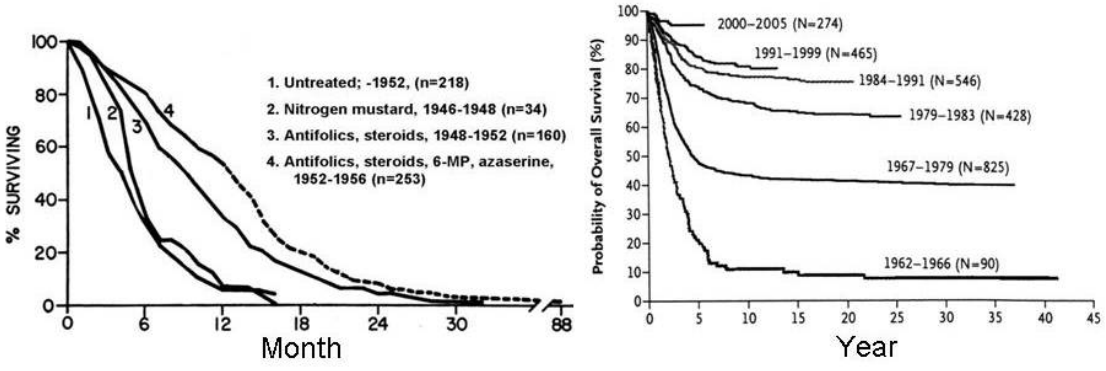
Boag Model and Its Extensions in Cancer Survival Analysis: Overview

What is the Best Measure of Survival Benefit for Cancer Patients

Common questions asked by patients who are diagnosed with cancer are "how great is my chance of being cured?" and "If not cured, how long will I live?" Whether cure is achieved or not makes a great difference in both quality of life of patients and their survival benefit since, if cured, patients are saved from physical and mental sufferings with relapse and can gain additional decades of life. Unfortunately, these basic questions have not been addressed by conventional survival tests such as the log-rank statistic[1] and the Cox regression[2], which have prevailed for the past 40 years. The conventional tests based on the Cox proportional hazards model fail to distinguish between cure and delaying of death. This problem is revealed by Gamel et al[3,4], and other investigators[5-7]. Cox himself[8] recognizes the limitations of his model in his comment on our editorial[9] which appeared in Surgical Oncology.

Limitations of the Cox Model

In 1972 Cox[2] evaluated the effect of 6-mercaptopurine (6-MP) compared with placebo in acute leukemia patients, who were mostly children with acute lymphoblastic leukemia (ALL). By fitting his model to the data from Freireich et al[10], Cox showed that the hazard ratio of 6-MP to placebo was about 0.2, a highly significant difference (log-rank χ^2=16. 79, P <0.0001). Generally, a hazard ratio of 0.2 is considered to mean that, 80% (1–0.2) of deaths occurring in the placebo group could be avoided in the treatment group (see, for example, the Glossary in BMJ Clinical Evidence 2011). In fact, extended follow-up proves to the contrary that almost all children treated before 1960 with 6-MP or other chemotherapeutics



died;[11] it merely delayed death from ALL.

a. Before 1960
(cited from Murphy, et al.[12])

b. After 1960
(cited from Pui CH, et al.[13])

Figure 1. Survival curves of acute lymphoblastic leukemia

Only after combination chemotherapy regimens had been developed was relapse-free cure achieved in the majority of ALL children. Figure 1 shows that before 1960 the survival curve shifted with time to the right, but after 1960 it progressively showed an upward shift, indicationg increasing cure and relevance of the Boag model..

It is likely that conventional tests also mislead clinicians and patients into overestimate of non-curative chemotherapeutics and their overuse since delaying of death is not distinguished from cure. Moreover, with the Cox model, the effect of curative treatment tends to be underestimated unless long-term follow-up is made.[7] The results of the Dutch D1 vs D2 trial could be an example of this sort; the advantage of D2 over D1 gastrectomy was not confirmed until after 15 years.[14] In contrast, using the Boag model, the non-curative nature of 6-MP[15] and curative impact of D2 resection[16] were reported much earlier.

Another limitation of the Cox model is that extrapolation of survival curve causes greater deviations from the actual curve than extrapolation using the Boag model.[17]

The Boag Log-Normal Cure Model

In 1949, Boag[18] proposed a survival model which is highly relevant to this problem. He postulated that of a group of cancer patients under study a fraction c are cured of the disease and the remaining (1- c) patients will die of the disease unless they succumb to other causes. He further postulated that log failure time of non-cured patients follow a normal distribution with mean m and variances s^2. Thus, using the maximum likelihood method he estimated these three parameters from cancer follow-up data, where only death from the disease was treated as event (disease-specific survival).

The primary task of this survival analysis is to estimate these three survival parameters (c, m and s) in a given group of cancer patients, so that the likelihood of cure can be inferred for this group, and also how long un-cured patients will live before dying from the disease. Such information is more important to patients and doctors than information provided by conventional survival tests.

Extension of the Boag Model to Mean Survival Analysis

It must be noted, however, that a high cure rate does not always assure a prolonged survival. Patients, even if cured of the disease, may succumb to other causes earlier than those with incurable disease. Such deaths are expected to be more common in older patients or those living in countries where the life expectancy of the general population is relatively short. It is therefore important to take into consideration the risks of all kinds of death. For this purpose, the mean survival (MS) of the whole patients may serve as another measure of survival

benefit, and is estimated as the area under the overall survival curve. To generate the overall survival curve, the life tables of the nation to which the patient group belongs are used.[19] Thus, the overall survival rates are calculated for the contemporaries who match the patients for age and sex (hereafter abbreviated as contemporaries). We then obtain the approximate value of the patient MS (Figure 2) using the competing risk model[20], which assumes that at any point in time the patient overall survival rate is the product of the disease-specific survival rate (estimated from the Boag model) and the overall survival rate for contemporaries. If there are operative deaths or early therapy-related deaths, this product must be multiplied by (1-therapy-related mortality) in order to obtain the overall survival rate.

Another rough estimate of the patients MS is made by what we call the survival limit model [21], assuming that contemporaries survive neither longer, nor shorter than their mean survival time; all die simultaneously at this point. Although this assumption does not fit the actual survival time distribution, MS estimates based on this model are reasonably close to those based on the competing risk model. Usually, the estimate based on the survival limit model is only a few percent greater than that based on the competing risk moel. Graphically, the MS estimate of the contemporaries is equal to the total area of the rectangle (black lines) in Figure 2, whereas the MS estimate of the patients based on the survival limit model is the stippled part of the rectangle, bordering on the disease-specific survival curve (Boag). These two estimates can thereby be visually compared. As the average age of patients increases, it can be seen that their MS decreases and the benefit of the curative treatment also reduces.

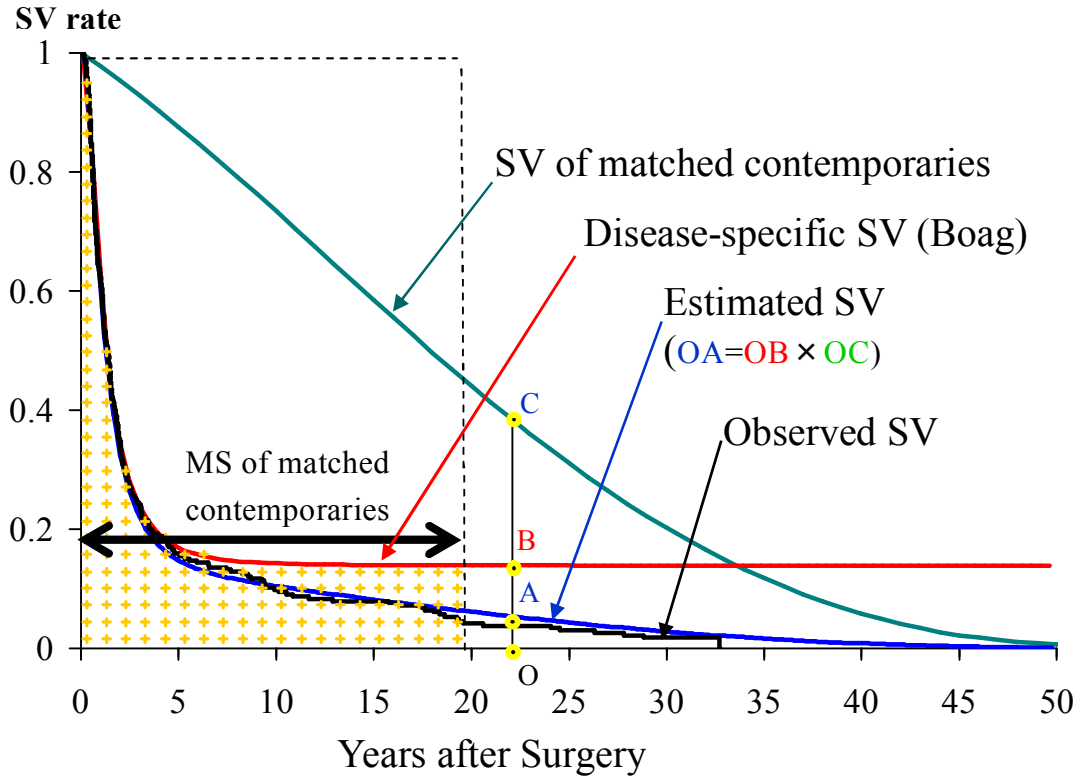


Figure 2. Survival curves and mean survival

. The predictability of overall survival and MS is supported by two long-term (>30 years) follow-up data from gastric cancer patients. They were classified into various subgroups, whose overall survival curved and MSs were predicted at 5 postoperative years and compared with the full follow-up data. [21-22] Further validation of the competing risk model is needed using life-long follow-up data from other cancers.

Extension of the Boag Model to Regression Analysis

Our third task is to evaluate the effects of predictor variables (explanatory variables) on the Boag parameters, particularly life-saving effect and death-delaying effect of the variables. This is done by extending the Boag model to three regressions (regression *c*, regression *m* and regression *s*) whose dependent variables are cure rate (c), mean (m) and SD (s) of log failure time (Gamel[23]).

Thus,

$$c = \frac{\exp(c_0 + c_1 x_1 + c_2 x_2 \cdots)}{1 + \exp(c_0 + c_1 x_1 + c_2 x_2 \cdots)}$$

$$m = m_0 + m_1 x_1 + m_2 x_2 \cdots$$

$$s = \exp(s_0 + s_1 x_1 + s_2 x_2 \cdots)$$

Suppose in this regression analysis the use of the test treatment is coded as x_1=1 while the control is coded as x_1=0. A positive regression coefficient c_1 with its 95% CI above 0 indicates that the test treatment significantly increases the likelihood of cure. In contrast, if only the regression coefficient m_1 is significantly positive, the new treatment is considered non-curative merely prolonging failure time.

Accelerated Failure Time Model

A situation may occasionally arise in which all patients in the group die from the disease, for example, those with leukemia before 1960. In such a group, the cure rate should be pre-specified as 0, so that only the parameters of the two regressions (m and s) are estimated. This is known as the accelerated failure time model[24].

Conclusions

Despite the increasing demand for patient-centered health care, survival information conveyed to cancer patients is still far from satisfactory. These computer programs are intended to help clinicians and patients to gain more accurate, relevant and comprehensible information so that they can accomplish better decision-makings.

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