

# A multistate survival model in rectal cancer surgery research for locally advanced patients

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**Background:** One of the most appropriate methods for analyzing longitudinal data is multistate model. This study has aimed to evaluate the risk factors of transfer to local recurrence (LR), distant metastasis (DM), and death in rectal cancer patients through multistate survival analysis. **Materials and Methods:** This is a retrospective cohort of rectal cancer patients in Mashhad, Iran. Multistate models were applied to show the difference between the significant risk factors affecting death and recurrence in different defined transitions. Risk factors include age, sex, primary surgical technique, tumor location, postoperative tumor stage, circumferential or distal resection involvement, surgery time, and surgical complications. **Results:** A total of 280 eligible patients with a median (interquartile range) survival time of 60 (42-76.2) months were investigated. Based on Cox proportional multistate model, the hazard ratio (HR) of DM increases by 3%/1-year increase in age ( $P = 0.018$ ). The HR of DM and the HR of LR in patients with postoperative disease Stage II/III were 3.06 and 2.53 times higher than patients with cancer Stage 0/I ( $P < 0.05$ ). When the resection margins of distal or circumferential were involved, the HR of DM was 3.58 times higher than those patients without involvement. In the extended multistate model, time of DM was a significant predictor of death ( $P = 0.006$ ). **Conclusion:** Age and margin involvement in DM path and stage in LR and DM path had a significant effect; however, no effective variable was seen on the death of patients with recurrence. The time of metastasis also had an effect on the path of death.

**Key words:** Distant metastasis, local recurrence, multistate model, rectal cancer, survival

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## INTRODUCTION

Rectal cancer is a major global burden worldwide that accounts for around one-third of colorectal cancers.<sup>[1,2]</sup> Over 1.4 million new cases and 180,000 deaths due to rectal cancer have been registered in Asia.<sup>[1,3]</sup> A significant proportion of patients with rectal cancer suffer from locally advanced tumors that attach to or attack nearby structures such as prostate, pelvic wall, bladder, or bone. In these cases, the tumors may be unresectable or resection may be associated with a significant risk of local recurrence (LR).<sup>[4,5]</sup>

Studies have shown that LR or distant metastasis (DM) occurs after surgery in about 30%–50% of colorectal

cancer cases.<sup>[6-8]</sup> The annual incidence of LR or DM in the 1, 2, and 5 years has been reported about 9.9%, 26.2%, and 31.5%, respectively. The highest rate is related to the first 2 years after surgery. However, the median time to LR or DM is steadily increasing, especially for rectal cancer.<sup>[9]</sup>

The survival and corresponding factors in cancer patients have always been the main subject in clinical studies. During the treatment course, patients experience different procedures such as surgery, chemoradiation therapy, and LR or DM from the diagnosis time to death. Each step affects the patients' survival;<sup>[10,11]</sup> hence, the standard survival analysis methods may lack the proper accuracy. A common method for simultaneous modeling of disease progression events is using multistate models

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that describe the progress and transitions over time. These models are widely used in medical fields where the stages of the disease are expressed by model states. Application of these models in medicine leads to a better understanding of the disease process.<sup>[12,13]</sup>

Subjects in a multistate model enter the study at different starting states but may experience one or several states until their final (absorbing) state. Some patients may be censored before the absorbing state.<sup>[10,14]</sup> Multistate models calculate the transition probability and intensity from one state to another by considering the effect of individual and clinical characteristics such as age, sex, tumor location, and surgical methods.<sup>[11]</sup>

Rectal cancer patients experience LR or DM as main determinants of patients' survival with a higher risk in the first five years after surgery, which causes major changes in the disease progression. Furthermore, multistate model is one of the most appropriate methods for analyzing these longitudinal data.<sup>[15,16]</sup> This study was designed with the aim of evaluating the risk factors of patients' transition to LR, DM, and death states through providing the application of the multistate survival model on rectal cancer data.

## MATERIALS AND METHODS

### Study design and participants

A total of non-metastatic 300 patients with locally advanced rectal cancer (LARC) who underwent neoadjuvant chemoradiotherapy followed by laparoscopic curative surgery were enrolled in this retrospective cohort at Omid, Ghaem, and Razavi hospitals in Mashhad, Iran, between July 2011 and March 2017. The follow-up sessions continued until 2021. Thirty-day mortality patients (N=2), loss to follow-up cases (N=9), and those who experienced both LR and DM or multiorgan metastases after surgery (N=9) were excluded from the study.

### Study variables

Variables include age at diagnosis, sex, primary surgical technique (transanal, transabdominal, and abdominoperineal), tumor location (upper, middle, and lower), postoperative tumor stage (0/I, II/III), circumferential or distal resection involvement, surgery time (based on minutes), and surgical complications (including pelvic collection, anastomotic failure, and intestinal obstruction). Rectal tumor location and time of surgery were not analyzed because these variables are related to the surgical technique.

### Statistical analysis

The quantitative results were presented as mean  $\pm$  standard deviation or median (inter-quartile range:IQR). Categorical data were expressed as frequency (percentage). Patient

survival analysis was performed using a multistate model based on Cox proportional hazards. Four states including onset state (curative surgery), intermediate state (LR and DM), and death due to rectal cancer (absorbing state) were adjusted based on the clinical events. The Cox proportional hazard model is the most common regression model for multistate data. Many hazard models are multiplicative; this means that the logarithm of hazard is linear with respect to the explanatory variables. In this case, the semi-parametric Cox regression model is considered. The proportional hazards hypothesis is considered for technical and interpretive convenience.<sup>[10,17]</sup> This model is as follows:

$$\lambda_{q,i}(t) = \lambda_{q,0}(t) \exp(X_i^T(t)\beta_q)$$

where  $q$  is the indicator of transition set;  $X_i$  is the vector of covariates;  $\beta_q$  is transition-specific covariate coefficient vectors; and  $\lambda_{q,0}(t)$  is transition-specific baseline hazard function.<sup>[18]</sup>

Once again, the model (state-arrival extended Markov stratified hazard) was fitted in the presence of a recurrence time variable (time-dependent variable).

Bayesian information criterion (BIC) evaluation was used to compare the two aforementioned multiple models (with and without time-dependent variable).<sup>[19]</sup> The BIC represents the amount of information lost by the model, and therefore, the smaller the BIC value, the better and more appropriate the model is. Cox proportional hazards multistate model was fitted to the data using the "mstate" package. This package calculates the probabilities of interstate transitions for any given patient according to the study variables. The analysis was performed using R<sup>[20]</sup> statistical software (version 4.1.1; R Core Team, 2021). The significance level was considered at  $P < 0.05$ .

## RESULTS

A total of 280 eligible patients with a median (IQR) survival time of 60 (42-76.2) months were included in the study. The descriptive information of the patients is summarized in Table 1. Among all patients, 29 (10.40%) and 43 (15.40%) patients experienced LR and DM during the follow-up, respectively. The median (IQR) survival time was reduced to 35 (25-47) and 40 (25-67) months in patients with DM and LR, respectively. Out of 72 (25.71%) patients with any recurrence, 58 (80.56%) died due to rectal cancer. The 3- and 5-year survival rates (95% confidence interval: CI) for patients with no recurrence were 97% (93.5, 98.7) and 95.4% (91, 97.7), respectively. The survival rates for patients with any recurrence significantly reduced to 51% (39, 61.9) and 23.7% (14.5, 34.2), respectively. The 3-year survival

rates (95%CI) for patients with DM and LR were 48.8% (33.3, 62.5) and 54.4% (34.7, 70.4), respectively, whereas the 5-year survival rates (95%CI) were 18.1% (8.2, 31) and 32.1% (16.1, 49.3), respectively. The patient status and transition between states are depicted in Figure 1.

**Transition hazard estimations**

The results of the multiple Cox proportional multistate model are summarized in Table 2. Considering the clinical significance of the research variables together and considering the lack of proportional hazards hypothesis for the four transitions in the study, the multiple stratified Cox proportional hazard model was fitted to the data. The surgical complication variable was not considered in the first and second transitions as it has no clinical meaning in these pathways. Furthermore, the variable of surgical technique in the second and fourth transitions is not examined because 86.2% of patients with LR have undergone transanal surgery.

The risk of DM increases by 3%/year increase in age at diagnosis ( $P = 0.018$ ) [Table 2]. The risk of DM and LR

in patients with postoperative disease Stages II/III was 3.06 and 2.53 times higher than those with cancer Stage 0/I ( $P = 0.001$  and  $P = 0.018$ , respectively). When the distal or circumferential resection margins were involved, the risk of DM was 3.58 times higher than that of patients without involvement. The state-arrival extended Markov model was fitted to the data, and the occurrence time of DM in DM to death transition as well as occurrence time of LR in LR to death transition were included. Since the fitted multistate model was stratified (model with different baseline hazards for each transition), estimation of the hazard ratio (HR) for the variables in the first and second transitions remained unchanged and only changes in the third and fourth transitions were observed. The risk of death in patients with DM increased by 13%/1-year delay in DM ( $P = 0.006$ ).

The BIC for the model without time dependence [Table 2] was equal to 980.09, while this criterion for the time-dependent model [Table 3] was 977.28. The smaller the BIC, the better fit of the model is. According to BIC, the time-dependent model (time to enter the metastasis state) was considered the model with better fit.

**Transition probability prediction**

The probabilities of transitions between states are studied graphically for convenient understanding. For illustrational purposes, we defined one reference patient with tumor, node, and metastasis (TNM) Stage 0/I, noninvolved circumferential, or distal margin in all transitions. He was 55 years old at the surgery time. LR or metastasis occurred in the 12<sup>th</sup> month after surgery, and he underwent transanal resection. The transition probabilities are presented in Figure 2a-a1 and a2, showing a low transition probability

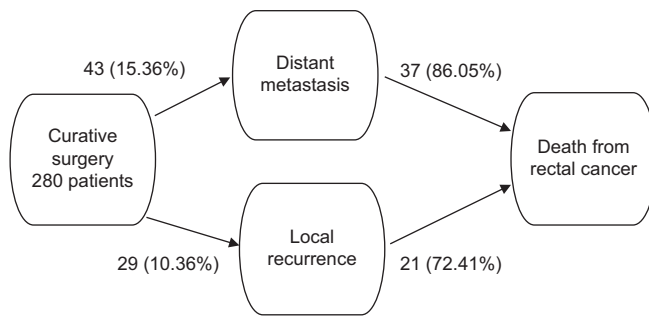


Figure 1: Four transitions for all 280 patients in the study

**Table 1: Descriptive statistics of rectal adenocarcinoma patients in this study**

Variables	Overall, n (%)	LR, n (%)	DM, n (%)	Survivor <sup>a</sup> , n (%)	Death, n (%)
Age at diagnosis, mean±SD	55.15±12.69	50±12.18	58.98±13.35	54.92±12.34	57.23±14.42
Sex					
Female	113 (40.40)	11 (37.90)	17 (39.50)	85 (40.90)	26 (38.80)
Male	167 (59.60)	18 (62.10)	26 (60.50)	123 (59.10)	41 (61.20)
TNM stage <sup>b</sup>					
0/I	145 (51.80)	10 (34.50)	13 (30.20)	122 (58.70)	17 (25.40)
II/III	133 (47.50)	19 (65.50)	30 (69.80)	84 (40.40)	50 (74.60)
Surgical techniques					
Transanal	163 (58.20)	25 (86.20)	20 (46.50)	118 (56.70)	37 (55.20)
Transabdominal	70 (25)	3 (10.30)	10 (23.30)	57 (27.40)	14 (20.90)
Abdominoperineal resection	47 (16.80)	1 (3.40)	13 (30.20)	33 (15.90)	16 (23.90)
Distal or circumferential margin					
Noninvolved	265 (94.60)	25 (86.20)	38 (88.40)	202 (97.10)	60 (89.60)
Involved	15 (5.40)	4 (13.80)	5 (11.60)	6 (2.90)	7 (10.40)
Surgical complication related to survival					
None	222 (79.30)	26 (89.70)	34 (79.10)	162 (77.90)	54 (80.60)
Experienced	58 (20.70)	3 (10.30)	9 (20.90)	46 (22.10)	13 (19.40)

<sup>a</sup> Survivor without experience of intermediate state; <sup>b</sup> Missing for two patients. SD=Standard deviation; TNM=Tumor, node, and metastasis; LR=Local recurrence; DM=Distant metastasis

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**Table 2: The different variable effect on hazard ratio of distant metastasis, local recurrence, and death due to rectal cancer (multistate Cox stratified hazard)**

Variables	HR (P)			
	Surgery → DM	Surgery → LR	DM → death	LR → death
Age at diagnosis	1.03 (0.018)*	0.98 (0.116)	0.99 (0.615)	1.02 (0.332)
Sex				
Male	-	-	-	-
Female	0.93 (0.829)	0.78 (0.525)	0.92 (0.867)	2.18 (0.128)
TNM stage				
0/I	-	-	-	-
II/III	3.06 (0.001)*	2.53 (0.018)*	1.41 (0.511)	3.61 (0.106)
Surgical resection techniques				
Transanal	-	-	-	-
Transabdominal	0.92 (0.840)		0.80 (0.710)	
Abdominoperineal	2.01 (0.078)		1.04 (0.944)	
Distal or circumferential margin				
Noninvolved	-	-	-	-
Involved	3.58 (0.010)*	2.48 (0.113)	1.11 (0.872)	0.34 (0.191)
Surgical complication related to survival				
None	-	-	-	-
Experienced			1.54 (0.398)	2.37 (0.336)

\*Significant at  $\alpha=0.05$ . LR=Local recurrence; DM=Distant metastasis; HR=Hazard ratio; TNM=Tumor, node, and metastasis

**Table 3: The different variable effect on hazard ratio of distant metastasis, local recurrence, and death due to rectal cancer (extended multistate Cox stratified hazard)**

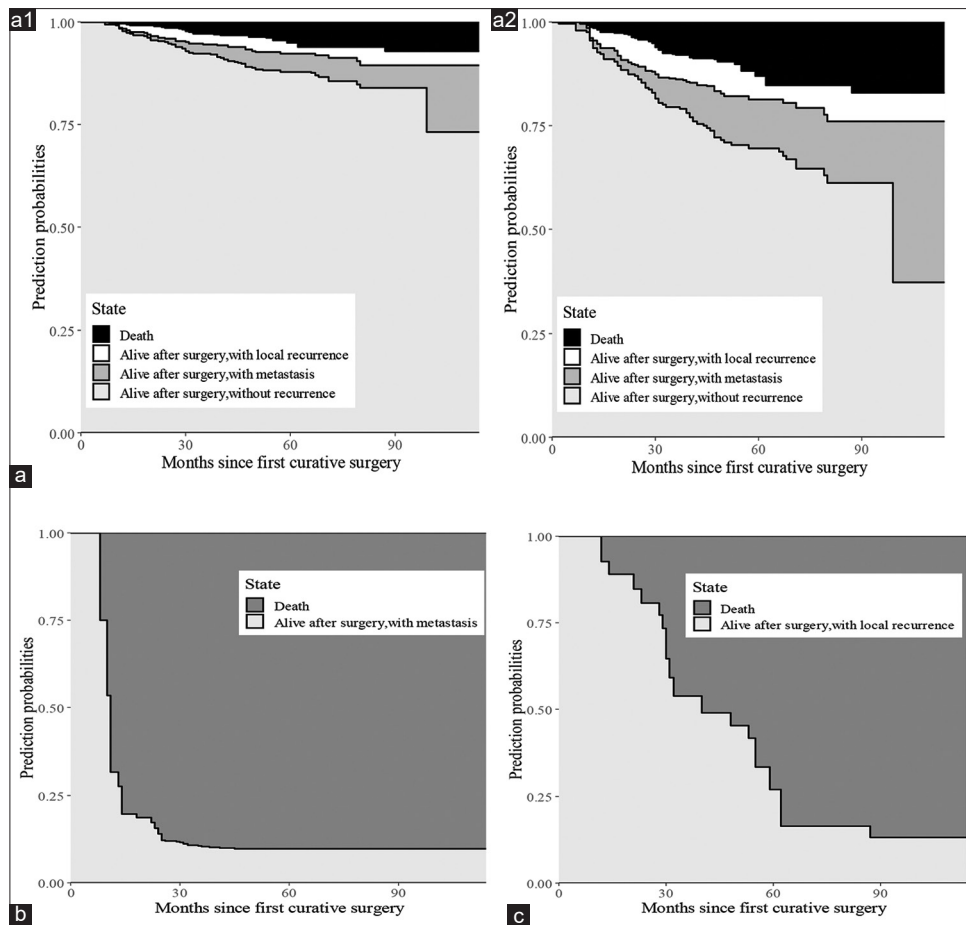
Variables	HR (P)			
	Surgery → DM	Surgery → LR	DM → death	LR → death
Age at diagnosis	1.03 (0.018)*	0.98 (0.116)	0.98 (0.253)	1.02 (0.345)
Sex				
Male	-	-	-	-
Female	0.93 (0.829)	0.78 (0.525)	0.95 (0.920)	2.18 (0.131)
TNM stage				
0/I	-	-	-	-
II/III	3.06 (0.001)*	2.53 (0.018)*	2.04 (0.213)	3.70 (0.103)
Surgical resection technique				
Trans-anal	-	-	-	-
Transabdominal	0.92 (0.840)		1.12 (0.845)	
Abdominoperineal	2.01 (0.078)		1.12 (0.838)	
Distal or circumferential margin involvement				
Noninvolved	-	-	-	-
Involved	3.58 (0.010)*	2.48 (0.113)	1.02 (0.974)	0.36 (0.214)
Surgical complication related to survival				
None	-	-	-	-
Experienced			1.34 (0.582)	2.40 (0.330)
Time of LR				0.99 (0.649)
Time of DM			1.13 (0.006)*	

\*Significant at  $\alpha=0.05$ . LR=Local recurrence; DM=Distant metastasis; HR=Hazard ratio; TNM=Tumor, node, and metastasis

from the initial (curative surgery) to intermediate states. However, the probability of death after recurrence in the reference patient is high [Figure 2b and c]. The difference between the two adjacent lines represents the probability of transition and remaining in that state. Figure 2a-a2 shows how different the stage of the disease was for the patient, considering that the patient stage was II/III in the first and second transitions.

## DISCUSSION

The classical survival models focus on the final event/s of a study and do not provide the details of the several intermediate states between enrollment and final outcome. This study was performed to determine the risk of LR and metastasis as the intermediate states as well as death from rectal cancer and its related factors.



**Figure 2:** Filled transition probability curves, (a) Filled transition probabilities. Transition probabilities starting from curative surgery – State 1, (a1) Reference patient (low risk), (a2) High-risk patient (Stage II/III in the first and second transitions). (b) Transition probabilities starting from distant metastasis – State 2. (c) Transition probabilities starting from local recurrence – State 3

In this longitudinal study on 280 LARC patients, a progressive illness–death multistate model with four states of surgery, local recurrence, distant metastasis, and death was used. Based on Cox model as a classic survival model, only the cancer TNM stage was found to be determinant for mortality. Our results were in line with a previous study by Omidvari *et al.*,<sup>[4]</sup> which examined 153 patients with middle/lower rectal cancer. However, after examining the univariate variables in different paths, the four-state model was fitted to the data with the candidate variables to enter the multiple model. In the surgery to metastasis transition, age, disease stage, and involvement of resection margins were the effective variables. In the surgery to LR, the disease stage was the only variable affecting patient transfer. In a previous study by Hajebi Khaniki *et al.* on colorectal cancer patients using a non-Markovian multistate model, in the disease to LR path, the disease TNM stage was the only variable affecting the transition, whereas, in the disease to death due to metastasis path, age and disease stage were identified as variables affecting this transition.<sup>[21]</sup>

The state-arrival extended Markov multistate model showed that the time of metastasis is significantly effective

in a patient’s transition to death from the metastasis state. Late recurrence was associated with worse survival in our study, whereas, in Guraya study, early or late recurrence did not affect patient survival rate.<sup>[7]</sup> This inconsistency was probably due to the late detection of metastasis in their patients. The patients may have actually received delayed salvage treatments due to late visits.

Multistate analysis with/without time dependence showed that considering the BIC, the time-dependent model had a better fit to our data. In Putter *et al.*’s study, adding time into platelet recovery transition to relapse/death state reduced the variance of the cumulative risk estimate.<sup>[10]</sup>

The mstate package provides transition probability estimation for a specified patient. A better insight into the patient’s condition based on different parameters is the advantage of this feature.<sup>[22]</sup> In our study, the transition probability of recurrence states (local or systemic) was very low, because the disease stage of the reference patient was 0/I. Furthermore, other variables of this specified patient were selected at low risk, so it seems rational that the transition probability to LR and DM was very low.

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However, as stated in previous studies, LR and DM were the most important events in rectal cancer patient mortality,<sup>[23-25]</sup> and according to our results, even when a low-risk patient experiences these events, the transition probability to death is very high.

Lack of sufficient observation in each transition is usually a main limitation of multistate models, resulting in problems such as sparse data. It leads to high standard deviations for HRs or probability estimates. In our study, the effect of resection margin involvement on surgery to LR transition was not significant due to the low sample size. Hence, the levels of 0 and I as well as II and III stages of the disease were integrated as 0/I and II/III, respectively, under the supervision of a clinician. Furthermore, the tumor location variable was changed to two levels at lower and middle/upper rectum. Furthermore, the variable of surgical complications was modified into the binary with/without variable. Anastomotic failure, intestinal obstruction, and pelvic collection were defined as “with surgical complications.” Nevertheless, from the recurrence and death point of view, accurate and long-term patient follow-ups in our study were positive points.

## CONCLUSION

According to our findings, age and margin involvement in DM path and stage in LR and DM path had a significant effect; however, no effective variable was observed on the death of patients with any type of recurrence. The time of metastasis also had an effect on the path of death. Careful and continuous surveillance in the recurrence and metastasis path should be performed.

### Author contributions

FS – substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content; AND MR – final approval of the version to be published; AND AA and MR – agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Sciences Ethics Committee (<https://ethics.research.ac.ir/IR.IUMS.REC.1399.861>).

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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