

Intraoperative monitoring of pelvic autonomic nerves during laparoscopic low anterior resection of rectal cancer

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Background: Some patients with low rectal cancer experience anorectal and urogenital dysfunctions after surgery, which can influence the long-term quality of life. In this study, we aimed to protect nerve function in such scenarios by performing intraoperative monitoring of pelvic autonomic nerves (IMPAN).

Patients and methods: We retrospectively investigated a series of 87 patients undergoing laparoscopic low anterior resection of rectal cancer. Nerve-sparing was evaluated both visually and electrophysiologically. IMPAN was performed by stimulating the pelvic autonomic nerves under processed electromyography of the internal anal sphincter. Urination, defecation, sexual function, and the quality of life were evaluated using validated and standardized questionnaires preoperatively and at follow-up, 12 months after surgery.

Results: Among a total of 87 patients (53 male and 34 female patients), IMPAN with simultaneous electromyography of the internal anal sphincter was performed in 58 (66.7%) patients. Bilateral positive IMPAN results for both measurements, indicating successfully confirmed pelvic autonomic nerve preservation, were obtained in 45 (51.7%) patients. No significant difference was found in terms of urogenital and anorectal functions between preoperative and postoperative patients with bilateral positive IMPAN ($P>0.05$). Compared to preoperative patients with IMPAN (unilateral) or without IMPAN, these patients exhibited higher International Prostate Symptom Score, a lower International Index of Erectile Function-5, and a lower Female Sexual Function Index score at 12 months postoperatively ($P<0.05$).

Conclusion: IMPAN is an appropriate method with which to laparoscopically protect nerve function.

Keywords: rectal cancer, low anterior rectal resection, intraoperative neuromonitoring, pelvic autonomic nerves

Introduction

The surgical procedure used for total mesorectal excision and the implementation of multimodal treatment strategies have considerably improved the prognosis of patients with low rectal cancer. However, following low anterior resection (LAR), some patients are known to experience anorectal and urogenital dysfunctions, which can exert significant impact upon the long-term quality of life,¹⁻³ regardless of whether open or laparoscopic LAR procedure was performed.⁴ The dominant cause of such dysfunction appears to be injuries incurred by the pelvic autonomic nerves during the surgical procedure.⁵ Therefore, it is very important to identify methods with which to protect the pelvic autonomic nerves during such procedures.

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Poor nerve visualization and a lack of neuroanatomical knowledge will inevitably result in inadvertent nerve damage. Furthermore, the intraoperative identification of nerve structures can be difficult due to the complex neuroanatomy involved, as well as the involvement of numerous surgical and patient-related factors, such as a narrow or deep pelvic cavity, severe obesity, a history of pelvic surgery, and neoadjuvant chemoradiotherapy.²⁻⁴ In order to reduce the rate of dysfunction following this form of surgery, Kneist et al introduced nerve-sparing surgery via the intraoperative neuromonitoring of pelvic autonomic nerves.⁶⁻⁸ Throughout this new technique, intraoperative neuromonitoring was performed via the electrical stimulation of pelvic autonomic nerves with concomitant electromyography of the internal anal sphincter and cystomanometry. Notably, better outcomes of anorectal and urogenital functions were evident in patients undergoing surgery with intraoperative neuromonitoring compared to patients who did not experience this method.⁹

Kneist et al were the first to demonstrate that laparoscopic intraoperative neuromonitoring is technically feasible.¹⁰ Laparoscopy may allow optimal visualization of neural structures in the narrow and deep pelvic cavity due to a number of specialist characteristics, including angled view, illumination, and magnification. Nerve preservation was usually evaluated visually. Few surgeons protected nerve through electrophysiological technique. The aim of the present study was to assess the effect of intraoperative monitoring of pelvic autonomic nerves (IMPAN) on accurate evaluation of nerve-sparing during laparoscopic LAR of rectal cancer.

Patients and methods

Patients

We retrospectively investigated 87 patients (53 male and 34 female patients) who underwent laparoscopic LAR for primary rectal cancer in Huashan Hospital, Fudan University between January 2012 and May 2016. Of these 87 patients, 58 underwent surgery with IMPAN; the rest did not. Written informed consent was obtained from all patients. This study was approved by the Ethics Committee of Huashan Hospital affiliated to Fudan University, and was conducted in accordance with the Declaration of Helsinki. Total mesorectal excision was carried out by the same team of surgeons using a standardized procedure. In cases of poor anastomosis, we fitted a diverting stoma.

Outcome assessment

Urinary function, anorectal function, sexual function, and quality of life were assessed in rectal cancer patients who underwent laparoscopic LAR over a 12-month follow-up

period (following stoma closure, patients were followed up for 6–9 months; and patients without a diverting stoma were followed up for 12 months). At the 12-month follow-up, stoma closure had failed in three patients with IMPAN (unilateral), five patients with IMPAN (bilateral), and six patients without IMPAN. These patients were eliminated from our analysis of anorectal function.

Urinary function

We ascertained the International Prostate Symptom Score ([IPSS], in which the total score ranges from 0 to 35 points) and the quality of life for urinary function (in which the total score ranges from 0 to 6 points) to assess urinary function for both male and female patients.¹¹ A higher score indicated more severe urinary dysfunction.

Sexual function

Assessment of sexual function differs according to gender. Male sexual function was evaluated using the International Index of Erectile Function-5 (IIEF-5) score (a five-item questionnaire in which total score ranges from 1 to 25 points).¹² A lower score indicated more severe erectile dysfunction. The Female Sexual Function Index (FSFI) has become a multi-dimensional self-reporting instrument for assessing sexual function in women and covers six domains: desire, subjective arousal, lubrication, orgasm, satisfaction, and pain. This is a 19-item questionnaire with a total score ranging from 2 to 36 points,¹³ with a higher score indicating better sexual function.

Anorectal function

Anorectal function was determined by the Wexner score, the total score of which ranges from 0 to 20 points, with a score of >9 indicating anorectal dysfunction resulting in a diminished quality of life.¹⁴

Electrophysiological assessment

Neuromonitoring was performed with an electromyograph (DK-2740; Medtronic, Minneapolis, MN, USA). For electromyography, the needle electrode was placed into the internal anal sphincter, and a reference electrode was placed on the left thigh. As shown in Figure 1, we developed a bipolar probe as

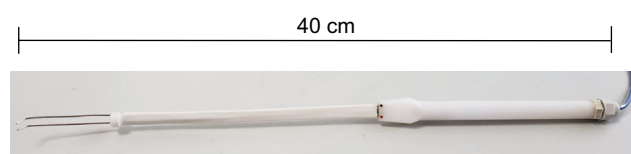


Figure 1 Bipolar probe for laparoscopic neuromonitoring in the pelvis.

the stimulating electrode. The stimulating electrode was placed into the abdominal cavity through the trocar. Any visualized pelvic autonomic nerves were directly stimulated after dissection of the lateral ligament of the rectum and Denonvilliers' fascia (Figure 2). The currents applied ranged from 5 to 10 mA, the frequency was 2 Hz, and stimulation lasted 5–20 seconds.

Statistical analysis

For statistical evaluation, *P*-values <0.05 were considered statistically significant. The Wilcoxon's signed-rank test was used to analyze paired random samples. All analyses were performed using SPSS 21.0 software (IBM Corporation, Armonk, NY, USA).

Results

Patient data

Out of the 87 patients (53 male and 34 female patients) included in this study, IMPAN with simultaneous electromyography of the internal anal sphincter was performed in 36 male patients and 22 female patients. Bilateral positive IMPAN results for both measurements indicating successfully confirmed pelvic autonomic nerve preservation were achieved in 45 patients (28 male and 17 female patients). In patients with IMPAN, if one side of the pelvic autonomic nerve can be successfully monitored and the other side failed, these patients belong to unilateral IMPAN group.

No significant differences were found in terms of the baseline characteristics of our patients. There were no major intraoperative or postoperative complications. None of the patients died as a result of the operation. Demographics, histopathological characteristics, and surgical data are summarized in Table 1.

Urinary function

In 45 patients with bilateral positive stimulation responses, the mean IPSS total score was 6.58 ± 3.19 preoperatively, and 6.76 ± 3.11 at the 12-month follow-up. The mean preoperative IPSS score was 6.08 ± 1.66 in 13 patients with a unilateral positive stimulation response, while the mean preoperative IPSS score was 6.28 ± 2.53 in 29 patients without IMPAN. At the time of the 12-month follow-up, the IPSS score had increased significantly to 10.23 ± 3.09 in patients with IMPAN (unilateral) and to 9.10 ± 4.08 in patients without IMPAN ($P < 0.05$). Assessment of the quality of life due to urinary symptoms in the 87 patients yielded a similar result for IPSS scores (Table 2).

Sexual function

Out of the 53 male patients, preoperative mean total IIEF-5 score was 18.29 ± 4.27 , 18.68 ± 5.38 , and 18.88 ± 3.69 in the unilateral IMPAN group, bilateral IMPAN group, and none-IMPAN group, respectively. At the 12-month follow-up, 2

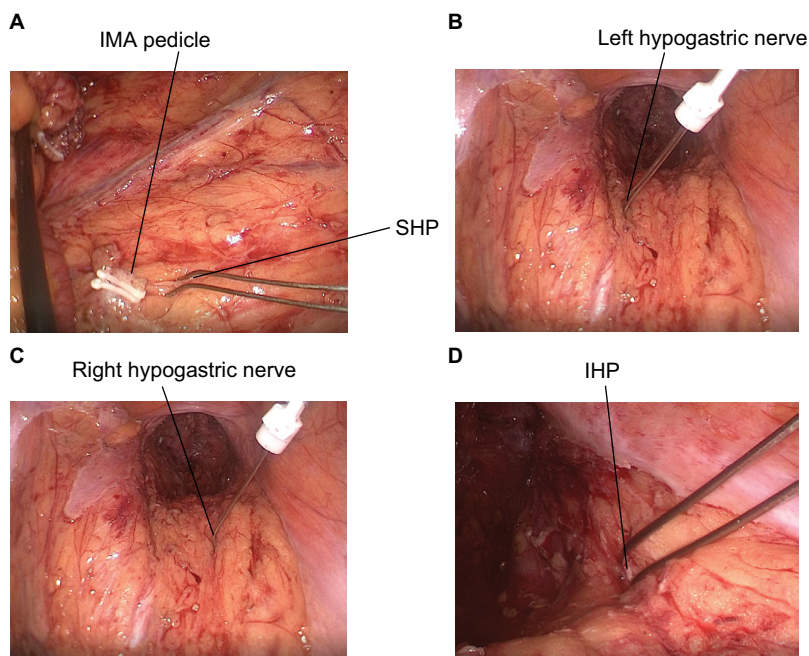


Figure 2 Pelvic autonomic nerves stimulated by a bipolar probe during surgery.

Note: (A) Intraoperative monitoring of SHP; (B) intraoperative monitoring of left hypogastric nerve; (C) intraoperative monitoring of right hypogastric nerve; and (D) intraoperative monitoring of right IHP.

Abbreviations: IHP, inferior hypogastric plexus; IMA, inferior mesenteric artery; SHP, superior hypogastric plexus.

Table 1 Characteristics of rectal cancer patients undergoing laparoscopic LAR with or without IMPAN

Patient characteristics		With IMPAN	Without IMPAN	P-value
Age (years) ^a		65 (45–80)	62 (55–78)	0.099
Gender	Male	36	17	0.565
	Female	22	12	
ASA grade	I	32	15	0.074
	II	21	8	
	III	5	6	
Previous pelvic surgery	Yes	12	5	0.442
	No	46	24	
Neoadjuvant chemoradiotherapy	Yes	19	7	0.083
	No	39	22	
Tumor location (from anal verge)	>7 cm	24	14	0.378
	≤7 cm	34	15	
Multi-visceral resection	Yes	14	9	0.198
	No	44	20	
Tumor category	T1/T2	23	11	0.754
	T3/T4	35	18	
Lymph node category	N negative	33	15	0.496
	N positive	25	14	
Operation time (min) ^b		156.72±33.32	150.69±32.06	0.327
Blood loss (mL) ^b		102.16±65.10	113.45±78.25	0.237

Notes: ^aResults are expressed as medians. Interquartile range is in parentheses. ^bResults are expressed as mean ± SD.

Abbreviations: ASA, American Society of Anesthesiologists; IMPAN, intraoperative monitoring of pelvic autonomic nerves; LAR, low anterior resection.

Table 2 IPSS and quality of life due to urinary symptoms in patients with rectal cancer before surgery and at follow-up after LAR

Evaluation of urinary function	With IMPAN (unilateral) 13 patients			With IMPAN (bilateral) 45 patients			Without IMPAN 29 patients		
	Before surgery	After surgery	P-value	Before surgery	After surgery	P-value	Before surgery	After surgery	P-value
IPSS	6.08±1.66	10.23±3.09	0.001	6.58±3.19	6.76±3.11	0.088	6.28±2.53	9.10±4.08	0.001
Quality of life	1.46±1.13	2.77±1.54	0.007	2.33±1.13	2.51±1.32	0.185	1.76±0.91	3.03±1.48	0.001

Notes: Results are expressed as mean ± SD at follow-up 6–9 months after stoma closure or 12 months after surgery in patients without a diverting stoma. P-values <0.05 are shown in bold.

Abbreviations: IMPAN, intraoperative monitoring of pelvic autonomic nerves; IPSS, International Prostate Symptom Score; LAR, low anterior resection.

out of 28 patients with IMPAN (bilateral), three out of seven patients with IMPAN (unilateral), and five out of 18 patients without IMPAN had postoperative erectile dysfunction. The differences in the IIEF-5 scores between patients with IMPAN (unilateral) and without IMPAN were highly significant compared to patients with IMPAN (bilateral) ($P < 0.05$). Similar results were observed in terms of FSFI scores among the three groups of female patients after surgery (six patients in the unilateral IMPAN group, 17 patients in the bilateral IMPAN group, and eleven patients in the none-IMPAN group). Impairment of female sexual function was significantly worse in patients with IMPAN (unilateral) and without IMPAN rather than in patients with IMPAN (bilateral) (Tables 3 and 4).

Anorectal function

Wexner score was evaluated in patients preoperatively and at the 12-month follow-up after LAR procedures. Three

patients with IMPAN (unilateral), five patients with IMPAN (bilateral), and six patients without IMPAN failed to achieve stoma closure by the 12-month follow-up appointment. These patients were not evaluated for Wexner score. No significant difference was found in Wexner score when compared between preoperative and 12-month follow-up assessments, regardless of IMPAN ($P > 0.05$) (Table 5).

Discussion

Total mesorectal excision is a standard technique for the treatment of rectal cancer and was first described in 1982 by Heald et al.¹⁵ During this procedure, sharp dissection, a negative circumferential resection margin, and pelvic autonomic nerve preservation are required to ensure radical resection and reduce postoperative anorectal and urogenital dysfunctions.

Over the past decade, various intraoperative pelvic neuromonitoring methods, aimed at identifying and preserving

Table 3 IIEF-5 scores in male patients before and at follow-up after LAR from rectal cancer

Evaluation of male sexual function	With IMPAN (unilateral) seven male patients			With IMPAN (bilateral) 28 male patients			Without IMPAN 18 male patients		
	Before surgery	After surgery	P-value	Before surgery	After surgery	P-value	Before surgery	After surgery	P-value
IIEF -5	18.29±4.27	12.43±5.53	0.039	18.68±5.38	18.04±5.67	0.074	18.88±3.69	12.82±4.43	0.001

Notes: Results are expressed as mean ± SD at follow-up 6–9 months after stoma closure or 12 months after surgery in patients without a diverting stoma. P-values <0.05 are shown in bold.

Abbreviations: IIEF, International Index of Erectile Function; IMPAN, intraoperative monitoring of pelvic autonomic nerves; LAR, low anterior resection.

Table 4 FSFI scores in female patients with rectal cancer prior to surgery and at follow-up after LAR

Evaluation of female sexual function	With IMPAN (unilateral) six female patients			With IMPAN (bilateral) 17 female patients			Without IMPAN eleven female patients		
	Before surgery	After surgery	P-value	Before surgery	After surgery	P-value	Before surgery	After surgery	P-value
FSFI	17.33±6.95	10.50±4.37	0.002	16.76±6.13	16.53±6.32	0.299	17.28±5.73	11.00±4.88	0.001

Notes: Results are expressed as mean ± SD at 6–9 months after stoma closure or 12 months after surgery in patients without a diverting stoma. P-values <0.05 are shown in bold.

Abbreviations: FSFI, Female Sexual Function Index; IMPAN, intraoperative monitoring of pelvic autonomic nerves; LAR, low anterior resection.

Table 5 Wexner score in patients with rectal cancer before and at follow-up after LAR

Evaluation of anorectal function	With IMPAN (unilateral) ten patients			With IMPAN (bilateral) 40 patients			Without IMPAN 23 patients		
	Before surgery	After surgery	P-value	Before surgery	After surgery	P-value	Before surgery	After surgery	P-value
Wexner	6.500±3.95	8.10±2.60	0.193	6.63±2.69	6.85±2.24	0.544	7.09±2.86	8.48±3.34	0.071

Notes: Results are expressed as mean ± SD at 6–9 months after stoma closure or 12 months after surgery in patients without a diverting stoma.

Abbreviations: IMPAN, intraoperative monitoring of pelvic autonomic nerves; LAR, low anterior resection.

pelvic autonomic nerves, have been developed and introduced to exenterative pelvic surgery.¹⁶ The anatomy of the pelvis is highly complex, particularly with respect to the autonomic nervous system and its interindividual variations.^{17–20} It is anticipated that pelvic nerve injury may occur at different sites, with different functional consequences.^{21,22} First, during ligation of the inferior mesenteric artery pedicle, unsuitable lymph node dissection at the root of the inferior mesenteric artery may increase the possibility of superior hypogastric plexus injury. Second, during initial posterior rectal dissection, when separating the parietal (presacral) and the visceral (perirectal) pelvic fascia at the level of the sacral promontory, it is possible to injure the hypogastric nerves due to working in the wrong anatomic plane; the magnification of laparoscopy, and vaporization from the ultrasonic knife, can help us to identify the posterior plane. Third, during anterolateral rectal dissection close to the lateral ligaments, inferior hypogastric plexus should be protected. Finally, during anterior rectal dissection at the lateral edge

of Denonvilliers' fascia, the three-dimensional structural integrity of the prerenal presacral fascia and Denonvilliers' fascia need be maintained in order to maintain the integrity of the mesorectum. Urogenital neurovascular bundles which are close to Denonvilliers' fascia are vulnerable to injury.

Due to its angled view and magnification, the surgical field in laparoscopic operations is clearer than in open surgeries. Laparoscopic procedures could, therefore, provide improved views and enable a more selective approach for repetitive electric stimulations of different sites compared to open surgery. In this study, we demonstrated that IMPAN was a more appropriate method for the reliable quality assurance of laparoscopic nerve-sparing during LAR for rectal cancer.

When compared preoperatively and at 12-month follow-up, the differences in IPSS score, quality of life, IIEF-5 score, and FSFI score among patients with IMPAN (bilateral), with IMPAN (unilateral), and without IMPAN, respectively, were highly significant. These results suggested that IMPAN could become a predictor of urinary and sexual dysfunctions in

patients undergoing laparoscopic LAR surgery. In patients without IMPAN, pelvic autonomic nerve preservation was assessed visually by the surgeon. Since the pelvic autonomic nerve was not damaged in some patients without IMPAN, the advantages of IMPAN may be greater than this result shows. Kneist et al reported similar improvements in urogenital and anorectal functions in patients undergoing surgery with monitoring of the autonomic pelvic nerves during laparoscopic LAR compared to patients who did not.¹⁰

In our study, three out of seven patients with IMPAN (unilateral) had positive erectile dysfunction compared to five out of 18 patients without IMPAN. Erectile dysfunction in the two patients with bilateral nerve-sparing may have been associated with adjuvant radiochemotherapy and severe reactive depression subsequent to surgery. Our findings suggested that bilateral nerve-sparing is an essential prerequisite for maintaining male erectile function, which is in accordance with previous studies of erectile function following nerve-sparing radical surgery for rectal cancer.^{23,24} We should also acknowledge study limitations, including possible selection bias. IMPAN can be performed in selected patients with no radiotherapy, no edema, female patients with large pelvis, thin patients, tumor size is small, no invasion of serosa, etc. On the contrary, IMPAN will not be performed in selected patients with pelvic autonomic nerves that are not easily exposed. Owing to the difficulty of nerve exposure, nerve is very easily damaged. Even performing IMPAN can lead to unilateral or bilateral nerve monitoring failure.

It is remarkable that no significant difference was found in Wexner score between the preoperative and 12-month follow-up assessments in patients receiving IMPAN and those who did not. As the *P*-values in unilateral IMPAN group and without IMPAN group are quite low, type I error may be smaller and type II error may be greater in Wexner scores. But if we increase the sample size, we can reduce type I and type II errors at the same time. The sample size of our study, however, was small; our next step will be to recruit more patients to participate in our research. Most patients came to our hospital because of bloody stools and anorectal disorders, while others were preoperative patients with locally advanced stages who already had anorectal dysfunction. We plan to use anorectal manometry as an objective indicator with which to evaluate anorectal function. We also aim to increase the frequency and duration of postoperative follow-up.

In addition, neoadjuvant chemoradiotherapy may affect the anorectal and urogenital functions of patients for a long time. In a recent retrospective study of 263 rectal cancer patients, it was demonstrated, after a median follow-up of

51 months, that fecal incontinence occurs more frequently in irradiated patients with a trend toward worse sexual function.²⁵ A further study reported the negative long-term effect of preoperative radiation on anorectal function with a mean follow-up of 14 years.²⁶ Similar results were found in the Dutch Total Mesorectal Excision Trial in which Lange et al evaluated anorectal and sexual functions preoperatively and at several time points up to 5 years after surgery; results showed that anorectal and sexual functions worsened significantly over time in the irradiated patients.^{5,27}

Conclusion

IMPAN may be of substantial value, because it provides the surgeon with direct feedback as to whether the plane of dissection is close to the pelvic autonomic nerves. Our retrospective study demonstrated that IMPAN is an appropriate and reliable method with which to assure laparoscopic nerve-sparing. However, up until now, there have been no published data from prospective randomized studies which compare the functional outcome after LAR for rectal cancer with and without IMPAN. Prospective randomized multicenter trials remain important for better demonstration of the efficacy, accuracy, and safety of IMPAN.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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