

# The Incidence and Mortality of Anastomotic Leakage after Colorectal Cancer Surgery

Gabriel Popescu<sup>1</sup>, Daniela Sala<sup>2</sup>, Miana Gliga<sup>1</sup>, Sergiu Ciulic<sup>1</sup>, Radu Mircea Neagoe<sup>1,2\*</sup> and Mircea Mureşan<sup>1,2</sup>

<sup>1</sup>Department of Surgery II, Emergency Mureş County Hospital, Târgu Mureş, Romania

<sup>2</sup>University of Medicine and Pharmacy of Târgu Mureş, Târgu Mureş, Romania

## Abstract

**Introduction:** Anastomotic leakage (AL) remains one of the most feared complications after colorectal surgery with high mortality rates, prolonged hospitalization, highly risk of readmission, finally generating important costs for any healthcare system. AL prediction and early detection are a considerable challenge for each surgeon as no well-established and reliable predictors and diagnosis protocols are currently available.

**Aims:** To determine the incidence and mortality of AL after colorectal surgery, with identification of possible predictors and improvement points in the management of this complication.

**Material and methods:** We included 431 patients with colorectal cancer who underwent surgical resection and restoration of the digestive tube's continuity, at the 2<sup>nd</sup> Department of Surgery, Emergency County Clinical Hospital of Târgu-Mureş, from January 2010-December 2015. The patients have been divided in two groups: AL group including 21 patients and no leak group with 410 patients. Demographic characteristics and comorbidities were recorded with clinical and laboratory follow-up in the postoperative period.

**Results:** There were no significant differences between the two groups in terms of demographic characteristics and comorbidities. The average age of patients with AL was  $65.9 \pm 11.6$  vs.  $65.0 \pm 10.3$  without AL. Male gender was predominant in both groups. No significant differences were recorded in terms of the localization and type of intervention between the two groups. Elevated C reactive protein levels were significantly more frequent in patients with AL ( $p=0.03$ ). The mortality rate in patients with AL was significantly higher compared to the no leak group  $28.6\%$  vs.  $1.9\%$  ( $p<0.0001$ ).

**Conclusions:** AL remains the most feared complication in colorectal surgery, with high mortality rates, regardless of the localization of the anastomosis and type of intervention. Elevated C reactive protein levels may predict AL being helpful for the early detection and treatment of this complication.

**Keywords:** Colorectal cancer; Colorectal resections; Anastomosis; Anastomotic leak; Postoperative morbidity; Postoperative mortality

## Introduction

Colorectal cancer is one of the most commonly diagnosed cancers worldwide. Its incidence increases with age and higher mortality rate is encountered in men [1]. Therapeutic approach refers to a complex surgical, chemo-and radiotherapy treatment.

In spite of numerous surgical techniques developed in the last decades-including new mechanical stapler based methods-anastomotic leakage (AL) remains one of the most feared complications in colorectal surgery. Its incidence ranges from 1.5% to 16% for "per primam" anastomoses with frequent need for redo interventions, longer hospitalization and high mortality rates [2]. AL prediction and identification are still difficult due to its different clinical manifestations, varying from vague abdominal symptoms and prolonged postoperative ileus to fulminant abdominal pain in case of peritonitis and sepsis [3]. It is still a challenging task to distinguish early after surgery the developing septic process from the physiological inflammatory response; however, early diagnosis, before the appearance of clinical symptoms, remains essential for a long term survival [4]. The literature recognizes several risk factors for AL development such as diabetes, smoking, obesity, chronic kidney disease, cardiovascular diseases but facts are still contradictory [5-7]. According to several authors [8,9] characteristics of AL depend on many aspects:

-The direction of the leakage has a major impact on the patient's symptoms; internal leakages are drained to organs such as the vagina, gallbladder or bladder and external leakages are drained through the teguments.

-AL's may develop intra or extra peritoneal.

-Localizations of the AL may be at the proximal or distal part of the anastomosis.

-The debit of the AL through the drain tube which could be small (<200 ml/24h), medium (200-500 ml/24h) or large (>500 ml/24 h).

-The severity of AL which might be minor (no clinical signs) or major (with clinical impact).

Numerous classifications are available, but no consensus exists over the medical world. The IMAGImE (International Multispecialty Anastomotic Leak Global Improvement Exchange) classification gives a simple clinical categorization of AL. Type A-with no or minimal clinical involvement, which does not need any active therapeutic intervention, Type B-which requires active treatment, but not surgical intervention and Type C-requiring surgical treatment [10].

\*Corresponding author: Radu Micea Neagoe, University of Medicine and Pharmacy of Târgu Mureş, 2nd Department of Surgery, Emergency Mureş County Hospital, Târgu Mureş, Romania, Tel: +40 (0) 652 12 11 12 73; E-mail: [neagoerm@gmail.com](mailto:neagoerm@gmail.com)

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This study aims to determine the incidence and mortality of AL after both elective and emergency procedures; we analyze possible AL's predictors trying to identify improvement points in the management of this complication.

## Material and Methods

In our study the clinical and operative charts (2<sup>nd</sup> Department of Surgery II, Emergency Mures County Hospital) were retrospectively analyzed between January 2010 and December 2015. We included 431 patients with colorectal cancer for whom surgical resection was performed with "per primam intentionem" restoration of the digestive tube's continuity. The group of patients who developed AL was comparatively analyzed with those who did not exhibit this complication. Demographic characteristics and comorbidities of both groups were recorded; the type of surgical intervention, the localization and type of the anastomosis and the in-hospital mortality was determined for both groups. Patients with derivative surgical procedures were excluded, even if a later anastomosis was performed. No distinction was made between the types of procedures (manual or mechanical, continuous or separate sutures). Preoperative work-up included prophylactic antibiotherapy, cardiology and pre-anesthesia examinations. The postoperative follow-up and diagnosis of AL was based on clinical signs (fever, ileus, abdominal pain, altered state of the patient), laboratory examinations (total blood count, urea, creatinine, procalcitonin, C reactive protein) and imaging studies (abdominal echography, abdominal computed tomography), according to local protocols. The study was approved by ethical commission of the institution and it was realized in accordance with ethical code of the Declaration of Helsinki.

## Statistical Analysis

Statistical analysis was carried out using the SPSS for Windows (v 20.0, IBM Corporation, Armonk, NY, USA) software program. The Kolmogorov-Smirnov test was used to assess the normal distribution of continuous numerical variables. The results were presented as numbers and percentages for qualitative variables and as average  $\pm$  standard deviation or median values for quantitative variables. Facts were compared using Student test (for quantitative variables) and  $\chi^2$  test (for qualitative variables). A value of  $p < 0.05$  was considered statistically significant.

## Results

Among 431 patients included 21 (4.9%) were identified with anastomotic leakage during hospitalization. All leakages were type C and needed surgical treatment. Primary emergency operation was performed for 1 patient (4.8%) from the group AL and for 33 patients (8%) in the group without AL ( $p=0.25$ ). The average time to AL diagnosis was 6 days after the operation, with the earliest diagnosis on day 5<sup>th</sup> and the latest on day 13<sup>th</sup>. There was no significant difference between groups as regards demographic characteristics, associated comorbidities and risk factors such as diabetes, cardiovascular diseases, chronic kidney disease and obesity. The average age of patients with AL was  $65.9 \pm 11.6$  vs.  $65.0 \pm 10.3$  in the comparative group. Male gender was predominant in both groups, but with no significant difference between the two groups (Table I).

The majority of the tumors were localized at the level of the left colon (vascularized by the inferior mesenteric artery), with no significant difference between groups-42.8% in patients with AL vs. 38.8%,  $p=0.89$ . This location was followed by right colon tumors (vascularized by the superior mesenteric artery) with 28.6% ( $n=6$ ) in the AL groups vs. 34.9%,  $p=0.72$ . No significant difference was observed in the incidence of rectal tumors between the two groups with 28.6% ( $n=60$ ) in the AL group vs. 26.3% ( $n=108$ ) in the no leak group ( $p=0.98$ ). No significant differences were observed as concerned

the type of intervention; right hemicolectomy was most frequently performed in both groups (33.3% in the leak group vs. 36.4% in no leak group,  $p=0.94$ ), followed by rectosigmoid resections (28.6% vs. 26.6%,  $p=0.95$ ). Segmental colon resection of the colon was more often performed in the group with no leaks, but no significant difference was recorded ( $p=0.92$ ). No left hemicolectomies and total colectomies were carried out in the anastomotic leak group. The type of anastomosis was identical in both groups, as proximal anastomoses (performed on the right colon) were more frequent than distal (performed on the left colon) ones (Table II).

The mortality rate was significantly higher in patients with AL compared to the no leak group (28.6% vs. 1.9%,  $p < 0.0001$ ). The average age of the deceased patients was  $72 \pm 12.52$  years vs.  $65 \pm 10.37$  years in the survivors of the AL group ( $p=0.11$ ). There were no significant differences recorded in terms of the above-mentioned risk factors and comorbidities. Elevated C reactive protein levels ( $>5\%$  over the accepted normal levels at the local laboratory) were significantly more frequently recorded in patients from the AL compared to the no leak group 85.71% ( $n=18$ ) vs. 62.68% ( $n=257$ ), ( $p=0.03$ ).

## Discussion

Anastomotic leaks still represent a major complication of colorectal surgery; however, no particular risk factors have been yet identified. It has been shown that male gender, smoking, obesity, and diabetes might represent risk factors for AL, due to the vulnerability of these patients [11]; none of these were associated with higher incidence of AL in our study. Furthermore, the location of the tumor and anastomosis along with the type of intervention and surgical technique might also influence the development of AL [12]; in the current study no certain location or type of intervention proved to influence the AL's appearance.

Usually AL is diagnosed between day 5<sup>th</sup> and 8<sup>th</sup> after the surgical intervention, those from first days being commonly associated with technical errors during surgery [13]. Early detection of this complication, thus avoiding a major peritonitis, is essential for the long-term survival of these patients [14]; in our study the average time of AL diagnosis was 6 days. Den Dulk et al. [15] proposed a clinical score for early detection of AL, so called "Dutch Leakage Score", which analyzes different clinical and laboratory parameters. General vital signs such as fever (1 point), tachycardia (1 point), respiration frequency over 30/minute (1 point), diuresis-under 700ml/day or 30ml/hour (1 point), psychical-agitation or lethargy-and altered general state of the patient (1 point) along with local symptoms such as ileus, gastric stasis, evisceration or abdominal pain (2 points) are included. Laboratory parameters such as leukocytosis, elevated C reactive protein, creatinine, urea levels and parenteral feeding (1 point) are also part of the scoring system. The authors claimed that no diagnostic or therapeutic actions are needed  $\leq 3$  point; between 4-7 points severe monitoring is recommended and over 8 points contrast computed tomography is needed for diagnosis. This, yet not widely used score, might represent a useful tool in the early diagnosis of anastomotic leaks.

Anastomotic leaks detection, prior to the onset of clinical symptoms, is of paramount importance for better outcomes. In this

	Anastomotic leak n=21 (%)	No leak n=410 (%)	p
Age	65.9 $\pm$ 11.6	65.0 $\pm$ 10.3	0.69
Male gender	12 (57.4%)	210 (51.2%)	0.59
Diabetes mellitus	8 (38%)	113 (36.2%)	0.29
Cardiovascular disease	13 (61.9%)	243 (59.2%)	0.81
Chronic kidney disease	5 (23.8%)	97 (23.6%)	0.98
Obesity	13 (61.9%)	261 (63.65%)	0.87

Table I: Study population.

		Anastomotic leak n=21	No leak n=410	P
Localization of the tumor no (%)	Right colon	6 (28.6)	143 (34.9)	0.72
	Left colon	<b>9 (42.8)</b>	159 (38.8)	0.89
	Rectum	6 (28.6)	108 (26.3)	0.98
Intervention no (%)	Subtotal colectomy	<b>6 (28.6)</b>	64 (15.6)	0.20
	Total colectomy	0 (0.0)	4 (1.0)	0.58
	Right hemicolectomy	7 (33.3)	149 (36.4)	0.95
	Left hemicolectomy	0 (0.0)	32 (7.8)	0.36
	Rectosigmoid resection	6 (28.6)	109 (26.6)	0.95
	Segmental colon resection	2 (9.5)	52 (12.7)	0.92
Type of anastomosis no (%)	Proximal	13 (61.9)	251 (61.2)	0.76
	Distal	8 (38.1)	159 (38.7)	

**Table II:** Characteristics of the surgical interventions.

perspective biomarkers could represent an objective indicator of the inflammatory process as a pathogenic substrate for AL development [16]. In a systematic review Su'a et al. [17] stated that systemic and peritoneal drainage fluid biomarkers cannot accurately predict the appearance of AL, but recommends the combination of these biomarkers for better results. In a recent study Smith et al. [18] defined the trajectory of C reactive protein as a possible gold standard biomarker for identification of anastomotic leaks after colorectal surgery. Our results also suggested that elevated C reactive proteins were significantly more frequently recorded in patients with AL than in the group without leakage.

The mortality rate after AL is high due to peritonitis with intense systemic inflammatory response and sepsis finally leading to multiple organ dysfunction or failure and death [19]. In our study, the mortality rate of patients with AL was highly significant in comparison with those who didn't present this complication. Higher mortality rates are recorded in elderly patients who develop AL as a reason of cumulative comorbidities and frail immune system [11]. In our study, the deceased patients were older than the survivors, but no significant differences were observed.

**Conclusion**

Anastomotic leaks still represent one of the major complications of colorectal surgery with high mortality rates regardless of the localization of the anastomosis or the type of intervention. Elevated C reactive protein levels might predict the appearance of this complication, thus facilitating an early diagnosis. Early detection and proper treatment remains a great challenge for every surgeon, because any delay in this process has a major impact on the survival of these patients with longer hospitalization and higher costs. Application of a score system which includes clinical, laboratory and imagistic parameters, along with detection of new risk factors should be useful for the reduction of the mortality of this feared complication.

**Conflict of Interest**

Authors have no conflict of interest to disclose.

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