Cancer Research Journal
2024, Vol. 12, No. 2, pp. 21-26
https://doi.org/10.11648/j.crj.20241202.11

Research Article

Predictive and Prognostic Factors Related to Chemoradioresistance in Neoadjuvant Treatment of Locally Advanced Rectal Cancer at Panama

Daliana Alcantara Jerez[1], Carla Eloy La Luz[1], Jose Pinto Llerena[1], Rafael Arauz[2, *]

[1]Department of Gastrointestinal Medical Oncology, Instituto Oncologico Nacional, Panama City, Panama
[2]Department of Radiation Oncology, Instituto Oncologico Nacional, Panama City, Panama

Abstract

Background: In Panama, and the rest of Latin America, there are few publications on chemoradioresistance, it leads to poor prognosis and represents the main reason for failure of therapy, ultimately it can lead to tumor recurrence and metastasis. *Objective:* Identify factors associated with chemoradioresistance in the neoadjuvant treatment of locally advanced rectal cancer at the Instituto Oncológico Nacional de Panamá, period 2016-2020. Methodology: This retrospective study included 71 patients with LARC who received neoadjuvant chemoradiotherapy and surgery. Chemoradioresistant patients were those who did not reach a higher pathological stage of ypT2NO and the results were compared. *Results:* Of the 71 patients, pathological complete response (pCR) was achieved in 34 patients (48%). 49% of patients met chemoradioresistance criteria. In this group, the median CEA was 136 ng/ml, the median hemoglobin was 12 g/dl, and the median BMI was 26 kg/m^2. The median radiation dose was 5000Gy. The time between completion of chemoradiotherapy and surgery was 110 days (16 weeks). Depending on the type of surgery, 65% who underwent low anterior resection were chemoradioresistant. The variables with statistical significance were the CEA value >5 ng/mL (OR=1.81, p=0.026) prior to the start of neoadjuvant treatment, with a lower pCR rate. Likewise, the ECOG scale (OR=2.51, p=0.015) was a risk factor related to chemoradioresistance, the lower the ECOG, the lower the risk of chemoradioresistance. The median overall survival and median recurrence-free survival was not reached in both groups and there was no statistically significant difference. *Conclusions:* Significant interactions were identified between CEA levels prior to the start of neoadjuvant treatment with the pathological complete response rate and the ECOG score with chemoradioresistance. Therefore, these factors can be used to predict patient outcomes, will help optimize personalized treatment strategies and improve patient outcomes.

Keywords

Locally Advanced Rectal Cancer, Chemoradiotherapy, Pathological Complete Response, Chemoradioresistance

[*]Corresponding author: radioarauz@gmail.com (Rafael Arauz)

Received: 5 March 2024; **Accepted:** 26 March 2024; **Published:** 12 April 2024

1. Introduction

The Colorectal cancer is the fourth most frequently diagnosed cancer and second leading cause of cancer death in the US [1]. Recent data show increased incidence in patients less than 65 years of age. The authors estimate that the incidence rates for rectal cancers will increase by 124.2%, for patients 20 to 34 [2]. The database at the Instituto Oncológico Nacional de Panamá for the year 2021 estimated that Rectal Cancer ranked ninth in frequency distribution for both sexes, representing 3.4% of all cancers diagnosed in that year [3], where the main management of Locally Advanced Rectal Cancer (LARC) of neoadjuvant chemotherapy and radiotherapy (nCRT). In Panama, and the rest of Latin America, there are few publications on chemoradioresistance, it leads to a poor prognosis and represents the main reason for therapy failure, which can lead to local recurrence and metastasis.

Identification of factors that influence histological response can help predict prognosis and propose organ preservation for good responders. Multiple studies have correlated pathological complete response with disease-free survival and overall survival [4-6]. It is essential to increase complete pathological responses, but it is unclear what clinical factors are involved.

The objective of the study is to evaluate the predictive and prognostic factors, as well as the incidence of chemoradioresistance, defined as patients who do not downstage to ypT2N0, after neoadjuvant treatment. These data would propose changes in the institutional practice if necessary and the departments that interfere in this management will benefit.

2. Materials and Methods

Retrospective, cross-sectional observational study who, data were obtained from electronic records of patients with Locally Advanced Rectal Cancer who received neoadjuvant treatment at the Instituto Oncológico Nacional de Panamá, between January 2016 and December 2020. The primary point of the study was to identify the predictive and prognostic factors related to chemoradioresistance in the neoadjuvant treatment of locally advanced rectal cancer of patients treated in the institution.

2.1. Patient Selection

The following inclusion criteria were used in this study:

1. Patients older than 18 years.
2. Diagnosis of locally advanced rectal cancer with histological type adenocarcinomas and treated with Neoadjuvant chemoradiotherapy therapy.

The following exclusion criteria were used in this study:

1. Patients who received total neoadjuvant chemotherapy.
2. Patients who received induction chemotherapy.
3. Patients who received chemotherapy other than fluoropyrimidines.
4. Patients with palliative colostomy prior to the start of treatment.
5. Patients with double primaries.

2.2. Statistical Analysis

The information were collected and analyzed using IBM SPSS Statistics version 23 and Stata 17. Patient characteristics were reported using frequency and descriptive statistics. The Kaplan-Meier method was used to analyze recurrence-free survival and overall survival.

3. Results

3.1. Patients' Characteristics

71 patients with LARC who were treated with nCRT and surgery were enrolled; 44 patients were male (62%), and 27 patients were female (38%), with a median age of 63 years (range 34 to 87). About 43% of all patients had a tumor located at middle rectum, 42% at lower rectum and 15% at upper rectum. Baseline characteristics are detailed in Table 1. There were 35 patients (49.3%) who were considered to have chemoradioresistance (patients who did not reduce their stage to ypT2N0 or lower after receiving neoadjuvant treatment). Regarding the ECOG scale, 27 patients were recorded with ECOG 1 in the first evaluation equivalent to 77%, 7 patients with ECOG 0 (20%) and only 1 patient was recorded with ECOG 2. In this study 34 patients (97%) presented with a locally advanced clinical stage compared to 1 patient (3%) who presented with a localized clinical stage. The most frequent grade of histological differentiation was moderately differentiated in 94% of patients, followed by well differentiated in the remaining 6%. Regarding the 36 patients (50.7%) considered responders, the ECOG scale were 0 in 20 patients, the remaining 16 patients had an ECOG of 1. In this group, 35 patients (97%) presented with a locally advanced clinical stage compared to 1 patient (3%) who is recorded with a localized clinical stage. The most frequent grade of histological differentiation was moderately differentiated in 94% of patients, followed by well differentiated in the remaining 6%.

Table 1. *Patient characteristics.*

Characteristics	No. of patients (%)	
	Chemoradioresistance	Chemoradiosensitive
Total, n (%)	35 (49)	36 (51)
Age (years), median [range]	63 [34-85]	62 [36-87]
Sex, n (%)		
Male	25 (71)	19 (53)
Female	10 (29)	17 (47)
Pretreatment ECOG performance status, n (%)		
0	7 (20)	20 (56)
1	27 (77)	16 (44)
2	1 (3)	0
Pretreatment CEA (ng/mL, median [range])		
	136 [122-396]	27 [4-51]
Pretreatment Hb (g/dL, median [range])		
	12 [11-12.8]	13 [12-14]
Pretreatment BMI (kg/m^2, median [range])		
	26 [24-29]	25 [24-27]
Stage, n (%)		
Localized	1 (3)	1 (3)
Locally Advanced	34 (97)	35 (97)
Histological Grade, n (%)		
Well differentiated	2 (6)	2 (6)
Moderately differentiated	33 (94)	34 (94)

*ECOG, the Eastern Cooperative Oncology Group; CEA, carcinoembryonic antigen; Hb, Hemoglobin; BMI, body mass index.

3.2. Treatment and Postoperative Pathological Features

All patients received 5-fluorouracil-based chemotherapy, CapeOx (capecitabine + oxaliplatin), orally or via intravenous infusion with concurrent radiotherapy to pelvis, followed by surgery and posterior adjuvant chemotherapy. The median dose of RT was 50 Gy. Of the 71 patients in the study, we obtained a total of 34 complete pathological responses (pCR) (48%) and 37 partial pathological responses (52%). In the Chemoradiosensitive patients, 34 patients obtained a complete pathological response (95%), and 2 patients had partial pathological response. As for the 35 chemoradioresistant patients, they only achieved a partial pathological response (Table 2).

Table 2. *Treatment and Postoperative pathological features.*

Characteristics	No. of patients (%)	
	Chemoradioresistance	Chemoradiosensitive
Radiotherapy dose, n (%)		

Characteristics	No. of patients (%)	
	Chemoradioresistance	Chemoradiosensitive
50 Gy	23 (68)	20 (56)
45 Gy	6 (18)	6 (16)
50.4 Gy	4 (12)	10 (28)
54 Gy	1 (2)	0
The neoadjuvant–surgery interval (day, median)	110	105
Types of surgical procedures, n (%)		
Low anterior resection	26 (74)	20 (56)
Abdominoperineal resection	9 (26)	16 (44)
Pathological response, n (%)		
Complete response	0	34 (95)
Partial response	35 (100)	2 (5)

3.3. Characteristic Parameters with Tumor Response

Univariate analysis showed significant associations between good tumor response and the preoperative pretreatment levels of CEA >5 ng/mL (OR=1.81, p=0.026) and the ECOG scale (OR=2.51, p=0.015). After a follow-up of 52 months, the median overall and recurrence-free survival was not reached in both groups and a statistically significant difference was not observed.

4. Discussion

To the best of our knowledge, this is the largest study to date on predictive and prognostic factors of response to preoperative chemoradiation in patients with rectal cancer in the region. Results show that the CEA value >5 ng/mL prior to the neoadjuvant treatment was significantly correlated with a lower rate of pCR. Likewise, the ECOG scale was a risk factor related to chemoradioresistance, the lower the ECOG, the lower the risk of chemoradioresistance.

The CEA marker is the most widely available and the most used in the management of colorectal cancer. Probst et al [7] examined 18,113 patients with locally advanced rectal cancer (LARC) selected from the National Cancer Database from 2006-2011, 47% had elevated CEA before treatment, which was significantly associated with a decrease in pCR (OR=0.65, $p < 0.001$), pathological regression of the tumor (OR=0.74, $p < 0.001$) and downstaging (OR=0.77, $p < 0.001$). A CEA level ≤5 ng/mL was a significant predictor of size reduction (OR=16.0, p=0.014) and was significantly associated with size reduction (>60%, p=0.012) in the study results by Yeo [8].

A recently published study on the prognostic importance of preoperative hematological parameters in patients with non-metastatic rectal cancer undergoing neoadjuvant chemoradiotherapy and radical surgery included 96 patients. Univariate analysis showed significant associations between poor overall survival and preoperative Hb level (≤11.2 g/dL vs. > 11.2 g/dL, P=0.030) [9]. In our study we found a trend towards significance between the Hb level < 9 g/dL and the development of chemoradioresistance (p=0.06).

Research on the best interval between the end of radiation and surgery began to appear as early as the 1990s, the most famous of which was the Lyon R90-01 randomized trial [10]. It was generally accepted that the interval should be extended to 6-8 weeks because the long interval group showed a better pathological response. Another phase II clinical trial to investigate interval extension and administration of additional mFOLFOX-6 during the waiting period found that the 11-week group showed a modest increase in pCR rate without increased complications [11]. When the median time interval reached 19.3 weeks, the pCR rate reached 38% [12]. However, the tumor response did not seem to obviously improve as the time interval increased in blinded fashion. Rombouts et al. [13] retrieved 1073 LARC patients from the population-based Netherlands Cancer Registry between 2006 and 2011, and the highest proportion of patients with stage ypT0-1N0 was 26.6% when the treatment interval ranged from 11 and 12 weeks. Slothaak et al. [14] also observed that the proportion of stage ypT0-1N0 reached a maximum of 23.2% with intervals of 10 to 11 weeks, followed by a decreasing trend, similar to this study cohort.

Previously, a multicenter study conducted in Italy indicated that radiation dose intensification (range 52.5–57.5 Gy) ap-

peared feasible, safe, and effective in terms of pathological response [15]. Of which the people who underwent local excision, one month later, reported no postoperative complications. More recently, a prospective observational study mentioned that radiation dose intensification, administered 60 Gy in 30 fractions, showed a better pathological response with acceptable toxicity related to neoadjuvant chemoradiotherapy in T3 tumors [16]. A longer follow-up period is warranted. Some potential factors may provide a higher probability for the choice of local excision in LARC and deserve further investigation.

In rectal cancer in stages II and III, management is based on chemoradiotherapy, currently knowing the importance and understanding the predictive factors involved in follow-up and treatment has great implications in predicting the results.

Among the limitations of the study, the data were derived from a single institution, with a low number of patients. It is necessary to perform prospective studies with a larger volume of patients to corroborate our findings.

5. Conclusions

Significant interaction were identified between CEA levels prior to the start of neoadjuvant treatment with the pathological complete response rate and the ECOG score with chemoradioresistance. Therefore, these factors can be used to predict patient outcomes, will help optimize personalized treatment strategies and improve patient outcomes.

Abbreviations

LARC: Locally Advanced Rectal Cancer
pCR: pathological Complete Response
CEA, carcinoembryonic antigen
BMI: Body Mass Index
ECOG: Eastern Cooperative Oncology Group
nCRT: neoadjuvant chemotherapy and radiotherapy
Hb: Hemoglobin

Conflicts of Interest

The authors declare no conflicts of interest.

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