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REVIEW

Intraoperative neuromonitoring in rectal cancer surgery: a systematic review and meta-analysis

Athina A. Samara[1] · Ioannis Baloyiannis[1] · Konstantinos Perivoliotis[1] · Dimitrios Symeonidis[1] · Alexandros Diamantis[1] · Konstantinos Tepetes[1]

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Abstract

Purpose The aim of this study is to evaluate the role of pelvic intraoperative neuromonitoring (pIONM) in rectal cancer surgery.
Methods A systematic review of the literature and a meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Cochrane Handbook for Systematic Reviews of Interventions.
Results Overall, nine studies were identified. Quantitative analysis was performed only in three trials. Bilateral pIONM improved postoperative anorectal and urogenital functional outcomes. However, unilateral pIONM displayed a significant effect only on erectile function ($p = 0.001$).
Conclusions Our findings suggest a positive effect of pIONM on postoperative functional outcomes and quality of life after rectal cancer surgery. Due to several limitations, further trials are required in order to elucidate the exact role of pIONM.

Keywords TME · Neuromonitoring · Fecal incontinence · Urogenital dysfunction · Pelvic

Introduction

A new era in rectal cancer surgery has been associated with the introduction of total mesorectal excision (TME) [1, 2]. The combination of neoadjuvant chemoradiotherapy with TME has allowed for the minimization of local recurrence risk and the enhancement of survival outcomes [1, 2]. Following these improvements, attention has been directed towards quality of life (QoL) and functional outcomes [3].

The impact of postoperative functional deficits on quality of life has been repeatedly confirmed [4, 5]. It is estimated that nearly one third of patients who undergo surgery for rectal cancer according to the TME principles will ultimately develop low anterior resection syndrome (LARS), with devastating consequences due to the deriving incontinence [5]. Additionally, the associated urinary and sexual dysfunction will further contribute to overall poorer QoL [6, 7].

Intraoperative injury of the pelvic autonomous nerves is considered as the primary risk factor for postoperative functional complications in rectal cancer surgery [8, 9]. The risk is further increased after previous neoadjuvant radiation, while advanced age and low tumor location have also been, identified as independent predictive factors for postoperative functional complications [8, 10, 11].

In recent years, pelvic intraoperative neuromonitoring (pIONM) has been adopted in rectal cancer surgery [10–14]. Overall, pIONM displays a favorable profile, with the technique being associated with optimal postoperative anorectal and urinary function. Several trials have evaluated the role of pIONM in rectal cancer surgery [11–15]. However, to the best of our knowledge, pooled data regarding the beneficial effect of pIONM after TME for rectal cancer are lacking.

Therefore, the present systemic review and meta-analysis were conducted to summarize current evidence and assess the efficacy of pIONM, concerning the functional outcomes after rectal cancer surgery.

Materials and methods

Study protocol

This meta- analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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✉ Athina A. Samara
at.samara93@gmail.com

[1] Department of Surgery, University Hospital of Larissa, Mezourlo Hill, 41112 Larissa, Greece

(PRISMA) guidelines [16] and the Cochrane Handbook for Systematic Reviews of Interventions [17].

Endpoints

The primary endpoint of this study was the assessment of anorectal functional improvement in patients receiving pIONM, compared to the respective controls. Anorectal functional comparisons were based on the Wexner score (ranging between 0 and 20 points, with a score > 9 indicating anorectal dysfunction) [18].

Secondary endpoints included urogenital dysfunction in terms of IPSS (International Prostate Symptom Score), Quality of Life for Urinary Function score [19], and IIEF-5 (International Index of Erectile Function) [20].

Eligibility criteria

All human prospective or retrospective studies reporting relevant and retrievable data regarding pIONM after TME for rectal cancer were considered as eligibile. No language restriction was applied in this study. Exclusion criteria included the following: [1] non-human trials, [2] irretrievable data, [3] pediatric patients, [4] studies in the form of expert opinion, editorials, conference abstracts, and letters.

Literature search

A systematic literature search was performed using the scholar databases Medline, Web of Science, and Scopus. The last literature search was performed on 1 December 2020; all studies published up to the last search date were included in the database screening. The following Boolean search algorithm was applied:

- [pelvic] AND [neuromonitoring]

Manual screening of reference lists from eligible studies was also performed.

Study selection and data collection

Following the removal of duplicate records, both titles and abstracts of the remaining studies were reviewed. The remaining records were submitted for a full-text review. All literature screening, data extraction, and quality assessment were completed in duplicate and blindly by two independent researchers (K.P. and A.S.). In the event that a discrepancy could not be resolved, the opinion of a third researcher was considered (I.B.).

Quality and methodology assessment was performed by Newcastle–Ottawa Scale (NOS) [21] and Case Series Quality Appraisal Checklist (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) for comparative studies and single group studies, respectively.

Statistical analysis

Analyses were performed using IBM SPSS version 23 and Cochrane Collaboration RevMan version 5.4. Continuous data were reported in the form of mean (standard deviation), whereas categorical variables were displayed as N. In cases where the continuous values were not provided, tthey were extracted following an established algorithm, from the respective median, range, or interquartile range [22].

Endpoint analysis was based on the weighted mean difference calculations. Evaluation of the two groups was based on the difference between postoperative and preoperative values of the respective score. These were estimated on the basis of the Cochrane guidance [17]. All analyses results were provided with the respective 95% confidence intervals (95%CI).

Both random effect (RE) and fixed effect (FE) models were calculated. The model that was finally presented was based on the results of the Cochran Q test. Heterogeneity was quantified by I^2. Statistical significance was considered at $p < 0.05$.

Risk of bias across studies

The presence of publication bias was evaluated by the visual inspection of the respective funnel plot.

Results

The literature search resulted in the retrieval of 168 records (Fig. 1). After removal of 93 duplicate articles, abstracts of the remaining records were reviewed. A total of 54 studies were excluded (11 review articles; 43 irrelevant articles) and therefore, 21 full-text articles were reviewed. Subsequently, nine studies [9, 11, 23–29] were included in the present qualitative analysis. Most of the trials were conducted by a single study group during overlapping time periods, thus increasing the risk of duplicate data. As such, only 3 trials were included in the quantitative analysis [23, 25, 27].

The characteristics of the studies included are displayed in Table 1. Seven prospective [9, 11, 24–29] and two retrospective [14, 25] trials were identified. A control group was introduced only in five studies [11, 23–25, 27]. Demographic data of the allocated patients are also displayed in Table 1.

Table 2 summarizes characteristics of the described neuromonitoring technique. The most common technique of pelvic autonomous nerve mapping included the use of repetitive electric stimulations using a hand-guided bipolar microfork probe, under continuously electromyography of the internal anal sphincter (IAS EMG) and urinary bladder

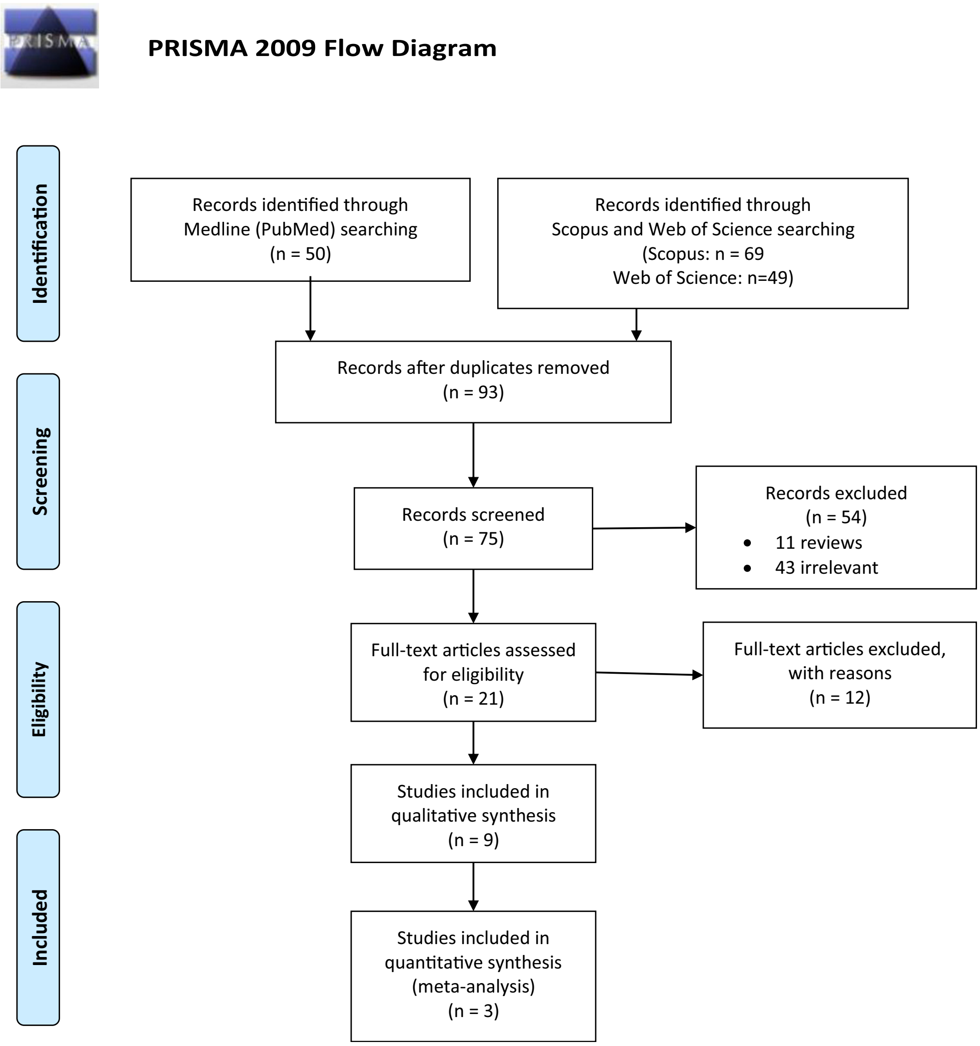


Fig. 1 PRISMA flow diagram

[9, 11, 24, 27]. Laparoscopic probes have also been designed for minimally invasive pIONM [11, 23–26] .

Four of the comparative trials were evaluated with 7 stars [11, 23, 25, 27] and one study with 6 stars [24] based on the Newcastle–Ottawa Scale (NOS) [21]. All four case series studies [9, 26, 28, 29] included in this systematic review were evaluated 7/9 in the Case Series Quality Appraisal Checklist (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).

Fecal incontinence (Supplementary Material Tables) rates ranged between 3.3% and 21% [24, 26] for TME under pIONM, whereas the corresponding incidence in the control group spanned between 35% and 50% [24]. Newly onset urinary dysfunction was reported between 3.3 to 20% [11, 26] and 40 to 54.7% [11, 27] of pIONM and control cases, respectively. Similarly, in terms of sexual dysfunction the pIONM group (38.5–60%) [11] displayed optimal results, compared to the non-pIONM (68.2–90.5%) [11].

Regarding the primary outcome, meta-analysis confirmed that patients who underwent TME surgery for rectal cancer under bilateral pIONM had a significantly ($p < 0.0001$) lower Wexner score difference (WMD: −1.29, 95%CI: −1.88, −0.70), compared to the control. However, when unilateral pIONM was applied, no significant effect was found ($p = 0.21$) (Fig. 2 A, B).

Similarly, the mean IPSS difference was significantly lower ($p < 0.0001$) when bilateral pIONM was used (WMD: −2.41, 95%CI: −2.89, −1.93). On the contrary, this was not the case for the unilateral pIONM group ($p = 0.82$) (Fig. 3 A, B). Similarly, in terms of the Quality of Life for Urinary Function score, only bilateral pIONM had a significant impact ($p < 0.0001$).

Regarding sexual dysfunction, bilateral pIONM application resulted in significant improvement ($p < 0.0001$) of IIEF-5 scores, and this effect remained even when unilateral pIONM was used ($p = 0.001$) (suplemantary material).

Visual inspection of the primary endpoint's funnel plot revealed a symmetrical distribution of the included studies (supplementary material).

Table 1 Study characteristics

Author	Year of publication	Study period	Type of study	Group	Sample	Age Median (sd)		Gender (males/ Females)	Follow-up (median)
Jin et al. [23]	2020	01/2012-12/2018	Retrospective	pIONM	43	Bilateral- male: 56 (6.5)	Unilateral-male: 55 (5.75)	29/14	12 months
				no pIONM	36	Bilateral- female:54 (3)	Unilateral female: 53 (6.75)		
Kauff et al.* [24]	2020	01/2008-10/2015	Prospective	pIONM no pIONM	29 52	63 (2.25)		26/3	24 months
Zhou et al. [25]	2019	01/2012–05/2016	Retrospective	pIONM no pIONM	58 87	65 (8.75)		36/22	12 months
Kauff et al.* [11]	2017	01/2008–08/2014	Prospective	pIONM no pIONM	43 85	65 (5)		35/8	24 months
Kauff et al.* [26]	2016	02/2008–05/2015	Prospective	pIONM	30	62 (5)		n/a	9 months (6–12 months)
Kneist et al.* [9]	2014	–	Prospective	pIONM	17	60 (4.75)		17/0	9 months (8–12 months)
Kneist et al.* [27]	2013	01/2008–11/2012	Prospective	pIONM no pIONM	35 150	65 (8.25)		n/a	9 months (7–14 months)
Kneist et al.* [28]	2012	–	Prospective	pIONM	11	67 (9.75)		10/1	6 months (2–12 months)
Kneist et al.* [29]	2004	04/2002-	Prospective	pIONM	17	61 (11.5)		11/6	2 months (1–4 months)

pIONM pelvic intraoperative neuromonitoring

*Studies conducted by the same research group

Table 2 Surgical and neuromonitoring techniques

Author	Type of primary surgery	Laparoscopic/ open	Neoadjuvant chemo/ radiotherapy (c/t, r/t)	Neuromonitoring procedure
Jin et al. [23]	LAR [34] APR [5] ISR [1]	43/0	n/a	Repetitive electric stimulations to map autonomic nerves with a laparoscopic handguided bipolar microfork probe under continuously electromyography of the internal anal sphincter neuromonitoring. After visualized pelvic autonomic nerves were directly stimulated after dissection of the lateral ligament of the rectum and Denonvilliers' fascia.
Kauff et al. [24]	LAR with TME	7/45	12/29	Bipolar electric stimulation of pelvic autonomic nerves at different sites along the pelvic side and above the level of the pelvic floor, under continuous electromyography of the internal anal sphincter and manometry of the urinary bladder.
Zhou et al. [25]	LAR	58/0	19/58	Repetitive electric stimulations to map autonomic nerves with a laparoscopic handguided bipolar microfork probe under continuously electromyography of the internal anal sphincter neuromonitoring. After visualized pelvic autonomic nerves were directly stimulated after dissection of the lateral ligament of the rectum and Denonvilliers' fascia.
Kauff et al. [11]	LAR [31] APR [11]	11/32	16/43	Repetitive electric stimulations to map autonomic nerves at different sites along the pelvic side and above the level of the pelvic floor, with a handguided bipolar microfork probe under continuously cystomanometry and online processed electromyography of the internal anal sphincter neuromonitoring
Kauff et al. [26]	LAR	30/0	n/a	Repetitive electric stimulations to map autonomic nerves at different sites along the pelvic side and above the level of the pelvic floor, with a laparoscopic handguided bipolar microfork probe under continuously cystomanometry and online processed electromyography of the internal anal sphincter neuromonitoring
Kneist et al. [9]	LAR	n/a	9/17 (all R/T)	Bipolar electric stimulation of pelvic autonomic nerves under continuous electromyography of the internal anal sphincter and manometry of the urinary bladder
Kneist et al. [27]	LAR	0/35	n/a	Bipolar electric stimulation of pelvic autonomic nerves under continuous electromyography of the internal anal sphincter and manometry of the urinary bladder
	LAR [11]	n/a	7/11	Electrical stimulation of the pelvic splanchnic nerves

Table 2 (continued)

Author	Type of primary surgery	Laparoscopic/ open	Neoadjuvant chemo/ radiotherapy (c/t, r/t)	Neuromonitoring procedure
Kneist et al. [28]	APR [3]		(6 R/T and 1 C/T)	with a handheld bipolar microfork probe sequentially on both pelvic sides. Additional nerve mapping was carried out if pelvic autonomic nerves could not be clearly identified macroscopically. IONM was performed after rectal resection in LAR, and after mesorectal dissection before perineal excision in APR
Kneist et al. [29]	LAR with TME [14] APR [2] MVR [1]	n/a	2/17	Monopolar unilateral right and left nerve stimulation of the parasympathetic pathways with insulated rigid probes of a neurostimulation device and bladder pressure measurement, either before or following rectal excision.

TME total mesorectal excision, *LAR* low anterior resection, *APR* abdomino-perineal resection, *MVR* multivisceral resection, *IONM* intraoperative neuromonitoring, *ISR* intersphincteric resection, *R/T* radiotherapy, *C/T* chemotherapy

Discussion

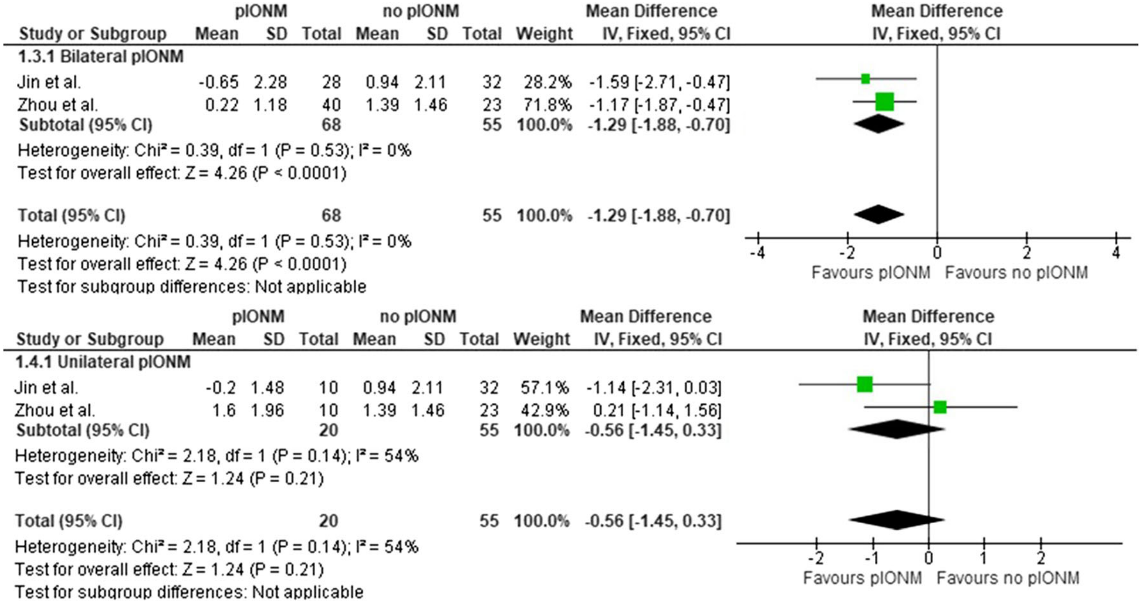
The optimal oncological outcomes of TME have rendered it the mainstay surgical approach for rectal cancer [30]. En bloc resection of the primary malignancy and the enveloping fatty tissue and lymph nodes, following the embryonical planes, allows a proper tumor clearance thus minimizing the risk of local recurrence [31]. However, the risk of intraoperative autonomous nerve injury during TME and the subsequent, adverse functional sequalae have long been established [3, 32, 33]. A predicted increase in the incidence of rectal cancer in the upcoming decades further highlights the significance of ameliorationg functional deficits through a nerve-sparing technique [31–36].

In order to maximize pelvic nerve preservation, the applied surgical approach should be optimized. Anatomical studies have confirmed several critical intraoperative keypoints, where the risk of nerve injury is considerably high. Typical examples include the high ligation of the inferior mesenteric artery, the mesosigmoid to mesorectum transition zone, and the dissection of the lateral rectal ligaments and the Denonvilliers fascia [37–39]. Additionally, the risk of injury is further enhanced by redundant use of electrocautery and energy sources [40].

Pelvic anatomy is characterized by considerable complexity, thus rendering surgical competence and structural familiarization necessary for optimal outcomes. Visual nerve identification can be quite challenging even for experienced surgeons [41]. The intraoperative difficulty is further increased in patients with a narrow and deep pelvis, or advanced tumors. Moreover, further anatomical obstacles include reoperated or irradiated cases, abdominal obesity, and a voluminous mesorectum [41]. Therefore, in contrast to the questionable visual identification of the pelvic nerves, pIONM was proposed as a more efficient technique for ensuring both the anatomical and functional preservation of the autonomous plexus [26].

Laparoscopic TME is considered to improve nerve-sparing, due to better visualization of the neural structures. Theoretically, magnification of the surgical site alongside meticulous tissue dissection decreases the risk of plexus injury, with a significant impact on QoL [14]. Several clinical trials investigated these assumptions, with mixed results [3]. In the COREAN trial, patients submitted to laparoscopic TME displayed improved physical functioning, fewer gastrointestinal and defecation problems and less frequent micturition disorders [42]. On the contrary, long-term QoL analysis of the COLOR II trial could not confirm any advantage related to the minimally invasive approach [43].

It is estimated that approximately up to 35% of patients submitted to TME will ultimately develop severe anorectal dysfunction. The renowned LARS syndrome is characterized by a debilitating fecal urgency, tenesmus and inconti-



Study or Subgroup	pIONM Mean	SD	Total	no pIONM Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 Bilateral pIONM								
Jin et al.	-0.65	2.28	28	0.94	2.11	32	28.2%	-1.59 [-2.71, -0.47]
Zhou et al.	0.22	1.18	40	1.39	1.46	23	71.8%	-1.17 [-1.87, -0.47]
Subtotal (95% CI)			**68**			**55**	**100.0%**	**-1.29 [-1.88, -0.70]**

Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 4.26 (P < 0.0001)

Total (95% CI)			**68**			**55**	**100.0%**	**-1.29 [-1.88, -0.70]**

Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 4.26 (P < 0.0001)
Test for subgroup differences: Not applicable

Study or Subgroup	pIONM Mean	SD	Total	no pIONM Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 Unilateral pIONM								
Jin et al.	-0.2	1.48	10	0.94	2.11	32	57.1%	-1.14 [-2.31, 0.03]
Zhou et al.	1.6	1.96	10	1.39	1.46	23	42.9%	0.21 [-1.14, 1.56]
Subtotal (95% CI)			**20**			**55**	**100.0%**	**-0.56 [-1.45, 0.33]**

Heterogeneity: Chi² = 2.18, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 1.24 (P = 0.21)

Total (95% CI)			**20**			**55**	**100.0%**	**-0.56 [-1.45, 0.33]**

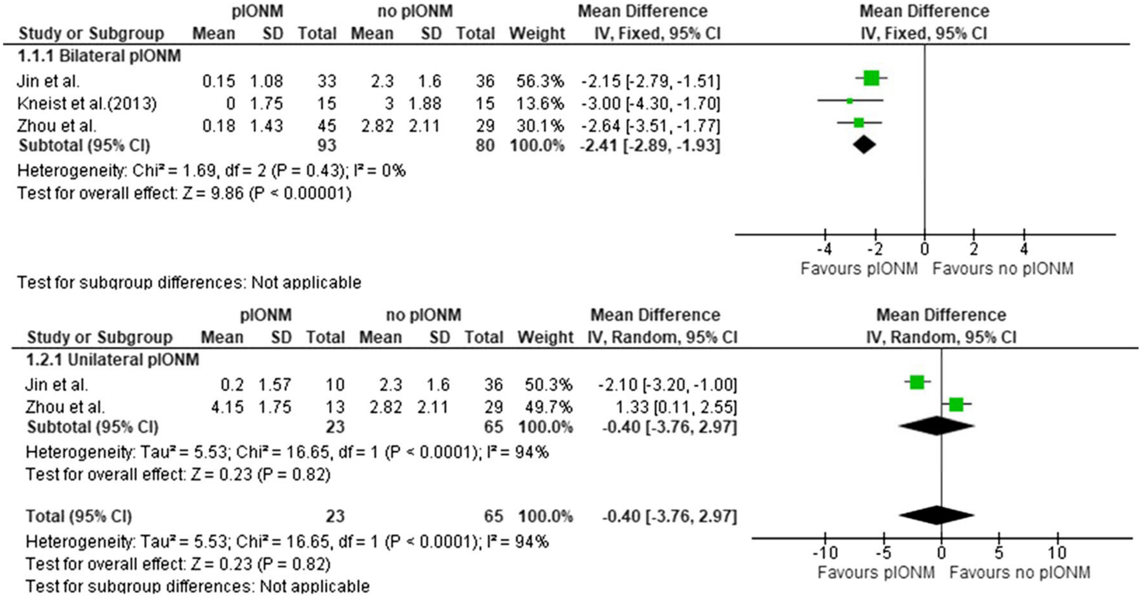
Heterogeneity: Chi² = 2.18, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 1.24 (P = 0.21)
Test for subgroup differences: Not applicable

Fig. 2 A, B: Wexner score for A. Bilateral and B. Unilateral pIONM compared to non-pIONM

nence [44]. Current literature reports regarding the true incidence of LARS are not conclusive [45, 46]. A recent population-based study by Pieniowski et al. [45] suggested that total or partial mesorectal excision resulted in a 77.4% LARS rate during a mean of 6.7 years of follow-up. Moreover, almost half of the patients developed a severe form of LARS, with a major impact upon all QoL components [45]. In contrast, a recent literature review by van der Heijden et al. [46] reported a 7–52% and a 10–84% rate of minor and major LARS, respectively, with no effect from the applied TME approach.

Several pathophysiologic disorders contribute to the development of LARS [47]. Among them, dysfunction of the internal anal sphincter (IAS), sensory denervation of the anal canal, and subsequent loss of the rectoanal inhibitory reflex (RAIR) are the most remarkable [47]. Application of pIONM enables the intraoperative identification of the splachnic neural contributors, thus avoiding an unnecessary pelvic denervation [13].

The clinical value of pIONM in postoperative anorectal function has been highlighted in several trials. In a cohort study by Kauff et al. [13], a two-dimensional IONM based on bladder manometry and IAS EMG displayed a 100% sensitivity and 96% specificity for the prediction of anorectal deficits. In another study by the same group, the omission of pIONM was characterized as an independent predictor of



Study or Subgroup	pIONM Mean	SD	Total	no pIONM Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Bilateral pIONM								
Jin et al.	0.15	1.08	33	2.3	1.6	36	56.3%	-2.15 [-2.79, -1.51]
Kneist et al.(2013)	0	1.75	15	3	1.88	15	13.6%	-3.00 [-4.30, -1.70]
Zhou et al.	0.18	1.43	45	2.82	2.11	29	30.1%	-2.64 [-3.51, -1.77]
Subtotal (95% CI)			**93**			**80**	**100.0%**	**-2.41 [-2.89, -1.93]**

Heterogeneity: Chi² = 1.69, df = 2 (P = 0.43); I² = 0%
Test for overall effect: Z = 9.86 (P < 0.00001)

Test for subgroup differences: Not applicable

Study or Subgroup	pIONM Mean	SD	Total	no pIONM Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 Unilateral pIONM								
Jin et al.	0.2	1.57	10	2.3	1.6	36	50.3%	-2.10 [-3.20, -1.00]
Zhou et al.	4.15	1.75	13	2.82	2.11	29	49.7%	1.33 [0.11, 2.55]
Subtotal (95% CI)			**23**			**65**	**100.0%**	**-0.40 [-3.76, 2.97]**

Heterogeneity: Tau² = 5.53; Chi² = 16.65, df = 1 (P < 0.0001); I² = 94%
Test for overall effect: Z = 0.23 (P = 0.82)

Total (95% CI)			23			65	100.0%	-0.40 [-3.76, 2.97]

Heterogeneity: Tau² = 5.53; Chi² = 16.65, df = 1 (P < 0.0001); I² = 94%
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable

Fig. 3 A, B: IPSS score for A. Bilateral and B. Unilateral pIONM compared to non-pIONM postoperative fecal incontinence, even after 24 months of follow-up [24]. Likewise, our pooled analyses suggest that bilateral pIONM compared to controls leads to a significantly lower increase of the postoperative Wexner scores. This effect however was not evident in unilateral pIONM.

Overall, the rate of post-TME urinary dysfunction is estimated to range between 4% and 28% [29]. In the Dutch trial, nearly 30% of patients developed long-term bladder emptying difficulties, with a considerable percentage requiring intermittent catheterizations [8]. Intraoperative preservation of the autonomous plexus has as a result the sustainment of the normal external urethral sphincter and detrusor muscle function [3]. It was estimated that application of pIONM retains the postoperative urinary dysfunction rates at 20%, compared to 51.2% in the non-pIONM patients, respectively. In a study by Kneist et al. [27], the omission of neural mapping led to a significant increase of the mean IPSS scores. Our findings are in parallel with this evidence. More specifically, pIONM retained urinary function as measured by both the IPSS and the Quality of Life for Urinary Function scores.

Postoperative sexual dysfunction presents a diverse clinical image, including unsatisfactory erection, retrograde ejaculation, decreased vaginal lubrication, and dyspareunia [3]. In a retrospective cohort study by Zhou et al. [25], the implementation of pIONM during lapararoscopic TME allowed for the preservation of sexual function in both genders. Interestingly, our meta-analysis found that both unilateral and bilateral nerve preservations were associated with a marked IIEF-5 improvement over the control group. However, these results were restricted only to males since female functional data were scarce.

The ongoing NEUROS trial is expected to provide solid evidence on the role of pIONM in TME; NEUROS is a multicenter RCT that will randomize 188 TME patients between pIONM and control groups [41]. The primary endpoint of the study is the evaluation of the urinary function on the basis of IPSS, whereas Wexner and IIEF scores are included as secondary outcomes [41]. Moreover, the incorporated histopathological and morbidity analyses will further elucidate the role of pIONM in rectal cancer surgery.

Acknowledging the additional operative time, the surgical technical requirements, and the equipment cost, a causiously selection of the patients who will, ultimately, benefit from pIONM, is essential. Rectal cancer patients with an increased risk for postoperative functional disorders are expected to receive the maximum benefit from pIONM. More specifically, obese male patients with a deep, narrow pelvis, that received neoadjuvant radiotherapy should be considered for pIONM use by a dedicated colorectal surgeon, to ameliorate postoperative functional outcomes. However, given the scarcity of evidence, further studies should address this research question.

This study is the first systematic review on the subject and provides pooled evidence regarding the role of pIONM in TME. However, prior to the appraisal of these results, several limitations should be considered. Due to the nature of the study, the validity of analyses is directly affected by the quality of the studies included. The lack of large randomized controlled trials and the small total patient sample contribute to underpowered results. Inconsistency in terms of patient and tumor characteristics is a considerable source of bias due to confounding. Moreover, the heterogeneity of data regarding the operative technique and the pIONM methodology further deteriorate the significance of our conclusions. In addition, the majority of included studies [9, 11, 24, 26–29] originated from the same research team, thus increasing the risk for duplicate data and prohibiting further analyses. We must also acknowledge the fact that the functional deficits were evaluated through questionnaires, which despite their validity, represent a subjective form of assessment. Finally, further extension of the eligible studies' follow-up period could have significantly altered the reported outcomes.

Conclusions

The findings of this study suggest the beneficiary role of bilateral pIONM in the preservation of postoperative anorectal and urogenital function after TME for rectal cancer. Surgeons specialized in rectal surgery should consider the use of pIONM in order to ameliorate postoperative functional outcomes and patients' quality of life. However due to several limitations of this meta-analysis as mentioned above, further validation of these results is essential.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00384-021-03884-z.

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