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Original Article

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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What's Known

- Understanding the prognostic factors affecting recurrence-free survival of patients with rectal cancer is the mainstay of care.
- Prognostic factors such as age, sex, genetic factors, pathologic variables, surgical techniques, and neoadjuvant therapy have been shown to affect the recurrence-free survival of patients with rectal cancer.

What's New

- The factors affecting short-term recurrence-free survival of patients with rectal cancer might be different from those affecting long-term recurrence-free survival.
- A lower body mass index was related to a poorer prognosis in patients with rectal cancer. Early diagnosis leads to a lower tumor-node-metastasis stage and could increase the probability of long-term recurrence-free survival.

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/m^2 (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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Keywords ● Cure model ● Rectal neoplasms ● Recurrence ● Lymph node ratio ● Survival

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.[6, 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 α_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

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/m^2 (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/m^2 was 1.98 (1.009-3.891), which indicated that patients

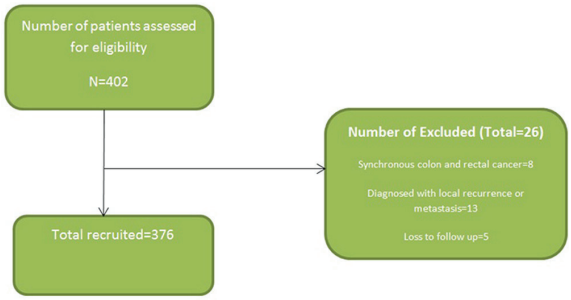

Figure 1: Flow diagram indicates the selection process of the patients.

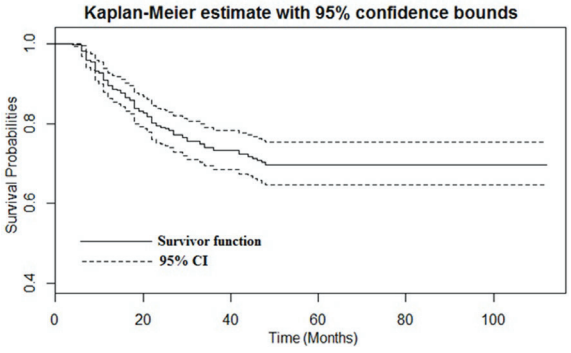

Figure 2: The stable pattern in the overall Kaplan-Meier survival curve for patients with rectal canceris observed from the 50th month.

Table 1: The effect of demographic characteristics on recurrence-free survival (N_{total}=376)

		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/m^2)	<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

Table 2: Radiological and pathological characteristics of patients with rectal cancer and their effect on recurrence-free survival (N_{total}=376)

Factor		No Recurrence n (%)	Recurrence n (%)	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

Table 3: Factors affecting short- and long-term survival using the mixture cure model

Short-term survival using the proportional hazards model				
Factor		**HR**	**95% CI**	**P value**
BMI≥25Kg/m²		-	-	-
BMI<25 Kg/m²		1.209	(0.613, 2.385)	0.584
CT-scan detected Pelvic lymph node	No	-	-	-
	Yes	0.930	(0.465, 1.865)	0.840
LNR	<0.2	-	-	-
	≥0.2	1.690	(0.333, 1.050)	0.074
Long-term survival using the logit link function				
Factor		OR	95% CI	P value
Intercept		0.192	(0.045, 0.818)	0.026*
Age		1.010	(0.988, 1.033)	0.340
BMI≥25Kg/m²		-	-	-
BMI <25 Kg/m²		1.980	(0.257, 0.991)	0.047*
TNM stage	I	-	-	-
	II	1.810	(0.896, 3.660)	0.097
	III	6.480	(3.037, 13.850)	<0.001*
Surgery type	APR	-	-	-
	LAR	0.598	(0.310, 1.140)	0.119
	VLAR	0.595	(0.240, 1.450)	0.254
Abdominal pain	No	-	-	-
	Yes	2.150	(1.235, 3.740)	0.007*
CT-scan detected Pelvic lymph node	No	-	-	-
	Yes	3.400	(1.338, 8.674)	0.010*

*P<0.05 was considered significant; BMI: Body mass index, HR: Hazard ratio, LNR: Lymph node ratio, OR: Odds ratio, TNM: Tumor-node-metastasis

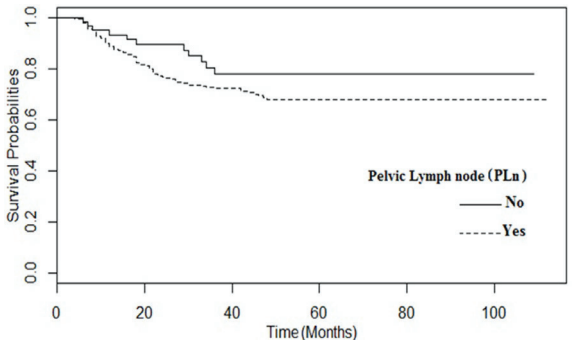

Figure 3: The figure illustrates the Kaplan-Meier curve for recurrence-free survival at lymph node ratios <0.2 and ≥0.2 (P=0.074).

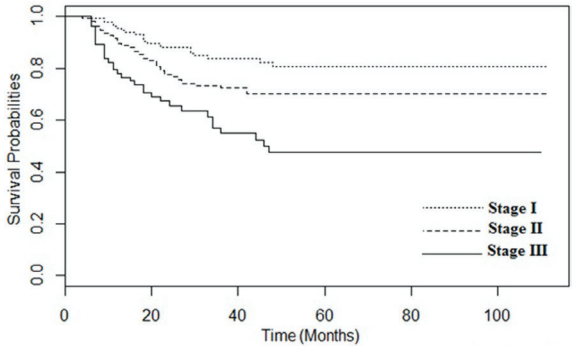

Figure 4: The survival probabilities are illustrated by the Kaplan-Meier curve for recurrence-free survival for tumor-node-metastasis stages I, II, and III.

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.[10, 12, 15] 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.[16-18] 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.[5, 11, 16] BMI had an important effect on long-term RFS. In line with previous studies,[5, 16] 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.[15] 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.[12] 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.[5, 19, 20]

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.[21] 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.[22] 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.[11, 23] 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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Conflict of Interest: None declared.

References

1 Fidler MM, Bray F, Soerjomataram I. The global cancer burden and human development: A review. Scand J Public Health. 2018;46:27-36. doi: 10.1177/1403494817715400. PubMed PMID: 28669281.

2 Chandrasinghe PC, Ediriweera DS, Hewavisenthi J, Kumarage SK, Fernando FR, Deen KI. Colorectal cancer burden and trends in a South Asian cohort: experience from a regional tertiary care center in Sri Lanka. BMC Res Notes. 2017;10:535. doi: 10.1186/s13104-017-2869-1. PubMed PMID: 29084610; PubMed Central PMCID: PMCPMC5663050.
3 Joseph DA, Johnson CJ, White A, Wu M, Coleman MP. Rectal cancer survival in the United States by race and stage, 2001 to 2009: Findings from the CONCORD-2 study. Cancer. 2017;123 Suppl 24:5037-58. doi: 10.1002/cncr.30882. PubMed PMID: 29205308; PubMed Central PMCID: PMCPMC6191027.
4 Tan WJ, Tan HJ, Dorajoo SR, Foo FJ, Tang CL, Chew MH. Rectal Cancer Surveillance-Recurrence Patterns and Survival Outcomes from a Cohort Followed up Beyond 10 Years. J Gastrointest Cancer. 2018;49:422-8. doi: 10.1007/s12029-017-9984-z. PubMed PMID: 28660522.
5 Akhoond MR, Kazemnejad A, Hajizadeh E, GAnbary Motlagh A, Zali MR. Comparison of influential factors affecting survival of patients with colon and rectum cancer using competing risks model. Koomesh. 2011;12:119-28. Persian.
6 Wu L, Pang S, Yao Q, Jian C, Lin P, Feng F, et al. Population-based study of effectiveness of neoadjuvant radiotherapy on survival in US rectal cancer patients according to age. Sci Rep. 2017;7:3471. doi: 10.1038/s41598-017-02992-7. PubMed PMID: 28615639; PubMed Central PMCID: PMCPMC5471198.
7 Orangio G, Gagliardi G. Corman's Colon and Rectal Surgery, 6th edition. Tech Coloproctol. 2013;17:335-. doi: 10.1007/s10151-013-0994-y.
8 de'Angelis N, Pigneur F, Martinez-Perez A, Vitali GC, Landi F, Torres-Sanchez T, et al. Predictors of surgical outcomes and survival in rectal cancer patients undergoing laparoscopic total mesorectal excision after neoadjuvant chemoradiation therapy: the interest of pelvimetry and restaging magnetic resonance imaging studies. Oncotarget. 2018;9:25315-31. doi: 10.18632/oncotarget.25431. PubMed PMID: 29861874; PubMed Central PMCID: PMCPMC5982752.
9 Smart N. Corman's Colon and Rectal Surgery, 6th Revised edition Edited by Corman ML, Nicholls RJ, Fazio VW, Bergamaschi R. Lippincott Williams and Wilkins, October 2012. Hardcover: 1584 pages, English. ISBN: 978-1451111149. Price £243.00 RRP hardback, £161.60 Kindle edition. Colorectal Disease. 2013;15:920. doi: doi:10.1111/codi.12287.
10 Grosek J, Velenik V, Edhemovic I, Omejc M. The Influence of the Distal Resection Margin Length on Local Recurrence and long- term Survival in Patients with Rectal Cancer after Chemoradiotherapy and Sphincter- Preserving Rectal Resection. Radiol Oncol. 2017;51:169-77. doi: 10.1515/raon-2016-0030. PubMed PMID: 28740452; PubMed Central PMCID: PMCPMC5514657.
11 Kim YS, Kim JH, Yoon SM, Choi EK, Ahn SD, Lee SW, et al. lymph node ratio as a prognostic factor in patients with stage III rectal cancer treated with total mesorectal excision followed by chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2009;74:796-802. doi: 10.1016/j.ijrobp.2008.08.065. PubMed PMID: 19289261.
12 Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, Nelson H, et al. Impact of body mass index and weight change after treatment on cancer recurrence and survival in patients with stage III colon cancer: findings from Cancer and Leukemia Group B 89803. J Clin Oncol. 2008;26:4109-15. doi: 10.1200/JCO.2007.15.6687. PubMed PMID: 18757324; PubMed Central PMCID: PMCPMC2654367.
13 Xu L, Zhang J. Multiple imputation method for the semiparametric accelerated failure time mixture cure model. Computational Statistics and Data Analysis. 2010;54:1808-16. doi: https://doi.org/10.1016/j.csda.2010.01.034.
14 Kleinbaum DG, Klein M. Survival Analysis A Self-Learning Text. 3th ed. 2012.
15 Asghari-Jafarabadi M, Hajizadeh E, Kazemnejad A, Fatemi SR. Site-specific evaluation of prognostic factors on survival in Iranian colorectal cancer patients: a competing risks survival analysis. Asian Pac J Cancer Prev. 2009;10:815-21. PubMed PMID: 20104971.
16 Hines RB, Shanmugam C, Waterbor JW, McGwin G, Jr., Funkhouser E, Coffey CS, et al. Effect of comorbidity and body mass index on the survival of African-American and Caucasian patients with colon cancer. Cancer. 2009;115:5798-806. doi: 10.1002/cncr.24598. PubMed PMID: 19937953; PubMed Central PMCID: PMCPMC2795032.
17 Russu PC, Molnar C, Gurzu S, Jung I, Voidazan TS, Copotoiu C. The role of clinical and pathological assessment in choosing the best therapeutic management to improve survival in rectal cancer. Rom J Morphol Embryol. 2016;57:1253-9. PubMed PMID:

28174791.
18 Mirzaee M, Azmandian J, Zeraati H, Mahmoodi M, Mohammad K, Etminan A, et al. Short-term and long-term survival of kidney allograft: cure model analysis. Iran J Kidney Dis. 2014;8:225-30. PubMed PMID: 24878946.
19 Fleshman J, Branda ME, Sargent DJ, Boller AM, George VV, Abbas MA, et al. Disease-free Survival and Local Recurrence for Laparoscopic Resection Compared With Open Resection of Stage II to III Rectal Cancer: Follow-up Results of the ACOSOG Z6051 Randomized Controlled Trial. Ann Surg. 2019;269:589-95. doi: 10.1097/SLA.0000000000003002. PubMed PMID: 30080730; PubMed Central PMCID: PMCPMC6360134.
20 Merchea A, Ali SM, Kelley SR, Duchalais E, Alabbad JY, Dozois EJ, et al. Long-Term Oncologic Outcomes of Minimally Invasive Proctectomy for Rectal Adenocarcinoma. J Gastrointest Surg. 2018;22:1412-7. doi: 10.1007/s11605-018-3751-8. PubMed PMID: 29594912.
21 Porter GA, Urquhart R, Bu J, Johnson P, Rayson D, Grunfeld E. Improving nodal harvest in colorectal cancer: so what? Ann Surg Oncol. 2012;19:1066-73. doi: 10.1245/s10434-011-2073-9. PubMed PMID: 21969083.
22 Sjo OH, Merok MA, Svindland A, Nesbakken A. Prognostic impact of lymph node harvest and lymph node ratio in patients with colon cancer. Dis Colon Rectum. 2012;55:307-15. doi: 10.1097/DCR.0b013e3182423f62. PubMed PMID: 22469798.
23 Rosenberg R, Friederichs J, Schuster T, Gertler R, Maak M, Becker K, et al. Prognosis of patients with colorectal cancer is associated with lymph node ratio: a single-center analysis of 3,026 patients over a 25-year time period. Ann Surg. 2008;248:968-78. doi: 10.1097/SLA.0b013e318190eddc. PubMed PMID: 19092341.