Prognostic Factors Affecting Short- and Long-Term Recurrence-Free Survival of Patients with Rectal Cancer using Cure Models: A Cohort Study

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Abstract

Background: Understanding the prognostic factors affecting the recurrence-free survival (RFS) of patients with rectal cancer (RC) is the mainstay of care. The present study aimed to identify factors affecting both short- and long-term RFS of patients with RC using semiparametric mixture cure models.

Methods: The data were obtained from the database of the Colorectal Research Center of Shiraz University of Medical Sciences, Shiraz, Iran, which was collected during 2007-2017. To determine the factors affecting recurrence, cure models were applied to short-term and long-term RFS of patients with RC separately. The cure rate was calculated using the smcure package in R 3.5.1 (2018-07-02) software. P<0.05 was considered statistically significant.

Results: Out of the 376 eligible patients with RC, 75.8% of men and 74.5% of women were long-term survivors. The mean age of the patients was 57.0±13.8 years. Lymph node ratio (LNR)≤0.2 increased the probability of short-term RFS. The prominent factors affecting long-term RFS were body mass index (BMI)<25 kg/m2 (OR=1.98, P=0.047), tumor-node-metastasis (TNM) stage (OR=6.48, P<0.001), abdominal pain (OR=2.15, P=0.007), and computed tomography (CT) scan detected pelvic lymph nodes (OR=3.40, P=0.01). Over a 9-year follow-up period, the empirical and estimated values of cure rates were 75.3% and 83.9%, respectively.

Conclusion: The results showed that factors affecting short-term RFS might be different from long-term RFS. A lower BMI was related to a poorer prognosis in patients with RC. Early diagnosis leads to a lower TNM stage and could increase the probability of long-term RFS.

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Introduction

Colorectal cancer (CRC) is the third most common malignancy in the world and the leading cause of cancer-related deaths in women after breast cancer.1-4 Rectal cancer (RC) constitutes one-third of all CRC cases.1, 3, 4 Age, family history of RC, and...
Western lifestyle have been reported as the major risk factors of RC.\(^5\) The epidemiology and treatment methods of RC have been continuously changing over time.\(^1\), \(^2\) To date, neoadjuvant chemoradiotherapy following total mesorectal excision (TME) is considered the standard treatment for locally advanced RC.\(^5\), \(^7\) Locally advanced RC is associated with a high risk of local recurrence (LR) and metastasis.\(^7\), \(^9\) Dissemination of the disease and recurrence have been reported as the leading causes of death in patients with RC.\(^10\)

Several studies have been conducted to specify the factors affecting recurrence in patients with RC.\(^11\), \(^12\) Most of these studies have mainly used the Cox-adjusted regression model for data analysis. In some of these studies, a large plateau on the estimated Kaplan-Meier curve indicated that a high percentage of patients did not experience the desired outcome at the end of the follow-up. Therefore, the multivariate cure model analysis might be more appropriate than the traditional Cox regression models provided that the follow-up period is long enough. Note that the hypothesis of a sufficient follow-up period is evaluated using the non-parametric $\alpha_n$-test. The two basic categories of cure models are non-mixture and mixture models.\(^13\), \(^14\) The benefit of mixture models over the Cox-adjusted regression model is the ability to separately seek for the effects of various factors on both short- and long-term survivals.

To the best of our knowledge, no studies have been conducted on short- and long-term recurrence-free survival (RFS) of patients with RC using multivariate cure models. Hence, the present study aimed to examine the impact of a wide range of clinical and pathological variables on RC recurrence in short-term (uncured cases) and long-term (cured cases) survivors.

### Patients and Methods

The current historic cohort survey aimed to assess the data of 376 patients with RC, collected during 2007-2017 at the Colorectal Research Center affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. This research center also gathered data from two other main referral centers for surgical/palliative treatment of CRC in Shiraz, Southern Iran (Colorectal Surgery Department of Shahid Faghihi Hospital and Radiotherapy Department of Nemazee Hospital).

Tumor-node-metastasis (TNM) staging is the most accepted classification system to define rectal tumor invasion and its prognostic implication.\(^9\) LR was defined as histologically, radiologically, and clinically ascertained tumor regrowth in the pelvis.\(^9\) All patients were diagnosed as new cases of RC and those with malignant lesions in the anal canal were enrolled in the study. The exclusion criteria were suffering from simultaneous malignancies of the colon and rectum or metastatic recurrence, those presented with recurrent cancer at the time of diagnosis, and loss to follow-up. Besides, cases with a considerable amount of missing data were excluded from the analysis. In cases where patients did not have any recurrences during the follow-up period, the interval between TME and the end of follow-up was considered the censored time. Concerning the method of treatment, some patients received neoadjuvant chemoradiotherapy, some had adjuvant radiotherapy after surgery, and others did not receive radiotherapy at all. Regarding follow-up, visits were scheduled according to the protocols of both the colorectal surgery and radiotherapy departments, which required patients to be followed up every three months during the first year, every six months during the second year, and then annually. The last update of the follow-up protocol was performed in December 2017. The study was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (code: IR.SUMS.REC.1395.S1103).

The probability of RFS in patients with RC was estimated using the Kaplan-Meier curve. The log-rank test was used to compare different groups of categorical variables of survival. Additionally, the mixture cure model was applied to calculate the percentage of patients with RC without recurrence (cured cases) and the probability of RFS among those with recurrence (uncured cases). The cure model is a mixed model; the Cox proportional and the logit models were used to model short- and long-term survival, respectively. The estimated cure rate could be immediately determined by long-term survival. The empirical cure rate (the ratio of individuals without recurrence at the end of the follow-up period) was calculated. The selection of variables for modeling was based on the clinical significance and statistical tests. If the $P$ value of the desired factor was $<0.2$ in the univariate cure model, that factor was a candidate for the multivariate cure model. All statistical analyses were performed using the smcure package in R 3.5.1 (2018-07-02) software. $P<0.05$ was considered statistically significant.

### Results

Out of 376 eligible patients with RC who were followed up during 2007-2017 (approximately
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112 months), 157 (41.8%) patients were female (figure 1). A total of 283 (75.3%) patients with RC did not have a recurrence, while the remaining patients (24.7%) had. As a result, the empirical cure rate over a 9-year follow-up period was 75.3%. The mean age and body mass index (BMI) of the patients were 57.0±13.8 years (range: 23-94) and 23.6±3.6 kg/m² (range: 15.6-35.8), respectively. The mean survival time was 49 months (range: 3-112). Demographic characteristics, radiological and pathological findings of the patients with RC and their effects on RFS are presented in tables 1 and 2. As shown, abdominal pain (P=0.011), TNM stage (P<0.001), and CT-scan detected pelvic lymph nodes involvement (P=0.017) had a significant impact on the overall RFS of the patients with RC.

Based on the estimated Kaplan-Meier curve (figure 2), the calculated survival probability inclined to reach a plateau after 48 months of follow-up. Therefore, there was evidence of long-term RFS; no event of interest occurred after 48 months and the overall estimated Kaplan-Meier curve was about 64 months as it leveled off. Moreover, 283 (75.3%) out of the 376 patients with RC were censored, i.e., they did not experience the desired outcome. Indeed, 50% of censoring occurred at the plateau phase. Furthermore, the result of a sufficient follow-up hypothesis test using α_n-test was significant (P<0.001). Therefore, the mixture cure model could be applied to explore the factors that significantly affected the recurrence in both short- and long-term groups.

The hazard ratio (HR) for uncured patients with RC (short-term RFS), odds ratio (OR) for cured patients (long-term RFS), and the associated 95% confidence interval (CI) are shown in table 3. The results of the cure model indicated that the lymph node ratio (LNR) values greater than 0.2 had no significant impact on the short-term RFS of patients with RC. However, a borderline P value was obtained (HR=1.690, CI: 0.952-3.003, P=0.074). For clarity, the estimated RFS curves for the two levels of LNR are illustrated in figure 3. The RFS values in patients with RC in each LNR level were almost the same within the initial 10 months after surgery. However, afterward, LNR<0.2 was accompanied by a higher RFS probability (lower risk of recurrence).

The results of the cure model analysis demonstrated that BMI, TNM stage III, abdominal pain, and CT-scan detected pelvic lymph nodes involvement had a significant impact on long-term RFS of the patients (P=0.047, P<0.001, 0.007, and 0.010, respectively). The OR (95% CI) for BMI<25 kg/m² was 1.98 (1.009-3.891), which indicated that patients

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Table 1: The effect of demographic characteristics on recurrence-free survival (N = 376)

| Characteristic   | No recurrence n (%) | Recurrence n (%) | P value*
|------------------|---------------------|------------------|---------|
| **Sex**          |                     |                  |
| Male             | 166 (44.2)          | 53 (14.1)        | 0.630   |
| Female           | 117 (31.0)          | 40 (10.7)        |         |
| **Age (years)**  |                     |                  |
| <50              | 75 (20.0)           | 29 (7.7)         | 0.470   |
| ≥50              | 208 (55.3)          | 64 (17.0)        |         |
| **BMI (Kg/m²)**  |                     |                  |
| <25              | 204 (54.3)          | 74 (19.7)        | 0.155   |
| ≥25              | 79 (21.0)           | 19 (5.0)         |         |
| **FHX of CRC**   |                     |                  |
| No               | 238 (63.3)          | 83 (22.0)        | 0.195   |
| Yes              | 45 (12.0)           | 10 (2.7)         |         |
| **FHX of OM**    |                     |                  |
| No               | 218 (58.0)          | 74 (19.7)        | 0.737   |
| Yes              | 65 (17.3)           | 19 (5.0)         |         |

*Log-rank statistic; P<0.05 was considered significant; BMI: Body mass index, FHX of CRCs: Family history of colorectal cancer, FHX of OM: Family history of other malignancies
| Factor                                      | No Recurrence | Recurrence | P value |
|---------------------------------------------|---------------|------------|---------|
| **Radiotherapy**                            |               |            |         |
| None                                        | 16 (4.3)      | 5 (1.3)    | 0.935   |
| Adjuvant                                    | 190 (50.5)    | 64 (17.0)  |         |
| Neoadjuvant                                 | 77 (20.5)     | 24 (6.4)   |         |
| **TNM stage**                               |               |            |         |
| I                                           | 118 (31.4)    | 21 (5.6)   | <0.001* |
| II                                          | 119 (31.6)    | 40 (10.7)  |         |
| III                                         | 46 (12.2)     | 32 (8.5)   |         |
| **Surgery type**                            |               |            |         |
| APR                                         | 78 (20.7)     | 36 (9.6)   | 0.075   |
| LAR                                         | 139 (36.9)    | 41 (10.9)  |         |
| VLAR                                        | 66 (17.6)     | 16 (4.3)   |         |
| **Grade**                                   |               |            |         |
| Moderately differentiated                   | 91 (24.3)     | 23 (6.1)   | 0.374   |
| Poorly differentiated                       | 20 (5.3)      | 9 (2.4)    |         |
| Well differentiated                         | 172 (45.7)    | 61 (16.2)  |         |
| **LNR**                                     |               |            |         |
| <0.2                                        | 231 (61.5)    | 82 (21.8)  | 0.140   |
| ≥0.2                                        | 52 (13.8)     | 11 (2.9)   |         |
| **Tumor size**                              |               |            |         |
| 0-1 cm                                      | 22 (5.9)      | 4 (1.1)    | 0.273   |
| 1-3 cm                                      | 96 (25.5)     | 28 (7.4)   |         |
| >3 cm                                       | 165 (43.9)    | 61 (16.2)  |         |
| **Radiation course**                        |               |            |         |
| None                                        | 14 (3.7)      | 5 (1.3)    | 0.804   |
| Short course                                | 4 (1.1)       | 2 (0.5)    |         |
| Long course                                 | 265 (70.5)    | 86 (22.9)  |         |
| **Chemotherapy session**                    |               |            |         |
| ≤6                                          | 224 (59.6)    | 79 (21.0)  | 0.203   |
| >6                                          | 59 (15.7)     | 14 (3.7)   |         |
| **Vascular invasion**                       |               |            |         |
| No                                          | 222 (59.0)    | 71 (18.8)  | 0.486   |
| Yes                                         | 22 (5.9)      | 10 (2.7)   |         |
| Unknown                                     | 39 (10.4)     | 12 (3.2)   |         |
| **Neural invasion**                         |               |            |         |
| No                                          | 200 (53.2)    | 68 (18.1)  | 0.750   |
| Yes                                         | 41 (10.8)     | 15 (4.0)   |         |
| Unknown                                     | 42 (11.2)     | 10 (2.7)   |         |
| **Lymphatic invasion**                      |               |            |         |
| No                                          | 197 (52.4)    | 72 (19.2)  | 0.438   |
| Yes                                         | 46 (12.2)     | 12 (3.2)   |         |
| Unknown                                     | 40 (10.6)     | 9 (2.4)    |         |
| **Proximal margin involvement**             |               |            |         |
| No                                          | 272 (72.3)    | 91 (24.2)  | 0.358   |
| Yes                                         | 11 (2.9)      | 2 (0.5)    |         |
| **Distal margin involvement**               |               |            |         |
| No                                          | 270 (71.7)    | 92 (24.5)  | 0.122   |
| Yes                                         | 13 (3.5)      | 1 (0.3)    |         |
| **Radial margin involvement**               |               |            |         |
| No                                          | 278 (73.9)    | 89 (23.7)  | 0.075   |
| Yes                                         | 5 (1.3)       | 4 (1.1)    |         |
| **Surgery method**                          |               |            |         |
| Laparotomy                                  | 120 (31.8)    | 33 (8.8)   | 0.382   |
| Laparoscopy                                 | 121 (32.2)    | 47 (12.5)  |         |
| Convert                                     | 42 (11.2)     | 13 (3.5)   |         |
| **CT-scan detected para-aortic lymph node** |               |            |         |
| No                                          | 269 (71.5)    | 90 (24.0)  | 0.693   |
| Yes                                         | 14 (3.7)      | 3 (0.8)    |         |
| **CT-scan detected pelvic lymph node**      |               |            |         |
| No                                          | 227 (60.4)    | 84 (22.3)  | 0.017*  |
| Yes                                         | 56 (14.9)     | 9 (2.4)    |         |
| **CT-scan detected wall thickness**         |               |            |         |
| No                                          | 55 (14.6)     | 20 (5.4)   | 0.505   |
| Yes                                         | 228 (60.6)    | 73 (19.4)  |         |
| **Residual tumor**                          |               |            |         |
| No                                          | 249 (66.2)    | 85 (22.6)  | 0.461   |
| Yes                                         | 34 (9.0)      | 8 (2.2)    |         |

*Log-rank statistic; P<0.05 was considered significant; TNM: Tumor-node-metastasis, APR: Abdominoperineal resection, LAR: Low anterior resection, VLAR: Very low anterior resection, LNR: Lymph node ratio
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with BMI<25 kg/m² had lower odds of remaining cured than those with BMI≥25 kg/m² (table 3). The TNM stage also had a significant effect on long-term survival. Based on the results, patients who were at stage III had lower odds of being cured than those at stage I (OR=6.480, CI: 3.037-13.850). Therefore, based on the calculated probability curve (figure 4), RFS was significantly higher in patients at stage I than those at stage III. Pelvic lymphadenopathy detected with a CT-scan was also a major prognostic factor for long-term survival. The patients with this finding had higher odds of remaining uncured (OR=3.40, 95% CI: 1.338-8.674). The estimated coefficients of all variables involved in the cure model analysis were applied to calculate the cure rate. The overall cure rate estimated with the mixture cure model using the logit link function was 0.839, indicating that 83.9% of the patients with RC were cured.

Discussion

The results showed that factors affecting short-term RFS might be different from long-term RFS. A lower BMI was related to a poorer prognosis in patients with RC. Early diagnosis resulting in a lower TNM stage increased the probability of long-term RFS.

Many studies have mainly highlighted and reported the overall survival rate of patients with rectal cancer. However, in the present study, we separately reported the short- and long-term survival rates. Previous studies used the
traditional Cox-adjusted regression model, which is an appropriate method for analyzing short-term survival. However, long term follow-up and high censoring (the ratio of patients without recurrence) make multivariate cure models more suitable than the Cox-adjusted regression analysis. In our dataset, the estimated Kaplan-Meier curve leveled off around 0.75 and a long plateau (almost 64 months) was observed over time. Therefore, we applied the mixture cure model analysis. The results of the cure model analysis indicated that BMI, TNM stage, abdominal pain, and pelvic lymph nodes involvement detected with a CT-scan had a significant effect on long-term RFS, while LNR affected short-term RFS of patients with RC. Since the incidence of RC follows an ascending trend, especially in developing countries, more attention has been paid to factors contributing to RFS. Recently, many studies have reported the effect of various prognostic factors on recurrence in patients with RC. BMI had an important effect on long-term RFS. In line with previous studies, we found that those patients with normal BMI had lower odds of being cured and only a few of them were long-term survivors. Jafarabadi and colleagues also reported a lower chance of survival for patients with a normal BMI compared with those with a higher BMI. In contrast, a prospective cohort study that examined the relationship between various BMI levels and RC recurrence reported that BMI was not associated with the risk of RC recurrence. The difference between the results might be attributed to differences in statistical analyses of the number of clinical and pathological factors associated with survival and the types of study populations. Moreover, the time at which the BMI was measured could have had an impact on survival.

The results showed that the TNM stage had a significant effect on long-term RFS of patients with RC. We found that patients in TNM stage III had lower long-term survival and odds of cure compared with those in stage I. Several studies have also reported that the TNM stage plays an important role in determining RFS and that the recurrence rate was higher in stage III than in stage I. Nodal involvement has been mostly accepted as the main risk factor for LR. In the current study, the number of involved lymph nodes had a significant prognostic effect on the recurrence of RC, which underlines the importance of precise preoperative evaluation of lymph nodes status. In the same vein, many previous studies highlighted an incremental risk of LR associated with lymph node involvement. The results of the present study showed that pelvic lymph node involvement, detected by a CT-scan, decreased the incidence of long-term RFS. Therefore, the metastasis of the pelvic lymph node had a significant effect on RC recurrence. Similarly, a previous study reported that patients with pelvic lymphadenopathy had poorer long-term RFS than those without pelvic lymph node involvement. We also found that patients with LNR>0.2 had a higher recurrence rate than those with LNR<0.2. Some other studies on patients with CRC also associated lower LNR with lower RC recurrence. We also found that patients with a primary complaint of abdominal pain had better RFS. However, there are no published reports to substantiate our findings.

One of the limitations of our study was due to incomplete clinical staging data (classification of tumor invasion before treatment), which only had been evaluated in some recent survivors of RC. The other limitation was related to incomplete registration of RC cases in the province, since some patients might not have been referred to our hospitals in Shiraz.

**Conclusion**

A lower BMI level was related to poorer prognosis in patients with RC. However, early diagnosis results in a lower TNM stage and a lower number of involved pelvic lymph nodes, which in turn increases the probability of long-term RFS in these patients. This should be considered by health policy-making bodies to enforce a strict screening program. The results showed that the factors affecting short-term RC recurrence might be different from those influencing its long-term recurrence. Therefore, further studies are required to expand on the existing knowledge beyond RC survivors and to develop more comprehensive cure models.

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