Pathological Response Has Survival Benefits for Rectal Cancer following Neoadjuvant Therapy

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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. The purpose of this study was to identify the prognostic factors of tumor response and outcome in rectal cancer patients. **Methods** The study was a retrospective analysis. Patients with locally advanced rectal cancer underwent nCRT followed by surgery from 2010 to 2014 with 5 years of follow-up. 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 counter-parts (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 adjuvant chemotherapy. **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, lymphovascular 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.

Methods

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 Status 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/m²; 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.

Conclusions

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.

Abbreviations

aHR = adjusted hazard ratio aOR = adjusted odds ratio ASA = American Society of Anesthesiologists BMI = body mass index CEA = carcinoembryonic antigen CAP = College of American Pathologists Hb = hemoglobin NCCN = National Comprehensive Cancer Network nCRT = neoadjuvant chemoradiation therapy NLR = neutrophil-lymphocyte ratio PCR = pathological completed response TME = total mesorectal excision

Declarations

I Ethics approval and consent to participate: The study was reviewed and approved by Taipei Medical University Institutional Review Board [Project number: N201904057]

I Consent for publication: Yes

I Availability of data and material: Not applicable

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I Authors' contributions:

Chen WC: writing the article

Kuo LJ: conception and design

Chen CC: participate in patients' treatment

Wei PL: data collection

Huang YM: data collection

Huang YJ: data collection

Tong YS: participate in patients' treatment

Chen RJ: data interpretation and analysis

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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=169)

	Pathological Complete Response			Downstaging		
	No (n= 139)	Yes (n= 30)	<i>p</i> <i>value</i>	No (n= 66)	Yes (n= 103)	<i>p</i> <i>value</i>
Age (y)	58.77 ± 13.05	56.6 ± 14.18	0.417	58.21 ± 13.17	58.5 ± 13.36	0.893
Sex			1.000			0.173
Male	96 (69.06)	21 (70)		50 (75.76)	67 (65.05)	
Female	43 (30.94)	9 (30)		16 (24.24)	36 (34.95)	
Body Mass Index (kg/m2)	24.11 ± 4.01	23 ± 3.91	0.168	24.27 ± 4.29	23.69 ± 3.81	0.356
Clinical Stage			0.400			<.0001
I	8 (5.76)	2 (6.67)		7 (10.61)	3 (2.91)	
II	34 (24.46)	7 (23.33)		24 (36.36)	17 (16.5)	
III	85 (61.15)	21 (70)		26 (39.39)	80 (77.67)	
IV	12 (8.63)	0 (0)		9 (13.64)	3 (2.91)	
Clinical T Stage			0.233			0.349
I- II	16 (11.51)	6 (20)		11 (16.67)	11 (10.68)	
III- IV	123 (88.49)	24 (80)		55 (83.33)	92 (89.32)	
Clinical N Stage			0.828			<.0001
N (+)	97 (69.78)	20 (66.67)		35 (53.03)	82 (79.61)	
N (-)	42 (30.22)	10 (33.33)		31 (46.97)	21 (20.39)	
Distance from anal verge (cm)	5.38 ± 2.71	5.67 ± 2.77	0.607	5.26 ± 2.46	5.55 ± 2.87	0.498
CRM (cm) [‡]	0.85 ± 0.74	n/a	n/a	0.64 ± 0.54	1 ± 0.82	0.016
Lymph-Vascular invasion			<.0001			<.0001
Positive	36 (25.9)	0 (0)		26 (39.39)	10 (9.71)	
Negative	103 (74.1)	30 (100)		40 (60.61)	93 (90.29)	
Adenocarcinoma			0.034			0.151
Yes	135 (97.12)	26 (86.67)		65 (98.48)	96 (93.2)	
No	4 (2.88)	4 (13.33)		1 (1.52)	7 (6.8)	
Differentiation			n/a			0.531
Well differentiated	95 (68.35)	n/a		44 (66.67)	51 (69.86)	
Moderately differentiated	40 (28.78)	n/a		19 (28.79)	21 (28.77)	
Poorly differentiated	4 (2.88)	n/a		3 (4.55)	1 (1.37)	
Pathological Stage			<.0001			<.0001
0	4 (2.88)	30 (100)		0 (0)	34 (33.01)	
I	47 (33.81)	0 (0)		5 (7.58)	42 (40.78)	
II	43 (30.94)	0 (0)		18 (27.27)	25 (24.27)	
III	35 (25.18)	0 (0)		33 (50)	2 (1.94)	
IV	10 (7.19)	0 (0)		10 (15.15)	0 (0)	
ASA Classification [¶]			0.188			0.832
1	7 (5.04)	3 (10)		3 (4.55)	7 (6.8)	
2	113 (81.29)	26 (86.67)		55 (83.33)	84 (81.55)	

3	19 (13.67)	1 (3.33)		8 (12.12)	12 (11.65)	
Pre-nCRT Hb (g/dL)	12.35 ± 1.54	12.83 ± 1.45	0.116	12.31 ± 1.69	12.51 ± 1.43	0.413
Pre-nCRT CEA (ng/mL)	13.04 ± 33.36	18.2 ± 63.41	0.668	14.3 ± 37.04	13.73 ± 42.2	0.928
Post-nCRT CEA (ng/mL)	4.89 ± 8.61	5.24 ± 10.7	0.845	5.57 ± 10.73	4.55 ± 7.67	0.506
Neoadjuvant Chemotherapy			0.168			0.020
Oxalip or Cape	20 (14.39)	3 (10)		9 (13.64)	14 (13.59)	
5FU+LV	99 (71.22)	26 (86.67)		43 (65.15)	82 (79.61)	
5FU alone	20 (14.39)	1 (3.33)		14 (21.21)	7 (6.8)	
Surgery type			0.905			0.553
Laparoscopy	61 (43.88)	14 (46.67)		26 (39.39)	49 (47.57)	
Robotic	71 (51.08)	15 (50)		37 (56.06)	49 (47.57)	
Open laparotomy	7 (5.04)	1 (3.33)		3 (4.55)	5 (4.85)	
Adjuvant Chemotherapy			0.463			1.000
Yes	111 (79.86)	22 (73.33)		52 (78.79)	81 (78.64)	
No	28 (20.14)	8 (26.67)		14 (21.21)	22 (21.36)	
Length of hospital stay (Day)	14.87 ± 8.4	14.41 ± 7.52	0.787	15.72 ± 10.16	14.18 ± 6.66	0.288
CAP Regression grade			<.0001			<.0001
Complete response	0 (0)	30 (100)		0 (0)	30 (29.13)	
Moderate response	54 (38.85)	0 (0)		21 (31.82)	33 (32.04)	
Minimal response	62 (44.6)	0 (0)		30 (45.45)	32 (31.07)	
Poor response	23 (16.55)	0 (0)		15 (22.73)	8 (7.77)	
Recurrence			0.139			0.012
Yes	33 (23.74)	3 (10)		21 (31.82)	15 (14.56)	
No	106 (76.26)	27 (90)		45 (68.18)	88 (85.44)	
Time to recurrence (Month)	47.56 ± 26.41	64.61 ± 21.04	0.001	42.13 ± 26.59	56.01 ± 24.76	0.001
Survival Status			0.071			0.001
Alive	96 (69.06)	26 (86.67)		38 (57.58)	84 (81.55)	
Death	43 (30.94)	4 (13.33)		28 (42.42)	19 (18.45)	
Time to survival (Month)	53.55 ± 24.09	65.9 ± 20.18	0.010	49.15 ± 25.71	59.97 ± 21.69	0.004

[‡]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=169)

	Survival Status			Recurrence		
	Alive	Death	<i>p</i> <i>value</i>	No	Yes	<i>p</i> <i>value</i>
	(n= 122)	(n= 47)		(n= 133)	(n= 36)	
Age (y)	56.39 ± 12.98	63.55 ± 12.62	0.002	57.71 ± 13.23	60.86 ± 13.18	0.207
Sex			0.062			0.425
Male	79 (64.75)	38 (80.85)		94 (70.68)	23 (63.89)	
Female	43 (35.25)	9 (19.15)		39 (29.32)	13 (36.11)	
Body Mass Index (kg/m2)	23.93 ± 3.96	23.88 ± 4.16	0.939	23.93 ± 3.97	23.84 ± 4.18	0.904
Clinical Stage			<.0001			0.371
I	6 (4.92)	4 (8.51)		6 (4.51)	4 (11.11)	
II	30 (24.59)	11 (23.4)		31 (23.31)	10 (27.78)	
III	84 (68.85)	22 (46.81)		87 (65.41)	19 (52.78)	
IV	2 (1.64)	10 (21.28)		9 (6.77)	3 (8.33)	
Clinical T Stage			1.000			0.261
I- II	16 (13.11)	6 (12.77)		15 (11.28)	7 (19.44)	
III- IV	106 (86.89)	41 (87.23)		118 (88.72)	29 (80.56)	
Clinical N Stage			0.854			0.309
N (+)	85 (69.67)	32 (68.09)		95 (71.43)	22 (61.11)	
N (-)	37 (30.33)	15 (31.91)		38 (28.57)	14 (38.89)	
Distance from anal verge (cm)	5.54 ± 2.75	5.17 ± 2.62	0.433	5.67 ± 2.77	4.58 ± 2.35	0.033
CRM (cm) [£]	0.84 ± 0.62	0.87 ± 1.01	0.899	0.88 ± 0.66	0.76 ± 0.95	0.598
Lymph-Vascular invasion			0.002			0.167
Positive	18 (14.75)	18 (38.3)		25 (18.8)	11 (30.56)	
Negative	104 (85.25)	29 (61.7)		108 (81.2)	25 (69.44)	
Adenocarcinoma			0.446			0.205
Yes	115 (94.26)	46 (97.87)		8 (6.02)	0 (0)	
No	7 (5.74)	1 (2.13)		125 (93.98)	36 (100)	
Differentiation			0.813			0.455
Well differentiated	64 (66.67)	31 (72.09)		73 (68.87)	22 (66.67)	
Moderately differentiated	29 (30.21)	11 (25.58)		29 (27.36)	11 (33.33)	
Poorly differentiated	3 (3.13)	1 (2.33)		4 (3.77)	0 (0)	
Pathological Stage			<.0001			0.160
0	30 (24.59)	4 (8.51)		31 (23.31)	3 (8.33)	
I	38 (31.15)	9 (19.15)		39 (29.32)	8 (22.22)	
II	28 (22.95)	15 (31.91)		30 (22.56)	13 (36.11)	
III	25 (20.49)	10 (21.28)		26 (19.55)	9 (25)	
IV	1 (0.82)	9 (19.15)		7 (5.26)	3 (8.33)	
ASA Classification [¶]			0.003			0.477
1	10 (8.2)	0 (0)		9 (6.77)	1 (2.78)	
2	103 (84.43)	36 (76.6)		107 (80.45)	32 (88.89)	
3	9 (7.38)	11 (23.4)		17 (12.78)	3 (8.33)	

Pre-nCRT Hb (g/dL)	12.69 ± 1.41	11.76 ± 1.65	<.0001	12.39 ± 1.54	12.57 ± 1.53	0.543
Pre-nCRT CEA (ng/mL)	9.53 ± 23.35	25.43 ± 65.33	0.110	14.28 ± 43.97	12.74 ± 21.1	0.767
Post-nCRT CEA (ng/mL)	3.55 ± 3.65	8.56 ± 15.48	0.033	5.19 ± 10.05	4.05 ± 2.32	0.235
Neoadjuvant Chemotherapy			0.023			0.964
Oxalip or Cape	12 (9.84)	11 (23.4)		9 (6.77)	1 (2.78)	
5FU+LV	97 (79.51)	28 (59.57)		107 (80.45)	32 (88.89)	
5FU alone	13 (10.66)	8 (17.02)		17 (12.78)	3 (8.33)	
Surgery type			0.024			0.682
Laparoscopy	51 (41.8)	24 (51.06)		57 (42.86)	18 (50)	
Robotic	68 (55.74)	18 (38.3)		70 (52.63)	16 (44.44)	
Open laparotomy	3 (2.46)	5 (10.64)		6 (4.51)	2 (5.56)	
Adjuvant Chemotherapy			0.058			0.021
Yes	101 (82.79)	32 (68.09)		23 (17.29)	13 (36.11)	
No	21 (17.21)	15 (31.91)		110 (82.71)	23 (63.89)	
Length of hospital stay (Day)	14.11 ± 7.2	16.67 ± 10.44	0.142	14.66 ± 8.31	15.26 ± 8.03	0.706
CAP Regression grade			0.003			0.219
Complete response	26 (21.31)	4 (8.51)		27 (20.3)	3 (8.33)	
Moderate response	43 (35.25)	11 (23.4)		44 (33.08)	10 (27.78)	
Minimal response	43 (35.25)	19 (40.43)		46 (34.59)	16 (44.44)	
Poor response	10 (8.2)	13 (27.66)		16 (12.03)	7 (19.44)	
Recurrence			0.006			
Yes	19 (15.57)	17 (36.17)				
No	103 (84.43)	30 (63.83)				
Time to recurrence (Month)	58.87 ± 22.63	29.1 ± 22.95	<.0001	57.47 ± 23.86	25.16 ± 18.12	<.0001
Survival Status						0.006
Alive				103 (77.44)	19 (52.78)	
Death				30 (22.56)	17 (47.22)	
Time to survival (Month)	64.01 ± 18.18	34.3 ± 23.64	<.0001	56.91 ± 23.87	51.44 ± 23.66	0.224

[‡]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 neoadjuvant chemoradiotherapy.

	Pathologic Complete Response			Downstaging		
	Odds Ratio	95% CI	<i>p value</i>	Odds Ratio	95% CI	<i>p value</i>
Age (y)	0.99	(0.96 - 1.02)	0.415	1.00	(0.98 - 1.03)	0.857
Sex						
Female v.s. Male	0.96	(0.41 - 2.26)	0.920	1.68	(0.84 - 3.36)	0.143
BMI (kg/m2)						
Non-Obese v.s. Obese	2.49	(0.31 - 20.07)	0.391	1.62	(0.50 - 5.24)	0.424
Clinical T Stage						
I-II v.s. III-IV	1.92	(0.68 - 5.41)	0.216	0.60	(0.24 - 1.47)	0.263
Clinical N Stage						
(+) v.s. (-)	0.87	(0.37 - 2.01)	0.737	3.46	(1.75 - 6.83)	<0.001
Adenocarcinoma						
No v.s. Yes	5.19	(1.22 - 22.09)	0.026	4.74	(0.57 - 39.38)	0.150
ASA Classification						
1 v.s. 3	8.14	(0.72 - 91.88)	0.117	1.56	(0.31 - 7.87)	0.554
2 v.s. 3	4.37	(0.56 - 34.15)	0.515	1.02	(0.39 - 2.65)	0.651
Pre-nCRT Hb (g/dL)						
Normal v.s. Abnormal	1.57	(0.67 - 3.69)	0.296	1.18	(0.63 - 2.23)	0.601
Pre-nCRT CEA (ng/mL)						
Normal v.s. Abnormal	0.95	(0.41 - 2.19)	0.900	1.51	(0.78 - 2.93)	0.227
Post-nCRT CEA (ng/mL)						
Normal v.s. Abnormal	1.02	(0.40 - 2.60)	0.962	1.80	(0.88 - 3.70)	0.107
Neoadjuvant Chemotherapy						
Oxalip or Cape v.s. 5FU alone	3.00	(0.29 - 31.35)	0.740	3.11	(0.92 - 10.69)	0.347
5FU+LV v.s. 5FU alone	5.25	(0.67 - 40.98)	0.082	3.81	(1.43 - 10.16)	0.036
Recurrence						
No v.s. Yes	2.80	(0.80 - 9.83)	0.108	2.74	(1.29 - 5.82)	0.009
Time to recurrence (Month)	1.03	(1.01 - 1.05)	0.002	1.02	(1.01 - 1.04)	0.001
Survival Status						
Alive v.s. Death	2.91	(0.96 - 8.86)	0.060	3.26	(1.62 - 6.54)	0.001
Time to survival (Month)	1.03	(1.01 - 1.04)	0.012	1.02	(1.01 - 1.03)	0.007
CI: Confidence Interval						

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

	Adjusted Hazard Ratio	95% Confidence Interval	<i>p value</i>
Downstaging	0.40	(0.21 - 0.71)	<0.001
Yes v.s. No			
Sex			0.003
Female v.s. Male	0.42	(0.12 - 0.88)	
Pre-nCRT Hb (g/dL)			0.021
Abnormal v.s. Normal	2.54	(1.41 - 4.58)	
Post-nCRT CEA (g/dL)			0.003
Abnormal v.s. Normal	1.91	(1.05 - 3.48)	

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

	Adjusted Hazard Ratio	95% Confidence Interval	<i>p value</i>
Downstaging			0.002
Yes v.s. No	0.42	(0.21 - 0.82)	
Received Adjuvant Chemotherapy			0.009
Yes v.s. No	0.35	(0.18 - 0.69)	

Figures

a

b

c

d

Figure 1

Adenocarcinoma; Chemoradiation; Downstaging; Neoadjuvant therapy; Pathological Completed Response; Rectal cancer; Survival