

**PREDICTIVE FACTORS OF ONCOLOGICAL AND SURVIVAL OUTCOME OF SURGERY
ON MID AND LOW RECTAL ADENOCARCINOMA IN MOROCCO:
-A SINGLE CENTER STUDY-**

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ABSTRACT

Introduction: The aim of our study is to assess the 3 years oncological outcomes (survival rates and predictive factors of impaired Overall survival) in low rectal cancer patients operated with curative intent in the National Oncology Institute of Rabat.

Patients and methods: We conducted a retrospective study, including all patients operated for low rectal cancer in the surgical department of the national oncology institute of Rabat from January 2011 to December 2015

Preoperative characteristics, clinical and pathological variables including the histological type, the grade of tumor and TNM staging as well as perioperative and postoperative outcomes were recorded and analyzed to determine the predictive factors of impaired overall survival using cox regression and Kaplan Meier representation .

Results: In 81 low rectal adenocarcinoma operated in this period, the average survival period was of 55. 8 months. The Overall survival rate after 1 year, 2 years and 3 years are respectively of 94%, 89. 1%, and 82. 8%.

Predictive factors of impaired survival were age and advanced tumor staging with respectively a HR: 3.5; 95CI:1.1-11.4; p=0.03 and HR: 3.9 95CI:1.2-12.4; p=0.01.

Conclusion: This study showed survival rates after curative surgery for low rectal adenocarcinoma similar to those reported in the literature. Independent factors associated with overall survival were high age and advanced T stage, highlighting the importance of early cancer detection particularly in elderly subjects in order to improve the overall survival in rectal cancer Moroccan patients.

Key words: Disease free survival; Overall survival; Predictive factors; Rectal cancer; Recurrence.

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INTRODUCTION

Colorectal cancer is a critical global health issue as it represents the first gastrointestinal cancer and the fourth most common cancer in the Moroccan population. [1-3]. It's the third most commonly diagnosed malignancy and the second leading cause of cancer-related deaths in the world with a percentage of

9.2% of all malignant deaths (Globocan 2018) [4]. Over time, rectal cancer treatment has shown a continuous evolution with the association of neoadjuvant radiochemotherapy alongside surgery. This Latter having also known a major leap with the introduction of the anterior rectal resection and total mesorectal excision [5].

Variations of survival and recurrence rates among different populations and ethnic groups have been underlined showing the impact of not only the tumor stage and extent but also the patient demographic characteristics, thereby emphasizing the analysis of cancer survival as an essential indicator to early detection benefits and an assessment tool of the therapeutic results.

The aim of our study is to assess the 3 years oncological outcomes (survival rates and predictive factors of impaired Overall survival) in rectal cancer patients operated with curative intent in the National Oncology Institute of Rabat. In our Moroccan context, only one study reported overall survival of rectal cancer, in very low rectal adenocarcinoma specifically after APR. This is the first study in Morocco to report the predictive factors of the oncological outcome.

MATERIALS AND METHODS

Our article is written accordingly to the STROBE [6] (Strengthening the Reporting of Observational studies in Epidemiology) directive lines for observational studies.

Study design:

We conducted a retrospective cross-sectional study, including all patients operated for low rectal cancer in the surgical department of the national oncology institute of Rabat from January 2011 to December 2015.

Patients:

Inclusion criteria were: (1) Patients aged older than 18 years, (2) preoperative Histological adenocarcinoma confirmation, (3) rectal cancer within 10 cm from the anal verge, (4) patients having received neoadjuvant treatment, (5) curative surgery with assessable distal, and circumferential margins (6) With or without adjuvant therapy.

Exclusion criteria :(1) Upper rectal cancer location, (2) palliative surgery.

Surgical procedures:

All patients underwent prior to surgery: (1) Clinical, biological and imaging explorations with Thoracoabdominopelvic computed tomography in addition to abdominopelvic magnetic resonance imaging when needed (2) 45 Gy neoadjuvant

chemoradiotherapy according to national guidelines (3) multidisciplinary meeting therapeutic decision. Conservative and non-conservative procedures were indicated on the basis of malignant sphincter involvement and the patient wishes. Colorectal or colo-anal anastomosis were performed in case of distant rectal tumor while an abdomino- perineal resection (APR) with definitive iliac colostomy (DIC) or pseudo-continent perineal colostomy (PCPC) was applied in case of proximally located tumors [7 8].

Follow up:

Preoperative characteristics, clinical and pathological variables including the histological type, the grade of tumor and TNM staging as well as perioperative and postoperative outcomes were recorded. Dworak classification was used to analyze the different regression grades in the pathological specimen. [9] Patients were contacted during their follow-up visits to the hospital or contacted via telephone. Deaths of subjects were confirmed via contact with their families and relatives. Survival periods were calculated from the date of surgery to the date of either last follow-up or death. Patients alive at the end of the follow-up and those lost to follow-up were censored either at the last contact or at death.

Statistical analysis:

Statistical analyses were performed using SPSS 21 software (IBM Statistics, SPSS Inc, Chicago, il). Survival curves and disease free curves were calculated using Kaplan Meier estimator. The differences in patient survival periods were determined in relation to socio-demographic, clinical and pathological parameters. The determination of prognostic factors influencing global survival rates was done through uni and multivariate studies on the Cox proportional-hazards model. The approval of this study was obtained by our local institutional review board.

RESULTS

Population:

During the study period, there were 99 patients with rectal cancer, 81 of which presented with tumors within 10 cm from the anal verge. Seventy-seven patients survived the post-operative period and were included in the survival analysis.

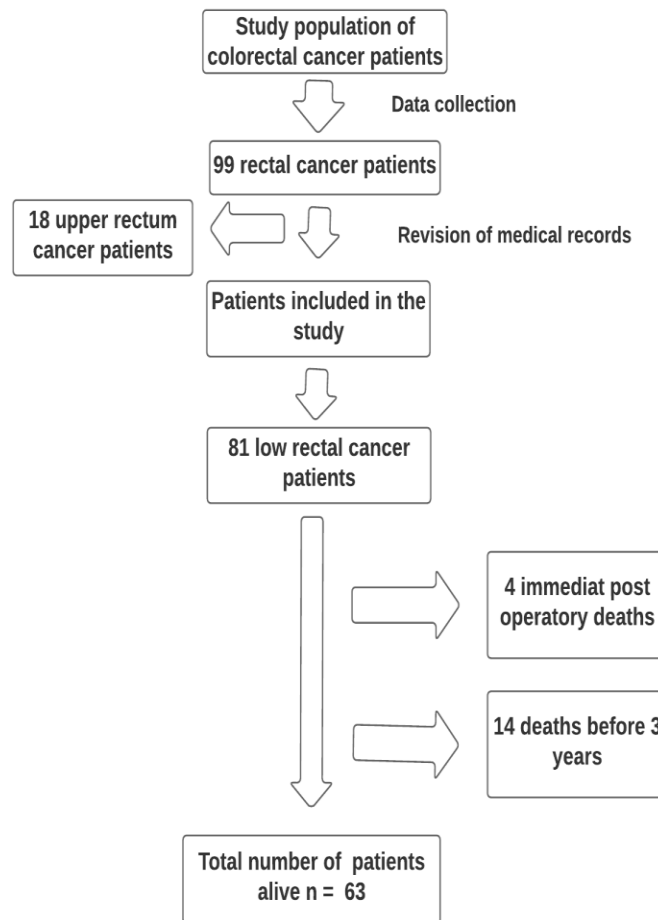


Figure 1: Flow chart of patient's recruitment

Demographics:

A total of 81 eligible patients were included in the analysis among which 43 males and 38 females. The median age was of 60.43 years (Quartiles 48.2; 67.8 with a range 25 and 90). (Table I)

Median survival rate:

The average survival period of our patients was of 55. 8 months. The survival rate after 1 year, 2 years and 3 years are respectively of 94%, 89. 1%, and 82.8%.

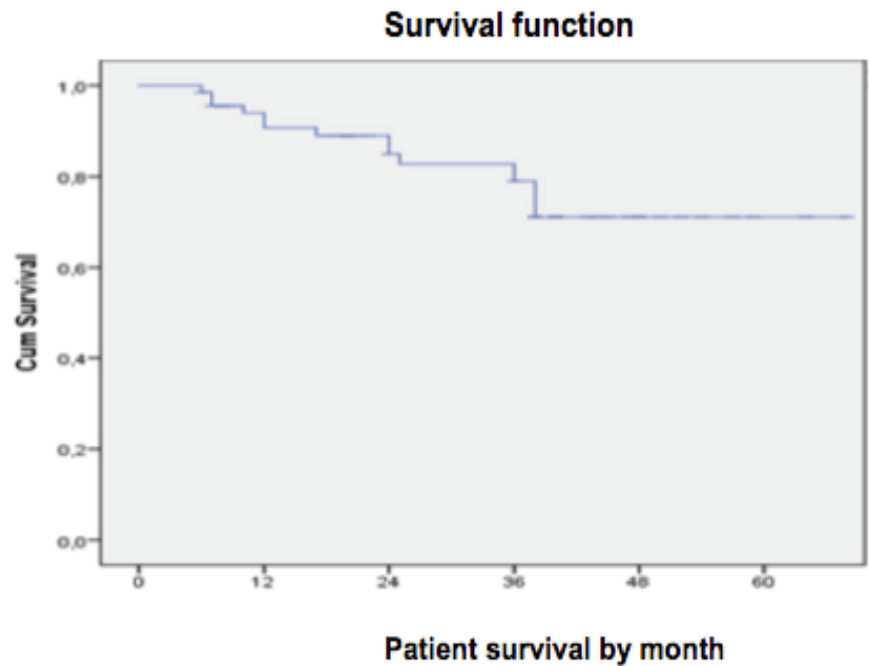


Figure 2: Overall 3-year survival in low rectal cancer patients

Univariate analysis:

Table I shows the results of the univariate analysis conducted in order to determine the impact of multiple factors such as sociodemographic (age, sex), clinical (tumor location, complication rate), pathological (TNM staging pre and post therapeutically, circumferential resection margin, nodal staging) and therapeutic impact (resection type, stoma type, neoadjuvant treatment).

Gender did not have a significant impact. Older patients (> 65 years) had lower survival rates, although not significant ($p = 0.08$).

Overall survival was the same for lower and middle rectum patients. Resection type was not associated with overall survival. All patients with Dworack 4 type had survived at least 5 years. The lymph node status and the circumferential resection margin were not considered as a factor influencing the overall survival. Patients with preoperative stages T1, T2 had better overall survival ($p = 0.02$) than patients with T3-T4 stage. Finally, overall survival was higher in patients without postoperative complications

Table I: Association of socio-demographical, clinical and pathological factors with overall survival in low rectal cancer patients (univariate analysis)

Variable	Nb (%)	Median survival in months (Quartiles 25-75)	p value
Gender			
Female	38 (46.9%)	54.1 (50.3-57.4)	0.281
Male	43 (53.1%)	53.2 (48.1-58.2)	
Age			
<65yo	54 (66.7%)	57.3 (51.1-60.2)	0.083
>65yo	27 (33.3%)	44.2 (40.1-51.2)	
Tumor location			
< 5cm	47 (58%)	58.5 (53.1-60.2)	0.753
> 5cm	34 (42%)	48.8 (41.1-58.2)	
Pre-therapeutical TNM staging			
T1-T2	29 (35.8%)	60.7 (58.4-63.9)	0.022
T3-T4	52 (64.1%)	40.3 (38.1-45.8)	
Post-therapeutical TNM staging			
T0-T1-T1			0.82
T3-T4	38 (44.1%) 43 (55.9%)	56.1 (52.5-62.7) 48.7 (43.1-56.2)	
Nodular staging			
N0	49 (63.6%)	56.2 (52.7-60.2)	0.7
N1	28 (36.4%)	48.8 (46.1- 56.3)	
Resection type			
AR	46 (56.8%)	49.4 (45- 54.7)	0,842
APR	35 (43.2%)	56.4 (51.3- 59.3)	
Complications			
Yes	14 (17.28%)	37.3 (34.2- 43.6)	0.09
No	67 (82.71%)	57.2 (52.1- 61.3)	
Circumferential resection margin			
R0	63 (81.8%)	53.9 (49.2- 56.1)	0.6
R1	14 (18.2%)	51.8 (47.4- 55.2)	
Response to neoadjuvant treatment			
Dworak 0-1-2-3	73 (94.8%)	52.8 (48.7- 55.9)	0.41
Dworak 4	6 (7.8%)	60 (56.4- 63)	

Multivariate analysis:

We included in the multivariate study all variables with a P< 0.2. Only age and advanced tumor staging

showed an impact with a HR of 3.5 and 3.9 respectively (**Table II**).

Table II: Prognostic factors for the 3 year survival in rectal cancer patients on multivariate analysis

	HR	95% CI	p
Age > 65 years	3.5	1.1 - 11.4	0.03
Complication occurrence	0.3	0.086 - 1.2	0.1
T3 T4 staging	3.9	1.2 - 12.4	0.01

Oncological results:

In our series, the disease-free survival at 1 year, 2 years and 3 years were respectively 75. 8%, 68.9%,

and 66.9%. Mean disease free survival period was 48.4 months.

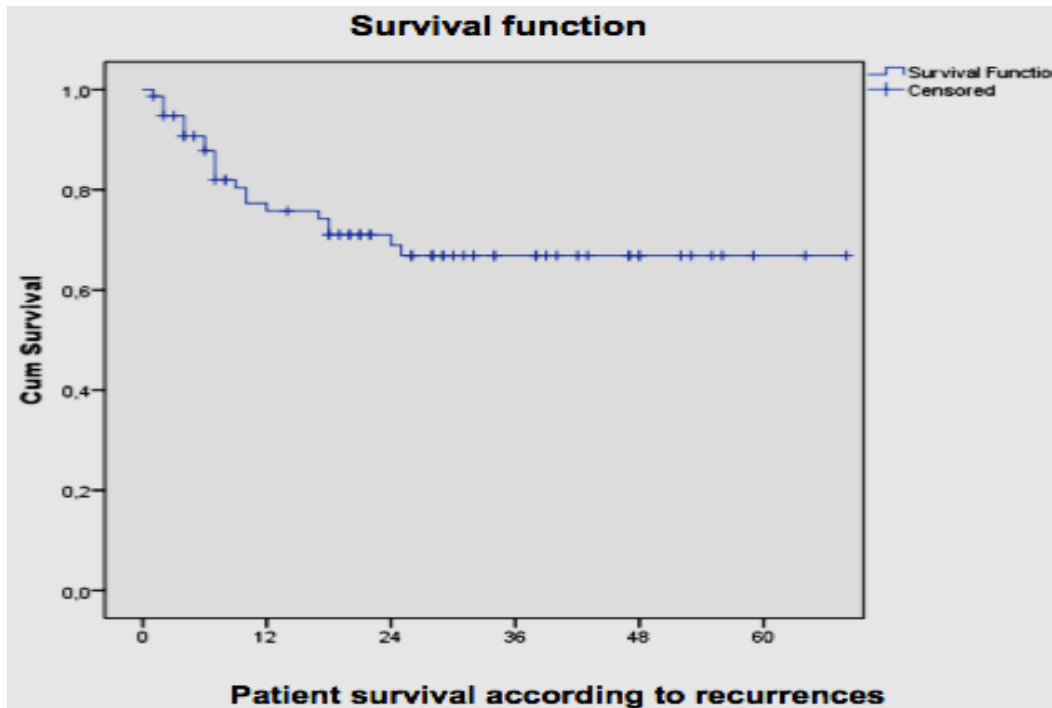


Figure 3 : 3 year Disease free survival of low rectal cancer patients

DISEASE RECURRENCE OCCURRENCE:

The median time limit for recurrence occurrence was 9 months post-operative with extremes going from 1 to 24 months and an occurrence peak from 6 to 24 months. (Fig. 4)

In our series 6 patients (7.8%) presented with local recurrences which occurred in a median time of 9

months after surgery, (Quartiles 6; 14 and extremes going from 2 to 24 months). As to distant recurrences, they were observed in 11 patients (14.3%) in a median postoperative period of 8.5 months (Quartiles 6; 13 and [1- 23] months). These distant recurrences were located in the liver (n=5), lungs (n=5), nodules (n=2) and bone (n=1).

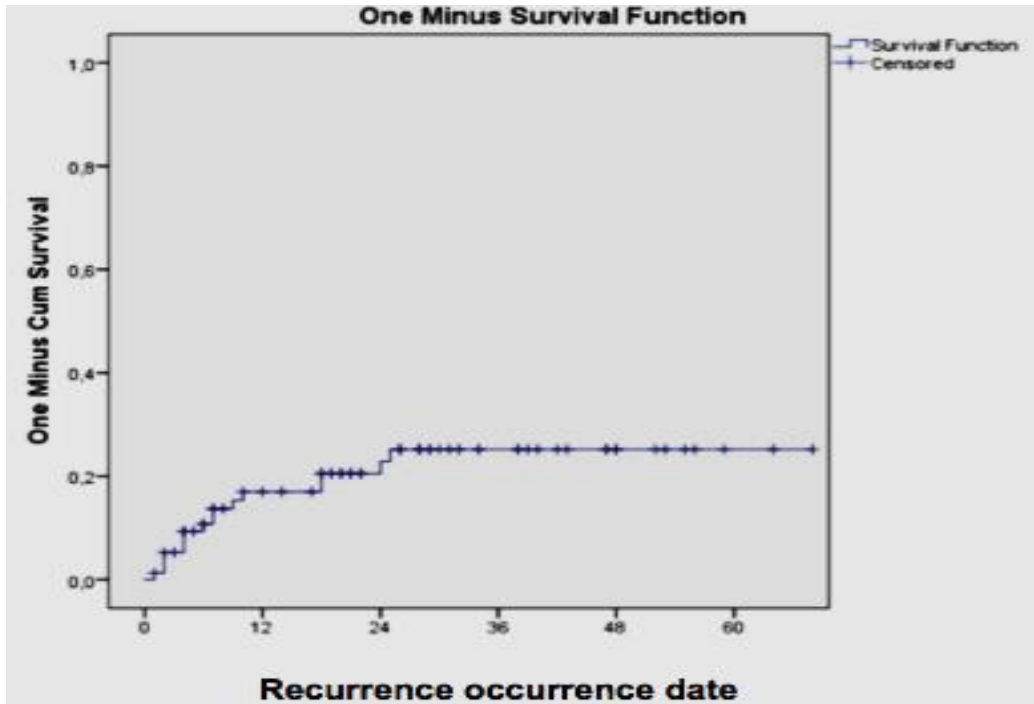


Figure 4: Recurrence occurrence in low rectal cancer patients

DISCUSSION

In the past decade, survival rates of colorectal cancer have improved due to early detection and more effective treatments. However, colorectal cancer remains a major cause of mortality in developing countries. Our study therefore in the first study in Morocco to investigate the predictive factors to the survival rate of colorectal cancer.

In this study, the overall survival at 1 year is of 94%, at 2 years of 89% and at 3 years is of 82.8% which corresponds to the average colorectal cancer 5 years overall survival rate of 60% to 70% [10], being thereby much higher than in sub-Saharan countries like the Gambia and Uganda where the survival was less than 8% [11]. Demographic factors such as the age of the patients influenced survival rates with an HR 3.5 (95%CI 1.1-11.4). Also numerous studies report on the role of patient's gender as a prognostic factor such as the study on gender differences in colorectal cancer survival in Japan where female patients had a better survival [12], but the majority of the available studies showed that gender had no significant role in predicting survival, being by that consistent with findings from our current study.

The tumor location in our study had no impact on survival, knowing that the results in the literature

showed adverse opinions to whether the ultra-low rectum location influenced or not overall survival. [13] Studies have shown that overall survival may be affected by the tumor staging with better survival for patients with stages T1-T2 than those with T3-T4, which was the case for our study (HR 3.5 95CI 1.2-12.4). In fact, the increased survival of patients with stages T1 and T2 compared to those staged T3-T4 has been reported to be an independent prognostic factor of survival. [14] Additionally, a great drop in survival has been proven to exist between stages T3 and T4 too. [15]

As to nodal invasion, it appeared to have no significant impact on the survival of our studied population which opposes to the results in literature indicating that when no nodular involvement was found, the 5-year survival rates were of 70%-80% in contrast to 30%-60% in cases of node-positive disease. [16] On another side, whether patients underwent anterior resection or abdominoperineal resection did not have an impact on survival.

Many studies have put great emphasis on the circumferential resection margins, with the minimum having to be superior to 1mm, on the overall survival [17, 18]. This wasn't the case for our study, which could be due to the small sample size of patients in our study.

As to the oncological outcomes, the postoperative tumor staging in the literature shows a response rate to neoadjuvant treatment from 5 to 25%. In our series, 7,5% of our patients presented with complete response. Local recurrences went from 30-40% with the normal procedure, 0 to 28% in ISR [19] and less than 10% with total mesorectal excision.

Ever since the adoption of neoadjuvant radiotherapy, recurrence rate went down 2 to 3 times. In fact, the effect of neoadjuvant radiotherapy has already been proven especially in tumors staged T3 or more [20] and also in Moroccan studies.

In our study, the overall survival was associated with complication occurrence, as it has been proven in other international studies where the difference in survival was very significant (84.9% vs. 69.8%, $p = 0.022$). [21] Another factor affecting overall survival was Age > 65 years. In fact, many studies showed the impact of age on the management and the outcome of colorectal cancer as it makes the patient more prone to postoperative complications as well as to mortality. [22]

Our analysis of the factors predictive of survival complements the findings in the literature as age and pathological T stage has been strongly linked to survival in German and French studies [23 24].

Disease-free survival after 3 years in our study was 66,9% and is similar to other studies. [25] Additively the median time limit for recurrence occurrence was 9 months which correlates with findings in literature stating that approximately 60%-80% of recurrences develop within the first 2 years after surgery and cases of recurrence 5 years after surgery are rare. [26 27]

STUDY LIMITATIONS

The primary limitation of our study is its retrospective design. Furthermore, the limited number of patients included was due to the single-center study and restrictive inclusion criteria (rectal adenocarcinoma within 10 cm of the anal verge). Finally, some interesting pathological characteristics such as lymphovascular and perineural invasion were not analyzed.

STRENGTH OF THE STUDY

This is the first study in Morocco to report the predictive factors of oncological outcomes. Although including a small population size, patients were treated according to national guidelines with adequate follow-up.

CONCLUSION

The study showed survival rates after curative surgery for mid and low rectal adenocarcinoma similar to those reported in the literature. Independent factors associated with overall survival were high age and advanced T stage, highlighting the importance of early cancer detection particularly in elderly subjects in order to improve the overall survival in rectal cancer Moroccan patients.

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