

A BAYESIAN META-ANALYSIS

**BAYESIAN META-ANALYSIS OF TRIALS OF CHEMOTHERAPY
WITH RADIOTHERAPY IN THE MANAGEMENT OF PATIENTS WITH
NEWLY DIAGNOSED LOCALLY ADVANCED SQUAMOUS CELL OR
UNDIFFERENTIATED NASOPHARYNGEAL CANCER**

By

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Abstract

Meta-analysis is a set of statistical procedures used to aggregate results from independent studies. These techniques are widely used in clinical research to get the overall picture from a series of trials addressing the same question. We used Bayesian hierarchical models to evaluate effect of the addition of chemotherapy to radiotherapy treatment in patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer. We also performed subgroup analysis to determine the best timing and regimen of chemotherapy.

It is demonstrated that the Bayesian model does not only efficiently incorporate all sources of variability, but is also robust under different likelihood functions.

The results based on Bayesian hierarchical models assuming a non-informative prior are similar to those from classical random effects models. A significant effect was observed in favour of patients who received radiochemotherapy versus those who received radiotherapy alone. The analysis revealed that neoadjuvant chemotherapy is the best timing for treatment.

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Chapter 1

Introduction

1.1 Background

Nasopharyngeal carcinoma (NPC) is a tumor of epithelial origin with a distinctive geographic and ethnic distribution. It has a specific high incidence rate for Southeast Asia, particularly the southern provinces in China, the Mediterranean basin, North Africa, Greenland, and Alaska. The annual incidence varies from 10 to 65 persons per 100,000 people in Asia to less than 1 per 100,000 people in North America⁽¹⁻⁴⁾. NPC occurs more frequently in males, with a gender ratio of male:female of 3:1. In contrast to other head and neck cancers, the vast majority of NPC tumors bear little or no causal association with heavy smoking or alcohol abuse. In addition, NPC patients are relatively younger and have a better performance status. The etiology of NPC is likely driven by several factors that include both genetic predisposition and environmental factors. Epidemiological evidence suggests that Epstein-Barr virus (EBV) is strongly associated with this malignancy, particularly in endemic areas, although the exact role of EBV in NPC

carcinogenesis remains to be unknown. The World Health Organization (WHO) has classified NPC into three types: Type 1, Keratinizing squamous cell carcinoma; Type 2, Nonkeratinizing carcinoma; Type 3, Undifferentiated carcinoma.

In North America, NPC is quite rare with approximately 2% of all cancers occurring in the head and neck regions. WHO type 1 is the most common type in North America, while WHO type 2 and 3 are most common in Asian countries. Regardless of tumor type, patients with stage I or II diseases usually have a reasonable rate of 5-year survival with radiotherapy (approximately 70% to 90%), although the prognosis for those with advanced disease (stage III or IV) is generally poor (approximately 45% to 55%)^(3,4). Unfortunately, the majority of patients with newly diagnosed NPC present with locally advanced diseases⁽³⁻⁵⁾.

As a curative strategy, radiotherapy is the standard treatment for this patient population. However, this strategy is generally poor with respect to overall survival rates and thus has led to further investigations for other alternatives. Several randomized trials have explored the role of chemotherapy in the neoadjuvant, adjuvant or concurrent settings, combined with radiotherapy versus the standard radiotherapy regimen alone. Since NPC tumors are known to be chemosensitive, any improvements in survival and local control typically come at the cost of increased toxicity. To date, optimal therapy for the treatment of NPC has not yet to be established. The Head and Neck Cancer Disease Site Group considered that a systematic review of the evidence comparing treatment options for patients with newly diagnosed squamous cell or undifferentiated nasopharyngeal cancer was warranted at this time⁽¹⁾.

1.2 Objectives

The purpose of this study is to perform a Bayesian meta-analysis to determine the additional value of neoadjuvant, concurrent or adjuvant chemotherapy to radiation in the curative treatment of locally advanced NPC, mainly with regard to the 2-year overall survival and 2-year disease-free survival. In this project, the 2-year overall survival and 2-year disease-free survival refer to the odds ratio of 2-year mortality and 2-year disease, respectively. If the addition of chemotherapy to radiotherapy treatment improves the overall survival or disease-free survival, then we need to find the best timing and regimen of chemotherapy. Also, a comparison between Bayesian meta-analysis and the classical random effects meta-analysis will be addressed.

1.3 Scope of the Study

In this study, we adopt the Bayesian approach to perform meta-analysis of the data. The thesis is arranged as follows. In Chapter 2, we construct hierarchical models based on non-informative priors. Then, we perform a sensitivity analysis with three different likelihood functions, Normal, Laplace, and Student's t with different degrees of freedom. We also perform a Bayesian subgroup analysis to determine the best timing and regimen of chemotherapy. In Chapter 3, we discuss the comparison of results of Bayesian meta-analysis and Bayesian subgroup analysis with those from the classical random effects models. Then, we discuss the robustness of the Bayesian results based on the sensitivity analyses. Finally, we discuss the advantages and disadvantages of Bayesian

meta-analysis in Chapter 4 and provide our conclusions.

1.4 Significance of the Study

The primary objective of this study is the development of guidelines for use of chemotherapy as an adjustment to radiotherapy in the treatment of patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer. The goal is to provide clear summarization of the treatment effect on different settings, and provide knowledge base for policy makers and clinicians. By performing Bayesian meta-analysis, all parameter uncertainty and other pertinent information are formally included in the modeling of the data, thus not only does it increase the statistical power by combining many studies, but it also improves the precision of the treatment effect. Non-informative priors are adopted in Bayesian analysis and thus final inferences are dominated by data from the trials.

1.5 Literature Search Strategy

The literature was searched using MEDLINE (OVID; 1966 through October 2004), EMBASE (OVID; 1980 through October 2004), the Cochrane Library (OVID; Issue 3, 2003), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse, as well as abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (1997-2003), the American Society for Therapeutic Radiology and Oncology (1992-2003), the Asian

Clinical Oncology Society (2001), the International Congress of Radiation, Oncology (1997 and 2001), the European Society of Therapeutic Radiology and Oncology (1992, 1994, 1996, 1998, 2000, 2002), and the European Society for Medical Oncology (2000, 2002). Article bibliographies and personal files were also searched to October 2003 for evidence relevant to this thesis.

1.6 Inclusion Criteria and Exclusion Criteria

The present study is a systematic review based on published reports or published abstracts of randomized controlled trials. To be eligible, published studies had to deal with newly diagnosed patients with locally advanced squamous cell or undifferentiated nasopharyngeal cancer who have received any combination of chemotherapy plus radiation in the neoadjuvant, concurrent, or adjuvant setting (intervention) versus radiotherapy alone (control). Also, results for the primary outcomes of interest should be disease-free survival (odds ratio of disease), or overall survival (odds ratio of mortality). Practice guidelines, meta-analyses, or systematic reviews explicitly based on randomized trials related to the guideline question were also eligible for inclusion in the systematic review of the evidence.

Thirty-four randomized trials with fifty-nine comparisons were eligible for inclusion in this systematic review of the evidence. Chemotherapy was delivered with radiotherapy in the neoadjuvant (13 trials), concurrent (9 trials), adjuvant settings (4 trials), or was delivered in the neoadjuvant plus adjuvant setting (6 trials), concurrent plus adjuvant therapy (2 trials), neoadjuvant and concurrent setting (3 trials), or neoadjuvant, concurrent

and adjuvant therapy (2 trials).

Articles were excluded from the systematic review of the evidence if they were trials that did not report separate results for patients with nasopharyngeal cancer.

Chapter 2

Methods

2.1 Methods of Analysis

The analysis adopted the Bayesian approach of meta-analysis is to pool the results from thirty-six studies on the effects of radiochemotherapy versus radiotherapy alone in treating NPC. The primary model used the Normal distribution as the likelihood function to estimate common treatment effect assuming non-informative priors for the model parameters. Secondary analysis involved sensitivity analyses using three different likelihood functions, that is, Normal, Student's t and Laplace distributions. Bayesian subgroup analysis was also done to find the best timing and regimen of chemotherapy. Comparisons between Bayesian hierarchical models and classical random effects model are made. Software WinBUGS (Windows Version of Bayesian Inference Using Gibbs Sampling) and Revman 4.2 (Review Manager) were used to help perform Bayesian and Classical meta-analysis respectively^(20, 21).

In the following sections, we describe the models and assumptions used in both the classical random-effects model (section 2.2) and Bayesian analysis (section 2.3, section 2.4). We also discussed the sensitivity analysis (section 2.5) and Bayesian subgroup analysis (section 2.6).

2.2 A Classical Random Effects Meta-Analysis Model

In a classical random effects model it is assumed that the treatment difference parameters in the r studies $(\theta_1, \dots, \theta_r)$ are a sample of independent observations from $N(\theta, \tau^2)$. The general random effects model is given by

$$\hat{\theta}_i = \theta + \nu_i + \varepsilon_i \quad (2.1)$$

for $i = 1, \dots, r$, where $\hat{\theta}_i$ is the estimate of θ_i , θ is the common underlying treatment effect, the ν_i are normally distributed random effects with mean 0 and variance τ^2 , the ε_i are error terms and are realizations of normally distributed random variables with expected value 0 and variance denoted by ξ_i^2 . The terms ν_i and ε_i are assumed to be independently distributed. It follows that

$$\hat{\theta}_i \sim N(\theta, \xi_i^2 + \tau^2) \quad (2.2)$$

Let $w_i^* = (w_i^{-1} + \hat{\tau}^2)^{-1}$, where w_i^{-1} is an estimate of ξ_i^2 and $\hat{\tau}^2$ is an estimate of τ^2 , if $(w_i^*)^{-1}$ is the true variance of $\hat{\theta}_i$, then the maximum likelihood estimate of θ is given by $\hat{\theta}$, where

$$\hat{\theta} = \frac{\sum_{i=1}^r \hat{\theta}_i w_i^*}{\sum_{i=1}^r w_i^*} . \quad (2.3)$$

This is the pooled point estimate of common treatment effect and an approximate 95% confidence interval (CI) for θ is given by

$$\hat{\theta} \pm 1.96 \sqrt{\frac{1}{\sum_{i=1}^r w_i^*}} . \quad (2.4)$$

For further details on classical random effects model see Whitehead A⁽²²⁾. For the classical meta-analysis, the results are expressed as odds ratio (OR) with corresponding 95% CI. The criterion for statistical significance is set *a priori* at $\alpha = 0.05$. Heterogeneity is assessed using χ^2 test with statistical significance set at $\alpha = 0.05$.

2.3 Bayesian Meta-Analysis

In the Bayesian approach, uncertainty about all unknown parameters is expressed through posterior distributions. The data consist of study estimates of treatment difference, $\hat{\theta}_i$, $i=1, \dots, r$, where

$$\hat{\theta}_i \sim N(\theta_i, \xi_i^2) . \quad (2.5)$$

The θ_i is the true treatment effect of the i^{th} study. The unknown parameters θ_i and ξ_i^2 are given prior distributions. In this model, it is assumed that the θ_i are exchangeable, there is no prior belief about their ordering. The vector of study estimates, $\hat{\theta}_i$, is denoted

by y , the corresponding vector of parameters, θ_i , by ψ , the vector of the variance of study estimates ξ_i^2 , by w . The joint density (likelihood) function for the data by $f(y|\psi, w)$, and the prior distributions for ψ and w by $p(\psi|\theta, \tau^2)$ and $p(w)$. Where θ is the common underlying treatment effect, τ^2 is the variability between treatment effects.

Considering θ and τ^2 as hyperparameters and giving them independent prior distributions, a hierarchical model can be constructed. The unknown parameters consist of w , ψ , θ and τ^2 , and their joint posterior distribution, using Bayes' theorem, is given by

$$P(\psi, w, \theta, \tau^2 | y) \propto f(y | \psi, w) p(\psi | \theta, \tau^2) p(w) p(\theta) p(\tau^2) \quad (2.6)$$

Where $p(\theta)$ and $p(\tau^2)$ are the prior distributions for θ and τ^2 .

Inference about each parameter can be obtained by integrating over the other parameters. Unless the prior distributions are very simple, these integrals cannot be calculated in closed form. Solutions to overcome this problem include the use of asymptotic methods to obtain analytical approximations to the posterior density, numerical integration and simulation. More recently much work has been carried and in developing simulation-based methods classified as Markov Chain Monte Carlo (MCMC) methods⁽²³⁾. Among these methods, Gibbs sampling has been increasingly used in applied Bayesian analysis within health care research settings^(24,25). The appeal of Gibbs sampling is that in wanting to summarize a marginal posterior density, simulating from a typically high dimensional joint posterior density is often difficult, but the posterior conditional distributions are often much easier to sample from. Gibbs sampling uses this fact, together with Ergodic theory, which ensures that if the marginal conditional densities are sampled from a sufficiently long period of time, then the realizations will approximate the

desired marginal posterior densities⁽²⁶⁾. The software package WinBUGS⁽²⁰⁾ was used to help get the posterior mean or median. It should be noticed that much care has to be taken in establishing convergence of the Markov chain and sensitivity to specific prior distributions when using WinBUGS.

2.4 Non-informative Prior Distribution

Non-informative priors were assumed for all model parameters. Non-informative priors, also known as vague priors of ignorance, attempt to impart little information about the parameters of interest, are commonly used because they often lead to inferences comparable to those obtained under classical approaches. The use of non-informative priors is quite common in Bayesian analysis^(27,28).

Since a prior normal distribution with a very large variance for θ will have little influence on the eventual posterior, and an inverse gamma (*IG*) prior distribution with parameters close to zero for τ^2 will have little effect, the non-informative prior distributions for the mean θ as $N(0, 1.0E+6)$ and for the variance between treatment effect τ^2 as $IG(0.001, 0.001)$ are used. Similarly, we assumed the variability within each trial has an inverse gamma distribution, i.e.

$$\xi_i^2 \sim IG(0.001, 0.001) \quad (2.7)$$

The inverse gamma distribution with parameters α and λ , $IG(\alpha, \lambda)$ has the density function

$$p(x) = \frac{\lambda^\alpha}{\Gamma(\alpha)} x^{-\alpha-1} \exp\left(\frac{-\lambda}{x}\right) \quad (2.8)$$

where

$$\Gamma(\alpha) = \int_0^{+\infty} x^{\alpha-1} \exp(-x) dx \quad (2.9)$$

for $\alpha > 0$.

It should be noted that WinBUGS parameterizes the variance in terms of precision. Precision is defined as the reciprocal of the variance. In WinBUGS, if X is distributed as a Normal distribution with mean μ and precision τ^2 , then the probability density function (pdf) of X is

$$\sqrt{\frac{\tau}{2\pi}} \exp\left(-\frac{\tau}{2}(x-\mu)^2\right); \quad -\infty < x < \infty \quad (2.10)$$

If the heterogeneity parameter is assigned a non-informative inverse Gamma distribution, then the inverse heterogeneity parameter will be a gamma distribution. In WinBUGS, the pdf of a gamma distribution with shape parameter r and scale parameter μ is

$$\frac{\mu^r x^{r-1} e^{-\mu x}}{\Gamma(r)}; r > 0 \quad (2.11)$$

For Bayesian analysis, the results are expressed as posterior mean with corresponding 95% credible interval (C_rI). Posterior densities, diagnostics summaries and diagnostics graphics are also provided.

2.5 Sensitivity Analysis

In order to check whether posterior inferences are robust to misspecification of the

likelihood function or not, three different likelihood functions, Normal, Student's t and Laplace, were used.

If X is distributed as a Student's t distribution with mean μ , precision τ , and k degrees of freedom, then the pdf of X is

$$\frac{\Gamma(\frac{k+1}{2})}{\Gamma(\frac{k}{2})} \sqrt{\frac{\tau}{k\pi}} \left[1 + \frac{\tau}{k}(x-\mu)^2\right]^{-\frac{k+1}{2}}; \quad -\infty < x < \infty; \quad k \geq 2 \quad (2.12)$$

Four different degrees of freedom of Student's t were used in the analysis, namely, $k = 4, 8, 12$ and 16 .

If X is distributed as a Laplace distribution, also called double exponential distribution, with mean μ and precision parameter τ , then the pdf of X is

$$\frac{\tau}{2} \exp(-\tau|x-\mu|); \quad -\infty < x < \infty \quad (2.13)$$

The Student's t and Laplace distributions were chosen because they fall in the same family of symmetric distribution with the Laplace knowing a heavy peak center and thinner tails (leptokurtic), while the Student's t is bell shaped like the Normal distribution but has thicker tails. For the Student's t distribution, the smaller the degrees of freedom, the thicker the tails are.

2.6 Bayesian Subgroup Analysis

In addition to a simple comparison of efficacy using the primary outcomes, clinical trial analysts often explore the possibility of different treatment effects within the study

population. This is referred to as subgroup analysis. The thirty-six randomized clinical trials were subdivided into seven subgroups on the basis of timing and regimen of chemotherapy. There are neoadjuvant, concurrent, adjuvant, neoadjuvant plus adjuvant, concurrent plus adjuvant, neoadjuvant plus concurrent, and neoadjuvant, concurrent plus adjuvant.

In each subgroup, the data consist of study estimates of treatment difference, $\hat{\theta}_i$, $i = 1, \dots, r$, where $\hat{\theta}_i \sim N(\theta_i, \xi_i^2)$. The θ_i are the true treatment effect of the i^{th} study. The unknown parameters θ_i and ξ_i^2 are given prior distributions as $\theta_i \sim N(\theta, \tau^2)$ and $\xi_i^2 \sim IG(0.001, 0.001)$. The non-informative prior distributions for the mean θ as $N(0, 1.0E+6)$ and for the variance between treatment effect τ^2 as $IG(0.001, 0.001)$ are used.

Chapter 3

Results

3.1 Results of Classical Random Effects Model

The two major outcomes are odds ratio of 2-year disease and odds ratio of 2-year mortality as 2-year disease-free survival and 2-year overall survival. Figures A.1 and A.2 display the results of these trials and the classical meta-analysis results⁽²⁹⁾.

There was a significant difference in 2-year disease-free survival in favor of patients who received radiochemotherapy versus those who received radiotherapy alone (OR = 0.66; 95% CI, 0.52 to 0.82). However, significant heterogeneity was detected using χ^2 statistics, the *p*-value is 0.0008. By timing of chemotherapy for 2-year disease-free survival, radiochemotherapy with neoadjuvant chemotherapy (OR = 0.76; 95% CI, 0.59 to 0.98), or concurrent plus adjuvant chemotherapy (OR = 0.25; 95% CI, 0.12 to 0.52) was significantly superior to radiotherapy alone.

Data on 2-year overall survival included thirty-four trials with thirty-six comparisons. Across thirty-six comparisons, there was a significant difference in favor of patients who

received radiochemotherapy versus those who received radiotherapy alone (OR = 0.70; 95 % CI, 0.59 to 0.84). Test for heterogeneity was not significant using χ^2 statistics, and the *p*-value is 0.07. By timing of chemotherapy, radiotherapy with neoadjuvant chemotherapy (OR = 0.78; 95 % CI, 0.62 to 0.97), or concurrent plus adjuvant chemotherapy (OR = 0.32; 95 % CI, 0.17 to 0.61), or neoadjuvant, concurrent plus adjuvant (OR = 0.44; 95 % CI, 0.21 to 0.92) was significantly superior to radiotherapy alone.

3.2 Results of Bayesian Non-informative Model

All the Bayesian results presented are based on 200,000 iterations following a burn-in of 1000. A logarithm transform of the odds ratios are done to make the data more normalized.

Bayesian meta-analysis for non-informative prior distribution included seventeen trials with twenty-two comparisons for 2-year disease-free survival, and thirty-four trials with thirty-six comparisons for 2-year overall survival. The odds ratios and 95% credible intervals are presented in Table 3.1. To get an easy comparison, we presented the classical results in Table 3.2.

| | | |
|--------------------------------------|---------------------------------|----------------------------|
| Bayesian non-informative model | 2-year disease-free survival | 2-year overall survival |
| Odds Ratio | 0.7151 | 0.7348 |
| CrI (95%) | 0.5275 - 0.9208 | 0.6034 - 0.8761 |

Table 3.1: Pooled analysis of radiochemotherapy versus radiotherapy alone: 2-year disease-free survival and 2-year overall survival (Bayesian non-informative model)

| | | |
|-----------------------------------|------------------------------|-------------------------|
| Classical Random effects model | 2-year disease-free survival | 2-year overall survival |
| Odds Ratio | 0.66 | 0.70 |
| CI (95%) | 0.52 - 0.82 | 0.59 - 0.84 |

Table 3.2: Pooled analysis of radiochemotherapy versus radiotherapy alone: 2-year disease-free survival and 2-year overall survival (classical random effects model)

3.3 Results of Sensitivity Analysis

After 200,000 iterations, the common underlying treatment effect parameter θ converges for Normal, Student's t , and Laplace likelihood functions. The kernel densities of θ for 2-year disease-free survival and 2-year overall survival are given in Figures A.3 and A.4. The odds ratio and confidence interval of common treatment effect θ for different likelihood functions are presented in Tables 3.3 and 3.4. From Figures A.3, A.4 and Tables 3.3, 3.4, we concluded that posterior inferences are robust to misspecification of the likelihood functions.

| Likelihood Function | Odds Ratio | C.I (95%) |
|--------------------------|------------|-----------------|
| Normal | 0.7151 | 0.5275 - 0.9208 |
| Laplace | 0.6874 | 0.5092 - 0.8941 |
| Student's t ($k=4$) | 0.7183 | 0.5269 - 0.9218 |
| Student's t ($k=8$) | 0.7196 | 0.5271 - 0.9186 |
| Student's t ($k=12$) | 0.7176 | 0.5281 - 0.9205 |
| Student's t ($k=16$) | 0.7161 | 0.5258 - 0.9208 |

Table 3.3: Pooled analysis of radiochemotherapy versus radiotherapy alone: 2-year disease-free survival (Bayesian non-informative model for different likelihood functions)

| Likelihood Function | Odds Ratio | C _r I (95%) |
|--------------------------|------------|------------------------|
| Normal | 0.7348 | 0.6034 - 0.8761 |
| Laplace | 0.7084 | 0.5824 - 0.8493 |
| Student's t ($k=4$) | 0.7356 | 0.6054 - 0.8755 |
| Student's t ($k=8$) | 0.7345 | 0.6034 - 0.8756 |
| Student's t ($k=12$) | 0.7337 | 0.6030 - 0.8745 |
| Student's t ($k=16$) | 0.7348 | 0.6040 - 0.8765 |

Table 3.4: Pooled analysis of radiochemotherapy versus radiotherapy alone: 2-year overall survival (Bayesian non-informative model for different likelihood functions)

Figures A.3, A.4, A.5 and A.6 provided the kernel density estimates of posterior distributions for parameter θ and τ using Normal, Laplace and Student's t distributions. Diagnostic graphs of time series, dynamic trace and autocorrelation are presented in Figures A.7, A.8, ..., A.18.

3.4 Results of Bayesian Subgroup Analysis

The results of subgroup analysis using Bayesian meta-analysis method for 2-year disease-free survival and 2-year overall survival are presented in Table 3.5 and Table 3.6. Results for 2-year disease-free survival included four subgroups according to the timing and regimen of chemotherapy, they are neoadjuvant, concurrent, adjuvant, and concurrent

plus adjuvant. Neoadjuvant plus adjuvant and neoadjuvant plus concurrent are excluded from the subgroup analysis because they contain only one estimable odds ratio respectively. In order to get a clear comparison of Bayesian subgroup analysis with classical subgroup analysis, results from classical meta-analysis are presented as well.

| Time of Chemotherapy | Classical Method | | Bayesian Method | |
|-----------------------------|------------------|-------------|-------------------|------------------------|
| | OR | CI (95%) | OR | C _r I (95%) |
| Neoadjuvant | 0.76 | 0.59 - 0.98 | 0.75 | 0.49 - 1.12 |
| Concurrent | 0.71 | 0.46 - 1.08 | 0.62 | 0.30 - 1.49 |
| Adjuvant | 0.82 | 0.56 - 1.19 | 0.80 | 0.48 - 1.35 |
| Concurrent plus adjuvant | 0.25 | 0.12 - 0.52 | Not convergent | Not convergent |

Table 3.5: Comparison of Bayesian subgroup analysis with classical subgroup analysis for 2-year disease-free survival

Table 3.5 suggested that by timing of chemotherapy, radiotherapy with concurrent chemotherapy and adjuvant chemotherapy were not significantly superior to radiotherapy alone from both Bayesian method and classical method. For neoadjuvant chemotherapy, the Bayesian model suggested no significant difference between radiochemotherapy and radiotherapy alone, while the classical model suggested that radiotherapy with neoadjuvant chemotherapy was significant superior to radiotherapy alone. Since there are only two trials in concurrent plus adjuvant subgroup, Bayesian method did not reach

convergence, but classical method suggested that it was significantly superior to radiotherapy alone.

| Time of Chemotherapy | Classical Method | | Bayesian Method | |
|---------------------------------------------|------------------|-------------|-------------------|-----------------------|
| | OR | CI (95%) | OR | C _r I(95%) |
| Neoadjuvant | 0.78 | 0.62 - 0.97 | 0.81 | 0.69 - 0.92 |
| Concurrent | 0.72 | 0.46 - 1.12 | 0.72 | 0.39 - 1.38 |
| Adjuvant | 1.14 | 0.65 - 1.98 | 1.03 | 0.42 - 2.67 |
| Neoadjuvant plus adjuvant | 0.73 | 0.47 - 1.13 | 0.67 | 0.39 - 1.13 |
| Concurrent plus adjuvant | 0.32 | 0.17 - 0.61 | Not convergent | Not convergent |
| Neoadjuvant plus concurrent | 0.47 | 0.19 - 1.18 | 0.42 | 0.05 - 4.55 |
| Neoadjuvant, concurrent plus adjuvant | 0.44 | 0.21 - 0.92 | Not convergent | Not convergent |

Table 3.6: Comparison of Bayesian subgroup analysis with classical subgroup analysis for 2-year overall survival

Table 3.6 suggested that by timing of chemotherapy, radiotherapy with neoadjuvant chemotherapy was significantly superior to radiotherapy alone, while concurrent chemotherapy, adjuvant chemotherapy, neoadjuvant plus adjuvant chemotherapy, and neoadjuvant plus concurrent chemotherapy were not significantly superior to radiotherapy alone from both Bayesian method and classical method. Since there are only two trials in concurrent plus adjuvant subgroup and neoadjuvant, concurrent plus adjuvant subgroup, the Bayesian method did not reach convergence, but the classical method suggested that both of them were significantly superior to radiotherapy alone.

Kernel density estimates, time series and dynamic trace for parameters θ and τ in neoadjuvant subgroup, concurrent subgroup, adjuvant subgroup, neoadjuvant plus adjuvant subgroup and neoadjuvant plus concurrent subgroup are presented in Figures A.19, A.20, ..., A.26.

Chapter 4

Discussion and Conclusion

4.1 Similarities and Differences Between Classical and Bayesian Meta-Analysis

Meta-analysis is a collection of statistical techniques for combining studies. It makes research findings more accessible to the general public, and provides a knowledge base for policy makers and practitioners. Both classical and Bayesian meta-analysis have the aforementioned goals and use the concept of probability as a measure of uncertainty. Both of them use sampling distributions to collect data and use likelihood functions to construct analysis models.

Classical meta-analysis is derived from a frequentist approach, which is concerned with an imagined infinite number of repetitions of the same inferential problem for fixed values of the unknown parameters. The Bayesian philosophy is fundamentally different from the frequentist. In the Bayesian approach, all unknown parameters are treated as random variables, such as the true treatment effect of the i^{th} study θ_i , the common

underlying treatment effect θ and the variability between treatment effects τ^2 , and they have a joint probability distribution specified prior to observation of data. In general, these prior distributions are reflections of subjective opinion. Since we know little about the model parameters, we adopted non-informative priors. The updating of the prior distribution in light of the data, governed by Bayes' theorem, leads to the posterior distribution. Bayesian inference is based on this posterior distribution. The analogue of a frequentist confidence interval is the credibility interval. The 95% credibility interval has the property that the Bayesian is 95% certain that the parameter lies within it; while a 95% confidence interval has the property that in 95% of repetitions it will include the true value of the parameter.

4.2 Advantages of Bayesian Meta-Analysis

An important advantage of the Bayesian approach is the ability to account for uncertainty of all relevant sources of variability in the model. In the Bayesian analysis, the posterior density is fully evaluated and exact posterior standard deviations and credibility intervals are obtained from the posterior distributions for each model parameter. By contrast, in the frequentist approach, the standard errors and CIs are computed using formulae which assume that the variance components are known. From Table 3.1 and Table 3.2, we can see that the odds ratio of common treatment effect θ in the Bayesian model is slightly bigger than that in the classical model, and the 95% credible interval derived from the posterior distribution is larger than confidence interval for 2-year disease-free survival and 2-year overall survival. That is because all unknown

parameters are included in the Bayesian model.

Furthermore, interpretation of Bayesian results is more intuitive than the classical results. Without the abstract p-values and the use of arbitrary choices of levels of significance, the Bayesian approach gives the probability of clinical benefit and the exact credible interval. For example, we calculated the probability of the odds ratio of common effect parameter θ smaller than 1, and we got $P(\text{OR} < 1) = 1$ for 2-year disease-free survival. That means that the probability of radiochemotherapy being more effective than radiotherapy is 1. In terms of 2-year disease-free survival, the probability that radiochemotherapy is more effective than radiotherapy is also 1. We cannot calculate these probabilities using the classical model.

4.3 Discussion of Subgroup Analysis

The purpose of doing subgroup analysis is the existence of variation in response of different timing and regimen of chemotherapy. It is helpful for clinical decision making. A clinician cannot recommend a treatment to a patient based on the average response. One must provide clinicians with enough information to assess the likely response of individual patients, against which they can weigh the risk and possibly cost.

From the subgroup analysis result, we can see that there is wide variation in the size of the effect. The treatment has a strong positive effect in two subgroups and no effect in the complementary subgroups for 2-year disease-free survival using classical method. For Bayesian method, all subgroups show no effect for 2-year disease-free survival. For

2-year overall survival, three subgroups show positive effect for classical method, one subgroup shows positive effect for Bayesian method, others either show no effect in classical model or do not converge in Bayesian model. This situation is often referred to as a qualitative subgroup effect as opposed to quantitative effects in which all subgroups show benefits of treatment.

One possible explanation of these qualitative subgroup effects is that the number of trials in most subgroups, which showed negative effect, is too small (less than five). Trials are always underpowered to detect true subgroup effects unless a priori and an appropriate sample size accommodations are incorporated; that is why we adopted Bayesian meta-analysis to explore subgroup effects.

Interpreting the findings requires caution. Until proven otherwise, one should assume that if a treatment shows benefit overall in a study, then the average treatment effect will apply to each recognizable subgroup.

4.4 Challenges of Bayesian Meta-Analysis

Like classical meta-analysis, Bayesian meta-analysis has some limitations. The first consideration is the Simpson's Paradox, whereby a reversal in the direction of the relationship may occur when different data from different sources is combined. The second limitation is the quality of the studies included in the meta-analysis. If the studies included in the meta-analysis are flawed or biased, so is the meta-analysis. The third limitation is publication bias. There is always a high likelihood for studies that did not achieve statistical significance not to be published. Therefore statistically significant

studies are more likely to be included in the meta-analysis, which will result in an overestimate of the treatment effect. In this Bayesian meta-analysis, efforts were put forth to obtain more information, such as contacting the authors of the abstract in an attempt to get unpublished papers.

4.5 Conclusion

In general, the Bayesian models agreed with the classical random effects model that for patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer, chemotherapy added to radiotherapy significantly improves the survival rate as compared with radiotherapy alone. A large survival benefit was detected for neoadjuvant chemotherapy therapy.

Bayesian non-informative model and classical random effects model gave the same conclusion for 2-year disease-free survival and 2-year overall survival. Odds ratios for the common treatment effect are all smaller than 1, and those credibility intervals and confidence intervals do not contain 1. That means a significant effect in favour of patients who received radiochemotherapy versus those who received radiotherapy alone has been achieved. The best timing for chemotherapy is neoadjuvant, or concurrent plus adjuvant therapy using classical random effects model for 2-year disease-free survival. For 2-year overall survival, the best timing for chemotherapy is neoadjuvant, concurrent plus adjuvant therapy, and neoadjuvant, concurrent plus adjuvant therapy using classical random effects model, while the Bayesian method concluded that only neoadjuvant therapy is the effective timing.

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Appendix A
Figures of Pooled Analysis of Classical
Model and Kernel density, Dynamict race,
time Series and Autocorrelation of
Bayesian Model

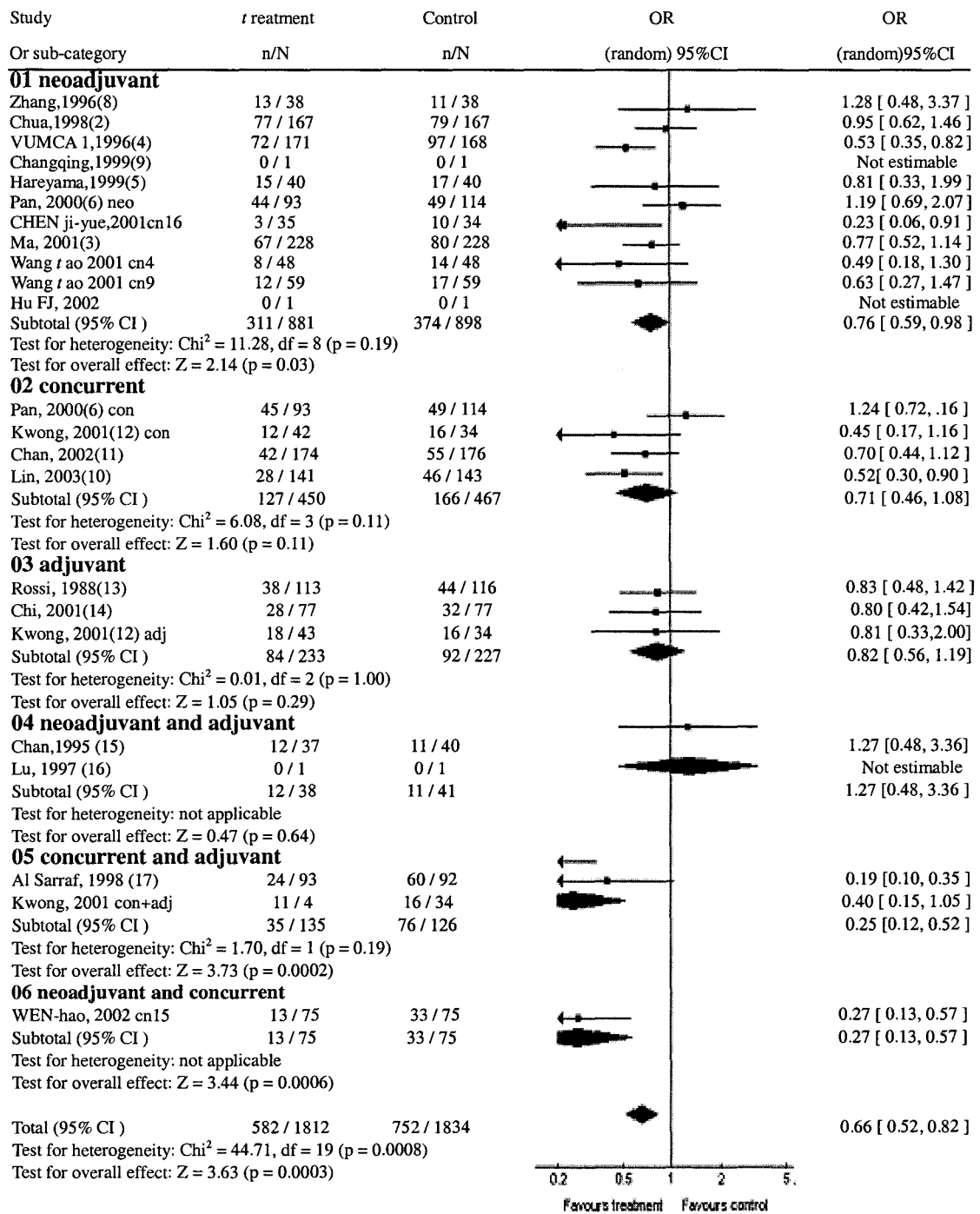


Figure A.1 Pooled analysis of radiochemotherapy versus radiotherapy alone: 2-year disease-free survival (classical random effects model)

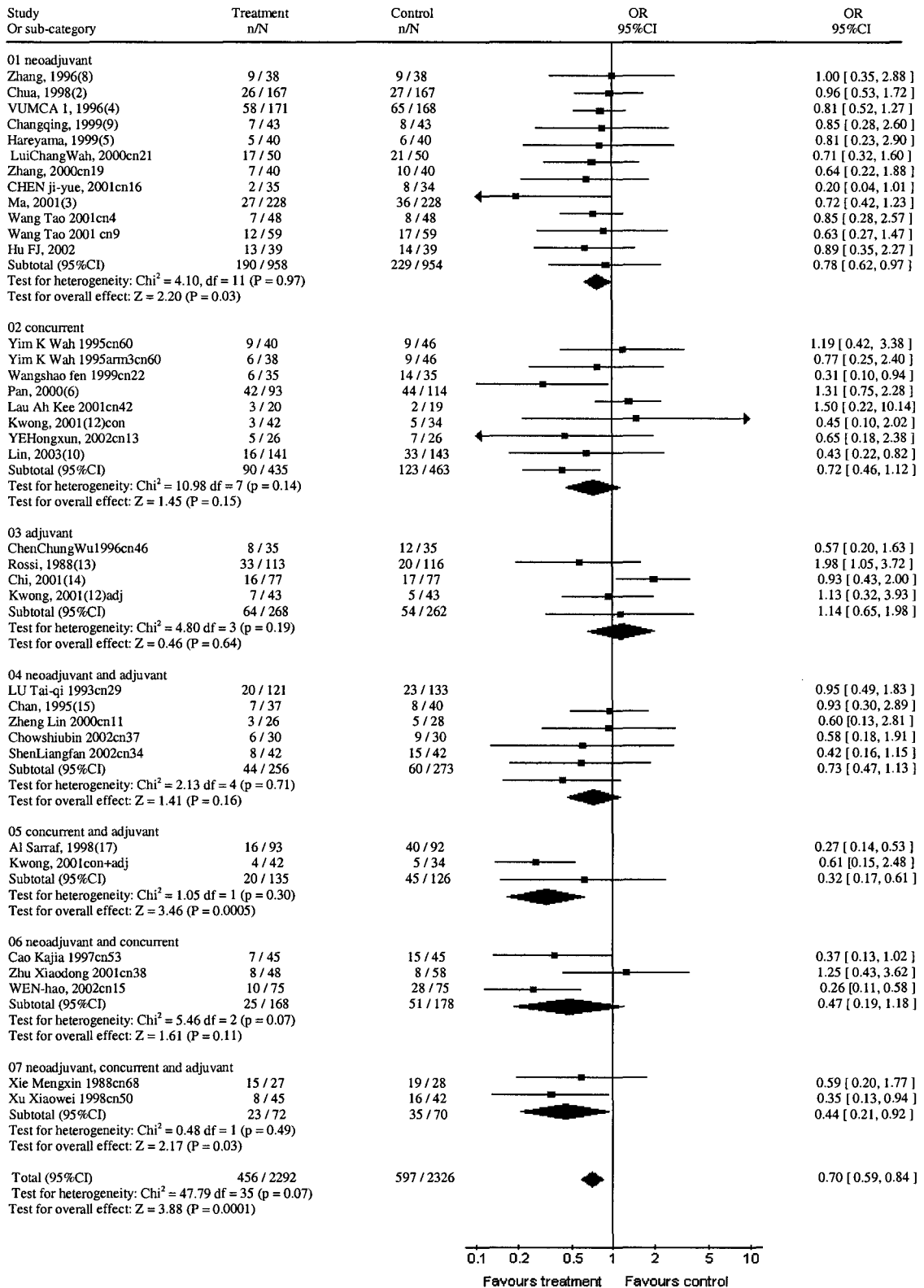
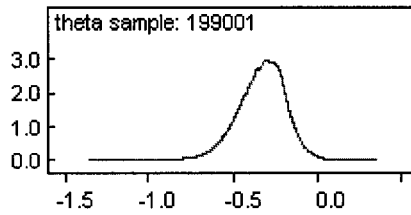
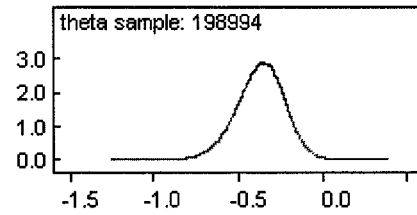


Figure A.2 Pooled analysis of radiochemotherapy versus radiotherapy alone: 2-year overall survival (classical random effects model)

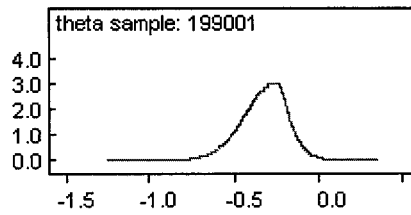
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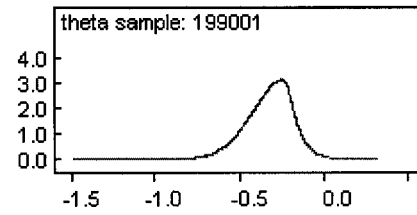
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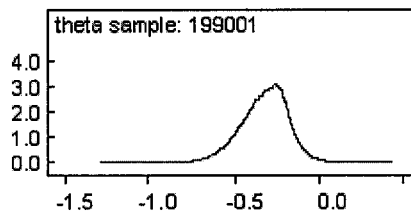
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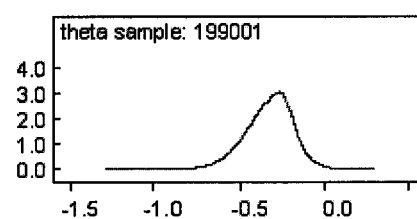
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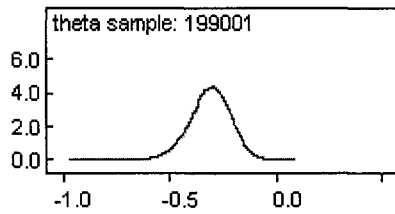


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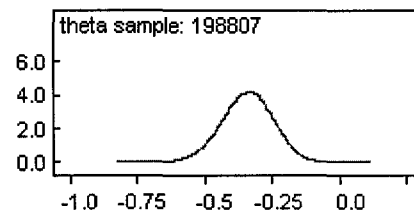


FigureA.3: Kernel density estimates of posterior distributions of parameter θ using Normal, Laplace and Student's t distributions with non-informative priors for 2-year disease-free survival

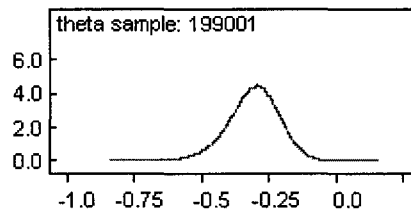
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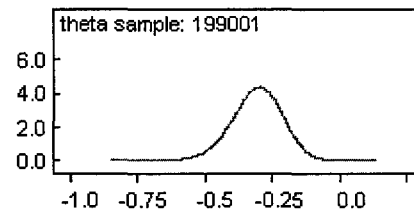
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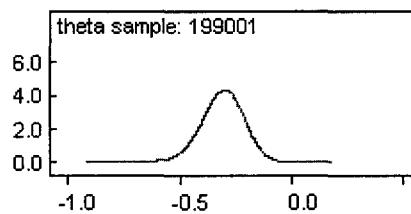
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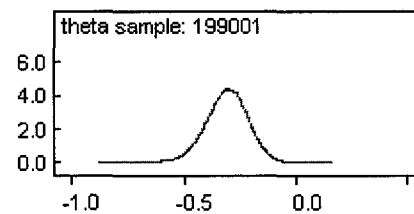
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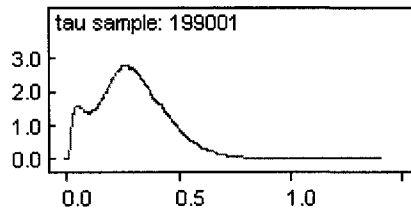


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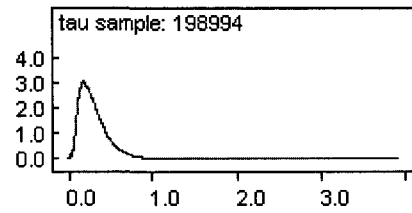


FigureA.4: Kernel density estimates of posterior distributions of parameter θ using Normal, Laplace and Student's t distributions with non-informative priors for 2-year overall survival

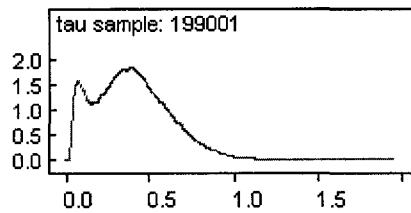
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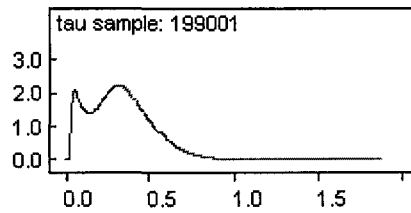
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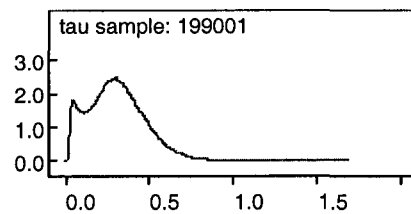
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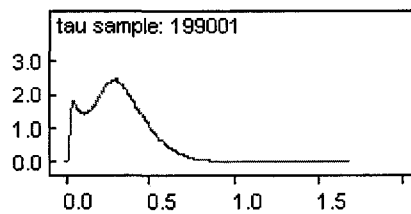
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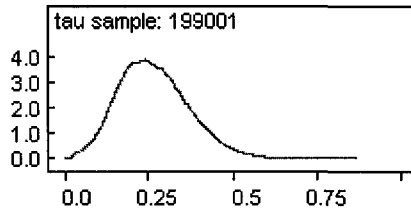


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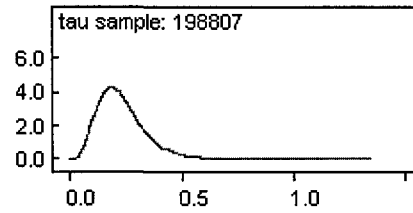


FigureA.5: Kernel density estimates of posterior distributions of parameter τ using Normal, Laplace and Student's t distributions with non-informative priors for 2-year disease-free survival

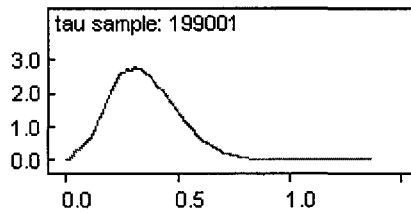
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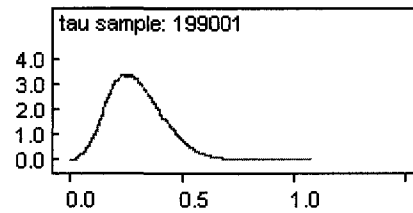
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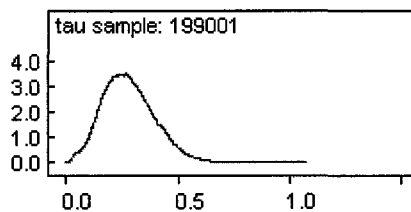
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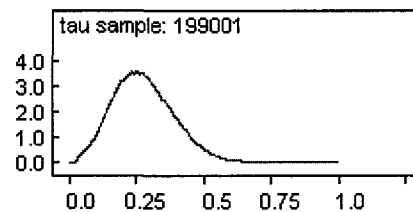
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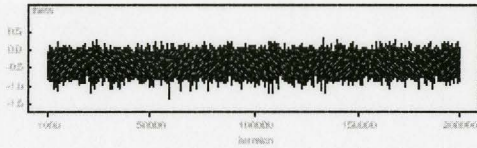


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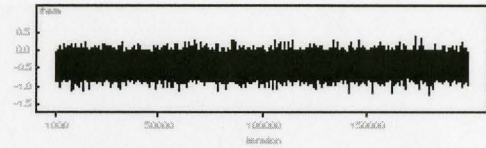


FigureA.6: Kernel density estimates of posterior distributions of parameter τ using Normal, Laplace and Student's t distributions with non-informative priors for 2-year overall survival

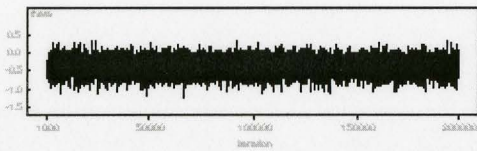
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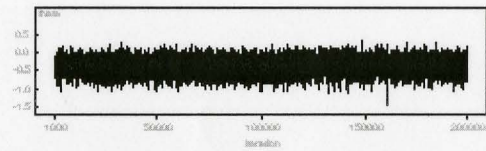
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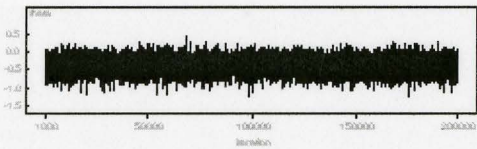
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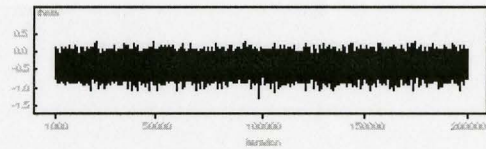
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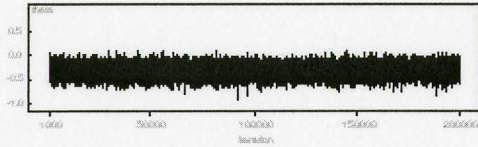


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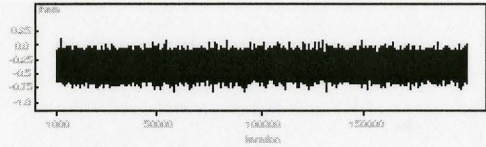


FigureA.7: The time series of parameter θ of Normal, Laplace and Student's t distributions with non-informative priors for 2-year disease-free survival

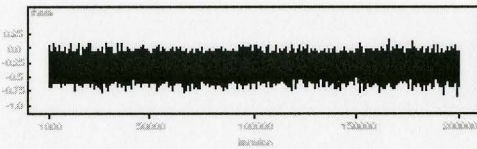
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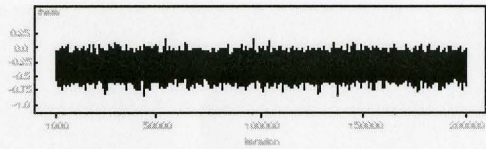
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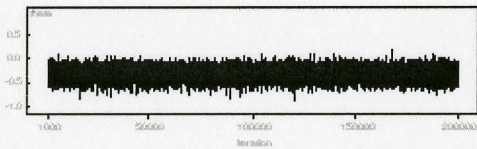
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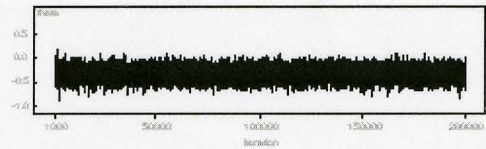
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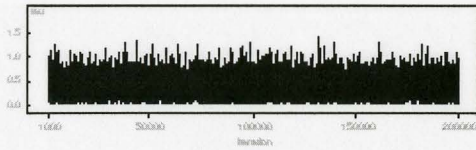


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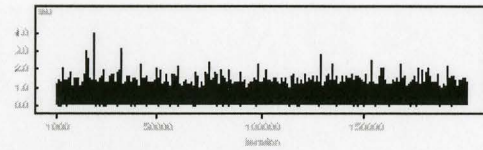


FigureA.8: The time series of parameter θ of Normal, Laplace and Student's t distributions with non-informative priors for 2-year overall survival

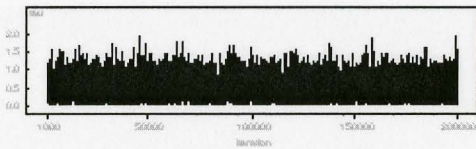
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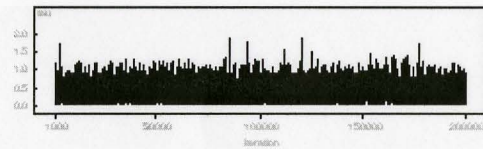
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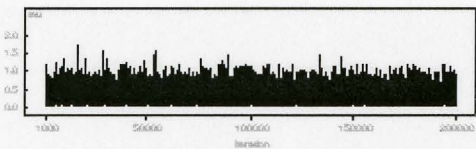
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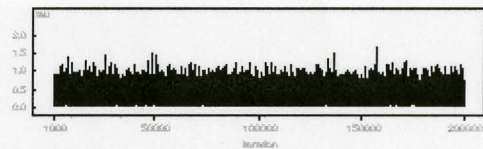
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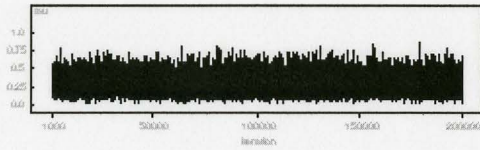


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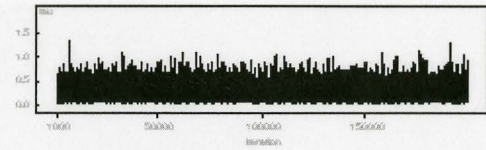


FigureA.9: The time series of parameter τ of Normal, Laplace and Student's t distributions with non-informative priors for 2-year disease-free survival

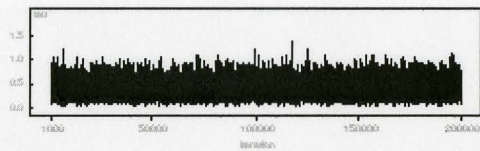
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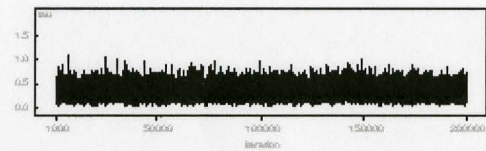
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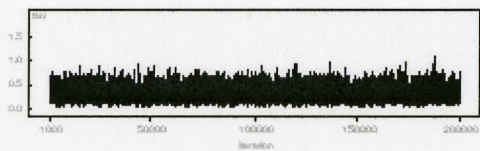
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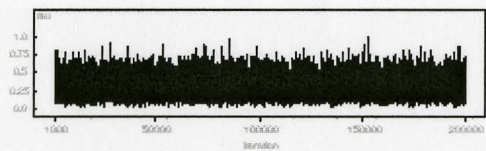
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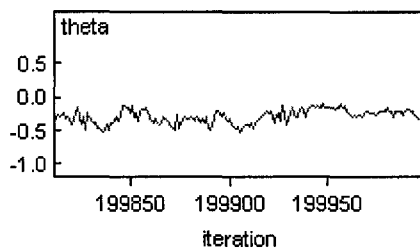


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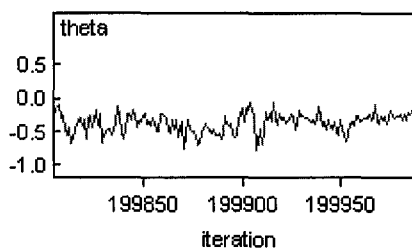


FigureA.10: The time series of parameter τ of Normal, Laplace and Student's t distributions with non-informative priors for 2-year overall survival

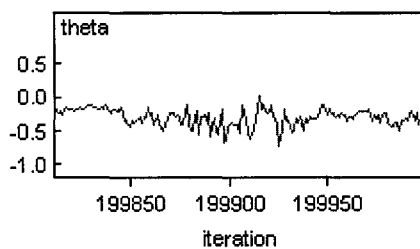
Normal



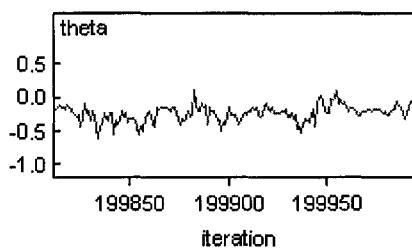
Laplace



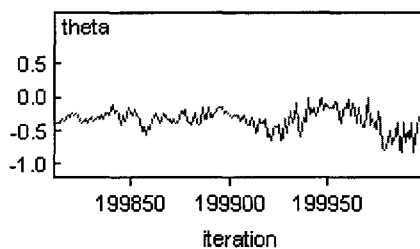
Student's t ($k = 4$)



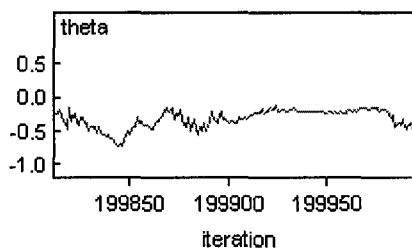
Student's t ($k = 8$)



Student's t ($k = 12$)

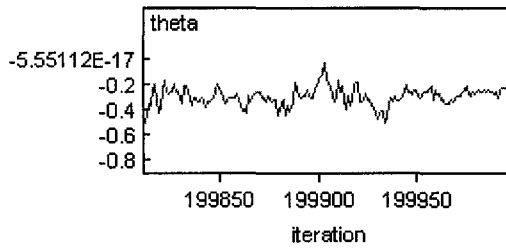


Student's t ($k = 16$)

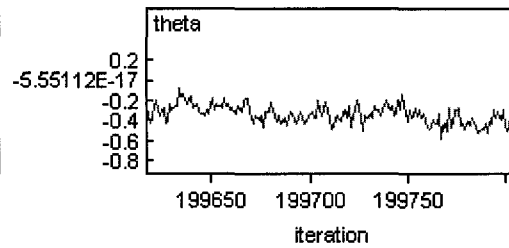


FigureA.11: Dynamic trace of parameter θ of Normal, Laplace and Student's t distributions with non-informative priors for 2-year disease-free survival

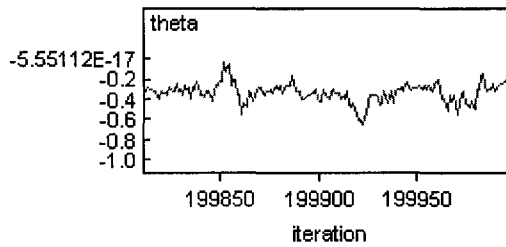
Normal



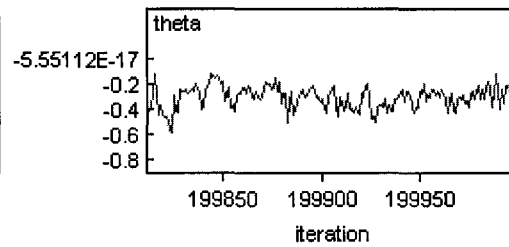
Laplace



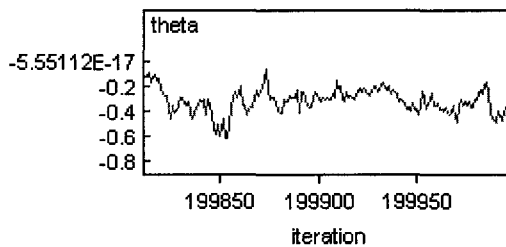
Student's t ($k = 4$)



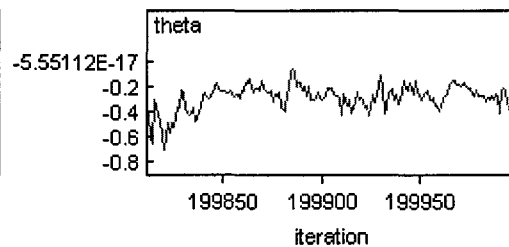
Student's t ($k = 8$)



Student's t ($k = 12$)

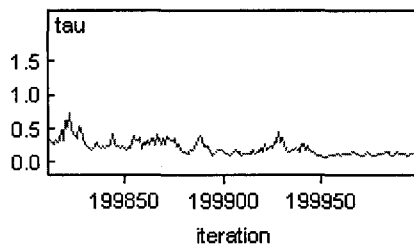


Student's t ($k = 16$)

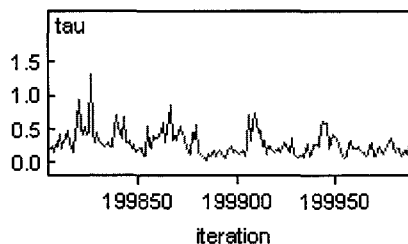


FigureA.12: Dynamic trace of parameter θ of Normal, Laplace and Student's t distributions with non-informative priors for 2-year overall survival

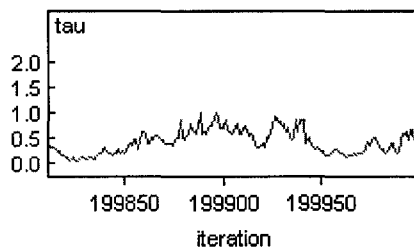
Normal



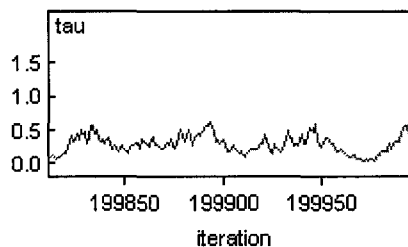
Laplace



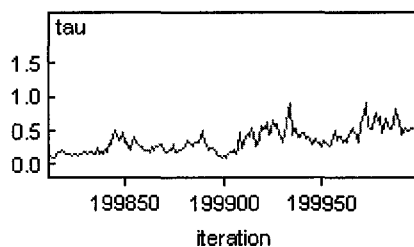
Student's t ($k = 4$)



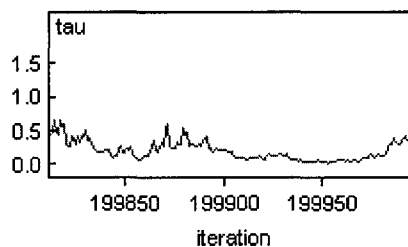
Student's t ($k = 8$)



Student's t ($k = 12$)

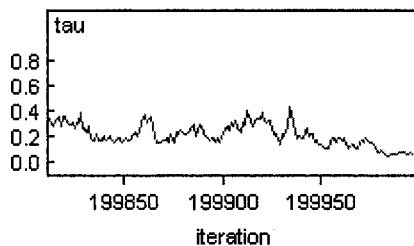


Student's t ($k = 16$)

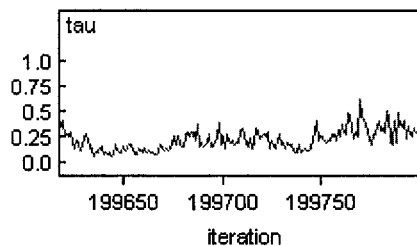


FigureA.13: Dynamic trace of parameter τ of Normal, Laplace and Student's t distributions with non-informative priors for 2-year disease-free survival

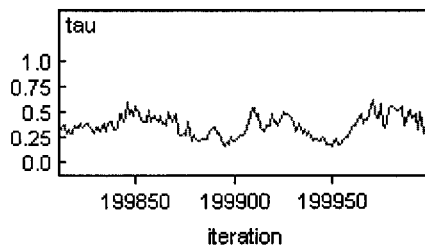
Normal



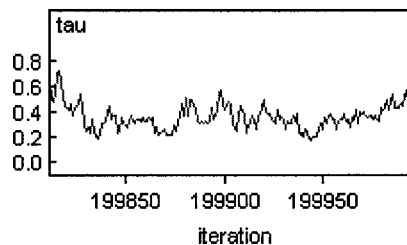
Laplace



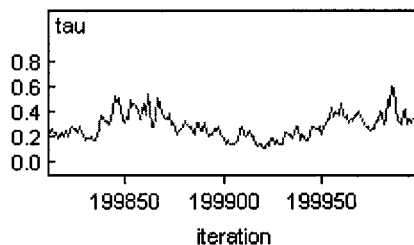
Student's t ($k = 4$)



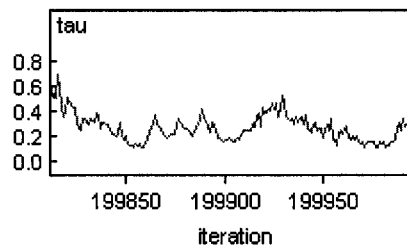
Student's t ($k = 8$)



Student's t ($k = 12$)

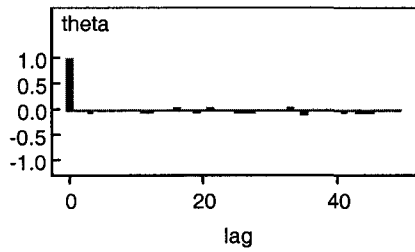


Student's t ($k = 16$)

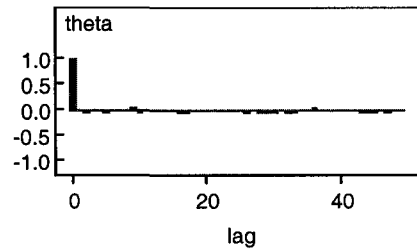


FigureA.14: Dynamic trace of parameter τ of Normal, Laplace and Student's t distributions with non-informative priors for 2-year overall survival

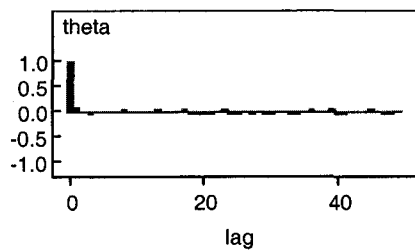
Normal



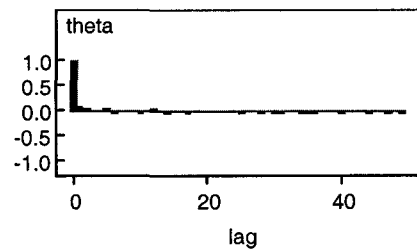
Laplace



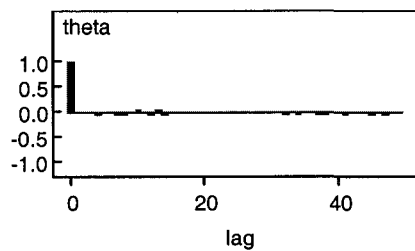
Student's t ($k = 4$)



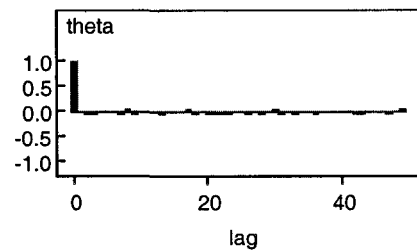
Student's t ($k = 8$)



Student's t ($k = 12$)

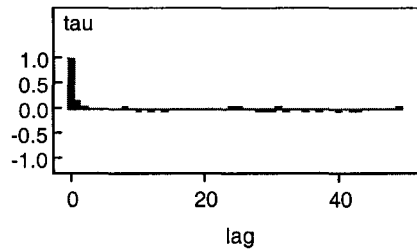


Student's t ($k = 16$)

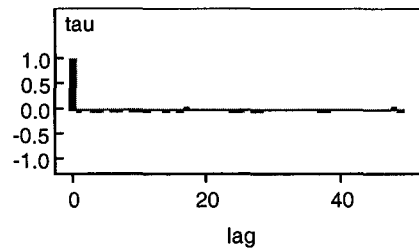


FigureA.15: Plots of the autocorrelation function of parameter θ for Normal, Laplace and student's t distributions with non-informative priors for 2-year disease-free survival

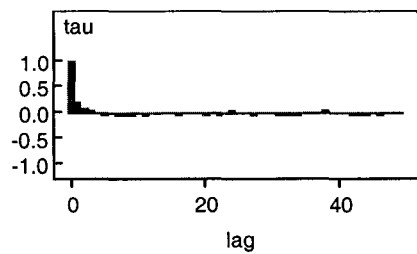
Normal



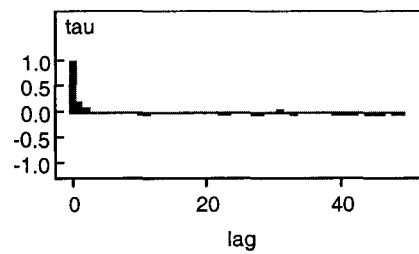
Laplace



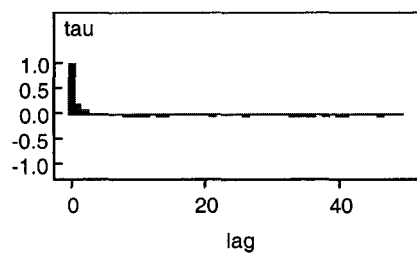
Student's t ($k = 4$)



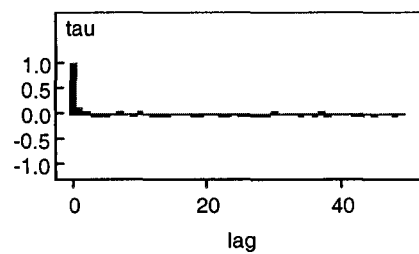
Student's t ($k = 8$)



Student's t ($k = 12$)

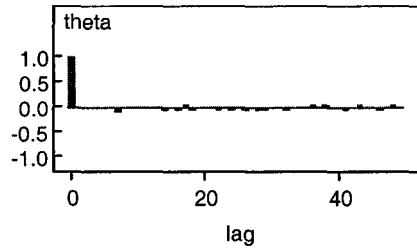


Student's t ($k = 16$)

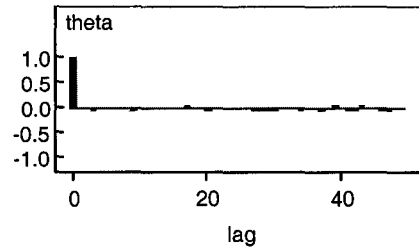


FigureA.16: Plots of the autocorrelation function of parameter τ for Normal, Laplace and student's t distributions with non-informative priors for 2-year disease-free survival

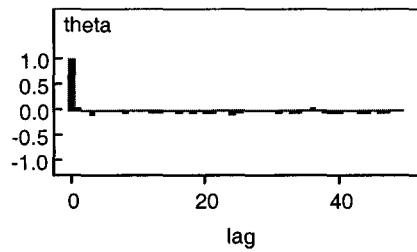
Normal



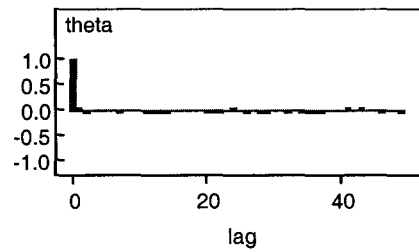
Laplace



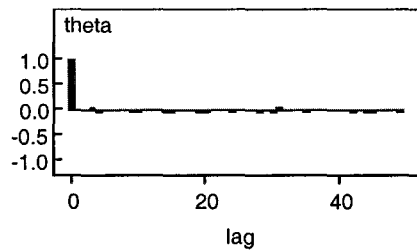
Student's t ($k = 4$)



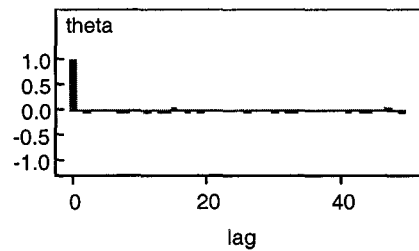
Student's t ($k = 8$)



Student's t ($k = 12$)

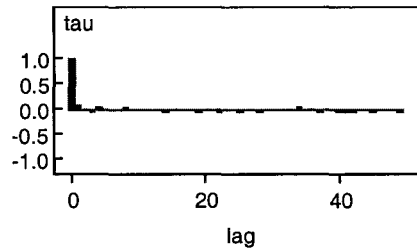


Student's t ($k = 16$)

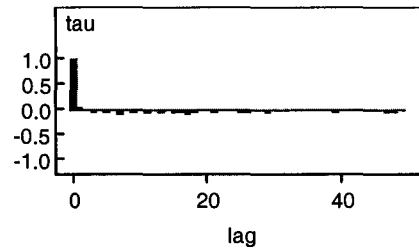


FigureA.17: Plots of the autocorrelation function of parameter θ for Normal, Laplace and student's t distributions with non-informative priors for 2-year overall survival

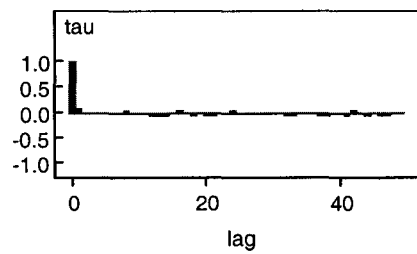
Normal



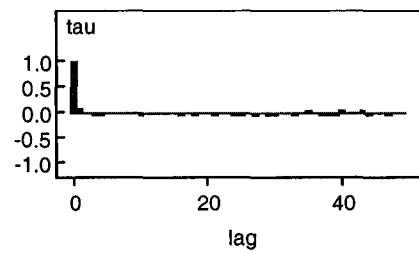
Laplace



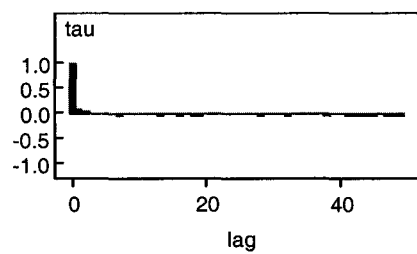
Student's t ($k = 4$)



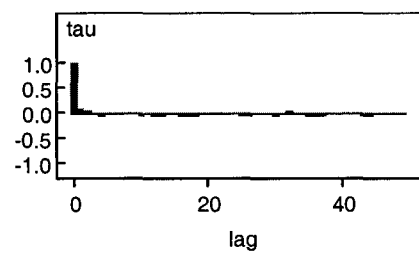
Student's t ($k = 8$)



Student's t ($k = 12$)

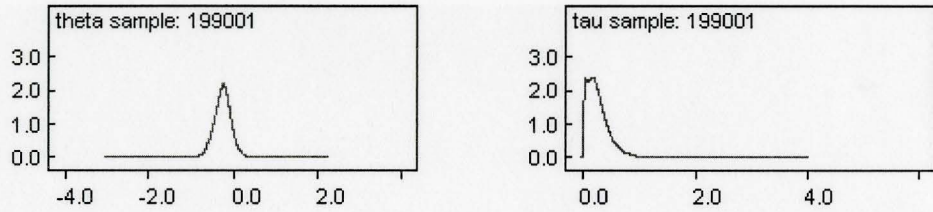


Student's t ($k = 16$)

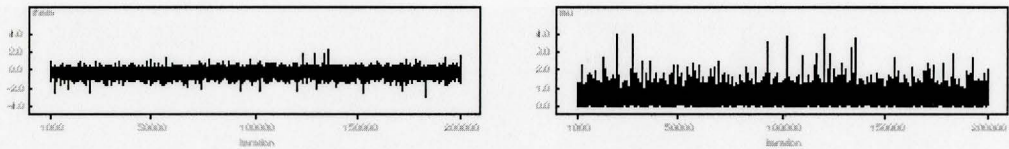


FigureA.18: Plots of the autocorrelation function of parameter τ for Normal, Laplace and student's t distributions with non-informative priors for 2-year overall survival

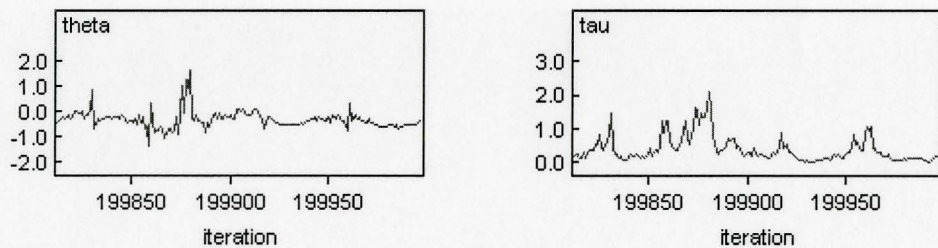
Kernel density estimates of posterior distribution:



Time series for θ and τ :

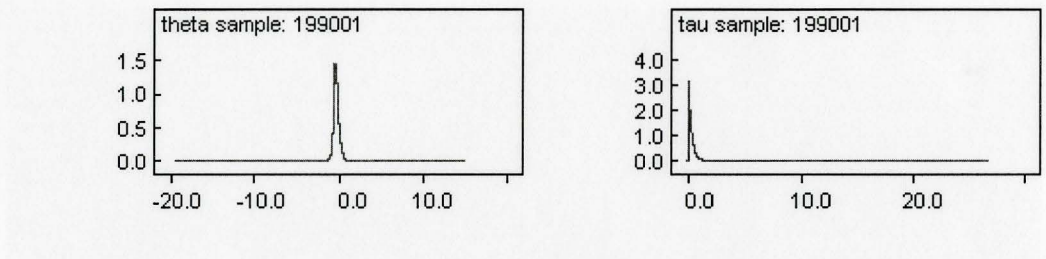


Dynamic trace for θ and τ :

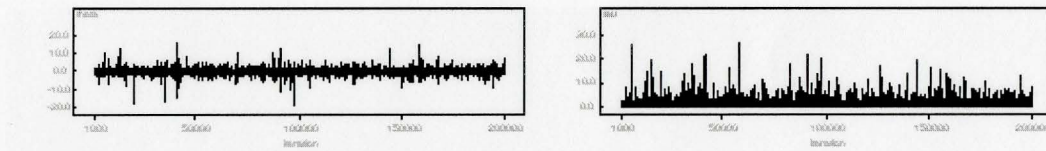


A.19: Kernel density estimates, time series and dynamic trace of parameters θ and τ for 2-year disease-free survival in neoadjuvant subgroup

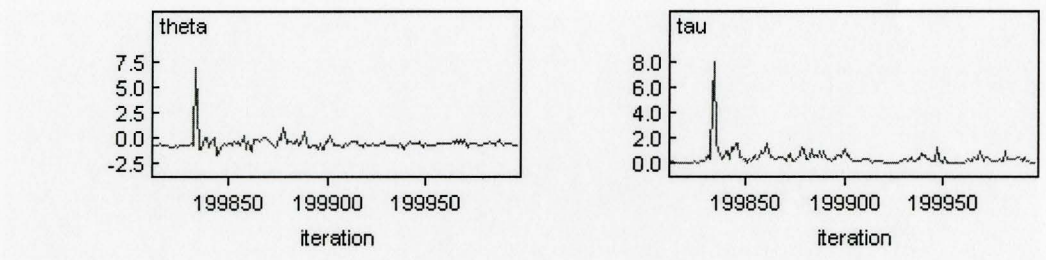
Kernel density estimates of posterior distribution:



Time series for θ and τ :

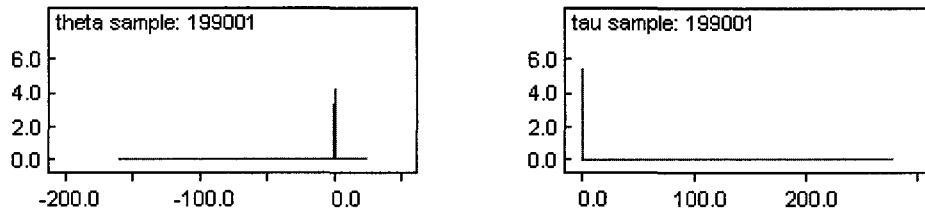


Dynamic trace for θ and τ :

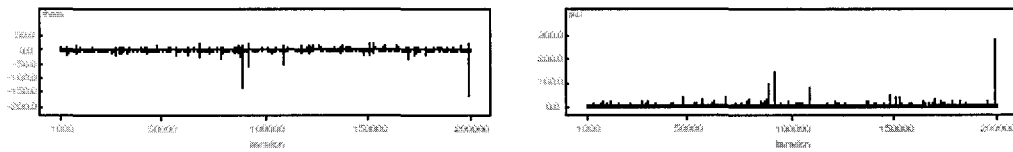


A.20: Kernel density estimates, time series and dynamic trace of parameters θ and τ for 2-year disease-free survival in concurrent subgroup

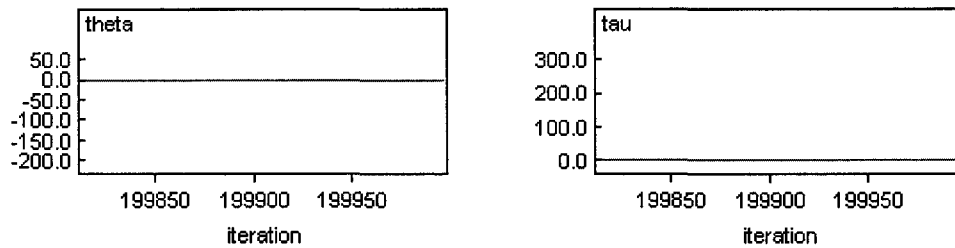
Kernel density estimates of posterior distribution:



Time series for θ and τ :

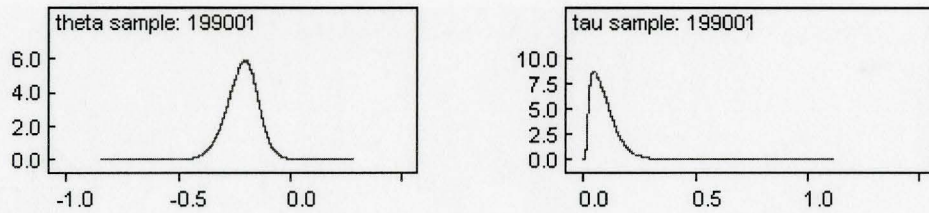


Dynamic trace for θ and τ :

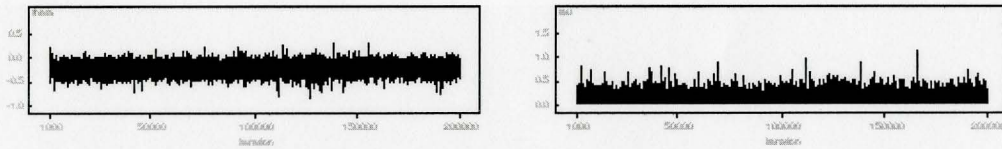


A.21: Kernel density estimates, time series and dynamic trace of parameters θ and τ for 2-year disease-free survival in adjuvant subgroup

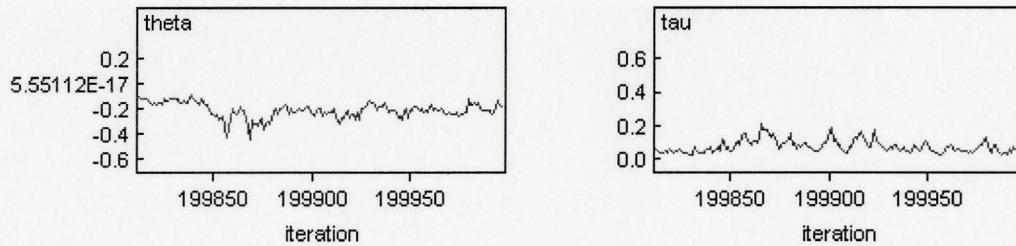
Kernel density estimates of posterior distribution:



Time series for θ and τ :

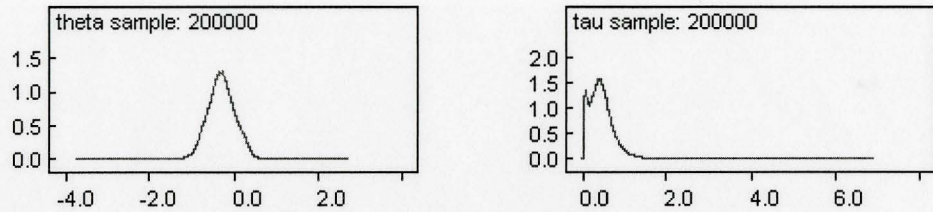


Dynamic trace for θ and τ :

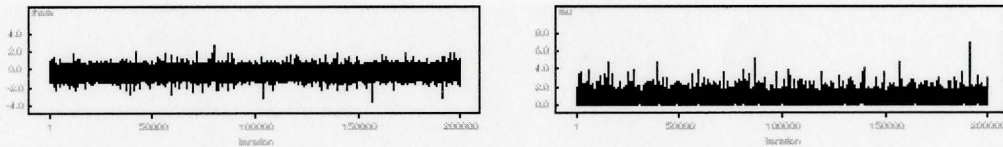


A.22: Kernel density estimates, time series and dynamic trace of parameters θ and τ for 2-year overall survival in neoadjuvant subgroup

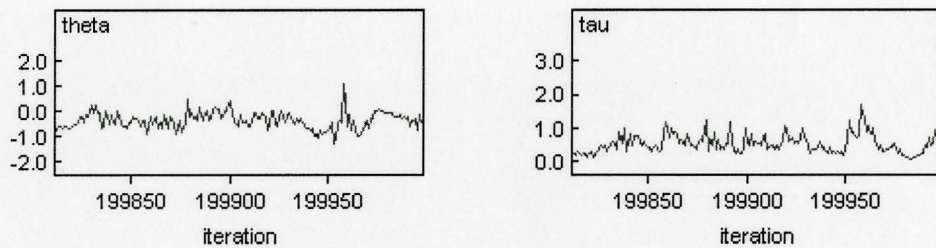
Kernel density estimates of posterior distribution:



Time series for θ and τ :

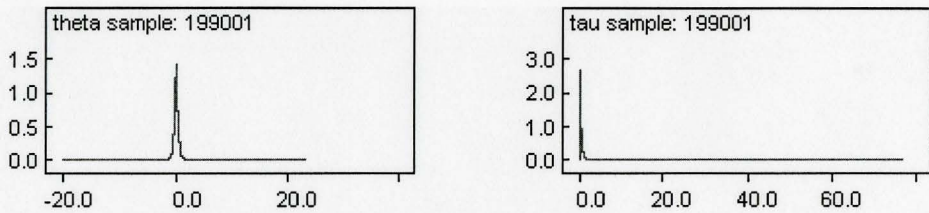


Dynamic trace for θ and τ :

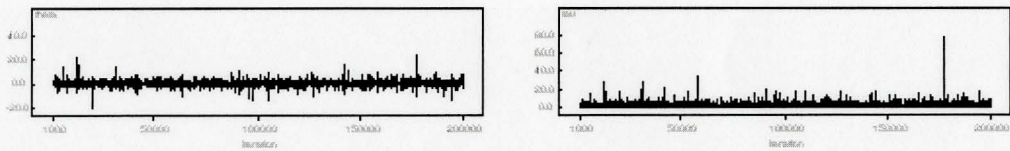


A.23: Kernel density estimates, time series and dynamic trace of parameters θ and τ for 2-year overall survival in concurrent subgroup

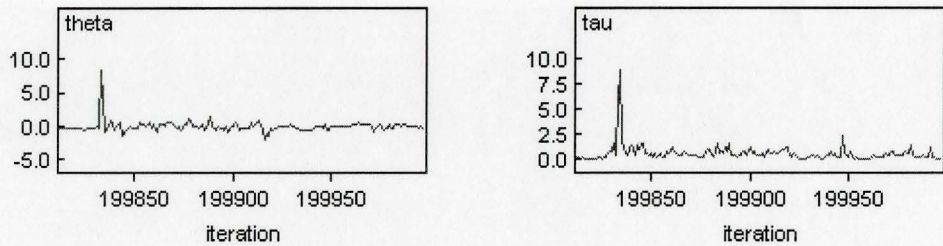
Kernel density estimates of posterior distribution:



Time series for θ and τ :

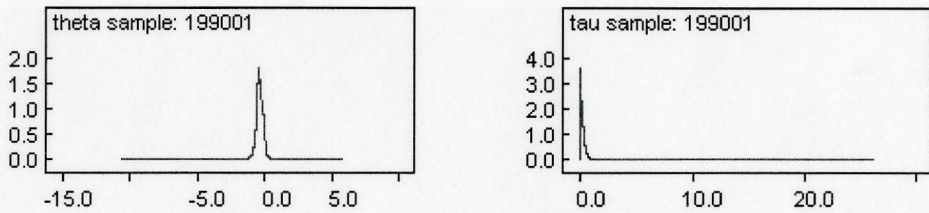


Dynamic trace for θ and τ :

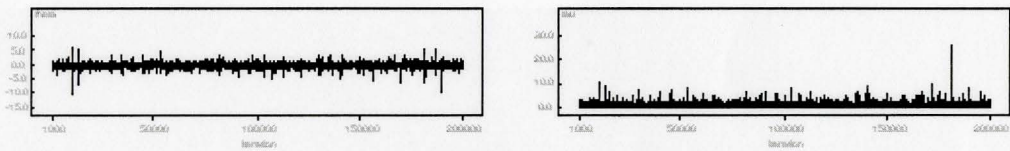


A.24: Kernel density estimates, time series and dynamic trace of parameters θ and τ for 2-year overall survival in adjuvant subgroup

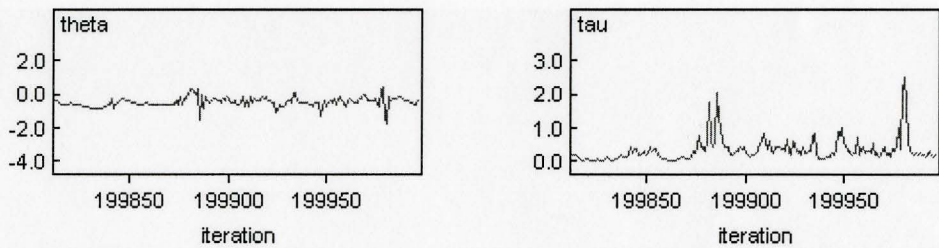
Kernel density estimates of posterior distribution:



Time series for θ and τ :

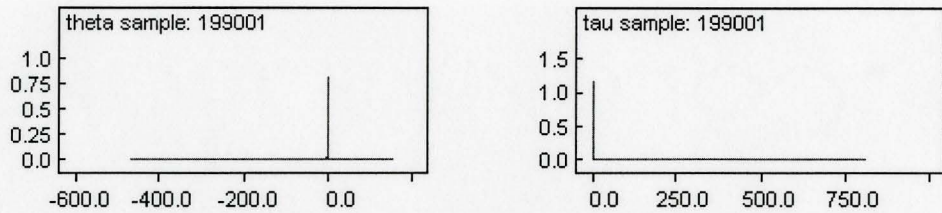


Dynamic trace for θ and τ :

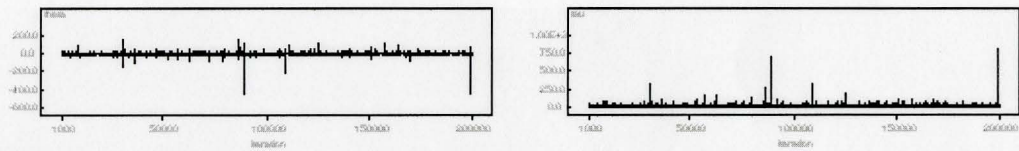


A.25: Kernel density estimates, time series and dynamic trace of parameters θ and τ for 2-year overall survival in neoadjuvant plus adjuvant subgroup

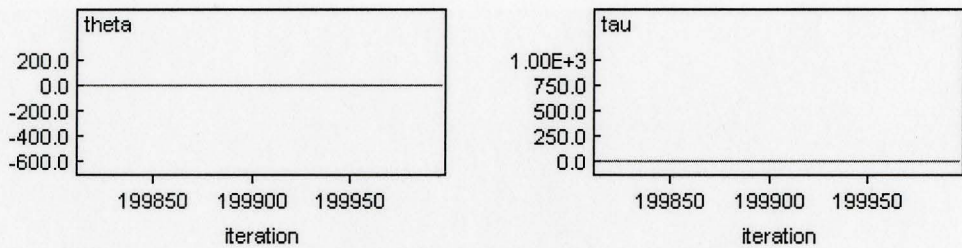
Kernel density estimates of posterior distribution:



Time series for θ and τ :



Dynamic trace for θ and τ :



A.26: Kernel density estimates, time series and dynamic trace of parameters θ and τ for 2-year overall survival in neoadjuvant plus concurrent subgroup

Appendix B

Related WinBUGS Code

```
model
{ # 2-year disease-free survival analysis
  # d <- 4 # degrees of freedom for k = 4, 8, 12, 16
  for (i in 1 : N) {
    Y[i] ~ dnorm(mu[i], w[i])
#    Y[i] ~ ddexp(mu[i], w[i])
#    Y[i] ~ dt(mu[i], w[i], k)

    mu[i] ~ dnorm (theta, t )
    w[i] ~ dgamma(0.001, 0.001)
  }

  #prior
  theta ~ dnorm(0, 1.0E-6)
  t ~ dgamma(0.001, 0.001)

# standard deviation of error distribution

  tau <- sqrt(1 / t ) # normal errors
# tau <- sqrt(2) / t # double exponential errors
# tau <- sqrt(d / (t * (k - 2))) # t errors on k degrees of freedom
  prob<-step(1-theta) # probability of theta less than one
}

Data list( N =20,
Y=c(0.24686, -0.05129, -0.63488, -0.21072, 0.17395, -1.46968, -0.26136,
-0.71335, -0.46204, 0.21511, -0.79851, -0.35667, -0.65393, -0.18633,
-0.22314, -0.21072, 0.23902, -1.66073, -0.91629, -1.30933))

Inits
list(theta = 0, t = 1, mu = c(0, 0, 0, 0,0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,
0, 0, 0, 0, 0, 0, 0), w=c(1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,
1, 1, 1, 1, 1))
```

```

model
{ # 2-year overall survival analysis
  d <- 4 # degrees of freedom for k = 4, 8, 12, 16
  for (i in 1 : N) {
    Y[i] ~ dnorm(mu[i], w[i])
#    Y[i] ~ ddexp(mu[i], w[i])
#    Y[i] ~ dt(mu[i], w[i], k)

    mu[i] ~ dnorm (theta, t )
    w[i] ~ dgamma(0.001, 0.001)
  }

#prior
theta ~ dnorm(0, 1.0E-6)
t ~ dgamma(0.001, 0.001)

# standard deviation of error distribution

  tau <- sqrt(1 / t ) # normal errors
# tau <- sqrt(2) / t # double exponential errors
# tau <- sqrt(d / (t * (k - 2))) # t errors on k degrees of freedom
  prob<-step(1-theta) # probability of theta less than one
}

Data list(N =36,
Y=c(-0.16252, -1.60944, -0.04082, -0.21072, -0.11653, -0.34249,
-0.3285, -0.21072, -0.16252, -0.46204, 0, -0.44629, -0.79851,
0.40547, -0.84397, 0.27003, -1.17118, -0.43078 , 0.17395, -0.26136,
-0.56212, -0.07257, 0.12222, 0.6831, -0.07257, -0.54473, -0.05129,
-0.8675, -0.51083, -1.30933, -0.4943, -0.99425, -1.34707, 0.22314,
-0.52763, -1.04982 ))

Inits

list(theta = 0, t = 1, mu = c(0, 0, 0, 0,0, 0, 0, 0, 0, 0, 0, 0, 0, 0,
0, 0, 0, 0,0, 0, 0, 0,0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,
1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,
1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1 ))

```

```

model
{
  # subgroup analysis for 2-year disease-free survival

  for (i in 1 : N) {
    Y[i] ~ dnorm(mu[i], w[i])
    mu[i] ~ dnorm (theta, t )
    w[i] ~ dgamma(0.001, 0.001)
  }

  #prior
  theta ~ dnorm(0, 1.0E-6)
  t ~ dgamma(0.001, 0.001)

  # standard deviation of error distribution
  tau <- sqrt(1 / t )          # normal errors
}

Data list( N =9,
Y=c(-1.46968, -0.05129, -0.21072, -0.26136, 0.17395, -0.63488, -0.71335,
-0.46204, 0.24686)) # neoadjuvant subgroup

Inits list(theta = 0, t = 1, mu = c(0, 0, 0, 0, 0, 0, 0, 0, 0), w=c(1,
1, 1, 1, 1, 1, 1, 1, 1))

# list (N=4, Y=c(-0.35667, -0.79851, -0.65393, 0.21511)) for concurrent
subgroup

# list( N =3, Y=c( -0.22314, -0.21072, -0.18633)) for adjuvant subgroup

# list (N=2, Y=c(-1.66073, -0.91629)) for concurrent and adjuvant subgroup

```

```

model
  { # subgroup analysis for 2-year overall survival
    for (i in 1 : N) {
      Y[i] ~ dnorm(mu[i], w[i])
      mu[i] ~ dnorm (theta, t )
      w[i] ~ dgamma(0.001, 0.001)
    }
    #prior
    theta ~ dnorm(0, 1.0E-6)
    t ~ dgamma(0.001, 0.001)
    # standard deviation of error distribution
    tau <- sqrt(1 / t ) # normal errors
  }
Data list(N =12, Y=c( -0.16252, -1.60944, -0.04082, -0.21072,
-0.11653, -0.34249, -0.3285, -0.21072, -0.16252, -0.46204, 0,
-0.44629))
# neoadjuvant subgroup
Inits list(theta = 0, t = 1, mu = c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,
0 ), w=c(1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1 ))

# list( N =8, Y=c(-0.79851, 0.40547, -0.84397, 0.27003, -1.17118,
-0.43078 , 0.17395, -0.26136)) for concurrent subgroup

# list (N=4, Y=c(-0.56212, -0.07257, 0.12222, 0.6831)) for adjuvant
subgroup

# list (N=5, Y=c(-0.07257, -0.54473, -0.05129, -0.8675, -0.51083)) for
neoadjuvant and adjuvant subgroup

# list(N=2, Y=c(1.30933, -0.4943)) for concurrent and adjuvant subgroup

# list (N=3, Y=c(-0.99425, -1.34707, 0.22314)) for neoadjuvant and
concurrent subgroup

# list (N=2, Y=c( -0.52763, -1.04982)) for neoadjuvant, concurrent and
adjuvant subgroup

```