

# Risk factors for anastomotic leakage after anterior resection for rectal adenocarcinoma

## Facteurs de risque de survenue de fistules anastomotiques après résection antérieure pour adenocarcinoma du rectum

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### RÉSUMÉ

**Prérequis :** La fistule anastomotique (FA) est une cause importante de morbidité après chirurgie pour cancer rectal.

**But:** Analyser les facteurs de risque associés à la survenue de FA après résection antérieure pour adénocarcinome du rectum.

**Méthodes:** Nous avons collecté les données de tous les patients qui ont eu une résection antérieure pour adénocarcinome du rectum à la Clinique Chirurgicale C (Hôpital Ibn Sina. Rabat, Maroc), entre janvier 2001 et décembre 2010. Les associations entre les variables et la FA ont été analysées en uni et multivariée.

**Résultats :** Notre travail a inclus 130 patients. Une FA est survenu chez 28 patients (21.5%). Les analyses uni et multivariées ont montré que le taux de FA était significativement supérieur après radiothérapie néoadjuvante (34.2% vs. 12 %,  $p = 0.002$  – OR 3.8 – CI 95%: 1.5 – 9.4). Il n'y avait de différence significative dans le taux de FA entre les patients avec et sans stomie de protection. Dans le groupe des patients avec FA, le taux de réinterventions était significativement inférieur en cas de stomie de protection (31.8% vs. 83.3%,  $p = 0.04$ ).

**Conclusion :** La radiothérapie est un facteur de risque de survenue de FA. La confection systématique d'une stomie de protection chez les patients recevant une radiothérapie néoadjuvante est conseillée afin de réduire le taux de réinterventions associées au FA.

### Mots-clés

Fistule anastomotique, cancer rectal, adenocarcinoma, morbidité, radiothérapie

### SUMMARY

**Background:** Anastomotic leakage (AL) is an important cause of morbidity after surgery for rectal cancer.

**Aim:** to analyze the risk factors associated with anastomotic leakage after anterior resection for rectal adenocarcinoma.

**Methods:** We collected data from all the patients who had surgical resection with an anastomosis, for rectal adenocarcinoma at the Surgical Clinic C (Ibn Sina Hospital, Rabat, Morocco), between January 2001 and December 2010. The associations between variables and anastomotic leakage were studied using univariate and multivariate analysis.

**Results:** Our study included 130 patients. Anastomotic leakage occurred in 28 patients (21.5%). Univariate and multivariate analysis showed that the rate of anastomotic leakage was significantly higher in patients who received preoperative radiotherapy (34.2% vs. 12 %,  $p = 0.002$  – OR 3.8 – CI 95%: 1.5 – 9.4). There was no significant difference in the rate of AL between patients with or without a protective stoma. In the group of patients with AL, the rate of reoperation was significantly lower in patients with a stoma protection (31.8% vs. 83.3%,  $p = 0.04$ ).

**Conclusion:** Radiotherapy is a risk factor for anastomotic leakage. The systematic design of a protective stoma in patients receiving neoadjuvant radiotherapy is advisable to reduce the rate of reoperations associated with AL.

### Key words

Anastomotic leakage; Rectal neoplasm, Adenocarcinoma, Morbidity, Radiotherapy

Anastomotic leakage (AL) is an important cause of morbidity after surgery for rectal cancer. In the literature [1], the rate of AL varies from 3 to 27%. Recently, with advances in the management of rectal cancer (neoadjuvant treatment, sphincter preservation, low anastomoses), sphincter-sparing operations became more frequent and the number of patients at risk of AL increased. Despite the advances in perioperative management of rectal cancer, this complication remains a major problem in rectal cancer surgery. Mortality associated with AL is estimated between 6 and 27% [1, 2]. Several studies also reported a significant increase in the rate of local recurrence and a decrease of five-years survival after AL [2][3-5]. Prevention is the best treatment and therefore, it is essential to understand the risk factors that predispose to AL [6].

The aim of this study is to analyze the risk factors associated with anastomotic leakage following anterior resection for rectal adenocarcinoma.

## PATIENTS AND METHODS

We collected data from all the patients who had surgical resection (curative or palliative) with an anastomosis, for rectal adenocarcinoma (0 to 15 cm from the anal verge) at the Surgical Clinic C (Ibn Sina Hospital, Rabat, Morocco), between January 2001 and December 2010. We identified in this group patients who had postoperative clinical anastomotic fistula (Pus or fecal discharge from the drain, pelvic abscess, peritonitis, recto-vaginal fistula, or discharge of pus per rectum) and excluded patients with another histologic type than adenocarcinoma, and patients with synchronous colonic cancer or tumor polyposis, requiring a total colectomy.

For statistical analysis, the software SPSS 13.0 (SPSS Inc. USA) was used. Quantitative variables were expressed as "mean +/- standard deviation" if the distribution was normal, or, as median if the distribution was not Gaussian. The qualitative variables were expressed as numbers and percentages. Univariate analysis was conducted using Pearson's chi-square test and logistic regression. Variables with "p" less than 0.1 were included in the multivariate analysis. The result was considered significant when "p" was less than 0.05.

## RESULTS

Between January 2001 and December 2010, 130 consecutive patients underwent anterior resections with the total mesorectal excision technique for adenocarcinoma of the rectum at the Surgical Unit C (Table 1). There were 68 men (52,3 %) and 62 women (47.7 %). The median age was 55 years (20 - 90 years, Interquartile 25-75: 46-65 years). Seventeen per cent of patients were younger than 40 years. There were thirty-three tumors (25.4%) of the lower rectum (between 0 and 5 cm from the anal verge), 64 tumors (42.2%) of the middle rectum (between 6 and 10 cm from the anal margin) and 33 tumors (25.4%) of the upper rectum (between 11 and 15 cm from the anal margin). The median distance of the tumor from the anal verge was 8 cm (Interquartile 25-75: 5 - 11 cm). Radiotherapy was performed in 55 patients (42.3%). The laparoscopic approach was used in 36 patients (27.7%). Protective stoma was performed in 85 patients (65.4 %). There was a predominance of T3 and T4 stages (74.6%).

## Anastomotic leakage

Anastomotic leakage occurred in 28 patients (21.5%). It was complicated by postoperative peritonitis in 12 patients (42.8%) who required revision surgery. The other clinical manifestations of the fistula were: pelvic abscess in 11 patients (39.3%), digestive fluid from drains in 3 patients (10.7%) and vaginal pus in 2 patients (7.2%). Two patients, who were both operated for postoperative peritonitis, died postoperatively due to septic shock (7.2%).

## Risk Factors (Table 1)

The rate of anastomotic leakage was significantly higher in patients who received preoperative radiotherapy (34.5% vs. 12%,  $p = 0.002$ ). The risk of occurrence of anastomotic leakage was 3.8 (95% CI: 1.5 - 9.4) higher in patients who received neoadjuvant radiotherapy. None of the factors related to the patient or the tumor were significantly associated with anastomotic leakage in our series. The rate of AL was higher after coloanal anastomosis but the difference was not significant (28,6 % Vs 14.9 %;  $p = 0.06$ ). Radiotherapy, anastomosis type (coloanal or colorectal) and level of the tumor (above or under 8 cm from the anal verge) were included in the multivariate analysis (Table 2). Only radiotherapy was statistically associated to the occurrence of AL ( $p = 0.022$  - OR 4.47 - CI 95%: 1.2 - 16.1).

There was no significant difference in the rate of AL between patients with or without a protective stoma. In the group of patients with AL, the rate of reoperation was significantly lower in patients with a stoma protection (31.8% vs. 83.3%,  $p = 0.04$  - OR 10,7 - IC 95%: 1 - 109,5) (Table 3).

Tableau 1 : Characteristics of patients and univariate analysis

1.	1.	Number	% AL	p
Age	< 40	6/22	27.3	0.57
	> 40	22/108	20.4	
Gender	Male	16/68	23.5	0.56
	Female	12/62	19.4	
Anemia	Yes	2/20	10	0.23
	No	23/97	23.7	
Tumor level	< 8 cm	20/76	26.3	0.1
	> 8 cm	8/54	14.8	
Surgery	Laparoscopy	7/36	19.4	0.7
	Open surgery	21/94	22.3	
IMA* ligation	At origin	11/57	19.3	0.42
	Not at origin	17/67	25.4	
Anastomosis	Coloanal	18/63	28.6	0.06
	Colorectal	10/67	14.9	
Anastomosis type	Stapled	5/35	14.3	0.22
	Hand-sewn	23/95	24.2	
Stoma	Yes	22/85	25.9	0.11
	No	6/45	13.3	
T in pathologic examination	T0 - T2	9/33	27.3	0.35
	T3 - T4	19/97	20.9	
Radiotherapy	Yes	19/55	34.5	0.002
	No	9/75	12	

\* IMA : Inferior mesenteric artery

**Tableau 2 :** Multivariate analysis

	p	OR	IC 95 %
Radiotherapy	0.022	4.475	1.2 – 16.1
Anastomosis	0.569	1.373	0.46 - 4
Level of tumor	0.476	0.606	0.15 – 2.3

**Tableau 3 :** Surgical revision and protective stoma after occurrence of anastomotic leakage

	Surgical revision		p
	Yes	%	
Protective stoma	7/21	31.8	0.04 (OR 10.7 IC 95% 1 – 109.5)
	5/6	83.3	

## DISCUSSION

Our study showed that radiotherapy (RT) was significantly associated with the occurrence of AL. In a prospective nonrandomized study including 1278 patients, neoadjuvant therapy was associated with the onset of symptomatic AL in univariate (23% vs. 11%,  $p = 0.003$ ) and multivariate analysis [7]. Other retrospective studies confirmed the results of the latter [8-10]. However, according to a German prospective study including 663, Sauer et al. randomized their patients into 2 groups: preoperative RCT and postoperative RCT. The rate of AL was similar in both groups (12% vs. 11%), but the authors did not specify the definition of AL in their article [11]. Enker et al. compared [12], in a prospective nonrandomized study, morbidity in patients receiving preoperative chemoradiation ( $n = 150$ ) and patients not receiving a preoperative treatment ( $n = 531$ ). The authors reported a similar rate of AL between the two groups (4% vs. 4%,  $p = 0.86$ ). However, this result is questionable because the definition of AL included the clinically apparent fistulas and asymptomatic diagnosed by radiology, while postoperative radiological examination was not systematic for all patients. Radiotherapy causes micro vascular [13] damage that could hinder the intestinal vasculature and cause AL. Our results were an argument in favor of the deleterious effect of radiotherapy.

The systematic design of a protective stoma after anterior resection is

controversial. The theoretical aim of fecal diversion is to reduce the rate of AL and reduce its gravity [26] (peritonitis, sepsis). In our work, the confection of a protective stoma reduced the rate of surgical reoperations (31.8% vs. 83.3%,  $p = 0.04$ ) in patients with AL. However, it did not statistically reduce the risk of occurrence of AL. A multicenter randomized study from Sweden [27] compared the rate of symptomatic AL (peritonitis, pelvic abscess, recto-vaginal fistula) in 234 patients operated on for rectal cancer, with ( $n = 116$ ) and without protective stoma ( $n = 118$ ). The AL rate was significantly decreased in cases of stoma (10% vs. 28%,  $p = 0.001$ ). Two recent metaanalysis [28, 29] showed that the realization of a protective stoma reduced the risk of AL. In contrast, several prospective nonrandomized studies did not confirm the protective effect of the stoma. Wong et al. [30] found no difference in the rate of AL in patients with or without stoma (1066 patients, 4% vs. 3%). In a German multicenter study [23] including 482 patients, the rate of AL was similar between patients with or without a protective stoma. However, all these studies showed that the rate of reoperation were significantly lower in patients who had a stoma. Arguments against the routine use of a protective stoma are [28] the significant morbidity and mortality associated with stomas that can reach 30% and 2.3% respectively; decreased quality of life in patients who have no complications and the need for a second surgery to close the stoma. For these reasons, several authors proposed the creation of a stoma only in patients at high risk of occurrence of AL [31, 32]. The definition of this group of patients is still different from one author to another. Our results suggested that the making of a stoma is advisable in patients who received neoadjuvant radiotherapy.

## CONCLUSION

Anastomotic leakage is the most feared complication after anterior resection of the rectum. Its consequences in the short and long term require any effort to prevent and reduce its severity. Our work shows that radiation therapy is a risk factor for occurrence of anastomotic leakage. The systematic design of a protective stoma in patients receiving neoadjuvant radiotherapy is advisable to reduce the rate of reoperations associated with AL.

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