Accounting for Cured Patients in Cost-Effectiveness Analysis

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ABSTRACT

Background: Economic evaluations often measure an intervention effect with mean overall survival (OS). Emerging types of cancer treatments offer the possibility of being “cured” in that patients can become long-term survivors whose risk of death is the same as that of a disease-free person. Describing cured and uncured patients with one shared mean value may provide a biased assessment of a therapy with a cured proportion. Objective: The purpose of this article is to explain how to incorporate the heterogeneity from cured patients into health economic evaluation. Methods: We analyzed clinical trial data from patients with advanced melanoma treated with ipilimumab (Ipi; n = 137) versus glycoprotein 100 (gp100; n = 136) with statistical methodology for mixture cure models. Both cured and uncured patients were subject to background mortality not related to cancer. Results: When ignoring cured proportions, we found that patients treated with Ipi had an estimated mean OS that was 8 months longer than that of patients treated with gp100. Cure model analysis showed that the cured proportion drove this difference, with 21% cured on Ipi versus 6% cured on gp100. The mean OS among the uncured cohort was 10 and 9 months with Ipi and gp100, respectively. The mean OS among cured patients was 26 years on both arms. When ignoring cured proportions, we found that the incremental cost-effectiveness ratio (ICER) when comparing Ipi with gp100 was $324,000/quality-adjusted life-year (QALY) (95% confidence interval $254,000–$600,000). With a mixture cure model, the ICER when comparing Ipi with gp100 was $113,000/QALY (95% confidence interval $101,000–$154,000). Conclusions: This analysis supports using cure modeling in health economic evaluation in advanced melanoma. When a proportion of patients may be long-term survivors, using cure models may reduce bias in OS estimates and provide more accurate estimates of health economic measures, including QALYs and ICERs. Keywords: cure models, oncology, overall survival, survival analysis.

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Introduction

Progress in the treatment of cancer has led to some patients being cured of their disease in the sense that they become long-term survivors whose risk of death is the same as that of a person who did not have cancer. Cured patients can induce heterogeneity in the overall survival (OS) of a patient population that may not be adequately described with traditional statistical analyses. For example, when some patients are cured, the mean OS of the full patient population is equal to the weighted average of the OS among cured and the OS among uncured patients, weighted by the relative proportions. The mean OS of cured patients is often much longer than the mean OS of uncured patients, and may in fact exceed the observation period of clinical studies. Grouping all patients together and reporting one shared mean value may provide an incomplete assessment of a therapy that cures a proportion of patients. In addition, statistical methods that do not account for cured patients may provide biased assessments of OS.

Mean OS is a measure frequently used in health economic evaluation, for example, in the evaluation of the mean effect of a treatment. This article aims to explain how to incorporate the heterogeneity from cured patients into health economic evaluation. In particular, we will explain how to modify the calculation of quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs) to account for cured patients. The ICER summarizes the additional value of a treatment and is defined as the ratio of the difference between mean treatment costs and the difference in mean treatment effects:

\[
\text{Mean cost treatment}_1 - \text{Mean cost treatment}_2)/(\text{Mean effect treatment}_1 - \text{Mean effect treatment}_2).
\]

Mean effects are often measured directly with mean OS or with survival weighted by quality of life, or QALYs. As an illustration, we will use clinical trial data from patients with advanced-stage melanoma treated with ipilimumab (Ipi) to show how health economic evaluations that explicitly account for cured patients can differ from standard analyses that do not model cured patients.

Cure Models

Statistical methodology for cure models has been an active area of research for more than 50 years. The most popular framework for cure models is to assume that the study population is a mixture of patients who are cured and patients who are not cured...
and to explicitly model this mixture [1–4]. In this framework, regression models can be used to estimate the probability that a patient is cured and to predict the survival of patients who are not cured.

At present, there are no diagnostic tests that can assess whether an individual patient is cured of his or her cancer. So, long-term follow-up is the ultimate way to determine whether an individual patient is cured of his or her cancer. So, not cured.

Logistic regression is a common choice to model the probability that a patient is cured [5]. Both patients who are cured and patients who are not cured are subject to “background” mortality not related to cancer. Patients who are not cured are subject to additional mortality from their cancer, and parametric survival models are often used to estimate this excess mortality. Mathematically, the survival for a population with a cure fraction can be written as follows:

\[ S(t, x) = S_0(t, x) \left[ 1 - p(x) \right] S_C(t, x), \]  

where \( S(t) \) denotes the survival at time \( t \), \( S_0(t, x) \) denotes the background mortality at time \( t \) conditional on covariates \( x \), \( p(x) \) denotes the probability of being cured conditional on covariates \( x \), and \( S_C(t, x) \) denotes the mortality due to disease (e.g., cancer) at time \( t \) conditional on covariates \( x \) [6,7]. We note that \( S_0, p, \) and \( S_C \) can be written more generally to depend on different covariates, but we focus on the scenario with shared covariates without loss of generality. \( S_C \) can be calculated from external data; for our application we used age- and sex-matched mortality data from the US Social Security life tables. We modeled \( p(x) \) with logistic regression and considered Weibull and lognormal parametric formulations of \( S_C \).

Cure Models and Health Economic Evaluation

Economic evaluations of competing interventions often estimate mean OS or QALYs for each intervention from clinical trials. However, for clinical trials with heterogeneity due to cured patients, the survival curves plateau and not drop to 0 during the finite follow-up of the trial. If the observed survival is not 0 at the end of the observation period, the mean value cannot be estimated without constructing a model. Parametric models such as the Weibull and lognormal can be used to calculate the mean. If a population contains a mixture of cured and uncured patients, the mean survival of the population should be calculated as the weighted average of the mean survival times of each of the cured and uncured subpopulations, weighted by the relative proportions. In the model in Equation 1, the mean OS of the cured population is the mean of the background mortality (\( S_0 \)), whereas the mean OS for the uncured patients is a function of both the background mortality (\( S_0 \)) and the disease-related mortality (\( S_C \)). In many cancer applications, the mortality from \( S_C \) is much higher than the background mortality (\( S_0 \)). The mean of a random variable with survival function \( S(t) \) is equal to \( \int_0^\infty S(t) dt \) and so the mean OS for cured patients is equal to \( \int_0^\infty S_0(t) S_C(t) dt \) and the mean OS for uncured patients is equal to \( \int_0^\infty S_C(t) S_C(t) dt \).

Cured and uncured patients will also have different costs because the cured patients will have long-term follow-up costs that are associated with long-term surveillance of their cancer and related medical costs. Similar to the calculation of mean OS, the mean costs associated with a therapy should be calculated as

\[ M = \sum_i S_i C_i, \]  

where \( C_i \) is the average cost over the \( i \)th interval conditional on surviving until the beginning of the interval and \( S_i \) is the probability of being alive at the beginning of the \( i \)th interval, estimated using the KMSA estimator. Lin et al. [9] demonstrated that the Kaplan-Meier estimator is unbiased and consistent as long as 1) censoring is independent in time and 2) the time intervals for the cost analysis are sufficiently narrow.

Statistical Methods

Survival was estimated using the Kaplan–Meier method. Parametric survival models without a cure fraction were estimated. Parameters for \( p(x) \) and \( S(t, x) \) from Equation 1 were estimated using the score equations from the log-likelihood in the study by Lambert [7] (a reference for implementing a version of Equation 1 in the statistical program Stata [StataCorp, College Station, TX]). Mean survival for uncured patients (equal to \( \int_0^\infty S_0(t) S_C(t) dt \)) was calculated by evaluating the numerical integral. CIs were calculated using the bootstrap percentile method on the basis of 10,000 bootstrap replicates.

Ipi Case Study

Ipi is a monoclonal antibody that targets cytotoxic T-lymocyte-associated antigen 4, a protein receptor that downregulates the immune system to allow cytotoxic T-lymocytes to continue to target cancer cells. Ipi has been approved by the United States for treatment of unresectable stage III and metastatic melanoma, by Canada for treatment of unresectable stage III and metastatic melanoma in patients who have failed or failed to tolerate other therapies, and by the European Union for first-line and second-line treatment of metastatic melanoma.

We considered patient-level data from a randomized trial in patients with unresectable stage III and IV melanoma [10]. The trial randomized patients to three arms: an Ipi arm, an active control arm with a cancer vaccine derived from the melanomasal glycoprotein 100 (gp100), and an Ipi + gp100 arm. In the following text, we focus attention on the gp100 and Ipi arms for clearer text, we focus attention on the gp100 and Ipi arms for clearer contact. The solid lines in Figure 1 display Kaplan-Meier estimates of OS. The median follow-up of censored patients is 1.8 years. The plateau at the tail of the curve indicates that more than 15% of the patients on the Ipi arm could be long-term survivors.

Because the Kaplan-Meier estimates do not drop to 0 at the end of follow-up, the empirical curve cannot be used to estimate the mean survival in this patient population. Previous work considered approaches to estimate the mean OS of this...
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