Conditional Survival and the Choice of Conditioning Set for Patients With Colon Cancer: An Analysis of NSABP Trials C-03 Through C-07

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ABSTRACT

Purpose

Colon cancer overall survival (OS) is usually computed from the time of diagnosis. Survival gives the initial prognosis but does not reflect how prognosis changes with changing hazard rates over time. Conditional survival (probability of surviving y additional years given they have survived x years [CS or OS|OS]) is an alternative measure that accounts for elapsed time since diagnosis, providing more relevant prognostic information. We extend the concept of CS to condition on the set of patients alive, recurrence-free, and second primary cancer-free (disease-free survival [OS|DFS]).

Patients and Methods

Using data from National Surgical Adjuvant Breast and Bowel Project trials C-03 through C-07, 5-year OS|DFS was calculated on patients who were disease free up to 5 years after diagnosis, stratified by age, stage, nodal status, and performance status (PS).

Results

For stage II, OS|DFS improved from 87% to 92% at 5 years. For stage III, OS|DFS improved from 69% to 88%. Patients younger than 50 years showed OS|DFS improvement from 79% to 95%; those older than 70 years showed no sustained increase in OS|DFS. Node-negative patients with ≥ 12 nodes resected showed little change (89% to 94%); those with more than four positive nodes showed an improvement (57% to 86%). Patients with a PS of 0 or 1 demonstrated a small improvement; those with a PS of 2 did not (64% to 58%).

Conclusion

Prognosis improves over time for almost all groups of patients with colon cancer, especially those with positive nodes. OS|DFS is a more relevant measure of prognosis for those who have already survived disease free a period of time after diagnosis.

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INTRODUCTION

As with many other malignancies, hazard rates for death among patients with colon cancer are relatively higher in the first few years after diagnosis, but then decrease markedly. Survival estimates for patients with colon cancer are traditionally reported from the time of diagnosis (eg, 5-year overall survival [OS]). These survival projections, however, are not necessarily applicable to patients who have survived a period of time after initial diagnosis and treatment. Such patients have a different prognosis than that estimated at the time of diagnosis. For them, prognosis is more accurately described using conditional survival (CS),¹ which is based on the concept of conditional probability and better reflects how changing hazard rates over time impact a

patient's prognosis. Representing the changing likelihood of demise over time, CS analysis seems to offer more relevant prognostic information for patients who are fortunate enough to have survived initial cancer management by providing more relevant estimates of their survival probability.

Several previously published cancer CS data series reveal distinct patterns of CS that vary substantially among diagnoses.² These studies have explored CS in cancer of the CNS,³⁻⁵ head and neck,⁶ breast,⁷⁻¹¹ lung,¹²⁻¹⁴ gallbladder,^{15,16} stomach,¹⁷ colorectum,¹⁸⁻²⁰ prostate,²¹ ovaries,²² and other sites.²³⁻²⁶ These studies have found that, in general, CS improves over time most significantly in patients with advanced disease, in whom the survival curve drops off rapidly in the first 1 or 2 years after diagnosis and then stabilizes.^{1-3,12,13,18,27} This

pattern can be less pronounced in early-stage disease for disease sites such as breast cancer, for which the hazard for recurrence (and subsequent death) remains relatively stable over time.

Sargent et al²⁸ showed that the pattern of decreasing hazard is present in early-stage colon cancer. His analysis of 20,898 patients pooled from 18 large randomized phase III colon cancer adjuvant clinical trials from 1977 to 1999 found that 88% of recurrences occurred within the first 3 years after diagnosis. Of these patients, 91% died within 5 years from diagnosis, indicating that disease recurrence can be used to predict subsequent OS fairly accurately. This finding inspired us to also examine the impact of disease-free survival (DFS) on CS estimates.

The specific aim of this study was to perform a secondary analysis of patients with colon cancer enrolled in National Surgical Adjuvant Breast and Bowel Project (NSABP) trials C-03 through C-07 to determine how CS changes for these patients as they survive longer periods of time from diagnosis. However, as one examines time from diagnosis, it should be noted that the number of patients in each subsequent risk set will become smaller and smaller, and thus caution should be taken when drawing inference about the effect of covariates over time.

PATIENTS AND METHODS

Written informed consent was obtained from patients who participated in NSABP trials C-03 through C-07. The human investigations were performed after approval by a local institutional review board and in accord with an assurance filed with and approved by the US Department of Health and Human Services. The NSABP is a National Cancer Institute–sponsored multicenter clinical trials cooperative group with randomizing institutions throughout the United States and Canada.

Definition of CS

CS is derived from the concept of conditional probability in statistics. CS can be calculated from traditional Kaplan-Meier or actuarial life-table survival data. The mathematical definition can be expressed as follows: Let $S(t)$ be the probability a patient survives to time t and $h(t)$ be the instantaneous hazard of death at time t . Conditional survival, $CS(y|x)$, is the probability of surviving an additional y years, given that the patient has already survived x years, and can be expressed as:

$$CS(y|x) = \exp \left[- \int_x^{x+y} h(t) dt \right] = \frac{S(x+y)}{S(x)} \quad (1)$$

For example, to compute the 5-year CS for a patient who has already survived 3 years, the absolute survival at 8 years is divided by the absolute survival at 3 years. When a survival curve has a changing hazard rate over time, this will be reflected as a change in CS as more time elapses from diagnosis.

Definition of Survival Conditional on Disease Status

The traditional definition of CS takes into account how long someone has survived, but it does not take into account the patient's present disease status relative to recurrence or second primary cancer (of any site). We propose extensions of the concept of CS where one conditions on the set of patients alive and free of recurrence (recurrence-free survival [RFS]) or on the set of patients alive and free of recurrence and second primary cancer (disease-free survival [DFS]). We use notation OS|DFS to generically denote the concept of OS on the set of patients alive and free of disease or OS(y)|DFS(x) for the probability of surviving an additional y years, given that the patient has already been alive and disease free x years. This expanded definition of CS cannot be directly calculated from survival estimates as CS can, but it can easily be estimated by applying Kaplan-Meier or life-table methods to the patients in the conditioning set. To do this, patients must be followed for recurrence,

Table 1. Number of Patients From Each NSABP Trial Arm Included in This Study

Study	Arm	Randomly Assigned	Ineligible	No Follow-Up	Included
C-03	LV + FU	539	19	2	518
C-04	LV + FU	719	26	2	691
C-04	LV + FU + LEV	717	20	2	695
C-05	LV + FU	1,088	18	1	1,069
C-05	LV + FU + IFN	1,088	21	8	1,059
C-06	LV + FU	803	27	6	770
C-06	LV + UFT	805	24	1	780
C-07	LV + FU	1,245	23	15	1,207
Total		7,004	178	37	6,789

Abbreviations: NSABP, National Surgical Adjuvant Breast and Bowel Project; LV, leucovorin; FU, fluorouracil; LEV, levamisole; IFN, interferon; UFT, tegafur and uracil.

secondary primary cancer, and death. van Houwelingen and Putter²⁹ discuss alternate estimation techniques. This definition can further be expanded to other conditioning sets including patients who are alive but have experienced a recurrence or second primary cancer. We refer to these patients as with disease (D) and use notation OS|D.

Data Selection Criteria

NSABP trials C-03 through C-07, conducted between 1987 and 2002, were a series of studies designed to evaluate the efficacy of different adjuvant chemotherapy regimens for Dukes' stage B and C colon cancer and compared fluorouracil (FU) plus leucovorin (LV) (or an equivalent regimen) with other chemotherapeutic agents.³⁰⁻³⁴ Because the general finding from these trials was that FU plus LV was more efficacious than comparison chemotherapy regimens and remains a major component of the current standard of care, for this CS study we selected only patients from these five trials who were enrolled on the FU + LV arms (or its equivalent; Table 1).

Survival, recurrence, and second primary cancer data for all eligible patients with follow-up as well as information on potential prognostic factors such as patient age at diagnosis, sex, race, tumor location, Dukes' stage, number of positive nodes, number of nodes resected, and Eastern Cooperative Oncology Group performance status (PS) were included in our analysis.

Survival Analysis

For all cohorts, we initially calculated 5-year CS, the probability of surviving at least 5 more years as a function of the number of years a patient had already survived since diagnosis, without regard to current disease status. To account for current disease status, we repeated the analysis for patients alive with disease at 1 to 5 years after diagnosis, OS|D. Finally, we calculated 5-year OS|DFS for patients alive and disease-free for up to 5 years after diagnosis.

All survival times were measured from the time of initial surgery, with the exception of patients in NSABP C-07, for whom date of randomization served as the anchor date. CS estimates were calculated using the Kaplan-Meier method in SAS (SAS Institute, Cary, NC). 95% CIs were also estimated using SAS.

The impact of prognostic covariates was evaluated by calculating OS DFS within strata defined by age (≤ 50 , 51 to 60, 61 to 70, and 71+ years), Dukes' stage (B, C), sex, tumor location (left colon, right colon, rectosigmoid, multiple locations), Eastern Cooperative Oncology Group PS (0 = normal activity, 1 = symptomatic but ambulatory, 2 = in bed $< 50\%$ of time), and number of positive and resected nodes (node-negative and ≥ 12 nodes resected, node-negative and < 12 nodes resected, one to three positive nodes, four or more positive nodes).

RESULTS

A total of 6,789 patients were identified in NSABP colon cancer trials C-03 through C-07 as meeting the inclusion criteria for this study

Fig 1. Five-year overall conditional survival for all patients as a function of (1) the total number of years survived since diagnosis ("Alive") and (2) the number of years survived without recurrence or second primary cancer. OS, overall survival; DFS, disease-free survival.

(Table 1). Figure 1 shows the results for 5-year CS as a function of years already survived since diagnosis. Error bars depict 95% CIs. Without regard to current disease status, the probability of surviving at least 5 more years as a function of the number of years a patient has already survived (5-year CS) increases modestly over the first 5 years, from 77% at diagnosis to 85% at 5 years postdiagnosis. For patients with disease at 1 to 5 years after diagnosis, the 5-year OS|D is very poor, ranging from 7% to 19% (data not graphed). For the set of patients alive and free of disease, the 5-year OS|DFS improves from 77% initially after surgery to 90% after 5 years. One can see that 5-year OS|DFS is consistently greater than the CS estimate. Because the prognosis for patients who have known recurrence or second primary is so much poorer than those who are disease-free, for the remainder of this

Fig 2. Five-year overall conditional survival stratified by age, as a function of the number of disease-free years survived.

Fig 3. Five-year overall conditional survival stratified by stage, as a function of the number of disease-free years survived.

analysis, we restricted our attention to patients who were alive and disease-free for up to 5 years after diagnosis.

Figures 2 to 5 show the 5-year OS|DFS estimates categorized by the levels of the prognostic covariates age, Dukes' stage, number of nodes positive and nodes resected, and PS. No substantial differences in 5-year OS|DFS were observed between male and female patients or among the tumor location categories (data not shown). For most subsets defined by the levels of prognostic covariates, 5-year OS|DFS estimates increase as time from diagnosis increases. OS|DFS improved with increasing time after diagnosis for all age groups (Fig 2) except for the oldest age group (> 70 years), which initially increases from 71% to 78% at 2 to 3 years, and then decreases again back to 70% at 5 years. As expected, Dukes' B patients (Fig 3) initially had better survival than Dukes' C patients (87% v 69%), but as time disease-free elapses from

Fig 4. Five-year overall conditional survival stratified by number of positive nodes, as a function of the number of disease-free years survived. Node-negative (N-) patients were further split into two groups based on the number of nodes resected (≥ 12 or < 12). N+, node positive.

Fig 5. Five-year overall conditional survival stratified by Eastern Cooperative Oncology Group performance status (PS), as a function of the number of disease-free years survived.

diagnosis, OS|DFS for Dukes' C improves and approaches the OS|DFS for Dukes' B patients (92% v 88% for Dukes' B and C at 5 years, respectively). Patients with four or more positive nodes (Fig 4) had markedly worse 5-year survival (57%) at diagnosis compared with other groups (76% to 89%), but as more time elapses from diagnosis, prognosis improves for all groups and the spread between the groups narrows (86% to 94%). When grouped by PS (Fig 5), prognosis improves over time for those with a PS of 0 or 1 but not for those with a PS of 2.

DISCUSSION

As time progresses from diagnosis, OS|DFS provides more relevant prognostic information for colon cancer survivors than traditional survival prognoses made at the time of diagnosis. In this analysis, we found that improvements in OS|DFS over time were seen for patients with higher stages of disease and for those with more positive nodes. On the other hand, older patients and those with poor PS did not necessarily show an improvement in OS|DFS over time.

To our knowledge, this is the first study of CS using a national cooperative group's clinical trial data. Previously published studies on CS have typically used cancer registry databases such as the Surveillance, Epidemiology, and End Results database³⁵ where information on recurrences is unavailable, thus making OS|DFS analyses impossible. Patients in the current analysis are a more select group who met the eligibility requirements for these NSABP trials and thus might reasonably be expected to have better CS than those in cancer registries, which are more all-inclusive. Also, the more detailed information available in the NSABP databases, such as recurrence and second primary cancer, allowed us to compute more relevant CS analyses in this study, OS|DFS.

A key observation from our analysis is that the differences in survival between strata tend to converge over time. For example, when categorized by number of positive nodes (Fig 4), 5-year survival shows a wide absolute range of 50% between groups (38% to 87%) at diag-

nosis, but this range decreases to 11% (81% to 92%) 5 years after diagnosis. This suggests that certain factors that are well known to have prognostic significance at diagnosis may lose some of their prognostic value as more time elapses from diagnosis. The diminishing importance of prognostic factors over time has been noted in previous NSABP studies; for example, in the B-14 data, an analysis of covariates over time showed this even in breast cancer, where hazard rates are considerably more persistent than in colon cancer.³⁶

Another factor contributing to this observed temporal change in CS is the natural selection effect over time of patients with better prognoses. The initial population contains a heterogeneous group of patients who have widely varying risks and prognoses. The portion of patients with highest inherent risk experience their greatest hazard in the initial years after diagnosis. Over time, as these patients expire, there is a natural selection of lower-risk patients and the surviving population becomes "healthier" with a better prognosis. The concept of CS is a way to quantify this phenomenon and make it easier for clinicians and patients to comprehend.

There are several limitations to this study. As more time elapses from diagnosis, the number of subjects in each group decreases as patients develop recurrence, second primary cancer, or die, and some apparent trends observed may actually be due to small patient numbers. This can be seen by the larger CI in some of the graphs. This precludes our ability to make more definite generalizations about the significance of some of the smaller trends observed. Also, secondary analyses of historical data dating back several decades may not reflect current treatment practices.

CS information is potentially of great interest to patients, their clinicians, and researchers. When patients who are seen in follow-up inquire about their current prognosis, CS can be used to give them a more relevant risk assessment that accounts for time already survived since diagnosis. The value of CS is that it is an easily understandable concept for patients and can be used to clearly portray their changing risk profile. Clinicians can also make use of CS to implement a more evidence-based approach to plan a post-therapy follow-up schedule based on a patient's actual current risk rather than simply relying on traditional schedules. It is important to remember, however, that CS only becomes relevant after the patient makes it to the given landmark year. The probability of reaching the landmark year depends on the patient's baseline prognosis at time zero.

When researchers design clinical trials, the study duration is often based on the estimated length of follow-up needed to see a significant result for a given end point. The study duration has important economic implications, particularly for large clinical trials, and it also affects the timeliness with which results can be published and translated into practice. Sargent et al^{28,37} proposed that alternative surrogate end points such as DFS may be appropriate in certain situations as a way to accelerate the completion of adjuvant clinical trials. In the current CS analysis, we observed little change in 5-year CS after 3 years of DFS in the majority of patient subsets, which is consistent with Sargent's findings.

In summary, for patients with colon cancer enrolled in the FU/LV arms of NSABP trials C-03 through C-07, we found that prognosis changed as more time elapsed from diagnosis. These changes in prognosis are a result of changing hazard rates over time and can be quantified and easily portrayed using the concept of CS, making the information more accessible to clinicians and more meaningful to patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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