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Original Research

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

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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.

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 Tabl 1. The study population was mostly females (57.5%) and had a median age of 56 years (range, 33 to 84 years). All the 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 involved more than 50% of the rectal circumference in 32.5% of the cases. During a digital rectal examination, the tumor was fixed in 25%. Almost all patients had a cT3 classification of their primary tumor (95%).

Variables	RESULTS
Sex	Male
	Female
Age	Mean [min-max]
Circumferential extent	≤ 50 %
	> 50 %

Fixation	fixed
	Not fixed
	Middle rectum
	Lower rectum
hemoglobin level < 12 g/dl	Yes
	No
Tumor differentiation	Well
	Moderate
	Poor
Clinical T stage	T3
	T4
Clinical N stage	N0
	N+

Table 1: Clinical and Pathological Characteristics of Patients

The patients then received preoperative CRT in the form of preoperative whole-pelvis radiotherapy. The mean dose was 46 Gy (range, 39 to 50 Gy): 15% of the patients received hypofractionated radiotherapy with the dose of 39 Gy in 13 fractions, 35% received 46 Gy in 23 fractions and 50% received 50 Gy in 25 fractions with a sequential boost of 4 Gy. All patients underwent CT simulation for three-dimensional radiotherapy planning. Delineation of the clinical target volume (CTV) included the gross tumor volume, mesorectum, presacral space, whole of the sacral hollow and regional lymphatics. The boost CTV included the gross tumor volume with 1 cm margins. The

relevant organs at risk volumes for this study were the bladder, femoral bones, and small bowel. The 6-MV or 18-MV photon beams were used for the treatment plan. Dosimetric parameters were calculated using cumulative dose volume histogram data. Preoperative chemotherapy was initiated on the first day of pelvic radiotherapy and was delivered concurrently with radiotherapy. All patients received 825 mg / m2 capecitabine orally twice daily, over the duration of radiotherapy with weekend breaks [7]. At the range of 32 to 137 days after the completion of preoperative RCT, all patients underwent a proctectomy associated with total mesorectal excision, with or without sphincter preservation. Anterior resection was performed in 19 patients (47.5%) and abdominoperineal resection in 21 patients (52.5%).

Histological examination of the operative specimen was performed to assess tumor type, histologic grade, number of retrieved and invaded LNs, maximum circumferential, distal extent, venous or perineural invasion, definitive staging (ypTNM after neoadjuvant treatment) evaluated according to the seventh edition of the UICC classification [8] Tumor regression grading (TRG) was done according to Dworak et al. (Tabl 2) [8].

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

Table 2: Dworak regression grade [9]

As previously used and validated in one study, the tumor response, whether complete or partial (downstaging), was characterized by a reduction in pathological staging (yp Stage) relative to the pre-therapeutic stage (c Stage) [9]. We defined the complete histological response as the total absence of tumor cells on the operative pathologic specimen at both the primary site and in regional LNs (ypT0 N0), grade 4 of the Dworak classification (Tabl 2) [9, 10]. The downstaging was defined as the lowering of the T classification to a stage less than or equal to ypT2.

A univariate analysis was done by the log-rank test. This analysis consists in studying the complete response and downstaging, after neoadjuvant treatment in middle and lower rectal cancer, as a function of various potential predictors 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 (Tabl 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%).

PRE (cTN)	POST (ypTN)	TOTAL
	T0N0	T0N+

T3N0	4	0
T3N+	2	0
T4N0	0	0
T4N+	0	0
TOTAL	6	0

Table 3. *Comparison between pre-treatment radiological TN stage and post-treatment pathological stage (ypT ypN stage).*

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 (Tabl 4 and Tabl 5).

Variables	pCR	No pCR	P
Sex	Male	3	4
	Female	3	20
Age	Mean [min-max]	54.83 [38-70]	
Circumferential extent	Mean [min-max]	32.5 [25-40]	69.56 [25-100]
Fixation	Fixed	1	9
	Not fixed	5	25
Distance from the anal verge	Middle rectum	4	13
	Lower rectum	2	21

hemoglobin level < 12 g/dl	Yes	2	19
	No	4	15
Tumor differentiation	Well	3	19
	Moderate to poor	3	15
Clinical T stage	T3	6	32
	T4	0	2
Clinical N stage	N0	4	22
	N+	2	12
Radiation dose	< 50 Gy	3	17
	≥ 50 Gy	3	17
delay between RCT and surgery	< 8 semaines	1	13
	≥ 8 semaines	5	21

Table 4: Unifactorial analysis of the complete histological response.

Variables	Downstaging	No downstaging	P
Sex	Male	8	9
	Female	11	12
Age	Mean [min-max]	60.63 [37-84]	52.57 [33-75]
Circumferential extent	Mean [min-max]	52.89 [25-100]	74.05 [25-100]
Fixation	fixed	3	7
	Not fixed	16	14
Distance from the anal verge	Middle rectum	8	9
	Lower rectum	11	12

hemoglobin level < 12 g/dl	Yes	7	14
	No	12	7
Tumor differentiation	Well	9	13
	Moderate to poor	10	8
Clinical T stage	T3	19	19
	T4	0	2
Clinical N stage	N0	13	13
	N+	6	8
Radiation dose	< 50 Gy	9	11
	≥ 50 Gy	10	10
the delay between RCT and surgery	< 8 weeks	2	12
	≥ 8 weeks	17	9

Table 5: Unifactorial analysis of the tumor response (downstaging)

Discussion

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 circumference 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 ≥ 8 weeks between treatment completion and surgical resection was significantly associated with a higher rate of PCR (p = 0.03). A study by D. A. M. Sloothaak et al. in 2013 [15]. showed that Delaying

surgery until 10-11 weeks after the end of RCT was significantly correlated with the complete histological response (p = 0.013). A recently published study using NCDB data provided the largest dataset focusing on the question of the interval from the end of CRT to surgery, and concurred with the published literature that an interval of more than 8 weeks is associated with increased rates of complete response [16]. In our study, the time between RCT and surgery was not correlated with a complete response (p = 0.3). However, a delay of ≥ 8 weeks was a predictor of downstaging (p = 0.02). These findings are consistent with other recent studies, where they observed more downstaging and better surgical results with a delay of more than 8 weeks [17]. The largest published dataset to date [18], dealing with predictive factors of PCR after preoperative RCT in 23747 patients with rectal cancer, is consistent with those findings but, furthermore, offer additional variables that can help identify those patients most likely to respond (lower tumor grade, lower clinical T and N stage and higher radiation dose, while lack of health insurance was linked with a lower likelihood of PCR). Other studies have reported some variables that were not included in this study, such as low pretreatment CEA level [19-24], low CEA level after RCT [25, 26], small pre- [27, 28] and post-treatment tumor size [29], pre-treatment tumor mobility on digital rectal examination [29], low clinical lymph node (N) classification [27], low tumor grade [30, 31], shorter distance from the anal verge [11, 30] , low neutrophil to lymphocyte ratio [28], type of concurrent chemotherapy used [32] and higher radiation dose [33]. These factors are subjective parameters that are susceptible to inter-observer variations, and it is difficult to assess these factors in a retrospective study.

In conclusion, the identification of predictive factors for tumor response could have potential therapeutic applications. The increase in the rates of complete or partial histological responses has led to the emergence of the concept of conservative approaches such as a wait-and-see strategy [34]. Further studies are required to determine strategies for optimizing the oncological outcome on an individual basis.

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