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RESEARCH ARTICLE

FIRST REPORT ON CLINICOPATHOLOGICAL CHARACTERISTICS, HISTOLOGICAL RESPONSE TO NEOADJUVANT THERAPY AND SURVIVAL OUTCOMES OF PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER IN NORTH-EST OF MOROCCO

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ABSTRACT

In this study, our aim was to provide a global overview of locally advanced rectal cancer (RC) epidemiology and its clinicopathologic characteristics as well as to identify predictive factors that may influence response to neoadjuvant therapy of a Moroccan population. Enrolled RC patients underwent neoadjuvant therapy, followed by surgery between 2011 and 2018 at the university hospital of Fez, Morocco. 250 patients were included in this observational retro-prospective cross-sectional study. 50.8% were women and 49.2% were men with a female to male ratio of 1.03. The average age at diagnosis was 56 years. Most of patients presented rectal bleeding as a revealing symptom (75.9 %). 84.8% were responders to neoadjuvant therapy and 51.2% were non responders. In univariate analysis, the responders group was found significantly associated with resection status, absence of perineural and vascular invasion, yp TNM, less metastasis, recurrence and long-term survival. In multivariate analysis, circumferential resection margins (HR: 3.154; 95% CI: 1.265-7.861; p=0.014), resection status (HR: 0.190; 95% CI: 0.042-0.849; p=0.030), ratio of positive lymph nodes (HR: 0.030; 95% CI: 0.002-0.391;p=007), and ypUICC stages (II: HR: 0.142; 95% CI: 0.021-0.974;p=0.047, III: HR: 0.050; 95% CI: 0.007-0.329;p=0.002, IV: HR: 0.172; 95% CI: 0.030-0.969; p=0.046) were found to be independent predictors of response to neoadjuvant therapy in RC.

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INTRODUCTION

Colorectal cancer (CRC) is the most frequent digestive cancer and represents the third most common cancer for men and the second for women worldwide(Bray et al.2018).

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Cancer is becoming a growing healthcare problem and a major cause of death worldwide. According to GLOBOCAN 2018, the mortality from cancer has increased from 8.8 million in 2015 to 9.6 million in 2018 with more than 18 million estimated new cases (Bray et al. 2018; Ferlay et al. 2015). Rectal cancer (RC) is the third most frequent cancer in men and the second in women and represents 10% and 9.2% of all cancers respectively (Bray et al. 2018). Moreover, RC alone is ranked as the 9th cancer worldwide after liver cancer, with 704,376 (3.9%) new cases and 310,394 (3.2%) death of all cancers reported in the latest updated GLOBOCAN report (Bray et al. 2018).

Notably, increased incidence of RC is seen in developed countries especially in the eastern of Europe (25.9%), Australia/New Zealand, and Eastern Asia compared with African and south Asian regions in both sexes (4.8%) (Deng 2017). In Morocco, CRC is the third cancer in women after breast, cervical and uterine cancers and the second in men after lung cancer (Elidrissi Errahhali et al. 2017). In addition, digestive cancers are mainly represented by CRC and gastric cancerwith a male predominance (Chbani et al. 2012). Current management of RC is difficult and requires multidisciplinary approaches including surgery, oncology and pathology as well as the growing impact of oncogenetics (Berho et al. 2015).

Basically, after diagnosis and staging of RC, curative carcinologic resection is performed after neoadjuvant chemoradiation therapy which has significantly improved 5-year survival by more than 50% (Nussbaum *et al.,* 2015). Optimal RC treatment depends upon a number of predictive and prognostic factors such as location in the rectum and local tumor extension (Rayan *et al.,* 2018). Efficacy of neoadjuvant treatment on tumor regression in Moroccan patients with RC has not been previously studied in addition to a lack of related epidemiological, clinical and pathological data. Our study was performed to provide clinical and histopathological characteristics of RC as well as to identify their association with therapy response and survival after neoadjuvant treatment for the first time in Morocco.

MATERIALS AND METHODS

Patient data: This is an observational retro-prospective cross-sectional study, performed at Hassan II university hospital (Fez, Morocco) in group colorec Fez, and enrolled 250 patients referred from different regions over 7 years between 2011 and 2018. Patients diagnosed with RC and treated with standard neoadjuvant chemoradiation therapy (45-50 Gy/25-28 fraction + capecitabine) or exclusive radiotherapy (39 Gy/3 fraction) followed by surgical resection were included.Demographic, clinical and pathological data were collected.

Ethics statement: The study protocol was approved by the local ethics committee under the reference number: 26/17 at the Faculty of Medicine and Pharmacy of Fez and Hassan II University Hospital and was conducted in accordance with the ethical standards of the Helsinki declaration. Informed consents were obtained from all patients.

Macroscopic and histological examination: After neoadjuvant treatment, all specimens were fresh or fixed in formalin 10% and were addressed to the department of pathology. Before cutting, the mesorectum was inked to assess the circumferential margins (Fig 1, a, b, c).After fixation, residual tumor and lymph nodes were totally included.Rectal carcinomas were staged according to the 8th edition of tumor node metastasis classification system.The commonly used Dworak tumor regression grading system (TRG) was employed to evaluate tumor response as previously described (Dworak, *et al.,* 1997; Langer *et al.,* 2018). TRG corresponding to complete and nearly complete regression were considered as responders group (Dworak 3 and 4), and TRG grades related to moderate, minimal, and no regression were considered as non-responders group (Dworak 0, 1 and 2). We also examined tumors for vascular and perineural invasions, circumferential resection margins and lymph node metastasis.

Follow-up: Patients with metastatic disease (ypUICC stage IV) were excluded as they may bias the survival analysis. Overall survival (OS) was defined as the time interval from the date of diagnosis until the date of death from any cause and was censored at the last follow-up if no death was recorded. Relapse-free survival (RFS) was defined as the time between the diagnosis to the first recurrence or metastasis.

Treatment: Patients diagnosed with rectal adenocarcinoma on biopsy are treated with long-course radiotherapy (45 Gy in 5 weeks) combined with concomitant chemotherapy (5-Fluoro-uracil in continuous infusion) or exclusive radiotherapy (39 Gy/3 fractions) followed by anterior resection or abdominoperineal excision indicated when the tumor involves the anal sphincter.

Statistical analysis: Chi-square and Student's t tests were used to compare data as appropriate. Survival rates were calculated using the standard Kaplan–Meier method, and the log-rank test was used to compare survival curves. Variables that were statistically associated with the 5% threshold were introduced intomultivariate analysis. In addition, p-values <0.05, <0.01, and <0.001 were considered statistically significant, very significant and highly significant respectively. All analyses were performed with SPSS Statistics version 21.0.

RESULTS

Demographic characteristics of our study population: Table 1 summarizes demographic, clinical, and histopathological characteristics of enrolled patients. 127 (50.8%) were women and 123 (49.2%) were men with a female to male ratio of 1.03. Patients were recruited to our university hospital from the six region of the country, including 199 (79.6%) patients living in Fez-Meknes region (Fig 2a). The average age at diagnosis was 56 years, ranging from 17 to 88 years including 58 years for males and 54 years for females (Fig 2b). 184 (65.6%) patients had an age above 50 years.

Clinical and histopathological characteristics: Globally (Table 1), the most common symptom in our RC cohort was rectal bleeding (75.9 %), followed by rectal syndrome (50%) (Fig 2c). The average diagnosis time was 7.35 months (0-31 months; median, 4 months). The average time between the end of the neoadjuvant treatment and surgery was 10.93 weeks (median, 8.5 weeks). 37 (14.8%) of deaths were recorded for 250 patients. Presence of metastases was reported in 75 patients (32%). The rate of recurrence was 7.6% (n=18). 22 tumors were located in the upper rectum, 108 in the middle rectum and 120 in the lower rectum. Average tumor size (longitudinal dimension) after treatment was 2.88 centimeter (cm) (0-10 cm; median: 3 cm). The most common histological type was adenocarcinoma which was seen in 235 cases (94%), and less frequently mucinous and signet ring cell carcinoma in 15 cases (6%). 233 tumors (93.6%) were well and moderately differentiated, and 17 (6.8%) were poorly or undifferentiated. 182 (72.2%) patients underwent long course of neoadjuvant chemoradiation and 68 (27.2%) were treated with exclusive radiation therapy. Low anterior, abdomino-perineal were performed in 198, and 52 respectively. Circumferential resection margin (CRM) was negative in 203 (81.2%) tumors and positive in 40 (16%) tumors. A vascular invasion was seen in 19 (7.6%) tumors. Perineural invasion was identified in 29 (11.6%) tumors after preoperative treatment. Moreover, according to Dworak grading system; 43 patients (17.2%) had

Table 1. Clinicopathological characteristics of study population

Clinicopathological characteristics	Total	n	Patients, n (%)
Patient characteristics			
Age (SD) Median Range Male Female	250	56 (14.54) 57 17-88 58.35 53.37	
Age ≤50 >50	250	86 164	34.4 65.6
Sex Male Female	250	 123 127	 49.2 50.8
Tumor characteristics			
Histotype Adenocarcinoma Mucinous/signet ring cell	250	 235 15	 94 6
Tumor location Upper Middle Lower	250	 22 108 120	 8.8 43.2 48
Tumor differentiation Well Moderate Poor Undifferentiated	250	 123 110 8 9	 49.2 44 3.2 3.6
Tumor Regression Grading (Dworak) 0 1 2 3 4	250	 8 42 78 79 43	 3.2 16.8 31.2 31.6 17.2
Perineural invasion No Yes	248	 219 29	 88.3 11.7
Vascular invasion No Yes	248	 229 19	 92.3 7.7
Treatment characteristics			
Neoadjuvant treatment nCRT (long course) Exclusive radiotherapy (RT)	250	 182 68	 72.8 27.2
Adjuvant treatment Yes No	228	 118 110	 51.75 48.25
Surgery Anterior resection Abdominoperineal resection	250	 198 52	 79.28 20.8
Circumferential resection margin (CRM) Negative≥2mm Positive< 2mm	243	 203 40	 83.5 16.5
Resection status Negative (R0) Positive (R+)	247	 231 16	 92.4 6.5
ypUICC stage 0 I II III IV	250	 39 58 72 69 12	 15.6 23.2 28.8 27.6 4.8
ypT 0 1 2 3 4	250	 43 9 71 118 9	 17.2 3.6 28.4 47.2 3.6
ypN N0 N1 N2	250	 175 49 26	 70 19.6 10.4
Number of dissected lymph nodes Average Median Range SD	245	 12.08 11 1-40 6.09	

Countine….

Number of lymph nodes	245		
<12		129	51.6
≥12+		121	48.4
Positive ratio of lymph nodes	152		
Average		0.09	
Range		0-0.8	
SD		0.18	
Time between diagnosis and last follow-up (months)	250		
Average		38	
Median		32	
Range		0-100	
SD		24	
Death	250		
Cases		37	14.8
Censored cases		213	85.2
Metastasis	229		
Yes		75	32
No		154	68
Recurrence	236		
Yes		18	7.6
Non		218	87.2

N: number of cases, SD: standard deviation, CRM: Circumferential resection margin, nCRT: neo adjuvant chemo radiotherapy, RT: Radiotherapy.

Table 2. Analysis of response to neoadjuvant treatment and clinicopathological characteristics

Age (mean; SD)	57 (128; 14.2)	54 (122;14.8)	0.217
Age			
≤50	40 (31.3)	46 (37.7)	0.173
>50	88 (68.8)	76 (62.3)	
Sex			
Male	63 (49.2)	60 (49.2)	0.548
Female	65 (50.8)	62 (50.8)	49,8
Histotype			
Adenocarcinoma	122 (95.3)	113 (92.6)	0.265
Mucinous/signet ring cell	6 (4.7)	9 (7.4)	
Tumor differentiation			
Well	59 (46.1)	64 (52.5)	0.266
Moderate	62 (48.4)	48 (39.3)	
Poor	2 (1.6)	6 (4.9)	
Undifferentiated	5 (3.9)	4 (3.3)	
Tumor location			
Lower	58 (45.3)	62 (50.8)	0.591
Middle	57 (44.5)	51 (41.8)	
Upper	13 (10.2)	9 (7.4)	
Neoadjuvant treatment			
nCRT (long course)	86 (67.2)	96 (78.7)	0.041
Exlusive radiotherapy (RT)	42 (32.8)	26 (21.3)	
Surgery			
Anterior resection	93 (72.7)	105 (86.1)	0.031
Abdominoperineal resection	35 (27,3)	17 (13.9)	
Circumferential resection margin (CRM)			
Negative			
Positive	90 (74,4)	113 (92.6)	<0.001
	31 (25,6)	9 (7.4)	
Resection status			
Negative(R0)	112 (89,6)	119 (97.5)	0.018
Positive(R1-R2)	13 (10,4)	3 (2.5)	
Perineural invasion			
Yes	23 (18.1)	6 (5)	0.001
No	104 (81.9)	115 (95)	
Vascular invasion			
Yes	15 (11.8)	4 (3.3)	0.016
No	112 (88.2)	117 (96.7)	
ypUICC stage			
0	0 (0)	37 (30.3)	<0.001
I	27(20.9)	33 (27)	
II	51 (39.8)	21 (17.2)	
III	46 (35.9)	23 (18.9)	
IV	4 (3.1)	8 (6.6)	
ypT			
0	0(0)	43 (35.2)	<0.001
1	2(1.6)	9 (7.4)	
2	38 (29.7)	33 (27)	
3	82 (64.1)	34 (27.9)	
4	6 (4.7)	3 (2.5)	
ypT			
0-2	40 (31.3)	83 (68)	<0.001
3-4	88 (68.8)	39 (32)	

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ypN	80 (62.5)	95 (77.9)	0.008
N0	28 (21.9)	21 (17.2)	
N1	20 (15.6)	6 (4.9)	
N2			
Tumor size after neoadjuvant treatment (average in cm)			
Mean (N;SD)	3.30 (106; 1.54)	2.48 (108;1.82)	<0.001
Number of Lymph Node dissected			
Average (N;SD)	12.71 (128; 6.69)	11.41 (122; 5.83	0.103
Ratio of positive lymph nodes			
Average (N;SD)	0.341 (48; 0.221)	0.228 (29; 0.218)	0.002
Number of lymph nodes			
<12	59 (46.1)	70 (57.4)	0.078
≥12	69 (53.9)	52 (42.6)	
Number of positive lymph nodes	1.48 (128; 2.74)		
Average (N;SD)		0.55 (122;1.33)	0.001
Mortality			
Death cases	26 (20.3)	11 (9)	0.013
Censored cases	102 (79.7)	111 (91)	
Metastasis			
Yes	42 (35.9)	33 (29.5)	0.326
No	75 (64.1)	79 (70.5)	
Recurrence			
Yes	13 (10.8)	5 (4.3)	0.059
Non	107 (89.2)	111 (47)	

N: number of cases, SD: standard deviation, CRM: Circumferential resection margin, nCRT: neoadjuvant chemo radiotherapy, RT: Radiotherapy.

Table 3. Multivariate analysis of different significance parameters

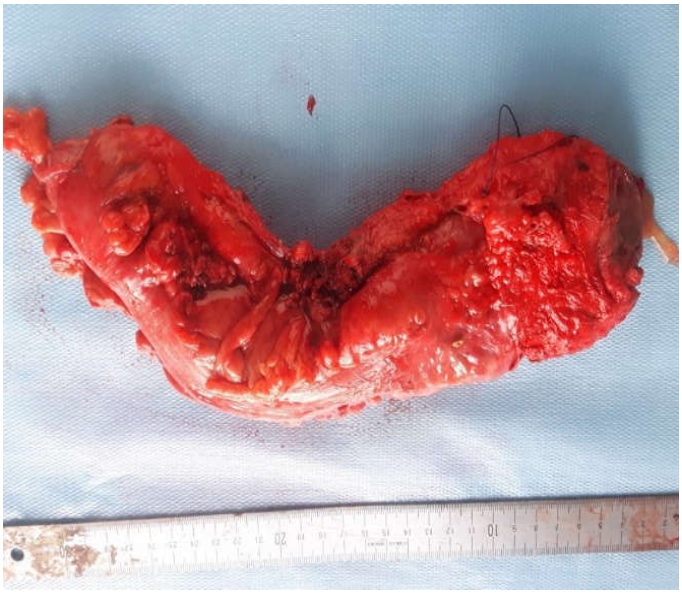
Significant variables	HR	95% CI	p value
Circumferential resection margin (CRM)	3.154	1.265-7.861	0.014
Resection status	0.190	0.042-0.849	0.030
Ratio of positive lymph nodes	0.030	0.002-0.391	0.007
ypUICC stage	reference	-	-
0	4.729	0.314-71.196	0.261
I	0.142	0.021-0.974	0.047
II	0.050	0.007-0.329	0.002
III	0.172	0.030-0.969	0.046
IV			

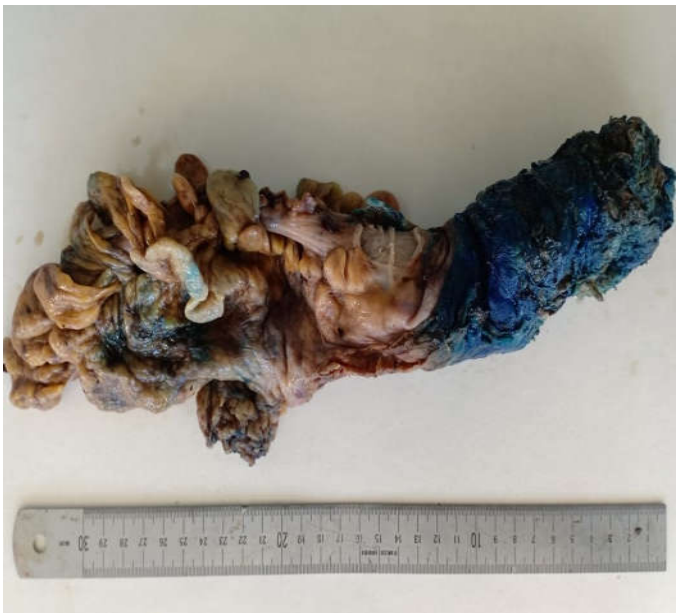
HR: Hazard ratio, CI: Confidence Interval

a complete regression and 242 (82.8%) presented an incomplete regression in which 8 (3.6%), 42 (16.6%), 78(31.2%), 79 (31.6%) were classified Dworak 0, 1, 2, 3 respectively. After neoadjuvant treatment, 43 (17.2%) subjects were ypT0, 9 (3.6%) ypT1, 71 (28.4%) ypT2, 118 (47.2%) ypT3 and ypT4 was present in 9 (3.6%) patients. In addition, 175 (70%) of cases were ypN0, 49 (19.6%) ypN1, and 26 (10.4%) ypN2. According to the classification of the International Union Against Cancer (UICC), 39 (15.6%) of tumors were classified as stage 0, 57 (22. 8%) as stage I, 69 (28.4%) as stage II, 67 (26.8%) as stage III and 16 (6 %) were stage IV. The average of tumor size after neoadjuvant treatment resection was 2.88 cm (0-10cm; median, 3cm). While its average size on pre-neoadjuvant treatment TDM was 6 cm (1.5-14; median, 6 cm). Average number of Lymph Nodes (LN) dissected was 12.08 (1-40; median, 11) of which 129 patients had dissected LN less than 12.

Patients' characteristics and histopathological response: Among 250 tumors analyzed, 128 (51.2%) were non responders, and 122 (84.8%) were responders Table 2. In the univariate analysis, neoadjuvant chemoradiation administration rate as long course was 78.7% in responders versus 67.2% in non responders (p=0.041). Low anterior resection was performed in 79.5% of responders versus 68% in non responders (p=0.031). Patients with tumors with negative circumferential resection were more likely to be classified as good responders in which 92.6% were responders and 74.4% were non responders (p<0.0001). Resection status was negative (R0) in 97.5 % of responders and 89.6% in non responders (p=0.018). Similarly, perineural invasion was negative in 95% of responders and 81.9% in non responders (p=0.001). Tumors with negative vascular invasion were seen in 96.7% of responders and 88.2% in non responders (p=0.016). In the responders, 31.1 % were pathological stage 0 as compared with non responders (0.8%) (p<0.0001).

Furthermore, there was also a very high significance in pathological T stage between the two groups, ypT1 was positive in 88.9% of responders groups, and 0.8% of non responders groups, and a 29.5% of ypT3 in responders versus 64.1% in non responders (p<0.0001). Furthermore, responders had a 77.9% of ypN0, versus 62.5% in non responders groups (p=0.008). Similar trends between the two treated groups were observed in other parameters such as tumor size after neoadjuvant therapy (p<0.0001), ratio of positive lymph nodes (p=0.002) and number of positive lymph nodes (p=0.001). The remaining clinic pathological features did not show significant results (Table 2). In multivariate analysis (Table 3), circumferential resection margins (HR: 3.154; 95% CI: 1.265-7.861; p=0.014), resection status (HR: 0.190; 95% CI: 0.042-0.849; p=0.030), ratio of positive lymph nodes (HR: 0.030; 95% CI: 0.002-0.391; p=0.007), and ypUICC stages (II: HR: 0.142; 95% CI: 0.021-0.974; p=0.047, III: HR: 0.050; 95% CI: 0.007-0.329; p=0.002, IV: HR: 0.172; 95% CI: 0.030-0.969; p=0.046) were the clinic pathological parameters significantly associated with response to therapy.





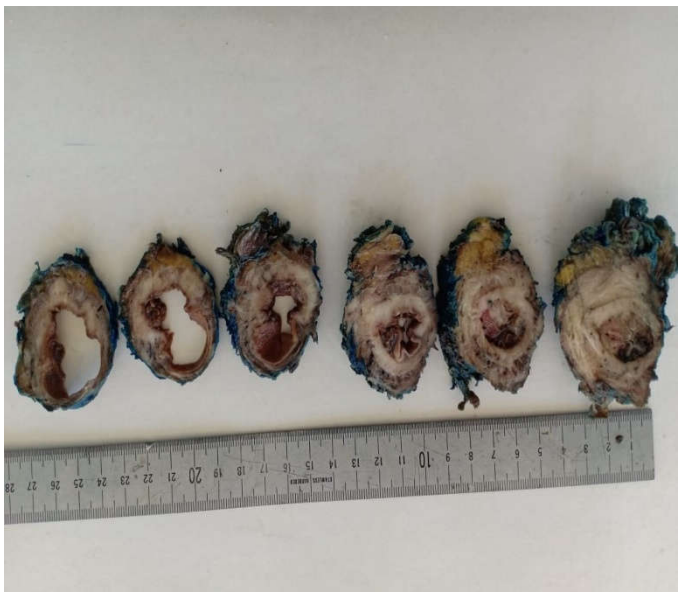
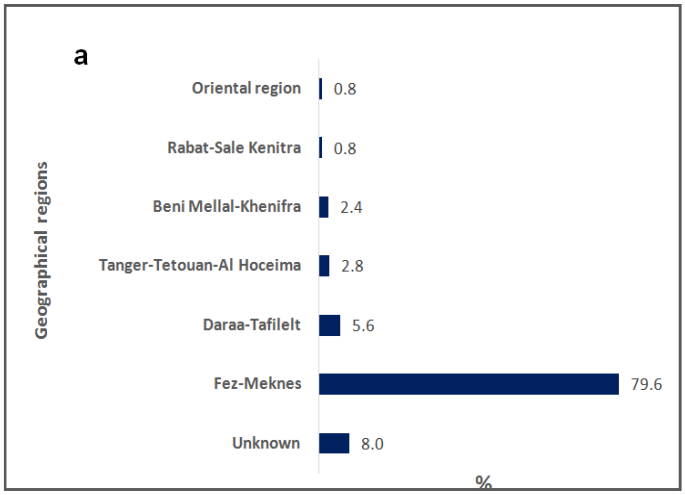
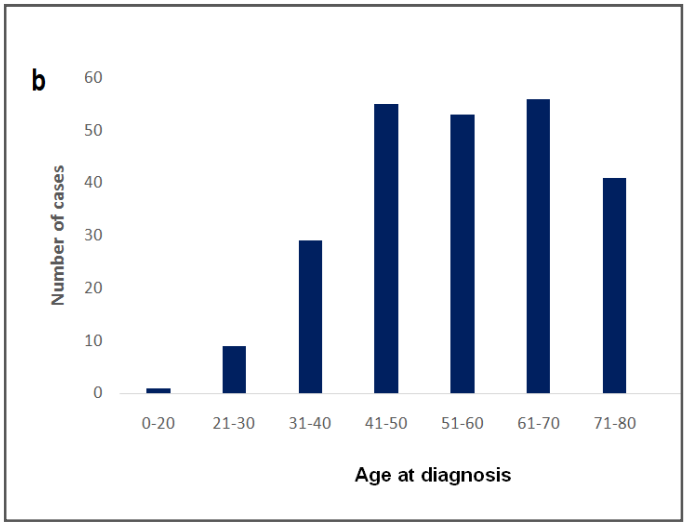


Figure 1. Example of abdominoperineal resection: (a) fresh resection, (b) surgical specimen fixed in 10% formalin and (c) procedure of dissection of rectal tumor resection





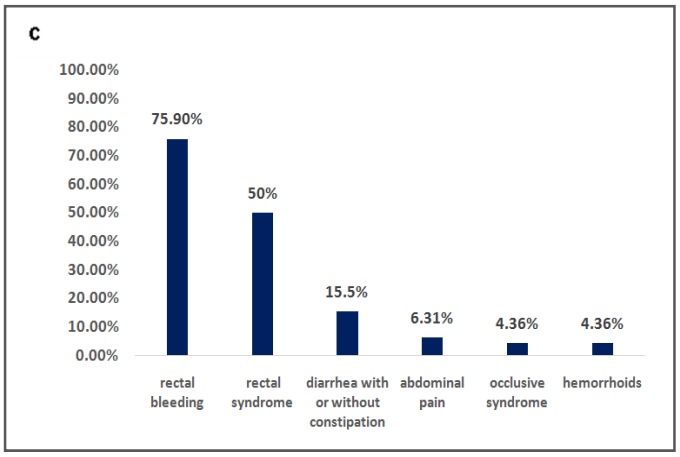


Figure 2. Distribution of study population by (a) geographical provenance, (b) age (c) and revealing symptoms

Follow-up and survival outcomes: The median follow-up period was 32 months with a range of 0-100 months in which 18 patients had recurrence (7.6%), 37 have died (14.8%) and 75 patients with metastasis (32%). Median RFS was 70 months with a range of 64.1-65.9 months. Median OS was 83.6 months with a range of 78.8-88.4 months. Moreover, 5-year survival for RFS and OS were 87% and 94.3% respectively. Fig 3 shows Kaplan-Meier curves of survival analysis of the treated population. When stratified according to pathologic response status (responders (Dworak 3 and 4) versus non responders (Dworak 0, 1 and 2) (Fig 4), global estimate of RFS

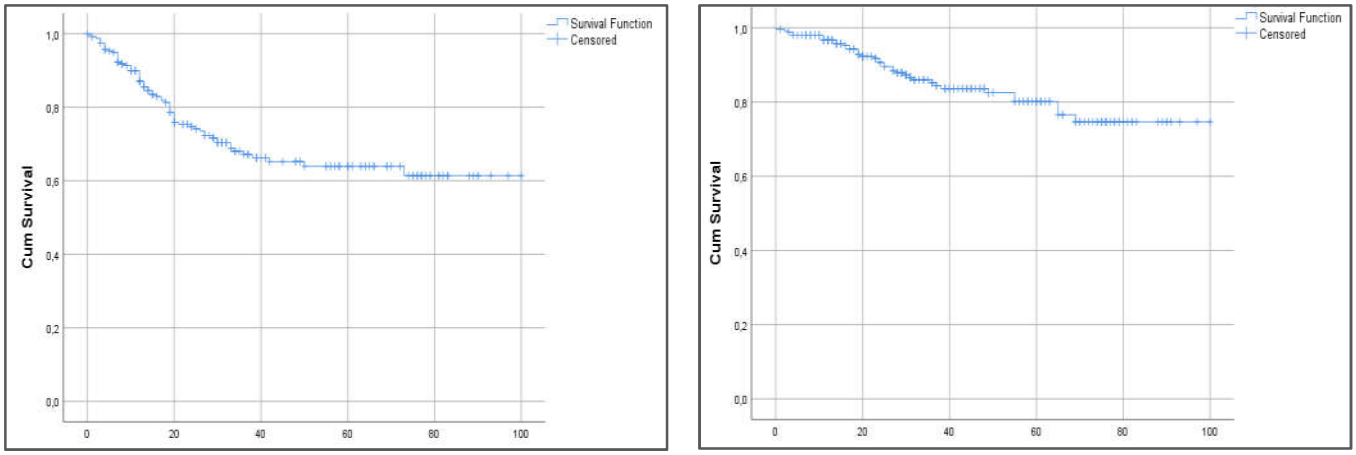


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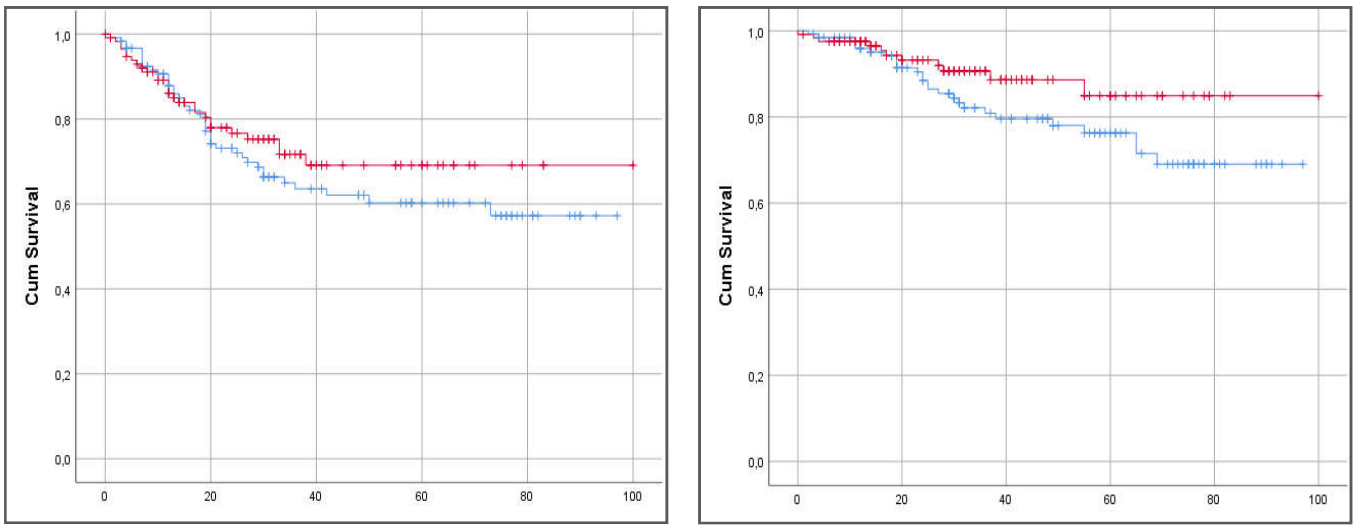
Figure 3. Kaplan-Meier curves of recurrence-free survival (RFS) and overall survival (OS) of our treated population. (A): RFS), (B): OS



a b

Figure 4. Kaplan-Meier curves of recurrence-free survival (RFS) and overall survival (OS) for response status of our treated patients. (a): RFS, (b): OS

in responders was superior compared with non responders (74.3% versus 65.5%). For OS, responders group showed higher rates (89.2%) compared to non responders (78%).At 5-years, RFS in the responding group was better compared with the non responders (75.3% versus 68.7%). However, this difference was not statistically significant (p=0.35). Similarly, OS in the two groups showed similar trends (p=0.088).

DISCUSSION

RC occupies an important place in digestive cancers in terms of prevalence and incidence. Pathological response to neoadjuvant treatment is known to be a key factor that determines outcomes and local recurrence. In this perspective, this preliminary report provides a global overview of RC in a Moroccan population. In addition, it demonstrates the relationship between therapeutic response after neoadjuvant treatment, clinicopathological features and prognosis.To our knowledge, this is the largest study to date in Morocco enrolling locally advanced RC patients alone. Regarding age at diagnosis, our report found 56 years with a female to male ratio of 1.03 which is relatively consistent with previous reports of North African countries such as Tunisia (Letaief *et al.,* 2017) , Libya (Elzouki *et al.,* 2014), and Algeria (Mesli *et al.,* 2016). Moreover, age is known to be a factor increasing risk of RC which was higher in men than in women in our cohort (58.35 versus 53.37 respectively) and thus, is consistent with the finding of the published epidemiological data (Marley *et al.,* 2016). RC occurs in the elderly population more than in young ones, accordingly, similar finding was observed in our study with 65.6% of patients with more than 50 years. 48 and 43.4 % of patients presented with RC in the lower and medium rectum. As expected, the most RC histological type was adenocarcinoma (94%) with rare perineural and vascular invasions (11.6 and 7.6 % respectively). After neoadjuvant chemoradiation therapy, our patients were responders in 78.7% (p=0.041) which is concordant with published trials (Gollin et al. 2016)[15]. It is well known that RC patients who undergo pathological assessment after neoadjuvant therapy have improved outcomes (Park et al.2012; Rodel et al. 2005; Fokas et al. 2014). Notably, this long course regimen significantly improved outcomes in the responding group compared with the non responding patients (p=0.041) suggesting its important place in the management of this subgroup of RC. Negative circumferential resection is known to be a good prognostic factor in this setting and influence survival of RC, our responding group showed higher rates of tumor response (92.6% versus 74.4%; p<0.0001)(Simillis et al.,2017).Moreover, perineural and vascular invasions were significantly different between the two groups (p=0.001 and

p=0.016 respectively) and may explain the low rate of recurrence in our RC cohort (Betge et al.,2011). Importantly, a very highly significant difference in pathological T stage between responders and non responders was seen including 88.9% of positive ypT1 compared with 0.8% respectively (p<0.0001) and thus, suggesting the effectiveness of the neoadjuvant therapy. In multivariate analysis, circumferential resection margins (HR: 3.154; 95% CI: 1.265-7.861;p=0.014), resection status (HR: 0.190; 95% CI: 0.042-0.849;p=0.03), ratio of positive lymph nodes (HR: 0.030; 95% CI: 0.002-0.391; p=0.007), and ypUICC stages (II: HR: 0.142; 95% CI: 0.021-0.974;p=0.047, III: HR: 0.050; 95% CI: 0.007-0.329;p=0.002, IV: HR: 0.172; 95% CI: 0.030-0.969;p=0.046) were found to be independent predictive factors of response to neoadjuvant therapy in RC. Notably,this confirms the current knowledge about the predictive value of these factors and also the similar results found by other teams (Simillis *et al.,* 2017; Mois et al.,2017;Zuo *et al.,* 2016) .In terms of survival, good outcomes were observed in concordance with the published literature (Goldenberg et al.,2018). Median OS exceeds 80 months with high rates of survival at 5-years (94.3%). Stratification of our RC patients according to Dworak response status demonstrated superiority in terms of RFS and OS but this was not statistically significant (p=0.35 and p=0.088 respectively) and was discordant with the current evidence which may be limited in our study by the retrospective design and the small sample size. However, our study has several strengths. First, the number of RC patients enrolled in our cohort is relatively large as well as a long period of follow-up. Remarkably, our report represents the largest in Morocco that shed light on clinical, epidemiological and pathological features in Moroccan patients with RC. Lack of data in some parameters, loss of follow-up and the retrospective design are the main limitations of our investigation and should be improved in a prospective study.

Conclusion

In our context, the responders group was found associated with resection status, absence of perineural and vascular invasion, ypTNM, less metastasis, recurrence and long-term survival. Notably, circumferential resection margins, resection status, ratio of positive lymph nodes, ypUICC stages were found to be independent predictive factors of response to neoadjuvant therapy in our RC patients. Further studies are needed to investigate biomarkers that could be associated with improved response to histopathological parameters in order to predict response to neoadjuvant therapy in RC.

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