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Predictors of pathological complete response after total neoadjuvant treatment using short course radiotherapy for locally advanced rectal cancer

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Abstract

Background Total neoadjuvant treatment (TNT) has become a standard treatment approach for locally advanced rectal cancer (LARC). Patients achieving pathological complete response (pCR) following TNT have better outcomes (overall survival, relapse free survival). However, not all patients treated for LARC with neoadjuvant treatment achieve pCR.

Aim The aim of our study was to assess the rate and predictors of pCR.

Materials and methods We performed a retrospective study at medical oncology unit in a tertiary care teaching hospital. All consecutive LARC patients without any evidence of distant metastasis who underwent neoadjuvant chemoradiotherapy and surgery between June 2020 and January 2023 were included in the research. Pathological response to neoadjuvant treatment was assessed using Mandard grading system and response was categorized as pCR or not-pCR. Two different standardized protocols for the neoadjuvant treatment were used: the first group was treated with induction chemotherapy followed by short course radiotherapy and the second group was treated with the RAPIDO protocol. Correlation between different studied parameters and pCR was determined using univariate and multivariate logistic regression analysis.

Results The mean age of the 91 included patients (46 men and 45 women) was 58.53 ± 10.3 years. Twenty (22%) were found to have a pCR (Mandard TRG1) in the operative specimen. In univariate analysis, patients less than 60 years, continuation of chemotherapy and patients treated with the induction chemotherapy followed by short course radiotherapy showed a better pCR as compared to patients treated with Rapido protocol ($p = 0.043$, $p = 0.0001$ and $p = 0.021$ respectively). Patients with mucinous component had low pCR rates ($p = 0.021$). On logistic regression analysis, chemotherapy continuation (OR = 10.27, 95% CI = 2,14–49.32), and absence of mucinous component (OR = 12.6, 95% CI = 3.1–40.32) were significant predictors of pCR. The median survival was 37.7 months.

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Conclusion Mucinous component and chemotherapy interruption are associated with lower pCR rates. Integrating these factors into personalized treatment algorithms may help optimize therapeutic strategies and improve outcomes for patients with LARC.

Keywords Pathological complete response, Locally advanced rectal cancer, Total neoadjuvant treatment, Radiotherapy, Chemotherapy

Introduction

Total neoadjuvant treatment (TNT) has become a cornerstone of treatment for locally advanced rectal cancer (LARC), aiming to increase rates of sphincter preservation, and improve oncological outcomes. Despite advancements in treatment modalities, the response to neoadjuvant treatment varies among patients, with only a subset achieving a pathological complete response (pCR), defined as the absence of viable tumor cells in the surgical specimen after surgery [1].

Patients who achieve pCR demonstrate significantly improved long-term oncological outcomes, including higher rates of relapse-free survival and overall survival. pCR can generally be achieved in 15–27% of the patients treated with NRCT, while as around 54–75% show partial or absence of response [2, 3]. The ability to predict which patients are more likely to achieve pCR following TNT holds substantial clinical implications. Moreover, identifying predictors of pCR can facilitate treatment decision-making, tailoring therapeutic strategies.

The primary aim of our study was to identify the impact of patient characteristics, tumor size, tumor stage, location at presentation, circumferential extent, and pre-treatment CEA levels, as possible predictive factors, on the occurrence of pCR after neoadjuvant treatment.

For our study, the primary measured outcome was pathologic complete response.

Patients and methods

We performed a retrospective study at medical oncology unit in a tertiary care teaching hospital. All consecutive locally advanced primary rectal adenocarcinoma patients without any evidence of distant metastasis who underwent neoadjuvant chemoradiotherapy and surgery between June 2020 and December 2022 were included in the research.

The study was approved by the institutional review board at the Salah Azaiez Institute of Tunisia.

All the information regarding demographic data (gender, age), stage at presentation, routine hemograms, biochemical test results, administrated treatment were obtained prospectively from the medical record.

A colonoscopy/flexible sigmoidoscopy and proctoscopy were performed on all patients at diagnosis and after neoadjuvant treatment (before surgery). Pre-treatment endoscopic evaluation was carried out to assess baseline tumor characteristics, and post-treatment endoscopy was done to evaluate the response to TNT. The confirmation of diagnosis was obtained after histopathological examination before starting treatment. Magnetic resonance imaging (MRI) of the pelvis and contrast-enhanced computed tomography of the chest, abdomen and pelvis were done for pre-operative staging.

MRI of the pelvis was performed to assess the local extent of the tumor (extension to the mesorectal fascia), the circumferential resection margin, extramural vascular invasion, and tumor deposits. CT scan was performed to evaluate for distant metastases.

Excluded patients from the study were those with metastatic disease, non-operated patients, and those treated with neoadjuvant radiation alone.

Neoadjuvant protocols

During the study period, two different standardized protocols for the neoadjuvant treatment were used. Patients were sanded into two groups:

The first group was treated with 6 injections of mFOLFIRINOX followed by short course radiotherapy at a dose of 25 Gy. External beam radiotherapy was given over 5 days a week with daily dose of 5 Gy. After radiotherapy patients received 2 injections of mFOLFOX (Oxaliplatin 85mg/m^2, 5-Fluorouracil: 2500 mg continuous infusion over 48 h (Days 1 and 2), leucovorin [folinic acid] 400mg/m^2. Surgery was performed after 8 weeks following last dose of radiotherapy.

The second group was treated with the RAPIDO protocol: patients received short-course radiotherapy (5*5 Gy over a maximum of 8 days) followed by 6 cycles of CAPOX chemotherapy (capecitabine 1000mg/m^2 orally twice daily on days 1–14, oxaliplatin 130 mg/m2 iv) or 9 cycles of FOLFOX4 (Oxaliplatin 85mg/m^2 on day 1, and fluorouracil 1600 mg/m2 iv continuous infusion over 48 h on days 1 and 2, leucovorin [folinic acid] 400mg/m^2).

Each regimen was selected with the aim of achieving optimal therapeutic outcomes while considering the tolerability and potential benefits of intensifying treatment. The RAPIDO protocol was preferred in elderly patients (age > 70 years) and/or those with a performance status of 2.

The chemotherapy interruption, defined as definitive cessation of chemotherapy, was decided for high grade toxicity.

Pathological staging

Three categories were used to categorize the tumor grade based on the initial tumor biopsy samples: low, moderate and high differentiated tumor. Histopathological features of mucinous component (>50%) and signet ring cells were also noted.

After surgery, resected specimens were subjected to histopathological examination, which was done by an experienced pathologist. According to Mandard grading system, treatment response was categorized as pCR (TRG1) or not pCR (TRG 2–5). Pathologic complete response was defined as the absence of viable tumor cells in the rectum and in any of the resected lymph nodes in the surgical specimen. Typically, five tumor blocks or more were initially assessed, and in cases where no viable tumor cells were identified, additional sections were examined. Regarding interobserver consistency, histological evaluation was performed by two experienced gastrointestinal pathologists.

Table 1 Baseline patients characteristics N (%)

Mean age (years)	58.53 ± 10.3
Gender	
Male	46 (50.5)
Female	45 (49.5)
Mean CEA (ng/ml)	6.97 ± 1.2
T stage	
T2	5 (5.5)
T3	71 (78)
T4	15 (16.5)
N stage	
N0	3 (3.2)
N1	44 (48.4)
N2	44 (48.4)
Grade	
Well differentiated	19 (20.9)
Moderately differentiated	37 (40.6)
Poorly differentiated	35 (38.5)
Mucinous	18 (19.8)
Signet ring cell	17 (18.7)
Site of the tumor	
Lower rectum	39 (42.9)
Middle rectum	52 (57.1)
Staging method	
Pelvic CT scan	11 (12.1)
Pelvic MRI	80 (87.9)
Neoadjuvant protocol	
Induction chemotherapy	61 (67)
Rapido protocol	30 (33)
Type of surgery	
Low anterior resection	67 (73.6)
Abdominoperineal resection	23 (25.3)
Hartmann operation	1 (1.1)
Average radiation dose (Gy)	25

CEA: Carcinoembryonic antigen, CT: computed tomography, MRI: Magnetic resonance imaging, Gy: Gray

Statistical analysis

All the Statistical analysis were carried through Statistical Package for the Social Sciences (SPSS) version 23, IBM SPSS Inc.; Chicago, IL, USA). Continuous variables that followed a normal distribution were expressed as mean ± standard deviation and range while results for the variables that did not follow a normal distribution have been shown in median and the interquartile range. The categorical variables were expressed in the form of frequency and percentage.

For comparisons, Student's t-test was used for quantitative variables. A univariate analysis using chi-squared tests for dichotomous variable was conducted to identify the possible associated factors between the categorical variables and pCR. A multivariate analysis was carried out with variables that achieved statistical significance using logistic regression modeling. *P* value ≤ 0.05 was the established level of statistical significance.

We defined disease free survival (DFS) as the time from diagnosis to local or distant recurrence or censored at date of last follow-up. DFS and OS curves were generated using the Kaplan-Meier method. Differences were assessed using the log-rank test. Given the potential non-proportional hazards, we have supplemented our analysis with Weighted Log-Rank Tests.

Results

Baseline patients characteristics

A total of 91 patients (46 men and 45 women) were included in the study. Mean age of patients was 58.53 ± 10.3 years [range 28–80 years]. The tumor histology consisted of well-differentiated adenocarcinoma in 19 (20.9%), moderately differentiated adenocarcinoma in 37 (40.6%), poorly differentiated adenocarcinoma in 35 (38.5%), and signet ring cell in 17 (18.7%) patients. The mean initial CEA concentration was 6.97 ng/ml (range from 0.55 to 139 ng/ml). Pelvic MRI was the most commonly performed staging method (87.9%). All patients underwent surgery: anterior resection in 67 (73.6%), abdominoperineal resection in 23 (25.3%) patients. The median duration of surgery following last dose of TNT was 9 weeks. pCR (TRG1) was achieved in 20 patients (22%). 71 patients (78%) showed some form of regression or no response (TRG 2–5). Baseline patient characteristics are summarized in Table 1. The mean follow-up of patients was 40.2 months. Distribution of pretreatment and treatment variables according to received protocol were summarized in Table 2.

Predictors of pCR

Young patients less than 60 years had significantly better pCR rates as compared to those more than 60 years ($p = 0.043$). Patients treated with the induction chemotherapy followed by short course radiotherapy showed a

Table 2 Distribution of pretreatment and treatment variables according to received protocol

Study variables	Induction chemotherapy (*n*,%)	Short course radiotherapy (*n*,%)	*P*
Gender			
Male	30 (49.2)	16 (53.3)	0.716
Female	31 (50.8)	14 (46.7)	
CEA pretreatment level (mean)	14.35	7.08	0.516
T stage			
T2	3 (4.9)	2 (6.7)	0.734
T3	51 (83.6)	20 (66.7)	
T4	7 (11.5)	8 (26.6)	
N stage			
N (-)	3 (4.9)	0(0)	0.287
N (+)	58 (95.1)	30(100)	
Grade			
Well differentiated	9 (14.7)	10 (33.3)	0.494
Moderately differentiated	27 (44.3)	10 (33.3)	
Poorly differentiated	25 (41)	10 (33.3)	
Signet ring cell	8 (13.1)	9 (30)	
Site of the tumor			
Lower rectum	38 (62.3)	14 (46.7)	0.167
Middle rectum	23 (37.7)	16 (53.3)	
Type of surgery			
Resection	60 (98.4)	30 (100)	0.380
Hartmann operation	1 (1.6)	0 (0)	
Chemotherapy interruption			
Yes	38(62.3)	1 (0.3)	**0.00001**
No	23(37.7)	29 (99.7)	
Mucinous component			
Yes	8 (13.1)	10 (33.3)	**0.015**
No	53 (86.9)	20(66.7)	

CEA: Carcinoembryonic antigen

better pCR as compared to patients treated with Rapido protocol ($p = 0.013$). Patients with mucinous component had low pCR rates ($p = 0.021$).

In univariate analysis, the differences in pCR rates among gender, initial carcino embryonic antigen (CEA) levels, T stage and N stage were not significantly associated with pCR.

Time to surgery (between the last dose of radiotherapy to surgery) was not a predictive factor for pCR (8.83 weeks in patient with pCR Vs 11.46 weeks in patients without pCR, $p = 0.246$). Table 3 summarizes univariate analysis of various predictive factors for pCR.

On logistic regression analysis, chemotherapy continuation (OR = 10.27, 95% CI = 2,14–49.32), and mucinous component (OR = 12.6, 95% CI = 3.1–40.32) were significant predictors of pCR[Table 4].

Overall survival (OS)

The median survival was 37.7 months. The OS is represented in Fig. 1a. There was no significant difference in OS between patients achieving pCR and those without achieving pCR (Fig. 1b) and patients treated with different protocols (Fig. 1c).

Table 3 Univariate analysis of predictors for pathologic complete response

Study variables	pCR (*n*,%)	No pCR (*n*,%)	*P*
Gender			
Male	10 (11)	36 (39.5)	0.956
Female	10 (11)	35 (38.5)	
Age			
< 60 years	16 (17.6)	39 (42.8)	**0.043**
≥ 60 years	4 (4.4)	32 (35.2)	
ECA pretreatment level (mean)	9.08	13.49	0.516
T stage			
T2	2 (2.2)	3 (3.3)	0.268
T3	13 (14.3)	58 (63.7)	
T4	5 (5.5)	10 (11)	
N stage			
N (-)	1 (1.1)	2(2.2)	0.629
N (+)	19 (31.2)	69(65.5)	
Grade			
Well differentiated	10 (11)	9 (9.9)	0.755
Moderately differentiated	18 (19.8)	19 (20.9)	
Poorly differentiated	17 (18.6)	18 (19.8)	
Signet ring cell	8 (8.8)	9 (9.9)	
Site of the tumor			
Lower rectum	11 (12.1)	41(45)	0.826
Middle rectum	9 (9.9)	30 (33)	
Time to surgery (weeks)	8.83	11.46	0.246
Neoadjuvant protocol			
Induction chemotherapy	18 (19.8)	43 (67)	**0.013**
Rapido protocol	2 (2.2)	28 (33)	
Type of surgery			
Resection	19 (20.9)	71 (78)	0.058
Hartmann operation	1 (1.1)	0 (0)	
Chemotherapy interruption			
Yes	1(1.1)	38 (31.4)	**0.0001**
No	19(31.2)	33 (36.3)	
Mucinous component			
Yes	0 (0)	18 (19.8)	**0.018**
No	18 (19.8)	55 (60.4)	

pCR = pathological complete response, CEA: Carcinoembryonic antigen

Discussion

Total neoadjuvant treatment (TNT) followed by total mesorectal excision for locally advanced rectal cancer (LARC) has become a standard treatment approach due to its good results in downstaging tumors. TNT increase the likelihood of sphincter preservation, and improve local control of the disease. However, not all patients treated for LARC with neoadjuvant treatment achieve a pathological complete response (pCR). pCR is associated with better long-term outcomes including improved relapse-free survival and overall survival. Understanding the predictors of pCR is crucial for optimizing treatment strategies and identifying patients who may benefit most from neoadjuvant therapy especially in the era of total

Table 4 Multivariate analysis of predictors for pathologic complete response

Study variables	pCR (*n*,%)	No pCR (*n*, %)	*P*	OR
Age				
< 60 years	16 (17.6)	39 (42.8)	0.450	1.88[0.36–9.81]
≥ 60 years	4 (4.4)	32 (35.2)		
Neoadjuvant protocol				
Induction chemotherapy	18 (19.8)	43 (67)	0.067	4.36[0.9-21.14]
Rapido protocol	2 (2.2)	28 (33)		
Chemotherapy interruption				
Yes	1(1.1)	38 (31.4)	**0.04**	**10.27**[2.14–49.32]
No	19(31.2)	33 (36.3)		
Mucinous component				
Yes	0 (0)	16 (18.8)	**0.021**	**12.6**[3.1-40.32]
No	18 (21.2)	69 (60)		

OR = Odds ratio, CI = Confidence interval, pCR = pathological complete response

neoadjuvant therapy and watch-and-wait surveillance approach [4, 5]. The watch and wait strategy may have the benefit of avoiding surgery [6].

The pathological response to TNT in most studies varies among individuals. Achieving pCR varies from 15 to 27% of the patients. However, around 54–75% show partial response or no response after TNT [2–3]. Mojca et al., reported in their study that pCR was obtained in 12.1% of patients treated with 3D conformal technique [7]. In our study, pCR was achieved in 22% of patients.

Recently, there has been increased interest in the concept of total neoadjuvant treatment. TNT is defined as chemotherapy induction and/or consolidation in conjunction with classical standard chemoradiotherapy prior to surgery. It is believed that TNT increases the rate of pCR by addressing occult micrometastatic disease. A meta-analysis published in 2020 showed a pCR rate of 22.4% in the TNT cohort, and it was associated with a 39% increase in the odds of achieving pCR compared to other strategies (1.40, 95% CI 1.08–1.81, $p = 0.01$) [8].

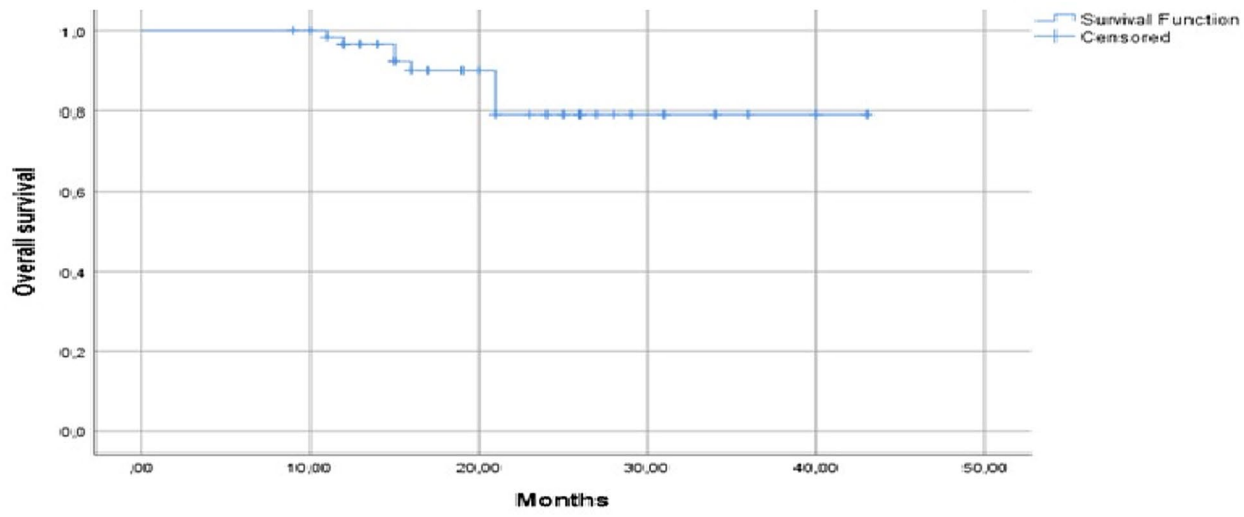
In this study, we investigated various clinical, biochemical, radiological, and pathological factors as potential predictors of pCR following TNT using short course radiation for LARC. The purpose of this study was to assess preoperative predictors of pCR after TNT using short course radiation.

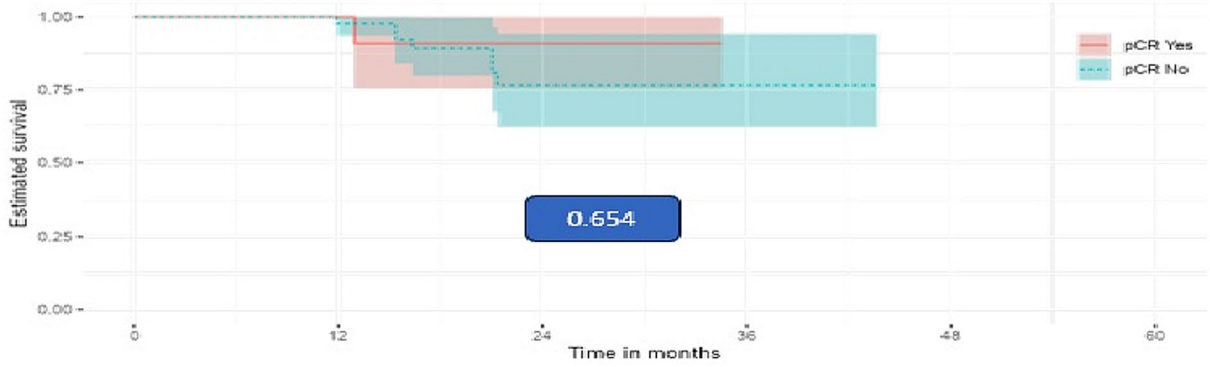
Patient-related factors play a crucial role in predicting pCR after TNT. Age, performance status (PS), nutritional status and comorbidities may influence clinical and pathological treatment outcomes (OS, DFS and pCR). Younger patients and those with PS ranging from 0 to 2 are more likely to achieve pCR. However, patients with significant comorbidities, impaired PS (3–4) may have reduced tolerance to treatment and consequently lower rates of pCR. In our study and in univariate analysis, we found that patient less than 60 years of age had significantly better pCR rates as compared to those more than 60 years of age ($p = 0.043$). The data in the literature concerning patient age as a predictive factor for pCR are discordant. In fact, a recent meta-analysis showed that elderly patients achieved higher pCR rates ($p = 0.0002$) [9]. Most studies have found lower CEA level are associated with pCR. A systematic review and meta-analysis confirmed these findings and concluded that CEA levels were inversely correlated with pCR rates [10].

In the literature, an association between interruption of chemotherapy and pCR has been demonstrated. Patients with an interruption in their neoadjuvant therapy due to treatment-related toxicity, were less likely to develop pCR [11].

Lymph node regression grade is a good indicator of response to preoperative TNT and several studies have shown that TNT is associated with a low pN (+) rate in locally advanced rectal cancer. Histopathological findings in positive lymph nodes after chemoradiotherapy include residual cancer cells, hemorrhage, areas of hyalinosis, cystic cell reactions, and pools of mucin [12, 13]. The impact of lymph node status on neoadjuvant chemoradiotherapy treatment response in LARC has been studied in several studies. Huang et al. showed that patient without lymph node involvement was a positive predictor of pCR ($P < 0.00001$) for rectal cancer following neoadjuvant chemoradiotherapy [9].

The treatment protocols for LARC are various. The addition of induction chemotherapy to concomitant neoadjuvant treatment in LARC could increase pCR rate. A systematic review showed that the addition of induction/consolidation chemotherapy to standard neoadjuvant treatment results in a higher pCR rate [14]. In our study, patients treated with induction chemotherapy followed by short course radiotherapy prior to surgery showed a better pCR as compared to patients treated with short course radiotherapy. This could be attributed to differences in patient selection, tumor biology, or chemotherapy regimen intensity. Additionally, we hypothesize that early systemic control of micrometastatic disease in the induction arm may have contributed to the improved pCR rate. The effect of TNT on oncological outcomes has





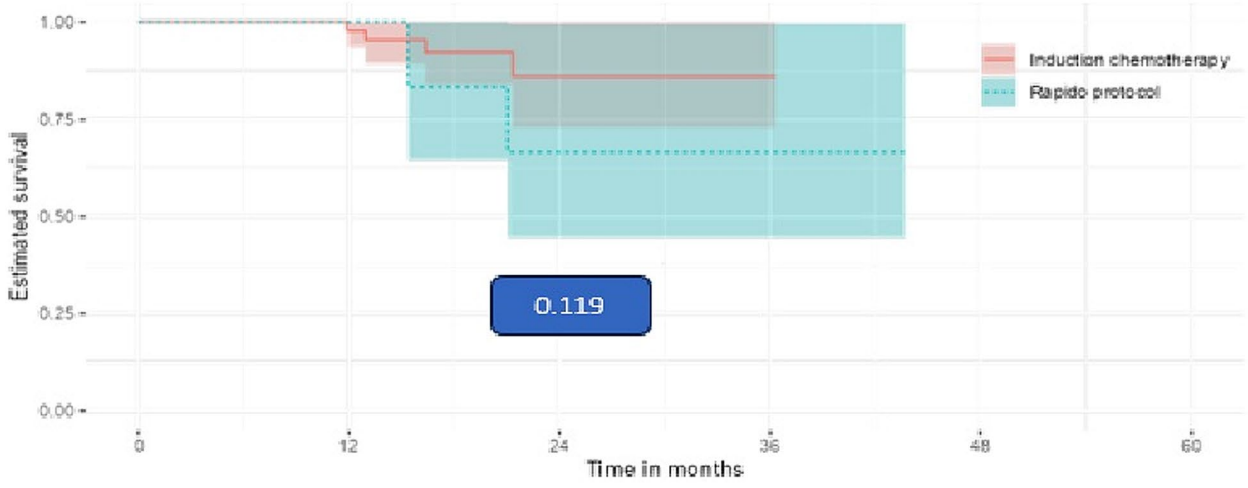


Fig. 1 (**a**) The Kaplan–Meier curve analysis of OS (**b**) Overall survival for pCR (**c**) Overall survival according to received protocol

not been fully investigated. Several studies and a meta-analysis showed that disease-free survival was not associated with the type of neoadjuvant treatment (hazard ratio [HR] 1.3; 95% CI: 0.93–1.80; $p = 0.12$) [15, 16].

Considering initial and definitive histopathological tumor features, three studies found no significant difference in terms of pCR [17–19]. A systematic review and meta-analysis found that mucinous component was associated with poor p CR [20].

In our study, a number of factors were independent predictors of pCR, including the absence of chemotherapy interruption (OR = 10.27, 95% CI = 2,14–49.32), and absence of mucinous component (OR = 12.6, 95% CI = 3.1–40.32). These factors predicting pCR require validation in prospective multicenter studies order to be incorporated into watch and wait strategies. The strength of this study lies in the fact that there is little data on real world outcomes of pCR after TNT using short course radiotherapy especially with induction chemotherapy.

Due to the retrospective nature of our study, there are certain limitations that it is important to acknowledge. Despite our efforts to minimize missing data, we encountered some challenges. Specifically, CEA levels were missing in some patient's records. Additionally, duration of chemotherapy interruption was not mentioned.

Despite advances in our understanding of predictors of pCR after TNT for LARC, several challenges are remaining. These challenges come from the fact that patient populations are heterogeneous, and there are big variations in treatment regimens. The differences in study methodologies make comparisons between studies difficult. Further research into novel biomarkers, personalized treatment approaches and risk models and algorithms based on artificial intelligence are required.

Conclusion

Our study identified several predictors of pathological complete response following TNT with short course for LARC. Mucinous component and chemotherapy interruption are associated with lower pCR rates. Integrating these factors into personalized treatment algorithms may help optimize therapeutic strategies and improve oncological outcomes for patients with LARC. Further prospective studies are warranted to validate these findings and refine predictive models.

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Author contributions
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Data availability
The data that support the findings of this study are available on request from the corresponding author, [HY]. The data are not publicly available due to [restrictions e.g. their containing information that could compromise the privacy of research participants].

Declarations

Ethics approval and consent to participate
This study was performed according to the Declaration of Helsinki, following the guidelines for good clinical practice. "Salah Azaiz institute ethics committee" approved the study protocol. All methods were carried out in accordance with relevant guidelines and regulations. Informed consent to participate in the study was obtained from participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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