Rectal cancer complete responders after neoadjuvant chemoradiation: when to spare their organs?

Ahmed M. Saleh[a], Mohamed Mazloum[a], Abdelsalam Ismail[b], Doaa Emara[c]

[a]Colorectal Surgery, Faculty of Medicine, Alexandria University, Alexandria, Egypt, [b]Medical Oncology and Nuclear Medicine, Faculty of Medicine, Alexandria University, [c]Diagnostic and Interventional Radiology, Faculty of Medicine, Alexandria University

Correspondence to Ahmed M. Saleh, MSc (legible now for MD and PhD), Department of surgery, Alexandria university, Champollion Street, El Raml Station, Alexandria 21111, Egypt. Tel: +0100 450 0725; fax: (03) 4847426; e-mail: dr.amgsaleh@gmail.com

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Objective
The aim of this study is to identify possible clinical predictors of complete response after neoadjuvant treatment (NAT) in locally advanced rectal cancer (LARC) patients.
Materials and methods
This study included 40 LARC patients (16 males and 24 females) who received NAT followed by total mesorectal excision (TME) in the period between August 2020 and February 2023. Two different NAT protocols were used; long-course chemoradiotherapy (LCRT) or consolidation total neoadjuvant treatment (TNT) according to the decision of the multidisciplinary team (MDT). Reassessment of response is done after completion of radiotherapy by digital rectal examination (DRE), proctoscopy, and pelvic MRI to define complete responders. All these responders received TME and were classified according to their pathology specimens into the pathological complete response group (pCR=22 patients) and nonpathological complete response group (non-pCR=18 patients). Statistical analyses were performed to compare the two groups and identify clinical factors associated with pCR.
Results
The significant clinical predictors of pCR in the univariate analysis were patients' age, preneoadjuvant carcinoembryonic antigen (CEA) level and preneoadjuvant lymphocytic ratio (P=0.030, 0.007, and 0.001, respectively). In multivariate analysis, lymphocytic ratio was the only independent predictor for pCR (P=0.017). Lymphocytic ratio (>26%) has high diagnostic performance for predicting pCR, while age (>50 years) and normal CEA (≤5 ng/ml) have lower diagnostic performance which can be much improved when both are used in combination to predict pCR.
Conclusion
Preneoadjuvant lymphocytic ratio and the combined use of age and preneoadjuvant CEA level are significant predictors of pCR, this may help the MDT select rectal cancer patients with complete clinical response (cCR), who are candidates for organ preserving strategies, to spare their rectum and avoid unnecessary radical surgeries.

Keywords:
complete response, lymphocytic ratio, rectal cancer

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Introduction

Rectal cancer (RC) represents more than one-third of colorectal tumors and it is the eighth most common malignancy worldwide [1]. Nowadays, the standard approach for RC management is total mesorectal excision (TME) followed by NAT, which aims at improving local control through downsizing and downstaging the tumor [2]. These treatment modalities of combined use of surgery and radiotherapy may have long-term functional effects on the pelvic organs which may be persistent especially low anterior resection syndrome, urinary dysfunction, sexual dysfunction, and the need for permanent stoma, which negatively impacts the quality of life of these patients [3].

With the continuous advances in the field of NAT and the adoption of more intensive regimens, 15–30% of LARC patients present with pathological complete response (pCR). Those with complete tumor regression represent a subset of patients with a particularly favorable outcome suggesting that disease management could be tailored according to the tumor stage after NAT rather than before it [4]. This has raised the interest in organ preserving strategies as the watch and wait approach, described

by Habr-Gama *et al.*, and local excision with the aim of avoiding the substantial morbidity and mortality of radical resection without compromising the oncological outcomes [5,6]. In this setting, complete clinical response (cCR) has become an intended outcome and a necessary condition to adopt this strategy in those patients [7].

The challenge in the management of RC when trying to consider an organ preserving approach remains in accurately identifying those who would likely achieve a sustained cCR after NAT without local re-growths. It is reported that 30% of complete responders are not recognized preoperatively at reassessment due to over staging of the residual tumor, with the consequence that these patients undergo a major radical surgery which could have been avoided [8].

Unfortunately, the currently available clinical, pathological, serological, and radiological predictor tools cannot precisely determine those patients who would benefit from this approach and no robust marker of pCR prediction has yet been identified [9,10]. Identification of accurate markers for pCR may help the MDT select the prober candidates for organ sparing strategies to avoid the consequences of radical surgeries.

Patients and methods

This study was prospectively conducted in Alexandria university hospital between August 2020 and February 2023, on 40 patients with middle or low LARC who had cCR after NAT. Patients with early, complicated, or metastatic RC were excluded from the study. After approval of the protocol by Alexandria faculty of medicine ethics committee, all patient were informed well about all the procedures done through the study and they all signed an informed consent before being enrolled in the study.

Demographic data of all patients were recorded. All patients in this study were subjected to thorough history taking, physical examination including abdominal examination, digital rectal examination (DRE) and rigid proctoscopy. Laboratory investigations included complete blood count, coagulation profile, lymphocytic count and ratio, random blood sugar, renal function tests, liver function tests and the tumor marker carcinoembryonic antigen (CEA). Radiological examination included pelvic MRI, computed tomography (CT) of the chest, abdomen, and pelvis with oral and intravenous contrast.

Two protocols of NAT were used according to the MDT team decision either standard NAT in the form of LCRT of 50.4 Gy divided into 28 fractions, with infusion 5-fluorouracil (1000 mg/m^2/day for 5 days in the first and fifth weeks of radiation) or consolidation TNT (4 cycles of full dose systemic chemotherapy-FOLFOX or CAPEOX-after chemoradiation) [11]. Then all patients were reevaluated at least 6 weeks after completion of radiotherapy sessions for having the criteria of cCR described by Habr-Gama [6], through DRE, rigid proctoscopy, and high-resolution pelvic MRI.

Surgeries were performed 8–12 weeks after completion of radiotherapy sessions for patients who recieved standard LCRT and after 4 weeks of completion of chemotherapy for patients who recieved consolidation TNT. Bowel preparation and stoma site marking were done the day before surgery. All patients were offered total mesorectal excision which included ultra-low anterior resection or abdominoperineal resection according to the tumor level. All surgeries were done using sharp dissection under direct vision through the proper pelvic facial planes. A diverting loop ileostomy was done for patients managed by ultra-low anterior resection.

Pathological examination of the resected specimens was done, the tumor and lymph nodes responses to NAT (ypT and ypN) were determined according to the American joint committee on cancer (AJCC)/college of American pathologists' regression grading system modified by Ryan *et al.* [12], and patients were classified into two groups: pCR group (22 patients), and non-pCR group (18 patients).

The two study groups were compared regarding demographic parameters (as sex and age), laboratory parameters (as lymphocytic ratio and CEA), preneoadjuvant parameters (as tumor differentiation, tumor size, affected mesorectal and lateral lymph nodes, and distance from anal verge), postneoadjuvant parameters (interval between radiotherapy and reassessment, MRI tumor regression grade (mrTRG), diffusion weighted images (DWI) and postneoadjuvant tumor size), operative parameters (type of surgery and complications) and postoperative pathology parameters (as mesorectal grading, number of retrieved LNs, follow-up period and recurrence). These different parameters were then included in the univariate analysis and parameters of P value less than 0.1 where included in the multivariate analysis for determining the possible predictors for pCR.

Statistical analysis

Statistical analysis was done using IBM SPSS statistics for windows, Version 23.0. Armonk, NY: IBM Corp). When the data were parametric, it was provided as mean, SDs, and ranges; when the data were nonparametric, it was presented as median and interquartile range. Numbers and percentages were also used to represent qualitative characteristics. When the predicted count in any cell was less than 5, the χ^2 test and/or Fisher exact test were used to compare the groups' qualitative data. The independent t test was used to compare two groups' quantitative data and parametric distributions, whereas the Mann–Whitney test was used to compare nonparametric distributions. The confidence interval was set to 95% and the margin of error accepted was set to 5%.

Results

The study included 24 (60%) women and 16 (40%) men, their ages ranged between 32 and 77 years, with a mean of 58.5±12 years for the pCR group and 49.9 ±10.4 for non-pCR (Table 1).

The lymphocytic ratio for the pCR group ranged between 24.9% and 53.7% with a mean of 33.6 ±8.8%, while that for the non-pCR group ranged between 11% and 35.8% with a mean of 19.1±5.1%. The difference between the two groups was statistically significant ($P<0.001$). The CEA level was high in 5 of 22 patients (22.7%) of the pCR group and 11 of 18 patients (61.1%) of the non-pCR group. The difference between the two groups was statistically significant ($P=0.005$) (Table 2).

Different tumor and management parameters are described in Tables 3–6. Nothing of these parameters showed a statistically significant difference between the two groups except for preneoadjuvant tumor size at P less than 0.1.

The pathological parameters and follow-up are described in Table 7. It is worth noting that the median number of retrieved LNs in the postoperative pathological specimen for the pCR group was 3 (1–20) LNs, while that for the non-pCR group was 8.5 (3–18) LNs. the difference between the two groups was statistically significant ($P=0.005$). The median for the follow-up period after surgery for the pCR group is 24 months, while that for the non-pCR group is 20 months, during which none of the patients in the pCR group showed any recurrence. For the non-pCR group, 2 (11.1%) patients showed recurrence at the anastomotic site and were offered APR (Table 7).

Parameters predicting pathological complete response

The logistic regression analysis was done for the total sample (22 patients with no tumor residual vs. 18 patients with tumor residual) to determine the different parameters predicting pCR (Table 8). The statistically significant parameters ($P<0.1$) in the univariate analysis were age of the patients, lymphocytic ratio, CEA, and preneoadjuvant tumor

Table 1 Demographic data of the two study groups

	Residual (n=18)	Free (n=22)	Test of Sig.	P
Sex				
Male	8 (44.4%)	8 (36.4%)	χ^2=0.269	0.604
Female	10 (55.6%)	14 (63.6%)		
Age (y)				
Mean±SD.	49.9±10.4	58.5±12	t=2.387*	0.022*
Median (Min–max)	49.5 (32–70)	60 (34–77)		

χ^2, Chi square test t: Student t-test; SD, Standard deviation. p: P value for comparing between the two studied groups. *Statistically significant at P less than or equal to 0.05.

Table 2 Laboratory parameters

	Residual (n=18)	Free (n=22)	Test of Significance	P
Lymphocytic ratio (%)				
Mean±SD.	19.1±5.1	33.6±8.8	t=6.515*	<0.001*
Median (Min–max)	19 (11–35.8)	30.4 (24.9–53.7)		
CEA				
Normal	7 (38.9%)	17 (77.3%)	χ^2=6.0774*	0.0137*
High	11 (61.1%)	5 (22.7%)		

χ^2, Chi square test t: Student t-test; SD, Standard deviation. p: P value for comparing between the two studied groups. *Statistically significant at P less than or equal to 0.05.

Table 3 Preneoadjuvant tumor parameters for the two study groups

	Residual (*n*=18)	Free (*n*=22)	Test of Significance	*P*
Colonoscopy biopsy				
Mucinous Adenocarcinoma	1 (5.6%)	4 (18.2%)	χ^2=1.385	^{MC}P=0.563
Moderately differentiated adenocarcinoma	13 (72.2%)	14 (63.6%)		
Well differentiated adenocarcinoma	4 (22.2%)	4 (18.2%)		
Tumor size (pre)				
Mean±SD.	5.5±1.3	4.84±1.1	t=1.754	0.088
Median (Min–max)	5.3 (3.5–9)	4.9 (2.3–6.8)		
Distance from anal verge (pre)				
Mean±SD.	5.8±2.8	6.4±2.6	*t*=0.708	0.483
Median (Min–max)	6 (1.5–10)	6.8 (1.5–11)		
Lymph nodes				
Mesorectal	14 (77.8%)	19 (86.4%)	χ^2=0.505	^{FE}P=0.680
Lateral	5 (27.8%)	5 (22.7%)	χ^2=0.135	^{FE}P=0.731

χ^2, Chi square test; FE, Fisher Exact; MC, Monte Carlo; SD, Standard deviation; *t*, Student *t*-test. p: *P* value for comparing between the two studied groups. *Statistically significant at *P* less than or equal to 0.05.

Table 4 Neoadjuvant type and interval to reassessment

	Residual (*n*=18)	Free (*n*=22)	Test of Significance	*P*
Type of neoadjuvant				
Total	7 (38.9%)	13 (59.1%)	χ^2=1.616	0.204
Standard	11 (61.1%)	9 (40.9%)		
Interval between radiotherapy and reassessment weeks				
Mean±SD.	11.9±5.2	14.2±6.2	*t*=1.244	0.221
Median (Min. – Max.)	9 (6–22)	15 (6–26)		

χ^2, Chi square test; SD, Standard deviation; t, Student t-test. p: *P* value for comparing between the two studied groups. *Statistically significant at *P* less than or equal to 0.05.

Table 5 Postneoadjuvant tumor parameters for the two study groups

	Residual (*n*=18)	Free (*n*=22)	Test of Significance	*P*
Distance from anal verge (post)				
Mean±SD.	7±2.8	7.3±2.6	*t*=0.433	0.667
Median (Min–max)	7.2 (3–11)	7 (3–12)		
Diffusion restriction				
No	9 (50%)	14 (63.6%)	χ^2=2.307	^{MC}P=0.375
Minimal	8 (44.4%)	5 (22.7%)		
High	1 (5.6%)	3 (13.6%)		
Minimal/ High	9 (50%)	8 (36.4%)	χ^2=0.753	0.385
Tumor regression grade				
Grade I	4 (22.2%)	4 (18.2%)	χ^2=1.595	^{MC}P=0.563
Grade II	12 (66.7%)	12 (54.5%)		
Grade III	2 (11.1%)	6 (27.3%)		
Tumor size (post)				
Mean±SD.	3.3±0.9	2.8±1.1	*t*=1.408	0.167
Median (Min–max.)	3.5 (2–5)	3 (1–5)		

χ^2, Chi square test; MC, Monte Carlo; SD, Standard deviation; *t*, Student *t*-test. p: *P* value for comparing between the two studied groups. *Statistically significant at *P* less than or equal to 0.05.

size (*P*=0.030, 0.001, 0.007, and 0.099, respectively). On including these parameters in the multivariate analysis, the lymphocytic ratio was the only significant independent parameter predicting pCR (*P*=0.017) (Table 9).

The diagnostic performance (sensitivity, specificity, PPV, NPV, and accuracy) of the parameters predicting pCR is described in Table 10. Age greater than 50 years is determined as a cut off value to predict pCR according to the receiver operating

Table 6 Type of surgery and postoperative complications

	Residual (*n*=18)	Free (*n*=22)	Test of Significance	*P*
Surgery type				
Open TME	9 (50%)	16 (72.7%)	χ^2=5.058	^{MC}P=0.134
Open APR	5 (27.8%)	2 (9.1%)		
Laparoscopic TME	4 (22.2%)	2 (9.1%)		
Trans-anal TME	0 (0%0	2 (9.1%)		
Postoperative complications				
Wound infection	5 (27.8%)	6 (27.3%)	χ^2=0.001	^{FE}P=1.000
Stoma complications	6 (33.3%)	5 (22.7%)	χ^2=0.559	^{FE}P=0.498
Leakage and pelvic collections	4 (22.2%)	4 (18.2%)	χ^2=0.101	^{FE}P=1.000
Anastomotic stricture	3 (16.7%)	3 (13.6%)	χ^2=0.071	^{FE}P=1.000
LAR syndrome	5 (27.8%)	9 (40.9%)	χ^2=0.750	^{FE}P =0.386
Mild Incontinence	6 (33.3%)	4 (18.2%)	χ^2=1.212	^{FE}P=0.300

χ^2, Chi square test; FE, Fisher Exact; MC, Monte Carlo; SD, Standard deviation; t, Student t-test. p: *P* value for comparing between the two studied groups. *Statistically significant at *P* less than or equal to 0.05.

Table 7 Pathological parameters and follow-up for the two study groups

	Residual (*n*=18)	Free (*n*=22)	Test of Significance	*P*
Mesorectal grading				
Incomplete	1 (5.6%)	1 (4.5%)	χ^2=2.635	^{MC}P=0.309
Near complete	5 (27.8%)	2 (9.1%)		
Complete	12 (66.7%)	19 (86.4%)		
LNs Retrieved				
Mean±SD.	9.1±4.2	5.7±5.3	U=97.500*	0.005*
Median (Min–max)	8.5 (3–18)	3 (1–20)		
LNs affected				
0	15 (83.3%)	22 (100%)	χ^2=3.489	^{MC}P=0.084
2	2 (11.1%)	0		
4	1 (5.6%)	0		
T stage			χ^2=46.597*	^{MC}P<0.001*
T0	0	22 (100.0%)		
T1	4 (22.2%)	0		
T2	14 (77.8%)	0		
N stage				
N0	15 (83.3%)	22 (100%)	χ^2=3.489	^{MC}P=0.084
N1	2 (11.1%)	0		
N2	1 (5.6%)	0		
Recurrence	2 (11.1%)	0	χ^2=2.573	^{FE}P=0.196
Period of follow-up (months)				
Mean±SD.	21.2±7.1	23.5±7.7	t=0.968	0.339
Median (Min–max)	20 (12–34)	24 (10–34)		

χ^2, Chi square test; FE, Fisher Exact; MC, Monte Carlo; SD, Standard deviation; *t*, Student *t*-test; U, Mann Whitney test. p: *P* value for comparing between the two studied groups. *Statistically significant at *P* less than or equal to 0.05.

characteristic (ROC) curve (Fig. 1), lymphocytic ratio greater than 26% as a cut off value (Fig. 2), and normal CEA less than or equal to 5 ng/ml. The specificity, PPV and overall accuracy of age (>50 years) and CEA increases when both are used in combination to predict pCR.

Discussion

Nowadays organ preserving strategies for rectal cancer patients with cCR after neoadjuvant chemoradiation are attractive options to avoid the substantial morbidities of radical surgeries with the same oncological and survival outcomes. The aim of this study was to determine the possible predictors of pCR in those patients and to assess the diagnostic performance of these predictors.

All patients in this study received total mesorectal excision after being defined as complete responders by digital rectal examination, rigid proctoscopy, and pelvic high-resolution MRI. The resected surgical

Table 8 Univariate logistic regression analysis for the parameters affecting polymerase chain reaction (*n*=22 vs. 18)

	P	OR (LL – UL 95%C. I)
Sex	0.604	1.400 (0.392–4.997)
Age (y)	0.030*	1.070 (1.007–1.138)
Lymphocytic ratio%	0.001*	1.637 (1.224–2.189)
CEA [Normal]	0.017*	5.343 (1.350–21.144)
Colonoscopy biopsy		
Presence of Mucinous adenocarcinoma	0.255	3.778 (0.383–37.282)
Presence of Moderately differentiated adenocarcinoma	0.565	0.673 (0.175–2.592)
Presence of well differentiated adenocarcinoma	0.751	0.778 (0.165–3.672)
Tumor size (pre)	0.099*	0.615 (0.345–1.096)
Distance from anal verge (pre)	0.472	1.091 (0.861–1.382)
Distance from anal verge (post)	0.658	1.056 (0.831–1.341)
Mesorectal nodes Pre neoadjuvant	0.481	0.553 (0.106–2.873)
Lateral nodes Pre neoadjuvant	0.714	1.308 (0.312–5.490)
Type of neoadjuvant [Total]	0.207	2.270 (0.636–8.106)
Interval bet. radiotherapy and reassessment weeks	0.217	1.074 (0.959–1.204)
No diffusion restriction (post)	0.387	1.750 (0.492–6.220)
Tumor regression grade		
Grade I	0.751	0.778 (0.165–3.672)
Grade II	0.438	0.600 (0.165–2.180)
Grade III	0.217	3.000 (0.525–17.159)
Tumor size (post)	0.168	0.625 (0.320–1.220)

C.I, Confidence interval; LL, Lower limit; OR, Odd's ratio; UL, Upper Limit. *Statistically significant at *P* less than or equal to 0.1.

Table 9 Multivariate logistic regression analysis for the parameters affecting polymerase chain reaction (*n*=22 vs. 18)

	P	OR (LL – UL 95% C.I)
Age (y)	0.099	1.276 (0.956–1.705)
Lymphocytic ratio%	0.020*	1.764 (1.094–2.846)
CEA [Normal]	0.261	0.086 (0.001–6.174)
Tumor size (pre)	0.386	0.403 (0.051–3.154)

C.I, Confidence interval; LL, Lower limit; OR, Odd's ratio; UL, Upper Limit. *Statistically significant at *P* less than or equal to 0.05.

Table 10 Diagnostic performance (sensitivity, specificity, positive predictive value, negative predictive value and accuracy) for age, carcinoembryonic antigen, and lymphocytic ratio to predict polymerase chain reaction (*n*=40)

	Sensitivity	Specificity	PPV	NPV	Accuracy
Age (>50 y)	77.27	55.56	68.0	66.70	67.50
CEA (Normal)	77.27	61.11	70.83	68.75	70.0
Lymphocytic ratio >26%	90.91	94.44	95.24	89.47	92.50
Age >50 y and normal CEA	72.72	94.44	94.12	73.91	82.50

NPV, Negative predictive value; PPV, Positive predictive value.

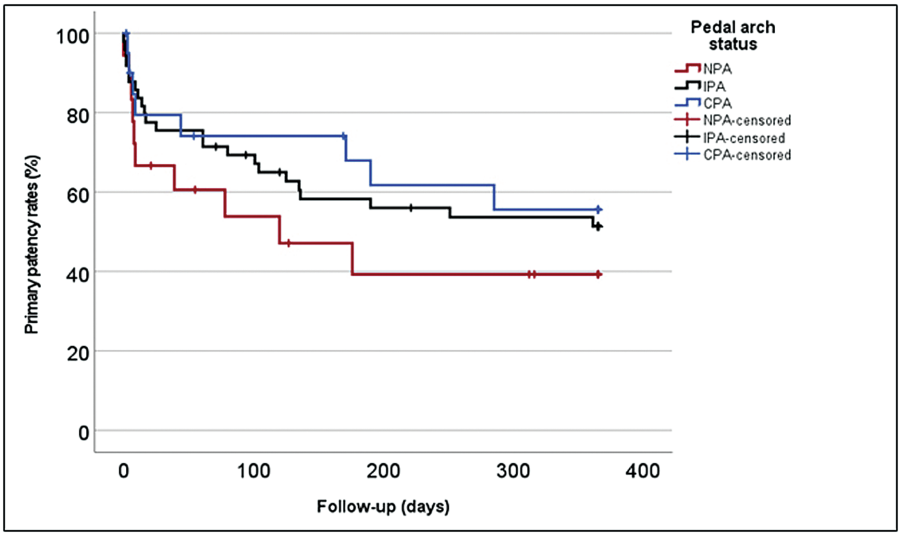
specimens were pathologically examined to determine the presence of pCR (*n*=22) or non-pCR (*n*=18).

The univariate regression analysis was done on the total sample to determine the different parameters predicting pCR. The statistically significant parameters ($P < 0.1$) were age of the patients, preneoadjuvant tumor size, preneoadjuvant normal CEA, and preneoadjuvant lymphocytic ratio %. The multivariate regression analysis was done on these significant parameters, and by then the preneoadjuvant lymphocytic ratio % was the only significant independent parameter predicting pCR.

The sensitivity, specificity, PPV, NPV, and accuracy of age for predicting pCR, when 50 years is determined as a cut off value, were 77.27%, 55.56%, 68%, 66.7%, and 67.5%, respectively. While that for CEA were 72.27%, 61.11%, 70.83%, 68.75%, and 70%. Lymphocytic ratio had much better diagnostic performance than age and CEA when 26% count is determined as a cut off value (90.91%, 94.44%, 95.24%, 89.47%, and 92.5%, respectively). The combined use of age and pre-neoadjuvant CEA level much improves their specificity, PPV and overall accuracy to predict pCR (94.44%, 94.12%, and 82.5%, respectively).

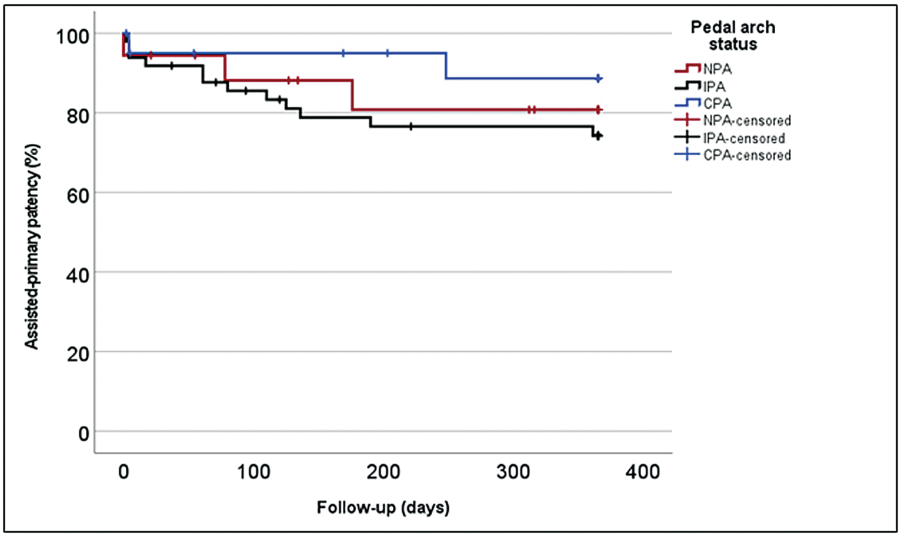
Age of patients in this study ranged between 32 and 77 years, with a mean of 58.5±12 years for the pCR group and 49.9±10.4 for non-pCR. This data is in line with other studies highlighting the correlation between age and pCR but with different cut off values. Mehraj *et al.* [13] stated that patients older than 60 years old have significantly better pCR rates as compared with patients younger than 60 years. Zhang *et al.* [14] reported that young age less than 40 years is a predictive factor for lower pCR rates following

Figure 1



Receiver operating characteristic curve for age to discriminate patients with pCR.

Figure 2



Receiver operating characteristic curve for lymphocytic ratio to discriminate patients with pCR.

NAT. Another recent meta-analysis conducted by Huang *et al.* [9], reported higher rates of pCR achieved in elderly patients.

The CEA level in this study was high in 5 of 22 patients (22.7%) of the pCR group and 11 of 18 patients (61.1%) of the non-pCR group, this difference between the two groups is statistically significant (P=0.0137). These results build on the existing evidence of the role of preneoadjuvant CEA for predicting pCR as reported by many studies. Zhang *et al.* [15] in a study on 432 patients, found that normal pretreatment CEA was significantly associated with pCR in both univariate and multivariate analyses. Probst *et al.* [16] conducted a large study on 18 113 patients and stated that elevated pretreatment CEA levels were associated with decreased pCR, decreased pathologic tumor regression and worse overall survival. Gash *et al.* [17] in a study on 13 742 patients reported that elevated pretreatment CEA is associated with poor pathological response, with a 50% lower pCR rate than when CEA was normal. Tan *et al.* [18] in a study on 6,555 patients developed a nomogram based on multivariate analysis and showed that positive pretreatment CEA is significant independent predictor for not achieving pCR.

The lymphocytic ratio in this study ranged between 24.9% and 53.7% for the pCR group with a mean of 33.6±8.8%, while for the non-pCR group, ranged between 11% and 35.8% with a mean of 19.1±5.1%. The difference between the two groups was statistically significant ($P<0.001$). Our study results are in concordance with a study reported by Mbanu *et al.* [19], on 322 patients, who stated that lymphocyte count was significantly associated with sustained cCR. Another study by Duo *et al.* [20], conducted on 88 patients, reported that high lymphocyte ratio (≥24.6%) is an independent predictor of good tumor response. Choi *et al.* [21], in a study on 51 patients, reported a significant association between peripheral lymphocyte level and downstaging of rectal tumors and suggested that the death of tumor cells after NAT is partially dependent on the host immune response. Kitayama *et al.* [22], also conducted a study on 73 patients with LARC and reported that preneoadjuvant lymphocyte ratio was an independent predictor to complete response and raised the possibility that a lymphocyte-mediated immune reaction may have a role in complete destruction of cancer cells.

The post-neoadjuvant distance of the tumor from the anal verge for the pCR group ranged between 3 cm and 12 cm with a mean of 7.3±2.6 cm, while that for the control group ranged between 3 cm and 11 cm with a mean of 7±2.8 cm. Although the results of this study did not find a significant correlation between the distance of the tumor from the anal verge and pCR, however, several studies as those reported by Novin *et al.* [23], Armstrong *et al.* [24], and Das *et al.* [25], have demonstrated higher odds of pCR with low rectal tumors less than 5 cm from the anal verge.

The results of this study failed to conclude a significant correlation between mrTRG and pCR. This is in line with a study by Sclafani *et al.* [26], who reported that mrTRG can distinguish between good and bad responder groups, but it does not correlate directly with pTRG with low sensitivity and specificity to detect complete responders. A recent meta-analysis by Jang *et al.* [27], including six studies on 916 patients, reported only a specificity of 64% and sensitivity of 70% of mrTRG score 1–2 to detect complete response. On the contrary, other studies have shown a correlation between mrTRG and pathological findings as that conducted by Bothady *et al.* [28], who suggested that mrTRG may identify nearly ten times more pCR rates when compared with clinical and endoscopic findings. Another study by Patel *et al.* [29], stated that mrTRG showed a significant correlation with pCR and patient survival. Further dedicated studies are needed to evaluate the diagnostic performance of mrTRG to predict pCR.

This study also did not conclude a significant correlation between DWI and pCR. These results are like those reported by Lambregts *et al.* [30], in a study of 222 patients with nonmucinous tumors, who stated that DWI alone may be valuable in subcircumferential scars, however in thick circumferential scars the likelihood of incomplete response is high even if DWI is negative (no diffusion restriction). Another meta-analysis of 14 studies by Wu *et al.* [31], showed a nonsignificant increase in sensitivity for prediction of tumor response when adding DWI to T2 WI. On the other hand, a meta-analysis by van der Paardt *et al.* [32], showed that the combined use of DWI with the standard T2 WI for reassessment after NAT increases the diagnostic performance of MRI and its sensitivity from 50% to 84% to differentiate between complete and incomplete responders.

The median number of retrieved LNs in the postoperative specimens for the pCR group is 3 (1–20) LNs, and 8.5 (3–18) LNs for the non-pCR group. This diminished yield of retrieved LNs after NAT was reported similarly by several studies like that conducted by Damin *et al.* [33], who noted a 26.8% decrease in the mean number of LNs harvested after NAT and TME. Another study conducted by Bustamante-Lopez *et al.* [34], reported that pCR was an independent factor associated with decreased LNs yield in surgical specimens of patients treated with NAT and TME. De Campos-Lobato *et al.* [35], found that RC patients who received NAT and achieved the best Tumor Regression Grade (pTRG) have less than 12 LNs in their surgical specimens.

Although the National Comprehensive Cancer Network (NCCN) [36] still recommends a minimum of 12 LNs to be harvested from the surgical specimens for proper staging of colorectal cancer, however, several investigators as Marks *et al.* [37], and Gurawalia *et al.* [38], suggested that retrieval of less than 12 LNs is related to tumor biologic factors and should be considered a good indicator of tumor response with better control of the local disease.

Several parameters are thought to affect the results of this study, and their standardization or modification would have resulted in better data interpretation. The number of patients in this study is relatively small compared with other similar studies, this is due to the prospective nature of the study with the relatively

few numbers of patients who fulfill the criteria of cCR within this time limit. Homogeneity of the patients (mainly Caucasian from the same city) and heterogeneity of treatment protocols (type of neoadjuvant and nonuniform administration of radiation boosts) are other shortcomings of this study. Serum CEA was only interpretated as normal or high in our analysis because this parameter is susceptible to interlaboratory variations and is recorded in our data base as only normal or high (>5 ng/ml).

Conclusion

This study demonstrated that age greater than 50 years, preneoadjuvant normal CEA level (≤5 ng/ml) and lymphocytic ratio greater than 26% are significant predictors of pCR in rectal cancer patients presenting with cCR after NAT. The combined use of age and preneoadjuvant CEA level increases their specificity and PPV to predict pCR than using each of them alone. This may help the multidisciplinary team select patients who are proper candidates for organ preserving strategies to spare their rectum and avoid unnecessary radical surgeries.

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Conflicts of interest

The authors declare that they have no competing interests.

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