28] Waggoner, S. E. Cervical cancer. Lancet. 2003; 361:2217-2225.

【計畫成果自評】

目標達成度：100%

學術價值：針對 One Parameter，One Nuisance Parameter，the Multi-parameter Case 的命題推導以及 Baseline Hazard 模擬，並完成以客觀貝氏參考分析卜瓦松程序於模式化復發性子宮頸癌。(出席印度 43 屆作業研究年會，並獲得最佳論文獎與 short list 推薦至期刊；計畫結果已整理投稿 Central European Journal of Operations Research/SCI)

臨床價值：為了反應學術價值，在臨床上不同治療方式的差異，我們蒐集放射化療與雷射治療法二個群別樣本在復發的徵候表現；根據共同主持人陳進典副院長以及醫院婦癌專家的嚴格審視，顯示本研究模式成果在不同的期別可以反應有不同的預後效果。(臨床發現已整理投稿 Archives of Medical Science /SCI)

後續研究發展：在學術理論部分：本研究模式的進一步發展可以針對參數不同的假設以推論不同的非主觀事前機率分配。在臨床實務部分：可以根據本研究模式為基底，進一步考慮研究放射劑量、腫瘤復發位置以及是否為非骨盆內移轉等因素加以研究其經濟效益。

計畫執行感言：對於任何的疾病言，預防勝於治療。換言之，有效監控評估子宮頸癌防治措施以及定期評估與監測機制，是現今世衛組織在疾病預防任務中重要的品質管控指標之一，也是世界各國新興的潮流與趨勢。相較於歐美國家，台灣的子宮頸癌發生率有偏高現象，因此如何運用整合的篩檢模式是現階段台灣所面臨的新問題，也是最值得努力的方向。

由近幾年醫學文獻發展的趨勢與臨床實務上的需求，作業研究方法將逐漸扮演重要的角色。由於跨領域的過程式相當艱辛，且涉及許多醫學專業的知識，本研究之成果受益於任職單位附屬醫院資源以及婦癌專家團隊的支持，更重要的是本學門審查委員們的青睞得以完成。展望未來研究生涯，將持續爭取國家研究經費補助以及獲得國內各醫療院所合作的機會與資源，自許成為工程處工業工程學門在醫療決策領域專家，並成為工業工程學門之研究主力；此外，藉由出席國際會議與論文發表等管道建立各種國際合作研究，以提升個人學術與台灣在醫療決策領域的國際地位。

國科會補助專題研究計畫項下出席國際學術會議心得報告

日期：99 年 12 月 20 日

計畫編號	**NSC99-2628-E-040-001-**		
計畫名稱	以客觀貝氏參考分析卜瓦松程序於模式化復發性子宮頸癌		
出國人員姓名	張啟昌	服務機構及職稱	中山醫學大學應用資訊科學學系 助理教授
會議時間	99 年 12 月 15 日至 99 年 12 月 17 日	會議地點	印度 madurai
會議名稱	43rd Annual Convention of Operational Research Society of India		
發表論文題目	Bayesian Inference for Cervical Carcinoma Cancer in Survival Analysis		

一、參加會議經過

2010年43rd Annual Convention of Operational Research Society of India年會在印度馬度賴市Thiagarajar College of Engineering召開。本次研討會的主題為Operational Research for Urban and Rural Development。 本次的年會為期三天，今年年會的主軸是針對作業研究在企業、工業以及醫療服務產業的應用與比較城鄉之間的差距，會議的第一天主要是召開Multi Criteria Decision Making (MCDM) techniques的workshop展開，而後從第二天下午開始則是presentation sections的行程，所有的作者一一上台報告今年最新發表的論文；而在各個Session、Workshop間則是會有許多的Keynote speech以及 Panel Discussion，讓世界各國的學者都可以參與主題的討論，做學術上的交流。在議程的安排，大會將一些業界的現今的作業研究應用進行座談可謂是一項與其他國際學術研討會最大與最有貢獻的特色。筆者的發表論文題目為 “Bayesian Inference for Cervical Carcinoma Cancer in

Survival Analysis”，許多學者前來詢問台灣的健保制度，並針對個人的研究展示高度的興趣。

二、與會心得

這是我第九次出國參加國際學術研討會，以往參與的研討會僅是發表自己的論文與傾聽國外學者的研究報告與分享經驗。此次得以出國參加學術研討會，以我個人而言，可以直接談論跨國際研究的合作事宜，收穫非常豐碩。

三、攜回資料名稱及內容

攜回資料名稱及內容（附件：與會手冊封面、論文暨海報發表時程等影本）43rd Annual Convention of Operational Research Society of India 年會大會手冊，內容包括研討會宗旨、大會議程、發表之論文摘要等相關資訊。

接受函

Dear Sir,

Sub: Your abstract has been accepted for presentation in ORSI 2010 conference

Abstract No: **OR 058**

Title: **Bayesian Inference for Cervical Carcinoma Cancer in Survival Analysis**

Dear Author Prof. Chi-Chang Chang

Thanks for submitting your abstract to ORSI 2010 conference.

We are pleased to inform that your Abstract titled "**Bayesian Inference for Cervical Carcinoma Cancer in Survival Analysis**" has been accepted for presentation. The abstract has been reviewed by three eminent experts.

The format for submitting full paper is attached with this email. The maximum page length is 8.

Please remember to submit the full paper along with registration form and demand draft on or before 17/10/2010.

Kindly send a soft copy of full paper as per the format and a copyright declaration form (attached) to emails (orsi2010@tce.edu and orsiorurd2010@gmail.com) a hardcopy to the Conference Secretary,

ORSI-2010-ORURD, Department of Mechanical Engineering, Thiagarajar College of Engineering, Madurai - 625015

In the meantime, please do not hesitate to contact us, if you have any queries.

Kind regards

Dr. SP. Nachiappan / Dr. K. Chockalingam

Conference secretary – ORSI -2010-ORURD

Department of Mechanical Engineering, Thiagarajar College of Engineering,

Madurai – 625015

orsi2010@tce.edu / orsiorurd2010@gmail.com. Web:www.tce.edu/orurd2010

Payment Details:

Category	Before 15th November	After 15th November
ORSI Member	Rs.2500	Rs.3500
Non-ORSI Member	Rs.3500*	Rs.4500*
Foreign Delegate	USD 250	USD300
Student Delegate		
*Domestic	Rs.1500	Rs.2000
*Foreign	USD100	USD150

(DD should be drawn in favour of "THE PRINCIPAL, THIAGARAJAR COLLEGE OF ENGINEERING", Payable at Madurai)

Bayesian Inference for Cervical Carcinoma Cancer in Survival Analysis

Chi-Chang Chang [*1], Gin-Den Chen[2], Su-Hsin Chang[3]

[1]*School of Applied Information Sciences, Chung Shan Medical University and Information Technology Office, Chung Shan Medical University Hospital, Taichung, Taiwan*

[2]*School of Medicine, Chung Shan Medical University and Cancer Treatment Prevention Center, Chung Shan Medical University Hospital, Taichung, Taiwan*

[3]*Department of Economics, Washington University in St. Louis, MO, USA*

[*1]threec@csmu.edu.tw

***Abstract*— All cancers are usually classified further according to the extent or stage of disease so that therapies may be tailored to the particular disease stage. Moreover, detection of asymptomatic recurrences is associated with prolonged overall survival and survival from the time of initial detection of recurrence. This project will applies Bayesian reference analysis, widely considered as the most successful method to produce objective, model-based, posterior distributions, to an inferential problem of recurrent cervical carcinoma in survival analysis. A formulation is considered where individuals are expected to experience repeated events, along with concomitant variables. In addition, the sampling distribution of the observations is modeled through a proportional intensity homogeneous Poisson process. The medical records and pathology were accessible by the Chung Shan Medical University Hospital Tumor Registry. Finally, this study attempts to improve surveillance after treatment might lead to earlier detection of relapse, and precise assessment of recurrent status could improve outcome.**

***Keywords*—Reference Analysis, Recurrent Cervical Carcinoma, Poisson process, Bayesian Inference**

I. INTRODUCTION

The theory for survival data has been sufficiently developed to analyze the function of risk or survival of a patient. The methodology is designed to determine which variables affect the form of the risk function and to obtain estimates of these functions for each individual. This papaer involves the following individuals until the occurrence of some event of interest. Frequently, this event does occur for some units during the period of observation, thus producing censured data. Another characteristic of survival data is that some events of interest are not terminal, events which are able to occur more than once for the same individual, producing the recurrent events. In fact, recurrent events pervade many studies in variety of fields, and hence it is of paramount importance to have appropriate models and methods of statistical analyses.

Lifetime data where more than one event is observed on each subject arise in areas such as, manufacturing and industrial reliability, biomedical studies, criminology, demography, the event of primary interest is recurrent, so that for a given unit the event could be observed more than once during the study (Chang and Cheng, 2007). For example, several tumors may be observed for an individual; medical settings include outbreak of disease (e.g., encephalitis), repeated hospitalization of end-stage renal disease patients, recurrent pneumonia episodes arise in patients with human immunodeficiency syndrome; and angina pectoris in patients with chronic coronary disease. That is, the data on the *i*-th individual consists of the total number, m_i of the events observed over the time period $(0, T_i]$ and the ordered epoch of the m_i event, $0 \le t_{i1} \le t_{i2} \le t_{i3} \le \cdots \le t_{im_i} \le T_i$. Additionally, we may have covariate information on each subject defined by a vector of censoring indicators. In more studies, interest may lie in understanding and characterizing the event illustrate process for individual subject or may focus on treatment comparisons based on the time to each distinct event, the number of events, the type of events and interdependence between events. The development of statistical models based on counting process data were originally introduced by Aalen (1978). Several methodologies have been proposed to analyze the problem of recurrent events. Lawless (1982) apply the Poisson process to develop models that focus on the expected number of events occurred in determined time interval. There is an extensive literature about point process models, (e.g., Cox and Isham 1980); this approach offers us tools powerful enough able to generalize several situations.

In this paper the problem is treated under the focus of punctual counting process. Poisson process has been well studied many recent discussion about lifetime and stochastic process transition data have focused on modeling and analyzing the effects of so called unobserved heterogeneity. In addition, the model presented will be studied under a Bayesian perspective. It is well known that under a Bayesian perspective the posterior distribution for the quantity of interest represents the most complete inference that can be made the respect of this quantity. The posterior distribution

combines the information contained in the data with the prior information about on the quantity of interest. The use of the prior function that represents lack of prior knowledge about the quantity of interest, has been a constant in the history of the Bayesian inference. Key pointers to the relevant literature include Bayes (1763), Laplace (1812). Reference analysis, introduced by Bernardo (1979) and widely developed by Berger and Bernardo [5-8] is widely considered today the most successful algorithm to derive non-informative prior. In this project, reference analysis is developed for a survival model based on proportional intensity Poisson process, where individuals may expected to experience repeated events and concomitant variables are observed. The methodology is illustrated using the recurrent cervical carcinoma data which medical records and pathology were reviewed for all patients accessible by the Chung Shan Medical University Hospital Tumor Registry. Approval for this retrospective study reviews by the Chung Shan Medical University Hospital Medical Institutional Review Board.

Section 2 presents a review of research problem relevant to the study. Section 3 contains an overview of reference analysis, where the definition is motivated, heuristic derivations of explicit expressions for the one parameter, two parameters, and multi-parameter cases are sequentially presented. In Section 4 we describe the survival model. In Section 5, the theory is applied to an inference problem, the parameters survival model, for which no objective Bayesian analysis has been previously proposed. Some work items and expected contributions are presented in Section 6.

II. STATEMENT OF THE PROBLEM

Cervical carcinoma remains one of the leading causes of cancer-related death among women globally [19, 24]. Even though the morbidity and the mortality have been decreasing in recent years, the morbidity rates of Cervical Carcinoma are the second leading type in women and the mortality rates are the sixth of the top ten cancers in Taiwan. The cure rate of cervical carcinoma is quite high if detected early, but approximately 30% of International Federation of Gynecology and Obstetrics (FIGO) stage IB2 to stage IV disease will ultimately recur with modern multimodality treatment [20, 28]. Once the primary treatment has failed, the opportunity of secondary cure is slim. Probably several factors exist which indeed affect the ultimate prognosis of early stage cervical carcinoma other than clinical staging. In other words, early detection of recurrence may impact survival. Moreover, detection of asymptomatic recurrences is associated with prolonged overall survival and survival from the time of initial detection of recurrence [12]. Therefore, this paper attempts to improve surveillance after treatment might lead to earlier detection of relapse, and precise assessment of recurrent status could improve outcome.

In Taiwan, cervical carcinoma is the second most common malignancy for women and contributing to a quarter of all female cancer cases. It remains one of the most pressing medical problems for women. The natural history of cervical carcinoma begins with a normal epithelium which progress through various stages of dysplasia - cervical intraepithelial neoplasia grade CIN 1, CIN 2, CIN 3 - and finally, to invasive cervical carcinoma (ICC). There is a long time interval for the progression to ICC, and consensus on the fact that regression occurs in CIN. The most important part of therapy is to detect and eradicate local CIN 3 lesions before the progression to ICC and metastasis can occur. In general, the Papanicolaou (Pap) smear has been used widely as the most effective screening tool for detecting precancerous cervical lesions. Though screening and treat in its early phase, cervical carcinoma will be decreased significantly to its rate of incidence as well as death. Because cervical carcinoma is a cancer which can be controlled and avoided, the studies related to the causes of and the treatment to the cervical carcinoma has been described sufficiently in lots of advanced researches. On the other hand, there are few researches on its relationship between recurrent events and the mortality and incidence rate. Indeed, recurrent cervical carcinoma is a devastating disease for those women unfortunate enough to suffer such an event. Patients with recurrent disease or pelvic metastases have a poor prognosis with a 1-year survival rate between 15 and 20% [4]. Since, the treatment of recurrent cervical carcinoma is still a clinical challenge. When the recurrence is not surgically resectable, and/or suitable for curative radiation, therapeutic options are limited. In some advanced countries, the combination of cisplatin and topotecan is preferred since this is the only regimen which was able to show a statistical significant improvement of overall survival (OS) (9.4 months) without impairing quality of life due to intolerable toxicity [22]. But one has to be careful, because due to a change in primary therapy since 1999, when concomitant chemotherapy and radiotherapy became standard [23, 25-27], and due to the current investigation of the role of neo-adjuvant chemotherapy (EORTC 55994 (Cochrane Database of Systematic Reviews, 2004)), most people with recurrent cervical carcinoma will have had some challenge with a chemotherapeutic agent. This will influence responses in secondary treatment lines and will limit comparison of new studies with older ones including more chemonaive patients. Therefore, in the absence of surgical/ radiotherapeutic indications, chemotherapy should be targeted to the prolongation of survival with minimum morbidity and to the improvement of subjective symptoms, thus preserving quality of life. Unfortunately, in these conditions, there is no evidence of a significant impact on survival or on quality of life. For these reasons, the role of chemotherapy in recurrent disease remains to be defined and the search for more active and less toxic agents must be continued.

However, the question remains: What is the rate of progression, regression, and/or stasis from one stage to another? What is the time interval in which these changes are detected? At stake is the considerable financial cost and cost-effectiveness of implementation; in other words, the rate of progression for all the stages of dysplasia from normal to ICC must be established and the frequency of progression for the

various stages of cancerous lesion must be known. In order to examine this issue, we would like to highlight the recurrent events frequently are not necessarily fatal on recurrent cervical carcinoma. This paper will apply Bayesian reference analysis to an inferential problem of recurrent cervical carcinoma in survival analysis. A formulation is considered where individuals are expected to experience repeated events, along with concomitant variables. In addition, the sampling distribution of the observations is modeled through a proportional intensity homogeneous Poisson process. This direction will give us hopefully some additional therapy strategies for patients with recurrent cervical carcinoma.

III. An Overview of Reference Analysis

The notion of a non-informative prior, that is, of a prior which describes lack of prior knowledge about the quantity of interest has been the object of many debates within the Bayesian community it is warranty that prior function which, by formal use of theorem Bayes produces a posterior distribution dominated by the information provided by the data [8, 11]. Objective reference priors do not depend on the data, but they depend on the probabilistic model that is assumed to have generated the data, the idea basic is by allows the amount of information about an amount of interest θ, that we expect to learn how a clinical record to provide information regarding θ, is obviously a function of our prior knowledge regarding θ. Thus, if we already have a good prior knowledge of θ then we do not expect to learn much the clinical experience; on the other hand, if the prior knowledge regarding θ is scarce, then the data may be expected to provide a large amount of useful information.

In other words, the bigger amount of available prior information, the lesser will be the quantity of information to be expected from the data. An infinitely larger clinical trial would eventually supply to all the information still regarding the amount of interest. Bernardo (2005) called this quantity missing information. Thus, it is natural to define a prior that determine no prior knowledge, or better, that becomes a posterior dominated for the data, as a prior that maximizes the missing information on the quantity of interest. However as missing information is defined as a limit that is not necessarily finite, the reference prior is defined as a type special of limit of a sequence of priors that maximize the expected information of successively having clinical trials. In this section we synthesize the formal construction reference priors as following [6].

A. One Parameter

Definition 1: Consider a clinical record ε which consists of one observation x from $p(x \mid \phi)$, $\phi \in \Phi \subset \Re$. Let $z_k = \{x_1, ..., x_k\}$ the result of k independent replications of ε .

Then, under suitable regularity conditions,

$$\pi_k(\phi) = \exp\left\{\int_{X^k} p(z_k|\phi) \log q(\phi|z_k) dz_k\right\} \qquad (1)$$

where $q(\phi \mid z_k)$ is an asymptotic approximation to the posterior distribution $p(z_k \mid \phi)$.

The reference posterior distribution is a function $\pi(\phi \mid x)$ such that

$\lim_{k\to\infty}[\int_\Phi \pi_k(\phi \mid x) \log\left\{\frac{\pi_k(\phi \mid x)}{\pi(\phi \mid x)}\right\} d\phi] = 0$, where

$$\pi_k(\phi \mid x) = \frac{p(x \mid \phi)\pi_k(\phi)}{\int_\Phi p(x\phi)\pi_k(\phi) d\phi}, \qquad k = 1,2,\ldots$$

A reference prior ϕ is a function which, for any data, provide the reference posterior $\pi(\phi \mid x)$ by formal use of Bayes theorem, i.e., a positive function $\pi(x)$ such that, for all $x \in X$,

$$\pi(\phi \mid x) = \frac{p(x \mid \phi)\pi(\phi)}{\int_\Phi p(x \mid \phi)\pi(\phi) d\phi} \qquad (2)$$

Thus the reference prior $\pi(\phi)$ is the limit of the sequence $\{\pi_k(\phi), k = 1,2,...\}$ defined by (1) in the precise sense that the information-type limit of the corresponding sequence of posterior distributions $\{\pi_k(\phi \mid x), k = 1,2,...\}$ is the posterior obtained from $\pi(\phi)$ by formal use of Bayes theorem.

■ Proposition 1: (Reference priors under asymptotic normality).

Let $p(x \mid \phi), x \in X$, be a probability model with one real-valued parameter $\phi \in \Phi \subset \Re$. If the asymptotic posterior distribution of ϕ given k replications of the clinical record is normal, with standard deviation $S(\hat{\theta})$ such that $\hat{\phi}_k$ is an estimator consistent and asymptotically sufficient of the ϕ . In this case the reference prior is given by

$$\pi(\phi) \propto \left\{\frac{1}{S(\phi)}\right\}$$

where under regularity conditions $S(\phi) = h(\phi)^{1/2}$ and $h(\cdot)$ is the Fisher information (please refer to Bernardo and Smith, 1994, p. 314). Notice, that in this case, the reference prior is Jeffrey's prior.

B. One Nuisance Parameter

Consider now the case where the statistical model $p(x \mid \phi, \omega), (\phi, \omega) \in \Phi \times \Omega \subseteq \Re \times \Re$ contains one nuisance parameter, where the quantity of interest is ϕ , and the nuisance parameter is ω . We shall only consider here regular

case where joint posterior asymptotic normality may be established.

■ Proposition 2: Let $p(x \mid \phi,\omega)$, $(\phi,\omega)\in\Phi\times\Omega\subseteq\Re\times\Re$ be a probability model with two real-valued parameters ϕ and ω, where ϕ is the quantity of interest, and suppose that the joint posterior distribution of (ϕ,ω) is asymptotically normal with covariance matrix $S(\hat{\phi},\hat{\omega})$, where $(\hat{\phi},\hat{\omega})$ is a consistent estimator of (ϕ,ω) .Let $S(\phi,\omega)=H^{-1}(\phi,\omega)$ is information Fisher matrix.

(i). the conditional reference prior of ω is

$\pi(\omega \mid \phi)\propto h_{22}(\phi,\omega)^{1/2},\ \omega\in\Omega(\phi)$

(ii). if $\pi(\omega \mid \phi)$ is not proper, a compact approximation $\{\Omega_i(\phi), i=1,2...\}$ to $\Omega(\phi)$ is required, and the reference prior of ω given ϕ is given by

$$\pi_i(\omega \mid \phi)=\frac{h_{22}(\phi,\omega)^{1/2}}{\int_{\Omega_i(\phi)} h_{22}(\phi,\omega)^{1/2}\,d\omega},\ \omega\in\Omega_i(\phi)$$

(iii). within each $A_i(\phi)$ the marginal reference prior of ϕ is obtained as

$\pi_i(\phi)\propto \exp\{\int_{\Omega(\phi)}\pi_i(\omega \mid \phi)\log[s_{11}^{1/2}(\phi,\omega)]d\omega\}$ where

$s_{11}^{1/2}(\phi,\omega)=h_{\phi}(\phi,\omega)=h_{11}-h_{12}h_{22}^{-1}h_{21}$

(iv). the reference posterior distribution of ϕ given data $\{x_1,...x_n\}$ is

$$\pi(\phi \mid x_1,...x_n)\propto\pi(\phi)\left\{\int_{\Omega(\phi)}[\prod_{l=1}^{n}p(x_1 \mid \phi,\omega)]\pi(\omega \mid \phi)d\omega\right\}$$

■ Corollary: If the nuisance parameter space $\Omega(\phi)=\Omega$ is independent of ϕ , and the functions $s_{11}^{-1/2}(\phi,\omega)$ and $h_{22}^{1/2}(\phi,\omega)$ factorize in the form, $\{s_{11}(\phi,\omega)\}^{1/2}=f_1(\phi)g_1(\omega)$, $\{h_{22}(\phi,\omega)\}^{1/2}=f_2(\phi)g_2(\omega)$

Then $\pi(\phi)\propto f_1(\phi)$, $\pi(\omega \mid \phi)\propto g_2(\omega)$. The reference prior relative the parametric value ordered (ϕ,ω) is given by $\pi(\omega,\phi)=f_1(\phi)g_2(\omega)$, and in this case, there is no need for compact approximation, even if the conditional reference prior is not proper [6].

C. The Multiparameter Case

The approach to the nuisance parameter are considered above was based on the use of an ordered parametrization whose first and second components were (ϕ,ω), respectively, referred as the parameter of interest and the nuisance parameter. The reference prior for the ordered parametrization (ϕ,ω) , was then successively constructed to obtain $\pi_{\omega}(\phi,\omega)=\pi(\omega \mid \phi)\pi(\phi)$.

When the model parameter vector θ has more than two components, this sequential conditioning idea can obviously be extended by considering θ as an ordered parametrization, $\theta=(\theta_1,...,\theta_m)$, and generating, by successive conditioning, a reference prior, relative to this ordered parametrization, of the form

$$\pi(\theta)=\pi(\theta_m \mid \theta_1,...,\theta_{m-1})...\pi(\theta_2 \mid \theta_1)\pi(\theta_1) \quad (3)$$

■ Proposition 3: Let $p(x \mid \theta)$, $\theta=(\theta_1,...,\theta_m)$ be a probability model with m real-valued parameters, let θ_1 be the quantity of interest, and suppose that the joint distribution of $(\theta_1,...,\theta_m)$ is asymptotically normal with covariance matrix $S(\hat{\theta}_1,...,\hat{\theta}_m)$. Then, if S_j is the $j\times j$ upper matrix of S, $H_j=S_j^{-1}$ and $h_{jj}(\theta_1,...,\theta_m)$ is the (j,j) element of H_j.

(i). the conditional reference priors are

$\pi(\theta_m \mid \theta_1,...,\theta_{m-1})\propto h_{mm}(\theta_1,...,\theta_m)^{1/2}$ for $i=m-1,m-2,...2$

$$\pi(\theta_i \mid \theta_1,...,\theta_{i-1})\propto \exp\left[\begin{matrix}\int_{\Lambda_{i+1}}...\int_{\Lambda_m}\log[h_{i+1,i+1}(\theta_1,...,\theta_m)^{1/2}] \\ [\prod_{j=1}^{m}\pi(\theta_j \mid \theta_1,...,\theta_{j-1})]d\theta_{i+1}\end{matrix}\right],$$

where $d\theta_j=d\theta_j\times...\times d\theta_m$

(ii). the marginal reference prior of θ_1 is

$$\pi(\theta_1)\propto\exp\left\{\begin{matrix}\int_{\Lambda_1}...\int_{\Lambda_m}\log[s_{11}(\theta_1,...,\theta_m)^{-1/2}] \\ [\prod_{j=1}^{m}\pi(\theta_j \mid \theta_1,...,\theta_{j-1})]d\theta_1\end{matrix}\right\}$$

(iii). after data $\{x_1,...,x_n\}$ have been observed, the reference posterior distribution of the parameter of interest θ_1, is

$$\pi(\theta_1 \mid x_1,...,x_n) \propto \pi(\theta_1) \propto \exp\left\{\begin{array}{l}\int_{\Lambda_1} \ldots \\ \int_{\Lambda_m} \prod_{j=1}^{m} p(x_1 \mid \theta_1,...,\theta_m)[\\ \prod_{j=1}^{m} \pi(\theta_j \mid \theta_1,...,\theta_{j-1})]d\theta_1\end{array}\right\}$$, For proof and details see Berger and Bernardo (1992a, 1992b, 1992c).

IV. Model Formulation

Suppose that n individuals may experience a single type of recurrent event. Let m_i denote the number of events occurring for the *i*-th individual. Assume that the *i*-th individual is observed over the interval $(0,T_i]$, where T_i is determined independently of m_i. Let $0 \le t_{i1} < t_{i2} < \ldots < t_{im_i} \le T_i$ where the variable of interest t_{ij} denote the continuous failure times for the i-th individual and the j-th occurrence events ($i = 1,...,n$ and $j = 1,...,m_i$). Besides that we are going to consider that individual carry a covariate vector represented by x, so data from i-th individual consist of the total number of events m_i observed about a time period $(0,T_i]$ in the ordered occurrence, $t_{i1},...,t_{im_i}$ and the covariate vector x.

It is assumed that the repeated events of an individual with $k \times 1$ covariate vector x occur according to a nonhomogeneous Poisson process with intensity function given by

$$\lambda_{x_i}(t) = \lambda_0(t)\exp(x_i'\beta), t \ge 0, \text{ i = 1,2,…,n} \quad (4)$$

where $\lambda_0(t)$ is a baseline intensity function and $x_i = (x_{i1}, x_{i2},..., x_{ik})$ and $\beta = \beta_1,...,\beta_k$ is a vector of unknown parameters.

The corresponding cumulative or integrated intensity function is

$$\Lambda_x(t) = \int_0^t \lambda_x(u)du = \Lambda_0(t)e^{x'\beta} \quad (5)$$

where $\Lambda_0(t) = \int_0^t \lambda_0(u)du$.

Methods of analysis will be considered semi parametric if $\lambda_0(t)$ is arbitrary, and completely parametric if $\lambda_0(t)$ is specified by a parameter vector θ. In the case of the function of baseline hazard to be constant, this is a homogeneous Poisson process (see Cox and Isham, 1980). The Poisson process model (4) is often known as Cox proportional risk model (see, Cox, 1972).

Considers a parametric Poisson process where $\lambda_0(t) = \lambda_0(t;\theta)$. Then, the likelihood function for the model (4) for θ and β is given by (see, Cox and Lewis 1996),

$$L(\theta,\beta) = \prod_{i=1}^{n}\left\{\prod_{j=1}^{m_i}\lambda_{x_i}(t_{ij},\theta)\right\}\exp\left\{-\Lambda_{x_i}(T_i,\theta)\right\} \quad (6)$$

which can be decomposed as $L(\theta,\beta) = L_1(\theta)L_2(\theta,\beta)$, where

$$L_1(\theta) = \left\{\prod_{i=1}^{n}\prod_{j=1}^{m_i}\frac{\lambda_0(t_{ij};\theta)}{\Lambda_0(T_i;\theta)}\right\}, \text{ and}$$

$$L_2(\theta,\beta) = \prod_{i=1}^{n}\exp\left[\Lambda_0(\theta,\beta)e^{x_i'\beta}\right]\left[\Lambda_0(T_i;\theta)e^{x_i'\beta}\right]^{m_i}$$

The first likelihood kernel $L_1(\theta)$ arises from the conditional distribution of the event times, given the counts and the second the likelihood kernel $L_2(\theta,\beta)$ arises form the Poisson distribution of the counts $m_1,...,m_n$.

A. Modeling the Baseline Hazard

The exponential distribution is one of the simplest and important probability distributions used in the modeling of data that represent the life time. It has been used intensively in the literature of survival and reliability, as for example in study areas on lifetime of items manufactured (Chang, 2008), in research involving survival or time of remission of chronic illnesses (see Feigl and Zelen, 1965). A characteristic of the exponential distribution say respect to the fact of the values next to one of the extremities of the random variable to present maximum probability and next to the other extremity to present probability zero. This characteristic is associated with a probabilistic mechanism that favors the events of higher intensity or lower.

The exponential distribution has been extensively used to model the baseline hazard function due to its simplicity and flexibility. This is the particular case where

$$\lambda_0(t) = \lambda_0(t;\theta) = \nu \quad (7)$$

The corresponding intensity function and integrated intensity function are $\lambda_x(t) = \nu e^{x'\beta}$, and

$$\Lambda_x(T) = T\nu e^{x'\beta} \quad (8)$$

Considering the decomposition in (6) the likelihood function for ν, β is given by

$$L(\nu,\beta) = \prod_{i=1}^{n} T_i^{-m_i}\exp[-\nu T_i e^{x_i'\beta}][\nu T_i e^{x_i'\beta}]^{m_i} \quad (9)$$

where $L_2(\nu,\beta) = \prod_{i=1}^{n}\exp[-\nu T_i e^{x_i'\beta}][\nu T_i e^{x_i'\beta}]^{m_i}$ is the nucleus of the regression model for which m_i has a Poisson distribution with average and variance $E(m_i \mid x_i) = Var(m_i \mid x_i) = \nu T_i e^{x_i'\beta}$.

The log-likelihood function (9) is given by

$$l(\nu,\beta) \propto \sum_{i=1}^{n} m_i \log(\nu) + \sum_{i=1}^{n} m_i x_i'\beta - \sum_{i=1}^{n} \nu T_i e^{x'\beta} \qquad (10)$$

Interval estimates and hypothesis tests for the parameters can be performed, in principle, by considering the asymptotic normal distribution of the maximum likelihood estimates and the asymptotic chi-squared distribution of the likelihood ratio statistics, respectively.

B. The Matrix of Information of Fisher Associated with the Model

The posterior distribution of the parameter is often asymptotically normal (see e.g., Bernardo and Smith, 1994, Sec.5.3). In this case, the reference prior is easily derived. If the posterior distribution is asymptotically normal, than reference prior only depends on Fisher information matrix.

Considering the log of the likelihood function (10) we have the first and second derivatives given by

$$\frac{\partial l}{\partial \nu} = \sum_{i=1}^{n} \frac{m_i}{\nu} - \sum_{i=1}^{n} T_i e^{x_i'\beta}$$

$$\frac{\partial l}{\partial \beta_r} = \sum_{i=1}^{n} m_i x_{ir} - \sum \nu T_i x_{ir} e^{x_i'\beta} \ , \ \text{r} = 0,1,\ldots,\text{k}$$

$$\frac{\partial l}{\partial \nu^2} = -\sum_{i=1}^{n} \frac{m_i}{\nu^2}$$

$$\frac{\partial l}{\partial \beta_r \beta_s} = -\sum_{i=1}^{n} \nu T_i x_{ir} x_{is} e^{x_{1i}'\beta} \ , \quad \text{r , s} = 0,1,\ldots,\text{k}$$

$$\frac{\partial l}{\partial \nu \partial \beta_r} = -\sum_{i=1}^{n} T_i x_{ir} e^{x_i'\beta}$$

In this way, the elements of the Fisher information matrix are given

by $I_{\nu\nu} = E[-\frac{\partial l(\nu,\beta)}{\partial \nu^2}] = \sum_{i=1}^{n} E[\sum_{i=1}^{n} \frac{m_i}{\nu^2}] = \frac{1}{\nu}\sum_{i=1}^{n} T_i e^{x_i'\beta}$

$I_{\beta_r\beta_s} = E[-\frac{\partial l(\nu,\beta)}{\partial \beta_r \beta_s}] = \nu \sum_{i=1}^{n} T_i x_{ir} x_{is} e^{x_i'\beta}$, r , s = 0 , 1 , … , k

$I_{\beta_r\nu} = E[-\frac{\partial l(\nu,\beta)}{\partial \beta_r \nu}] = \sum_{i=1}^{n} T_i x_{ir} e^{x_i'\beta}$, r , s = 0 , 1 , … , k

Thus, Fisher information matrix associated with the model is given by

$$H(\theta) = H(\nu,\beta) = \begin{bmatrix} \frac{1}{\nu}\sum_{i=1}^{n} T_i e^{x_i'\beta} & \sum_{i=1}^{n} T_i x_{ir} e^{x_i'\beta} \\ \sum_{i=1}^{n} T_i x_{ir} e^{x_i'\beta} & \nu \sum_{i=1}^{n} T_i x_{ir} x_{is} e^{x_i'\beta} \end{bmatrix} \qquad (11)$$

V. Reference Analysis for Survival Model Parameters

Following the methodology described in section 3, now we derive the reference prior considering two potential groups (with surgically hysterectomy or not), which corresponds to the ordered partition $\{\nu,\beta\}$, where $\beta = \{\beta_1,\beta_2,...,\beta_k\}$ and ν is considered to be the quantity of interest (to see Berger and Bernardo, 1992b). Hence the joint posterior distribution of the parameter is often asymptotically normal (see e.g., Bernardo and Smith, 1994. Sec.5.3). In this case, the reference prior is easily derived and reference prior only depends on Fisher information matrix found in (11).

So the reference prior relative to this ordered parametrization is of the following form $\pi(\nu,\beta) = \pi(\beta \mid \nu)\pi(\nu)$. From Corollary of Proposition 3 where the nuisance parameter space $\Lambda(\beta) = \Lambda$ is independent of ν, it is easy to see that

$$\pi(\beta \mid \nu) = |h_{22}|^{1/2} = \nu^{1/2}\left[\sum_{i=1}^{n} T_i x_{ir} x_{is} e^{x_i'\beta}\right]^{1/2}$$
$$= f_1(\nu) g_1(\beta)$$

and

$$h_\nu(\nu,\beta) = h_{11} - h_{12}h_{22}^{-1}h_{21} =$$
$$\nu^{-1/2}\left[\sum_{i=1}^{n} T_i e^{x_i'\beta} - \frac{[\sum_{i=1}^{n} T_i x_{ir} e^{x_i'\beta}]^2}{\sum_{i=1}^{n} T_i x_{ir} x_{is} e^{x_i'\beta}}\right]^{1/2}$$
$$= f_2(\nu) g_2(\beta)$$

This implies that the conditional reference prior of the nuisance parameter β given the parameter of interest ν is

$$\pi(\beta \mid \nu) \propto g_1(\beta) = [\sum_{i=1}^{n} T_i x_{ir} x_{is} e^{x_i'\beta}]^{1/2} \qquad (12)$$

The reference prior needed to obtain a reference posterior for the parameter of interest ν is

$$\pi(\nu) \propto f_2(\nu) = \nu^{-1/2} \qquad (13)$$

The figure 1 represents the reference prior (13).

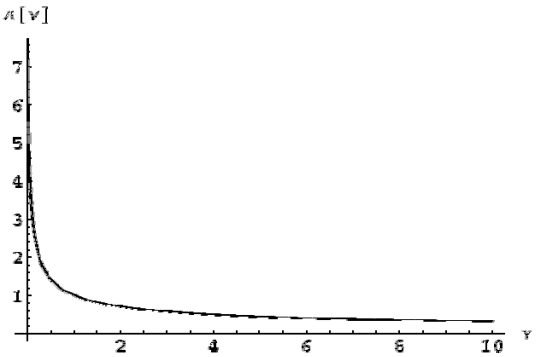


Fig. 1. Reference prior for the parameter ν

It follows that the joint reference prior for parameters ν and β is given by

$$\pi(\nu,\beta)=\pi(\beta\mid\nu)\pi(\nu)$$
$$\propto[\sum_{i=1}^{n}T_i x_{ir}x_{is}e^{x_i'\beta}]^{1/2}\nu^{-1/2} \quad (14)$$

The figure 2 represents the joint reference prior (14), considering in the particular case where T = 100, n = 30, x = 1.

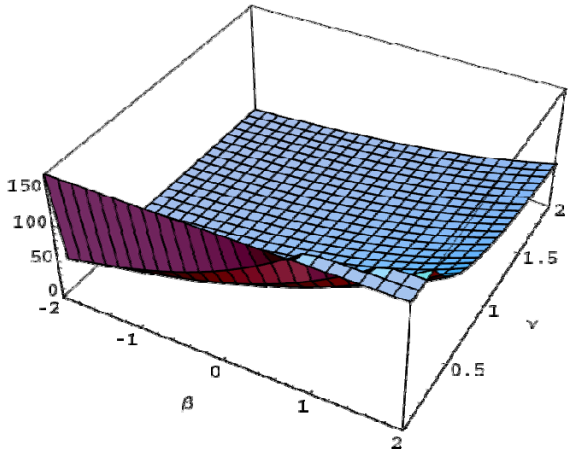


Fig. 2. Joint reference prior for the parameter ν and β

The corresponding reference posterior for ν after data $T=\{t_1,...,t_n\}$ have been observed is

$$\pi(\nu|t_1,...,t_n)\propto\pi(\nu)\int_{\Lambda}L(\nu,\beta)\pi(\beta|\nu)d\beta$$

$$\propto\nu^{-1/2}\int_{\Lambda}\prod_{i=1}^{n}T_i^{-m_i}\exp[-\nu T_i e^{X_i'\beta}]$$
$$[\nu T_i e^{X_i'\beta}]^{m_i}[\sum_{i=1}^{n}T_i x_{ir}x_{is}e^{X_i'\beta}]^{1/2}d\beta \quad (15)$$

The marginal reference posterior densities (15) cannot be obtained explicitly. We will overcome this difficulty by making use of the Markov Chain Monte Carlo (MCMC) methodology to obtain approximations for such densities. In order to make Bayesian inference for the parameters of interest ν we implement the MCMC methodology considering the Metropolis-Hastings (see, Hastings, 1970; Chib and Greenberg, 1995)

VI. Conclusions

The purpose of this retrospective analysis of cervical carcinoma is to determine the factors associated with morbidity and survival for recurrent event. In order to analysis survival, this proposed methodology is illustrated using the recurrent cervical carcinoma data which medical records and pathology were reviewed for all patients accessible by the Chung Shan Medical University Hospital Tumor Registry from 1995 to 2008. Approval for this retrospective study reviews by the Chung Shan Medical University Hospital Medical Institutional Review Board for now. Patient demographics evaluated were age at the time of initial stage and site of cancer, treatment history, time from diagnosis to relapse, and time and status from surgery until last follow-up or death. Exclusion criteria for this study include prior treatment with interferon, retinoid, or chemotherapy (except as radiation sensitization); and lactating females. Further, the goal is to afford the patient the opportunity to have a reasonable quality of life in addition to providing the chance for a cure in the future.

References

[1] Aalen, O.O. Nonparametric inference for a family of counting processes, The Annals of Statistics, 1978, 6, 701–726.

[2] Bayes, T. 1763. An essay toward solving a problem in the doctrine of chances.Published posthumously in Phil. Trans. Roy. Soc. London 53, 370–418 and 54, 296–325. Reprinted in Biometrika 45 (1958), 293–315, with a biographical note by G. A. Barnard.

[3] Laplace, P. S. (1812). Th´eorie Analytique des Probabilit´ıes. Paris: Courcier. Reprinted as Oeuvres Compl´etes de Laplace 7, 1878–1912. Paris: Gauthier-Villars.

[4] Berek, J. S. and Hacker, N. F. Practical gynaecologic oncology. New York: Lippincott Williams & Wilkins 2005.

[5] Berger, J. O. and Bernardo, J. M. On the development of reference priors. Bayesian Statistics 1992c; 4 (J. M. Bernardo, J. O. Berger, A. P. Dawid and A. F. M. Smith, eds.) Oxford: University Press, 35-60 (with discussion).

[6] Berger, J. O. and Bernardo, J. M. Ordered group reference priors with applications to a multinomial problem. Biometrika. 1992a; 79:25-37.

[7] Berger, J. O. and Bernardo, J. M. Reference priors in a variance components problem. Bayesian Analysis in Statistics and Econometrics (P. K. Goel and N. S. Iyengar, eds.) Berlin: Springer, 1992b; 323–340.

[8] Berger, J. O., Bernardo, J. M., and Sun, D. Reference priors from first principles: A general definition. 2005 Tech. Rep., SAMSI, NC, USA.

[9] Bernardo, J. M. and Smith, A. F. M. Bayesian Theory. Chichester: Wiley 1994.

[10] Bernardo, J. M. Reference analysis. Handbook of Statistics 2005; 25 (D. K. Dey and C. R. Rao eds.). Amsterdam: Elsevier, 17-90

[11] Bernardo, J. M. Reference posterior distributions for Bayesian inference. J. Roy. Statist. Soc. 1979; B 41, 113-147 (with discussion).

[12] Bodurka-Bevers, D., Morris, M., Eifel, P. J., et al. Posttherapy surveillance of women with cervical cancer: an outcomes analysis. Gynecol Oncol. 2002; 78:187-193.

[13] Chang, C. C. and Cheng, C. S. A Structural Design of Clinical Decision Support System for Chronic Diseases Risk Management. CEJ Med. 2007; 2(2):129-139.

[14] Chang, C. C. Bayesian Value of Information Analysis with Linear, Exponential, Power law Failure Models for Aging Chronic Diseases JCSE. 2008; 2(2): 201-220.

[15] Cochrane Database of Systematic Reviews. Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration

(NACCCMA) Collaboration. Neoadjuvant chemotherapy for locally advanced cervix cancer. John Wiley & Sons 2004.
[16] Cox, D. R. and Isham, V. Point Process, London: Chapman & Hall 1980.
[17] Cox, D. R. Regression models and life tables (with discussion), J. Roy. Statist. Soc. 1972; B 34: 187-220.
[18] Feigl, P. and Zelen, M. Estimation of exponential survival probabilities with concomitant Information. Biometrics 1965; 21:826-837.
[19] Goldie, S. J., Kuhn, L., Denny, L., Pollack, A. and Wright, T. Policy analysis of cervical cancer screening strategies in low-resource setting: clinical benefits and cost effectiveness. JAMA. 2001; 285:3107-3115.
[20] Lai, C. H., Hong, J. H., Hsueh S, et al. Preoperative prognostic variables and the impact of postoperative adjuvant therapy on the outcomes of stage IB or II cervical carcinoma patients with or without pelvic lymph node metastases. Cancer. 1999; 85:1537-1546.
[21] Lawless, J. F. Statisctical Models and Methods for Life Time Data. New York: Jonh Wiley 1982.
[22] Long III, H. J., Bundy, B. N., Grendys, E. C., Benda, J. A., McMeekin, D. S. and Sorosky, J., et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. J Clin Oncol. 2005; 23(21):4626-33.
[23] Morris, M., Eifel, P. J., Lu, J., Grigsby, P. W., Levenback, C. and Stevens, R. E., et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med. 1999; 340(15):1137-43.
[24] Parkin, D. M., Bray, F. I. and Devesa, S. S. Cancer burden in the year 2000: the global picture. Eur J Cancer. 2001; 37 (suppl):S4-S66.
[25] Pearcey, R., Brundage, M., Drouin, P., Jeffrey, J., Johnston, D. and Lukka, H., et al. Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. J Clin Oncol. 2002; 20(4):966-72.
[26] Peters III, W. A., Liu, P. Y., Barrett, R. J., Stock, R. J., Monk, B. J. and Berek, J. S., et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol. 2000; 18(8):1606-13.
[27] Rose, P. G., Bundy, B. N.,Watkins, E. B., Thigpen, J. T., Deppe, G. and Maiman, M. A., et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med. 1999; 340(15):1144-53.
[28] Waggoner, S. E. Cervical cancer. Lancet. 2003; 361:2217-2225.

AUTHORS BIOGRAPHY

First Author, Chi-Chang Chang is currently an assistant professor in the School of Information Sciences at Chung Shan Medical University. He received his Ph.D. from Yuan-Ze University in 2006. His primary research interests are in the areas of medical decision analysis, reliability engineering, stochastic processes. He has published in EJOR, JUCS, IJTM, CEJM, etc.

Second Author, Gin-Den Chen is currently a professor in the school of medicine at Chung Shan Medical University. His primary research interests are in the areas of Gynecologic oncology. He has published in Prenat Diagn, International journal of gynaecology and obstetrics, Journal of clinical laboratory analysis, Journal of the Society for Gynecologic Investigation, etc.

Third Author, Su-Hsin Chang is Post-doctoral Research Associate in Washington University School of Medicine. She received his Ph.D. from Johns Hopkins University in 2010. His primary research interests are in the areas of Health Economics, Applied Econometrics, medical decision analysis, and Statistics.

國科會補助計畫衍生研發成果推廣資料表

日期:2011/10/21

國科會補助計畫	計畫名稱: 以客觀貝氏參考分析卜瓦松程序於模式化復發性子宮頸癌
	計畫主持人: 張啟昌
	計畫編號: 99-2628-E-040-001- 學門領域: 作業研究

無研發成果推廣資料

99 年度專題研究計畫研究成果彙整表

計畫主持人：張啟昌	計畫編號：99-2628-E-040-001-
計畫名稱：以客觀貝氏參考分析卜瓦松程序於模式化復發性子宮頸癌	

成果項目			量化			單位	備註（質化說明：如數個計畫共同成果、成果列為該期刊之封面故事...等）
			實際已達成數（被接受或已發表）	預期總達成數(含實際已達成數)	本計畫實際貢獻百分比		
國內	論文著作	期刊論文	0	0	100%	篇	
		研究報告/技術報告	1	1	100%		
		研討會論文	0	0	100%		
		專書	0	0	100%		
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（本國籍）	碩士生	1	1	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		
國外	論文著作	期刊論文	0	0	100%	篇	
		研究報告/技術報告	0	0	100%		
		研討會論文	1	1	100%		出席印度 43 屆作業研究年會，並獲得最佳論文獎與 short list 推薦至期刊
		專書	0	0	100%	章/本	
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（外國籍）	碩士生	0	0	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		

其他成果 (無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。)	1.出席印度43屆作業研究年會，並獲得最佳論文獎與short list推薦至期刊；計畫結果已整理投稿Central European Journal of Operations Research/SCI 2.為了反應學術價值，在臨床上不同治療方式的差異，我們蒐集放射化療與雷射治療法二個群別樣本在復發的徵候表現；根據共同主持人陳進典副院長以及醫院婦癌專家的嚴格審視，顯示本研究模式成果在不同的期別可以反應有不同的預後效果。(臨床發現已整理投稿Archives of Medical Science /SCI) 3.計畫執行感言：對於任何的疾病言，預防勝於治療。換言之，有效監控評估子宮頸癌防治措施以及定期評估與監測機制，是現今世衛組織在疾病預防任務中重要的品質管控指標之一，也是世界各國新興的潮流與趨勢。相較於歐美國家，台灣的子宮頸癌發生率有偏高現象，因此如何運用整合的篩檢模式是現階段台灣所面臨的新問題，也是最值得努力的方向。 由近幾年醫學文獻發展的趨勢與臨床實務上的需求，作業研究方法將逐漸扮演重要的角色。由於跨領域的過程式相當艱辛，且涉及許多醫學專業的知識，本研究之成果受益於任職單位附屬醫院資源以及婦癌專家團隊的支持，更重要的是本學門審查委員們的青睞得以完成。展望未來研究生涯，將持續爭取國家研究經費補助以及獲得國內各醫療院所合作的機會與資源，自許成為工程處工業工程學門在醫療決策領域專家，並成為工業工程學門之研究主力；此外，藉由出席國際會議與論文發表等管道建立各種國際合作研究，以提升個人學術與台灣在醫療決策領域的國際地位。

	成果項目	量化	名稱或內容性質簡述
科教處計畫加填項目	測驗工具(含質性與量性)	0	
	課程/模組	0	
	電腦及網路系統或工具	0	
	教材	0	
	舉辦之活動/競賽	0	
	研討會/工作坊	0	
	電子報、網站	0	
	計畫成果推廣之參與（閱聽）人數	0	

國科會補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估

■達成目標

□未達成目標（請說明，以 100 字為限）

□實驗失敗

□因故實驗中斷

□其他原因

說明：

2. 研究成果在學術期刊發表或申請專利等情形：

論文：□已發表 ■未發表之文稿 □撰寫中 □無

專利：□已獲得 □申請中 ■無

技轉：□已技轉 □洽談中 ■無

其他：(以 100 字為限)

3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）(以 500 字為限)

研究問題：子宮頸癌症在臨床實務的診療原則，視疾病的發展並藉由階段化的分類以提供適合的進程治療。依據 International Federation of Gynecology and Obstetrics (FIGO) 的數據顯示，若能早期發現 IB2 到 IV 的病期，有 30%的治癒機率，儘管如此，臨床上無法避免的問題是高度復發的疾病特徵。

研究目標：運用貝氏參考分析方法，基於卜瓦松程序模式與後驗分佈的發展以推論復發性子宮頸癌的存活問題。

目標達成度：100%

學術價值：針對 One Parameter，One Nuisance Parameter，the Multi-parameter Case 的命題推導以及 Baseline Hazard 模擬，並完成以客觀貝氏參考分析卜瓦松程序於模式化復發性子宮頸癌。(出席印度 43 屆作業研究年會，並獲得最佳論文獎與 short list 推薦至期刊；計畫結果已整理投稿 Central European Journal of Operations Research/SCI)

臨床價值：為了反應學術價值，在臨床上不同治療方式的差異，我們蒐集放射化療與雷射治療法二個群別樣本在復發的徵候表現；根據共同主持人陳進典副院長以及醫院婦癌專家的嚴格審視，顯示本研究模式成果在不同的期別可以反應有不同的預後效果。(臨床發現

已整理投稿 Archives of Medical Science /SCI）

後續研究發展：在學術理論部分：本研究模式的進一步發展可以針對參數不同的假設以推論不同的非主觀事前機率分配。在臨床實務部分：可以根據本研究模式為基底，進一步考慮研究放射劑量、腫瘤復發位置以及是否為非骨盆內移轉等因素加以研究其經濟效益。

計畫執行感言：對於任何的疾病言，預防勝於治療。換言之，有效監控評估子宮頸癌防治措施以及定期評估與監測機制，是現今世衛組織在疾病預防任務中重要的品質管控指標之一，也是世界各國新興的潮流與趨勢。相較於歐美國家，台灣的子宮頸癌發生率有偏高現象，因此如何運用整合的篩檢模式是現階段台灣所面臨的新問題，也是最值得努力的方向。

由近幾年醫學文獻發展的趨勢與臨床實務上的需求，作業研究方法將逐漸扮演重要的角色。由於跨領域的過程式相當艱辛，且涉及許多醫學專業的知識，本研究之成果受益於任職單位附屬醫院資源以及婦癌專家團隊的支持，更重要的是本學門審查委員們的青睞得以完成。展望未來研究生涯，將持續爭取國家研究經費補助以及獲得國內各醫療院所合作的機會與資源，自許成為工程處工業工程學門在醫療決策領域專家，並成為工業工程學門之研究主力；此外，藉由出席國際會議與論文發表等管道建立各種國際合作研究，以提升個人學術與台灣在醫療決策領域的國際地位。