Anastomotic leakage and septic complications: impact on local recurrence in surgery of low rectal cancer.

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Michelangelo Miccini, Ottavia Borghese, Massimo Scarpini, Diletta Cassini, Matteo Gregori, Stefano Amore Bonapasta, Adriano Tocchi

Department of Surgery, "La Sapienza" University Medical School, Rome, Italy

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PURPOSE: *We thought to determine the influence of anastomotic leakages (AL) and septic complications (SC) on the incidence of local recurrence (LR) in patients undergoing curative surgery for rectal cancer.*
METHODS: *The records of 479 patients (286 male, 193 female; median age 67 years) who received, between 1966 and 1975 (Group A) and 1976 and 1985 (Group B), curative surgery for middle to low rectal cancer were retrospectively reviewed. All patients received mesorectal excision in the course of abdominoperineal excision (Group A) and of anterior resection with colorectal anastomosis (Group B). The outcome of SC in both groups and that of AL in Group B were investigated. AL were divided into clinical leaks (CL) and radiological leaks (RL). All patients surviving surgery were followed up for a mean period of 71 months. The development of pelvic recurrence was registered. The effect of SC and AL on LR was statistically analyzed.*
RESULTS: *LR was diagnosed in 24 (9.3%) patients of Group A. No difference was detected between patients with SC (9.3%) and those without (9.3%). In Group B, LR occurred in 28 (12.7%) patients: 12.5% without SC and 12.7% with SC. A significant difference in the prevalence of LR was found between patients with CL (14.2%) and those with RL (30.0%). When CL were excluded, RL resulted as an independent predictor of LR.*
DISCUSSION: *Many factors have been shown to affect the rate of LR, including operative technique and surgeon expertise as well as margins of clearance and tumor stage. In our study, overall LR rate of Group B was 13.2%. The incidence of this event in patients with AL (24%) was significantly higher than that in the nonleakage group (11.1%). Correspondent results have been reported by some authors who evidenced RL as a negative prognostic factor for higher rates of LR. The mechanism by which AL affects LR remains to be elucidated.*
CONCLUSIONS: *All were found to be associated with higher rates of LR, especially if associated with prolonged inflammatory local reaction.*

KEY WORDS: Anastomosic leakage, Local recurrence, Rectal cancer

Introduction

Various variables have been implicated in the local recurrence (LR) rate of patients who had undergone curative surgery for rectal cancer[1–3]. Tumor stage is paramount.[4–7] However, the search has continued to identify other factors. Anastomotic leakages (AL) and septic complications (SC) have well-documented, immediate clinical consequences on rectal surgery [8,9,10]. Whether these complications, either separately or in conjunction, are prognostic factors for LR after resection of carcinoma of the middle and low rectum remains open to speculation[11–15]. The aim of this study was to determine the frequency of SC and AL and their relationship as potential predictors of LR in patients with middle to low rectal cancer treated by curative surgical resection alone.

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Corresponding to: Adriano Tocchi, Via Bruno Bruni n. 94, 00189 Rome, Italy (e-mail: adriano.tocchi@uniroma1.it)

Materials and methods

Clinical, operative, pathological, and follow-up information on patients undergoing surgery for rectal adenocarcinoma from 1965 has been stored in a computer database maintained at the First Department of Surgery of the University of Rome La Sapienza. The database includes [1] the name, gender, age, and major medical problems of the patients, [2] location, size, and Dukes' stage of the tumors, [3] the types of operation, complications, and operative morbidity and mortality, and [4] long-term outcomes. The records of patients admitted between January 1966 and December 1975 (Group A) and between January 1976 and December 1985 (Group B) who underwent curative resection for tumors with low margins anywhere up to 8 cm from the anal verge were extracted for analysis. The choice of these periods was made in order to select two groups of patients that, although undergoing different procedures, could be characterized by the same oncological radicality and could, in such a way, permit the distinct analysis of the incidence of SC and AL and of the influence of these two complications on LR. Patients with synchronous cancers or cancers complicating familial adenomatous polyposis or inflammatory bowel disease were excluded. Distance of growths from the anal verge was measured with rigid rectoscopy. Abdominoperineal excision was performed in the first period and low anterior resection in the second. Both procedures included total mesorectal excision. Operations were all performed or assisted by senior colon rectal surgeons. During the second period a small number of patients were treated with adjuvant therapy, and they were excluded from analysis. Patients were deemed to have had a potentially curative resection if there was

TABLE I - *Demographie and Clinical Data.*

	Group A (258 Patients)	Group B (221 Patients)	P Value
Gender			
Male	155 (60.0%)	131 (59.0%)	
Female	103 (40.0%)	90 (41.0%)	.92
Age (years)	66.4 ± 9.4	65.6 ± 8.6	.33
Comorbidity*			
CAD	15 (5.8%)	16 (7.2%)	
COPD	9 (3.5%)	11 (5.0%)	.91
ESRD	6 (2.3%)	6 (2.7%)	
DIAB	18 (7.0%	13 (5.9%)	
EPAT	6 (2.3%)	6 (2.7%)	
Tumor site			
Low	123 (47.7%)	98 (44.3%)	.52
Middle	135 (52.3%)	123 (55.7%)	
Dukes' stage			
A	104 (40.3%)	87 (39.4%)	
B	79 (30.6%)	74 (33.5%)	.78
C	75 (29.1%)	60 (27.1%)	
Blood units			
0	196 (76.0%)	165 (74.7%)	
1	36 (13.9%)	28 (12.7%)	.77
2	21 (8.1%)	24 (10.8%)	
3	5 (2.0%)	4 (1.8%)	
Morbidity			
No	227 (88.0%	197 (89.1%)	
Cardiac	36 (13.9%)	5 (2.3%)	.88
Pulmonary	11 (4.3%)	9 (4.0%)	
Urinary	11 (4.3%)	10 (4.6%)	
Mortality	7 (2.7%)	5 (2.5%)	.98

*CAD = Coronary artery disease; COPD = Chronic Obstructive pulmonary disease; ESRD Endstage renal disease; DIAB= Diabetes; EPAT= Hepatic diseases.

TABLE II - *Postoperative Data*

	Group A	Group B	*P* Value
Septic complications			
No	107 (41.5%)	207 (93.7%)	<.001
Yes	151 (58.5%)	14 (6.3%)	
Anastomotic leakage			
No		187 (84.6%)	–
Radiological	–	20 (9.0%)	
Clinical		14 (6.4%)	

TABLE III - *Univariate Analysis.*

	No Local Recurrence	Local Recurrence	P Value
Group			
A	234 (54.8%)	24 (46.1%)	
B	193 (45.2%)	28 (53.9%)	.24
Gender			
Male	256 (59.9%)	30 (57.7%)	
Female	171 (41.1%)	22 (42.3%)	.76
Age	66.0 ± 8.9	66.0 ± 9.7	.99
Dukes' stage	183 (42.8%)	8 (15.4%)	
	136 (31.8%)	17 (32.7%)	
A	108 (25.4%)	27 (51.9%)	
			<.001
B			
C			
Tumor site	200 (46.8%)	21 (40.4%)	
Low	227 (53.2%)	31 (59.6%)	.46
Middle			
Morbidity	376 (88.0%)	47 (90.4%)	
No	51 (12.0%)	5 (9.6%)	.82
Yes			
Septic complications	278 (65.1%)	36(69.2%)	
No	149 (34.9%)	16(30.8%)	.64
Yes			
Anastomotic leakage	401 (93.9%)	44 (84.6%)	
	26 (6.1%)	8 (5.4%)	
No			.016
Yes			

no evidence of metastatic disease at the time of surgery and if the surgeon considered that there was no residual tumor following resection. The outcomes of postoperative AL and SC were investigated. Radiologic assessment of anastomotic integrity was made, using a water-soluble contrast enema, between days 6 and 8 postoperatively. The definition of AL included all patients who developed any clinical or radiologic evidence of dehiscence of the anastomosis. A clinical leak (CL) was defined as the appearance of fecal material from drains or the development of any systemic sepsis associated with general or local peritoneal signs. A radiological leak (RL) was defined as a subclinical leak detected merely by contrast radiology. In Group A, SC was defined as a per-

TABLE IV - *Multivariate Analysis.*

	BETA	SE BETA	B	SE B	t	p
Dukes' stage	–0.114	0.045	–3.113	1.235	–2.519	**.012**
Anastomotic leakage	–0.092	0.045	–5.321	2.617	–2.032	**.043**

ineal infection, that is, an abscess in the perineal wound, associated with high swinging pyrexia above 38 °C and a raised white cell count that either discharged spontaneously or required surgical drainage. In Group B, SC was defined as clinical evidence of localized or generalized signs of peritonitis with the following clinical parameters: high swinging pyrexia above 38 °C and a raised white cell count. One pathologist reviewed all the pathology slides from the surgical specimens without knowledge of clinical patterns or long-term outcomes. Operation was confirmed as potentially curative when no residual tumor in the circumferential or distal margins of resection could be detected at microscopy. The extent of tumor spread was assessed by Dukes' classification. Mean follow-up was 71.7 ± 22.2 months (9–134 months). Twenty-eight patients were lost at follow-up. All patients were reviewed in the outpatient department approximately every 3 months in the first year after resection, every 6 months in the second year, and annually thereafter. Protocol comprised, in Group A, physical examination and chest radiography. In Group B, protocol comprised physical examination, digital rectal examination and rectoscopy, and chest radiography twice a year in the first year and once a year thereafter. LR was defined as clinical, histologic, or autopsy evidence of recurrent disease in the region of previous surgery with or without newly diagnosed distant metastases. When a LR was suspected, biopsy confirmation was obtained whenever possible. Time to LR was measured from the date of resection until the date of confirmation of recurrence. In patients without LR the censoring date was the date of death for those who died or the date when last known to be alive. The separate influence of SC on LR was investigated in Group A, whereas that of both SC and AL were investigated in Group B.

The results of parametric and nonparametric data were expressed, respectively, as means and medians ± standard deviations. Confidence intervals were set at 95%. A two-sided *P* value of <.05 was considered statistically significant. Univariate comparisons were carried out using Fisher tests and the test for discrete variables, the Mann–Whitney test for continuous variables.

Multivariate analysis was performed with a logistic regression test.

Results

This study is based on 2429 patients who had a resection for primary rectal adenocarcinoma, 1359 of whom underwent radical removal of their primary tumor. In these, 479 patients with growths with lower margins anywhere up to 8 cm from the anal verge were finally recruited: 258 in the first period (Group A) and 221 in the second (Group B). Men composed 61% and 59% of Groups A and B, respectively. The age range was 41-83 years (mean 66.0 ± 9.0), and there was no significant difference between the two groups (Table I). The prevalence of stages A, B, and C were 40.3% , 30.6%, and 29.1% and 39.4% , 33.5%, and 27.1% in Groups A and B, respectively. Demographic and clinical data are shown in Table I. Perineal infections occurred in 140 patients of Group A (58.5%). In Group B, SC due to AL occurred in 14 patients, and RL occurred in a further 20 patients. LR overall rate in Group A was 9.3%: 9.3% in patients with perineal infection and 9.3% in those with an uncomplicated postoperative course. LR rate in Group B was 12.7%: 12.5% in patients without SC and 12.7% in those with postoperative SC (Table II). However, in Group B, there was a significant difference in prevalence of LR between patients with CL (13.2%) and those with RL (30.0%). The stage-adjusted LR rates were 4.2%, 11.7%, and 20.0% in Group A and 6%, 14.9%, and 25.4% in Group B for Dukes' stages A, B, and C, respectively. No LR developed inside the intestinal lumen at the suture line. Age and sex were found to be unrelated to the incidence of LR. Univariate analysis results are shown in Table III.

The range of disease-free survival in Group A was 14.4 ± 12.6 months (5–64 months) and 12.4 ± 9 months (6–56 months) in Group B (*P* = .56). No difference in the range of disease-free survival (0.7–5.2 months) was observed in Group A between patients with and without SC.

The resulting statistical model showed a significant and relatively strong independent effect of AL on LR. The only other independent variable associated with LR was tumor stage (Table IV).

Discussion

The rates of LR after curative resection of rectal cancer have been reported as widely varying[16,17]. Many factors have been shown to affect the rate of LR, including operative technique and surgeon expertise [18-20] as well as margins of clearance and tumor stage [2,3]. Strategies to reduce LR have included the use of specific operative techniques, with particular reference to dissecting in

defined anatomical planes [21,22]. However, whether it is clear that surgical variability is important, it is not entirely clear which margins of clearance are determinants of outcome. Although the importance of circumferential margins and radial clearance has progressively increased [23,24], mesorectal excision has long been evidenced as an independent prognostic variable influencing LR [25-28]. Whatever might be considered the more radical technique, it is essential that studies include only patients submitted to procedures targeting the same clearing. Mesorectal excision assured in both groups of our series the same locoregional clearing. The surgical procedures adopted, actually depending not on a patient's state or tumor stage, but only on current technology, did not influence locoregional clearing. As LR is principally related to tumor stage [29,30], series with different proportions of stages will have different rates. It is therefore essential that studies report a stage-specific LR rate as well as an overall rate. The overall recurrence rates were 10% and 13% in Groups A and B, respectively. Stage-specific recurrence rates were 3%, 9.7%, and 20.5% in Group A and 6%, 14%, and 22.4% in Group B when referring to Dukes' staging system. These results, all within the standards usually reported in literature, suggest the absence of any tumor stage selection. Recurrence is time-dependent. Follow-up lasting less than 5 years has been evidenced to underestimate the rate of LR occurring in as much as 36% of cases after the first 2 years since curative surgery for rectal cancer[9,31]. It is therefore essential that follow-up be conducted for a sufficiently long period to allow most recurrences to occur. There are, then, good reasons to believe that the great majority of recurrences had been detected, in our series, by a follow-up lasting far more than 5 years.

An end point of the study was to verify the influence of AL on LR. The overall LR rate of Group B was 13.2%. The incidence of this event in patients with leakage (24%) was significantly higher than that in the non-leakage group (11.1%). Furthermore, an appreciable shortening of the interval from operation to disease recurrence was observed in patients with AL. However, the correlation between AL and LR did not apply to all leaks. The incidence of LR in patients with SC secondary to CL was not different from that of patients without leakage. When CL were excluded and RL examined alone, the latter resulted as an independent predictor for LR. Correspondent results have been reported by some authors who evidenced subclinical AL as a negative prognostic factor for higher rates of LR.[31] The mechanism by which AL affects LR remains to be elucidated. However, there is evidence that viable cells may be present in the bowel lumen of patients with rectal cancer at the time of operation[33,34]. The effect of AL on cancer-specific LR was similar in patients with Dukes' A, B, and C tumors, thus suggesting a pathophysiological mechanism affecting homogeneous progression and poor outcome in different stages of disease. In the event of AL, this may lead to a washout through the anastomotic dehiscence of viable cancer cells. Raw areas, surrounding the anastomosis and resulting from pelvic dissection, provide a suitable surface for cancer cells to adhere and grow, thus favoring LR[35].

A further end point of our study was to analyze the possible influence of local postoperative infectious events on the development of LR. In Group A, where the influence of SC on LR could be studied independently from that of AL, no increased risk for recurrences was evidenced in patients who experienced SC in the immediate postoperative course. However, the influence of inflammation on LR remains unclear. Actually, while LR has resulted, in both Groups A and B, unrelated to SC, significantly higher rates of LR were found in Group B in patients with localized, subclinical AL. Since even subclinical AL are likely to be associated with some degree of inflammatory response, it may be argued, contradicting a long-held view, that it is not as much the magnitude as the duration of SC that influences, in the case of AL, the occurrence of LR. In the case of acute sepsis following general breakdown of the anastomosis, the opportunity of cancer cells to implant is minimized by prompt intestinal diversion and peritoneal washing breaking off the intestinal spillage and moving away from the pelvic environment the intestinal content together with viable cancer cells. In the case of subclinical leaks, in contrast, intestinal spillage is not interrupted, and intestinal collections are either left in place, in case of expectant treatment, or are only partially removed when percutaneous drainage is adopted. In both cases the length of stay and the opportunity of cancer cells to implant are prolonged, and tumor spread is possibly enhanced, as previously suggested, by the inflammatory response [36-38].

Conclusions

In light of our results, while there is no evidence that isolated, postoperative pelvic sepsis is a risk factor for LR, subclinical leakages have been determined, after tumor stage, to be the second most important prognostic factor for pelvic failure after curative surgical resection for rectal cancer. Further studies are needed to confirm whether prolonged inflammatory reaction acts as a boost of AL in favoring LR.

Riassunto

OBIETTIVO: Determinare l'influenza della deiscenza anastomotica (DA) e della complicanza settica (CS) sull'incidenza della recidiva locale (RL) in pazienti sottoposti a chirurgia curativa per cancro del retto.

MATERIALE E METODO: Sono stati analizzati i dati relativi a 479 pazienti (286 maschi, 193 femmine; età media 67 anni) sottoposti, tra il 1966-1975 (Gruppo A) e il

1976-1985 (Gruppo B), ad intervento chirurgico con intento curativo per cancro del retto. In tutti i pazienti è stata eseguita l'escissione completa del mesoretto in corso di amputazione addominopelvica (Gruppo A) e di resezione anteriore (Gruppo B). Sono state calcolate le incidenze della CS in entrambi i gruppi e della DA nel Gruppo B. La DA è stata suddivisa in deiscenza clinica e radiologica. Il follow up ha avuto una durata media di 71 mesi. L'insorgenza di recidiva locale (LR) è stata calcolata. Infine, è stato analizzato il valore predittivo della CS e della DA sulla recidiva di malattia neoplastica.
RISULTATI: Nel Gruppo A la RL si è verificata in 24 casi (9.3%) senza mostrare differenze statisticamente significative in riferimento alla presenza o meno di CS. Nel Gruppo B la RP è occorsa in 28 casi (12.7%): 12.5% senza CS e 12.7% senza CS. In questo gruppo è stata osservata una differenza significativa nella prevalenza di RL tra pazienti con deiscenza clinica (14.2%) e quelli con deiscenza radiologica (30.0%). Quando la deiscenza clinica è stata esclusa dall'analisi, la deiscenza radiologica è risultata essere un fattore predittivo indipendente di RL.
DISCUSSIONE: Molteplici fattori, tra cui la tecnica operatoria, l'esperienza del chirurgo, i margini di resezione e lo stadio del tumore risultano correlati all'incidenza di RL di cancro del retto dopo chirurgia curativa. Nel Gruppo B dei nostri pazienti, il rateo di RL è risultato del 13.2% con percentuali significativamente maggiori nei pazienti con DA (24%) rispetto a quelli senza DA (11.1%). Risultati analoghi sono riportati da altri autori seppure il meccanismo fisiopatologico attraverso cui la DA favorisca la RL resta ancora da chiarire.
CONCLUSIONE: La DA è risultata associata a ratei maggiori di RL, soprattutto quando associata a prolungati tempi di reazione infiammatoria locale.

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