Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/21272
DOI URL: http://dx.doi.org/10.21474/IJAR01/21272

RESEARCH ARTICLE

FACTORS PREDICT COMPLETE HISTOLOGICAL RESPONSE FOLLOWING NEOADJUVANT RADIOCHEMOTHERAPY FOR RECTAL CANCER

Imane Lahlali[1,2], Fatimazahra Babaouyoub[1,2], Karima Nouni[1,2], A. Lachgar[1,2], Hanan Elkacemi[1,2], Tayeb Kebdani[1,2] and Khalid Hassouni[1,2]

1. Department of Radiotherapy, National Institute of Oncology.
2. Faculty of Medicine and Pharmacy, Mohamed V University, Rabat, Morroco.

Manuscript Info

Manuscript History
Received: 01 May 2025
Final Accepted: 04 June 2025
Published: July 2025

Key words:-
Rectal Tumor,
NeoadjuvantChemoradiotherapy,
Pathologic Complete Response

Abstract

Introduction and Objective: Radiotherapy combined withconcomitant chemotherapy, followed by surgery, is currently the standard treatment for locally advanced rectal cancer. This therapeutic strategy improves local control and increases the sphincter preservation rate. In addition, a pathological complete response (pCR) can be achieved in up to 20% of cas. The objective of our study was to determine the predictive factors for pCR after neoadjuvant RCT.

Methods: This is a retrospective study of a series of 430 patients with rectal carcinoma, collected from January 2018 to December 2023 at the National Institute of Oncology in Rabat, who received radiotherapy with concomitant chemotherapy based on Capecitabine and subsequent surgery.

Results: In this study, 430 consecutive patients with rectal carcinoma were treated with RCC, 315 underwent surgery performed 6 to 8 weeks after the end of radiotherapy.The median age was 55 years (15–88 years).Regarding the stage of the primary tumour, 0 cases had T1 disease, 38 cases had T2 disease, 280 cases had T3 disease and 112 cases had T4 disease. 106 cases had N0 disease, 324 cases had N+ disease. The pathological stages of the patients were as follows: 16 cases with ypT1 disease, 92 cases with ypT2 disease, 116 cases with ypT3 disease, and 23 cases with ypT4 disease. 68 had ypT0N0M0 disease (ypCR). The total ypCR rate for the 315 patients with LARC was 21.58%. The predictive factors for p CR were as follows: tumour location: middle rectum, tumour size less than 3 centimetres, clinical stage T, and well-differentiated tumours.

Conclusions: Pathological characteristics that have been reported to significantly influence patient outcomes after neoadjuvant RCC include post-treatment pathological stage (ypTNM). They provide a good indicator of tumourradiosensitivity and chemosensitivity. The incidence of complete histological response in our study was 21%. Tumour site, size and differentiation were clinical predictors of a complete histological response associated with a very good prognosis.

Corresponding Author:-ImaneLahlali
Address**:-**Department of Radiotherapy, National Institute of Oncology.

……..

Introduction:

The management of locally advanced cancers of the middle and lower rectum (stage T3 or T4 with or without lymph node metastases) is based on neoadjuvant treatment (preoperative neoadjuvantchemoradiotherapy (nCRT)). This strategy has been shown to reduce the rate of local recurrence and facilitate surgical resection [2].

The selection of patients for nCRT is based on preoperative staging, with the aim of identifying those at risk of marginal resection margins and positive lymph node involvement. These patients have higher recurrence rates, which can be reduced through a combination of nCRT and total mesorectal excision.

A complete pathological response (pCR) has been observed in approximately 20% of patients, suggesting a potential survival benefit [9-11]. It is conceivable that this group of patients could be exempted from the morbidity and risks associated with surgery. However, it should be noted that there is a paucity of case series reporting this approach [12]. The preoperative prediction of pCR may be possible based on a number of tumour-related factors, including clinical, pathological, radiological and molecular markers [18-20].
The objective of this study was to identify predictive factors for histological response to neoadjuvant treatment of locally advanced rectal cancer.

Patients and Methods:

Patient selection

This is a retrospective, cross-sectional study conducted at the National Institute of Oncology in Rabat over a five-year period between 2018 and 2023. Data was collected from 430 patients with rectal cancer who were referred to the radiotherapy department for preoperative chemoradiotherapy. 73,25 %, 315 underwent surgery 6 to 8 weeks after the end of radiotherapy.

Patients were recruited according to the following criteria:
- tumour located within the first 15 centimetres of the anal margin
- presented with rectal adenocarcinoma confirmed by histological examination.
- All patients underwent curative surgery after nCRT

The study excluded patients
- with distant metastases,
- patients who did not undergo surgery after neoadjuvant treatment.

Data collection:
- Medical history and clinical findings: age, gender, medical history, suggestive clinical signs and time to consultation.
- Endoscopy and diagnostic biopsy
- Imaging: pre-treatment staging and pelvic MRI, which allowed the tumour size, degree of rectal wall infiltration and lymph node status to be determined.
- The nature of neoadjuvant treatment
- Type and timing of surgery
- Anatomopathological results of the surgical specimen: the degree of differentiation of the ADK according to the 2010 World Health Organisation (WHO) classification, the presence or absence of vascular and perineural invasion, the ypTNM stage. The tumour classification system used to assess tumour response was the Dworak TRG system.

  The information also included data relating to patient follow-up.

The information was collected from paper and computerised patient records on ENOVA.

Treatments

All of the patients received:

Radiotherapy: Radiotherapy was administered at a dose of 50 Gray (46 Gray at the site of the primary tumour and lymph nodes, followed by a 2 Gy boost, in fractions of 2 Gray 5 days a week.

Determination of target volumes and organs at risk
- GTV T = Macroscopic tumour (based on clinical, endoscopic and radiological examinations)
- GTV N = Suspicious ADP
- CTV 50: GTV T + 2 cm cranio-caudal margin including the mesorectum at this level,

- CTV 46: CTV HR + entire mesorectum + entire presacral space + 1-1.5 cm anterior margin in adjacent organs opposite the GTV + CTV N.
- CTV N: Iliopsoas areas + (presacral) + external iliac if adjacent organs (prostate, vagina, uterus, bladder) are affected + Inguinal: to be discussed in case of extension to the anal canal or lower third of the vagina
- PTV: CTV + 10 mm

The concomitant chemotherapy protocol was 800 mg/m2 of oral capecitabine (twice daily) during the radiotherapy period.
Patients received surgical treatment 6 to 8 weeks after neoadjuvant treatment. Surgical intervention consisted of low anterior resection surgery or abdominoperineal resection surgery.

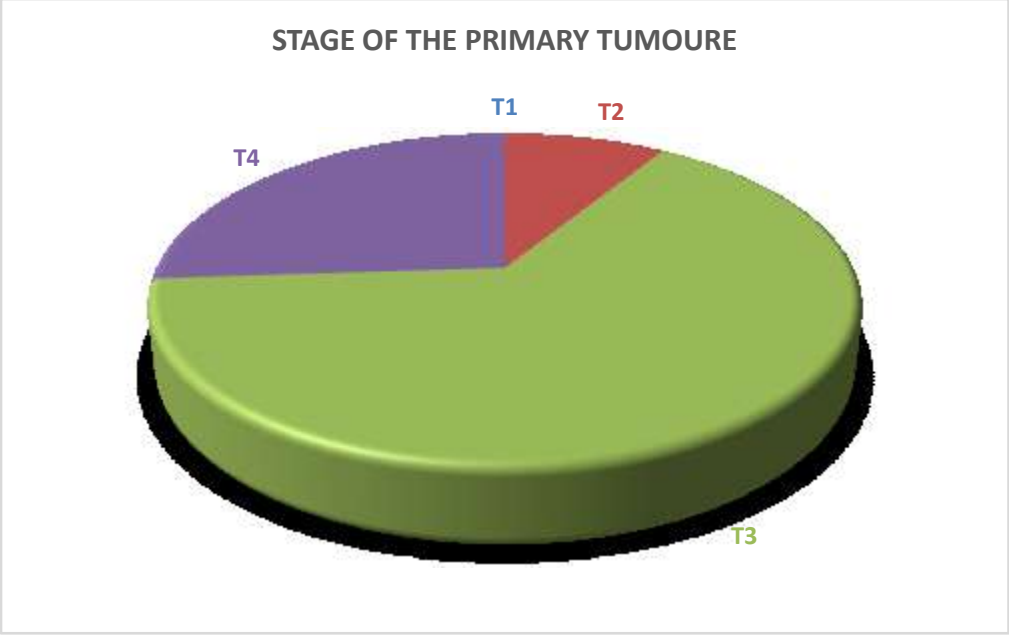
Statistical analysis
Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 for Windows. The chi-square test to explore the independent effects of potential predictors on pCR rate.
The predictive factors studied in the univariate analysis were age, sex, TNM stage, tumour diameter, differentiation, nodal involvement, and the association of chemotherapy with radiotherapy.

Results:

Anatomical and clinical characteristics:
The study involved 315 patients with locally advanced ADK of the lower or middle rectum, with or without lymph node metastases, who underwent concomitant chemoradiotherapy followed by surgery.

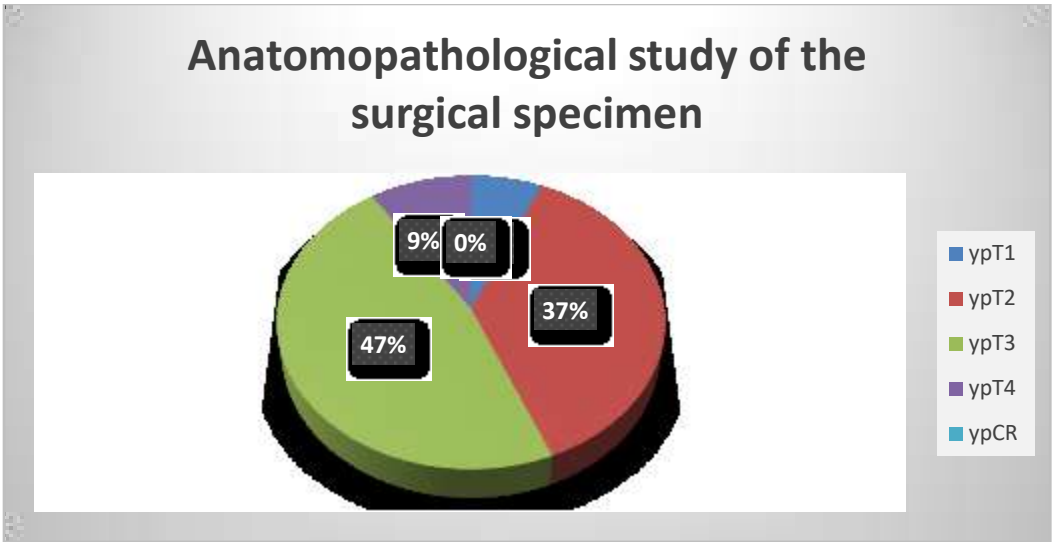
The average age of the patients was 55 years, ranging from 15 to 88 years. Male predominance with 52% of cases. More than 90% of patients exhibited good performance status of <2. On endoscopy, the rectal tumour was budding in more than 80% of cases. TAP CT scan was requested in 91% of cases, and an abdominal-pelvic MRI was performed in 74% of patients before neoadjuvant treatment.

Regarding the stage of the primary tumour, 0 cases had T1 disease, 38 cases had T2 disease, 280 cases had T3 disease, and 112 cases had T4 disease. 106 cases had N0 disease, 324 cases had N+ disease.



Treatement
A total of 315 patients (75%) had surgery after receiving neoadjuvant CCRT, which took between 6 and 8 weeks.
The following techniques are used:
A total mesorectal excision with two types of resection: an abdominoperineal amputation (ACAD) or an anterior low anastomosis (AAP), with or without additional pelvic lymph node dissection (CPC).
The most common complication after neoadjuvant treatment was gastrointestinal (GI) diseases.

Anatomopathological study of the surgical specimen
The patient's illness progressed as follows: There were 16 cases of ypT1 disease, 92 cases of ypT2 disease, 116 cases of ypT3 disease, and 23 cases of ypT4 disease. 68 patients had ypT0N0M0 disease (i.e., ypCR). The overall ypCR rate for the 315 patients with LARC was 21.58%.



pCR
In univariate analyses, patients with well-differentiated histology had a higher pCR rate than patients with poorly differentiated or undifferentiated histology.

The pCR rate was also higher in patients with tumour size less than 3 centimetres and T2 stage cancer than in patients with T3 or T4 stage cancer.

The predictive factors for pCR were as follows: tumour location: middle rectum, tumour size less than 3 centimetres, clinical stage T, well-differentiated tumours, absence of lymph node involvement (cN0).

Discussion:

Over the past decade, significant advances have radically changed the management of locally advanced rectal cancer. Currently, the therapeutic approach is based on three methods: chemotherapy, radiotherapy and surgery. The combination of these approaches and the selection of treatments are determined by initial prognostic factors and tumour response. It is known that treatment outcomes may differ depending on whether or not patients achieve pCR, and it has been proven that pCR is associated with a better prognosis. It therefore seems reasonable to determine the clinical, biological and therapeutic factors associated with pCR. Previous research has highlighted significant variations in pCR rates and the potential predictive factors identified. According to our research, the pCR rate of 21.58% is within the range of pCR rates documented in scientific publications.

The search for predictive factors for treatment response ideally allows the selection of ‘good’ and ‘poor’ responders in order to adjust subsequent therapeutic management. It allows certain patients to be spared treatment without benefits, with added perioperative morbidity, high costs and unnecessary loss of time. These patients could benefit from an alternative therapeutic strategy or more aggressive treatment from the outset.

Table1: Patientcharacteristics.

Characteristics	*n*=430
Age,years	Median55 (rangingfrom15to88)
Gender	
Male	223 (52)
Female	107 (48)
Clinicalstage	
T2	38 (22)
T3	280 (78)
T4	112
Lymphnodeinvolvement	
N-	106 (27)
N+	342 (73)
histological response	
ypT1	16
ypT2	92
ypT3	116
ypT4	23
pCR	68 (21.58%)

Clinical predictive factors

The main clinical factors studied in the literature that influence pCR are: tumour size, circumferential extent, pre-treatment clinical stage T and N, tumour fixity and distance of the tumour from the anal margin.

Size

Some studies have reported that tumour size prior to treatment was a predictive factor for achieving pCR. In studies conducted by De Felice et al. and Bozkaya et al., it was indicated that a tumour size ≤ 5 cm was associated with a higher pCR rate (P = 0.035; P = 0.03, respectively) [1,2]. Furthermore, in the study by Bitterman et al., a tumour size ≥ 3 cm was predictive of a poor response to nCRT (P = 0.023). Our study also indicates that a tumour size ≥ 6 cm was associated with a poor tumour response in univariate analysis (P = 0.017).

The disparity in the results found in the different studies could be partly explained by differences in techniques or interpretation thresholds for the same factor. Indeed, for tumour size, some authors use endoscopic size [3,4]. while others use rectal examination or imaging size, as in our case [5].

T stage

Clinical T stage and clinical lymph node involvement have been studied as predictors of pCR in previous studies. Several studies have found that the absence of lymph node involvement at initial evaluation was predictive of pCR [2]. The study by Yoon et al. [6], which included 351 patients, found that a cN0 classification before treatment was a predictive factor for good tumour regression (p = 0.044). In our study, T2 classification and cN0 lymph node status were independent predictors of pCR.

N stage
We also demonstrated that cN0 in patients with rectal cancer was associated with high rates of pCR in univariate (p = 0.021) and multivariate (p = 0.03) analyses. In previous studies, Yoon et al [8]. and Choi et al [7]. both identified cN0 as an independent predictor of pCR and that the use of TME decreased the recurrence rate in patients with rectal cancer (< 10%) [8].

Distance from the anal margin
The distance from the tumour to the anal margin has been studied as a predictor of histological response by several authors; a distance from the tumour to the anal margin > 5 cm is thought to be less favourable for tumour stage reduction (P = 0.01) [9]. In our study, tumour location was significantly associated with histological response. The histological type of rectal tumour has rarely been implicated in the histological response to neoadjuvant treatment due to the low representativeness of types other than Lieberkuhn adenocarcinoma. However, Bitterman et al. noted in their study that none of the ten patients with mucinous carcinoma achieved pCR, without being able to demonstrate a statistical association between these two factors [10].

Differentiation
We also found that the pCR rate was significantly higher in patients with well-differentiated tumours; these results were consistent with those reported in the literature [11]. A well-differentiated tumour would be more favourable for tumoursterilisation according to the study by Bozkaya et al. (P = 0.002) [2]. In our study, tumour differentiation was linked to tumour regression.

IHC
Numerous biomarkers were also tested on pre-treatment biopsies, using IHC in the majority of cases. According to Reerink and Kuremsky, there is no relationship between the expression of p53, bcl-2 or Ki-67 on pre-treatment biopsies and response to treatment [12,13].. In our series, we did not test biomarkers but rather clinical, histological and radiological data.

Treatment-related predictive factors
Over the past two decades, the management of locally advanced rectal cancer has seen considerable progress thanks to three major revolutions in therapeutic strategies: TME, neoadjuvant radiotherapy and neoadjuvant chemotherapy. These therapeutic methods have improved local control of the disease and thus increased overall patient survival.

Preoperative radiotherapy
Several trials have demonstrated the benefits of preoperative radiotherapy on local disease control and survival. The Stockholm I trial, which randomised 849 patients between surgery alone and short-course radiotherapy at a dose of 25 Gray followed by surgery after one week, found a significant difference in terms of local recurrence (p < 0.001) [14]. The Swedish trial and the Stockholm II trial demonstrated the role of short-course preoperative radiotherapy in reducing local recurrence and increasing overall survival [15,11]. After standardisation of surgery with total mesorectal excision (TME), the Dutch trial confirmed the benefit of short-course radiotherapy followed by surgery with TME on the local recurrence rate compared with TME alone.

Currently, intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) and adaptive radiotherapy techniques make it possible to irradiate target volumes while preserving neighbouring organs at risk, particularly the small intestine, the bladder and the bone marrow, and to increase the dose to the tumour through sequential or integrated dose boosting. A review of the literature published by Burbach et al., which included 487 patients treated with radiotherapy doses >= 60 Gy, showed higher pCR levels. The advantage of intensity-modulated radiotherapy combined with an additional dose above 45 Gray and a low rate of acute toxicity [16,17].

In addition, the combination of neoadjuvant chemotherapy and radiotherapy increases the pCR rate and reduces local recurrence compared to neoadjuvant radiotherapy alone, but does not affect overall survival or disease-free survival [18,19,20,21].

Chemotherapy
The PROSPECT trial compared neoadjuvant chemotherapy with FOLFOX and selective use of CRT with preoperative CRT before TME for patients with rectal cancer with a good prognosis [22].. Eligibility criteria included: tumour between 5 and 12 centimetres from the anal margin on rectoscopy, classified as T2N1, T3N0 or

T3N1 (by MRI, CT scan or endoscopic ultrasound) justifying preoperative CRT, circumferential margin ≥ 3 mm, eligible for sphincter preservation, and managed by a surgeon accredited in TME. T4 tumours, tumours of the lower rectum and tumours with more than 4 perirectal lymph nodes > 10 mm or lateral lymph nodes on imaging were excluded. Tumours were considered N0 if there were no perirectal lymph nodes ≥ 5 mm.

Some studies have indicated that the combination of oxaliplatin and 5FU is not superior to 5FU alone, is not well tolerated, and is associated with increased toxicity. Another interesting therapeutic strategy for patients with advanced rectal cancer is neoadjuvant chemotherapy followed by chemoradiotherapy. Numerous clinical trials have reported favourable results, such as higher pCR rates, higher progression-free and disease-free survival, and improved overall survival in enrolled patients.

PRODIGE 23 is an ongoing phase 3 trial evaluating the benefits of neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy compared to preoperative chemoradiotherapy alone in patients with locally advanced, resectable rectal cancer. The primary outcome of this trial is expected by next year.

In the phase II trial: EXPERT-C, whose primary endpoint was complete histological response. The results of this trial showed no difference in terms of complete histological response. The results of this trial showed no difference in terms of complete histological response with or without cetuximab (9% vs 11%; P = 0.1), however, cetuximab improved the radiological response rate after chemotherapy (51% vs. 71%; P = 0.038) and RT-CT (75% vs. 93%; P = 0.028) as well as overall survival (P = 0.034) [23].

Delay between chemoradiotherapy and surgery

In 2016, a meta-analysis by Petrelli et al., involving 3,584 patients from 13 studies, revealed that a waiting period before surgery longer than the standard 6 to 8 weeks would increase the pCR rate by 6% [24]. Another meta-analysis conducted in 2017, involving 19,652 patients, showed that the pCR rate was significantly higher in patients who underwent surgery after a delay of ≥ 8 weeks compared to those who underwent surgery after a delay of < 8 weeks (p = 0.0001), without a significant increase in the rate of postoperative complications [25].

In the GRECCAR-6 trial, the results showed that waiting 11 weeks after CCRT does not increase the pCR rate after surgical resection. A longer waiting period could be associated with higher morbidity and more difficult surgical resection [26].

Conclusions:

The evolution of rectal cancer treatment has been observed to increasingly gravitate towards conservative approaches. Consequently, a significant body of research is currently examining various methods for intensifying neoadjuvant therapy. The identification of predictive factors for histological response has the potential to assist clinicians in estimating prognosis and suggesting organ preservation for patients who respond well.

The pathological features that have been identified as having a significant impact on patient outcomes after neoadjuvant CRC treatment include post-treatment pathological stage (ypTNM). These indicators have been demonstrated to be reliable predictors of tumourradiosensitivity and chemosensitivity. In the present study, the complete histological response rate was found to be 21%. The location, size, and degree of differentiation of the tumour were clinical indicators of a complete histological response, which was associated with a very favourable prognosis.

In this study, emphasis was placed on the significance of accurate disease staging prior to therapy by routinely performing pelvic MRI accurately within the TNM classification. Furthermore, emphasis was placed on the enhancement of neoadjuvant radiotherapy, the necessity of evaluating tumour response within a designated time frame, the standardisation of pathology reports, and the implementation of a unified score for tumour regression. Furthermore, emphasis was placed on the significance of close collaboration between radiotherapists, medical oncologists, and surgeons at every stage of treatment, with the objective of enabling the adjustment of the therapeutic strategy if necessary.

References:

[1] De Felice F, Izzo L, Musio D, Magnante AL, Bulzonetti N, Pugliese F, et al. Clinical predictive factors of pathologic complete response in locally advanced rec tal cancer. Oncotarget [Internet] 2016:7 [cité 15 juin 2019] Disponible sur: http://www.oncotarget.com/fulltext/8133.
[2] Bozkaya Y, Özdemir NY, Erdem GU, Güner EK, Ürün Y, Demirci NS, et al. Clinical predictive factors associated with pathologic complete response in locally advanced rectal cancer. J OncolSci2018;4:5–10.
[3] Brenner H, Bouvier AM, Foschi R, Hackl M, Larsen IK, Lemmens V, et al. Progress in colorectal cancer survival in Europe from the late 1980s to the early 21st century: the EUROCARE study. Int J Cancer. 2012; 131: 1649-58.
[4] Carlson RW, Jonasch E. NCCN evidence blocks. J Natl ComprCancNetw. 2016; 14: 616-9.
[5] Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med. 1997; 336: 980-7.
[6] Yoon SM, Kim DY, Kim TH, Jung KH, Chang HJ, Koom WS, et al. Clinical parameters predicting pathologic tumor response after preoperative chemoradiotherapy for rectal cancer. Int J RadiatOncol2007;69:1167–72. [11] Letaief F, Nasri M, Ayadi M, Meddeb K, Mokrani A, Yahyaoui Y, et al. Potential predictive factors for pathologic complete response after the neoadjuvant treatment.
[7] Choi CH, Kim WD, Lee SJ, Park WY. Clinical predictive factors of pathologic tumor response after preoperative chemoradiotherapy in rectal cancer. RadiatOncol J. 2012; 30: 99-107.
[8] Yoon SM, Kim DY, Kim TH, Jung KH, Chang HJ, Koom WS, et al. Clinical parameters predicting pathologic tumor response after preoperative chemoradiotherapy for rectal cancer. Int J RadiatOncolBiol Phys. 2007; 69: 1167-72.
[9] Das P, Skibber JM, Rodriguez-Bigas MA, Feig BW, Chang GJ, Wolff RA, et al. Predictors of tumor response and downstaging in patients who receive preoperativechemoradiation for rectal cancer. Cancer 2007;109:1750–5.
[10] Bitterman DS, Resende Salgado L, Moore HG, Sanfilippo NJ, Gu P, Hatzaras I, et al. Predictors of complete response and disease recurrence follow ingchemoradiation for rectal cancer. Front Oncol [Internet] 2015;5 [cité 15 juin 2019] Disponible sur: http://journal.frontiersin.org/Article/10.3389/ fonc.2015.00286/Abstract.
[11] Martling A, Holm T, Johansson H, Rutqvist LE, Cedermark B. The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. Cancer 2001;92:896–902.
[13] Park JW, Lim SB, Kim DW, Jung KH, Hong YS, Chang HJ, et al. Carcinoembryonic antigen as predictor of pathologic response and a prognostic factor in locally advanced rectal cancer patients treated with preoperative chemoradiotherapy and surgery. Int J RadiatOncolBiol Phys. 2009; 74: 810-7.
[14] Cedermark B, Johansson H, Rutqvist LE, Wilking N, The Stockholm I. trial of preoperative short term radiotherapy in operable rectal carcinoma. A prospective randomized trial. Stockholm Colorectal Cancer Study group. Cancer 1995;75:2269–75.
[15] Improved Survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997;336:980–7.
[16] Liu Q, Feng L, Qu B, Ma L, Jia B, Dai G, et al. Efficacy of preoperative neoadjuvant simultaneous integrated boost IMRT radiation therapy combined with preoperative chemotherapy for locally advanced rectal cancer: a prospective II clinical study. Int J RadiatOncol 2018;102:S65.
[17] Hernando-Requejo O, López M, Cubillo A, Rodriguez A, Ciervide R, Valero J, et al. Complete pathological responses in locally advanced rectal cancer after preoperative IMRT and integrated-boost chemoradiation. StrahlentherOnkol2014;190:515–20.
[18] Ceelen W, Fierens K, Van Nieuwenhove Y, Pattyn P. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer: a systematic review and meta-analysis. Int J Cancer. 2009; 124: 2966-72.
[19] Braendengen M, Tveit KM, Berglund A, Birkemeyer E, Frykholm G, Påhlman L, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J ClinOncol. 2008; 26: 3687-94.
[20] Bosset JF, Collette L, Calais G, Mineur L, Maingon P, RadosevicJelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med. 2006; 355: 1114-23.
[21] Gérard JP, Conroy T, Bonnetain F, Bouché O, Chapet O, ClosonDejardin MT, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J ClinOncol. 2006; 24: 4620-5.
[21] par E Basch · 2023 · Cité par 102 — 20 juillet 2023 ;41(21):3724-3734. estce que je: 10.1200/JCO.23.00903. Publication enligne le 4 juin 2023. Auteurs. Ethan Basch ,
[23] Dewdney A, Cunningham D, Tabernero J, Capdevila J, Glimelius B, Cervantes A, et al. Multicenter randomized phase ii clinical trial comparing neoadjuvantoxaliplatin, capecitabine, and preoperative radiotherapy

with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). J ClinOncol2012;30:1620–7.
[24] Petrelli F, Sgroi G, Sarti E, Barni S. Increasing the Interval between neoadjuvantchemoradiotherapy and surgery in rectal cancer: a meta-analysis of published studies. Ann Surg2016;263:458–64.
[25] Du D, Su Z, Wang D, Liu W, Wei Z. Optimal Interval to surgery after neoadjuvantchemoradiotherapy in rectal cancer: a systematic review and meta-analysis. Clin Colorectal Cancer 2018;17:13–24.
[26] Chau I, Brown G, Cunningham D, Tait D, Wotherspoon A, Norman AR, et al. Neoadjuvantcapecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging–defined poor-risk rectal cancer. J ClinOncol2006;24:668–74. [33] Chua YJ, Barbachano Y, Cunningham D, Oates JR, Brown G, Wotherspoon A, et al. Neoadjuvantcapecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. Lancet Oncol2010;11:241–8.