Japanese Journal of Gastroenterology and Hepatology

Research Article ISSN 2435-1210 |Volume 6

# Weight Loss May be a Predictive Factor of Not Achieving Pathological Complete Response After Neoadjuvant Radiochemotherapy for Low Rectal Adenocarcinoma

**Malki HOEL[1,2,3*], Essangri H[3,4], Kassou O[3,4], Manzeki GB[1], Ifrine L[1,3], Belkouchi A[1,3] and Souadka A[3,4]**

[1]University Mohammed V[th] in Rabat Morocco, Medical School, Surgery Department "A" Ibn Sina Hospital, Rabat Morocco

[2]University Mohammed V[th] in Rabat Morocco, Medical School, Biostatical, clinical research and epidemiological laboratory (LBRCE), Morocco

[3]University Mohammed V[th] in Rabat, Morocco, Medical School, Research Team of Hepato-Pancreato Biliary, Digestive and Endocrine Surgeries, Morocco

[4]University Mohammed V[th] in Rabat, Morocco, Medical School, Department of surgical oncology, National Institut of Oncology, Rabat, Morocco

**[*]Corresponding author:**
Hadj Omar El Malki,
Guiche Oudaya Oulad Mtaâ Temara,
Tel: 00 212 661 215977, Morocco,
E-mail : oelmalki@hotmail.com

Received: 11 Apr 2021
Accepted: 14 May 2021
Published: 19 May 2021



**Citation:**
Malki HOEL. Weight Loss May be a Predictive Factor of Not Achieving Pathological Complete Response After Neoadjuvant Radiochemotherapy for Low Rectal Adenocarcinoma. Japanese J Gstro Hepato. 2021; V6(14): 1-5

**Keywords:**
Rectal adenocarcinoma; Complete response; Neoadjuvant radiochemotherapy; Prognosis factors

## 1. Abstract

**1.1. Background and Aims:** Chemoradiotherapy represents one of the cornerstones of colorectal cancer management as not only it improves the local control but can also induce the histological resolution of the disease also known as the pathological complete response. The aim of this study is to identify predictive factors for cPR after chemoradiotherapy in patients with rectal adenocarcinoma.

**1.2. Patients and Methods:** We conducted a retrospective study, including all patients operated on for rectal cancer in the period from January 1st, 2004 to December 31st, 2013 in a single tertiary gastrointestinal surgical unit in Morocco. Preoperative characteristics, clinical and pathological variables including the histological type, the grade of tumor and TNM staging as well as chemoradiotherapy regimen and interval from surgery were recorded and analysed to determine the predictive factors of cPR using univariate and multivariate analysis.

**1.3. Results:** Pathological complete response was encountered in 16 patients (18.18%), 60 (68.18%) patients had incomplete response and 12 patients (13.64%) had no pathological response. The results from the univariate analysis showed that general status deterioration (p = 0.004), weight loss ≥10% (p= 0.011), asthenia (0.050) and anorexia (0.021) were associated significantly with not achieving pCR. The results from the multivariate analysis showed that the great weight loss independently predicted a low percentage of pCR OR = 0.259 (95% CI 0.06 - 0.982).

**1.4. Conclusion:** This study showed that weight loss is associated with low pathological complete response after chemoradiotherapy in colorectal cancer patients. The knowledge of the association of this factor with low chances of achieving pathological response could lead to following more adapted therapeutic strategies and preventing unnecessary procedures.

## 2. Introduction

Rectal neoplasms are one of the most common cancers, with a crude incidence of 3.5 per 100,000 persons and the four rank among all cancers in the moroccan population according to Rabat cancer Register [1]. The anatomical features of the rectum and pelvic region are, among others, contributive to the diagnostic delay and the important amount of cases pinpointed at an advanced stage, thereby requiring a more aggressive therapeutic approach. In fact the standard of care for locally advanced stage II and stage III (T3, T4 and or positive lymph

nodes) rectal adenocarcinoma relies on the association of neoadjuvant chemotherapy and radiotherapy as well as surgery followed by adjuvant chemotherapy with as a main purpose the improvement of local control.[2] In this sense, neoadjuvant chemoradiotherapy (CRT) is not only responsible for a significant downstaging and downsizing of tumors, but also for increasing tumor resection rate and the possibility of sphincter preserving procedures without being detrimental to the obtain of negative margins [2-4]. Additively a proportion of patients (18.1% to 30.2%) experience the histological resolution of disease, also known as pathologic complete response (pCR). Obtaining pCR did not only improve the overall survival and decrease local recurrence but also inspired a more conservative method relying on the close monitoring of these patients and only offering surgery in the event of relapse, also known as the watch and wait strategy. This approach permitted avoiding the morbidity and mortality of unnecessary surgery, as it has been proven that there is no significant difference in survival outcomes between the 'watch and wait' patients and those who were identified as pCR after resection [5].

Besides pCR, patients can have varying treatment responses ranging from no response to even resistance [6, 7]. This disparity in results has been the subject of many studies which attempted to identify potential factors affecting pCR such as clinical prognostic factors, tumor size, compounds of chemotherapy, radiation protocols, interval between radiochemotherapy and surgery as well as the timing of tumour assessment. Some molecular biomarker namely carcinoembryonic antigen (CEA), epidermal growth factor receptor and p21 have also been shown to affect the extent of the pathological response [8, 9]. The better understanding of the factors at the origin of response differences will definitely allow surgeons to choose the best therapeutic strategy tailored to each patient. The aim of this study is to identify predictive factors for complete tumour response after chemoradiotherapy for rectal adenocarcinoma.

## 3. Materials and Methods

We retrospectively reviewed all patients with rectal cancers from January 1st, 2004 to December 31st, 2013 in a single tertiary gastrointestinal surgical unit. We reviewed and collected the data on comorbidities, family and personal history, clinical examination, imaging and explorations as well as blood and pathological exams. Weight loss was defined as loss more than 10 % of patient's body initial weight in 6 months or loss of 5% in 1 month. We included in the study patients with cT2-T4 or cN1-N2 adenocarcinoma of the rectum (stage II or III) and who are concurrently candidates for receiving neoadjuvant chemoradiotherapy. The lower tumour border has to be located less than 10 cm from the anal verge. Patients with stage I tumour, recurrent disease, previous chemotherapy or pelvic radiotherapy, hereditary or synchronous colorectal cancers, metastatic disease as well as those having refused to undergo neoadjuvant chemoradiation were excluded from the study. Preoperative staging was determined clinically by digital rectal examination, rigid proctoscopy, colonoscopy, thoraco-abdominopelvic CT, pelvic MRI, a complete blood cell count, liver function tests and serum CEA level. Patients with cancer related anorexia cachexia syndrome (CACS) in our study were defined by those who had a weight loss superior to 10%.

All patients received prior to surgery 5-fluorouracil-based chemotherapy with concomitant radiation. Preoperative radiotherapy consisted of 45 to 50 Gy in 23 to 25 fractions delivered to the pelvis in long course protocoles. For logistical and technical consideration, some patients received 25 Gy during 5 days or 39 Gy in 13 days according to short course protocole. Concurrent chemotherapy consisted of intravenous 5-Fluorouracil (400mg/m2 per day) and Leucovorin (20mg/m2 per day) during the first and fifth weeks of the initiation of radiotherapy; or concurrent Capecitabine (1.650mg/m2 per day) during each one of the days of the long course radiotherapy protocol.

The surgical procedure consisted of patients undergoing total mesorectal excision one week after the end of the short-course protocol and 6 to 8 weeks after the end of the long course protocol. The procedure either consisted of low anterior resection with colorectal or coloanal anastomosis or abdomino-perineal resection.

Tumor response assessment to chemoradiotherapy was performed by two experienced gastrointestinal pathologists and was categorized as pathological complete response (pCR) or not. Absence of viable adenocarcinoma cells in the surgical specimen defined the pCR, "Dworak" tumor regression grade 4.

As for statistical analysis, continuous variables were presented as mean value ± Standard Deviation (SD) or as median (IQR). Categorical variables were expressed as frequency and percentage. We have conducted a univariate association between each liable factor and the pCR using the $\chi 2$ test for categorical data or Mann–Whitney U test for continuous data. Univariate binary logistic regression analysis was done. All P values are two-tailed and a $p<0.05$ was considered significant. Multivariate analysis was performed using variable $p$ inferior or equal to 0.02. However, if factors relating to the same state and are elligible they were substituted to the more relevant. In this model we included also the strongest factor described in the litterature (Intervall from chemoradiotherapy and surgery) it was not All statistical analyses were performed using SPSS version 13 (IBM, Armonk, New York, USA).

## 4. Results

A total of 290 patients were managed for rectal neoplasm among which 88 (57.51%) met the inclusion criteria and were thereby included in our study. The median age was 53.5 years IQR (44 - 61) with 41 men (46.6%) and 47 women (53.4%). Demographical, clinical and pathological characteristics as well as treatment modality is characterized in (Table 1).

Pathological complete response was encountered in 16 patients (18.18%), 60 patients (68.18%) had incomplete response and 12

patients (13.64%) had no response. Clinical complete response was observed in only 6 patients, among which 5 were confirmed by pathology and only 1 showed tumor microscopic residue.

After univariate analysis general status deterioration was significantly associated to low pCR rate ($p = 0.004$). Weight loss ≥10%, asthenia and anorexia had respectively $p = 0.011$, $p = 0.050$ and $p = 0.021$. Other assessed variables did not show correlation to pCR namely sexe, age, Tumor stage, clinical nodular staging, tumor size and location, distance from anal margins, tumor aspect and differentiation, mucinous component, anemia, CEA ≥ 5 ng/ml, chemotherapy type and radiotherapy type. Chemoradiotherapy surgery interval as 8weeks was not statistically significant. General status deterioration as Weight loss was predictive factors in non cPR after chemoradiotherapy with odds ratios of 4,32 (95% CI 1,32 -16,07) $p$=0.016. Predictive factors of cPR in univariate analysis are shown in (Table 3).

Multivariate logistic regression analysis of candidate factors (CRT to surgery interval and Weight loss) showed that presence of Weight loss was statistically significant predictors of complete response occurrence with OR of 0.259 (95% CI 0.06 - 0.982).

**Table 1:** Demographic, clinical and therapeutic features of patients

| Variable | | Number (%) |
|---|---|---|
| Gender | | |
| Male | | 41 (46,6 %) |
| Female | | 47 (53,4%) |
| Age median | | 52,92 +/- 12,96 (21-87) |
| Distance from anal margin (cm) | | |
| Low rectum | | 63 (71,6 %) |
| middle rectum | | 25 (28,4 %) |
| Tumor size (cm) | | 3,08 +/- 2 (1- 8) |
| Tumor Localization | | |
| Anterior | | 1 (33,3 %) |
| Posterior | | 2 (66,7%) |
| Lateral | | 1 (6,3%) |
| Circumferential | | 15 (93,7%) |
| Tumor aspect | | |
| Budding | | 21 (51,2%) |
| Ulcero-budding | | 20 (48,8%) |
| Circumferential extension | | |
| ≤ 50 % | | 6 (75%) |
| >50% | | 2 (25%) |
| Pretherapeutic CEA concentration | | 2,23 (1,52 – 5,82) |
| Tumor grade | | |
| Well differentiated | | 40 (45,45 %) |
| Moderately differentiated | | 34 (38,64 %) |
| Poorly differentiated | | 11 (12,5 %) |
| Chemoradiotherapy | | |
| Concomitant chemoradiotherapy | | 67 (76.13%) |
| Radiotherapy alone | | 21 (23.86%) |
| Radiotherapy | | |
| *Short* | 25 Gy (5Gy x 5 fractions) | 9 (10,23%) |
| | 39 Gy (3Gy x 13 fractions) | 8 (9,1%) |
| *Long* | 45 Gy (1,8Gy x 25 fractions) | 1 (1,13%) |
| | 46 Gy (2Gy x 23 fractions) | 58 (65,9%) |
| | 50 Gy ((2Gy x 23) + (2Gy x 2 fractions)) | 12 (13,64%) |
| Time interval before surgery (weeks) | | 7 weeks |
| Surgery | | |
| Laparosscopy | | 23 (26,14%) |
| Laparotomy | | 65(73,86%) |
| Resection type | | |
| Anterior resection | | 48 (%) |
| Abdominoperineal resection | | 40 (%) |
| Resection quality | | |
| R0 | | 71 (80,68%) |
| R1 | | 3 (3,41%) |
| R2 | | 14 (15,91%) |

**Table 2:** Tumor node classification before and after radiochemotherapy

| | Before therapy (cT) | After therapy (ypT) |
|---|---|---|
| T category | | |
| Tx | 16 (18,18 %) | 0 ( 0%) |
| T0 | 0 (0%) | 16 (18,18%) |
| T1 | 0 (0%) | 2 (2,27%) |
| T2 | 24 (27,27 %) | 21 (23,86%) |
| T3 | 40 (45,45 %) | 40 (45,45%) |
| T4 | 8 (9,1 %) | 9 (10,24%) |
| N category | | |
| Nx | 16 (18,18 %) | 0 (0%) |
| N o | 49 (55,68 %) | 55 (62,5%) |
| N 1 | 23 (26,14 %) | 21 (23,86%) |
| N 2 | - | 12 (13,64%) |

**Table 3:** Univariate analysis of complete pathologic response; CRT Chemoradiotherapy

| | **Complete response** | | ***p*** |
|---|---|---|---|
| | Yes | No | |
| **Sex** | | | 0.801 |
| Male | 7 (17.1%) | 34 (82.9%) | |
| Female | 9 (19.1%) | 38 (80.9%) | |
| **Age in year median +/-SD** | 53.06 +/- 12.87 | 52.88+/- 13.08 | 0.988 |
| **Weight loss** | | | 0.011 |
| No | 11 (30.6%) | 25 (69.4%) | |
| Yes | 4 (8.7%) | 42 (91.3%) | |
| **Asthenia** | | | 0.05 |
| No | 9 (11.8%) | 22 (88.2%) | |
| Yes | 6 (12%) | 45 (88%) | |
| **Anorexia** | | | 0.021 |
| No | 10 (30.3%) | 23 (69.7%) | |
| Yes | 5 (10.2%) | 44 (89.8%) | |
| **Anemia ( Hb < 12 g/dl)** | | | 0.503 |
| No | 4 (14.3%) | 24 (85.7%) | |
| Yes | 6 (22.2%) | 21 (77.8%) | |
| **Tumor location** | | | 0.541 |
| Low rectum | 13 (20.6%) | 50 (79.4%) | |
| Middle rectum | 3 (12%) | 22 (88%) | |
| **Tumor size in cm (Median +/-SD)** | 2.25 +/- 1.06 | 3.25 +/-2.1 | 0.406 |
| **Tumor aspect** | | | 0.200 |
| Budding | 4 (19%) | 17 (81%) | |
| Ulcero- budding | 2 (6.3%) | 30 (93.7%) | |
| **CEA (ng/ml)** | | | 0.655 |
| <5 | 5 (16.7%) | 25 (83.3%) | |
| ≥5 | 1 (8.3%) | 11 (81.7%) | |
| **Initial tumor differentiation** | | | 0.459 |
| Well | 6 (15%) | 34 (85%) | |
| Moderately | 8 (23.5%) | 26 (76.5%) | |
| Poorly | 1 (9.1%) | 10 (90.9%) | |
| **Mucinous component** | | | 0.683 |
| No | 13 (17.3%) | 62 (82.7%) | |
| Yes | 1 (9.1%) | 10 (90.9%) | |
| **cT staging** | | | 0.264 |
| 2 | 6 (25%) | 18 (75%) | |
| 3 | 4 (10%) | 36 (90%) | |
| 4 | 1 (12.5%) | 7 (87.5%) | |
| **c N staging** | | | 0.306 |
| 0 | 6 (12%) | 44 (88%) | |
| + | 5 (21.7%) | 18 (78.3 %) | |
| **Chemotherapy** | | | 0.999 |
| 5 FU | 1 (35%) | 3 (65%) | |
| Capécitabine | 13 (20.6%) | 50 (79.4%) | |
| **Radiotherapy** | | | |
| Short | | | 0.370 |
| 25 Gy | 0 | 9 (100%) | |
| 39 Gy | 3 (37.5%) | 5 (62.5%) | |
| Long | | | |
| 45 Gy | 0 | 1 (100%) | |

| | | | |
|---|---|---|---|
| 46 Gy | 11 (19%) | 47 (81%) | |
| 50 Gy | 2 (16.7%) | 10 (83.3%) | |
| **CRT and surgery interval** | | | 0.356 |
| <8 | 11 (23.9%) | 35 (76.1%) | |
| ≥8 | 3 (13%) | 20 (87%) | |

## 5. Discussion

In this study 16 patients (18.18%) with locally advanced rectal cancer achieved pathologic complete response after being treated with neo-CRT, and weight loss remains the only risk factor for not achieving pCR.

The knowledge of the clinical factors predicting pCR is useful as they are already part of the initial investigations offering therefore the possibility of an initial prediction of the type of response. In our serie a slightly higher pCR rate has been noted between bulging tumors and ulcerative or infiltrating ones without being statistically significant in the univariate analysis (P = 0.200). The tumor size and distance from anal margins showed no statistical correlation either. On the other hand, the greater circumferential extent of tumor, although not statistically significant in our study, is associated in literature with a low percentage of pCR [10]. CEA is widely used in monitoring the diagnosis, treatment and prognosis of colorectal cancer. In our study the rate pCR was higher in patients with CEA levels < 5 ng/ml then those with higher CEA, although no statistical significance was proven, which could be due to the fact that we only had the CEA levels of 44 patients. Tomono et al demonstrated that CEA ≤5 ng/m before neoadjuvant radiochemotherapy is associated with high levels of pCR [11]. Moreover, a study by Kalady et al. showed that a CEA ≤2.5 ng/mL before treatment was not correlated with pCR [12]. This same study also showed no other correlation to radiotherapy treatment fields and dose, nor chemotherapy modalities. This was the case for our study as well, as there was no proven statistical difference in pathological response between different types of neoadjuvant radiochemotherapy protocoles.

The interval between radiochemotherapy and surgery wasn't statistically significant but we noticed a difference in the percentage of pCR between patients who were operated before and after 8 weeks. This observation has been subject to many studies linking a longer interval to a better chance of achieving pCR. One large study of 17,255 patients from the national cancer database found that waiting > 8 weeks after the conclusion of nCRT to perform surgery was associated with higher odds of attaining pCR [13]. Several studies confirmed this association in addition to demonstrating that the percentage of patients attaining pCR does not increase further after 11 weeks. Furthermore, some studies have proven that waiting for a superior period could have a negative impact on the quality of the mesorectal excision and the surgical outcome [13, 14].

Many other clinical factors have been assessed in literature among which are the tumor distance from the anal verge, the impact of post-nCRT tumor size, and post-nCRT circumferential extent of tumor.

Other predictors had been assessed. The study of molecular pathways associated with pCR, especially with the promising role of oncogenes, tumor suppressors and DNA repair genes in the cellular response to radiochemotherapy. Furthermore, the study of stem cell markers has also been able to provide more insight on the factors either increasing or decreasing the chances of achieving pCR, which is the case for CD133 and CD44 which have been correlating to minimal tumor response in many studies [15, 16]. We could not analyse these variables for this study.

By the way, cancer is a state of high physiological stress accompanied by tumor hypoxia/necrosis and local tissue damage, which is counterbalanced by the host body through the systemic release of proinflammatory cytokines and growth factors provoking the release of C reactive protein and the decrease of albumin production by hepatocytes (hypoalbuminemia). This latter is not only correlated to systemic inflammation but also associated to cancer prognosis, in addition to reflecting malnutrition, cancer cachexia and patient status alteration. In fact, cancer cachexia is the result of a disrupted equilibrium between reduced food intake through anorexia and an abnormal metabolism with depletion of the total body fat as well as the loss of body protein manifested in skeletal muscle atrophy. The glucose metabolism is also impacted through an increased glucose production, reduced hepatic gluconeogenesis, decreased glucose oxidation and insulin resistance, all responsible for an excess glucose. This anorexia–cachexia [17], has already proven to hold a prognostic significance in cancer patients in addition to affecting the immune system and its role as an extrinsic tumor suppressor and facilitator of tumor growth and progression [18, 19]. All these factors could justify the low pCR rate in patients with malnutrition observed in our multivariate analysis.

Our study was retrospective thus, had certain inherent limitations. Since the study was conducted on a period of 9 years, there is some therapeutic variations in chemoradiotherapy regimens between patients as well as concerning the clinical and pathological assessment. Not all patients were able to benefit from some investigations such as CEA levels which could have limited the proper assessment of the relationship between pCR and this factor. Prognostic tools can be used to guide clinical decisions, such as palliative care referral or chemotherapy discontinuation.

In conclusion, developing the ability to predict pathological response could open the possibility for discussing individualized therapeutic protocols based on the predicted response of a patient either before the start of treatment through clinical predictors or after, which will prevent unnecessary and aggressive therapy. The knowledge of such factors could also allow the establishment of predictive nomograms which could be included in each patient's therapeutic plan.

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