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Original Article

# Analyzing the Long-Term Survival of Colon and Rectal Cancer Patients Using Non-Mixture Cure Rate Model

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ABSTRACT

**Introduction:** Colorectal cancer is the most common cause of cancer mortality in Iran. There are differences in the etiology, clinical behavior and pathological features in cancer of the colon versus the rectum. The aim of this study was to evaluate the factors related to survival and cure probability of patients with colon and rectal cancer using a semi-parametric non-mixture cure rate model.

**Methods:** This retrospective cohort study was conducted on 311 patients, with colorectal cancer. Data of all patients with colon and rectum malignances who underwent the first treatment in Omid Hospital, Mashhad, between 2006 and 2011 were gathered through medical records. Patients were followed-up for 9 years until September 2020. Semi-parametric non-mixture cure model was implemented using miCoPTCM package in the R software.

**Results:** The mean survival time was 2973.94 days (95% confidence interval [CI]: (2694.96, 3252.93). The 5-year survival rates for colon and rectal cancer patients were 0.54 (%95 CI:(0.45, 0.61)) and 0.57 (%95 CI:(0.48,0.65)), respectively. The proportion of cured colon cancer patients was 44.0%, while it was 40.0% for the ones with rectal cancer. Age and stage of the disease were determined as the common related factors of survival and cure fraction for both colon and rectal cancers. Ethnicity and type of first treatment were distinguished as factors related to survival and cure fraction of rectal cancer. Whereas the history of drug abuse increased the hazard of death in colon cancer patients; Also, overweight played a protective role in the survival and cure fraction of rectal cancer patients.

**Conclusion:** Because the factors associated with colorectal cancer are not necessarily equal to the risk factors for colon and rectal cancer, it is recommended to obtain more accurate and valid results in the survival analysis of colorectal cancer patients, the colon and rectum should be considered separately. It is also appropriate to use cure rate models when there is a cure fraction in the data.

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## Introduction

Cancer is the second leading cause of death in the world.[1] After cardiovascular disease and accidents, cancer is the third leading cause of death in Iran.[2] Colorectal cancer is the third most common cancer and the second leading cause of cancer related death in the world.[3] It is also the third and second diagnosed malignancy among men and women respectively.[4] Colorectal cancer is the most common cause of cancer mortality in Iran.[5] The incidence of colorectal cancer has increased dramatically over the past 25 years.[6] Although this cancer usually occurs after the age of 55, half of patients with colorectal cancer in Iran are younger than 50 years.[6] Adenocarcinoma accounts for 85% of all colorectal cancers, which originate from benign adenomatous polyps. These polyps turn into carcinomas after 26 years, and can be identified during this time.[7] Since the colorectal cancer is asymptomatic for a long time, it is often treatable if diagnosed during this period.[8] The mortality rate of this disease has decreased significantly over the last 2 decades, which is the result of development in different treatments and early detection.9 Some of the screening methods for early detection of the disease include annual fecal occult blood testing, colonoscopy every 10 years or double-contrast barium enema every 5 to 10 years and flexible sigmoidoscopy every 5 years.[10] There is difference in the etiology, clinical behavior and pathological features in cancer of the colon versus the rectum.[11]

Classical survival analysis models assume all included individuals will finally experience the event of interest if they are followed sufficiently enough. However, the assumption of susceptibility of all individuals may not always be true as a fraction of patients may not experience the event of interest even after sufficient follow-up; consequently, the use of ordinary survival models and ignoring such long term survivors (cured subjects) would lead to overestimation of the survival of the susceptible subjects.[12] For such data, the Kaplan-Meier survival curve will tend to a stable plateau at the end of study.[13] In such conditions the use of cure models is recommended.[14] There are two main categories for cure models including mixture and non-mixture cure rate models.[15]The non-mixture cure models or promotion time cure models, have the proportional hazards structure. They also have biological interpretation and easier computational application compared to mixture cure models.[16]

Since the colorectal cancer is the most common cause of cancer mortality in Iran and its resulting mortality in adults imposes a great economic burden on society, we aimed to analyze the long-term survival of colon and rectal cancer patients and to evaluate the relationship between variables such as gender, body mass index (BMI), age at the time of diagnosis, marital status, ethnicity, family history, type of first treatment, history of smoking and the history of drug abuse and American Joint Committee on cancer (AJCC) staging with survival and cure probability of patients with colon and rectal cancer as well as the estimation the cure rate of patients using non-mixture cure rate model.

The advantage of this study is to employ a semi-parametric non-mixture cure model as a suitable model to predict cure rate of colon and rectal cancer patients that can not be done by popular models such as cox model.

## Methods

This retrospective cohort study was conducted on 311 patients, with colorectal cancer. Information was obtained from all patients with colon and rectum malignances who underwent the first treatment in Omid Hospital, Mashhad, between 2006 and 2011. They were followed-up until September 2020 and the latest status of these patients in terms of death due to colorectal cancer was evaluated. All patients with colorectal cancer who received their first treatment at Omid Hospital were included in the study; while, the exclusion criteria were previous history of colorectal cancer. Also, all cases with incomplete medical records were not included in the analysis. The start time of the study was the date of tumor resection or the first chemotherapy and the end time was the date of death due to colorectal or the last confirmed date of censorship. The variables included in this study were gender, body mass index (BMI), age at the time of diagnosis, marital status, ethnicity, family history of cancer, type of first treatment, history of smoking, the history of drug abuse and American Joint Committee on cancer (AJCC) staging.[17] The current study approved by the Ethics Committee of the Mashhad University of Medical Sciences (approval code: IR.MUMS.REC.1399.356).

Frequency (percentage) and mean (SD) were used to describe qualitative and quantitative variables, respectively. The presence of a cured fraction in the sample before fitting the cure model, as well as sufficient follow up, were evaluated using the Kaplan-Meier plot and the tests introduced by Maller and Zhou.[14] The semi-parametric non-mixture cure model was fitted to the data. Selection of variables was done via the use of backward method. This model is based on the number of cancer cells that remain after treatment. Assume N indicates the number of defective tumor cells (cells which have could be metastasized) for a person which remain unchanged after the first treatment. We consider N has a Poisson distribution with parameter $\theta$ and $T_i$ is the random time variable for the $i^{th}$ defective tumor cell to produce traceable metastatic cancer. The time to relapse of cancer can be specified by random variable $T = \min\{T_i, 0 \le i \le N\}$ where $P(T_0 = \infty) = 1$ in which $T_0$ denotes the time to detectable metastatic when there is no defective tumor cell. Since with a specified N, the random variables $T_i$ , i = 1, 2, . . . are considered to be independent and identically distributed, their common distribution function would be regarded as $F_0$ (t) which does not depend on N. So, the survival function for T would be as:

$S_{pop} = P(T > t) = P(N = 0) + P(T_1 > t,...,T_N > t, N \ge 1)$

$= P(N = 0) + P(T_1 > t) \times ... \times P(T_N > t) \times P(N \ge 1)$

$$= \exp(-\theta) + \sum_{N=1}^{\infty} S(t)^N \frac{\theta^N}{N!} \exp(-\theta)$$

$$= \exp(-\theta) + \exp(-\theta) \sum_{N=1}^{\infty} S(t)^N \frac{\theta^N}{N!}$$

$= \exp(-\theta) + \exp(-\theta) \times [\exp(S(t)\theta) - 1] = \exp(-\theta + \theta S(t))$

$= \exp(-\theta F_0(t))$ (1),

which $F_0(t) = 1 - S_0(t)$, where $F_0(t)$ is a proper baseline distribution function.[16] If $x$ and $\beta$ are respectively the vectors of independent variables and coefficients of parameters then using $\theta = \exp(x'\beta)$ the cure probability is

exp(-θ)[13]; Thus a negative regression coefficient leads to a larger cure fraction and larger hazard for susceptible patients when the corresponding covariate takes a positive value.[18] The "density" corresponding to[1] is given by[16]:

$$f(t) = \theta f_0(t)\exp\{-\theta F_0(t)\} \quad (2)$$

And the hazard function is given by:

$$h(t) = \theta f_0(t) \quad (3)$$

in which h(t) has the proportional hazards structure.[16] Considering this model, the contribution of the $i^{th}$ subject in the likelihood function is given by:

$$L_i = [h(t_i)]^{\delta_i} S(t_i) = [\theta f_0(t_i)]^{\delta_i} \exp[-\theta F_0(t_i)] \quad (4)$$

Where $\delta_i$ is a censoring indicator variable, that is, $\delta_i = 0$ if the subject is censored, otherwise $\delta_i = 1$.[19] Analysis of the data was performed in R software (version 3.6) and the non-mixture cure model was implemented with miCoPTCM package (https://cran.r-project.org/). The significance level for all statistical tests was set at 0.05.

## Results

A total of 311 patients with mean age of 55.51 ± 14.05 years (range from 16 to 84 years) were included in the study. Most patients were in the normal range of BMI and 54% of the patients were males. The mean survival time was 2973.94 days (95% CI:(2694.96 ,3252.93)). There were 169 cases with colon cancer (54.34%) and 142 cases with rectal cancer (45.66%). Patients characteristics are presented in Tables 1 and 2.

The 1, 3, and 5-year survival rates for colon cancer patients were 0.85 (%95 CI, 0.79 to 0.89), 0.62 (%95CI, 0.54 to 0.69), and 0.54 (%95 CI, 0.45 to 0.61), respectively. Similarly, the 1, 3, and 5-year survival rates for rectal cancer patients were 0.89 (%95 CI, 0.82 to 0.93), 0.65 (%95 CI, 0.56 to 0.73), and 0.57 (%95 CI, 0.48 to 0.65), respectively. The Kaplan-Meier survival plots of both the colon and rectal cancers were plateau at the end of the study, indicating the possibility of cured individuals in the study (Figure 1). The results of Maller and Zhou tests confirmed the two basic assumptions of cure models, i.e. the existence of patients with long-term survival and the sufficiency of follow up. The survival graphs of both groups were almost the same, except that the survival rate of rectal cancer patients was slightly higher than the colon, while the graph for the colon flattened out sooner. Plot of the survival function estimated from the non-mixture model versus Kaplan-Meier survival estimate in colon and rectal cancer patients showed the appropriateness of the use of non-mixture cure model (Figure 2 & 3).

Based on the non-mixture cure model and backward elimination feature selection, the variables of age, stage of the disease and history of drug abuse were selected as the significant factors in colon cancer dataset and type of first treatment, ethnicity, age, the stage of the disease and BMI were chosen in rectal cancer. The results were presented in Table 3.

According to Table 3, age and the stage of disease had significant effects on cure probability and survival of susceptible patients with either colon or rectal cancer. Patients who were in stages I or II, had a better chance of being cured and the susceptible patients with advanced stage (III and IV) experienced

Table 1. Descriptive Statistics for quantitative variables by colon and rectal cancers

| Quantitative Variables | Colon cancer | Rectal cancer |
|---|---|---|
| Age (y)* | 56.35±14.20 | 54.51±13.91 |
| Body mass index (kg/m²)* | 23.04±4.61 | 22.68±4.59 |
| The survival time (day)** | 2695.61(95%CI: 2363.13, 3028.08) | 3015.92(95% CI: 2600.07, 3431.76) |

*Data were presented as Mean±standard deviation
**Mean (95% confidence interval)

Table 2. Patients Characteristics by Colon and Rectal Cancer

| Variables* | Colon cancer | Rectal cancer |
|---|---|---|
| Gender | | |
| Male | 86 (50.9%) | 82 (57.7%) |
| Female | 83 (49.1%) | 60 (42.3%) |
| BMI | | |
| <18.5 | 27 (16.0%) | 27 (19.1%) |
| 18.5-24.9 | 94 (55.6%) | 70 (49.6%) |
| 25-29.9 | 30 (17.8%) | 36 (25.5%) |
| ≥ 30 | 18 (10.7%) | 8 (5.7%) |
| Type of first treatment | | |
| Surgery | 123 (72.8%) | 76 (53.5%) |
| Chemotherapy | 46 (27.2%) | 66 (46.5%) |
| Ethnicity | | |
| Fars | 149 (88.2%) | 120 (84.5%) |
| Other | 20 (11.8%) | 22 (15.5%) |
| Stage | | |
| I-II | 65 (38.5%) | 59 (41.8%) |
| III-IV | 104 (61.5%) | 82 (58.2%) |
| Marital status | | |
| Single | 4 (2.4%) | 4 (2.8%) |
| Married | 152 (89.9%) | 133 (93.7%) |
| Other | 13 (7.7%) | 5 (3.5%) |
| Family history of cancer | | |
| Yes | 50 (29.6%) | 27 (19.0%) |
| No | 119 (70.4%) | 115 (81.0%) |
| History of smoking | | |
| Yes | 18 (10.7%) | 30 (21.1%) |
| No | 151 (89.3%) | 112 (78.9%) |
| History of drug abuse | | |
| Yes | 20 (11.8%) | 19 (13.4%) |
| No | 149 (88.2%) | 123 (86.6%) |
| Death due to cancer | | |
| Yes | 83 (49.1%) | 66 (46.5%) |
| No | 86 (50.9%) | 76 (53.5%) |

*Frequency (percentage)

Table 3. The Results Based on Non-Mixture Cure Rate Model by Colon and Rectal cancer

| Variables | Estimate | S.E | P-value |
|---|---|---|---|
| Colon Cancer | | | |
| Age | 0.018 | 0.008 | 0.020 |
| Stage of disease | | | |
| I-II | Reference | - | - |
| III-IV | 1.209 | 0.263 | <0.001 |
| History of drug abuse | | | |
| Yes | - | Reference | - |
| No | -0.649 | 0.278 | 0.020 |
| Rectal Cancer | | | |
| Age | 0.035 | 0.010 | 0.001 |
| BMI | | | |
| <18.5 | 0.046 | 0.345 | 0.893 |
| 18.5-24.9 | | Reference | |
| 25-29.9 | -0.954 | 0.410 | 0.020 |
| ≥ 30 | -0.467 | 0.458 | 0.308 |
| Type of first treatment | | | |
| Surgery | - | Reference | - |
| Chemotherapy | 0.559 | 0.262 | 0.033 |
| Stage of disease | | | |
| I-II | | Reference | |
| III-IV | 1.148 | 0.305 | 0.0001 |
| Ethnicity | | | |
| Fars | - | Reference | - |
| Other | 0.973 | 0.331 | 0.003 |

S.E, Standard error.

the event earlier. In terms of age, younger individuals had a more chance of being cured. Colon cancer patients with history of drug, had less chance to be cured. Table 3 also showed the significant impact of type of first treatment, ethnicity and BMI on rectal cancer patients. Patients who had received chemotherapy as the first therapeutic action had less chance to be cured comparison to patients who underwent surgery. In terms of ethnicity, individuals who were Fars, had more cure probability. Likewise, patients with BMI between 25 and 29.9 kg/m$^2$ had a higher probability of being cured.

The estimated cure fractions for colon and rectal cancer patients were 44.0%, and 40.0% respectively. According to Table 4 disease progression (increased in the stage of cancer) in both studied cancers was associated with a reduced cure proportion. Also, the cure proportions at all stages of the disease were higher in patients with colon cancer compared to rectal cancer.

Table 4. Cure Proportion of Colon and Rectal cancer by stage of disease

| Variable | Cure proportion |
|---|---|
| Colon cancer | |
| Stage of disease | |
| I-II | 0.69 |
| III-IV | 0.29 |
| Rectal cancer | |
| Stage of disease | |
| I-II | 0.63 |
| III-IV | 0.23 |

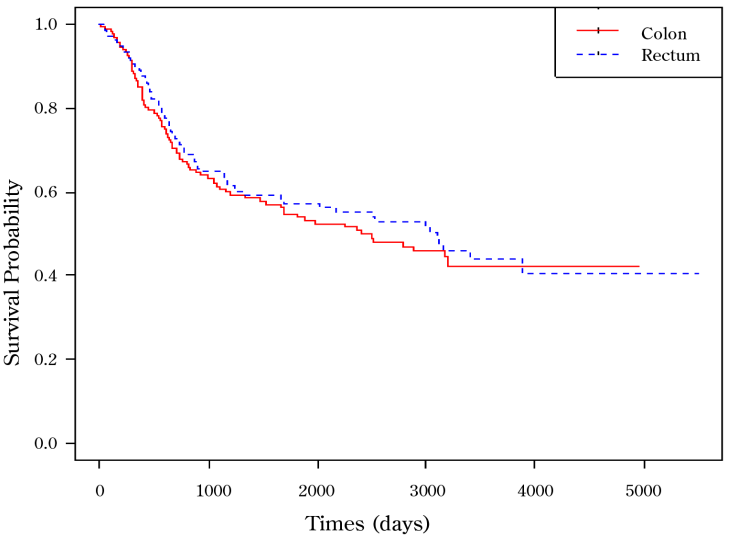


Figure 1. Kaplan-Meier survival estimate of patients by colon and rectal cancer

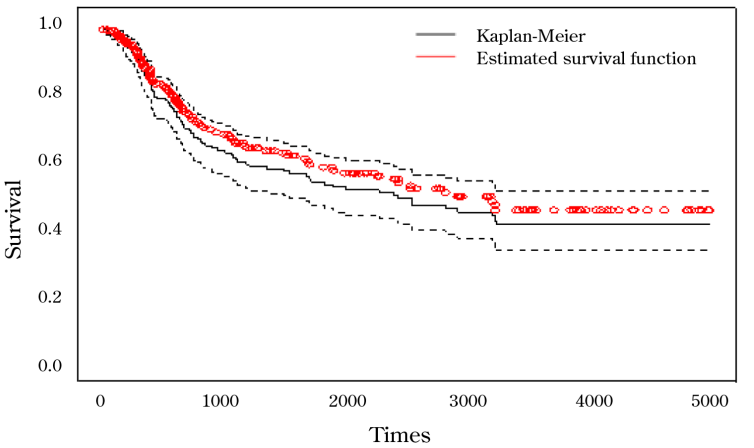


Figure 2. Survival function estimated from the non-mixture cure model (dotted line) versus Kaplan-Meiersurvival estimate (solid line) with 95% confidence interval (dashed line) in colon cancer patients.

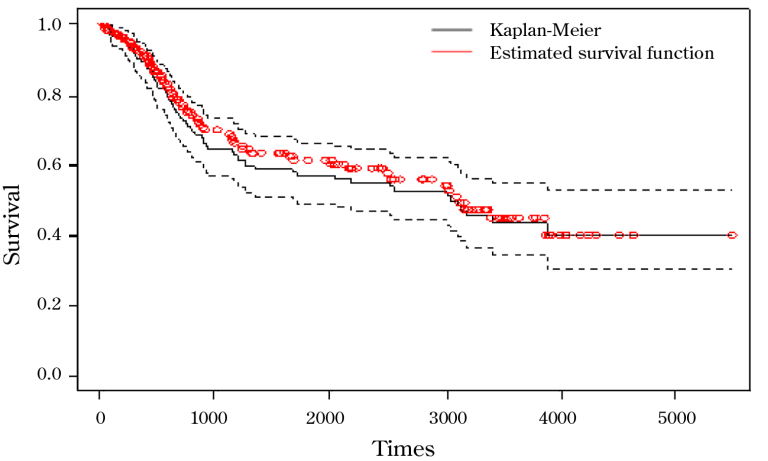


Figure 3. Survival function estimated from the non-mixture cure model (dotted line) versus Kaplan-Meiersurvival estimate (solid line) with 95% confidence interval (dashed line) in rectal cancer patients.

## Discussion

Identifying the factors associated with death due to a particular disease, especially cancer, is important for both patients and physicians. This helps patients to avoid the health threatening factors and is a guide for doctors to choose a specific treatment method based on the patients characteristics.[20] The treatment of various diseases, including cancer, has been significant progress in recent years, leading to the recovery of a fraction of patients, and as a result, these individuals may not experience the event of death or recurrence.[21] Cure rate models consider this cure fraction in survival analysis.[18] Our aim in this study was to analyze the long-term survival of patients with colon and rectal cancer and also to investigate the factors associated with death in each of them using non-mixture cure rate models. Colorectal cancer is one of the major concerns in the developed countries where malignant cells are found in the colon or rectum.[22]

Based on the results of this study advanced stages of the disease and older age were considered related factors to survival and cure probability of patients with colon and rectal cancer. Likewise, in the study of van der Sijp et al. age has been identified as predictor of short-term mortality and more complications in colon and rectal cancer.[23] Age, in the study of Morrison et al. was identified a predictor of death due to colon and rectal cancer.[24] In the study of van Eeghen et al. the age was reported to be related to the survival of colon cancer patients.[25] However, in the study by Looha et al. there was no significant relationship between age and survival of colorectal cancer patients.[26] On the basis of this study, early diagnosis of colorectal cancer is associated with a higher cure fraction and survival of these patients, which necessitates a more complete understanding of the disease progression and its early diagnosis. The study conducted by Li et al. was in accordance with ours and the stage was related to the survival of patients with colon and rectal cancer.[27] Also, in the study of Liska et al. the stage was reported to be effective on the recurrence of colon cancer patients.[28] Similarly, in the studies of Chu et al. and Looha et al. stage of cancer was related to the survival of patients suffering from colorectal cancer.[29, 30]

According to the results, being overweight increased the cure probability in patients with rectal cancer, the higher resistance of overweight patients to cancer may be due to their better nutrition. However, in the study by Morrison et al. there was not any significant relationship between BMI and patient survival in both cancers.[24]

The study conducted by Sabouri et al. showed a lower survival of people with a history of drug abuse.[31] This significant relationship was also mentioned in the studies of Gohari et al. and Parsaee et al.,[32, 33] whereas in our study, history of drug abuse was only related to the lower survival of colon cancer patients.

In the present study, history of smoking had no effect on colon and rectal cancer survivorship. In the study by Morrison et al., smokers had higher risk of death due to colon and rectal cancer compared to never-smokers.[24]

Based on the results, patients who first had received chemotherapy have a higher risk of rectal cancer death. In the study by Sanoff et al., among patients aged 75 years or more with colon cancer, chemotherapy was considered appropriate, and those who received chemotherapy had a lower risk of death;[34]

however, no association was found between it and colon cancer in our study.

Racial and ethnic differences affect the prevalence of colorectal cancer risk factors, and individuals' responses to the disease vary across races and ethnicities.[35] In our study, ethnicity was only associated with death due to rectal cancer. Similarly, the result of the study by Berger et al. was consistent with our study.[36] Based on the results, there was no significant relationship between family history of cancer and gender with colon or rectal cancer. Differences in results with previous studies may be due to the type of patients included in the study in terms of metastasis.

The strength of this study is the long-term follow-up and so far, no study has examined the factors related to the survival of colon and rectal cancer patients separately. The present study was able to examine the factors affecting the long-term survival of these two cancers with non-mixture cure rate model. One of the limitations of this study was the lack of information of some variables that were confirmed as factors related to the treatment of colorectal cancer patients in other studies, such as tumor grade, metastasis and alcohol consumption. It is suggested that further studies be performed to examine other clinical variables, and evaluation of factors effecting the survival of colon and rectal cancer patients using mixture cure rate model and non-mixture cure rate model with a Bayesian approach.

## Conclusion

Based on our results, considering a sufficient follow up, a fraction of patients with colon or rectal cancers have been cured. The cure fraction of patients with early stages of cancer was higher than those patients with advanced stage of disease, which suggest the early screening of these two types of cancer. According to our findings, age and stage of cancer were determined as risk factors affecting survival and cure fraction of both colon and rectal cancers. In addition, ethnicity and type of first treatment were related to the rectal cancer mortality. While the history of drug abuse only increased the risk of colon cancer death; overweight as a protective variable increased the survival and cure fraction of rectal cancer patients.

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## Conflict of interests

None

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