

Defecatory Dysfunction After Colon Cancer Resection: The Role of Inferior Mesenteric Artery Tie

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Abstract. *Background:* Although oncological results for resection of colon cancer with inferior mesenteric artery (IMA) ligation at its origin (high tie) or immediately below the left colic artery (low tie) are similar, injury of the superior hypogastric plexus may be caused when the IMA is tied at its origin, thus impairing defecatory functions. *Aim:* The importance of IMA tie location on defecatory dysfunction in patients undergoing laparoscopic sigmoidal resection without preoperative radiation therapy was studied. *Patients and Methods:* From February 2013 to December 2018, 56 consecutive patients submitted to curative laparoscopic resection for stage II and III, M0, sigmoidal cancer were randomized to a high or low tie of the IMA. All demographic data and information on symptoms and comorbidity, intra- and post-operative outcomes and defecatory function before and after surgery [according to the following scales: Fecal Incontinence Quality of Life (FIQL) scale, Jorge-Wexner incontinence and Agachan-Wexner constipation scores] were collected into a computerized database. *Results:* All patients completed the questionnaires. The educational and social status, and lifestyle habits (defined as active or sedentary) of our groups were similar. A significant difference in total score of FIQL scale was observed between the high and low tie groups at 1 month [88 ± 6 and 93 ± 7 , $p=0.005$, confidence interval for the difference between mean values (CI_{Δ})= $1.706-9.065$] and 6 months (93 ± 7 and 97 ± 6 , $p=0.030$, $CI_{\Delta}=0.390-7.547$). The Jorge-Wexner incontinence scores showed a significant

decrease in patients of the high group (1 month: 0.59 ± 0.76 and 6 months: 0.62 ± 0.79 , respectively) when compared to those of the low tie group (1 month 0.17 ± 0.38 and 6 months 0.17 ± 0.38 , respectively) ($p=0.008$ and $p=0.006$ at 1 and 6 months, respectively). At 1, 6 and 12 months, the overall Agachan-Wexner constipation scores were significantly higher in patients of the high tie group when compared to those of the low tie group (1 month: 5.1 ± 1.1 and 4.3 ± 0.86 , $p=0.002$, $CI_{\Delta}=-1.350--0.316$; 6 months: 7.4 ± 1.4 and 6.2 ± 1.4 , $p=0.003$, $CI_{\Delta}=-1.959--0.436$; and 12 months: 7.2 ± 1.3 and 6 ± 1.1 , $p=0.001$, $CI_{\Delta}=-1.840--0.576$, respectively). Conclusion: Patients affected with stage II and III sigmoidal cancer had a better fecal continence at the short- to medium-term and less abdominal pain in the medium- to long-term when a low tie technique was utilized.

Colonic resection for cancer can be performed either tying the inferior mesenteric artery (IMA) at its origin (high tie) or immediately below the left colic artery (LCA) (low tie). Two recent meta-analyses have focused on these interesting technical aspects of colon surgery to determine if morbidity, mortality, disease-free interval and long-term survival rates were influenced by these two different techniques. Zeng *et al.* demonstrated that the level of IMA ligation does not affect postoperative mortality, number of harvested lymph nodes, overall recurrence rate, and 5-year survival rate (1). Fan *et al.* reported the results of trials comparing preservation and non-preservation of the LCA (2). The comparisons studied three aspects: intraoperative, oncological, and safety outcomes. The authors demonstrated no significant difference in the 5-year mortality rate and in the operative time between high and low ligation groups and showed that LCA preservation can be successful in reducing the incidence of anastomotic leakage (2-5).

Although the oncological results of these two technical options are similar, during the dissection maneuvers, injury of the superior hypogastric plexus may be more frequent

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when the IMA is tied at its origin, leading to alteration of defecatory functions (6). The theoretical basis of these alterations is strictly linked to the sacrifice of the plexus arising from the root of the IMA and to the reduction of the blood flow to the stump when the ligation is performed at this level (4, 7, 8). The use of laparoscopic and robotic surgery for colon cancer resection, which provide a 3-dimensional view, ergonomic instrumentation and facilitate fine dissection with movement stability (7), seems not to reduce the risk of defecatory dysfunction in patients submitted to colorectal surgery (9). Furthermore, preoperative radiotherapy is another known risk factor for defecatory dysfunction, which is also associated with sexual incontinence data are inconclusive (16).

Based on the improved rates for cure of colon cancer because of multidisciplinary oncological treatments, we have been encouraged to became more focused on combining the definitive cure for colonic tumor with an improvement in patient quality of life (8, 17, 18). We believe that, at present, defecatory dysfunction should be considered an important negative outcome of colorectal surgery, in addition to the traditional endpoints such as complications, tumor recurrence, and survival.

In the present controlled randomized trial, we aimed to study the specific role of IMA tie location on defecatory dysfunction in a selected group of patients who underwent laparoscopic sigmoidal resection without preoperative radiation therapy.

Patients and Methods

Fifty-six consecutive patients undergoing curative laparoscopic resection for stage II and III, M0, sigmoidal cancer at our Institution from February 2013 to December 2018 were enrolled into this prospective randomized open label parallel trial.

Patient data were collected according to the principles laid down in the Declaration of Helsinki and a formal ethic approval from our Institutional Research Committee was obtained. The protocol was registered at a public trial registry, www.clinicaltrials.gov (trial identifier: NCT03451643). Written informed consent for treatment and the analysis of data for scientific purposes was obtained from all patients.

In order to prospectively collect demographic data and information on symptoms and comorbidity, intra- and post-operative outcomes and defecatory function before and after surgery were collected according to the following scales: Fecal Incontinence Quality of Life (FIQL) scale (19), Jorge–Wexner incontinence score (20) and Agachan–Wexner constipation score (21) and a computerized database was created. The questionnaires were administered before treatment and thereafter at 1, 6 and 12 months. Comorbidities were defined as follows: Specific colon cancer familiarity, active smoking, anamnestic cardiac disease (prior myocardial infarction, stable or unstable angina, or ST segment alteration on electrocardiogram), hypertension (diastolic blood pressure, ≥ 85 mmHg), renal disease (blood urea nitrogen > 7.1

Table I. Patient demographics, comorbidities, plasma level of tumor markers, and tumor stage according to ligation of the inferior mesenteric artery at its origin (high tie) or immediately below the left colic artery (low tie) during curative laparoscopic resection for stage II and III, M0, sigmoidal cancer.

Characteristic	High tie (n=32)	Low tie (n=24)	p-Value
Age, years			
Mean \pm SD	67 \pm 9	68 \pm 10	0.905
Gender, n (%)			
Male	24	13	0.103
Female	8	11	
Familiarity, n (%)			
Yes	4 (12%)	4 (17%)	0.713
Risk factor, n (%)			
Active smoking	10 (31%)	11 (46%)	0.282
Cardiac disease	17 (53%)	9 (37%)	0.288
Hypertension	19 (59%)	12 (50%)	0.590
Renal disease	7 (22%)	3 (12%)	0.489
Pulmonary disease	8 (25%)	3 (12%)	0.319
Obesity	8 (25%)	8 (33%)	0.558
CEA, ng/ml			
Mean \pm SD	4 \pm 1	5 \pm 1	0.442
TPA, ng/ml			
Mean \pm SD	95 \pm 12	94 \pm 13	0.817
CA19-9, U/ml			
Mean \pm SD	44 \pm 6	42 \pm 6	0.108
ASA physical status, n (%)			
I	4 (12%)	2 (8%)	0.684
II	22 (69%)	19 (79%)	
III	6 (19%)	3 (13%)	
Stage, n (%)			
IIB	10 (31%)	8 (33%)	0.939
IIIA	7 (22%)	4 (17%)	
IIIB	13 (41%)	11 (46%)	
IIIC	2 (6%)	1 (4%)	

SD: Standard deviation; CEA: carcinoembryonic antigen; TPA: tissue polypeptide specific-antigen; CA19-9: carbohydrate antigen; ASA: American Society of Anesthesiologists (23).

mmol/l; creatinine level, > 266 μ mol/l; creatinine clearance, < 50 ml/min), pulmonary disease (pO_2 , < 60 mmHg; pCO_2 , > 50 mmHg; pulmonary function tests, $< 80\%$ of predicted; tested with arterial blood gas test and spirometry), and obesity (body mass index BMI- $kg/m^2 > 20\%$ of ideal).

Serum samples for analysis of carcinoembryonic antigen (CEA), tissue polypeptide specific antigen (TPA), and carbohydrate antigen (Ca 19-9) were obtained by direct venipuncture of an antecubital vein of the arm at each patient's admission to hospital before surgery.

Criteria for exclusion were stage I and stage IV sigmoidal cancer, emergency surgery or previous stenting for colonic obstruction, metastatic disease, laparotomic approach and conversion to laparotomy, history of fecal incontinence.

According to the type of surgical treatment, the patients were randomly assigned into two groups: high IMA tie (n=32), and low IMA tie (n=24).

Preoperative work-up evaluation consisted of endoscopy with biopsy, whole-body computed tomographic (CT) scan, and blood sampling. Preoperative tumor stage (TNM classification designated by American Joint Committee on Cancer) (22), comorbidities and the physical status according to the American Society of Anesthesiologists (ASA) classification system were reported (Table I) (23). Mean operative time, number of lymph nodes excised, postoperative complications according to Clavien–Dindo classification (24), pathological tumor stage and number of positive lymph nodes at the origin of IMA were also reported.

FIQL scale. This scale is made up of a total of 29 items (19) in four domains: Lifestyle (10 items), coping/behavior (9 items), depression/self-perception (7 items), and embarrassment (3 items). The highest overall score is 119, whereas scores for individual domains are 40 for lifestyle, 36 for coping/behavior, 31 for depression/self-perception and 12 for embarrassment domain. A lower score corresponds to a compromised quality of life, whereas higher scores correspond to a better quality of life.

Jorge–Wexner incontinence score. The Jorge–Wexner scoring system (20) cross-tabulates frequencies and different anal incontinence presentations (gas/liquid/solid/pad use/need for lifestyle alterations) and sums the returned score to a total of 0–20 (where 0=perfect continence and 20=complete incontinence). In this scoring system, each of the incontinence presentations is graded equally. No psychometric items are included, other than the non-specific ‘Lifestyle Alterations’ item.

Agachan–Wexner Constipation score. The Agachan–Wexner constipation score (21) explores the following eight areas of investigation: Frequency of bowel movements; difficulty: painful evacuation effort; completeness: feeling incomplete evacuation; pain: abdominal pain; time: minutes in lavatory per attempt; assistance: type of assistance; failure: unsuccessful attempts for evacuation per 24 hours; history: duration of constipation (years). Based on the questionnaire, scores ranged from 0 to 30, with 0 indicating normal bowel function and 30 indicating severe constipation.

Surgical technique. Briefly, standard laparoscopic anterior rectosigmoidal resection was performed as previously reported (3, 4, 25, 26). High IMA ligation was achieved through a medial access after sectioning of the inferior mesenteric vein. After the identification of the IMA root, it was divided, and the colon mobilized. After rectal division, the proximal colon was exteriorized through a mini-Pfannestiel incision, resected and then stapled with an end-to-side anastomosis. A similar approach was used for patients of the second group, however, the low IMA ligation was performed after the identification and preservation of the LCA. The surgical techniques were successfully completed in all cases with a radical oncological resection.

Chemotherapy. Adjuvant chemotherapy was based on the standard FOLFOX scheme [85 mg/m² oxaliplatin intravenously (*i.v.*) day 1; 400 mg/m² leucovorin (*i.v.*) day 1; 400 mg/m² 5-fluorouracil (5-FU) bolus on day 1, then continuous infusion with 1,200 mg/m² day for 2 days (total 2,400 mg/m² over 46–48 h)] or FOLFOXIRI regimen (165 mg/m² irinotecan day 1; 85 mg/m² oxaliplatin day 1; 200 mg/m² leucovorin day 1; 48-h continuous infusion with 2,400 mg/m² 5-FU starting on day 1) plus cetuximab (400 mg/m² first infusion, 250

mg/m² thereafter) or panitumumab (6 mg/kg) or bevacizumab (5 mg/kg) based on wild-type (cetuximab/panitumumab) or mutated (bevacizumab) Rat sarcoma viral oncogene homolog (*RAS*), B-Raf murine sarcoma viral oncogene homolog B1 (*BRAF*) status (27).

Statistical analysis. SPSS (Ver. 25.0.0.1; IBM, Armonk, NY, USA) was used to analyze our data. Non-parametric tests were used because of the sample sizes. The Mann–Whitney *U*-test was used to analyze the continuous variables, with the confidence interval reported for the size of the effect, *i.e.* the difference between mean values (CI_A). The chi-square test or Fisher’s exact test was used for the categorical variables. Data are expressed as the mean±standard deviation, median, interquartile range (IQR) and mode because of the heterogeneity of the sample. Actuarial survival rate and disease-free interval were assessed by the Kaplan–Meier method at 5 years. The standard error (SE) of survival rates and disease-free interval were estimated at each censored case. Differences with α -level of <0.05 were considered statistically significant.

Results

Demographics and clinical findings. There were 37 males and 19 females. The mean age at presentation was 68±10 years (range=41–84 years; median=69 years; IQR=16 years; mode=66 years). Demographic, comorbidities, plasma level of tumor markers, ASA, TNM and tumor stage are given in Table I. No significant differences between the two groups were noted.

Early results. There were no postoperative mortality and major complications within 30 days. Overall, we recorded five (9%) minor complication; three patients in the high tie group had urinary bladder retention, postoperative vomiting needing nasogastric tube positioning, and superficial wound infection of the mini-Pfannestiel which resolved with medication; and in the low tie group, two cases had superficial wound infection of the mini-Pfannestiel which resolved with medication in one and with drainage and antibiotic therapy in the other. Oral feeding was resumed on the first or second postoperative day by all patients. The overall length of stay was 7±1 days (range=5–12 days; mode=7 days, IQR=2 days).

Long-term results. No patients were lost to follow-up (mean 37±20 months; range=3–77 months; mode=3 months, IQR=32.5 months). All patients underwent adjuvant chemotherapy. There were no major or life-threatening complications related to chemotherapy but chemotherapy was stopped for three (5%) patients because of significant deterioration of the liver function tests after the first cycle. Symptoms, potentially related to chemotherapy (fatigue, partial hair loss, decreasing liver function) were common (47 patients, 84%), and equally distributed between the two groups (26 and 21, respectively).

Overall, the 5-year survival rate was 63% (SE=0.1) and disease-free rate was 60% (SE=0.9).

Defecatory function outcome. All patients completed the questionnaires. The educational and social status, and lifestyle habits (defined as active or sedentary) of our population were similar for both groups. Most of them (48-86%) had a basic education (up to secondary), while 30 (54%) had college or master education. Social status was also similar: 41 (73%) patients were retired from work, and 15 (27%) were active (eight were manual workers and seven were employees). Twenty-five (45%) had an active lifestyle and 31 (55%) a sedentary one.

FIQL score. No differences in FIQL score were observed preoperatively between the two groups (99 ± 6 and 100 ± 7 , respectively, $CI_{\Delta} = -2.911-4.598$; $p = 0.653$). A significant difference in total score of FIQL scale was observed at 1 month (88 ± 6 and 93 ± 7 , respectively, $p = 0.005$, $CI_{\Delta} = 1.706-9.065$) and 6 months (93 ± 7 and 97 ± 6 , respectively; $p = 0.030$, $CI_{\Delta} = 0.390-7.547$). Specifically, the scores were significantly lower for patients of the high tie group when compared to those of the low tie group for each domain. The scores were similar between the two groups at 12 months after surgery (96 ± 4 and 95 ± 4 , respectively; $p = 0.437$, $CI_{\Delta} = -3.379-1.483$).

Jorge–Wexner incontinence score. No differences in Jorge–Wexner incontinence score were observed preoperatively between the two groups (0.17 ± 0.38 and 0.12 ± 0.34 , respectively; $p = 0.426$; $CI_{\Delta} = -1.552-0.238$). At 1 and 6 months, the scores showed a significant decrease in patients of the high tie group (0.59 ± 0.76 and 0.62 ± 0.79 , respectively) when compared to those of the low tie group (0.17 ± 0.38 and 0.17 ± 0.38 , respectively, $p = 0.008$, $CI_{\Delta} = -0.738--0.116$; and $p = 0.006$, $CI_{\Delta} = -0.780--0.136$, respectively). The scores were similar among the two groups at 12-month after surgery (0.25 ± 0.62 and 0.12 ± 0.34 , respectively; $p = 0.340$, $CI_{\Delta} = -0.386-0.136$).

Agachan–Wexner constipation score. No differences in Agachan–Wexner constipation score were observed preoperatively between the two groups (6.3 ± 1.2 and 5.8 ± 1.1 , respectively; $p = 0.115$, $CI_{\Delta} = -1.103-0.124$). At 1, 6 and 12 months, the overall scores were significantly higher for patients of the high tie group (5.1 ± 1.1 and 4.3 ± 0.86 , $p = 0.002$, $CI_{\Delta} = -1.350--0.316$; 7.4 ± 1.4 and 6.2 ± 1.4 , $p = 0.003$, $CI_{\Delta} = -1.959--0.436$, and 7.2 ± 1.3 and 6 ± 1.1 , $p = 0.001$, $CI_{\Delta} = -1.840--0.576$, respectively).

Discussion

The treatment of colorectal cancer, although it has greatly improved the overall disease-free and survival rates in the past decades, may impair an important aspect of the lifestyle and social habits of these patients: the defecatory function. Preoperative radiation therapy and surgery are known factors

implicated in this serious complication. Among these risk factors, we chose to investigate the role of IMA tie location in a series of patients who had no other confounding factors (no *i.e.* radiation therapy, neoadjuvant chemotherapy or open surgery). We chose to study the defecatory function with well-standardized and accepted scales and our population was also homogeneous for education, social status and lifestyle habits. These factors have an important role in the perception of eventual impairment of defecatory function (8).

Overall, our results demonstrated that a high IMA tie negatively affected the risk of defecatory disturbance after sigmoidal resection for cancer. Specifically, at 1 and 6 months, we found that the total score of FIQL was statistically significantly lower in patients of the high IMA tie group for each domain of the scoring system. The results from the Jorge–Wexner incontinence score are extremely interesting and need specific speculation. The overall analysis of the questionnaires showed a significant increase of the total score at 1 and 6 months in patients of this group when compared to those of the low tie one, but this significance was reached because patients of the high tie group specifically reported an increase in gas incontinence. Again, the results of the Agachan–Wexner constipation score similarly deserve attention. A significantly higher total Agachan–Wexner constipation score was observed in the high IMA tie group at 1, 6 and 12 months. However, this was mainly influenced by the abdominal pain item.

Our findings corroborate the hypothesis of a denervation of the pre-anastomotic colon with consequent hypomotility, inefficient transport of intestinal contents (contributing to feelings of incomplete evacuation) and retention of upstream colonic gas on the left side causing abdominal pain. We postulated that a long denervation occurring when the IMA is transected at its origin when compared to a short denervation when the LCA is preserved might be the cause of this complication (6). Denervation may lead to the loss of propagation of contraction waves, thus causing an alteration in gas continence. A direct injury of the superior hypogastric plexus may be hypothesized when this event happens (9). High IMA ligation may damage either the inferior mesenteric ganglion, which is situated immediately lateral to its origin, or the dense network of fibers (predominantly sympathetic) around the artery innervating the left colon (28-33), thus resulting in minor colonic contractions and loss of the propagating wave, with consequent diarrhea, urgency and soiling (34-36). No differences in FIQL and Jorge–Wexner incontinence scores were observed at 12 months between the two groups. We theorized that since bowel function is controlled by several factors, including rectal compliance and anal sphincter function, after an initial settling period, an insufficiency of the superior hypogastric plexus may be compensated for by the recruitment of additional existing nerve roots.

This study has several limitations but also some strengths. Firstly, this was a single-center investigation with a small number of patients, thus a significant heterogeneity, although unpredictable, might be present, thus limiting our observations. Secondly, functional studies such as anorectal manometry were not performed before and after surgery. Functional studies might improve and confirm the results. Thirdly, genitourinary and sexual dysfunction, which undoubtedly represent other serious complications linked to colorectal surgery, were not included in the present study. We expect, in fact, an even higher incidence of these dysfunctions when analyzing all spheres of disturbances linked to denervation due to injury of the superior hypogastric plexus. Conversely, the strengths of our study were the randomization of our population, the absence of patients lost to follow-up, and the completeness of all questionnaires with formally validated scales.

In conclusion, our study demonstrated that patients affected with stage II and III sigmoidal cancer had better fecal continence in the short- to medium-term and less abdominal pain in the medium- to long-term after surgery when a low tie technique was used.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Enrico Fiori: Conception, design and data analysis; Daniele Crocetti: Analysis, interpretation of data and writing the article; Antonietta Lamazza: Analysis and interpretation of data; Francesca De Felice: Conception and design; Giorgia Burrelli Scotti: Collection of data; Antonio V. Sterpetti: Conception, design and data analysis; Andrea Mingoli: Conception design and data analysis; Paolo Sapienza: Conception, design and writing the article; Giorgio De Toma: Conception and design).

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