A Comparison between Kaplan-Meier and Weighted Kaplan-Meier Methods of Five-Year Survival Estimation of Patients with Gastric Cancer

Ali Zare, Mahmood Mahmoodi, Kazem Mohammad,
Hojjat Zeraati, Mostafa Hosseini, and Kourosh Holakouie Naieni

Department of Epidemiology and Biostatistics, Tehran University of Medical Sciences, Tehran, Iran

Received: 5 May. 2013; Received in revised form: 28 Dec. 2013; Accepted: 4 Jan. 2014

Abstract- The 5-year survival rate is a good prognostic indicator for patients with Gastric cancer that is usually estimated based on Kaplan-Meier. In situations where censored observations are too many, this method produces biased estimations. This study aimed to compare estimations of Kaplan-Meier and Weighted Kaplan-Meier as an alternative method to deal with the problem of heavy-censoring. Data from 330 patients with Gastric cancer who had undergone surgery at Iran Cancer Institute from 1995- 1999 were analyzed. The Survival Time of these patients was determined after surgery, and the 5-year survival rate for these patients was evaluated based on Kaplan-Meier and Weighted Kaplan-Meier methods. A total of 239 (72.4%) patients passed away by the end of the study and 91(27.6%) patients were censored. The mean and median of survival time for these patients were 24.86±23.73 and 16.33 months, respectively. The one-year, two-year, three-year, four-year, and five-year survival rates of these patients with standard error estimation based on Kaplan-Meier were 0.66 (0.0264), 0.42 (0.0284), 0.31 (0.0274), 0.26 (0.0264) and 0.21 (0.0256) months, respectively. The estimations of Weighted Kaplan-Meier for these patients were 0.62 (0.0251), 0.35 (0.0237), 0.24 (0.0211), 0.17 (0.0172), and 0.10 (0.0125) months, consecutively. In cases where censoring assumption is not made, and the study has many censored observations, estimations obtained from the Kaplan-Meier are biased and are estimated higher than its real amount. But Weighted Kaplan-Meier decreases bias of survival probabilities by providing appropriate weights and presents more accurate understanding.

Acta Medica Iranica, 2014;52(10):764-767.

Keywords: Censoring; Gastric Cancer; Kaplan-Meier; Survival Rate; Weighted Kaplan-Meier

Introduction

Gastric cancer is defined as the uncontrolled growth of malignant cells in the stomach. Most people show no symptoms until the advanced stage of the disease; therefore, Gastric cancer is one of the most common causes of cancer deaths all over the world. Gastric cancer is usually treated with surgery, radiotherapy, or chemotherapy. The primary treatment of gastric cancer in initiative stages is surgery; so it is regarded as the best treatment for cancer. Radiotherapy and chemotherapy will be used as renewed treatments, if necessary. In advanced stages of the disease, surgical procedures, radiotherapy and chemotherapy are also used for the treatment but they do not usually achieve good outcomes. The chances of patients' full recovery depend on the surgery, but the time when the disease passes through the mucous membrane, it is possible to spread to the lymph nodes and to causes relapse in spite of the successful surgery (1-4).

One of the most important prognostic indicators which are considered after diagnosis and treatment for patients with gastric cancer is an increase in patients' survival rate particularly the 5-year survival rate. Different methods have been designed to estimate the survival rate among which the most common one is the non-parametric Kaplan-Meier method. This method is severely affected by censoring assumption, so that if the patients under study were followed after the time in which they were censored, the rate of occurrence of the event among them will be the same as those subjects who were not censored at that time, in other words, it can be said that the censoring has occurred randomly and is independent of the event (5). The reliability of

Corresponding Author: M. Mahmoodi
Department of Epidemiology and Biostatistics, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 88950185, Fax: +98 21 88989127, E-mail address: mahmoodim@tums.ac.ir

Kaplan-Meier estimations is affected by censoring assumption (6-7).

For example, a study may be terminated with a large number of censoring, which could be due to loss to follow up, withdrawal and alternative outcome than the focused event.

The large number of censored observations results in reducing the number of patients at risk in the following time-points, and the estimations produced by Kaplan-Meier of the survival function would not be reliable anymore. High levels of censoring can suggest a number of problems in the study. The Quick end (by which most patients do not have an outcome at the end of the study) and a pattern of censoring that makes a lot of subjects be excluded from the study in a specific time, are among these problems. Hence, a large number of censored observations make the survival estimations contain error and be estimated higher than their real amounts. Unfortunately, no suitable test determines the validity of the censoring assumption, and this is just a judgment made by researchers. To modify Kaplan-Meier estimations, Jan *et al.,* presented a method named Weighted Kaplan-Meier (8-9). Their study revealed that if there is high censorship (27% in their study), Kaplan-Meier estimations will contain an error, and their amounts will be estimated more than actual. Other methods were also presented by Shafiq *et al.,* and Huang to resolve the problem of Kaplan-Meier unreliable estimations (8-11).

Ramadurai *et al.,* investigated and reported in the paper all methods and procedures which had been proposed to estimate the survival function up to the time of their study. Their results showed that Weighted Kaplan-Meier is a suitable method to estimate the survival probability (12).

Thus, this study aimed to determine the five-year survival rate of patients with gastric cancer undergone surgery at the most important Cancer Institute in Iran using the standard Kaplan-Meier method and Weighted Kaplan-Meier as an alternative method to deal with the problem of high level of censorship.

Materials and Methods

In this study, 330 patients with Gastric cancer with the following data were studied: 1) the patients had been hospitalized and had undergone surgery from 1995-1999 in surgical wards of Cancer Institute of Iran at the Imam Khomeini Hospital, 2) they had records in the archives of the hospital, and in their files, their addresses and phone numbers were available for subsequent follow-ups. The survival time of patients was determined after surgery and those patients who were still alive at the end of study period or the ones whose data were not available after a specific time-period were censored.

Kaplan-Meier and Weighted Kaplan-Meier were used to estimate the survival rate of patients after surgery. According to Kaplan-Meier, n is the total number of monitored participants in the study and $t_1, t_2, ..., t_n$ are the observed times. The survival time of some of these patients may have been censored. So we assumed that the number of focused outcomes is r in which $r \le n$ and $t_{(1)} \le t_{(2)} \le ... \le t_{(r)}$ will be patients' ordered event times. Now, the number of patients who have survived before $t_{(j)}$ (including those who have died at this time) is n_j, and the number of those who have focused outcome at $t_{(j)}$, is $d_j, (1 \le j \le r)$. Therefore, in the time interval less than t which is shown in $\hat{s}(t)$, the Kaplan-Meier estimator is as follows:

$$\hat{s}(t) = \prod_{j:t_{(j)} \le t} \left\{ \frac{n_j - d_j}{n_j} \right\}$$

If $t \le t_{(1)}$, in which $t_{(1)}$ is the smallest survival time observed, so $\hat{s}(t) = 1$, and if $t \ge t_{(r)}$, in which $t_{(r)}$ is the largest survival observed, thus $\hat{s}(t) = 0$.

To calculate the Weighted Kaplan-Meier method in this study, a method provided by Jan *et al.,* was used (8-9). They showed that when a considerable proportion of observations were censored, Kaplan-Meier estimation would be unreliable and inefficient. As in Kaplan-Meier we assumed, c_j is the number of censored patients at $t_{(j)}$ and w_j is the weights of censored observations. As the rate of un-censoring will be as follows:

$$w_j = \left\{ \frac{n_j - c_j}{n_j} \right\}$$

If $t_{(j)}$ is one event-time, $w_j = 1$, and if $t_{(j)}$ is a censored time, $0 < w_j < 1$. Now, the Weighted Kaplan-Meier estimation is defined as follows:

$$s^*(t) = \prod_{j:t_{(j)} \le t} w_j \left\{ \frac{n_j - d_j}{n_j} \right\}$$

In this formula, $s^*(t)$ solves the problem of overestimation (that existed in the Kaplan-Meier estimations) by proper weighing.

Results

This study was conducted on 330 patients with Gastric cancer undergone surgery. Among these patients 239 (72.4%) died by the end of the study and 91 (27.6%) were censored. The survival mean and median of these patients were 24.86±23.73 and 16.33 months, respectively. One-year, two-year, three-year, four-year and five-year survival rates of these patients, as well as standard error and a 95% confidence interval for both methods, are presented in Table 1. Based on Kaplan-Meier method these estimations were 0.66 (0.0264), 0.42 (0.0284), 0.31 (0.0274), 0.26 (0.0264), and 0.21 (0.0256) months and the estimations calculated according to Weighted Kaplan-Meier were 0.62 (0.0251), 0.35 (0.0237), 0.24 (0.0211), 0.17 (0.0172), and 0.10 (0.0125) months, respectively. The results showed that Weighted Kaplan-Meier presents better estimations (lower standard errors and shorter confidence intervals). Survival probabilities derived from both methods are shown in Figure 1.

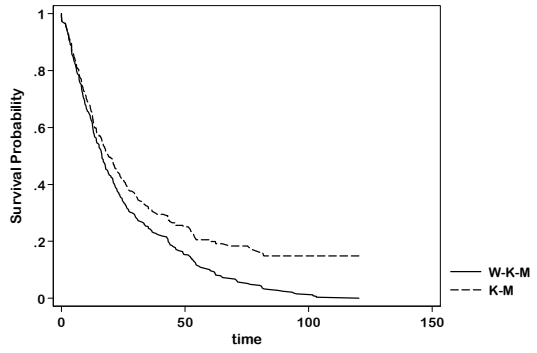

Figure 1. The Survival Curves for Gastric Cancer Data by Kaplan-Meier (K-M) and Weighted Kaplan-Meier (W-K-M) Methods

As Figure 1 illustrates, the estimations derived from both methods are approximately close to each other at the beginning of the study where the rate of censoring was low. But as time passes and the rate of censoring increases, Kaplan-Meier estimations always estimate the survival probabilities more than their real amounts whereas Weighted Kaplan-Meier presents more accurate estimations for patients' survival by placing appropriate weights for censored observations.

Discussion

The 5-year survival rate of patients with gastric cancer was estimated 10% based on Weighted Kaplan-Meier in this study which is lower than Kaplan-Meier estimation (21%) of current study and the results obtained in other studies in America (37%), Switzerland (22%), China (26%), and France (30%) (13-20). The high 5-year survival rate estimated by Kaplan-Meier is not unexpected because Kaplan-Meier—known as a standard method for estimating such probabilities—is severely affected by the censoring assumption. In cases where this assumption is violated (high levels of censoring), it causes biased estimations in the results of the study. Therefore, high levels of censoring affect the reliability of Kaplan-Meier estimations. Unfortunately, no good test is available to check the censoring assumption except the judgment made by the researchers.

Generalization of Kaplan-Meier method with proper weights causes unbiased estimations of survival probability at any time. As shown in Figure 1, at the beginning of the study the rate of censoring is low and the estimations of both methods are nearly identical, but as time goes by the end of the study and as the censored observations increase, the discrepancy between the estimations of two methods arises. Table 1 also showed that Weighted Kaplan-Meier estimations had lower standard errors and shorter confidence intervals and revealed that a more accurate statistical analysis can be made based on them. Moreover, one of the problems existing in Kaplan-Meier survival curve with the last censored observation is the fact that the survival function for observations after that time is indefinable (21). But the survival curve of Weighted Kaplan-Meier by the use of proper weighing reaches the horizontal axis even if the last observation is censored.

Large amounts of censoring in Kaplan-Meier method causes survival probability to be constant at these time-points whereas the number of subjects at risk decreases markedly. The constancy of survival probabilities leads in overestimation but Weighted Kaplan-Meier-using appropriate weights-reduces bias in survival probabilities in censored time-points and resolves the problem of overestimation. Censoring assumption is necessary to estimate survival probabilities; moreover, it is indispensible for common tests in survival analysis. Furthermore, the need for more research has been much felt on alternative methods in cases where the study is teemed with censored observations.

Table 1. Five-years survival rate estimation and 95% confidence interval by K-M and W-K-M

Year	Kaplan-Meier Estimation (SE)	Weighted Kaplan-Meier Estimation (SE)	95%CI K-M	95%CI W-K-M
1	0.66(0.0264)	0.62(0.0251)	0.6051-0.7086	0.5781-0.6765
2	0.42(0.0284)	0.35(0.0237)	0.3683-0.4791	0.3082-0.4011
3	0.31(0.0274)	0.24(0.0211)	0.2615-0.3685	0.2010-0.2839
4	0.26(0.0264)	0.17(0.0172)	0.2085-0.3089	0.1330-0.2004
5	0.21(0.0256)	0.10(0.0125)	0.1576-0.2574	0.0756-0.1245

References

1. Gunderson LL, Sosin H. Adenocarcinoma of the stomach: areas of failure in a re-operation series (second or symptomatic look) clinicopathologic correlation and implications for adjuvant therapy. Int J RadiatOncol BiolPhys 1982;8(1):1-11.
2. Wisbeck WA, Becker EM, Russell AH. Adenocarcinoma of the stomach: Autopsy observations with therapeutic implications for the radiation oncologist. Radiother Oncol 1986;7(1):13-8.
3. Sadighi S, Mohagheghi M, Haddad P, et al. Life expectancy with perioperative chemotherapy and chemoradiotherapy for locally advanced gastric adenocarcinoma. Tehran Univ Med J 2008;66(9):664-9.
4. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 2011;14(2):113-23.
5. Young KD, Menegazzi JJ, Lewis RJ. Statistical methodology. Acad Emerg Med 1999;6(3):244-9.
6. Murray S. Using Weighted Kaplan‐Meier Statistics in Nonparametric Comparisons of Paired Censored Survival Outcomes. Biometrics 2001;57(2):361-8.
7. Zare A, Mahmoodi M. Modified Kaplan-Meier Estimator Based on Competing Risks for Heavy Censoring Data. Int J Statist Med Res 2013;2(4):297-304.
8. Jan B, Shah SWA, Shah S, et al. Weighted Kaplan Meier estimation of survival function in heavy censoring. Pak J Stat 2005;21(1):55-63.
9. Jan B. Improved Inferences in the context of Survival/Failure Time [Dissertation]. Peshawar Univ., 2004.
10. Huang ML. A weighted estimation method for survival function. App Math Sci 2008;2(16):753-62.
11. Shafiq M, Shah S, Alamgir M. Modified Weighted Kaplan-Meier Estimator. Pak J Stat Operat Res 2007;3(1):39-44.
12. Ramadurai M, Ponnuraja C. Non-parametric estimation of the survival probability of children affected by TB meningitis. Int Refereed Res J 2011;II(2):216-27.
13. Ding YB, Chen GY, Xia JG, et al. Correlation of tumor-positive ratio and number of perigastric lymph nodes with prognosis of patients with surgically-removed gastric carcinoma. World J Gasrtroenterol 2004;10(2):182-5.
14. Thong-Ngam D, Tangkijvanich P, Mahachai V, et al. Current status of gastric cancer in Thai patients. J Med Assoc Thai 2001;84(4):475-82.
15. Schwarz RE, Zagala-Nevarez K. Recurrence patterns after radical gastrectomy for gastric cancer: prognostic factors and implications for postoperative adjuvant therapy. Ann Surg Oncol 2002;9(4):394-400.
16. Adachi Y, Tsuchihashi J, Shiraishi N, et al. AFP-producing gastric carcinoma: multivariate analysis of prognostic factors in 270 patients. Oncology 2003;65(2):95-101.
17. Triboulet J, Fabre S, Castel B, et al. Adenocarcinomas of the distal esophagus and cardia: Surgical management. Cancer Radither 2001;5(Suppl 1):90s-7s.
18. Wang CS, Hsieh CC, Chao TC, et al. Resectable gastric cancer: operative mortality and survival analysis. Chang Gung Med J 2002;25(4):216-27.
19. Zare A, Mahmoodi M, Mohammad K, Zeraati H, Hosseini M, Naieni KH. Survival Analysis of Patients with Gastric Cancer Undergoing Surgery at the Iran Cancer Institute: A Method Based on Multi-State Models. Asian Pacific journal of cancer prevention. 2013; 14(11):6369-73.
20. Zare A, Mahmoodi M, Mohammad K, Zeraati H, Hosseini M, Naieni KH. Factors Affecting the Survival of Patients with Gastric Cancer Under¬ gone Surgery at Iran Cancer Institute: Univariate and Multivariate Analyses. Iranian Journal of Public Health. 2014;43(6):800-8.
21. Klein JP, Moeschberger ML, editor. Survival analysis: techniques for censored and truncated data. 1st ed. New York, NY, USA: Springer; 2003: p. 92-104.