Bayesian Decision Analysis for Recurrent Ovarian Cancer

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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 study applied Bayesian decision theorem to an inferential problem of recurrent ovarian cancer in survival analysis. A formulation is considered where individual was expected to experience repeated events, along with concomitant variables. In addition, the sampling distribution of the observations is modelled through a proportional Nonhomogeneous Poisson process. Finally, this paper develops a systematic way to integrate the expert's opinions which will furnish clinician with valuable support for quality medical decision making.

Keywords: Bayesian Decision Analysis; Recurrent Ovarian Cancer; Nonhomogeneous Poisson process

1. Introduction

Ovarian cancer remains one of the leading causes of cancer-related death among women globally [1, 2]. Even though the morbidity and the mortality have been decreasing in recent years, the morbidity rates of ovarian cancer are the second leading type in women and the mortality rates are the fifth of the top ten cancers in Taiwan. The studies related to the causes of and the treatment to the ovarian cancer has been described sufficiently in lots of advanced researches. The cure rate of ovarian carcinoma is quite high if detected early, International Federation of Gynecology and Obstetrics (FIGO) stage IB2 to stage IV disease will ultimately recur with modern multimodality treatment [3, 4]. There are few researches on its relationship between recurrent events and the mortality and incidence rate. Indeed, recurrent ovarian cancer is a devastating disease for those women unfortunate enough to suffer such an event. Limitations in the number of active agents in ovarian cancer management make it more important for oncologists to manage the available treatment options [5].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

ovarian carcinoma other than clinical staging. Since, the treatment of recurrent ovarian cancer is still a clinical challenge. When the recurrence is not surgically resectable, and/or suitable for curative radiation, therapeutic options are limited. 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 [6, 7, 8]. 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.

2. Nonhomogeneous Possion Process (NHPP)

In order to model the recurrent ovarian cancer, the Nonhomogeneous Poisson process (NHPP) was introduced to make the time-dependent behavior of more ovarian cancer tractable [9]. The assumption that the survival after a medication is essentially the same as it was immediately before the recurrent event is plausible. Based on the assumption, the recurrent ovarian cancer is time-dependent [9]. The intensity function of the failure process is usually assumed to be of the form $\lambda(x)=\lambda_0 h(\beta;x)$, where λ_0 is the scale factor, β is the aging rate, x is the elapsed time, and $h(.)$ can be any function that reflects the recurrent ovarian cancer.

Suppose we have a patient with ovarian cancer who recurrent process is given by a NHPP. We observe ovarian cancer for x^* units of time, during which we observe N recurrent events. In this (time-truncated) case, x^* is a constant and N is a random variable. It is known for such an NHPP that the joint density function of the first N recurrent times is

$$f_{X_1,X_2,\cdots,X_N,N}(x_1,x_2,\cdots,x_n,n)=[\prod_{i=1}^{n}\lambda(x_i)]\,exp(-\Lambda(x^*)] \quad (1)$$

where $\Lambda(x)=\int_0^x \lambda(u)du$ is the mean number of recurrent events by time x in the nonhomogeneous Poisson process. If we instead observe the ovarian cancer until the n^*th recurrent event (rather than until time x^*), and the n^*th recurrent time occurs at time X_{n^*} (i.e., the recurrent event-truncated case, where n^* is a constant and X_{n^*} is a random variable), then the joint density function of the first n^* recurrent times is

$$f_{X_1,X_2,\cdots,X_{n^*}}(x_1,x_2,\cdots,x_{n^*})=[\prod_{i=1}^{n^*}\lambda(x_i)]\,exp(-\Lambda(x_{n^*})] \quad (2)$$

The recurrent ovarian cancer is modeled by a power law failure model if it is given by an NHPP with an intensity function of the form

$$\lambda(x)=\lambda_0\beta x^{\beta-1} \qquad \lambda_0>0, \quad \beta>0 \quad (3)$$

where β is effectively unit. When β is equal to one, the NHPP degenerates to an HPP with a constant λ_0. For $\beta<1$ the failure intensity is decreasing (corresponding to survival growth), and for $\beta>1$ the failure intensity is increasing. Note that for $1<\beta<2$ the failure intensity is concave downward, and for $\beta>2$ the failure intensity is concave upward.

The nonhomogeneous Poisson process is often used because it is mathematically tractable. Cook et al. [10] developed a robust test for kidney transplant based on recurrent event responses. Wang et al. [11] using a nonhomogeneous poisson process to analyze the times between failures to determine the optimum first metastases.

Aggarwal et al. [12] also investigated the mean time between failures for dorsal cochlear nucleus neurons. They stated a necessary and sufficient condition for the mean time until the next failure to be asymptotically proportional to the reciprocal of the intensity function, and verified their theorem for power law and log-linear processes.

Other failure models have also been proposed to model recurrent process, but in more complicated ways. Unlike the power law failure model given above, these models often have more than two parameters. This makes the analysis more difficult. But since some of these models are generated by combining two of the three commonly used models. For example, the exponential polynomial rate model proposed by Cox [13] is of the form $\lambda(x) = \exp(\sum_{m=0}^{r} \alpha_m x^m)$, the Weibull and log-linear rate model proposed by Lee [14] is of the form $\lambda(x) = \alpha\gamma x^{\gamma-1} \exp(\beta x)$, the nonlinear failure rate model proposed by Salem [15] is of the form $\lambda(x) = (\alpha_1 + \alpha_2 \beta x^{\beta-1})$, the bounded intensity model proposed by Hartler [16] is of the form $\lambda(x) = \eta[1-(1+\eta x)^{-1}]$, the gamma type intensity model proposed by Yamada et al. [17] is of the form $\lambda(x) = \alpha\eta^2 x exp(-\eta x)$, and the bathtub type failure rate models $\lambda(x) = \delta x + \theta/(1+\beta x)$ and $\lambda(x) = \alpha_1 x^{\beta_1-1} + \alpha_2 + \alpha_3 x^{\beta_2-1}$ are proposed by Calvin [18] and Hjorth [19], respectively.

In this paper, we develop a Bayesian decision process for the power law failure model, since the power law intensity function allows for a wide variety of shapes (including both concave upward and concave downward, as well as decreasing) and tends not to increase very steeply, which may make it more realistic for clinical practices.

3. Bayesian inference

Suppose a patient with recurrent ovarian cancer that behaves according to the nonhomogeneous Poisson process with intensity function $\lambda(x)=\lambda_0 h(\beta;x)$. The crucial two-action decision is whether after some period of time *t*, the failure rate of the recurrent ovarian cancer will be too high (in which case some undertaking the intervention treatment needs to be taken), or will still be within an acceptable range (in which case we can wait according to the status quo). Another option is to gather additional information. The decision should be made on the basis of expected cost-effectiveness with respect to some loss function [20, 21]. We also assume that the decision maker is risk neutral, and can therefore make the decision on the basis of expected monetary value. The basic elements of the Bayesian decision process are as follows:

Parameter space Θ: $\{(\lambda_0, \beta)| \ \lambda_0>0\}$, where λ_0 is the scale factor and β is the aging rate. Both parameters are uncertain and can be estimated through physicians' opinions.

Action space *A*: $\{a_1,a_2\}$, where a_1 is the status quo, and a_2 is the risk reduction action. (We eventually expand this to consider a third possible action, the collection of additional information).

Loss function *L*: a real function defined on $\Theta \times A$. If we decide to keep continuing the status quo, then the loss we face is $L(\theta,a_1)$; if we decide to take the risk reduction action, then the loss we face is $L(\theta,a_2)$.

Sample space *S*: The additional information available to be collected. With recurrent event-time endpoints, it is common to schedule analyses at the times of occurrence of specified landmark events, such as the 5*th* event, the 10*th* event, and so on. The collecting of this additional data or information should also be reflected in the decision process.

The cost of collecting this additional information should also be reflected in the decision process. The detailed analysis descriptions of each phase are as follows:

Prior analysis

The available prior clinical knowledge (e.g., physician's opinion, past experience, or the similar clinical status) about the parameter space, Θ:{(λ_0,β)| λ_0>0}, can be represented by a joint distribution indicating the relative likelihood of each state of nature. Loss functions appropriate for the status quo a_1 and risk reduction action a_2 can be derived by taking all cost-related data into account. Once the prior distribution and loss function have been specified, it is easy to perform a prior analysis by simply comparing the expected losses for the options a_1 and a_2. Therefore, if $E\{L(\theta,a_1)\} > E\{L(\theta,a_2)\}$, then option a_2 is optimal, and if $E\{L(\theta,a_1)\} \leq E\{L(\theta,a_2)\}$, then option a_1 is optimal.

Preposterior analysis

When the expected losses associated with options a_1 and a_2 are fairly close, we might not feel very confident about a decision based solely on a prior analysis, and gathering additional information might be desirable. However, before collecting additional information, we have to investigate the possible outcomes and costs of each candidate sampling plan, and to determine the first stage decision of whether collecting additional information is worthwhile and also which sampling plan is the best in terms of cost-effectiveness. The Expected Value of Sample Information (EVSI) can be calculated according to $EVSI(S_i) = \underset{j=1,2}{Min}\, \boldsymbol{E}\{L(\theta, a_j)\} - \boldsymbol{E}_{s}\{\underset{j=1,2}{Min}\, E\{L(\theta, a_j) \mid S_i\}\}$, where S_i is the ith sampling plan under consideration. The Expected Net Gain of Sample information (ENGS) is defined as $ENGS(S_{i^*}) = EVSI\{S_{i^*}\} - C_I\{S_{i^*}\}$, where $C_I\{S_{i^*}\}$ is the cost of the ith sampling plan. Therefore, if $ENGS \leq 0$, then it is not worthwhile collecting additional information; conversely, if $ENGS > 0$, then we can start collecting data and prepare for a posterior analysis, and the i^*th sampling plan should be adopted in order to satisfy the condition $ENGS(S_{i^*}) = \underset{i}{Max}\{ENGS(S_{i^*})\}$.

Posterior analysis

Once the optimal sampling plan, say $S^{(k)}$, has been selected based on the preposterior analysis. After the data collection is complete, the observed data $S^{(k)}=s^{(k)}$ can then be used to perform a posterior analysis. The decision should then be made in accordance with the strategy that if $\boldsymbol{E}\{L(\theta, a_1) | S^{(k)} = s^{(k)}\} \geq \boldsymbol{E}\{L(\theta, a_2) | S^{(k)} = s^{(k)}\}$, then option a_2 is optimal, and if $\boldsymbol{E}\{L(\theta, a_1) | S^{(k)} = s^{(k)}\} < \boldsymbol{E}\{L(\theta, a_2) | S^{(k)} = s^{(k)}\}$, then option a_1 is optimal.

By exploring the relationships among the optimal decision and the extent of uncertainty about recurrent trends, the conditions under which gathering additional information is worthwhile can be determined, and more generally in developing guidelines for the use of isolating trends in data in risk management. The following terminology will be used throughout this paper:

C_A: the cost of a recurrent event if it occurs.
C_R: the cost of the proposed risk reduction action.
C_I: the cost of collecting additional information.
ρ: the reduction in failure rate that would result from the proposed risk reduction action ($0<\rho<1$).
M: the expected number of failures during the time period $[t,T]$ under the status quo.

Suppose that patient has a planned lifetime T, and the decision of whether to keep the status quo or perform some intervention treatment must be made at time t. The decision variable we are dealing with is then the expected number of recurrent event during the time period $[t,T]$.

Sincerecurrent times are assumed to be drawn from a nonhomogeneous Poisson process with intensity function $\lambda(t)=\lambda_0 h(\beta;t)$, the expected number of recurrent events in $[t,T]$ under the status quo is given by

$$M \equiv M(T,t,\lambda_0,\beta) = \int_t^T \lambda(s)ds = \int_t^T \lambda_0 h(\beta;s)ds = \lambda_0[H(\beta;T)-H(\beta;t)] = \lambda_0 \mathsf{H}, \quad (4)$$

where $H(\beta; y) = \int_0^y h(\beta; s)ds$, and $\mathsf{H} \equiv H(\beta) = H(\beta;T) - H(\beta;t)$. Suppose that undertaking the intervention treatment will reduce the failure intensity by a fraction ρ, where $0 < \rho < 1$. Then the expected number of recurrent events in $[t,T]$ if undertaking the intervention treatment is performed is given by

$$\int_t^T \lambda(s)(1-\rho)ds = (1-\rho)\lambda_0 \quad \mathsf{H} = (1-\rho)M \quad (5)$$

On the basis of the assumptions given above, we therefore have a two-action problem with a linear loss function, where the loss for taking action a_1 (i.e., continuing with the status quo) is $C_A M$ and the loss for taking action a_2 (i.e., undertaking the intervention treatment) is $C_A(1-\rho)M + C_R$. The expected loss for the status quo is simply $C_A \boldsymbol{E}\{M\}$, and the expected loss for undertaking the intervention treatment is $C_A(1-\rho)\boldsymbol{E}\{M\} + C_R$, and $M_C = C_R/(C_A\rho)$ is the cutoff value of $E\{M\}$ for undertaking the intervention treatment.

As a simplistic assumption, one can assume that λ_0 and β are independent of each other. For example, if the prior distributions for λ_0 and β are Gamma(α; γ) and Uniform (a,b), respectively, and the power-law failure model is assumed to be suitable under consideration, then the joint distribution of λ_0 and β is just the product of the individual distributions of λ_0 and β. The joint posterior distribution for λ_0 and β obtained by Bayesian updating is simply proportional to the product of the joint prior distribution for λ_0 and β and the likelihood function, which is given by

$$f(\lambda_0, \beta \mid x_1, x_2, \cdots, x_{n^*}) = K\lambda_0^{a+n^*-1}\beta^{n^*}\left(\prod_{i=1}^{n^*} x_i\right)^{\beta-1} exp[-\lambda_0(\gamma + x_{n^*}^{\beta}) - 1)] \quad \lambda_0 > 0, a < \beta < b \quad (6)$$

where K is the normalizing constant.

Since the prior and posterior density functions for M are functions of λ_0 and β, some prior and posterior mean values of M can be derived by the bivariate transformation technique. However, closed forms for the prior and posterior means of M are not always available, which is typically the case for the Bayesian analysis. Nevertheless, Bayesian prior and posterior analyses can still be performed by computing the prior and posterior mean values of M using the numerical integration technique and comparing them with the cutoff value $M_C = C_R/(C_A\rho)$ (i.e., the cutoff value of $E\{M\}$ for taking the risk reduction action). If the relevant mean is smaller than M_C, then we should keep the status quo; if not, then we should perform the risk reduction action.

4. Simulation Study

We have used the recurrent ovarian cancer case study to illustrate the use of the models developed in the previous sections. The medical records and pathology were accessible by the Chung Shan Medical University Hospital Tumor Registry. The

birth date of the studied subject was 1-May-1943, and the observation period was from 24-Sep -2010, to 23- August-2011. The recurrent dates for the subject during the observation period were: {24-Jan-2011, 24-Apr-2011, 24-May-2011, 23-Jul-2011, 22-Aug-2011}. An application is performed with the assumption that $E\{\lambda_0\}$=0.2 and $SD\{\lambda_0\}$=0.03, and that β is *Uniform*[1,2.8]. In addition, we have C_A=238,000, C_R=196,000, C_I=102,000, ρ=0.08, T=75, and t=62. We use the entire failure data for the posterior analysis. Prior and posterior analyses are performed by comparing the prior and posterior mean values of M with the cutoff value M_C.

Since the recurrent data are already available, we assume that the cost of analyzing the recurrent data is associated with tasks such as reviewing records and interviewing physicians. As can be seen in the table 1, prior and posterior analyses can be performed by comparing the prior and posterior mean values of λ_0 with the cutoff value M_C. The observed data support the adoption of the risk reduction action, whereas the priors support the status quo. This can be explained by the fact that the observed data indicate greater deterioration than was assumed by the prior distributions.

Table 1 Summary the result of Bayesian inference

Prior $E\{M\}$	4.9500
Optimal sampling number of failure	7
Actual sampling number of failure	4
Prior $E\{\lambda_0\}$	0.2
Posterior $E'\{\lambda_0\}$	0.1532
Prior $E\{\beta\}$	1.49
Posterior $E'\{\beta\}$	1.7314
Cutoff Value of $E\{M\}$ for Risk Reduction	6.9400
Prior Decision	Status quo
Posterior $E'\{M\}$	9.6983
Posterior Decision	Risk Reduction

5. Conclusions

In medical decision making, the event of primary interest is recurrent, so that for a given unit the event could be observed more than once during the study. In general, the successive times between recurrent events are not necessarily identically distributed. However, if any critical deterioration is detected, then the decision of when to take the intervention, given the costs of diagnosis and therapeutics, is of fundamental importance. In this paper, Bayesian inference of a nonhomogeneous Poisson process with power law failure intensity function is used to describe the behavior of recurrent ovarian cancer. Finally, this paper develops a systematic way to integrate the expert's opinions which will furnish clinician with valuable support for quality medical decision making.

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