Is Low Inferior Mesenteric Artery Ligation Worthwhile to Prevent Urinary and Sexual Dysfunction After Total Mesorectal Excision for Rectal Cancer?

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Abstract. *Background/Aim: We studied the role of high or low inferior mesenteric artery (IMA) tie on defecatory, sexual and urinary dysfunctions in patients who underwent laparoscopic TME for early rectal cancer. Patients and Methods: Forty-six consecutive patients undergoing curative laparoscopic resection for pT2N0M0, rectal adenocarcinoma from February 2013 to March 2019 were enrolled into this prospective randomized open label parallel trial to have a laparoscopic TME with a high (Group 1) or low IMA ligation (Group 2). Demographic data and information on symptoms and comorbidity, intra- and post-operative outcomes and defecatory, sexual and urinary functions before and after surgery according to the validated International quality of life questionnaires. Results: A significant difference in postoperative total score of FIQL scale, Jorge-Wexner incontinence score and Agachan-Wexner constipation score were observed between the high and low tie groups at 1, 6, and 12 months after surgery. ICIQ-UI short form, FSFI, and IIEF demonstrated at 1, 6 and 12 months, the scores were significantly higher for patients of Group 1 as compared to those of Group 2. Conclusion: A low IMA ligation permits a better fecal continence, less abdominal pain, and less genito-urinary and sexual dysfunctions in patients submitted to TME for rectal cancer.*

Urinary, sexual and defecatory functional disorders are often related to total mesorectal excision (TME) performed during anterior rectal resection for rectal cancer, thus significantly impairing the quality of life (QoL) of the patients (1, 2). At present, rectal surgery should include R0 resection, appropriate lymphadenectomy, low incidence of anastomotic leakage and sphincter preservation after preoperative or postoperative pelvic radiotherapy. Previous studies have shown that sexual and urinary dysfunction due to pelvic nerve injury after surgery and pelvic radiotherapy can have a significant impact on patients' quality of life (QoL) (3). Moreover, the position of arterial ligation during laparoscopic anterior rectal resection with total mesorectal excision can affect genito-urinary and bowel functions, oncological outcomes, and incidence of anastomotic leakage. Rectal resection for cancer can be performed either by tying the inferior mesenteric artery (IMA) at its origin (high tie) or just below the left colic artery (LCA) (low tie). Recent metanalyses (4, 5) focused on morbidity, mortality, disease-free interval and long-term survival rates demonstrated that the level of IMA ligation does not affect oncological outcomes and showed that LCA preservation can be successful in decreasing the incidence of anastomotic leakage (6-8). Furthermore, during dissection maneuvers, an injury of the superior hypogastric plexus may be provoked more frequently when the IMA is tied at its origin, thus determining an alteration of the defecatory functions (9, 10). In the present prospective randomized open label trial, we aimed to study the role of high or low IMA tie on defecatory, sexual and urinary dysfunctions in patients who underwent laparoscopic TME for early rectal cancer without neoadjuvant radiation therapy.

Patients and Methods

Forty-six consecutive patients undergoing curative laparoscopic resection for pT2N0M0 (Stage I) (11), rectal adenocarcinoma at our Institution from February 2013 to March 2019 were enrolled into

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this prospective randomized open label parallel trial to have a laparoscopic TME with a high or low IMA ligation.

Patients' data were carried out 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 properly registered at a public trial registry, www.clinicaltrials.gov (Trial identifier NCT03451643). A written informed consent for the treatment and the analysis of data for scientific purpose was obtained from all patients.

Demographic data and information on symptoms and comorbidity, intra- and post-operative outcomes and defecatory, sexual and urinary functions before and after surgery according to the following scales: Fecal incontinence quality of life (FIQL) scale (12), Jorge-Wexner incontinence (13), Agachan-Wexner constipation (14) scores, international consultation on incontinence questionnaire urinary incontinence short form (ICIQ-UI Short Form) (15), female sexual function index (FSFI) (16) and international index of erectile function (IIEF) (17), were collected into a computerized database. These questionnaires were administered before treatment and thereafter at 1, 6 and 12 months. Comorbidities were defined as follows: specific rectal 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 mmol/l; creatinine level, >266 μmol/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/m² >20% of ideal).

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

Criteria for exclusion were T1, T3 and T4 rectal cancer or N+ rectal cancer, neoadjuvant/adjuvant radio-chemotherapy, rectal cancer lower than 5 cm, emergent surgery or previous stenting for rectal obstruction, metastatic disease and laparotomic approach or conversion to laparotomy, history of sexual or urinary dysfunction.

According to the type of surgical treatment, the patients were assigned into two groups: Group 1, high IMA tie, (n=22) and Group 2, low IMA tie (n=24).

Preoperative work-up evaluation consisted of endoscopy with biopsy, endorectal ultrasound, whole body contrast enhanced computed tomography (CT)-scan, pelvic magnetic resonance imaging (MRI), and blood samples. Preoperative tumor stage (TNM classification designated by American Joint Committee on Cancer) (11), comorbidities and the physical status class according to the American Society of Anesthesiologists (ASA) (18) classification system were reported (Table I). Mean operation time, number of lymph nodes excised, postoperative complications, according to Clavien-Dindo classification (19), pathological tumor stage and number of positive lymph nodes at the origin of IMA were also reported.

FIQL scale. A total of 29 items make the FIQL scale (12). These items form four domains: Lifestyle (10 items), Copying/Behavior (9 items), Depression/Self-Perception (7 items), and Embarrassment (3 items). The highest overall score is 119, whereas for individual domains are 40 for lifestyle, 36 for copying/behavior, 31 for depression/self-perception and 12 for embarrassment domain. Lower

Table I. *Patients demographics, comorbidities, plasma level of tumor markers 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 IIA rectal cancer.*

	Group 1 (n=22)	Group 2 (n=24)	*p*-Value
Age (SD)	68 (9)	68 (11)	0.990
Gender (Male/Female)	12/10	14/10	0.796
Familiarity	8 (36)	7 (29)	0.603
Active smoking	8 (36)	10 (41)	0.713
Cardiac disease	8 (36)	8 (33)	0.829
Hypertension	10 (45)	9 (37)	0.584
Renal diseases	3 (13)	3 (12)	0.909
Pulmonary diseases	2 (9)	4 (17)	0.446
Obesity	9 (41)	8 (33)	0.595
CEA, ng/ml (SD)	5 (1)	6 (1)	0.406
TPA, ng/ml (SD)	95 (12)	95 (12)	0.997
CA 19-9, U/ml (SD)	47 (6)	44 (6)	0.085
ASA			0.396
I	0 (0)	1 (4)	
II	18 (82)	16 (67)	
III	4 (18)	7 (29)	

SD: Standard deviation; CEA: carcinoembryonic antigen; TPA: tissue polypeptide specific antigen; CA 19-9: carbohydrate antigen 19-9; ASA: American Society of Anesthesiologists.

score corresponds to a compromised quality of life whereas higher scores corresponds to a better quality of life.

Jorge-Wexner incontinence score. Jorge-Wexner scoring system (13) 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. Agachan-Wexner constipation score (14) explores the following areas of investigations: 1-frequency of bowel movements; 2-difficulty: painful evacuation effort; 3-completeness: feeling incomplete evacuation; 4-pain: abdominal pain; 5-time: min in lavatory per attempt; 6-assistance: type of assistance; 7-failure: unsuccessful attempts for evacuation per 24 h; 8-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.

ICIQ-UI short form. The aim of ICIQ (15) is to assess urinary incontinence and its impact on quality of life (QoL). The ICIQ-UI Short Form is a brief and psychometrically robust patient-completed questionnaire for evaluating the frequency, severity and impact on quality of life (QoL) of urinary incontinence in men and women in research and clinical practice across the world. It is scored on a scale from 0-21. The ICIQ-UI Short Form provides a brief and robust measure to assess the impact of symptoms of incontinence on outcome.

Sexual function questionnaire. Female sexual function was evaluated with the FSFI (16) and male sexual function with the IIEF (17). FSFI assesses different domains of sexual female function (desire, arousal, lubrication, orgasm, satisfaction and pain). The FSFI is a 19-item questionnaire with a total score ranging from 2 to 36 points. The IIEF is a multidimensional scale, which addresses the most relevant aspects of male sexual function, such as erectile strength, orgasm, desire, satisfaction with intercourse, and overall satisfaction. The IIEF is a 19-item questionnaire with a total score ranging from 5 to 75 points. Lower scores indicate for both scales a decreased sexual function.

Surgical technique. Briefly, standard laparoscopic anterior rectal resection was performed as previously reported (6, 7, 20, 21). In group 1 the high IMA ligation was gained through a medial access after the section of the inferior mesenteric vein. After the identification of the IMA root, it was divided, and the left colon mobilized using, in all cases, the Harmonic Focus device (Ethicon Endo-Surgery, Johnson & Johnson Inc, NJ, USA) to reduce bleeding (22). Total mesorectal excision was always performed. After rectum division, the rectum was exteriorized through a mini-Pfannestiel incision, resected and then stapled with a colorectal end-to-side anastomosis. A similar approach was used for patients of group 2, 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 an oncologic radical resection.

Statistical analysis. Our data were inserted into a computer software program (SPSS Ver. 25.0.0.1; SPSS Chicago, IL, USA for MacOS High Sierra ver. 10.13.4, Apple Inc., Cupertino, CA, USA) and statistically analyzed. Non-parametric tests were used because of the sample sizes. Continuous variables were analyzed with the Mann-Whitney U-test with the 95% confidence interval reported for the size of the effect, *i.e.* the difference between mean values (CI_Δ). Categorical variables were studied with the Chi-square test or the Fisher's exact test. Data were expressed as 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. 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. Twenty-six (56%) were males and 20 (44%) females (mean age 68 ± 10 years; range=39-84 years; median=69.5 years; IQR=13 years; mode=78 years). Table I gives the demographic, comorbidities, plasma level of tumor markers, and ASA showing no significant differences between the two groups.

Early results. No postoperative mortality and major complications within 30 days were observed. Three (6%) minor complications were observed. One patient in Group 1 had superficial wound infection of the mini-Pfannestiel, which resolved with medication; and 2 in Group 2 (1 acute urinary retention and 1 superficial antecubital arm vein phlebitis). Oral feeding was resumed on the first or second postoperative day by all patients with no statistical differences between the two groups (p=0.873). The overall length of stay was 7±2 days (range=5-11 days; median=7 days; mode=7 days, IQR=2 days) and no statistical differences were recorded among the two groups (p=0.213).

Long-term results. No patients were lost to follow-up (mean 40±21 months; median=39.5; months; range=5-72 months; mode=55 months, IQR=30 months). No patients underwent adjuvant treatment. The 5-year survival rate was 91% (SE=0.5) and disease-free rate was 81% (SE=0.7). No differences were recorded among the two groups (p=0.462 and p=0.896, respectively).

Defecatory, urinary and sexual function outcome. All patients completed the questionnaires. The social and educational status, the lifestyle habits (defined as active or sedentary) of our population were similar for both groups. Thirty-five (76%) completed a basic education (up to secondary), while 11 (24%) had college or master's degree. A similar social status was observed: 37 (80%) patients were retired from work, and 9 (20%) were active (6 were manual workers and 3 were employees). Seventeen (37%) had an active lifestyle and 29 (63%) a sedentary one.

FIQL score. Preoperatively, the score was similar among the two groups (Group 1: 101±6; Group 2: 102±7; p=0.662; 95%CI_Δ=−3.118-4.951). A significant difference in the total score was observed at 1 month (87±6 and 94±7, respectively; p=0.001; 95% CI_Δ=2.892-11.047), 6 months (92±8 and 98±6, respectively; p=0.006; 95%CI_Δ=1.868-10.495), and 12 months after surgery (92±5 and 95±5, respectively; p=0.024; 95% CI_Δ=0.473-6.262). The scores were significantly lower for patients of Group 1 when compared to those of Group 2 for each domain.

Jorge–Wexner incontinence score. No preoperative differences were recorded among Group 1 and 2 (0.4±0.5 and 0.2±0.4, respectively; p=0.256; 95%CI_Δ=−0.428-0.117). At 1, 6 and 12 months, the scores showed a significant decrease in patients of Group 1 (0.6±0.8, 0.7±0.8, and 0.6±0.9 respectively) when compared to those of Group 2 (0.2±0.4, 0.2±0.4, and 0.1±0.3 respectively) (p=0.017; 95%CI_Δ=−8.49- −0.091; p=0.013; 95%CI_Δ=−0.914- −0.116; and p=0.019; 95%CI_Δ=−0.931- −0.092, respectively).

Agachan–Wexner constipation score. No differences were observed preoperatively among the two groups (Group 1: 6±1 and Group 2: 6±1; p=0.437; 95%CI_Δ=−0.906-0.398). At 1, 6 and 12 months, the scores were significantly higher for patients of Group 1 when compared to those of Group 2 (5±1 and 4±1, p=0.002; 95%CI_Δ=−1.720- −0.424; 8±1 and 6±1,

p=0.001; 95%CI$_\Delta$=–2.489- –0.913, and 8±1 and 6±1, p=0.001; 95%CI$_\Delta$=–2.626- –1.291, respectively).

ICIQ-UI short form. No statistical differences were observed preoperatively (Group 1: 0.4±1 and Group 2: 0.5±1; p=0.809; 95%CI$_\Delta$=–0.636-0.811). At 1, 6 and 12 months, the scores were significantly higher for patients of Group 1 as compared to those of Group 2 (2±2 and 0.5±1, p=0.0025; 95%CI$_\Delta$=–2.593- –0.505; 2±2 and 0.5±1, p=0.002; 95%CI$_\Delta$=–2.466- –0.618, and 2±2 and 0.6±1, p=0.018; 95% CI$_\Delta$=–2.084- –0.204, respectively).

FSFI. No statistical differences were observed preoperatively (Group 1: 19±3 and Group 2: 18±3; p=0.839; 95%CI$_\Delta$=–3.143-2.583). At 1, 6 and 12 months, the scores were significantly lower for patients of Group 1 as compared to those of Group 2 (11±3 and 17±4, p=0.001; 95% CI$_\Delta$=3.315-10.085; 12±3 and 17±4, p=0.007; 95% CI$_\Delta$=1.465-7.935, and 13±3 and 18±3, p=0.002; 95% CI$_\Delta$=2.022-7.778, respectively).

IIEF. No statistical differences were observed preoperatively (Group 1: 42±16 and Group 2: 43±19; p=0.894; 95%CI$_\Delta$=–13.199-15.032). At 1, 6 and 12 months, the scores were significantly lower for patients of Group 1 as compared to those of Group 2 (27±11 and 39±17, p=0.036; 95%CI$_\Delta$=0.878-24.122; 28±11 and 40±18, p=0.048; 95%CI$_\Delta$=0.134-24.319, and 28±11 and 40±18, p=0.041; 95%CI$_\Delta$=0.541-24.864, respectively).

Discussion

Although TME, radio- and chemotherapy have greatly improved the survival rates of patients affected with rectal cancer, they represent two known factors negatively influencing defecatory, urinary and sexual function. Specifically, from one side, the combination of neoadjuvant radiotherapy followed by TME with nerve sparing, permits an extremely low local recurrence (<5%) and high 5-year survival rates (80%) (23), to the other, a defecatory, urinary and sexual impairment, is recorded from 5 to 40% of the patients (24, 25). Specifically, the rate of urinary dysfunction (*i.e.* urinary incontinence, difficulty in voiding or neurogenic bladder), reported in the current literature, reaches 30% (25), whereas sexual dysfunctions (*i.e.* erectile dysfunction and ejaculation problems in men and decreased vaginal lubrication, dyspareunia and difficulty reaching orgasm in women) are reported in more than 50% of the patients (24, 25). On the other hand, in men, radiotherapy causes an obliterative endarteritis of the penile bulb small blood vessels, which reduces blood flow and impairs erectile function, whereas, in females, determines a persistent detrimental effect on the vaginal mucosa impacting negatively on sexual function (24). Although preoperative

chemo-radiation therapy or adjuvant chemotherapy deteriorate the defecatory, urinary and sexual functions, the most important factor influencing these occurrences is an intraoperative nerve damage because of a lack of anatomical knowledge or poor visualization of the pelvic nerve fibers (26). Therefore, an improvement of the surgical technique and pelvic radiotherapy fields may, at least theoretically, reduce the incidence of these complications (27-29). In particular, the introduction in clinical practice of a standardized technique for TME performed with a minimally invasive approach have significantly improved surgical visibility, thus helping in recognizing the abdominal and pelvic nerves (24). Their recognition, more easily accomplished with this approach, seems, in fact, to permit a significant reduction in these dysfunctions when compared to conventional open surgery (1, 23, 30).

In our study, we aimed to investigate the role of high and low IMA ligation and no other confounding factors (*i.e.* radiation therapy, neoadjuvant chemotherapy and open surgery, benign lesions, emergency setting) (9, 31-35) in the impairment of the defecatory, sexual and urinary function after TME. The ligation of the IMA at its origin may accidentally damage the superior hypogastric plexus, which is interconnected with the inferior hypogastric plexus. The regulation of normal defecatory, sexual and urinary function depends, in fact, on sympathetic and parasympathetic nerve supply originating from the superior and inferior hypogastric plexus. In our previous study, we demonstrated (9) that a high IMA tie negatively affects the risk of defecatory disturbances because 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. Furthermore, an injury to the superior hypogastric plexus and hypogastric nerves may also lead to retrograde ejaculation, incomplete or lack of ejaculation (23, 36). We also observed that patients of Group 1 had a higher incidence of urinary incontinence, seriously impacting their quality of life. We postulated that the urinary involvement is due to interconnections between sympathetic and parasympathetic fibers from the superior and inferior hypogastric plexus.

The total score of FIQL was significantly lower for Group 1 patients when compared to those of Group 2 for each domain, and similar results were obtained with the Jorge-Wexner incontinence score. In particular, the analysis of the questionnaires showed a significant increase in the total score at follow-up in Group 1 patients; but this significance was reached because these patients reported an increase in gas incontinence. Furthermore, the total score of the Agachan-Wexner constipation questionnaire was significantly higher for patients of Group 1 when compared to those of Group 2, because of a loss of propagated

contraction waves causing abdominal pain. Furthermore, we showed a better genito-urinary and sexual outcome in patients who underwent a low IMA ligation.

This study has several limitations but also some strengths. This is a single center study with a small number of patients, thus a significant heterogeneity, although unpredictable, might be present, thus limiting our observations. Functional studies, such as anorectal manometry, urodynamic test (*i.e.* uroflowmetry, flow cystometry, abdominal leak-point pressure), penile dynamic color Doppler ultrasound, nocturnal penile tumescence test, were not performed before and after surgery. Functional studies might improve and confirm the results. Conversely, the strengths of our study were the randomization of our population, the analysis of all spheres of disturbances linked to the denervation of the superior hypogastric plexus, 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 who underwent TME for rectal cancer with a low IMA ligation had a better fecal continence, less abdominal pain, and experienced less genito-urinary and sexual dysfunctions when compared to those having a high IMA ligation. Since no differences in long-term survival and disease-free rates are recorded, we recommend a low IMA ligation to decrease the risk of these complications significantly impairing patients' quality of life.

Conflicts of Interest

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

Authors' Contributions

Enrico Fiori (Conception, design and data collection), Daniele Crocetti (Conception, design and writing the manuscript), Antonietta Lamazza (Data analysis and interpretation of data), Francesca De Felice (Writing the manuscript), Antonio V Sterpetti (Conception and design), Luigi Irace (Interpretation of data), Andrea Mingoli (Interpretation of data), Paolo Sapienza (Conception, design and writing the manuscript), Giorgio De Toma (Conception and design).

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