Pathological Response Has Survival Benefits for Rectal Cancer following Neoadjuvant Therapy

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Research

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Abstract

Background: Studies reporting the results of associated factors of pathological completed response (PCR) and tumor regression response in patients with rectal cancer following neoadjuvant chemoradiation therapy (nCRT) are inconsistent. Objective: The purpose of this study was to identify the prognostic factors of tumor response and outcome in rectal cancer patients. Design: The study was a retrospective analysis. Settings: The study was conducted in a single large institution in Taiwan. Patients: Newly diagnosed rectal cancer patients who underwent nCRT followed by surgery from 2010 to 2014 with 5 years of follow-up. Main Outcome Measures: The primary outcomes were associated factors of pathological completed response and downstaging. The risk factors of survival outcome and disease recurrence were also observed. Results: A total of 169 rectal cancer patients were included. The PCR rate was 17.8%, and the downstaging rate was 60.9%. Patients with a histology type of adenocarcinoma associated with PCR, and patients positive for clinical N stage were associated with downstaging. Kaplan-Meier analysis showed the PCR group performed better to a statistically significant level both in overall survival and disease recurrence free survival than the no PCR group ($p= 0.033$ & 0.025, respectively). Patients with a downstaging response also showed better overall survival benefits and disease recurrence free survival benefits than their counterparts (both $p<0.001$). After controlling confounding variables, the risk factors of overall survival were downstaging [Hazard Ratio (HR): 0.40, 95% CI: 0.21-0.74], male, abnormal post-nCRT CEA level and abnormal Hb level. In addition, the protective factors of recurrence were downstaging and having received adjuvant chemotherapy. Limitations: Modest sample size and limited genetic bio-markers information. Conclusions: Among rectal cancer patients who received the neoadjuvant therapy, histology type and clinical N stage were associated with PCR and downstaging, respectively. Downstaging was an important protective factor for better overall survival and recurrence free survival.

Background

According to the National Comprehensive Cancer Network (NCCN) guidelines, the current standardized management among locally advanced rectal cancer patients is neoadjuvant chemoradiation therapy (nCRT) followed by total mesorectal excision (TME) and adjuvant chemotherapy [1]. Various studies found the association factors of better survival include tumor response regression, tumor stage, lymph-vascular invasion, cancer biomarkers, type of operation, chemotherapy regimen, radiation therapy dosage, and follow-up adherence [2–6].

The evidence shows presented approximately 10–38% of rectal cancer patients achieved a pathological completed response (PCR) after receiving neoadjuvant chemoradiation therapy [7]. Moreover, patients who achieved PCR obtained the benefits of overall survival and disease-free survival [7]. However, some studies argued PCR did not improve the survival outcomes due to the invasive treatment of resection and staging [8]. Despite the inconsistent outcomes of PCR after nCRT, it is beneficial in clinical practice to identify the predictive factors of PCR and optimize the following treatments for rectal cancer patients.

Recent research has aimed to discover the predictive factors of PCR and how to achieve a better PCR rate in rectal cancer patients [9]. In past studies, the biological and genetic characteristic predictive factors of PCR included carcinoembryonic antigen (CEA) levels, hemoglobin (Hb) levels, neutrophil-lymphocyte ratio (NLR), and obesity [10–14]. In addition, the clinical predictive factors of PCR included the tumor size, nodal status, tumor histology, treatment type of chemotherapy and radiation therapy, as well as the interval from the completion of nCRT to surgery [6, 15–17].

There are discrepancies in the predictors for PCR from the previous research and disparities of the risk factors as well as survival outcome among rectal cancer patients who underwent nCRT and TME. Therefore, this comprehensive research was conducted to identify the factors influencing PCR and downstaging after receiving nCRT and to explore the risk factors of survival and recurrence among rectal patients from a single institution's experience.

Method

We retrospectively reviewed the medical records of patients with newly diagnosed rectal cancer who underwent neoadjuvant chemo-radiation therapy followed by surgery at Taipei Medical University Hospital in Taiwan from January 2010 to July 2014. Patients were followed up until July 2019 with five years follow- up duration. Patients who received the short course of neoadjuvant radiation therapy were excluded from the study. The degree of tumor response following neoadjuvant CRT was observed, including pathological completed response (PCR) with no viable cancer cells and downstaging. Downstaging was defined as any occurrence of decreasing pathological stage status from the initial stage status. Additionally, the College of American Pathologists (CAP) tumor regression grade [18] was abstracted from the medical record as follows: grade 0 (complete response), no viable cancer cells; grade 1 (moderate response), single or small groups of cancer cells; grade 2 (minimal response), residual cancer outgrown by fibrosis; and grade 3 (poor response), minimal or no tumor kill, extensive residual cancer. The follow-up status and duration of disease recurrence and survival status after the primary operation date were recorded.

The patient characteristics included age at diagnosis, sex, body mass index (BMI), initial clinical stage, clinical primary tumor (T) stage, clinical regional lymph node (N) stage, tumor histology type from the colonoscopy report prior to the surgery, histology differentiation grade after the surgery, American Society of Anesthesiologists (ASA) physical Statius Classification [18], lymph vascular invasion, number of lymph nodes involved, tumor size, circumferential resection margin (CRM), pre-nCRT hemoglobin (Hb) level, and pre-nCRT CEA level. The post-nCRT CEA concentration level was recorded following the nCRT and prior to surgery. The surgery type was categorized in to three types as open laparotomy, robotic surgery using the Da Vinci surgical system, and laparoscopy surgery. The neoadjuvant chemotherapy regimen was classified as the regimen containing (1) Oxaliplatin or Capecitabine, (2) fluorouracil (5FU) and leucovorin, (3) 5FU alone. If the patient received adjuvant chemotherapy, it was logged into a binary variable. We further classified the BMI value into a non-obese group and obese group at a cutoff point of

30 kg/m^2; also, we divided the Hb value into normal and abnormal at a cutoff point of 12 g/dL. The CEA concentration level was analyzed for normal and abnormal levels at a cut-off point of 5 ng/mL.

All variables were analyzed by t-test or chi-square test. Univariate and multivariate logistic regression models were used to evaluate the associated factors of tumor regression response and survival outcomes. Kaplan-Meier analysis was performed for the survival and disease recurrence outcome between the tumor response group and non-response group. The Cox proportional hazard model was used to analyze the risk factors of overall survival and recurrence free survival. Statistical analysis was performed using SAS 9.4.

The study was reviewed and approved by Taipei Medical University Institutional Review Board [Project number: N201904057].

Results

A total of 169 newly diagnosed rectal cancer patients who underwent neoadjuvant chemo-radiation therapy and surgery were included in the study. Overall, 30 (17.8%) patients achieved PCR and 103 (60.9%) patients displayed downstaging. In addition, the average age at diagnosis was 58.4±13.2 years old, and 67.2% (117/174) were male. The majority of patients in the analysis were diagnosed with clinical stage II (29%) and clinical stage III (71%) cancer. Among those patients, the rate of PCR and downstaging were 18% and 65%, respectively. Additionally, of the four patients showing no PCR but (y) p stage 0, the (y)pT stage was found carcinoma in situ (Tis).

As a result, there was a statistically significant difference between the PCR and no PCR group among the histology type of adenocarcinoma (p=0.034) and lymph-vascular invasion (p<0.001). However, there were no statistically significant difference in age at diagnosis, sex, BMI, tumor staging, distance from anal verge, surgery type, ASA classification, the type of neoadjuvant chemotherapy regimen, pre and post nCRT CEA status, and pre-nCRT Hb level between patients with PCR or no PCR (all p> 0.05) (table 1). Moreover, there was a significant difference between the downstaging group and non-response group in clinical stage, clinic N stage, CRM, and lymph-vascular invasion.

PCR and downstaging for survival and disease recurrence outcome

The mean duration of survival among the PCR group was 12 months longer than the no PCR group, which is statistically significant (p= 0.010); also, the mean time of disease recurrence following surgery was 17 months longer in the PCR group than the no PCR group (p= 0.001). According to the results of Kaplan-Meier analysis, the PCR group had better survival benefits, to a level of statistical significance, both in overall survival and disease recurrence free survival than the no PCR group with p values of 0.033 and 0.025, respectively (Figure 1A and 1B). Moreover, the group displaying downstaging also demonstrated significantly better overall survival benefits and disease recurrence free survival benefits than the group without a downstaging response (both *p* values were <0.001) (Figure 1C and 1D).

Further, between the mortality and survivor groups, there were significant differences in age, sex, clinical stage, pre-nCRT Hb level, pre-nCRT and post-nCRT CEA level, lymph vascular invasion, time to survival and disease recurrence, surgery type, ASA classification, CAP regression grade, received adjuvant chemotherapy (all $p< 0.05$) (Table 2). Distance from the anal verge was marginally but still significantly lower in the recurrence population (5.67 ± 2.77 cm) than the non-recurrence patients (4.68 ± 2.35 cm). Among the recurrence group, there were significantly more patients who received adjuvant chemotherapy than the non-recurrence group (62.16%).

Associated factors of tumor response

According to the results of multivariate logistic regression, the histology type of adenocarcinoma appeared to be the only predictive factor of PCR when controlling other clinical factors [adjusted Odds ratio (aOR): 5.385, 95% Confidence Interval (CI): 1.27-22.9, p-value=0.023, AUC: 0.55]. Moreover, after controlling other clinical factors, a positive clinical N stage was associated with the downstaging rate (aOR: 3.458, 95%CI: 1.77-6.73, p-value<0.001, AUC: 0.63). However, various clinical factors, including age, sex, BMI, regimen of chemotherapy or radiation therapy, CEA concentration levels and Hb level, as well as tumor size, had no statistically significant association with PCR or downstaging (Table 3).

Further, patients with PCR were 2.9 times more likely to survive (OR: 2.91, 95% CI: 0.96-8.86) than the residual group. Patients with downstaging were 3.2 times more likely to survive (OR: 3.26, 95% CI: 1.62-6.54) and less likely to have disease recurrence (OR: 2.79, 95% CI: 1.29-5.92] than the non-response group (Table 3).

Risk factors and protective factors of outcomes

After controlling the confounding variables, downstaging was revealed to be the important protective factor for survival [adjusted hazard ratio (aHR): 0.40, 95% CI: 0.21-0.71] in female patients (aHR: 0.42, 95%CI: 0.12-0.88). In addition, the multivariate Cox proportional analysis selected variables of the abnormal post CEA level (aHR:1.91, 95%CI:1.05-3.48) , and abnormal pre-nCRT Hb level (aHR: 2.54, 95% CI: 1.41-4.58) as risk factors of survival among rectal cancer patients (Table 4). Similarly, downstaging also appeared to be the important protective factor of disease recurrence after controlling all the confounding variables (aHR: 0.42, 95% CI: 0.21-0.82). In addition, patients who received adjuvant chemotherapy were 65% less likely to relapse (aHR: 0.35, 95% CI: 0.18-0.69) (Table 5).

Discussion

This single institution, retrospective, cohort study proved the promising survival benefits of rectal cancer patient who had PCR treated with neoadjuvant therapy and surgery. Despite PCR not being proven to be a significant predictor of better survival rate or recurrence-free survival rate by univariate logistic regression, PCR was still proven to be a significant predictor of a longer survival length and remaining recurrence-free. Moreover, patients showing pathological downstaging had a significantly better survival rate and recurrence-free survival rate in the survival analysis. Our results are consistent with previous findings [6,

15]. Therefore, the implication is patients with either a pathological completed response or downstaging exhibit the benefits of better survival and recurrence free outcome.

We found rectal cancer patients with a histology type of adenocarcinoma tumor had a significant association with achieving PCR. However, the AUC value from the analysis showed a weak predictive power of PCR. This relevant study [17] suggested adenocarcinoma in rectal cancer was more resistant to both chemotherapy and radiotherapy than non- adenocarcinoma. Further, previous studies advised mucinous adenocarcinoma has a higher mortality risk and warrants more aggressive treatment regimens [19, 20]. Hence, awareness of the rectal cancer histology type before administering an effective treatment regimen might improve the PCR rate and survival outcome in clinical practice.

Various studies have shown clinical factors such as type of nodal positive, neoadjuvant chemotherapy, obesity, CEA concentration level, Hb level are associated with an improved PCR rate in rectal cancer patients who received neoadjuvant CRT [7, 9–12, 14, 17, 21]. However, none of the predictive factors in our study demonstrated an improved PCR rate. In addition to PCR, the positive clinical N stage was the only predictive factor of downstaging. The finding could be explained by patients with clinical stage III being the highest proportion in this cohort. Thus, the response of patients with early stage to nCRT was marginal, which was not enough to achieve minimal downstaging. Second, the false positive imaging diagnosis of the node metastatic could also influence the clinical staging. We also examined both pre and post nCRT CEA levels using the cut-off point of 5 ng/ml. The results showed no difference between normal and abnormal CEA levels in predicting PCR and downstaging.

We further explored other risk factors of survival outcome and disease recurrence. Our multivariate logistic regression demonstrated a best fit prediction model of survival including tumor downstaging, sex, pre-nCRT Hb level, and post-nCRT CEA level. The outcome of our experience was consistent with previous studies [3, 4, 22]. However, contrary to our survival outcome predictor of tumor downstaging, a study in Singapore did not show a survival benefit from tumor downstaging [8]. In addition, regardless of whether PCR was achieved, patients who received adjuvant chemotherapy were more likely to have better survival outcome and less likely to relapse following surgery (Table 5). The past evidence also suggested patients who achieved PCR after neoadjuvant chemoradiation therapy followed by surgery [and adjuvant chemotherapy?] increased the likelihood of survival and recurrence free survival [5, 23].

Controversially, many studies have suggested different types of surgery among rectal cancer resulted in different short-term and long-term survival outcomes [24–26]. The univariate analysis suggested patients who received the traditional open laparotomy had no significantly higher mortality risk than patients who underwent laparoscopy or robotic surgery. The univariate Cox proportional hazard model found significantly less overall survival risk for patients who received a laparoscopy (HR:0.30, 95%CI:0.11–0.79) or robotic surgery (HR:0.28, 95%CI:0.10–0.75) than an open laparotomy. In clinical practice, patients with higher severity or metastatic tumor were more likely to receive an open laparotomy than laparoscopy or robotic surgery. Therefore, the surgical approach should consider the high-risk patients in the practice.

We found an abnormal post-nCRT CEA level was also a risk factor in survival (aOR: 1.91, 95%CI: 1.05–3.48) according to the multivariate logistic regression. Similarly, the evidence [11] proved a low post-nCRT CEA level was a strong predictor of PCR, which also pointed to a better survival outcome. In addition to predicting survival and PCR, regular follow-up surveillance of the CEA level among rectal cancer patients is recommended by the guidelines [27]. The study also points to the importance of proactive follow-up surveillance of CEA level monitoring, which benefits rectal cancer survivorship.

Limitations

Although this study had a larger sample size to evaluate the associated factors of PCR and outcome than past single institution studies, the current sample size is still inadequate to perform further analysis. In addition, some clinical data such as genetic biomarkers could not be obtained due to the retrospective study design and the data not being in the routine clinical practice at that time. Therefore, future study is recommended to obtain more recently diagnosed patients for increasing the sample size and obtaining more comprehensive parameters for identifying the potential associated factors.

Conclusion

In conclusion, our findings suggest histology and clinical N stage are associated with PCR and downstaging among rectal cancer patients after nCRT followed by surgery. Patients with tumor response, PCR and downstaging, had a better overall survival and recurrence free survival outcome. Downstaging is an important protective factor of both overall survival and recurrence free survival. Received adjuvant chemotherapy could reduce mortality and disease recurrence. The risk factors were lymph-vascular invasion and abnormal biomarkers. Future research is needed to recognize the potential predictors of tumor regression and survival outcome as well as provide awareness and insights into precision management in clinical practice.

Declarations

Ethics approval and consent to participate:

The study was reviewed and approved by Taipei Medical University Institutional Review Board [Project number: N201904057].

Consent for publication:

All authors have read and approved this manuscript and agree to publish this article.

Availability of data and materials:

The dataset for this study is not publicly available but can be made available upon reasonable request.

Competing interests:

The authors do not have any conflicts of interest to disclose.

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Authors' contributions

WCC and LJK drafted the manuscript and provided the original pictures. CCC, PLW, YMH, YJH, YST and RJC reviewed the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Demographic and clinical characteristics among rectal cancer patients underwent neoadjuvant chemoradiotherapy (nCRT) by pathological complete response and downstaging. (n=174)

	Pathological Complete Response			Downstaging		
	No (n= 144)	Yes (n= 30)	*p value*	No (n= 69)	Yes (n= 105)	*p value*
Age (y)	58.77 ± 13.02	56.6 ± 14.18	0.415	58.17 ± 13.27	58.54 ± 13.24	0.858
Sex			0.893			0.139
Male	99 (68.75)	21 (70)		52 (75.36)	68 (64.76)	
Female	45 (31.25)	9 (30)		17 (24.64)	37 (35.24)	
Body Mass Index (kg/m2)	24.09 ± 3.99	23 ± 3.91	0.175	24.34 ± 4.24	23.61 ± 3.81	0.244
Clinical Stage			0.395			<0.001*
I	8 (5.56)	2 (6.67)		7 (10.14)	3 (2.86)	
II	37 (25.69)	7 (23.33)		26 (37.68)	18 (17.14)	
III	87 (60.42)	21 (70)		27 (39.13)	81 (77.14)	
IV	12 (8.33)	0 (0)		9 (13.04)	3 (2.86)	
Clinical T Stage			0.183			0.289
I- II	16 (11.11)	6 (20)		11 (15.94)	11 (10.48)	
III- IV	128 (88.89)	24 (80)		58 (84.06)	94 (89.52)	
Clinical N Stage			0.823			<0.001*
N (+)	99 (68.75)	20 (66.67)		36 (52.17)	83 (79.05)	
N (-)	45 (31.25)	10 (33.33)		33 (47.83)	22 (20.95)	
Distance from anal verge (cm)	5.42 ± 2.69	5.67 ± 2.77	0.651	5.26 ± 2.44	5.6 ± 2.86	0.426
CRM (cm)[£]	0.83 ± 0.73	n/a	n/a	0.63 ± 0.54	0.98 ± 0.81	0.023*
Lymph-Vascular invasion			0.002*			<0.001*
Positive	36 (25)	0 (0)		26 (37.68)	10 (9.52)	
Negative	108 (75)	30 (100)		43 (62.32)	95 (90.48)	
Adenocarcinoma			0.012*			0.108
Yes	140 (97.22)	26 (86.67)		68 (98.55)	98 (93.33)	
No	4 (2.78)	4 (13.33)		1 (1.45)	7 (6.67)	
Differentiation			n/a			0.542
Well differentiated	99 (68.75)	n/a		47 (68.12)	52 (69.33)	
Moderately differentiated	41 (28.47)	n/a		19 (27.54)	22 (29.33)	
Poorly differentiated	4 (2.78)	n/a		3 (4.35)	1 (1.33)	
Pathological Stage			<0.001*			<0.001*
0	4 (2.78)	30 (100)		0 (0)	34 (32.38)	
I	48 (33.33)	0 (0)		5 (7.25)	43 (40.95)	
II	46 (31.94)	0 (0)		20 (28.99)	26 (24.76)	
III	36 (25)	0 (0)		34 (49.28)	2 (1.9)	
IV	10 (6.94)	0 (0)		10 (14.49)	0 (0)	
ASA Classification[¶]			0.191			0.813

1	7 (4.86)	3 (10)		3 (4.35)	7 (6.67)	
2	118 (81.94)	26 (86.67)		58 (84.06)	86 (81.9)	
3	19 (13.19)	1 (3.33)		8 (11.59)	12 (11.43)	
Pre-nCRT Hb (g/dL)	12.33 ± 1.53	12.83 ± 1.45	0.100	12.25 ± 1.68	12.52 ± 1.42	0.256
Pre-nCRT CEA (ng/mL)	12.8 ± 32.8	18.2 ± 63.41	0.498	13.91 ± 36.27	13.61 ± 41.8	0.961
Post-nCRT CEA (ng/mL)	4.96 ± 8.5	5.24 ± 10.7	0.874	5.54 ± 10.52	4.66 ± 7.65	0.525
Neoadjuvant radiation therapy			0.300			0.345
Long course	139 (96.53)	30 (100)		66 (95.65)	103 (98.1)	
Short course	5 (3.47)	0 (0)		3 (4.35)	2 (1.9)	
Neoadjuvant Chemotherapy			0.130			0.045
Oxalip or Cape	20 (13.89)	3 (10)		9 (13.04)	14 (13.33)	
5FU+LV	101 (70.14)	26 (86.67)		45 (65.22)	82 (78.1)	
5FU alone	23 (15.97)	1 (3.33)		15 (21.74)	9 (8.57)	
Surgery type			0.933			0.552
Laparoscopy	65 (45.14)	14 (46.67)		28 (40.58)	51 (48.57)	
Robotic	72 (50)	15 (50)		38 (55.07)	49 (46.67)	
Open laparotomy	7 (4.86)	1 (3.33)		3 (4.35)	5 (4.76)	
Adjuvant Chemotherapy			0.427			0.901
Yes	115 (79.86)	22 (73.33)		54 (78.26)	83 (79.05)	
No	29 (20.14)	8 (26.67)		15 (21.74)	22 (20.95)	
Length of hospital stay (Day)	14.72 ± 8.29	14.41 ± 7.52	0.856	15.49 ± 10	14.11 ± 6.61	0.284
CAP Regression grade			<0.001*			<0.001*
Complete response	0 (0)	30 (100)		0 (0)	30 (28.57)	
Moderate response	54 (37.5)	0 (0)		21 (30.43)	33 (31.43)	
Minimal response	65 (45.14)	0 (0)		33 (47.83)	32 (30.48)	
Poor response	25 (17.36)	0 (0)		15 (21.74)	10 (9.52)	
Recurrence			0.097			0.006*
Yes	34 (23.61)	3 (10)		22 (31.88)	15 (14.29)	
No	110 (76.39)	27 (90)		47 (68.12)	90 (85.71)	
Time to recurrence (Month)	47.66 ± 26.06	64.61 ± 21.04	0.001*	42.25 ± 26.1	56.06 ± 24.58	0.001*
Survival Status			0.055			0.001*
Alive	100 (69.44)	26 (86.67)		40 (57.97)	86 (81.9)	
Death	44 (30.56)	4 (13.33)		29 (42.03)	19 (18.1)	
Time to survival (Month)	53.86 ± 23.94	65.9 ± 20.18	0.011*	49.86 ± 25.69	59.93 ± 21.54	0.006*

£CRM: Circumferential resection margin; ¶ASA: American Society of Anesthesiologists physical status

Values are presented as mean ± standard deviation or number (%) by t-test or chi-square test.

Table 2. Clinical characteristics among rectal cancer patients underwent neoadjuvant chemoradiotherapy (nCRT) by survival status and disease recurrence. (n=174)

	Survival Status			Recurrence		
	Alive (n= 126)	Death (n= 48)	*p value*	No (n= 137)	Yes (n= 37)	*p value*
Age (y)	62.98 ± 13.11	56.65 ± 12.88	0.004*	57.7 ± 13.23	60.97 ± 13.01	0.182
Sex			0.031*			0.543
Male	81 (64.29)	39 (81.25)		96 (70.07)	24 (64.86)	
Female	45 (35.71)	9 (18.75)		41 (29.93)	13 (35.14)	
Bode Mass Index (kg/m2)	23.89 ± 4.11	23.91 ± 3.96	0.977	23.92 ± 3.97	23.84 ± 4.12	0.919
Clinical Stage			<0.001*			0.330
I	6 (4.76)	4 (8.33)		6 (4.38)	4 (10.81)	
II	33 (26.19)	11 (22.92)		33 (24.09)	11 (29.73)	
III	85 (67.46)	23 (47.92)		89 (64.96)	19 (51.35)	
IV	2 (1.59)	10 (20.83)		9 (6.57)	3 (8.11)	
Clinical T Stage			0.972			0.196
I- II	16 (12.7)	6 (12.5)		15 (10.95)	7 (18.92)	
III- IV	110 (87.3)	42 (87.5)		122 (89.05)	30 (81.08)	
Clinical N Stage			0.950			0.188
N(+)	86 (68.25)	33 (68.75)		97 (70.8)	22 (59.46)	
N(-)	40 (31.75)	15 (31.25)		40 (29.2)	15 (40.54)	
Distance from anal verge (cm)	5.13 ± 2.61	5.59 ± 2.73	0.310	5.68 ± 2.75	4.68 ± 2.38	0.046*
CRM (cm)[£]	0.84 ± 1	0.83 ± 0.62	0.968	0.86 ± 0.65	0.76 ± 0.95	0.605
Lymph-Vascular invasion			0.001*			0.126
Positive	18 (14.29)	18 (37.5)		112 (81.75)	26 (70.27)	
Negative	108 (85.71)	30 (62.5)		25 (18.25)	11 (29.73)	
Adenocarcinoma			0.328			0.132
Yes	119 (94.44)	47 (97.92)		129 (94.16)	37 (100)	
No	7 (5.56)	1 (2.08)		8 (5.84)	0 (0)	
Differentiation			0.790			0.477
Well differentiated	67 (67)	32 (72.73)		76 (69.09)	23 (67.65)	
Moderately differentiated	30 (30)	11 (25)		30 (27.27)	11 (32.35)	
Poorly differentiated	3 (3)	1 (2.27)		4 (3.64)	0 (0)	
Pathological Stage			<0.001*			0.146
0	30 (23.81)	4 (8.33)		31 (22.63)	3 (8.11)	
I	39 (30.95)	9 (18.75)		40 (29.2)	8 (21.62)	
II	31 (24.6)	15 (31.25)		32 (23.36)	14 (37.84)	
III	25 (19.84)	11 (22.92)		27 (19.71)	9 (24.32)	
IV	1 (0.79)	9 (18.75)		7 (5.11)	3 (8.11)	
ASA Classification[¶]			0.003*			0.482

1	10 (7.94)	0 (0)		6.57 (111)	2.7 (33)	
2	107 (84.92)	37 (77.08)		81.02 (17)	89.19 (3)	
3	9 (7.14)	11 (22.92)		12.41 (0)	8.11 (0)	
Pre-nCRT Hb (g/dL)	11.72 ± 1.65	12.67 ± 1.4	<0.001*	12.38 ± 1.53	12.52 ± 1.53	0.625
Pre-nCRT CEA (ng/mL)	24.98 ± 64.7	9.44 ± 22.98	0.020*	14.04 ± 43.34	12.58 ± 20.83	0.843
Post-nCRT CEA (ng/mL)	8.45 ± 15.33	3.68 ± 3.74	0.001*	5.22 ± 9.93	4.21 ± 2.47	0.538
Neoadjuvant radiation therapy			0.700			0.944
Long course	122 (96.83)	47 (97.92)		133 (97.08)	36 (97.3)	
Short course	4 (3.17)	1 (2.08)		4 (2.92)	1 (2.7)	
Neoadjuvant Chemotherapy			0.038*			0.838
Oxalip or Cape	12 (9.52)	11 (22.92)		18 (13.14)	5 (13.51)	
5FU+LV	98 (77.78)	29 (60.42)		99 (72.26)	28 (75.68)	
5FU alone	16 (12.7)	8 (16.67)		20 (14.6)	4 (10.81)	
Surgery type			0.022*			0.650
Laparoscopy	54 (42.86)	25 (52.08)		60 (43.8)	19 (51.35)	
Robotic	69 (54.76)	18 (37.5)		71 (51.82)	16 (43.24)	
Open laparotomy	3 (2.38)	5 (10.42)		6 (4.38)	2 (5.41)	
Adjuvant Chemotherapy			0.047*			0.011*
Yes	104 (82.54)	33 (68.75)		114 (83.21)	23 (62.16)	
No	22 (17.46)	15 (31.25)		23 (16.79)	14 (37.84)	
Length of hospital stay (Day)	16.48 ± 10.4	14.02 ± 7.11	0.085*			
CAP Regression grade			0.007*			0.249
Complete response	26 (20.63)	4 (8.33)		27 (19.71)	3 (8.11)	
Moderate response	43 (34.13)	11 (22.92)		44 (32.12)	10 (27.03)	
Minimal response	45 (35.71)	20 (41.67)		48 (35.04)	17 (45.95)	
Poor response	12 (9.52)	13 (27.08)		18 (13.14)	7 (18.92)	
Recurrence			0.005*			
Yes	20 (15.87)	17 (35.42)				
No	106 (84.13)	31 (64.58)				
Time to recurrence (Month)	29.51 ± 22.88	58.61 ± 22.46	<0.001*	57.42 ± 23.56	25.28 ± 17.88	<0.001*
Survival Status						0.007*
Alive				106 (77.37)	20 (54.05)	
Death				31 (22.63)	17 (45.95)	
Time to survival (Month)	34.58 ± 23.47	64.07 ± 18.16	<0.001*	56.85 ± 23.57	52.57 ± 24.31	0.332

£CRM: Circumferential resection margin; ¶ASA: American Society of Anesthesiologists physical status

Values are presented as mean ± standard deviation or number (%) by t-test or chi-square test.

Table 3. Logistic regression for the pathologic complete response and downstaging after received neoadjuvant chemoradiotherapy among rectal cancer patients.

	Pathologic Complete Response			Downstaging		
	Odds Ratio	95% CI	*p value*	Odds Ratio	95% CI	*p value*
Age (y)	0.99	(0.96 - 1.02)	0.413	1.00	(0.98 - 1.03)	0.857
Sex						
Female vs. Male	0.94	(0.40 - 2.22)	0.893	1.66	(0.85 - 3.28)	0.141
BMI (kg/m2)						
Non-Obese vs. Obese	2.40	(0.30 - 19.31)	0.411	1.57	(0.49 - 5.09)	0.451
Clinical T Stage						
I-II vs. III-IV	2.00	(0.71 - 5.63)	0.189	0.62	(0.25 - 1.51)	0.292
Clinical N Stage						
(+) vs. (-)	0.91	(0.39 - 2.10)	0.823	3.46	(1.78 - 6.73)	<0.001*
Adenocarcinoma						
No vs. Yes	5.39	(1.27 - 22.90)	0.023*	4.85	(0.58 - 40.32)	0.144
ASA Classification						
1 vs. 3	8.14	(0.72 - 91.89)	0.111	1.56	(0.31 - 7.87)	0.541
2 vs. 3	4.19	(0.54 - 32.69)	0.559	0.99	(0.38 - 2.57)	0.603
Pre-nCRT Hb (g/dL)						
Normal vs. Abnormal	1.62	(0.69 - 3.78)	0.265	1.36	(0.730 - 2.52)	0.336
Pre-nCRT CEA (ng/mL)						
Normal vs. Abnormal	0.97	(0.42 - 2.23)	0.942	1.45	(0.75 - 2.78)	0.267
Post-nCRT CEA (ng/mL)						
Normal vs. Abnormal	1.10	(0.43 - 2.77)	0.847	1.65	(0.82 - 3.31)	0.158
Neoadjuvant Chemotherapy						
Oxalip or Cape vs. 5FU alone	3.45	(0.33 - 35.85)	0.667	2.59	(0.80 - 8.41)	0.413
5FU+LV vs. 5FU alone	5.92	(0.76 - 45.90)	0.069	3.04	(1.23 - 7.49)	0.072
Recurrence						
No vs. Yes	2.78	(0.79 - 9.74)	0.110	2.81	(1.33 - 5.92)	0.007*
Time to recurrence (Month)	1.03	(1.01 - 1.05)	0.002*	1.02	(1.01 - 1.04)	0.001*
Survival Status						
Alive vs. Death	2.86	(0.94 - 8.68)	0.064	3.28	(1.65 - 6.54)	0.001*
Time to survival (Month)	1.02	(1.01 -	0.013*	1.02	(1.01 -	0.007*

	1.04)	1.03)

CI: Confidence Interval

Table 4. Cox proportional hazard model of overall survival among rectal cancer patients.

	Adjusted Hazard Ratio	95% Confidence Interval	*p value*
Downstaging	0.40	(0.20 - 0.74)	<0.001*
Yes vs. No			
Surgery type			0.025*
Laparoscopy vs. Open laparotomy	0.24	(0.09 - 0.67)	
Robotic vs. Open laparotomy	0.25	(0.09 - 0.67)	
Lymph-Vascular invasion			0.034*
Positive vs. Negative	2.00	(1.05 - 3.94)	
Pre-CRT Hb (g/dL)			0.045*
Abnormal vs. Normal	2.10	(1.20 - 3.77)	

Table 5. Cox proportional hazard model of recurrence free survival among rectal cancer patients.

	Adjusted Hazard Ratio	95% Confidence Interval	*p value*
Downstaging			0.001*
Yes vs. No	0.40	(0.20 - 0.74)	
Received Adjuvant Chemotherapy			0.004*
Yes vs. No	0.35	(0.18 - 0.68)	

Figures

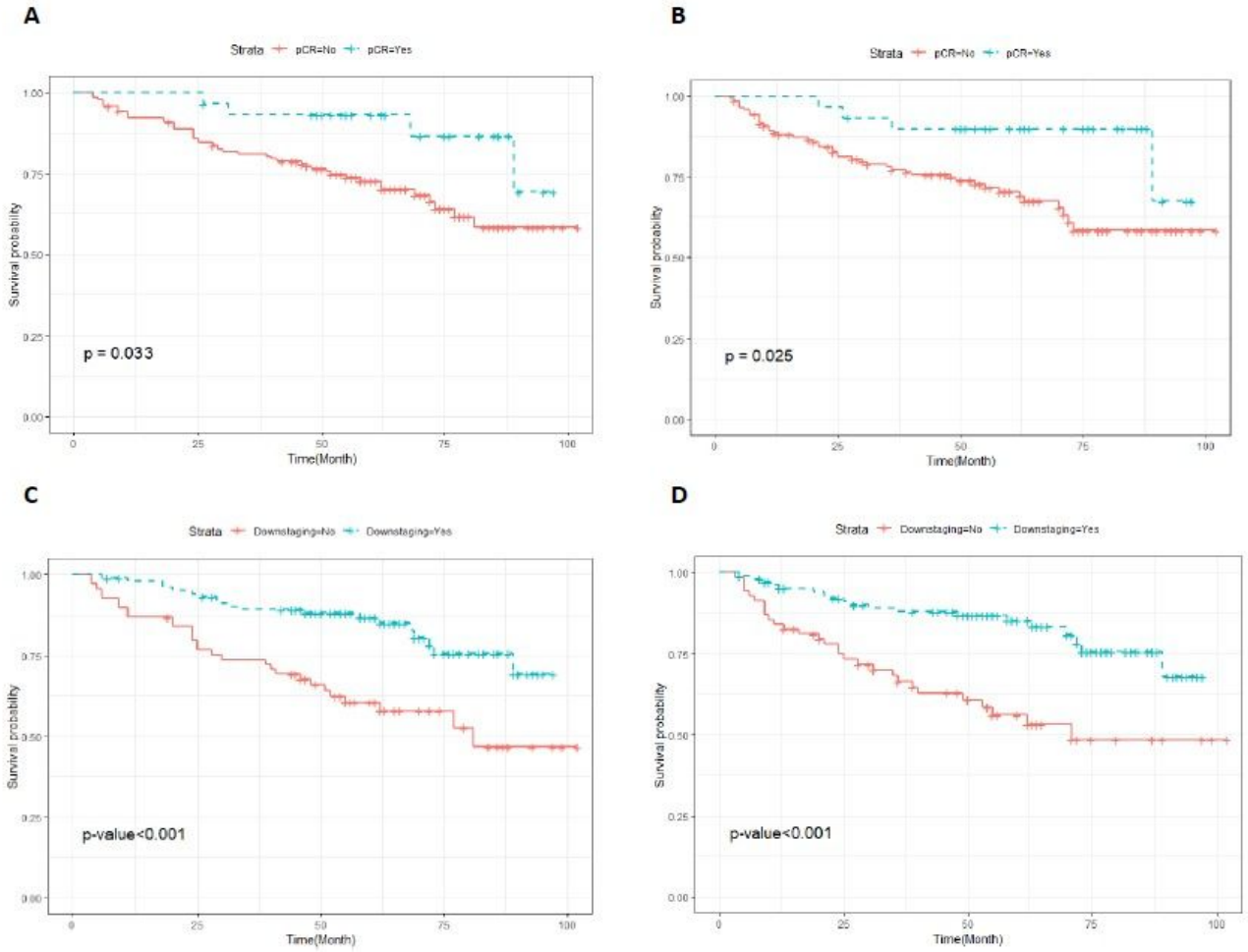

Figure 1

Kaplan-Meier analysis for A) overall survival by pathological completed response (PCR), B) recurrence free survival by pathological completed response (PCR), C) overall survival by downstaging, D) recurrence free survival by downstaging.