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Review Article

Predictors of pathological response and clinical outcome following chemoradiation for locally advanced rectal cancer – a systematic review

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ABSTRACT

Background: Colorectal cancer is one of the most common types of cancer and is associated with a high lethality rate. Treatment is multidisciplinary, and neoadjuvant chemoradiation is recommended in locally advanced rectal cancer. About 15% of patients answer favorably to neoadjuvant chemoradiation, so it is important to determine the predictors of response.
Objective: To review the results of studies that analyzes the predictors of complete pathological response to neoadjuvant chemoradiation in patients with locally advanced rectal cancer.
Search methods: We searched for eligible articles in data bases Pubmed and Scopus, between the 12th and the 20th of March 2020. The following key words were used: "predictors of response", "chemoradiation" and "locally advanced rectal cancer".
Selection criteria: Inclusion criteria: Studies including patients with locally advanced rectal cancer, patients receiving neoadjuvant chemoradiation as treatment, studies including predictors of response to neodjuvant chemoradiation, overall survival as an outcome and regarding language restrictions, only articles in English were accepted, only studies published until the 31st of December 2019 were accepted.
Main results: Fourteen studies fulfilled the inclusion criteria. Thirteen are cohort studies and one is a clinical trial. Four groups of predictors were defined: blood markers, tumors, histopathological and patients' characteristics.
Author's conclusions: During the analysis of the articles, there were several predictors identified as potential candidates for clinical practice, such as high pre neoadjuvant chemoradiation Carcinoembryonic Antigen levels and small post neoadjuvant

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chemoradiation tumor size. Nevertheless, it is difficult to make definitive conclusions about the most reliable predictors. That is why it is crucial to initiate further studies with standardized cut-off values and a methodology homogenization.

Preditores de resposta patológica e de *outcome* clinico após quimioradioterapia neoadjuvante para cancro do reto localmente avançado -uma revisão sistemática

Palavras-chave:
CRLA
Quimioradioterapia neoadjuvante
Preditores de resposta

R E S U M O

Introdução: O cancro colorretal é um dos cancros mais prevalentes em Portugal e tem associada uma alta taxa de letalidade. Atualmente, o tratamento é multidisciplinar, e a quimioradioterapia neoadjuvante está indicada no Cancro do Reto Localmente Avançado. Sabe-se que cerca de 15% dos doentes responde favoravelmente à quimioradioterapia neoadjuvante, sendo por isso importante determinar quais os preditores de resposta a este tipo de tratamento.

Objetivo: Rever os resultados dos estudos que analisam os preditores de resposta completa à quimioradioterapia em pacientes com Cancro do Reto Localmente Avançado.

Métodos de pesquisa: Pesquisamos artigos elegíveis nos bancos de dados Pubmed e Scopus, desde o dia 12 a 20 de Março de 2020. Foram utilizadas as seguintes palavras chave: "preditores de resposta", "quimioradioterapia neoadjuvante" e C̈ancro do Reto Localmente Avançado:.

Critérios de seleção: Critérios de inclusão: Estudos que incluam pacientes com Cancro do Reto Localmente Avançad, pacientes sujeitos a quimioradioterapia neoadjuvante, preditores de resposta à quimioradioterapia, que avaliem a sobrevivência como outcome, escritos em inglês e publicados até dia 31 de Dezembro de 2019.

Resultados principais: Catorze estudos preencheram os critérios de inclusão. De todos os artigos, treze são Cohort e um é Clinical Trial. Foram definidos quatro grupos de preditores: marcadores de sangue e caraterísticas do tumor, histopatológicas e dos pacientes.

Conclusões dos autores: Durante a análise dos artigos, foram identificados vários preditores como potenciais candidates para a prática clínica, tais como o valor elevado de antigénio carcinoembrionário pré- quimioradioneoaajuvância e tamanho reduzido. Contudo, é arriscado elaborar conclusões concretas relativamente aos preditores mais confiáveis. Por isso, é crucial iniciar novos estudos com valores de cut-off estandardizados e métodos com maior homogeneidade.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and it is the fourth cause of death by cancer in the world. According to predictions, by 2030, CCR will be responsible for 2.2 million of new cancer cases and 1.1 million of cancer deaths.[1]

Rectal cancer (RC) corresponds approximately to one third of the CRC cases[2,3] and presents unique characteristics in terms of staging and treatment.

Locally advanced rectal cancer (LARC) represents RC stage II and III,[4,5] with and 5 year survival rate between 52% and 65%.[6,7]

In the past, local recurrence was a major problem, after LARC surgical treatment, but nowadays, thanks to improvements in surgical techniques and a multidisciplinary approach with the association of neoadjuvant treatment, the major concern is the risk of distant relapses.[8]

The Ryan Tumor Regression Grade (TRG) system evaluates the response to Neoadjuvant Chemoradiation (nCRT). This model has 3 grades (TRG 1, 2 and 3) and analyzes characteristics such as the presence of cancer cells and the existence of fibrosis.[9]

After nCRT about 15% of patients have a Pathological Complete Response (pCR), defined by the absence of viable tumor cells (ypT0N0M0) in the surgical resection specimen and these patients present a better 5 year Disease Free Survival (DFS). The problem is that the ascertainment of the pathological response can only be determined thought the evaluation of the surgical specimen.[4,10]

Current investigation in RC aims to find the best therapeutic strategies regarding the patient's characteristics. Therefore,

it is crucial to make a selection of the patients, in order to adjust the type and dose of nCRT. Many factors have been proposed as predictors of response and survival, but to this day, it has not been possible to propose a model with the capacity of predicting clinically or pathologically tumor response to the nCRT.

This is an important issue concerning therapeutic decisions, enabling the development of risk-adapted treatment strategies; for example, other strategies may be considered in patients who are less likely to answer to standard nCRT. As well, local excision or *wait-and-see* strategies may be useful in patients more likely to have a pCR.[11]

The objective of this study is to review the results of articles that analyze the predictors of pCR and clinical outcome after nCRT in patients with LARC.

Materials and methods

Criteria for considering studies for this review

Types of studies: Studies that analyzes predictors of the response to nCRT and clinical outcome in patients with LARC.

Types of participants: Studies including patients >8 years old with LARC who have undergone chemoradiation.

Types of interventions: Trials investigating treatment with neoadjuvant chemoradiation.

Search methods for identification of studies

Data sources and searches

A systematic review of the literature was carried out according to a predefined protocol, in order to identify studies assessing predictors of pathological response and survival of patients with LARC who have received nCRT. Pubmed and Scopus database were searched for eligible articles. The following keywords were used in the search: "predictors of response", "chemoradiation" and "locally advanced rectal cancer". In case of duplicate publications, the most recent papers and those with the most data provided were selected.

Selection of studies, data extraction and management

Three review authors (EA, MB and SR) independently evaluated all yielded titles and abstracts for eligibility. We resolved disagreements by consensus and by involvement of a fourth review author (SM). When several reports described the same trial, we chose the most complete report as the main report and checked the remaining ones for complementary data on clinical outcomes, descriptions of study participants or design characteristics. We extracted the type of control used, authors names', year of publication, sample size, primary endpoint, results on Overall Survival (OS), Progression Free Survival (PFS) and when these data were not available we would extract DFS or any other that gave us information on survival. We also extracted important conclusions from the publication status.

Study eligibility criteria

Studies investigating the associations between predictors of response to nCRT and OS in patients with LARC were initially reviewed. Three review authors (EA, MB and SR), working independently and in parallel, scanned the abstracts and then obtained and reviewed in full only studies that appeared to meet predefined inclusion and not exclusion criteria.

Inclusion criteria: Studies including patients with LARC, patients receiving nCRT as treatment, studies including pathological predictors of response, OS as an outcome and regarding language restrictions, only articles in English were accepted, only studies published until the 31st of December 2019 were accepted.

Exclusion criteria: Types of paper that weren't primary studies, studies that didn't have patients assigned to nCRT, patients that didn't have LARC, studies that don't include predictors of response to nCRT, papers that have genetic markers and PET exam as predictors of OS, papers that didn't measure survival as an outcome, studies not performed on humans, papers that weren't in English language and studies considered gray literature.

Quality assessment of included studies

Three review authors (EA, MB and SR) independently assessed the adequacy of randomization, blinding and analyzes, verifying methodological validity for every study that met the inclusion criteria. Any disagreements were resolved through consensus-based discussion or with a third review author (SM). Quality assessment of included studies was based on the recommendations given by the Critical Appraisal Skills Programme (CASP) checklists for Cohort Study[12] and Randomized Controlled Trial.[13] Based on the information given by the journal publications, we judged each domain in each study as high quality, moderate quality and low quality.

Data synthesis

The primary endpoints were PFS and OS. The OS was defined as the time between randomization and any death. PFS was defined as the time between randomization and the first occurrence of progression or relapse or death from any cause. When these weren't available we would extract the DFS, which was measured from the date of surgical resection until the date of CT scan detection of recurrence or last follow-up.

Results

A summary of our research is presented in Fig. 1. We initially collected 215 potentially relevant articles, of which we excluded 180 for not meeting our criteria and 5 articles that were not found.

Quality assessment

The overview of the studies' quality analysis is presented in Tables 1 and 2. The analysis was divided in three distinct groups: high quality, moderate quality and low quality.

The evaluation of the cohort studies showed that 2 of the 13 studies were classified as moderate quality. The absence of two criteria was transversal to nearly all the studies: the identification of confounding factors and the way these factors were taken into account in the analysis. Another criterion that wasn't totally fulfilled in all the articles was the implication of this study in the clinical practice: considering that we

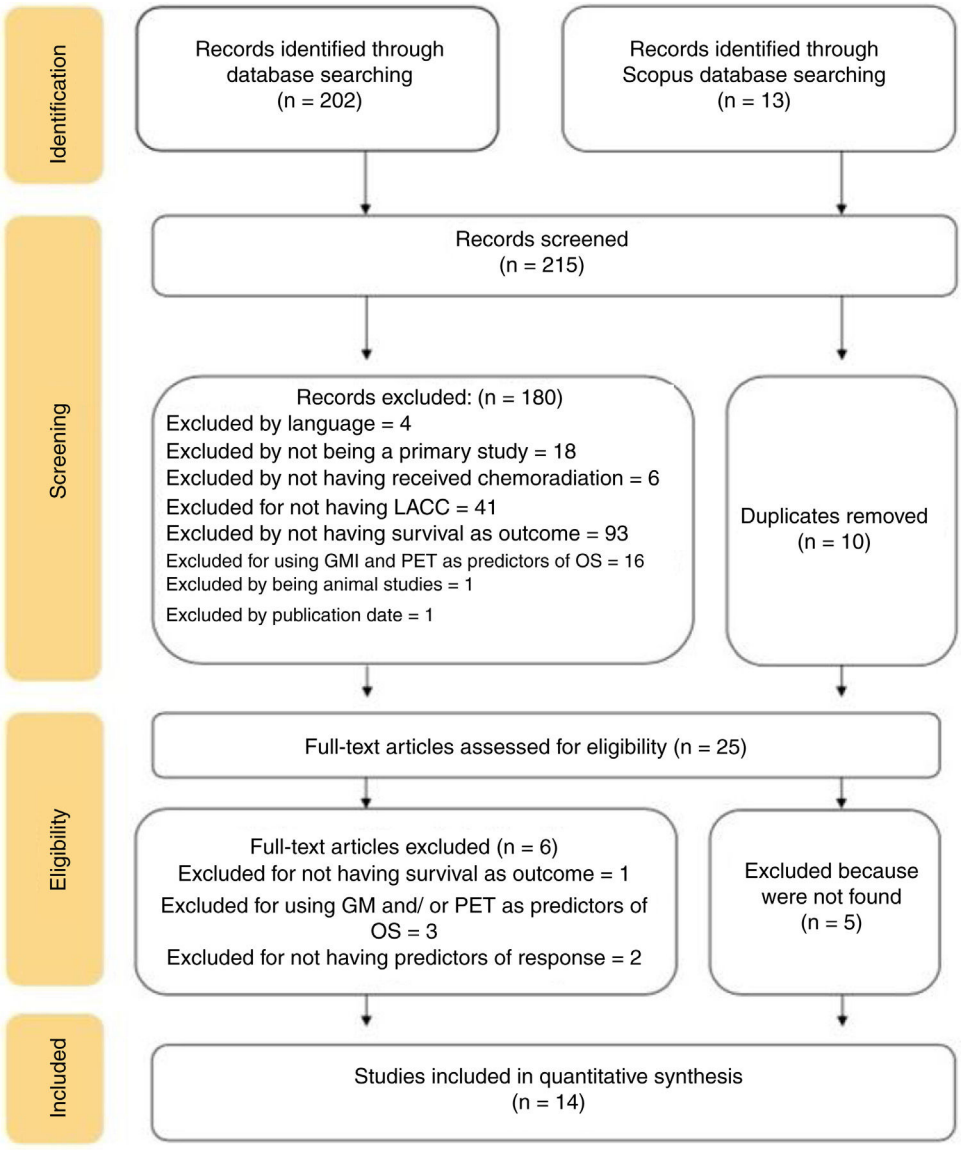

Fig. 1 – Flow chart – following PRISMA statement.

only want to evaluate the response of the "exposed group" and that on a cohort study there's always an "exposed" and "not exposed" group, there was always a group whose results weren't relevant.

The only article that was a clinical trial had moderate quality. There were several criteria failing, standing out the lack of randomization of the patients included in the study.

Description of the population

This review included 14 studies, which met the inclusion criteria. After analysis, the reviewed studies presented a total population of 2585 patients, in which 1684 were men and 901 women. The mean age was 61.05 years. The studies included were 13 cohorts and 1 clinical trial. Studies analyzed a wide range of predictors: 10 analyzed patients' characteristics, 9 studies analyzed blood markers, 10 analyzed tumor characteristics, 13 analyzed histopathological characteristics and 3 analyzed types of nCRT.

Studies Summary Information is described in Table 3.

Analyzed predictors

After analyzing the articles, the predictors that obtained significant results ($p < 0.05$) were divided into four groups. In each group, parameters were evaluated in order to understand if they were useful to predict the OS/DFS and/or the pCR.

Patients' characteristics

There are some characteristics of the population that may have an impact on the survival rate. Ten articles that were reviewed included patients' characteristics such as gender and age, and only one obtained a significative result regarding the gender of the patients. The results show that gender was a prognostic factor for DFS, and that males have a higher rate of DFS.[14]

Table 1 – Quality evaluation of the cohort studies.

CASP cohort	1	2	3	4	5	6	7	8	9	10	11	12	13
William H. Ward, et al.	√	√	√	X	X	√	√	√	√	√	√	√	?
Tseng M., et al.	√	√	√	X	X	√	√	?	√	√	√	?	?
Sun Y., et al.	√	√	√	√	√	√	√	√	√	√	√	√	?
Nakamura T., et al.	√	√	√	X	X	√	√	?	√	√	√	√	?
Runau F., et al.	√	√	√	X	X	√	√	?	√	√	√	√	?
Yanwu Sun, et al.	√	√	√	X	X	√	√	?	√	√	√	√	?
Braun L., et al.	√	√	√	X	X	√	√	?	√	√	√	√	?
Toiyama Y., et al.	√	√	√	X	X	√	√	?	√	√	√	√	?
Abdul-Jail K., et al.	√	√	√	X	X	√	X	√	√	√	√	√	?
Xue Dou, et al.	√	√	√	X	X	√	√	?	√	√	√	√	?
A.S. Dahadda, et al.	√	√	√	X	X	√	√	?	√	√	√	√	?
Jong Hoon Lee, et al.	√	√	√	X	X	√	√	?	√	√	√	√	?
Stanley K.T. Yu, et al.	√	√	√	X	X	√	√	√	√	√	√	√	?

1, focused issue; 2, selection of cohort; 3, assessment of outcome to minimize bias; 4, identification of confounding factors; 5, confounding factors taken into account in the analysis; 6, adequacy of follow up; 7, follow up long enough; 8, quality of the results; 9, precision of the results; 10, believing the results; 11, application to the local population; 12, results fits with available evidence; 13, implication of this study for practice; √, yes;?, can't tell; X, no.

Table 2 – Quality evaluation of the clinical trial.

CASP clinical trial	1	2	3	4	5	6	7	8	9	10	11
Klautke G., et al.	√	X	√	?	?	√	√	?	?	√	√

1, focused issue; 2, randomized assignment; 3, all patients were accounted for conclusion; 4, patients, health workers and study personnel blind to treatment; 5, similar groups at the start; 6, equality of treatment; 7, how large was the effect of the treatment; 8, how precise; 9, can the results applied to the local population; 10, all important outcomes considered; 11, benefits worth the harms and cost; √, yes; ?, can't tell; X, no.

Blood markers

These markers were evaluated as predictors of clinical outcome and of pathological response. Nine of the articles that were reviewed included some type of blood marker, and seven of these obtained significative results ($p < 0.05$).

Hemoglobin and Carcinoembryonic Antigen (CEA) were analyzed as predictors of pathological response.

Higher values of pre-operative hemoglobin were associated with the achievement of pCR and also revealed a better survival outcome.[15]

Relatively to CEA, the value of pre and post CRT, patients who present elevated pre-CRT CEA levels are less likely to achieve pCR.[12,16]

Low levels of post-CRT CEA are associated with a favorable prognostic.[12]

Regarding clinical outcomes, several ratios have been analyzed. WBC ratio (white blood cell) was studied in five articles, and the results revealed that patients with increased LMR (lymphocyte-to-monocyte ratio) have a better prognosis and greater OS than patients with lower values. Patients with decreased NLR (neutrophil-to-lymphocyte ratio) and PLR (platelet-to-lymphocyte ratio) have improved DFS compared to those with higher ratios ($p < 0.05$).[15,17–20]

Histopathological markers

The histopathological markers were also evaluated has predictors by a wide range of articles included in this review. A total of nine articles had this type of marker in account.

Sun et al. [21] studied acellular mucin pools, and showed that tumor pathology, including the presence of mucin, is independently associated with pCR. According to Sun et al.,[21] patients who had acellular mucin pools had a similar 5 year OS rate, but a significantly decreased DFS rate, when compared with patients without acellular mucin pools.

One of the most analyzed parameters was TRG, being studied in three different studies. Nakamura et al.[14] and Dahadda et al.[22] showed that a TRG grade 0/1 had a significantly increased DFS when compared to TRG grade 2/3. Dou et al.[20] compared the TRG in each patient before and after the surgery and concluded that patients with a poor response had lower 5 year DFS.

Extramural Venous Invasion (EMVI) conversion from positive to negative after CRT was associated with pCR and showed a higher 3 year DFS and 3 year OS when compared with patients who did not have that transition pos-CRT.[23] According to Dahadda et al.,[22] the presence of perineural invasion independently and significantly predicted for disease-free survival.

Regarding circumferential resection margin, Sun et al.,[21] post-CRT circumferential extent of tumor is independently associated with pCR. In another perspective, Dahadda et al.[22] concluded that circumferential margin status independently and significantly predict DFS ($p < 0.05$).

Klautke et al.[24] evaluated the extent of resection and determined that patients with R0 had a significantly higher 4 years DFS compared to patients with R1.

Pathological nodal status is mentioned as a good predictor of DFS, associating patients with ypN2 disease with extremely

Table 3 – Studies summary information.

Authors	Year	Study type	Exclusion criteria	Inclusion criteria	n	Median age	Predictors evaluated (in bold predictors with significance)	Survival	Summary
William H. Ward, et al.	2018	Cohort study	Patients with incomplete laboratory data, staging information, survival, or recurrence status.	Patients with AJCC stage II or III disease who underwent neoadjuvant chemoradiation and subsequent surgical resection.	146	58.6	LMR	Low LMR: OS 68.7% DFS 73.3%.	A query was completed for clinical stage II–III rectal adenocarcinoma patients treated from 2002 to 2016.
					Men: 89		NLR	High LMR: OS 86.3% DFS 87.4%.	Patients who had a complete blood count collected before neoadjuvant chemoradiation and again before surgery were included.
					Female: 57		PLR	Low NLR: OS 83% DFS 84.6%.	
			Patients who didn't receive neoadjuvant chemotherapy or chemoradiation.	Patients with a CBC within 60 days of chemoradiation initiation or definitive surgery.				High NLR: OS 41.5% DFS 40.4%.	
			Patients who had an AJCC clinical stage other than II–III.					Low PLR: OS 83.6% DFS 83.6%.	The LMR, NLR, and PLR were calculated for the pre-CRT and post-CRT time points.
			Patients without a CBC result within 60 days of chemoradiation start.					High PLR: OS 65.7% DFS 75.1%	Potential cut points associated with OS differences were determined using maximally selected rank statistics. Survival curves were compared using log-rank tests and were adjusted for age and stage using Cox regression.
			Patients without a CBC result within 60 days of TME.						Within the pretreatment group, a "low" (<2.86) LMR was associated with decreased OS. In the same group, a "high" (>4.47) NLR and "high" PLR (>203.6) were associated with decreased OS. With covariate adjustment for age, and separately for final pathologic stage, the associations between OS and LMR, NLR, and PLR each retained statistical significance.

– Table 3 (*Continued*)

Authors	Year	Study type	Exclusion criteria	Inclusion criteria	n	Median age	Predictors evaluated (in bold predictors with significance)	Survival	Summary
Tseng M., et al.	2018	Cohort study	Patients who received cetuximab with 5-FU.	Patients who were diagnosed with clinically staged T3/4, N0/+, M0 rectal cancer according to TNM classification of malignant tumors.	117	60	Age at diagnosis	5-year local recurrence: 4.5%; 5-year DFS: 65.7%; OS: 80.6%.	From April 2002 to December 2014, 117 patients with LARC received neoadjuvant CRT followed by TME surgery. The treatment regimen compromised a total radiotherapy dose of 50.4 Gy in 28 daily fractions delivered concurrently with 5-FU and capecitabine chemotherapy over 5.5 weeks. All patients were planned for TME surgery. Local control, disease-free survival, overall survival and treatment toxicities were analyzed. Median follow-up was 34 months. 11.5% of patients achieved pCR and 72.6% had either tumor or nodal downstaging following neoadjuvant QRT.
			Patients who received intensity-modulated radiotherapy instead of conventional radiotherapy.		Men: 78 Female: 39		Gender Chemotherapy regimen		
							Margin positivity	Patients with LARC who achieved pCR after preoperative CRT had an improved 5-year disease survival rate of 83.3% versus 65.6% for patients who did not achieve pCR.	
			Patients who declined neoadjuvant CRT.	Patients who received neoadjuvant CRT followed by TME surgery at Nacional University Hospital, Singapore, from April 2002 to December 2014.			Tumor downstaging Nodal positivity		

– Table 3 (*Continued*)

Authors	Year	Study type	Exclusion criteria	Inclusion criteria	n	Median age	Predictors evaluated (in bold predictors with significance)	Survival	Summary
							Pathological response		Multivariate analysis showed that nodal positivity was a predictor of poor disease-free survival and poor overall survival. Tumor downstaging and pCR did not improve outcomes.
Sun Y., et al.	2019	Cohort study	Patients with distant metastasis at diagnosis.	Patients who had histologically proven rectal adenocarcinomas, rectal tumors located <12 cm from anal verge, clinically staged as cT3-4 and/or N+ rectal tumors.	118	54.3	Acellular mucin pools	Patients with acellular mucin pools had a similar 5-year OS but a decreased DFS rate.	A retrospective analysis of 118 LARC patients who achieved pCR following nCRT and TME from 2008 to 2015.
			Patients with synchronous malignancy or a history of other malignant tumors.		Men: 63 Female: 55		MUC1immunostaining Serum post-CRT CEA levels	Patients with positive MUC1 staining had a similar 5-year OS but a lower DFS rate.	Clinicopathological and therapeutic parameters were evaluated as possible predictors of distant metastasis-free survival, and COX regression analysis was performed. After a median follow-up of 57 months, the 5-year OS and disease free survival rates were 94.7% and 88.1%, respectively.
			Patients with emergency surgery or palliative surgical resection, local excision or a "Watch-and-Wait" strategy.				Tumor distance from the anal verge		

– Table 3 (*Continued*)

Authors	Year	Study type	Exclusion criteria	Inclusion criteria	n	Median age	Predictors evaluated (in bold predictors with significance)	Survival	Summary
				Patients treated with nCRT and radical surgery and pathological staged as T0N0M0 (ypCR).					On univariate analysis, tumor distance from the anal verge (HR = 0.706; $p = 0.039$), acellular mucin pools (HR = 6687; $p = 0.002$) and MUC1 expression (HR = 8280; $p < 0.001$) were independently associated with DMFS. COX regression demonstrated that MUC1 expression (HR = 3812; $p = 0.041$) remained to be an independent predictor of DMFS in pCR patients. Tumor distance from anal verge, acellular mucin pools, and MUC1 expression were associated with distant metastasis in patients with pCR. MUC1 staining remained to be an independent risk factor for DMFS. Such information could facilitate treatment decision in this patient.
Nakamura T., et al.	2019	Cohort study	No info	Patients with a histopathologically confirmed diagnosis of previously untreated rectal adenocarcinoma.	105	64	Sex Age Preoperative tumor diameter cStage Preoperative CEA, CA19-9 Tumor site	Male patients had a decreased 5r-DFS.	105 patients with LARC who received NCRT followed by radical surgery. NCRT consisted of pelvic radiotherapy (45 Gy in 25 fractions over a period of 5 weeks), S-1 (80 mg/m^2) given concurrently for 25 days, and irinotecan (60 mg/m^2), given once a week as a continuous intravenous infusion. Radical surgery was performed 8 weeks after treatment.

– Table 3 (*Continued*)

Authors	Year	Study type	Exclusion criteria	Inclusion criteria	n	Median age	Predictors evaluated (in bold predictors with significance)	Survival	Summary
				Eastern Cooperative Oncology Group performance status of 0–3.	Men: 64		CRT treatment completion	Patients with tumors with a pre-treatment diameter <40 mm or histopathological treatment response grade 0/1 or ypN1 and ypN2 had a decreased 5DFS.	A pathological complete response was confirmed in 23.8%. The 5-year recurrence-free survival rate was 79.3%, and the 5-year overall survival rate was 87.1%. Multivariate analysis showed that the following 4 variables were independent predictors of recurrence-free survival: sex (male: $p = 0.0172$), pre-treatment tumor diameter (<40 mm: $p = 0.0223$), histopathological treatment response (grade 0/1: $p = 0.0169$), and ypN (ypN1: $p = 0.1995$; ypN2: $p = 0.0007$). Only ypN was an independent predictor of overall survival (ypN1: $p = 0.0009$; ypN2: $p = 0.0012$).
							Perioperative transfusion		
				Age 20–82 years at the time of enrollment.	Female: 41		Surgical procedure		
							Histological grade		
				Patients without dysfunction of major organs (bone marrow, heart, lung, liver and kidneys).			ypN	Patients with ypN1 ou ypN2 had also a decreased 5-year-OS.	
							ypCR		

– Table 3 (*Continued*)

Authors	Year	Study type	Exclusion criteria	Inclusion criteria	n	Median age	Predictors evaluated (in bold predictors with significance)	Survival	Summary
Runau F., et al.	2016	Cohort study	No info	Patients with locally advanced disease (T3/4 ± nodal disease) and deemed medically fit for long-course neoadjuvant CRT followed by an aim of curative surgical resection of tumor.	277 Men: 190 Female: 87	65.3	Length Tumor width Distance from closest margin Tumor height above anal verge Examined lymph nodes Involved lymph nodes Pre-operative hemoglobin Pre-operative neutrophil Pre-operative platelets Pre-operative lymphocytes NLR PLR	Patients with a pCR have a significantly improved OS and DFS compared to a non-pCR	Retrospective study (2000–2012). 380 patients diagnosed with primary rectal adenocarcinoma were identified, 277 received neoadjuvant chemoradiotherapy followed by curative ressection. 46 patients obtained a pCR (ypT0N0) with no local recurrence and two metastatic recurrences on follow-up. Patiens with a pCR have a significantly improved OS and DFS compared to a non-pCR. On univariate analysis, increased tumor height above anal verge, low lymph node yield, high pre-operative hemoglobin and a low neutrophil-lymphocyte ratio are significant factors identifying a pCR. Multivariable analysis of the above factors confirmed tumor height above anal verge as significant in obtaining a pCR.

– Table 3 (*Continued*)

Authors	Year	Study type	Exclusion criteria	Inclusion criteria	n	Median age	Predictors evaluated (in bold predictors with significance)	Survival	Summary
Yanwu Sun, et al.	2017	Cohort study	Patients with previous or concurrent malignancies.	Patients with LARC undergoing nCRT and curative resection between 2008 and 2014.	522	53.9	Age	5-year OS (pCR vs. non-pCR: 92.0% vs. 76.1%)	A total of 522 locally advanced rectal cancer patients undergoing nCRT and curative resection between 2008 and 2014 were included. A uni and multivariate analysis was developed to identify predictors of pCR.
					Men: 334 Female: 188		Sex		
			Patients treated with emergent surgery, palliative resection.				ASA scores	DFS (pCR vs. non-pCR: 92.7% vs. 66.5%)	
							Distance from the anal verge		
			Patients treated with local excision or “watch and wait” strategy.				Gross type		These post-CRT clinicopathologic and treatment-related factors were identified and used to develop a predictive nomogram for pCR. Logistic regression showed that post-CRT distance from the anal verge, post-CRT tumor, post-CRT circumferential extent of tumor, pre-CRT CEA level, and post-CRT CEA level were independently associated with pCR. Then, with a median follow-up of 55 months, pCR was associated with better 5-y OS and DFS.
							Histopathology		
							Tumor differentiation		
							Clinical T and N stage		
							Pretreatment CEA levels		
							Surgical approach		
							Post-CRT distance from the anal verge		
							Post-CRT tumor size		
							Post-CRT circumferential extent of tumor		
							Tumor pathology		
							Post-CRT CEA level		

– Table 3 (*Continued*)

Authors	Year	Study type	Exclusion criteria	Inclusion criteria	n	Median age	Predictors evaluated (in bold predictors with significance)	Survival	Summary
Braun L., et al.	2019	Cohort study	No info	Patients with LARC treated with preoperative long-course 5-fluorouracil based RCT between 2006 and 2013	220	65.5	Primary tumor location	DFS was significantly worse in patients with larger primary tumors ($p = 0.003$), an elevated NLR (>4.06) ($p = 0.001$), an elevated neutrophil count ($p = 0.019$), and an elevated leukocyte count ($p = 0.023$).	A retrospective analysis of patients with locally advanced rectal cancer treated with preoperative long-course 5-fluorouracil-based RCT was performed. Potential clinical and hematological prognostic factors for disease free survival (DFS) were studied using uni- and multivariate analysis. A total of 220 patients were included in the analysis. Median follow-up was 67 months. Five-year DFS and overall survival (OS) were 70% and 85%, respectively. NLR with a cut-off value of 4.06 was identified as optimal to predict DFS events. In multivariate analysis, only tumor volume (HR 0.33, 95% CI (0.14–0.83), $p = 0.017$) and NLR (HR 0.3, 95% CI (0.11–0.81), $p = 0.017$) remained significant predictors of DFS. An elevated pretherapeutic NLR was associated with higher T stage, inferior DFS, and poor pathological response to neoadjuvant RCT.
					Men: 142 Female: 78		T-stage N-stage Gross tumor volume Age CEA Grading CRP NLR Absolut neutrophil count Absolut leukocyte count	Among these, only tumor volume (HR 0.33, 95% CI (0.14–0.83), $p = 0.017$) and NLR (HR 0.3, 95% CI (0.11–0.81), $p = 0.017$) remained significant on multivariate analysis.	

– Table 3 (*Continued*)

Authors	Year	Study type	Exclusion criteria	Inclusion criteria	n	Median age	Predictors evaluated (in bold predictors with significance)	Survival	Summary
Toiyama Y., et al.	2015	Cohort Study	No info	Patients with tumors in the lower two thirds of the rectum and staged over T2 or T1 (tumor invading to submucosa) with clinical N1, which represent clinical stages I–III.	89	64.5	Age	OS rates were signifcantly lower in rectal cancer patients with elevated PLT counts, elevate NLR counts and pathologic TNM stage III (ypN+).	This retrospective study enrolled 89 patients with lLARC who underwent neoadjuvant CRT for whom platelet (PLT) counts and SIR status [neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR)] were available. Both clinical values of PLT and SIR status in rectal cancer patients were investigated. Elevated PLT, NLR, PLR, and pathologic TNM stage III [ypN(+)] were associated with significantly poor overall survival (OS). Elevated PLT, NLR, and ypN(+) were shown to independently predict OS. Elevated PLT and ypN(þ) significantly predicted poor disease-free survival (DFS). Elevated PLT was identified as the only independent predictor of DFS. PLT counts are a promising pre-CRT biomarker for predicting recurrence and poor prognosis in rectal cancer.
							Gender ypT ypN Tumor Pathology		
					Men: 66 Female: 23				
							Radiation effect PLT NLR PLR		
				Aged 80 years or younger.				DFS rate were significantly lower in rectal cancer patients with elevated PLT counts than in those with lower levels.	
				No invasion of the external sphincter muscle or elevator muscle of the anus. No evidence of deep venous thrombosis.					

– Table 3 (*Continued*)

Authors	Year	Study type	Exclusion criteria	Inclusion criteria	n	Median age	Predictors evaluated (in bold predictors with significance)	Survival	Summary
Abdul-Jail K., et al.	2013	Cohort Study	No info	Patients with T3/4 and/or node-positive rectal cancer who underwent neoadjuvant 5-Fluorouracil-based CRT followed by surgical resection.	153	63	Age	pCR: 5-year DFS = 100% and OS rate = 88%	The aim of this study was to evaluate the prognostic impact of TRG in a cohort of patients with LARC treated with neoadjuvant CRT. The lack of standardization of TRG is the major source of variability in published studies. In order to understand which system that evaluates TRG is the most informative, 4 systems were tested. One-hundred and 53 patients were included in this cohort. 23.5% of patients achieved pCR had a 5-year DFS rate of 100% compared with a DFS rate of 74% for 76.5% of patients without pCR ($p = 0.003$). The Royal College of Pathologists TRG condenses the Mandard 5 point TRG by stratifying patients into three groups with distinct 5-year DFS rates of 100%, 86% and 67% respectively ($p = 0.001$). In multivariate analysis, pathological nodal status and circumferential resection margin, but not TRG, remained significant predictors of DFS ($p = 0.002$, $p = 0.035$, $p = 0.310$, respectively). Findings support the notion that pCR status, nodal status after neoadjuvant CRT and CRM status are predictors of long-term survival in patients with LARC.
							Sex		
					Men: 105 Female: 48		Tumor location		
							Radiological nodal stage (pretreatment)	Cum survival: TRG (1 = 100%, 2 = 82%, 3 = 68% 4 = -no info; 5 = 62%);	
							Radiological nodal status (pretreatment)	Modified Mandard 3 point TRG system (1 = 92%, 2 = 68%, 3 = 65%)	
							Dose of radiotherapy	RC path (A = 100%, B = 86%, C = 67%); CAP system (0 = 100%, 1 = 86%, 2 = 68% 3 = 65%);	

– Table 3 (*Continued*)

Authors	Year	Study type	Exclusion criteria	Inclusion criteria	n	Median age	Predictors evaluated (in bold predictors with significance)	Survival	Summary
							Type of surgery Pathological tumor stage pCR	Modified Mandard 4-point TRGN system (N1 = 100%, N2 = 95%, N3 = 60%, N4 = no info);	
							Pathological nodal status CRM RC path tumor regression grade (Mandard system) Nodal downstaging status	Pathological nodal status (ypN0 = 94%, ypN1/2 = 46%); RC path system stratified to pathological nodal status (A = 100%, B node negative = 96%, B node positive = 87%, C node negative = 71%); Nodal status (N0-ypN0 = 94%, N0-ypN1/2 = 87%, N1/2-ypN1/2 = 31%)	
Xue Dou, et al.	2013	Cohort Study	Patients with WBC greater than 10×10^9/L or lower then 4×10^9/L.	Patients with clinical T3–T4 stage low rectal cancer, treated in Shandong Cancer Hospital and Institute, China between June 2004 and December 2007.	88	50 < 50 years old and 38 ≥50 years old	Age	5-Year DFS: cN stage (negative – 71.30%; positive – 50.80%);	All factors were evaluated in 88 patients with LARC treated with pre-operative long course nCRT at Shandong Cancer Hospital and Institute, China, between June 2004 and December 2007. High lymphocyte ratios before nCRT and good tumor regression (TRG 3–4) were significantly associated with 5-year DFS ($p < 0.05$). Pretreatment nodal status was also associated with 5-year DFS and 5-year OS ($p < 0.05$). Multivariate analysis confirmed that the pretreatment lymphocyte ratio and lymph nodal status were independent prognostic factors. The study suggests that patients with high lymphocyte ratios before nCRT will have good tumor response and high 5-year DFS and OS.

– Table 3 (*Continued*)

Authors	Year	Study type	Exclusion criteria	Inclusion criteria	n	Median age	Predictors evaluated (in bold predictors with significance)	Survival	Summary
					Men: 53 Female: 35		Gender Histology cT stage cN stage Tumor size Distance from anal verge	Tumor response (TRG 0–2 – 63.70%; TRG 3–4 – 80.20%);	
				All patients were diagnosed with primary rectal adenocarcinoma and no evidence of metastasis was found.			WBC (lymphocyte, neutrophil, monocyte, eosinophil and basophil count and ratio)	Lymphocyte ratio (<24.6%–55.70%; ≥24.6%–70.10%).	
							Tumor response	5-Year OS: cN stage (negative- 78.00%; positive- 59.10%); Lymphocyte ratio (<24.6%- 72.60%; ≥24.6%- 83.30%)	
A.S Dahadda et al.	2011	Cohort Study	Patients that refused to have surgery upon the completion of radiotherapy.	Patients with LARC, cT3/4 and/or N+ and that were considered inoperable or of borderline resectability due to potential CRM involvement.	158	65	Age	5-Year DFS: TRG2 node negative – 57%; TRG2 node positive – 39%; TRG3–5 node negative – 50%; TRG3-5 node positive – 20%	The study involved 158 patients with LARC treated with pre-operative long course nCRT at Nottingham University Hospital between April 2001 and December 2008. Surgery was performed after an interval of 6–10 weeks.
					Men: 105 Female: 53		Gender Site of tumor Pre-op treatment Type of resection Resection margin		

– Table 3 (*Continued*)

Authors	Year	Study type	Exclusion criteria	Inclusion criteria	n	Median age	Predictors evaluated (in bold predictors with significance)	Survival	Summary
							TRG		
				Referred to Nottingham City Hospital, UK, between April 2001 and December 2008 for long course preoperative chemo/radiotherapy.			CRM	5-Year OS: TRG2 node negative- 60%; TRG3–5 node negative – 49%; TRG3–5 node positive – 32%	The response to the pre-operative treatment was graded by a single pathologist using the five point Mandard score.
							Nodal status Perineural invasion		The Mandard score was clearly related to both DFS ($p < 0.001$) and OS ($p < 0.012$). On multivariate analysis perineural invasion, nodal status, TRG and CRM were the most powerful predictors of DFS. The Mandard tumor regression score is an independent prognostic factor and predicts for long-term outcome following pre-operative QT/RT in rectal cancer.
Jong Hoon Lee, et al.	2011	Cohort Study	Patients that had previous cancer other than non-melanoma skin cancer.	Patients with LARC who had been treated with preoperative CRT plus curative laparoscopic surgery between January 2003 and January 2009.	274	60	Age	5-Year OS: non-pCR group – 71.2%; pCR group – 86.0%	The study involved 274 patients with LARC who had been treated with preoperative CRT plus curative laparoscopic surgery between January 2003 and January 2009. At the time of analysis (September 2009), a follow-up period of ≥6 months was available for all patients, and the median follow-up time was 43 months.
					Men: 193		Gender Tumor stage		
			Patients that had evidence of distant metastases.		Female: 81		Nodal stage	5-year DFS: non-pCR group – 73.3%; pCR group – 88.4%	
							Distance of tumor from anal verge		
			Patients that had previously received radiotherapy to the pelvis.				Pre-CRT CEA		
							CRT operation interval		

– Table 3 (*Continued*)

Authors	Year	Study type	Exclusion criteria	Inclusion criteria	n	Median age	Predictors evaluated (in bold predictors with significance)	Survival	Summary
							Tumor grade		From all the predictors evaluated, a significant statistical difference was found in the pre-CRT CEA level. It is possible to conclude that preoperative CRT and laparoscopic surgery are related to favorable long-term outcomes.
Klautke G., et al.	2005	Clinical Trial	Pregnant or lactating women, patients with unresolved bowel obstruction or ileus.	Male and female patients with histologically confirmed adenocarcinoma of the rectum with nonmetastatic disease at locally advanced stage that made R0 resection and sphincter preservation uncertain.	37	62	Extent of resection	OS at 4 years: Resection: R0 = 81%, R1 = 0% Nodal status: pN0/1 = 80%, pN2 = 33%	This study aimed to evaluate the feasibility and efficacy of neoadjuvant CRT intensified with irinotecan in patients with LARC.
					Men: 27		Postoperative nodal status		
			Patients with a history of chronic diarrhea.		Female: 10		Pathohistological response rate	Disease specific OS at 4 years: Resection: R0 = 84%, R1 = 0% 4-Year DFS Nodal status: pN0: 92%, pN1 = 80%, pN2 = 0%	Extent of resection and postoperative nodal status were significant predictors of overall and disease free survival.
									Intensified neoadjuvant CRT with irinotecan can be safely administered and results in a high pCR rate.
				Measurable disease (at least one bidimensional measurable tumor lesion). Performance status ≤2.				DFS at 4 years: pCR or MDR = 88% Partial response = 58%	

– Table 3 (*Continued*)

Authors	Year	Study type	Exclusion criteria	Inclusion criteria	n	Median age	Predictors evaluated (in bold predictors with significance)	Survival	Summary
				Aadequate haematologic, hepatic and renal function. Life expectancy of at least 3 months.					
Stanley K.T. Yu, et al.	2013	Cohort study	Patients who received short-course preoperative RT or RT alone.	Patients diagnosed with LARC that underwent clinical examination, colonoscopy, MRI pelvis and CT chest, abdomen and pelvis (CT CAP) as staging.	281	63	Age	3-Year OS: responders – 90%; nonrespon. – 70%	The study involved 281 patients with LARC who were diagnosed and received neoajuvant CRT and surgical treatment, and underwent clinical examination, colonoscopy, MRI pelvis and CT chest, abdomen and pelvis (CT CAP) as staging. The study concluded that rectal tumor height and MR extramural venous invasion (EMVI) status are more important than baseline size and stage of the tumor as predictors of response to chemoradiation. Both magnetic resonance imaging (MRI) and pathologic- defined responders have significantly improved survival.
			Had no MRI performed before and after CRT. Did not undergo surgery after CRT. Incomplete histology data. Other malignancies.		Men: 175 Female: 106		Gender Neoadjuvant CRT Pre-CRT tumor characteristics MRI staging Post-CRT tumor characteristics **mrEMVI positive pre CRT to negative status post-CRT** **mrCRM positive pre-CRT to negative status post-CRT**	3-Year DFS: responders – 79%; nonrespon. – 63%	

CEA, cardioembryonic antigen; CRM, circumferential resection margin; DFS, disease free survival; LARC, locally advanced rectal cancer; LMR, lymphocyte-to-monocyte ratio; *n*, number of patients; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PLR, platelet-to-lymphocyte ratio; RCT, radiochemotherapy; RT, radiation therapy; TME, total mesorectal excision; TRG, tumor regression grade.

poor long-term prognosis.[14,25] Postoperative nodal status was taken into account in one of studies, showing that patients with no pathologic evidence of lymph node involvement (pN0) after CRT had a higher 4 year PFS compared with patients with pN1/pN2. 4 year OS was also significantly superior among patients with pN0 and pN1 status when compared to patients with pN2.[24]

Tumor characteristics

Tumor characteristics are another major group of factors that potentially have an effect on pCR and survival. Ten of the articles that were reviewed analyzed at least one characteristic as a possible predictor of pCR, although only nine showed a significant effect of one of these factors.

Regarding the size of the tumor, according with two studies, a tumor diameter <40 mm before treatment and a smaller post-CRT tumor size is independently related to Pcr.[12,14] The distance of the tumor from the anal verge was also approached in two studies, which concluded that tumors further from the anal verge were more likely to develop a pCR.[12,15]

Discussion

This review included 14 studies that analyzed predictors of pCR and survival in LARC, with a total population of 2585 patients in which 1684 were male and 901 were female whose mean age was 61.05 years. Concerning the quality of the studies, 3 of the 14 articles were classified as moderate quality and the other 11 had high quality.

The standard treatment for LARC is nCRT combined with radical resection. However, this therapy has a significant morbidity rate and 90 day mortality of approximately 4%.[26]

On the other hand, we observe that there are patients submitted to nCRT, that when resection specimen is analyzed, no tumor is found on surgical specimen, this can be achieved in about 15% of patients with pCR.[6,12] At the other end, there are patients that nCRT, not result in a downstaging of the tumor, with patient exposed to a higher morbimortality resulting from nCRT and from the surgery after nCRT.

For this reason, these studies are crucial, in order to understand who are the patients that can beneficiate from this treatment, so as to neither overtreat nor subtreat these patients.

Our main goal was to review the results of studies that analyze the predictors of response to nCRT evaluated in terms of pCR and OS in patients with LARC. pCR is itself a predictor of clinical outcome and influences the OS and DFS rates, which is supported by Tseng et al.[27] that verified that patients with LARC who achieved pCR after preoperative nCRT had an improvement of 5 year DFS rate of 83.3% vs. 65.6% for patients who do not achieve pCR. 11.5% of patients achieved pCR and 72.6% had either tumor or nodal downstaging following nCRT.

The predictors, found in literature, were divided into four groups: patients' characteristics, blood markers, tumors and histopathological characteristics. Literature is extensive in other kind of predictors, like genetic markers, realization of PET scan, but we have excluded these articles (see exclusion criteria) because they are not applicable to the clinical practice in the majority of the institutions.

Relatively to predictors of pCR, the literature reviewed documented that: high pre-operative hemoglobin,[15] tumors further from the anal verge,[12,15] tumor diameter <40 mm before treatment,[12] a smaller post-CRT tumor size,[14] the presence of mucin,[12] EMVI conversion from positive to negative after nCRT[23] and a post-nCRT circumferential extent of tumor[12] were associated with the achievement of pCR. On the other hand, pre-operative CEA is less likely to achieve pCR.[12]

Regarding predictors of clinical outcome, the literature reviewed documented that: males, patients with decreased NLR and PLR and resections R0 have improved DFS.[14] On the other hand, presence of acellular mucin pools,[21] lower TRG grades (0/1),[22] presence of perineural invasion,[22] ypN2 disease[24] have a significantly decreased DFS rate.

Low levels of post-nCRT CEA levels are associated with a favorable prognostic[12] and LMR,[14] pN0 and pN1 status (vs. pN2)[24] have a better prognosis and greater OS.

During the analysis of the results of the studies, we faced some difficulties. For starters, the method used to evaluate the survival was different between the articles, which made it hard to compare the results. Also, the studies didn't clearly define the outcomes (OS, DFS, PFS and pCR). This disparity may constitute a bias, because it makes it impossible to properly compare the values between them. In addition, some of the articles revealed significant results, but did not specify the differences and the effect that it could have on survival and pCR. Lastly, different cut-offs were used to evaluate the same predictor, and that makes it difficult to understand which value should be considered in clinical practice.

We also found it hard to make definitive conclusions about the significance of some predictors, because literature is controversial, the same predictor was considered significative in some studies and not significative in others. This was probably due to lack of homogenization in the methods that were used in the different studies, and the variation in the sample size.

Author's conclusions

Our data suggests that there are several predictors that may be potential candidates for clinical practice. The results of this review have shown that patients with increased pre-nCRT CEA levels are less likely to achieve pCR. On the contrary, tumors further from the anal verge and higher values of preoperative hemoglobin after nCRT are associated with a higher chance to reach pCR. Concerning the survival outcome, patients with increased LMR prior to nCRT, pN0 nodal status and EMVI Conversion from positive to negative after nCRT are associated with a better OS. However, regarding the limitations that were discussed previously, it is difficult to make definitive conclusions relatively to the best predictors.

In order to obtain less conflicting data, it is necessary to develop further studies with standardized cut-off values and more homogeneous methods.

Conflicts of interest

The authors declare no conflicts of interest.

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