Oncological outcomes in extended time intervals between preoperative chemoradiotherapy with capecitabine and surgery in operable rectal adenocarcinoma

Resultados oncológicos en intervalos extendidos de tiempo entre quimioradioterapia preoperatoria con capecitabina y cirugía en adenocarcinoma rectal operable

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ABSTRACT

Objective: To assess whether extended time intervals (8-12, 13-20 and >20 weeks) between the end of neoadjuvant chemoradiotherapy and surgery affect overall survival, disease-free survival. **Materials and methods:** Retrospective study in 120 patients with rectal adenocarcinoma without evidence of metastasis (T1-4/N0-2/M0) at the time of diagnosis that underwent surgery with curative intent after neoadjuvant chemoradiotherapy with capecitabine and obtained R0 or R1 resection between January 2010 to December 2014 at the National Cancer Institute of Peru. Dates were evaluated by Kaplan-Meier method, log-rank test and Cox regression analysis. **Results:** Of the 120 patients, 70 were women (58%). The median age was 63(26-85) years. All received neoadjuvant chemoradiotherapy. No significant difference was found between the association of the median radial (0.6, 0.7 and 0.8 cm; p=0.826) and distal edge (3.0, 3.5 and 4.0 cm; p=0.606) with time interval groups and similarly the mean resected (18.8, 19.1 and 16.0; p=0.239) and infiltrated nodules (1.05, 1.29 and 0.41); p=0.585). The median follow-up time of overall survival and desease free survival was 40 and 37 months, respectively. No significant differences were observed in overall survival (79.0%, 74.6% and 71.1%; p=0.66) and disease-free survival (73.7%, 68.1% and 73.6%; p=0.922) according to the three groups studied at the 3-year of follow-up. **Conclusions:** We found that widening the time intervals between the end of neoadjuvant chemoradiotherapy and surgery at 24 weeks does not affect the overall survival, disease-free survival and pathological outcomes. It allows to extend the intervals of time for future studies that finally will define the best time interval for the surgery.
Keywords: *Neoadjuvant treatment; Chemoradiotherapy; Rectal cancer; Time Intervals (source: MeSH NLM).*

RESUMEN

Objetivo: Evaluar si los intervalos de tiempo extendidos (8-12, 13-20 y >20 semanas) entre el fin de la quimioradioterapia neoadyuvante y la cirugía afectan la sobrevida global, y la sobrevida libre de enfermedad. **Material y métodos:** Estudio retrospectivo de 120 pacientes con adenocarcinoma rectal sin evidencia de metástasis (T1-4/N0-2/M0) al momento del diagnóstico que se sometieron a cirugía con intención curativa luego de quimioradioterapia neoadyuvante con capecitabina y tuvieron resección R0 o R1 entre enero 2010 y diciembre 2014 en el Instituto Nacioanal de Enfermedades Neoplásicas de Perú. El análisis se hizo con el método de Kaplan-Meier, la prueba log-rank y la regresión de Cox. **Resultados:** De 120 pacientes, 70 fueron mujeres (58%). La mediana de la edad fue 63 años (26-85 años). Todos recibieron quimioradioterapia neoadyuvante. No hubo diferencia significativa entre la asociación de las medianas de los bordes radial (0,6, 0.7 y 0,8 cm; p=0,826) y distal (3,0, 3,5 y 4,0 cm; p=0,606) con los intervalos de tiempo de los grupos y similarmente con la media de los ganglios resecados (18,8, 19,1 y 16,0; p=0,239) e infiltrados (1,05, 1,29 y 0,41; p=0,585). No se observaron diferencias significativas en sobrevida global (79,0%, 74,6% y 71,1%; p=0,66) y sobrevida libre de enfermedad (73,7%, 68,1% y 73,6%; p=0,922), en los tres grupos estudiados a 3 años de seguimiento. **Conclusiones:** Encontramos que aumentar los intervalos de tiempo entre el fin de la quimioradioterapia neoadyuvante y la cirugía hasta 24 semanas no afecta la sobrevida global, sobrevida libre de enfermedad ni los desenlaces patológicos. Esto permitiría extender los intervalos de tiempo en estudios futuros para definir el mejor intervalo de tiempo para la cirugía.
Palabras clave: *Tratamiento neoadyuvante; Quimioradioterapia; Cáncer del recto (fuente: DeCS BIREME).*

INTRODUCTION

In the world, colorectal cancer ranks third in frequency in men (746,000 cases, 10.0% of the total) and the second in women (614,000 cases, 9.2% of the total) [(1)]. In Peru, it is the fourth most frequent in men (standardized rate for the age of 10.2 per. 100000) representing 7.2% of all the cancers (1318 cases). In women it is also the fourth in frequency (ASR 11.9 per 100,000) representing 7.1% of all cancers (1735

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cases) [2]. In the 2010-2012 period, 1046 new cases of rectum cancer were diagnosed among residents of Metropolitan Lima, with an age-standardized incidence rate of 3.8 cases per 100,000 inhabitants [3].

Korean group determined that the optimal period of time to perform surgery with curative intention in patients with response to neoadyuvant neoadjuvant chemoradiotherapy (CRT) is between 7 to 10 weeks (4). Probst, concluded that performing the surgery after 8 weeks increased the possibility of pathologic complete response (pCR) without association with the increase of surgical complications compared to the interval 6 - 8 weeks [5]. Rombouts, reports that there is no difference in the rate of pCR obtained in patients with early tumor stages evaluated at intervals ranging from 5-14 weeks, but in patients with locally advanced disease the interval of 9-12 weeks between neoadyuvant CRT and surgery improves pCR rate with no effect on overall survival [6]. Petrelli, reports in a meta-analysis that the pCR rate increases by 6%, if the surgery is performed in a greater interval of 6-8 weeks, with similar results and rate of complications [7]. Maas M. reports that patients with pCR have better oncologic outcomes than those who do not [8]. There are few studies evaluating cancer outcomes after 14 weeks and the closest reported by Habr-Gamma determined that delaying surgical resection after neoadjuvant CRT for the distal rectum did not increase the risk of relapse of the disease or affect survival but this study does not consider patients with clinical complete response (cCR) [9].

Pathologic complete response (pCR) is defined as the complete absence of intact tumor cells in the resected specimen of patients with neoadjuvant CRT [10].

The primary objective of this study was to assess whether extended time intervals (8-12, 13-20 and >20 weeks) between neoadjuvant CRT and surgery affect overall survival (OS) and disease-free survival (DFS). The secondary objective is to assess the same association with clinicopathological variables.

MATERIALS AND METHODS

Ethics statement

This study was approved by the Institutional Committee on Ethics and Research of Instituto Nacional de Enfermedades Neoplasicas (INEN) (Protocol Number #INEN17-07).

Data source

Medical records of patients with rectal cancer who were operated in the Department of Abdominal Surgery at the INEN between January 2010 to December 2014.

Patient population

Between January 2010 to December 2014, a total of 336 patients with rectal cancer underwent surgery with curative intent in the Department of Abdominal Surgery at the INEN. From this initial cohort, we selected a series of 120 patients with rectal adenocarcinoma without evidence of metastasis (T1-4/N0-2/M0) according to the American Joint Committee on Cancer Staging (AJCC) manual seventh edition, at the time of diagnosis; Who underwent surgery with curative intent after neoadjuvant CRT with capecitabine and obtained R0 or R1 resection. Patients undergoing emergency surgery, patients with R2 surgery, different histology of adenocarcinoma, neoadjuvant CRT with intravenous 5-FU, neoadjuvant CRT in other institution, incomplite treatment with capecitabine and underwent surgery before 8 weeks have been excluded. We got 6 patients with R2 resection and 4 who underwent surgery before 8 weeks. Patients were categorized into 3 groups based on time intervals (8-12, 13-20 and >20 weeks) between the end of neoadjuvant CRT and the day of surgery. The only reason for delay in surgery was hospital bed availability. Demographic, clinical and pathological data were collected on a collection sheet.

Study variables

Time interval between the end of neoadjuvant CRT and surgery was the variable of interest, which included 8-12,13-20 and >20 weeks. The first interval was chosen to compare with previous studies and the others by author's choice because these intervals were not evaluated in previous studies.

Other variables used in this study included overall survival, disease-free survival, demographic variables, tumor clinical and pathological characteristics. Demographic variables included age and sex. Tumor clinical characteristics included pretreatment carcinoembryonic antigen (CEA) level, clinical T, clinical N, clinical stage, location by colonoscopy and distance from the tumor to anal verge. Tumor pathological characteristics included, histological type, tumor pathological response, pathological T, pathological N, pathological stage, proximal, radial and distal edge, histological grade, limphovascular invasion, perineural invasion, type of resection, preservation sphincter rate, compromised and resected nodes.

Tumor clinical and pathological stage was determined according to the American Joint Committee on Cancer staging manual seventh edition. The primary objectives of the study were to assess whether extended time intervals (8-12, 13-20 and >20 weeks) between neoadjuvant CRT and surgery improve OS and DFS.

Evaluation

For diagnosis and clinical workup, history taking and digital rectal examination were done and complete blood counts, blood chemistry for liver and kidney functions, and CEA level were checked. Imaging studies included abdomen and pelvis computed tomography (CT), chest radiography and colonoscopy with biopsy in all cases, only in some cases include pelvic MRI and chest CT. All patients had a performance status of one according to the WHO, prior to treatment.

Neoadjuvant CRT

These regimens consisted of radiotherapy (RT) concomitant with chemotherapy (QT); which in all cases was capecitabine at doses of 825 mg/m^2 orally 5 or 7 days per week (twice per day) during RT. The radiotherapy technique was external RT in pelvic fields, with a 4-field box technique at 45 Gy doses in 25 sessions, with 180 cGy / day + boost 540 (total dose 5,040 cGy), five days a week, for five weeks concurrent to QT. In some cases, the doses of RT were individualized. Seven neoadjuvant regimens were applied, the most frequent being 5040 cGy/28 sessions + QT in 94 patients (78.3%), and the other were 6,600 cGy/36, 5,400 cGy/30, 5,000 cGy/25, 6,000 cGy/32, 4,500 cGy/25 and 3,900 cGy/13 sessions in 1 (0.8%), 8 (6.7%), 3 (2.5%), 1 (0.8%), 12 (10.0%) and 1 (0.8%), respectively.

Surgery

All patients underwent pelvic examination under anesthesia on the day of surgery and some of them prior to surgery. The procedures included abdominoperineal resection (APR), low anterior resection (LAR), ultra-low anterior resection (ULAR), local resection (LR), pelvic exenteration (PE) and Hartmann´s procedure (HP) in 49.2% (n=59), 29.2% (n=35), 16.7% (n=20), 2.5% (n=3), 0,8% (n=1) and 1.7% (n=2) respectively. All patients received total mesorectal excision, except LR. Conventional open surgery were performed in 106 patients (88.3%), laparoscopic approach in 11 (9.1%) and transanal resection in 3 (2.5%). The mean interval time between neoadjuvant CRT and surgery was 17.86 weeks (range, 8-160). Patients with pathological stage III (pTx/N1–2/M0) were referred to a medical oncologist for adjuvant therapy. Adjuvant chemotherapy was required in 34 patients (28.3%) after surgery.

Patients' follow-up

The patients underwent a regular checkup every 3-4 month during the first 2 years after leaving the hospital, then every 6 months during the third and fourth year and finally every twelve months after the fifth year. The controls include rectal examination, CEA serum level, abdominal ultrasound and chest radiographs. Control colonoscopy and additional imaging exams to rule out distant metastasis were done by the clinician's decision. All patients who do not attend to their scheduled follow-up are considered lost. Patients were followed until December 2016, the date on which the number of deceased patients in our sample was determined, checking the data with those of the National Registry of Identification and Civil Status (RENIEC). So, in the end we had 36 dead, 82 alive and 2 lost control.

Statistical analysis

Continuous variables were represented by means, medians and range, and categorical variables with frequencies and percentages. The analysis between the variable of interest with continuous variables, were developed using the ANOVA or Kruskal Wallis test; And Chi-square test to associate with categorical variables, as well as categories of these variables were grouped in the case that was considered necessary. Kaplan-Meier method, log-rank test and Cox Regression Analysis were used to determine the relationship between possible significant risk factor for overall survival (OS) and disease-free survival (DFS). Multivariate data analysis includes only the factors identified as significant in univariate analysis and the variable of interest was include in both analysis. OS was defined as the period between surgery to death, DFS was defined as the time between surgery to recurrence and patients who did not die or who did not recur were censored. OS was calculated using the number of deaths prior to December 31, 2016. Differences were considered significant if $p<0.05$. The data were evaluated using SPSS v. 22 [11,12].

Pathology report

Pathologic specimens were evaluated using the standardized protocol of colon-rectum of the pathology department of INEN, based on protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum of the College of American Pathologists and this instrument is used since the last months of 2012 that is the reason why we could not get the tumor pathological response grade of 36 patients (29.0%), but we are sure that they did not get pCR because pathologic report confirm adenocarcinoma. Pathological complete response (pCR) is the same as tumor pathological response grade 0 in our study.

RESULTS

The mean pretreatment CEA level was 15.3 ng/ml (range 0.32-308.8). The most frequent clinical stage was cT4 (58.3%), cN0 (55%) and IIIB (35%). Fifty-one percent were localized in low rectum and the mean distance from the tumor to anal verge was 2.3 cm (range 0-5 cm) (Table 1).

Table 1. Shows the distributions of demographic variables and clinical tumor characteristics by time intervals between neoadjuvant CRT and surgery in patients with rectal cancer.

	Total (n=120, 100.0%)	8 - 12 weeks (n=39, 32.5%)	13 - 20 weeks (n=52, 43.3%)	>20 weeks (n=29, 24.2%)	*p*
Time, weeks					
Mean / Median / Range	17.86 / 14.5 / [8-160]	10.33 / 11 / [8-12]	15.65 / 15 / [13-20]	31.93 / 24 / [21-160]	-
Age, years					
Mean / Median / Range	59.37 / 63 / [26-85]	63.23 / 65 / [36-82]	55.33 / 56.5 / [26-85]	61.41 / 63 / [27-84]	**0.019**
Sex					
Female	70 (58.3)	22 (56.4)	32 (61.5)	16 (55.2)	
Male	50 (41.7)	17 (43.6)	20 (38.5)	13 (44.8)	0.819
Pretreatment CEA level, ng/ml (n=110)					
Mean / Median / Range	15.324 / 4.29 / [0.32-308.8]	11.16 / 3.38 / [0.6-85.43]	22.72 / 4.36 / [0.32-308.8]	8.0 / 4.6 / [0.5-42.1]	0.536
Clinical T					
cT1	2 (1.7)	1 (2.6)	1 (1.9)	-	
cT2	11 (9.2)	5 (12.8)	4 (7.7)	2 (6.9)	
cT3	36 (30.0)	10 (25.6)	19 (36.5)	7 (24.1)	
cT4	70 (58.3)	23 (59.0)	28 (53.8)	19 (65.5)	NE
TX	1 (0.8)	-	-	1 (3.4)	
Clinical N (groups)					
cN0	66 (55.0)	22 (56.4)	26 (50.0)	18 (62.1)	
cN1-cN2	54 (45.0)	17 (43.6)	26 (50.0)	11 (37.9)	0.565
Clinical N					
cN0	66 (55.0)	22 (56.4)	26 (50.0)	18 (62.1)	
cN1	52 (43.3)	17 (43.6)	25 (48.1)	10 (34.5)	
cN2	2 (1.7)		1 (1.9)	1 (3.4)	NE
Clinical stage (groups)					
cI-cII	65 (54.2)	22 (56.4)	26 (50.0)	17 (58.6)	
cIII	54 (45.0)	17 (43.6)	26 (50.0)	11 (37.9)	
None*	1 (0.8)	-	-	-	0.632
Clinical stage					
cI	8 (6.7)	4 (10.3)	2 (3.8)	2 (6.9)	
cII	57 (47.5)	18 (46.2)	24 (46.2)	15 (51.7)	
cIII	54 (45.0)	17 (43.6)	26 (50.0)	11 (37.9)	NE
None*	1 (0.8)	-	-	1 (3.4)	
Clinical stage					
cI	8 (6.7)	4 (10.3)	2 (3.8)	2 (6.9)	
cIIA	26 (21.7)	7 (17.9)	13 (25.0)	6 (20.7)	
cIIB	30 (25.0)	11 (28.2)	11 (21.2)	8 (27.6)	
cIIC	1 (0.8)	-	-	1 (3.4)	
cIIIA	5 (4.2)	2 (5.1)	3 (5.8)	-	
cIIIB	42 (35.0)	14 (35.9)	21 (40.4)	7 (24.1)	
cIIIC	7 (5.8)	1 (2.6)	2 (3.8)	4 (13.8)	NE
None*	1 (0.8)	-	-	1 (3.4)	
Location by colonoscopy					
Upper rectum	7 (5.8)	1 (2.6)	4 (7.7)	2 (6.9)	
Middle rectum	52 (43.3)	24 (61.5)	21 (40.4)	7 (24.1)	
Low rectum	61 (50.8)	14 (35.9)	27 (51.9)	20 (69.0)	NE
Distance from the tumor to anal verge, cm					
Upper rectum	13.86 / 12 / [11-20]	12	13.5 / 12 / [12-18]	15.5 / 15.5 / [11-20]	NE
Middle rectum	7.769 / 7 / [5-10]	7.46 / 7 / [5-10]	8 / 8 / [6-10]	8.14 / 8 / [6-10]	0.361
Low rectum	2.295 / 3 / [0-5]	2.79 / 3 / [0-5]	2.33 / 3 / [0-5]	1.9 / 2 / [0-5]	0.292

CEA: carcinoembryonic antigen, * One case TXN0, NE: No evaluable

There is significant difference between the mean ages of the three groups (63; 55 and 61 years; $p=0.019$). The association between clinical T, tumor location by colonoscopy and the mean distance from the upper rectum tumor to anal verge in the three time intervals groups could not be assessed because sample size was small for this stratified analyses. The median time interval between neoadjuvant CRT and surgery in the three groups (8-12, 13-20 and >20 weeks) was 11, 15 and 24 weeks respectively (Table 1).

There is not significant difference between pathological variables on the three intervals groups. The association between tumor pathological response, pathological T, histological type and grade, perineural invasion, residual tumor and pCR status with time intervals groups could not be assessed because sample size were small for this stratified analyses (Table 2).

The pCR rate in all patients were 10.8% (n=13) and the incidence was 10.3% (n=4), 7.7% (n=4) and 17.2% (n=5) in time interval groups (8-12, 13-20 and >20 weeks) respectively. The most frequent pathological stage was pT3 (40.8%), pN0 (69.2%) and III (30.8%). The predominant histological type was adenocarcinoma sp (24.2%). The average radial and distal edge was 0.87 cm (range 0.05-3 cm) and 3.62 cm (range 0.2-9.5 cm) respectively. High histological grade, lymphovascular invasion and perineural invasion was found in 5.8% (n=7), 22.5% (n=27) and 11.7% (n=14) respectively. Only 6.7% (n=8) has R1 resection. The average resected and infiltrated lymph nodes was 18.3 (range 0-85) and 1.0 (range 0-30) respectively (Table 2).

The clinical N ($p=0.049$), pathological N ($p=0.002$), pathological stage by groups ($p=003$), distal edge ($p=0.002$), lymphovascular invasion ($p=0.041$), distal edge ($p=0.019$) and infiltrated nodes ($p=0.003$) were the variables significantly associated with overall survival (Table 3).

Clinical N by groups ($p=0.027$), clinical stage by groups ($p=0.031$), tumor pathological response ($p=0.036$), tumor pathological response by groups ($p=0.014$), pathological T ($p<0.05$), pathological N ($p<0.05$), pathological stage by groups ($p<0.05$), lymphovascular invasion ($p<0.05$), perineural invasion ($p=0.014$), infiltrated nodes ($p<0.05$) and pathologic complete response ($p=0.025$) were the variables significantly associated with disease-free survival (Table 3).

There is not significant difference ($p=0.66$) in overall survival between the three groups of time intervals between neoadjuvant CRT and surgery at 3-year of follow-up (Table 3). The median OS follow-up time was 40 months and no significant differences were observed according to the three groups studied at the 5-year of follow-up (Figure 1).

There is not significant difference ($p=0.922$) in disease-free survival in patients with R0 between the three groups of time intervals between neoadjuvant CRT and surgery at 3-year of follow-up (Table 3). The median DFS follow-up time was 37 months no significant differences were observed according to the three groups studied at 5-year of follow-up. (Figure 2).

In the univariate analysis, variables associated with a higher likelihood of overall survival were lower pathological N ($p=0.039$), lower pathological stage by groups ($p=0.008$), distal edge ≥3.5 cm ($p=0.024$), without lymphovascular invasion ($p=0.046$) and without infiltrated nodes ($p=0.005$). On multivariable analysis, lower tumor pathological stage by groups ($p=0.009$) and distal edge ≥3.5 cm ($p=0.024$) remained significant prognostic factors of overall survival (Table 4).

In the univariate analysis, variables associated with a higher likelihood of disease-free survival were lower clinical N by groups ($p=0.031$), lower clinical stage by groups ($p=0.035$), lower pathological N ($p<0.05$), lower pathological stage by groups ($p=0.029$), without lymphovascular invasion ($p<0.05$), without perineural invasion ($p=0.021$) and without infiltrated nodes ($p<0.05$). On multivariable analysis, lower tumor pathological stage by groups ($p=0.037$) and without lymphovascular invasion ($p=0.013$) remained significant prognostic factors of disease-free survival (Table 5).

DISCUSSION

Our study examined whether long-term (8-12, 13-20 and >20 weeks) intervals between the end of neoadjuvant CRT and surgery affect overall survival (OS) and disease-free survival(DFS). Our results suggest that the OS and DFS are not affected by extending the time intervals. The univariate and multivariate analysis of the variable time interval shows that it is not a prognostic factor for OS and DFS. On multivariable analysis we determined that lower tumor pathological stage by groups and distal edge are independent prognostic factor of OS and tumor pathological stage by groups and lymphovascular invasion are independent prognostic factor of DFS.

We found that the highest OS and DFS at 3 years of follow-up was 79% and 73.7%, respectively. Our findings have similar outcomes with the studies reported by Wang, reported a 3-year OS rate of 92% and a DFS of 76% [13]. Sauer, reported an OS at 5 years of 76% and DFS of 68% in the group with neoadyuvant CRT prior to surgery [14]. Krishnan, reported a 2 years OS and DFS rate of 98% and 76% respectively [15]. Chan, reported a 3-year OS rate of 86% with a median follow-up time of 2.3 years in the group receiving RT and capecitabine [16].

Table 2. Shows the distributions of pathological characteristics by time intervals between neoadjuvant CRT and surgery in patients with rectal cancer.

	Total (n=120, 100.0%)	8 - 12 weeks (n=39, 32.5%)	13 - 20 weeks (n=52, 43.3%)	>20 weeks (n=29, 24.2%)	*p*
Time, weeks					
Mean / Median / Range	17.86 / 14.5 / [8-160]	10.33 / 11 / [8-12]	15.65 / 15 / [13-20]	31.93 / 24 / [21-160]	-
Tumor pathological response					
Grade 0	13 (10.8)	4 (10.3)	4 (7.7)	5 (17.2)	
Grade 1	14 (11.7)	6 (15.4)	5 (9.6)	3 (10.3)	
Grade 2	28 (23.3)	4 (10.3)	15 (28.8)	9 (31.0)	
Grade 3	29 (24.2)	6 (15.4)	15 (28.8)	8 (27.6)	
None*	36 (30.0)	19 (48.7)	13 (25.0)	4 (13.8)	
Tumor pathological response (Groups)					
Grade 0	13 (10.8)	4 (10.3)	4 (7.7)	5 (17.2)	
Grade 1/2/3	71 (59.2)	16 (41.0)	35 (67.3)	20 (69.0)	
None*	36 (30.0)	19 (48.7)	13 (25.0)	4 (13.8)	
Pathological T (pT)					
pT0	14 (11.7)	4 (10.3)	5 (9.6)	5 (17.2)	
pT1	7 (5.8)	2 (5.1)	4 (7.7)	1 (3.4)	
pT2	41 (34.2)	18 (46.2)	15 (28.8)	8 (27.6)	
pT3	49 (40.8)	12 (30.8)	24 (46.2)	13 (44.8)	
pT4	8 (6.7)	2 (5.1)	4 (7.7)	2 (6.9)	
TX	1 (0.8)	1 (2.6)	-		
Pathological N (pN)					
pN0	83 (69.2)	25 (64.1)	35 (67.3)	23 (79.3)	
pN1	(20.8)	10 (25.6)	11 (21.2)	4 (13.8)	
pN2	12 (10.0)	4 (10.3)	6 (11.5)	2 (6.9)	
Pathological N (Groups)					
pN0	83 (69.2)	25 (64.1)	35 (67.3)	23 (79.3)	0.377
pN1/pN2	37 (30.8)	14 (35.9)	17 (32.7)	6 (20.7)	
Pathological stage					
pI	37 (30.8)	15 (38.5)	17 (32.7)	5 (17.2)	
pIIA	28 (23.3)	5 (12.8)	13 (25.0)	10 (34.5)	
pIIB	1 (0.8)	-	-	1 (3.4)	
pIIC	3 (2.5)	1 (2.6)	1 (1.9)	1 (3.4)	
pIIIA	9 (7.5)	4 (10.3)	2 (3.8)	3 (10.3)	
pIIIB	20 (16.7)	8 (20.5)	8 (15.4)	4 (13.8)	
pIIIC	8 (6.7)	2 (5.1)	6 (11.5)	-	NE
None[a]	14 (11.7)	4 (10.3)	5 (9.6)	5 (17.2)	
Pathological stage (groups)					
pI	37 (30.8)	15 (38.5)	17 (32.7)	5 (17.2)	
pII	32 (26.7)	6 (15.4)	14 (26.9)	12 (41.4)	
pIII	37 (30.8)	14 (35.9)	16 (30.8)	7 (24.1)	0.107
None[a]	14 (11.7)	4 (10.3)	5 (9.6)	5 (17.2)	
Histology					
Adenocarcinoma sp	29 (24.2)	17 (43.6)	10 (19.2)	2 (6,9)	
Signet ring cell carcinoma	1 (0,8)	-	-	1 (3,4)	
Mucinous adenocarcinoma	21(17,5)	5 (12,8)	12 (23,1)	4 (13,8)	
Adenocarcinoma NOS	25 (20,8)	1 (2,6)	15 (28,8)	9(31,0)	
Tubular adenocarcinoma	25 (20,8)	11 (28,2)	8 (15,4)	6 (20,7)	
Tubular adenocarcinoma with mucinous-like areas	3 (2,5)	1 (2,6)	1 (1,9)	1 (3,4)	
Adenocarcinoma sp with mucinous component	2 (1,7)	-	1 (1.9)	1 (3,4)	
None[a]	14 (11,7)	4 (10.3)	5 (9,6)	5 (17,2)	NE
Proximal edge, cm (n=110)					
Mean / Median / Range	25.62 / 24.95 / [5-56]	26.91 / 25.25 / [5-56]	23.85 / 23.5 / [5-43]	27.22 / 27 / [13.5-45]	0.248

(Next)

Table 2. Shows the distributions of pathological characteristics by time intervals between neoadjuvant CRT and surgery in patients with rectal cancer *(continuation)*.

	Total (n=120, 100.0%)	8 - 12 weeks (n=39, 32.5%)	13 - 20 weeks (n=52, 43.3%)	>20 weeks (n=29, 24.2%)	*p*
Distal edge, cm (n=109)					
Mean / Median / Range	3.629 / 3.5 / [0.2-9.5]	3.44 / 3.0 / [0.5-8.5]	3.59 / 3.5 / [0.2-9.5]	3.98 / 4 / [0.5-9]	0.606
Radial edge, cm (n=79)					
Mean / Median / Range	0.8715 / 0.7 / [0.05-3]	0.81 / 0.6 / [0.05-3]	0.92 / 0.7 / [0.1-2.5]	0.83 / 0.8 / [0.1-2.5]	0.826
Histological grade					
Low	56 (46.7)	13 (33.3)	28 (53.8)	15 (51.7)	
High	7 (5.8)	4 (10.3)	2 (3.8)	1 (3.4)	NE
None*	57 (47.5)	22 (56.4)	22 (42.3)	13 (44.8)	
Lymphovascular invasion					
Yes	27 (22.5)	9 (23.1)	13 (25.0)	5 (17.2)	
No	81 (67.5)	26 (66.7)	35 (67.3)	20 (69.0)	0.797
None*	12 (10.0)	4 (10.3)	4 (7.7)	4 (13.8)	
Perineural invasion					
Yes	27 (22.5)	9 (23.1)	8 (15.4)	5 (17.2)	
No	81 (67.5)	26 (66.7)	16 (30.8)	13 (44.8)	NE
None*	12 (10.0)	4 (10.3)	28 (53.8)	11 (37.9)	
Residual tumor					
R0	112 (93.3)	38 (97.4)	50 (96.2)	24 (82.8)	
R1	8 (6.7)	1 (2.6)	2 (3.8)	5 (17.2)	NE
Resected lymph nodes (n=117)					
Mean / Median / Range	18.33 / 13 / [0-85]	18.85 / 14 / [1-67]	19.16 / 15 / [4-85]	16.04 / 11 / [0-69]	0.239
Infiltrated nodes (n=118)					
Mean / Median / Range	1.008 / 0 / [0-30]	1.05 / 0 / [0-9]	1.29 / 0 / [0-30]	0.41 / 0 / [0-6]	0.585
Pathologic complete response (pCR)					
No	107 (89.2)	35 (89.7)	48 (92.3)	24 (82.8)	
Yes	13 (10.8)	4 (10.3)	4 (7.7)	5 (17.2)	NE

* No registered, [a] One case pT0N2a and fourteen cases got pCR, NE: No evaluable.

The pCR rate in studies in which capecitabine was used as concurrent chemotherapy varies from (10.5% - 27%) reported by De Paoli, Krishnan, kim, korkolib, Conde, kocakova and Wong [10,15,17-19]. The rate of pCR in all patients of our study is 10.8% that is into the range. The pCR rate in one of the largest studies was 13.5% reported by Hartley (10). Our study is the first study in which the pCR rate is reported at time intervals between [13-20 weeks] and [>20 weeks].

Other oncological outcomes analyzed were the association between radial and distal edge with time intervals, and no significant differences were found. The mean distal edge in our study was 3.62 cm [0.2-9.5 cm] and distal edge ≥3.5 cm (p=0.024) resulted an independent prognostic factor of overall survival in the multivariate analysis. The literature reports that distal margin of 2 cm is suitable for most rectal cancers. The mean radial edge in our study was 0.87 cm [0.05-3] and we know that radial edge of 1 mm have a high risk of distant metastases (37.6 vs 12.7%, p=0001) [20].

No significant differences were found in the association between resected and compromised nodes with time interval groups, but the observation of interest is that the mean of the resected and compromised nodes decreases if we extend the time interval until surgery. That point requires further investigation. The mean number of resected and compromised nodes in all our patients was 18.3 and 1.0 respectively. These findings are similar to those reported by Codina Cazador in 162 patients, with an average of resected and compromised nodes of 19.6±11.8 and 0.6±1.9 respectively [21]. Wichmann, reported in 42 patients, an average of 13.6 and 1.4 nodes, respectively [22]. The AJCC and UICC recommend at least 12 lymph nodes in the surgical specimen to confirm lymph node staging [23]. Our patients had a pathological lymph node involvement of 30.8% (37 of 120). Rivas reported 47.6% (10 of 21) [24]. Chan reported 44% (15 of 34) with concurrent RT + capecitabine [16]. Kim reports 38.7% (48 of 124) with concurrent RT + capecitabine [25].

Sauer reports in a randomized study in which patients requiring abdominoperineal resection at baseline after neoadjuvant CRT + surgery achieved a higher rate of sphincter preservation than those who did not receive CRT prior to surgery (39% vs. 19%, p=0.004) [14]. Our sphincter preservation rate in

Table 3. Shows the results of the influence of the clinicopathological variables on the overall survival (OS) in all patients (n=120) with rectal cancer; and disease-free survival (DFS) in patients with R0 (n=112) at 3-years of follow-up.

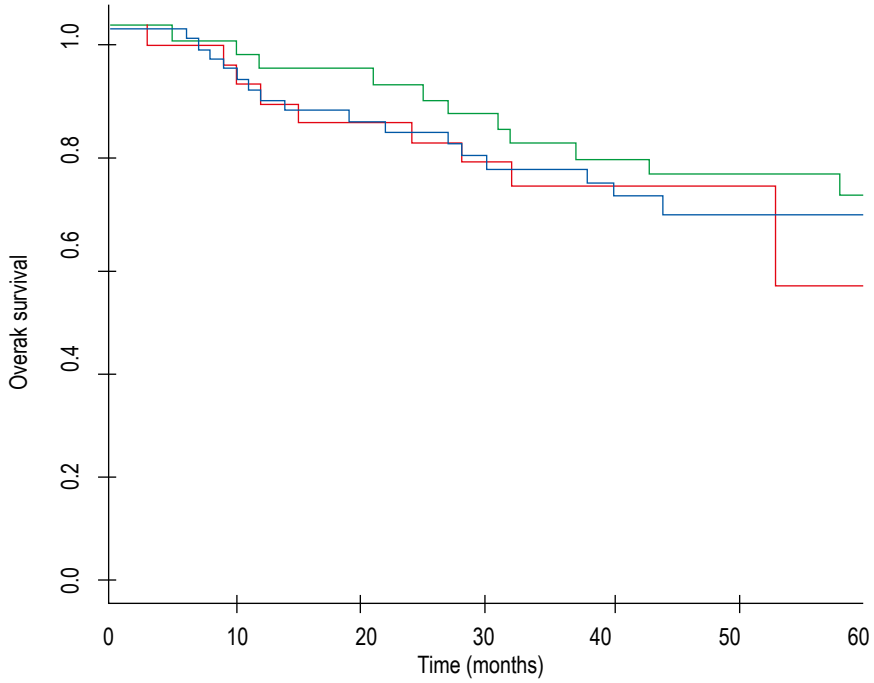
	Number of events	OS at 3-years	*p*	Number of events	DFS at 3-years	*p*
Age, years						
<60	15	71.8%		13	73,6%	
≥60	21	77.9%	0.952	18	69,4%	0.937
Sex						
Female	20	75.3%		17	73,7%	
Male	16	74.8%	0,84	14	67,6%	0.733
Pretreatment CEA level, ng/ml (n=110)						
<5	15	80.1%		15	73.7%	
≥5	16	71.8%	1,191	14	67.5%	0.404
Clinical T						
cT1	0	100.0%		0	100.0%	
cT2	2	90.0%		2	80.8%	
cT3	13	67.9%		12	61.6%	
cT4	21	75.4%	0,484	17	73.2%	0.486
Clinical T (groups)						
cN0	16	80.0%		13	78.9%	
cN1-cN2	20	69.8%	**0,049**	18	61.3%	**0.027**
Clinical N						
cN0	16	89.4%		13	78.9%	
cN1	20	75.0%		17	61.7%	
cN2	0	-	0,085	1	-	0,061
Clinical stage (groups)						
cI-cII	16	79.7%		13	78.6%	
cIII	20	69.8%	0.055	18	61.3%	**0.031**
Clinical stage						
cI	2	87.5%		2	75.0%	
cII	14	78.6%		11	79.1%	
cIII	20	69.8%	0.158	18	61.3%	0.096
Clinical stage						
cI	2	87.5%		2	75.0%	
cIIA	8	71.7%		8	66.4%	
cIIB	5	86.7%		3	89.5%	
cIIC	1	0.0%**		-	-	
cIIIA	0	100.0%		0	100.0%	
cIIIB	18	66.1%		16	56.8%	
cIIIC	2	-	0.082	2	-	0.031
Location by colonoscopy						
Upper rectum	2	71.4%		2	66.7%	
Middle rectum	16	73.5%		14	70.7%	
Low rectum	18	76.8%	0.988	15	72.2%	0,952
Tumor pathological response						
Grade 0	1	90.9%		0	100.0%	
Grade 1	5	71.4%		4	71.4%	
Grade 2	7	74.4%		7	70.9%	
Grade 3	12	63.4%	0.172	12	47.7%	**0.036**
Tumor pathological response (Groups)						
Grade 0	1	90.9%		0	100.0%	
Grade 1/2/3	24	69.6%	0,062	23	62.0%	**0.014**
Pathological T (pT)						
pT0	2	84.4%		0	100.0%	
pT1	1	85.7%		1	85.7%	
pT2	7	94.9%		6	85.4%	
pT3	21	57.0%		22	44.8%	
pT4	4	62.5%	**0.002**	1	85.7%	**<0.05**

(Next)

Table 3. Shows the results of the influence of the clinicopathological variables on the overall survival (OS) in all patients (n=120) with rectal cancer; and disease-free survival (DFS) in patients with R0 (n=112) at 3-years of follow-up *(continuation)*.

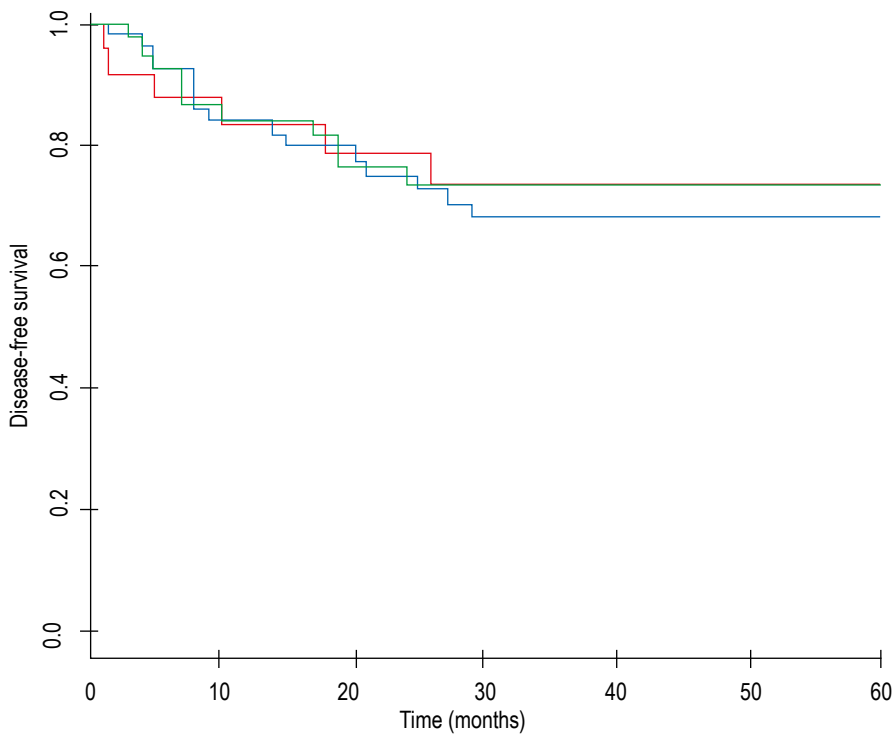
	Number of events	OS at 3-years	*p*	Number of events	DFS at 3-years	*p*
Pathological N (pN)						
pN0	18	81.2%		14	81.7%	
pN1	11	67.5%		12	49.1%	
pN2	7	48.6%	**0,002**	5	31.1%	**<0.05**
Pathological N (groups)						
pN0	18	81.2%		14	81.7%	
pN1/pN2	18	61.3%	**0,002**	17	45.2%	**<0.05**
Pathological stage						
pI	5	94.5%		4	89.2%	
pIIA	10	62.0%		9	61.8%	
pIIB	0	100.0%		0	100.0%	
pIIC	2	-		0	-	
pIIIA	2	88.9%		2	77.8%	
pIIIB	11	53.6%		15	16.7%	
pIIIC	4	62.5%	**0.003**	1	83.3%	**<0.05**
Pathological stage (groups)						
pI	5	94.5%		4	89.2%	
pII	12	60.2%		9	65.1%	
pIII	17	64.0%	0,003	18	43.3%	**<0.05**
Proximal edge, cm						
<24.95	16	77.7%		11	75.5%	
≥24.95	18	71.4%	0,619	19	60.5%	0.068
Distal edge, cm						
<3.5	10	86.1%		13	72.3%	
≥3.5	22	67.1%	**0.019**	15	67.4%	0.736
Radial edge, cm						
<0.7	11	76.5%		9	64.6%	
≥0.7	12	76.4%	0.827	11	73.3%	0.903
Histological grade						
Low	17	73.8%		15	69.3%	
High	3	57.1%	0.527	4	33.3%	0.126
Lymphovascular invasion						
Yes	12	62.1%		14	42.1%	
No	20	78.2%	**0.041**	12	83.2%	
Perineural invasion						
Yes	7	45.0%		7	38.9%	
No	9	68.2%	0.079	7	71.6%	**0.014**
Residual tumor						
R0	33	76.3%		-	-	
R1	3	-	0.271	-	-	-
Resected lymph nodes						
<13	18	73.4%		17	65.2%	
≥13	18	75.1%	0.586	14	72.4%	0.33
Infiltrated nodes(n=118)						
0	35	79.6%		16	79.9%	
>0	16	61.3%	**0.003**	15	41.8%	**<0.05**
pCR						
No	35	73.2%		31	67.4%	
Yes	1	90.9%	0.077	0	100.0%	**0.025**
Time intervals						
8 - 12 weeks	11	79.0%		10	73.7%	
13 - 20 weeks	16	74.6%		15	68.1%	
>20 weeks	9	71.1%	0.660	6	73.6%	0,922

CEA: carcinoembryonic antigen, pCR: pathologic complete response



Time intervals between neodjuvant CRT and surgery	12 months	36 months	60 months	p value
8-12 weeks	92,3%	79,0%	69,8%	
13-20 weeks	86,5%	74,6%	66,1%	
>20 weeks	86,2%	71,1%	53,3%	0,66%

Figure 1. Displays overall survival by time interval between neoadjuvant CRT and surgery in patients with rectal cancer.



Time intervals between neodjuvant CRT and surgery	12 months	36 months	60 months	p value
8-12 weeks	84,2%	73,7%	73,7%	
13-20 weeks	83,8%	68,1%	68,1%	
>20 weeks	83,1%	73,6%	73,6%	0,922%

Figure 2. Disease-free survival by time interval between neoadjuvant CRT and surgery in patient with rectal cancer.

Table 4. Shows the results of the Cox regression model for significant variables in the univariate and multivariate analysis of overall survival in patients with rectal cancer.

	Univariate			Multivariate		
	P	HR	CI 95%	P	HR	CI 95%
Clinical N (groups)						
cN0		1.000				
cN1-cN2	0.053	1.917	0.992-3.706			
Pathological T						
pT0		1.000				
pT1	0.893	0.848	0.077-9.364			
pT2	0.925	1.079	0.224-5.194			
pT3	0.059	4.054	0.948-17.335			
pT4	0.080	4.554	0.833-24.898			
Pathological N						
pN0		1.000				
pN1	0.039	2.204	1.039-4.672			
pN2	0.002	4.024	1.673-9.679			
Pathological stage (groups)						
pI	0.008	1.000			1.000	
pII	0.003	4.130	1.445-11.81	0.009	5.804	1.564-21.538
pIII		4.579	1.687-12.43	0.225	4.526	0.395-51.849
Distal edge, cm						
<3.5		1.000			1.000	
≥3.5	0.024	2.367	1.12-5.001	0.024	3.167	1.160-8.647
Lymphovascular invasion						
No		1.000			1.000	
Yes	0.046	2.071	1.012-4.24	0.595	1.293	0.501-3.341
Infiltrated nodes						
0		1.000			1.000	
>0	0.005	2.577	1.334-4.977	0.883	1.181	0.128-10.875
Time intervals						
8 - 12 weeks		1.000			1.000	
13 - 20 weeks	0.504	1.302	0.601-2.819	0.585	1.289	0.520-3.190
>20 weeks	0.415	1.448	0.594-3.530	0.928	1.055	0.332-3.352

patients with tumor located in the lower rectum by colonoscopy (≤5 cm of anal verge) was 29.5% (18 of 61 patients). Similar results were reported by De Bruin, reports a rate of 25% (8 of 32) of distal rectal tumors, where LAR was performed [26]. CHAN, reports a rate of 23% (6 of 26) after capecitabine + RT and 31% (16 of 52) after 5-FU, leucovorin, mitomycin + RT in tumors 7 cm from the anal margin [16]. Fernández-Martos reports a rate of 25% (11 of 43) in patients with tumors 2 cm from the anal margin that would initially be submitted to APR [27].

These findings have important clinical and logistic implications, especially in state institutes with a high degree of specialization and a large number of patients such as ours. The present study is the only one that reports these results in time intervals beyond 14 weeks and it allows to extend the intervals of time between the end of neoadjuvant CRT and surgery for future studies. These future studies would ultimately define the best time interval for surgery.

In conclusion, we found that amplifying the time intervals between the end of neoadjuvant chemoradiotherapy and surgery at 24 weeks does not affect the overall survival, disease-free survival and pathological outcomes. The present study is the only one that reports these results at these time intervals. Our pathologic and survival outcomes in these amplified intervals are within the range reported in the time intervals recommended by the world literature. It allows to extend the intervals of time for future studies that finally will define the best time interval for the surgery.

Table 5. Shows the results of the Cox regression model for significant variables in the univariate and multivariate analysis of disease-free survival in patients with rectal cancer.

	Univariate			Multivariate		
	P	HR	CI 95%	P	HR	CI 95%
Clinical N (groups)						
cN0		1.000				
cN1-cN2	0.031	2.196	1.074-4.49			
Clinical stage (groups)						
cI-cII		1.000				
cIII	0.035	2.157	1.055-4.41			
Tumor pathological response						
Grade 1		1.000				
Grade 2	0.870	0.902	0.264-3.083			
Grade 3	0.306	1.807	0.582-5.614			
Pathological T (pT)						
pT1		1.000				
pT2	0.986	0.981	0.118-8.149			
pT3	0.118	4.955	0.667-36.826			
pT4	0.852	1.303	0.081-20.847			
Pathological N (pN)						
pN0		1.000				
pN1	**<0.05**	3.746	1.728-8.123			
pN2	**0.004**	4.563	1.633-12.753			
Pathological stage (groups)						
pI		1.000			1.000	
pII	**0.029**	3.714	1.142-12.08	0.037	4.097	1.091-15.382
pIII	**<0.05**	7.612	2.567-22.57	0.016	7.446	1.451-38.226
Lymphovascular invasion						
No		1.000			1.000	
Yes	**<0.05**	4.779	2.206-10.36	0.013	2.984	1.263-7.048
Perineural invasion						
No		1.000				
Yes	**0.021**	3.465	1.207-9.951			
Infiltrated nodes						
0		1.000			1.000	
>0	**<0.05**	3.688	1.814-7.499	0.467	0.616	0.167-2.269
Time intervals						
8 - 12 weeks		1.000			1.000	
13 - 20 weeks	**0.654**	1.201	0.539-2.673	0.275	1.668	0.666-4.177
>20 weeks	**0.982**	1.012	0.368-2.785	0.304	1.896	0.559-6.420

Conflict of interest: None of the authors has any conflict of interest.

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