Predictive Factors of Histological Response after Preoperative Concomitant Radiochemotherapy in Middle and Low Rectal Cancer

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Abstract

Objective: The aim of our study was to identify potential predictive factors beyond pathologic response after neoadjuvant radiochemotherapy. Patients and Methods: Between January 2009 and December 2014, 40 patients with rectal carcinoma were included in the study. The treatment consisted of radiation ranging between 39 and 50.4 Gy associated with a concomitant chemotherapy with capecitabine. The correlation between histological response (complete response and downstaging) and potential predictive factors were investigated. Results: Complete response was 15% (06 patients), tumor regression of 32.5% (13 patients), and the absence of tumor response of 52.5% (21 patients). In univariate analysis, the circumferential extension of the tumor was significantly associated with tumor downstaging (p = 0.007) and complete tumor response (p = 0.001). However, the delay between the RCT and the surgery was a significant predictor for downstaging (p = 0.02). Conclusion: the parietal circumferential extension was a potential predictor of pathologic complete response (PCR) and downstaging after neoadjuvant chemoradiation. The time between the radiochemotherapy and the surgery was a significant predictor for downstaging. Delaying surgery beyond 8 weeks seems to result in the highest probability of PCR.

Keywords: Rectal cancer- adenocarcinoma- neoadjuvant radiochemotherapy- histologic response- predictive factors

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Introduction

Colorectal cancer (CRC) is the fourth most frequently diagnosed malignancy in both sexes and the second most common cause of cancer death in the world [1]. The advent of neoadjuvant radiotherapy in association with TME (Total Mesorectal Excision) surgery described by RJ Heald in 1982 [2]. has transformed the management of locally advanced forms (T3 T4 and/or N +) of middle and low rectal cancer, with a significant gain on local recurrence and an improvement in overall survival [3]. The association of chemotherapy with radiotherapy has further improved the carcinological and functional prognosis of this disease, favoring tumor regression (downstaging) or even tumor sterilization in some cases [4]. An interval of six to eight weeks between the end of radiochemotherapy (RCT) and surgery is recommended to optimize this tumor response and minimize toxicity [5]. In the literature, the tumor response correlates with recurrence-free survival and overall survival [6]. However, not all patients have the same sensitivity to this RCT: some tumors may not respond well to this treatment when others respond well.

The aim of this retrospective study was to identify the potential clinical, pathological, and therapeutic that could predict tumor response (complete pathologic response or downstaging to neoadjuvant RCT).

Materials and Methods

Between January 2009 and December 2014, 90 patients underwent preoperative RCT at the radiotherapy
department at University Hospital Mohamed VI, Oujda, Morocco.

Inclusion criteria for this study were included
biopsy-proven rectal cancer, the tumor of the lower and middle rectum, classified as cT3-T4 with or without regional lymph node metastasis and no evidence of distant metastasis. Among reviewed 90 patients, 50 patients were excluded for the following reasons: patients had no curative surgery (the tumor is unresectable or the patients refuse surgery), and patients who were transferred to other hospitals could not be traced by medical records. Therefore, 40 patients who met the inclusion criteria were analyzed in this study.

Patients underwent Pre-therapeutic staging workups, including digital rectal examination, full blood counts, biochemical tumor markers (but the concentration of pre-therapeutic ACE was not routinely required in all patients), colonoscopy with biopsy, chest radiography, abdominopelvic computed tomography (CT), pelvic magnetic resonance imaging (MRI). Endorectal ultrasonography (ERUS) was executed for one patient. The preoperative clinical stage was determined by CT scan, MRI, physical examination, or a combination of these.

Clinical and pathological characteristics of a population are described in Table 1. The study population was mostly females (57.5%) and had a median age of 56 years (range, 33 to 84 years). All patients had a tumor within 10 cm from the anal verge: 57.5% of the tumors were in the lower rectum and 42.5% in the middle rectum. The tumors had a mean diameter of 3 cm (range, 1 to 5 cm). The tumors were classified as cT3-T4 with or without hemorrhagic content. The tumors had a median number of retrieved and invaded LNs, with an average of 5 LNs invaded per patient. The tumors were classified based on the tumor regression grading (TRG) of Dworak et al. (Table 2) [8].

The univariate analysis indicated that the circumferential extent of the tumor was significantly associated with the histological response, whether complete or partial (downstaging), as a function of various potential predictive factors: age, sex, circumferential extent of tumor, tumor fixation, Distance from anal verge, Tumor differentiation, Hemoglobin level, clinical T classification, clinical lymph node (N) classification, radiation dose, and time between RCT and surgery. Multivariate analysis could not be done due to the lack of power due to low numbers. The analysis was performed with IBM SPSS statistics trial ver. 20.0 (IBM, Armonk, NY, USA). A p-value of < 0.05 was considered to indicate a significant difference.

Results
Pathologic examination of resected specimens revealed a complete histopathological response (PCR) in 06 patients (15%). Downstaging to ypT2 or less was observed in 19 patients (47.5%). Twenty-one patients (52.5%) showed no downstaging of either T or N stage and were classified as non-responders (Table 3). The tumor was classified as ypT0 in 6 patients (15%), ypT1 in 4 (10%), ypT2 in 9 (22.5%), ypT3 in 19 (47.5%) and ypT4 in two (5%).

The univariate analysis indicated that the circumferential extent of the tumor was significantly associated with tumor downstaging (p = 0.007) and with a complete tumor response (p = 0.001). However, a delay between RCT and surgery ≥ 8 weeks was a significant predictive factor for downstaging (p = 0.02). Other variables (sex, age, Tumor localization, tumor fixation, anemia, Distance from the anal verge, Tumor differentiation, clinical T classification, clinical lymph node (N) classification, radiation dose) were not significantly correlated with downstaging (Table 4 and 5).
Table 1. Clinical and Pathological Characteristics of Patients

| Variables                      | Results                  |
|--------------------------------|--------------------------|
| Sex                            |                          |
| Male                           | 17 (42.5 %)              |
| Female                         | 23 (57.5 %)              |
| Age Mean [min-max]             | 56.4 [33-84]             |
| Circumferential extent ≤ 50 %  | 27 (67.5 %)              |
| Circumferential extent > 50 %  | 13 (32.5 %)              |
| Fixation fixed                 | 10 (25 %)                |
| Fixation Not fixed             | 30 (75 %)                |
| Distance from anal verge       |                          |
| Middle rectum                  | 17 (42.5 %)              |
| Lower rectum                   | 23 (57.5 %)              |
| Hemoglobin level < 12 g/dl     |                          |
| Yes                            | 21 (52.5 %)              |
| No                             | 19 (47.5 %)              |
| Tumor differentiation          |                          |
| Well                           | 22 (55 %)                |
| Moderate                       | 18 (45 %)                |
| Poor                           | 4 (10 %)                 |
| Clinical T stage               |                          |
| T3                              | 38 (95 %)                |
| T4                              | 2 (5 %)                  |
| Clinical N stage               |                          |
| N0                              | 26 (65 %)                |
| N+                              | 14 (35 %)                |

Table 2. Dworak Regression Grade [9]

| Grade   | Description                                                                 |
|---------|-----------------------------------------------------------------------------|
| 0       | No regression                                                               |
| 1       | Dominant tumor mass with obvious fibrosis and/or vasculopathy               |
| 2       | Dominantly fibrotic changes with few tumor cells or groups (easy to find)   |
| 3       | Very few (difficult to find microscopically) tumor cells in fibrotic tissue or without mucous substance. |
| 4       | No tumor cells, only fibrotic mass (total regression or response)           |

Table 3. Comparison between Pre Treatment Radiological TN Stage and Post Treatment Pathological Stage (ypT ypN stage).

| PRE (cTN) | POST (ypTN) | TOTAL |
|-----------|-------------|-------|
| T0N0      | T0N+        | T1N0  | T1N+  | T2N0  | T2N+  | T3N0  | T3N+  | T4N0  | T4N+  |
| 4         | 0           | 0     | 2     | 7     | 0     | 6     | 6     | 0     | 0     | 25    |
| 2         | 0           | 0     | 2     | 0     | 2     | 3     | 4     | 0     | 0     | 13    |
| 0         | 0           | 0     | 0     | 0     | 0     | 0     | 0     | 1     | 0     | 1     |
| 0         | 0           | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 1     | 1     |
| TOTAL     | 6           | 0     | 2     | 2     | 7     | 2     | 9     | 10    | 1     | 40    |

Discussions

The factors that predict the response to neoadjuvant radiation chemotherapy in rectal cancer has not yet been well determined. Some recent studies also have investigated potential predictors of PCR and downstaging.

Tumor circumferential can serve as an important predictor of pathological tumor response. This was demonstrated in the study by Das et al. [11]. In this study, the results of the univariate and multivariate analysis indicate that the circumferential extent of tumor (less than 60%) predicts significantly the complete response rate and downstaging. These results agree with those of our study, the circumferential extent of a tumor was significantly predicted for PCR and downstaging with a p of 0.001 and 0.007 respectively.

The interval from the end of radiation to surgery has been of special interest and has been directly addressed by multiple studies as well as a meta-analysis [12]. Although the exact ideal interval to optimize PCR has not been identified, the overall conclusion from these studies is that PCR rates improve with delaying surgery by more than 6–8 weeks after the end of RCT. In this context, curative surgical treatments performed at six weeks from the end of the RCT may have interrupted ongoing necrosis, which means that some patients may achieve complete tumor regression if waiting times were longer [13]. Kalady et al. in 2009 [14] had shown that interval
Table 4. Unifactorial Analysis of the Complete Histological Response

| Variables                        | pCR   | No pCR  | P    |
|----------------------------------|-------|---------|------|
| Sex                              | Male  | 3       | 4    | 0.51 |
|                                  | Female| 3       | 20   |      |
| Age                              | Mean [min-max] | 54.83 [38-70] | 56.68 [33-84] | 0.76 |
| Circumferential extent           | Mean [min-max] | 32.5 [25-40] | 69.56 [25-100] | 0.001 |
| Fixation                         | Fixed | 1       | 9    | 0.52 |
|                                  | Not fixed | 5       | 25   |      |
| Distance from anal verge         | Middle rectum | 4       | 13   | 0.19 |
|                                  | Lower rectum | 2       | 21   |      |
| hemoglobin level < 12 g/dl       | Yes   | 2       | 19   | 0.28 |
|                                  | No    | 4       | 15   |      |
| Tumor differentiation            | Well  | 3       | 19   | 0.56 |
|                                  | Moderate to poor | 3     | 15   |      |
| Clinical T stage                 | T3    | 6       | 32   | 0.71 |
|                                  | T4    | 0       | 2    |      |
| Clinical N stage                 | N0    | 4       | 22   | 0.65 |
|                                  | N+    | 2       | 12   |      |
| Radiation dose                   | < 50 Gy | 3       | 17   | 0.66 |
|                                  | ≥ 50 Gy | 3       | 17   |      |
| delay between RCT and surgery    | < 8 semaines | 1       | 13   | 0.3  |
|                                  | ≥ 8 semaines | 5       | 21   |      |

Table 5. Unifactorial Analysis of the Tumor Response (Downstaging)

| Variables                        | Downstaging | No downstaging | P    |
|----------------------------------|-------------|----------------|------|
| Sex                              | Male        | 8              | 9    | 0.60 |
|                                  | Female      | 11             | 12   |      |
| Age                              | Mean [min-max] | 60.63 [37-84] | 52.57 [33-75] | 0.60 |
| Circumferential extent           | Mean [min-max] | 52.89 [25-100] | 74.05 [25-100] | 0.007 |
| Fixation                         | fixed       | 3              | 7    | 0.18 |
|                                  | Not fixed   | 16             | 14   |      |
| Distance from anal verge         | Middle rectum | 8              | 9    | 0.60 |
|                                  | Lower rectum | 11             | 12   |      |
| hemoglobin level < 12 g/dl       | Yes         | 7              | 14   | 0.58 |
|                                  | No          | 12             | 7    |      |
| Tumor differentiation            | Well        | 9              | 13   | 0.27 |
|                                  | Moderate to poor | 10      | 8    |      |
| Clinical T stage                 | T3          | 19             | 19   | 0.26 |
|                                  | T4          | 0              | 2    |      |
| Clinical N stage                 | N0          | 13             | 13   | 0.46 |
|                                  | N+          | 6              | 8    |      |
| Radiation dose                   | < 50 Gy     | 9              | 11   | 0.50 |
|                                  | ≥ 50 Gy     | 10             | 10   |      |
| delay between RCT and surgery    | < 8 weeks   | 2              | 12   | 0.02 |
|                                  | ≥ 8 weeks   | 17             | 9    |      |
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