

# Estimating short-term and long-term survival in rectal cancer patients using cure model

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## ABSTRACT

**Background:** A large number of rectal cancer patients are cured after treatment. In such cases, cure models are used for survival analysis. This study aims to investigate factors that affect survival in rectal cancer using the Cox mixture cure model. **Methods:** Following a retrospective design, medical documents and pathological findings of newly diagnosed rectal cancer cases hospitalized at Imam Hossein Hospital, Tehran, Iran, from 2005 to 2013 were reviewed. The patients were followed up with until May 2018. The Cox mixture cure model was used. Data analysis was carried out using Statistical Analysis System (SAS) version 9.4. The statistical significance level was considered to be 0.05. **Results:** Four hundred nine patients were included in this study. The mean of disease-free survival was  $87.08 \pm 3.2$  months. The hazard of the event for the patients who were drug abusers was 2.37 (95% CI: 1.30-4.31) times more than the other cases ( $P = 0.005$ ). The odds ratio of the event for patients of stage III was 3.04 (95% CI: 1.51-6.12) times more than the cases of stage I ( $P = 0.002$ ), and for the patients of stage IV, it was 12.42 (95% CI: 4.17-37.01) times more than patients of stage I ( $P < 0.001$ ). **Conclusions:** The results of this cure model indicate that the tumor stage, tumor grade, and history of drug abuse are the risk factors for the survival of patients with rectal cancer. These results can attract the attention of doctors and patients who want to be aware of their physical status and prognosis.

**Keywords:** Disease-free survival, epidemiologic methods, rectal neoplasms, survival analysis

## Background

Colorectal cancer (CRC) is one of the most prevalent gastrointestinal cancers whose main etiologies are not yet precisely known. After skin cancers, lung and breast cancers in females (9.4%) and lung and prostate cancers in males (10%) are the most prevalent cancers. CRC is the third most common cancer in both genders. Seventy-two percent of such cancers are of colon type, and 28% are rectal.<sup>[1]</sup> The major risk factors

of CRC are high body mass index (BMI) and low-fiber diet, low physical activity, and smoking.<sup>[2]</sup> Studies indicate that the consequences of CRC depend not only on the anatomical site of the disease but also on other factors related to the patient's and tumor's characteristics.<sup>[3,4]</sup>

Common multivariate survival models (Cox model or parametric survival models) have been used for the prognostic analysis of patients suffering from CRC and investigating factors affecting cancer. Such models are based on the assumption that the final event occurs for all patients, whereas this assumption is not used for diseases when a considerable percentage of patients are cured after treatment.

Researches on rectal cancer indicate that many patients are treated successfully, particularly by using the three modalities

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of treatment: surgery, radiotherapy, and chemotherapy.<sup>[5]</sup> In this case, the use of common models leads the survival rate to be overestimated.<sup>[6]</sup> This cure in patients means treat successfully but cure model is a term in biostatistics. It is worth noting that this definition is conceptually different from “clinical cure” for patients.<sup>[7]</sup>

In order to analyze such data, functional cure models can be used. These models have been designed to analyze the high rate survival data.<sup>[8,9]</sup> A cure model is a mixture model and consists of two parts. The first part is the cure part which estimates the cure proportion and also the variables that affect the odds ratio (OR) of cured individuals (for long-term survivors). The second part provides the survival estimates by using variables that affect the risk ratio of those who have experienced the event (for short-term survivors). This research aimed to study the effect of prognostic factors on long-term survival (non-susceptible individuals) and short-term survival (susceptible individuals).

## Materials and Methods

### Study design

Following a retrospective design, medical documents and pathological findings of newly diagnosed rectal cancer cases hospitalized at Imam Hossein Hospital, Tehran, Iran, from 2005 to 2013 were reviewed. All newly diagnosed rectal cancer cases aged 18 to 75 years were included. Cases whose medical records were not complete, and those without a previous history of cancer and history of radiotherapy to pelvis and chemotherapy were excluded from the study. All of the cases had filled the informed consent form at admission in the hospital and before any diagnostic workup or treatment. They filled the part in that form that their innominate data provided in medical files such as demographic, pathologic reports, and treatment data, which could be used for future results. This study was a retrospective trial which used medical data and no procedure was done on patients. The study was confirmed by a local committee of medical ethics, Shahid Beheshti University of Medical Science with approval code IR.SBMU.RE/TECH.REC.1399.330.

During the period of study, 445 medical files were reviewed. Totally, 36 cases were excluded from the study due to partial follow-up (8 cases), wrong contact number (18 cases) or incomplete medical records (10 cases). We studied the remaining 409 cases. All eligible participants were routinely followed up every three months for two years, every six months for five years, and then every twelve months. The telephone interview was used to follow patients. The deadline for phone calls was May 2018. Patients' causes of death and their time of death were either extracted from their medical records or were asked from their first-order relatives by telephone. Patients were considered censored at their last follow-up or the date of telephone contact if they were alive.

The definition of survival outcomes is provided in the following. The period between data of pathological diagnosis

and death (due to any reason) was defined as the overall survival (OS). Additionally, the period between the dates of pathological diagnosis and the date of diagnosis of local recurrence, distant metastases, or death was considered as the disease-free survival (DFS). Variables of the study were age, gender, drug abuse, family history of cancers, BMI, stage of the tumor, tumor grade, primary symptoms of the disease, carcinoembryonic antigen (CEA) marker, and the location of metastasis.

### Statistical analysis

Cure models (CMs) are classified into mixture cure models and non-mixture cure model. Mixture CMs explicitly model survival as a combination of two types of cases: cured and non-cured cases. In this study, logistic regression was used to model the probability of curing a patient (long-term survival). Another component is the survival model of non-cured cases (short-term survival).<sup>[10]</sup> In this study, a Cox mixture cure model has been used with a logit link, while collinearity and proportional hazard assumption of included covariates were checked. Data analysis was carried out using Statistical Analysis System (SAS) version 9.4. The statistical significance level was considered to be 0.05.

## Results

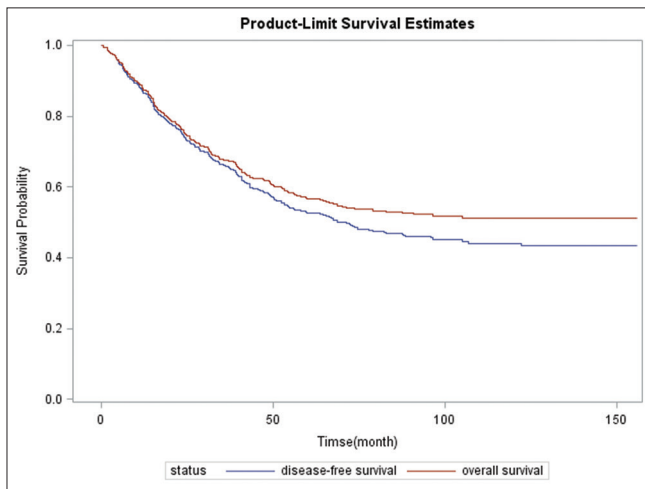
A total of 409 patients were included in the study. The median follow-up time was 63.34 months. The mean age of cases at the time of diagnosis was  $52.5 \pm 12$  (ranging from 18 to 75 years). The mean and median DFS were  $87.08 \pm 3.2$  and  $70.11 \pm 12.18$  months, respectively. The mean OS was  $119.69 \pm 3.93$  months and the median OS was 125 months. Local recurrence occurred in 120 patients and distant metastasis was observed in 139 patients, the latter of which included 45 liver metastases, 36 lung metastases, 14 bone metastases, and 37 metastases in other organs. In all cases reviewed, 189 patients died. The three, five, and ten-year DFS were 66%, 50%, and 44%, respectively. The three, five, and ten-year OS were 67%, 57%, and 51%, respectively.

The most common primary symptoms of patients were, rectal bleeding, change in bowel movement, melena, and abdominal pain. The baseline characteristics of patients and the results of a logrank test are shown in Table 1. Gender, family history, BMI and comorbidity had no significant association with DFS. Survival in patients younger than 50 years and survival in patients who had CEA less than 5 were more than the others, but these differences were not statistically significant. There were three factors which had a significant effect on DFS: disease stage, tumor grade, and drug abuse. There were significant differences in the cure fraction for tumor stage ( $P = 0.001$ ) and tumor grade.

In this study, a high percentage of patients had long-term survival according to Kaplan–Meier's curve plateau on the y-axis [Figure 1]. In this study, cure models were used to identify factors affecting survival. Variables such as gender, family

history, drug abuse, age, comorbidity, BMI, CEA, tumor stage, and tumor grade were entered into the Cox multivariate cure model. The result of the short-term survival part showed that the hazard of the event of interest (including local recurrence, distant metastasis, or death) in men was 1.3 times more than women ( $P = 0.07$ ). This hazard was 2.37 times more in patients who were drug abusers ( $P = 0.005$ ).

Furthermore, the risk of event in patients who had moderate differentiated tumors (grade II according to pathologic report) was 1.42 times more than cases who had well-differentiated tumors. In the long-term (cure) survival part, the OR of the event in stage III patients was 3.04 times more than that in stage I patients ( $P = 0.002$ ).



**Figure 1:** Kaplan–Meier curve for disease-free survival and overall survival

The OR of the event for stage IV patients was 12.42 times more than that for stage I patients ( $P < 0.001$ ) [Figure 2].

Patients older than 50 years had about 30% higher chance to experience the event [Table 2]. Also, patients who had poorly and moderately differentiated tumors developed metastasis more than cases with well-differentiated tumors; however, it was not statistically significant, based on the Chi-squared test result ( $P = 0.052$ ).

## Discussion

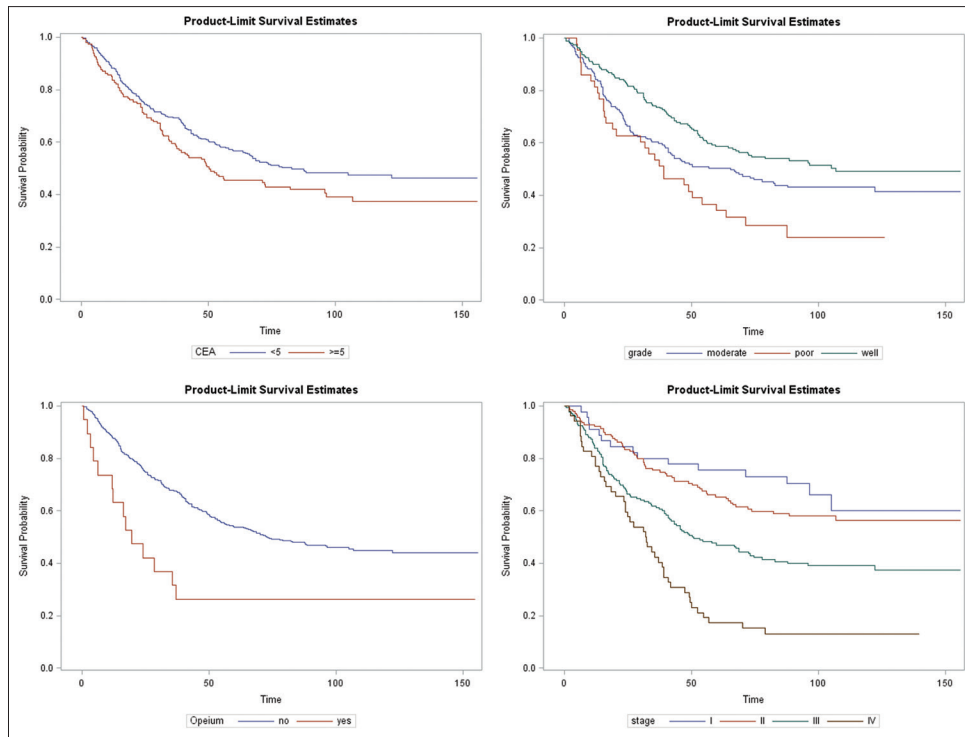
CMs provide an interesting technique to investigate patient prognosis in oncology as such models provide the opportunity to know the cure rate of cases. The clinical utility of the cure fraction lies on informing cases concerning the probability of the success of a particular intervention, in an understandable manner, as compared to the survival.<sup>[10]</sup> This measure would be of high use, particularly regarding the high prevalence of CRCs and the relatively high probability of metastasis and recurrences.<sup>[11,12]</sup> The majority of cancer survivors worry about the risk of recurrence or metastasis of the disease and live with the uncertainty of their ability to start a normal life. The ability to provide an accurate estimate of the probabilities of tumor recurrence would assist healthcare professionals to provide a more precise answer to patients.

In the present study, factors such as stage and tumor grade, as well as the history of opium abuse, were recognized as risk factors for patients with rectal cancer. The overall cure fraction of the patients was 43%. By way of explanation, 43% of the patients survived until the end of the study without any symptom

**Table 1: Descriptive statistics, the results of the logrank test and cure fraction**

Variable	Categories	Number of Patients	Number of Deaths	P*	Cure fraction% (95% CI)	P
Sex	Female	182 (44.5)	92 (50.5)	0.132	45 (39,52)	0.431
	Male	227 (55.5)	129 (49.5)		41 (35,47)	
Age	≤50	175 (42.8)	86 (38.9)	0.067	48 (41,55)	0.078
	>50	234 (57.2)	135 (61.1)		39 (34,45)	
Family History	No	377 (92.2)	201 (91)	0.429	44 (39,44)	0.352
	Yes	32 (7.8)	20 (9)		35 (20,50)	
Opium use	No	390 (95.4)	207 (93.7)	0.003	44 (39,47)	0.141
	Yes	19 (4.6)	14 (6.3)		26 (11,47)	
BMI	<25	216 (52.8)	119 (53.8)	0.838	42 (41,55)	0.643
	25-29.9	112 (27.4)	60 (27.1)		44 (35,53)	
	>29.9	81 (19.8)	42 (19)		45 (34,55)	
Comorbidity	No	335 (81.9)	175 (79.2)	0.197	45 (40,50)	0.081
	Yes	74 (18.1)	46 (20.8)		34 (24,45)	
CEA	<5	263 (64.3)	135 (61.1)	0.066	46 (40,52)	0.118
	≥5	146 (35.7)	86 (38.9)		38 (30,45)	
TNM Stage	I	45 (11)	15 (6.8)	0.001	64 (51,77)	0.001
	II	139 (34)	58 (26.2)		55 (47,63)	
	III	173 (42.3)	103 (46.6)		37 (31,44)	
	IV	52 (12.7)	45 (20.4)		12 (5,21)	
Tumor Grade	Well	190 (46.5)	91 (41.2)	0.002	49 (43,56)	0.004
	Moderate	176 (43)	99 (44.8)		41 (34,48)	
	Poor	43 (10.5)	31 (14)		25 (13,37)	

\*P-values calculated based on the logrank test. TNM, Tumor node metastasis; BMI, Body mass index; CEA, Carcinoembryonic antigen; CI, Confidence interval



**Figure 2:** Kaplan–Meier curve based on disease-free survival for CEA, tumor grade, opium and stage

**Table 2: Multivariate cure model and estimates of odds ratio and hazard ratio with confidence intervals for patients**

Variable	Categories	Odds Ratio (95%CI)	P	Hazard Ratio (95%CI)	P
Gender	Female	ref		ref	
	Male	1.13 (0.73, 1.76)	0.582	1.39 (0.98, 1.72)	0.07
Age	≤50	ref		ref	
	>50	1.28 (0.83, 1.98)	0.266	1.21 (0.90, 1.62)	0.209
Family History	No	ref		ref	
	Yes	1.21 (0.53, 2.74)	0.656	0.92 (0.56, 1.45)	0.734
Opium	No	ref		ref	
	Yes	1.44 (0.46, 4.51)	0.537	2.37 (1.29, 4.31)	0.005
BMI	<25	ref		ref	
	25-29.9	1.03 (0.62, 1.69)	0.917	0.96 (0.69, 1.34)	0.82
	>29.9	0.97 (0.54, 1.74)	0.922	1.10 (0.75, 1.62)	0.616
Comorbidity	No	ref		ref	
	Yes	1.55 (0.87, 2.76)	0.136	0.85 (0.59, 1.22)	0.389
CEA	<5	ref		ref	
	≥5	1.09 (0.68, 1.73)	0.716	1.09 (0.82, 1.48)	0.533
TNM Stage	I	ref		ref	
	II	1.45 (0.71, 2.94)	0.31	1.05 (0.57, 1.92)	0.876
	III	3.04 (1.51, 6.12)	0.002	1.29 (0.72, 2.33)	0.385
	IV	12.42 (4.17, 37.01)	<0.001	1.22 (0.63, 2.35)	0.557
Tumor Grade	Well	ref		ref	
	Moderate	1.19 (0.76, 1.88)	0.446	1.42 (1.04, 1.94)	0.025
	Poor	2.59 (1.16, 5.78)	0.02	1.35 (0.88, 2.05)	0.165

TNM, Tumor node metastasis; BMI, Body mass index; CEA, Carcinoembryonic antigen; CI, Confidence interval

of local relapse or metastasis. Lambert *et al.*<sup>[5]</sup> reported a lower cure fraction of about 40% whereas Cucchetti *et al.*<sup>[13]</sup> indicated a cure fraction of 20%. However, in another study in Japan, a cure fraction of 57% was seen. This was about 53% in another study in 2018.<sup>[14,15]</sup> There are factors that may affect the diversity of the results in studies. These factors can be the difference in the

follow-up period of cases and different facilities and experiences in treatment strategies in various centers and may also be because of having different comorbidity. This study demonstrated that men have lower OR regarding being cured of rectal cancer compared to women, but gender did not have a significant effect on cure fraction and survival.

A large number of studies have indicated that tumor grade affects the survival of rectal cancer patients.<sup>[16–19]</sup> In this study, the odds of the cure for patients with well-differentiated tumors was 2.59 times more than patients with poorly differentiated tumors. It seems that the risk of short-term survival for the patients with moderately differentiated tumors was significantly more than cases with well-differentiated tumors. Also, this risk in patients with poorly differentiated tumors was more than cases with well-differentiated tumors; however, it was not statistically significant, which can be attributed to the small sample size or the type of analysis that has been employed.

The tumor stage is the most important variable to predict the survival of those suffering from rectal cancer. In this research, those who were in stages I and II had an observed survival higher than 55%. In addition, for those at stages III and IV, survival was <40%. Nevertheless, in this study, we did not observe a low survival rate among stage IV patients. In similar studies, the survival of stage IV patients in CRC patients (4%) was much lower than what we achieved.<sup>[20]</sup> The effect size of the American Joint Committee on Cancer (AJCC) staging on survival and cure fraction of cases with rectum cancer was significant. The findings of the present study are consistent with several other studies.<sup>[21,22]</sup>

For cases who suffered from CRC, serum tumor marker CEA was of crucial importance to manage and follow-up with patients.<sup>[23]</sup> Generally, serum CEA measurements are often applied both before and after surgery. Enhanced concentration of serum CEA in the follow-up of the patients strongly indicated recurrences. In addition, measuring the CEA before the surgery was important. High concentrations of CEA before the surgery indicate progressed disease with distant metastasis or locally advanced disease.<sup>[24]</sup> Wiratkapun *et al.* reported that the cumulative DFS of cases with preoperative normal serum CEA concentration was significantly better compared to cases with enhanced serum CEA concentration (5 ng/ml or more).<sup>[25]</sup> In our study, patients with CEA less than 5 ng/ml had better survival, but it was not statistically significant.

The present study demonstrated a significant association between the consumption of opium and rectal cancer, which is in line with the study conducted by Kim *et al.*<sup>[26]</sup> Several cases with an addictive behavior may not report drug abuse when noting their history. Hence, drug abuse is probably underestimated.

The Cox mixture cure model demonstrated differences among factors that contribute to short- and long-term survival. The effect of age on the patients' survival is a controversial variable in the studies.<sup>[27,28]</sup> In the present study, the patients were categorized into two age groups: younger or older than 50 years. Patients who were younger than 50 years old survived longer than the older group. However, it was not statistically significant. One of the limitations of this study was being uni-centric and the patients' incomplete information.

## Conclusion

The results of this cure model indicate that the stage, tumor grade, and history of drug abuse are the risk factors for shortening the survival of patients with rectal cancer. Physicians should pay attention to these factors while taking the patient's history. It can help to estimate the prognosis of cases. Also, this study demonstrated differences among factors that contribute to short- and long-term survival.

## List of abbreviations

DFS: Disease-free survival

OS: Overall survival

CEA: Carcinoembryonic antigen

BMI: Body mass index

CRC: Colorectal cancer

AJCC: American Joint Committee on Cancer

TNM staging: Tumor, node, metastasis staging system

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the consent form, the patients permit the researchers to use their images and other clinical information to be reported in the journals anonymously.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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