Laparoscopic total mesorectal excision (L-TME) for rectal cancer surgery: does elective diverting ileostomy really protect?

An observational retrospective cohort study

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Laparoscopic total mesorectal excision (L-TME) for rectal cancer surgery: does elective diverting ileostomy really protect? An observational retrospective cohort study.

AIMS: *Elective diverting ileostomy may reduce consequences of anastomotic leakage after laparoscopic total mesorectal excision (L-TME); however, its safety is debated because of morbidity related to stoma creation and closure. We aimed to investigate the impact of diverting ileostomy on clinical behavior of anastomotic leakage and complications related to stoma itself.*
MATERIAL OF THE STUDY: *We retrospectively evaluated 150 L-TMEs with (Group 1, 100 patients) or without (Group 2, 50 patients) elective ileostomy for rectal cancer.*
RESULTS: *Overall anastomotic fistula rate was 26% without significant differences between the two groups (28% in the Group 1 and 22% in the Group 2, respectively). In all the series, NAD was significantly associated with higher risk of postoperative complications (OR=2.14, p=0.02). In Group 2, NAD particularly increased the risk of anastomotic fistula (OR=6.6, p=0.014). Instead, patients of Group 1 showed higher odd of post-operative complications (OR: 3.8; CI 95%: 1.8483-8.0492; p = 0.0003) and notably 79 (79%) developed complications related to the ileostomy itself (hydro-electrolytic, metabolic and peristomal skin disorders). Moreover, thirty-two (32%) ileostomies were never reversed; among the reversed patients, 27 (39.7%) developed at least one postoperative complication and in 9 (33.3%) cases an urgent re-intervention was needed.*
DISCUSSION: *Diverting ileostomy may mitigate clinical behavior of anastomotic leakage after L-TME. However, there is non-negligible morbidity of stoma creation and closure.*
CONCLUSION: *Diverting ileostomy should be selectively considered in higher risk patients as those who received NAD.*

KEY WORDS: Anastomotic leakage, Ileostomy, Rectal cancer

Introduction

Colorectal cancer is one of the most common tumors in Western Countries and rectal localization amount for about one third of the cases [1]. Anastomotic leakage represents the main complication of major surgery performed for colorectal cancer. Although less frequent after elective procedures with intraperitoneal anastomosis, its incidence increases up to 24% in low rectal surgery with Total Mesorectal Excision (TME) and primary anastomosis [2,3]. In addition to tumor location, also advanced age, male sex, malnutrition, use of steroids, tumor size and neoadjuvant treatment (NAD), perioperative blood transfusions and conversion of mini-invasive procedures have been identified as other significant risk factors for the development of anastomotic fistula [4-8].

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Ileostomy reduces clinical entity and septic complications (peritonitis and abscesses) deriving from the leakage and often allows avoiding other invasive treatments [9]. However, the ileostomy itself can lead to complications, reported in 21% to 70% of the cases. These complications include dehydration, acute renal failure, obstruction, prolonged hospitalization, and peristomal skin disorders [10-12]. Moreover, even morbidity related to ileostomy closure is not trivial since it has been reported in up to 30% of the cases [13]. Small bowel obstruction is reported in up to 15% of the cases, while wound infection is reported in up to 18.3% and anastomotic fistula rate has been described in 8% [14]. The overall reoperation rate in patients who undergo ileostomy reversal is reported in up to 10% [15]. Mortality has also been reported in 0.5-3.5% of cases of ileostomy reversal [13,16]. Lastly, 20-30% of patients will never be submitted to stoma reversal [14,17].

For these reasons, the current role of elective diverting ileostomy in oncological rectal surgery is still debated. In order to verify pros and cons of elective diverting ileostomy in TME, the aim of this retrospective study was to investigate the impact of diverting ileostomy on the incidence and clinical behavior of anastomotic leakage and to focus on complications related to the presence of the ileostomy itself and to its take down.

Materials And Methods

Population

From a prospective collected database, data regarding patients who underwent to laparoscopic TME, with (Group 1) or without (Group 2) elective diverting ileostomy for rectal cancer from 2012 to 2017 at University Campus Bio-Medico di Roma, have been retrospectively analyzed. The Ethical Committee of University Campus Bio-Medico di Roma approved this study (11.17 OSS ComET CBM) and the methods were carried out in accordance with the principles of Good Clinical Practice, with the ethical standards of the Ethical Committee of University Campus Bio-Medico di Roma and national research committee and with the Helsinki declaration (as revised in Brazil 2013). The study was retrospectively registered in the ClinicalTrials.gov database (NCT04169425) and the work is compliant with the STROBE Statement [18]. Eligibility was restricted to adult patients (aged 18 years and over) who underwent to laparoscopic elective TME for rectal cancer. Exclusion criteria included abdominoperineal resection (APR), chronic use of immunosuppressant agents and urgent surgery. Patients who received NAD (radio-chemotherapy performed by intensity-modulated radiation therapy associated with pyrimidine based chemotherapy) were included in this study.

Operative technique, postoperative complications of primary surgery, length of stay, ileostomy related complications (dehydration, acute renal failure, obstruction, prolonged hospitalization and peristomal skin disorders), morbidity due to its reversal (anastomotic leakage, bowel obstruction, anastomotic bleeding, surgical site infection and need for re-operation) and patient-related factors as age, gender, BMI, ASA score, have been evaluated.

Surgical procedure

In all patients, Anterior Rectal Resection (ARR) with TME was performed with a colorectal anastomosis according to the "double stapling" technique described by Knight and Griffen in 1980 [19] and the integrity of the anastomotic donuts was checked. According to surgeon's choice, based mainly on previous NAD and on patient's comorbidities, elective diverting ileostomy was performed. Anastomotic leakage was defined on the basis of perianastomotic drain appearance and/or of radiological findings during postoperative X-Ray or abdominal CT scan enema performed in case of clinical suspect (*i.e.* fever, postoperative acute abdomen) of dehiscence in absence of sinister appearance of surgical drains fluid. Patients were followed up until the reversal of ileostomy. If the ileostomy was not reversed during the first 5 years after primary surgery, the stoma was considered permanent.

Table I - *Patients demographic characteristics*

	Group 1 (100 patients)	Group 2 (50 patients)	P value
Median age, yr (range)	68 yr (42 – 86 yr)	67 yr (52 – 85 yr)	0.93
Male, n (%)	60 (60%)	26 (52%)	0.35
Female, n (%)	40 (40%)	24 (48%)	
Median BMI (kg/m2) (range)	25.2 (18 – 42.5)	24 (20 – 36.9)	0.22
NAD (RCT), n (%)	67 (67%)	12 (24%)	< 0.0001***
ASA 1-2	66 (66%)	40 (80%)	0.35
ASA 3-4	34 (34%)	10 (20%)	
Median length of stay in days (range)	8 d (3-49 d)	7 d (4-70 d)	0.83

Statistical analysis for Age, BMI and length of stay was performed according to Student's t test.Statistical analysis for Sex, NAD, ASA score and tumor location was performed according to χ^2 test.

Statistical analysis

Descriptive statistical analysis was performed. Odds Ratio (OR) and their 95% interval of confidence (95% CI) were calculated to evaluate the association between different variables. Timing to reversal of ileostomy was considered as probable predictor, and it was assessed by receiver operating characteristic (ROC) analysis. Then, according to the optimal cut-off value, an association was investigated. c^2 and Student's *t* test were used to confirm the statistical significance. A P value ≤ 0.05 was considered statistically significant. Statistical analysis was performed using the MedCalc v.18.11.

Results

One-hundred-fifty patients (median age 67.5 years, range 42-86) were eligible for the present study. Eighty-six (57.3%) were male and 64 (42.7%) were female. One-hundred patients joined Group 1 and 50 Group 2 (Fig. 1). In the Group 1, the median age was 68 years (range 42 - 86 years), 60 (60%) were male, 40 (40%) were female, the median BMI was 25.2 kg/m^2 (range 18 - 42.5 kg/m^2), 67 (67%) received neoadjuvant radio-chemotherapy. A total of 66 patients (66%) had an ASA score of I-II and 34 patients (34%) ASA III-IV. Anastomotic fistula was observed in 28 (28%) cases. In the Group 2, the median age was 67 years (range 52 - 85 years), 26 (52%) males and 24 (48%) females, the median BMI was 24 kg/m^2 (20 - 36.9 kg/m^2), neoadjuvant radio-chemotherapy was performed in 12 (24%) patients. Forty patients (80%) had an ASA score of I-II and 10 (20%) ASA III-IV.

Anastomotic fistula was observed in 11 (22%) patients. Patients' characteristics for each group are listed in Table I.

Notably, patients of Group 1 showed higher odd of post-operative complications after laparoscopic ARR (OR: 3.8; CI 95%: 1.8483-8.0492; *P* = 0.0003), as reported in Table II.

In the Group 1, 79 (79%) patients developed at least one complication related to the ileostomy itself; hydro-electrolytic or metabolic disorders and peristomal skin disorders were found in 34 (34%) and 68 (68%) of cases respectively. ROC curve analysis showed with a sensitivity of 76.3% and a specificity of 66.7% that patients who underwent to ileostomy reversal later than 7.9 months presented more skin complications (OR: 3; CI 95%: 1.0216 - 8.8098; *P* = 0.045) and hydro-electrolytic and metabolic disorders (OR: 3.6; CI 95%: 1.0449 - 12.4033; *P* = 0.042) (Fig. 2).

Thirty-two (32%) ileostomies were never reversed. The median time to ileostomy take down was 8.6 months (range 1 - 27 months). Among the reversed patients, 27 (39.7%) developed at least one postoperative complication. Particularly, we observed 12 (17.6%) anastomotic leakage, 13 (19.1%) bowel obstruction, 3 (4.4%) anas-

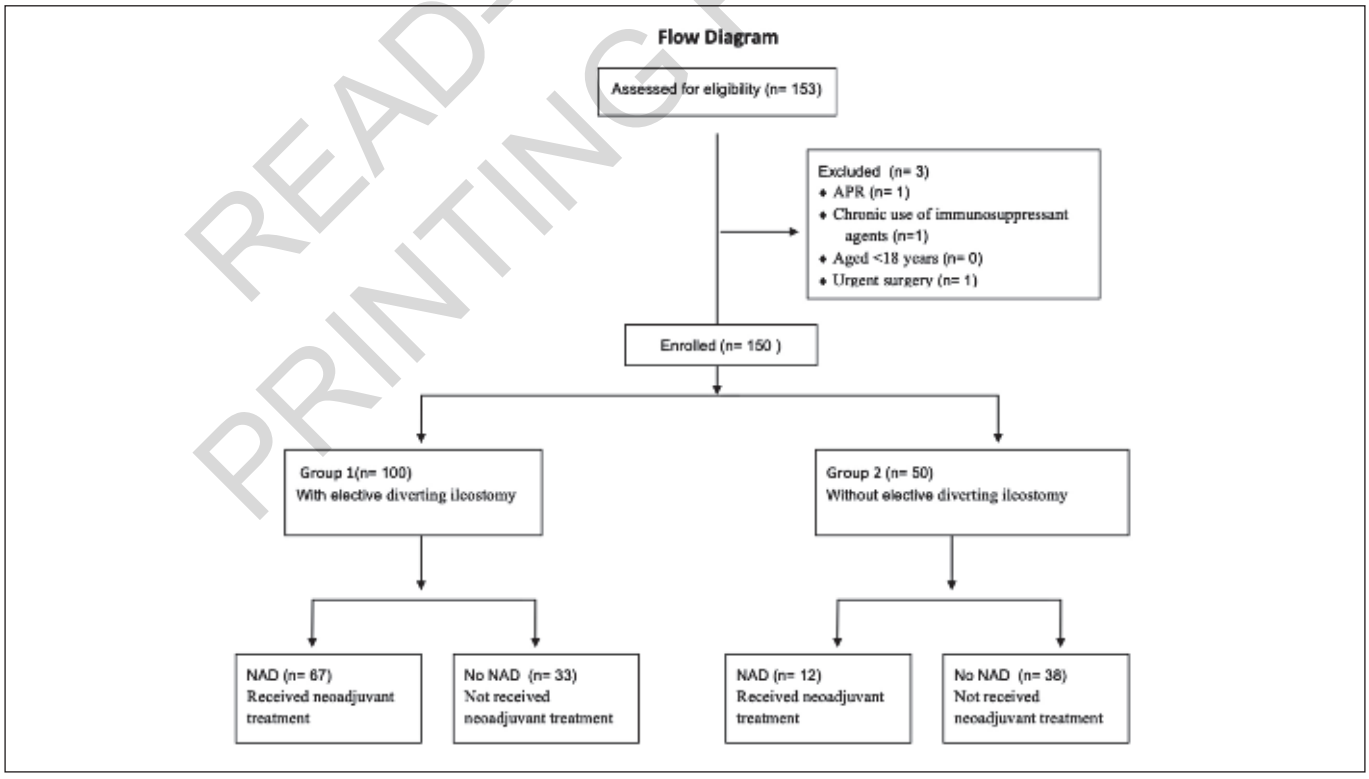

Fig. 1: Flow diagram of participants recruited.

TABLE II - *Post operative complications after ARRs*

	Group 1 (100 patients)	Group 2 (50 patients)	P value
Overall complications, n (%)	60 (60%)	14 (28%)	0.0003***
Fever, n (%)	45 (45%)	11 (22%)	0.006**
Surgical site infection, n (%)	12 (12%)	4 (8%)	0.45
Abdominal collections, n (%)	15 (15%)	4 (8%)	0.22
Anastomotic leakage, n (%)	28 (28%)	11 (22%)	0.42
Anastomotic bleeding, n (%)	1 (1%)	2 (4%)	0.21
Perforation, n (%)	3 (3%)	1 (2%)	0.72
Anastomotic stenosis, n (%)	3 (3%)	2 (4%)	0.74
Re-operation, n (%)	14 (14%)	5 (10%)	0.48

Statistical analysis was performed according to χ^2 test.

Table III - *Complications after ileostomy closure*

Patients, n	68
Overall complications, n (%)	27 (39.7%)
Anastomotic leakage, n (%)	12 (17.6%)
Bowel obstruction, n (%)	13 (19.1%)
Anastomotic bleeding, n (%)	3 (4.4%)
Surgical site infection, n (%)	5 (7.3%)
Re-operation, n (%)	9 (13.2%)

tomotic bleeding and 5 (7.3%) surgical site infections. In 9 (33.3%) patients, conservative treatment was not possible and urgent re-operation needed: 8 of these subjects had an anastomotic leakage and 1 bowel obstruction (Table III).

Overall, postoperative complications and anastomotic leakage rates were higher among patients who underwent to NAD (79 patients, 52.6%). The odd to develop at least one post-operative complication was higher among NAD patients with an OR of 2.14 (CI 95%: 1.11 - 4.11; P = 0.02). In detail after laparoscopic TME among those who received NAD, 46 (58%) developed at least one post-operative complication and 25 (31.6%) an anastomotic leakage. Among the 71 No-NAD patients (47.4%) the rates were lower (39.4% and 19.7%, respectively). Overall anastomotic fistula rate was 26% (39 patients). In detail, among those who received NAD, anastomotic leakage rates were similar in the overall population and in Group 1 (31.6% and 28.3%, respectively). In the Group 2, rates of anastomotic leakage were 50% and 13% in NAD and No-NAD patients respectively showing how NAD significantly increased the risk of anastomotic fistula (OR: 6.6; CI 95%: 1.5 - 28.74; P = 0.014). This difference was not detected in the Group 1 where rates of anastomotic leakage were 28.3% and 27.3 % in NAD and No-NAD patients respectively (P = 0.43) (Table IV).

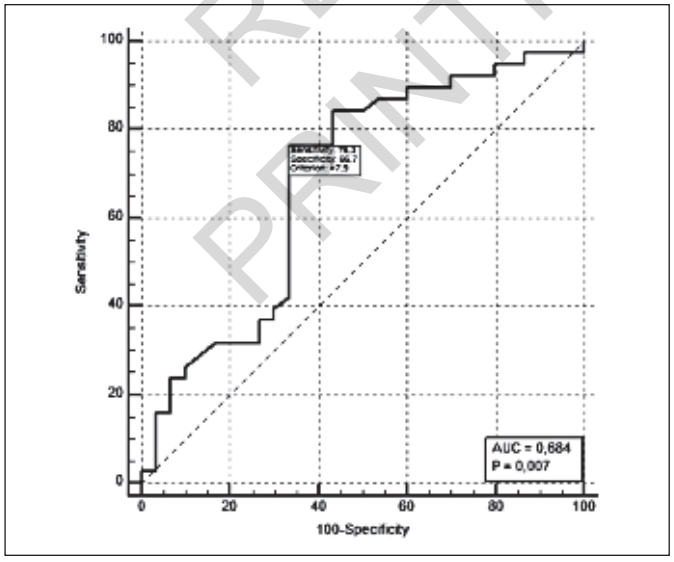

Fig. 2: Cut-off to ileostomy reversal.

Discussion and Comments

Major rectal cancer surgery is burdened with non-negligible postoperative morbidity. Among these, anastomotic fistula, reported in about one fourth of the cases, can lead to severe consequences. For this reason, colorectal anastomosis is often protected with elective diverting ileostomy. However, the ileostomy does not decrease the rate of anastomotic leakage but may reduce the severity of its clinical behavior and the risk of re-operation [20]. Moreover, morbidity in up to 70% of the cases and a non-negligible mortality have been described in presence of ileostomy and after the surgical procedure needed for its reversal. For these reasons, nowadays the real "protective" role of the elective diverting ileostomy is still an object of discussion [9,21,22]. An analysis and a clear selection of patients who truly can benefit from an elective diverting ileostomy are needed.

To tackle this issue, the present retrospective analysis study comparing patients submitted to ARR with (Group 1) and without (Group 2) elective ileostomy has been carried out. An overall anastomotic fistula rate of 26% was found. According to what has already been reported in literature [2], anastomotic failure was one of the main complications in both Groups and no differences

Table IV - *Complications and anastomotic leakage according to NAD*

OVERALL (150 patients)	NAD (79 patients)	NO NAD (71 patients)	P value
Overall complications, n (%)	46 (58%)	28 (39.4%)	0.02*
Anastomotic leakage, n (%)	25 (31.6%)	14 (19.7%)	0.09
GROUP 1 (100 patients)	NAD (67 patients)	NO NAD (33 patients)	P value
Overall complications, n (%)	40 (59.7%)	20 (60.6%)	0.93
Anastomotic leakage, n (%)	19 (28.3%)	9 (27.3%)	0.90
GROUP 2 (50 patients)	NAD (12 patients)	NO NAD (38 patients)	P value
Overall complications, n (%)	6 (50%)	8 (21%)	0.06
Anastomotic leakage, n (%)	6 (50%)	5 (13%)	0.014*

Statistical analysis was performed according to χ^2 test.

were observed between the two groups (28% and 22% respectively). Nevertheless, a higher postoperative complications rate was observed in the Group 1. Notably in this Group, 79% of the patients developed at least one complication related to the ileostomy. Some of them were mild and generally easy to manage (*e.g.*, peristomal skin disorders), but others were severe (*e.g.*, metabolic disorders and acute renal failure) and often needed hospital readmission.

According to the Authors that have already reported how early ileostomy reversal reduces complications [23], such as dehydration, metabolic and motility disorders [24], in the present experience, ileostomy related morbidity increased with the length of its permanence. However, according to those who suggest a late ileostomy take down, in order to allow resolution of inflammation and edema [25], reversal could be suggested after primary surgery, but earlier than 7.9 months post-surgery, based on our findings. Nevertheless, as we observed, ileostomy take down also showed non-negligible morbidity and re-operation rates. Moreover, 32% of patients in the present series were never reversed, mostly because of advanced age and comorbidity. This data is in agreement with other Authors that reported a rate of permanent stoma up to 30% [14,17,26].

According to previous studies [23,25], our findings showed that neoadjuvant radio-chemotherapy represents an independent risk factor for both post-operative complications and anastomotic leakage.

This could be due to the local and systemic effects induced by NAD as collagen deposition, impairment of wound healing, architectural distortions, inflammation, loss of the activity of blood cells, and blood supply linked to decreased microvessel density [27]. Our data shows that NAD significantly increased the risk of anastomotic failure in patients who did not receive elective ileostomy, while the presence of the ileostomy after NAD reduced the clinical impact of the anastomotic failure as reported in a decreased incidence of anastomotic leakage and overall complication. Based on these results, we can assume that the elective ileostomy during laparoscopic TME for rectal cancer should not routinely be considered, while patients who can benefit from elective ileostomy after laparoscopic TME are those who received NAD. We are aware that this study is limited by its retrospective design and by the small sample size, however, it should be considered that this is a monocentric study that avoids the heterogeneity related to surgical skills. Furthermore, it has to be considered that, since a radiological study of anastomotic integrity was not performed routinely, we cannot exclude the loss of some anastomotic leakage.

Conclusion

Further prospective studies are needed to define the actual role of diverting ileostomy and to identify, in addition to NAD, other high-risk classes of patients who can benefit from it after laparoscopic TME for rectal cancer.

Riassunto

Il reale ruolo protettivo della ileostomia derivativa in chirurgia laparoscopica del retto è ancora controverso. L'ileostomia derivativa può mitigare le manifestazioni cliniche della deiscenza anastomotiche ma non ne riduce l'incidenza. Inoltre, la non trascurabile incidenza di complicanze legate alla presenza della stessa ileostomia ed alla procedura di ricanalizzazione comportano la necessità di una attenta selezione dei pazienti per i quali il confezionamento di una stomia di protezione è realmente vantaggioso. Obiettivo di questo studio è quello di investigare l'impatto dell'ileostomia derivativa sugli effetti della deiscenza anastomotica e sulla morbilità legata alla stomia stessa.

Sono stati analizzati retrospettivamente 150 pazienti con cancro del retto che sottoposti a *TOTAL MESORECTAL EXCISION LAPAROSCOPICA* (TME-L) con (Gruppo 1, 100 pazienti) o senza (Gruppo 2, 50 pazienti) ileostomia elettiva per cancro del retto dal 2012 al 2017 presso l'Università Campus Bio-Medico di Roma.

Di questi due gruppi sono state analizzate le caratteristiche demografiche (età, sesso, punteggio dell'American Society of Anesthesiologists (ASA), indice di massa corporea (BMI)), le dimensione e la localizzazione del tumore, i trattamenti neoadiuvanti (NAD), la tecnica operatoria, complicanze della chirurgia primaria, durata della degenza, e complicanze correlate all'ileostomia.
La percentuale complessiva di fistole anastomotiche è stata del 26% senza differenze significative tra i due gruppi (28% nel Gruppo 1 e 22% nel Gruppo 2). In entrambi i gruppi, il trattamento neoadiuvante era significativamente associato a un rischio più elevato di complicanze postoperatorie (OR = 2,14, p = 0,02). Nel Gruppo 2, la NAD ha aumentato in modo particolare il rischio di fistole anastomotiche (OR = 6,6, p = 0,014). Invece, i pazienti del Gruppo 1 hanno mostrato una maggiore probabilità di complicanze post-operatorie dopo resezione anteriore del retto laparoscopica (OR: 3,8; CI 95%: 1,8483-8,0492; p = 0,0003) e in particolare 79 (79%) hanno sviluppato complicanze correlate a l'ileostomia stessa (disturbi della cute peristomale, squilibri idroelettrolitici e metabolici). Inoltre, trentadue (32%) ileostomie non sono mai state ri-canalizzate; tra i pazienti ri-canalizzati, 27 (39,7%) hanno sviluppato almeno una complicanza postoperatoria e in 9 (33,3%) casi è stato necessario un re-intervento urgente.
Il confezionamento dell'ileostomia può mitigare il comportamento clinico della deiscenza anastomotica dopo TME-L. Tuttavia, a causa della morbilità non trascurabile relativa alla presenza stessa della stomia ed alla sua ricanalizzazione, il confezionamento di una ileostomia derivativa dovrebbe essere considerato selettivamente nei pazienti a rischio più elevato come ad esempio coloro i quali hanno ricevuto una radio-chemioterapia neoadiuvante.

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