A Nonparametric Comparison of Conditional Distributions with Nonnegligible Cure Fractions

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Abstract. Survival data with nonnegligible cure fractions are commonly encountered in clinical cancer clinical research. Recently, several authors (e.g. Kuk and Chen, Biometrika 79 (1992) 531; Maller and Zhou, Journal of Applied Probability, 30 (1993) 602; Peng and Dear, Biometrics, 56 (2000) 237; Sy and Taylor, Biometrics 56 (2000) 227) have proposed to use semiparametric cure models to analyze such data. Much of the existing work has been emphasized on cure detections and regression techniques. In contrast, this project focuses on the hypothesis testing in the presence of a cure fraction. Specifically, our interest lies in detecting whether there exists survival differences among noncured patients between treatment arms. For this purpose, we investigate the use of a modified Cramér-von Mises statistic for two-sample survival comparisons within the framework of cure models. Such a test has been studied by Tamura et al., (Statistics in Medicine 19, 2000, 2169) using bootstrap procedure. We will focus on developing asymptotic theory and convergent algorithms in this paper. We show that the limiting distributions of the Cramér-von Mises statistic under the null hypothesis can be represented by stochastic integrals and a weighted non-central chi-squares. Both representations lead to concrete numerical schemes for computing the limiting distributions. The algorithms can be easily implemented for data analysis and significantly reduce computing time compared to the bootstrap approach. For illustrative purposes, we apply the proposed test to a published clinical trial.

Keywords: cure model, Cramér-von Mises statistics, asymptotic theory

1. Introduction

In cancer trials the idea of ‘cure from cancer’ is that the disease would be completely eliminated so that it never recurs, and the patient’s lifespan is the same as that of someone who has never suffered cancer. Treatments are typically developed to increase patients’ chances of being cured, but considerable interest has also been given to pursue treatments that prolong survival among noncured patients as well. Because the study population is essentially an unobservable mixture of patients deemed curable and noncurable, evaluation of treatment effects in such a scenario is often complicated. A recently published study is presented below as an illustrative example.
Between 1992 and 1999, a phase III clinical trial was conducted by Adelstein et al. (2003) of the Eastern Cooperative Oncology Group (ECOG) to evaluate treatment effects in patients with unrespectable head and neck cancer. Patients were randomized among the following treatment arms: a standard single daily fractionated radiotherapy (control arm), and a split course of single daily fractionated radiotherapy and chemotherapy (experimental arm). One primary endpoint was whether these treatments had survival benefit in terms of preventing death from head and neck cancer. In this trial, a number of long term survivors have been observed. But, in addition to the comparison of the cure rates, the investigators were also interested in evaluating the treatment effect in terms of survival among patients who were not cured.

The concept of cure brings new clinical interests as well as statistical challenges. For instance, clinical objectives are not only focused on the comparison of unconditional distributions of the time to a medical event of interest (e.g. death), but also on that of the conditional distributions within uncured patients (e.g. Berkson and Gage, 1952; Farewell, 1982; Greenhouse and Wolfe, 1984, Gray and Tsiatis, 1989; Laska and Meisner, 1992). Meanwhile, other characteristic problems in survival analysis need to be addressed. For example, random accrual and patients’ dropout or loss to follow up are to be modeled through random right censoring processes. Several authors (e.g. Kuk and Chen, 1992; Peng and Dear, 2000; Sy and Taylor, 2000) have proposed using semiparametric cure models to analyze such data, with emphasis placed on regression modeling. A complete review of the statistical methods using censored failure time to determine the presence of a cure fraction can be seen in Maller and Zhou (1992, 1993).

In this article, we will take a different perspective by focusing on the characterization of the conditional distribution among uncured individuals. That is, we are interested in studying the distribution of the time-to-event variables given the event (e.g. disease-related death) will occur before a clinically meaningful terminal time \( t \). Explanations of these types of models from medical viewpoints, together with some available statistical methods (e.g. likelihood ratio tests and rank tests) can be found in, for example, Laska and Meisner (1992) and Gray and Tsiatis (1989), and the likelihood ratio test has been used to analyze a clinical trial (Laska et al. 1991).

Indeed, the past two decades has seen a rapid development of statistical tools for detecting survival differences in clinical trials, but log-rank type tests, most powerful under proportional hazards alternatives, are routinely performed by practitioners in the absence of cure fractions. Schumacher (1984), however, demonstrated via simulation that Cramér-von Mises statistics have decent power under proportional hazards alternatives and are superior to log-rank tests in other cases. A Cramér-von Mises type statistic was proposed by Tamura et al. (2000) for a two-sample survival comparison within the framework of cure models, and