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ORIGINAL ARTICLE

Risk Factor Analysis for Newly Developed Urogenital Dysfunction after Total Mesorectal Excision and Impact of Pelvic Intraoperative Neuromonitoring—a Prospective 2-Year Follow-Up Study

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Abstract
Aim Urogenital dysfunction is a common sequela following total mesorectal excision for rectal cancer. This prospective study analyzed potential risk factors and investigated the impact of pelvic intraoperative neuromonitoring.
Method Included were 85 patients undergoing total mesorectal excision for rectal cancer, 43 under the control of pelvic intraoperative neuromonitoring. Urogenital function was assessed with validated questionnaires within a 2-year follow-up period. Potential risk factors were identified by multivariate analysis.
Results Overall, approximately one-third of treated patients suffered from new onset of urinary dysfunction. Initially, half of the sexually active patients were affected by sexual dysfunction; after 2 years, almost three quarters were affected. In the pelvic intraoperative neuromonitoring group, urinary and sexual dysfunction rates including minor and major disturbances were significantly lower (2-year follow-up 20% vs. 51% ($p = 0.004$) and 56% vs. 90% ($p = 0.010$)). Throughout the survey, non-performance of pelvic intraoperative neuromonitoring was found to be an independent risk factor. Neoadjuvant chemoradiotherapy was identified as an independent predictor for urogenital dysfunction in the further course one and 2 years after surgery.
Conclusion Pelvic intraoperative neuromonitoring is associated with significantly lower rates of urinary and sexual dysfunction in the short and long run, whereas neoadjuvant chemoradiotherapy has a negative impact only in the long run.

Keywords Rectal cancer · Autonomic nervous system · Neoadjuvant therapy · Urogenital dysfunction · Intraoperative monitoring

Introduction

Urinary (UD) and sexual dysfunction (SD) is a common and serious sequela following total mesorectal excision (TME) for rectal cancer, which can severely impact patients' quality of life. The rates of UD and SD reach up to 70 and 90%, respectively, with a great variety in range attributed to study design and definition of functional assessment.[1–6] Most studies are limited to retrospective analysis, small sample size, missing of baseline data, short-term follow-up, and the use of non-validated instruments. Several predicting factors, for instance, advanced age, tumors located less than 12 cm from the anal verge, radiotherapy, and injury to pelvic autonomic nerves were reported under these circumstances.[7–10]

The patient desires precise information about the risk of developing such disturbances.[11] Only few could recall any specifics regarding their probability. In the context of the complexity of multimodal rectal cancer therapy, a profound knowledge is important for a focused preoperative discussion on functional outcome. Therefore, well-conducted prospective studies concerning long-term dysfunction rates are needed.

This prospective 2-year follow-up study aimed to investigate potential patient-, tumor-, and operation-related risk factors for urogenital dysfunction at specific time intervals after

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TME in order to rule out their relevance in the long run. The impact of pelvic intraoperative neuromonitoring (pIONM) on functional outcome was analyzed.

Materials and Methods

Patients

Among a consecutive series of 146 prospectively investigated patients undergoing elective TME for primary rectal cancer between January 2008 and August 2014, 85 were included. Of those, 43 underwent pIONM-controlled surgery (within a monocentric clinical trial, "IKONA" ISRCTN06042867).[12] There was no randomization. Within this translational research project, the patients needed to undergo a standardized pIONM procedure for accurate data acquisition. Thus, patients were more likely to undergo pIONM if optimum conditions were achieved, such as first operation of the day, performance of total intravenous anesthesia, and no use of a thoracal epidural catheter. Furthermore, the surgical team strived for intraoperative and postoperative support in data analysis by a team of specialized medical engineers and assistants trained in pIONM. For safety reasons, patients with cardiac pacemaker did not undergo pIONM. Excluded were patients undergoing Hartmann's procedure and those with previous history of open prostatectomy, T4 rectal cancer, postoperative adjuvant chemoradiotherapy (CRT), or missing follow-up on urogenital function. The patients undergoing pIONM within the ongoing prospective randomized controlled multicenter trial "NEUROS" (Clinicaltrials.gov: NCT01585727) were also excluded.

In the present study, all patients underwent standardized nerve-sparing TME with dissection in front of the Denonvilliers' fascia performed by colorectal surgeons. Those patients with indication for neoadjuvant CRT were treated using 50 Gy in 5 weeks with accompanying chemotherapy followed by surgery 6 to 8 weeks later.

Written informed consent was obtained from all patients. The study was approved by the local Ethics Committee (Ethics Committee of the Medical Association of Rhineland-Palatinate, Germany).

Pelvic Intraoperative Neuromonitoring

The pIONM was performed using the standard methodological setup.[12] Repetitive electric stimulations were carried out to map the autonomic nerves at different sites along the pelvic side and above the level of the pelvic floor, ensuring adequate nerve identification and functional verification during the operation. The neuromapping was performed with a hand-guided probe right after posterolateral mesorectal dissection in order to identify the pelvic splanchnic nerves and exposed nervous tissue of the inferior hypogastric plexus. Further stimulations were carried out after lateral and anterolateral dissection. After full mobilization of the rectum, stimulations were additionally performed at the level of the pelvic floor in order to identify nerve branches heading to the internal anal sphincter. Bilateral repetitive stimulations were finally carried out after rectal resection for quality control of the nerve-sparing technique. Currents of 6 mA, frequency of 30 Hz, and monophasic rectangular pulses of 200 μs were used. The electrophysiological stimulation was observed under simultaneous cystomanometry and online processed electromyography of the internal anal sphincter. Signals were continuously visualized on the monitor of the system.

Urogenital Function

Patients were asked to complete the validated International Prostate Symptom Score (IPSS) and Quality of life index (Qol).[13] Higher scores indicated lower urinary function and quality of life. New onset of urinary dysfunction was defined by worsening of the IPSS combined with diminished quality of life (minor dysfunction) or the need of long-term catheterization (major dysfunction).

Male sexual function was evaluated using the validated International Index of Erectile Function (IIEF) score, which covers five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction.[14] The questionnaire includes 15 questions, which are each scored from 0 to 5, with lower scores indicating greater dysfunction. The severity of erectile dysfunction (questions 1–5 and 15) can be classified into five categories: no dysfunction (score 26–30), mild (score 22–25), mild to moderate (score 17–21), moderate (score 11–16), and severe dysfunction (score 6–10).[15] A reduced score leading to a more severe classification of erectile dysfunction indicated new onset of erectile dysfunction. Female sexual function was evaluated using the Female Sexual Function Index (FSFI), which covers six domains: desire, subjective arousal, lubrication, orgasm, satisfaction, and pain.[16] The total score ranges from 2.0 to 36.0 points, with a higher score indicating better sexual function. A score of 26.55 was considered to be the optimal cut-off for differentiating women with and without sexual dysfunction.[17] Thus, a postoperative total score that was newly below 26.55 was considered to indicate new onset of female sexual dysfunction with severe dysfunction at values ≤ 15.

Preoperative urogenital function was compared to the functional outcome at 3 or 6 months after stoma closure (median time interval between TME and stoma closure was 3 months) or at 6 and 9 months after surgery in patients with a permanent stoma. Further follow-ups were performed at 12 and 24 months after surgery.

Statistical Analysis

The data were analyzed using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). The influence of the predictor variables on the risk of new onset of urogenital dysfunction following surgery was calculated using univariate analysis. Therefore, functional data were transformed into a binary outcome (new onset of dysfunction vs. no new onset of dysfunction). To examine the independent influence of these variables, all variables significantly associated with urogenital dysfunction in the univariate analysis were included in a logistic regression analysis. For comparisons of function between the non-pIONM and pIONM group, the Chi-square test

Table 1 Patients' characteristics

	Non-pIONM group (n = 42)	pIONM group (n = 43)	p
Sex, M/F	24/18	35/8	0.014
Age, years	66 (57, 75)	65 (54, 74)	0.823
Body mass index, kg m^{-2}	26 (23, 29)	27 (23, 30)	0.394
ASA classification, I/II/III/IV	2/26/13/1	1/21/20/1	0.505
pT-category (n)			0.314
yT0	3	1	
T1 (yT1)	3 (1)	6 (3)	
T2 (yT2)	6 (4)	9 (4)	
T3 (yT3)	11 (9)	16 (9)	
UICC classification (n)			0.448
I	14	21	
II	13	8	
III	7	6	
IV	8	8	
Tumor site (n)			0.373
Middle rectal third (<6 cm from the anal verge)	22	20	
Lower rectal third (6 to ≤12 cm from the anal verge)	20	23	
Anterior quadrant involvement (n)	31	32	0.572
Neoadjuvant CRT	16	16	0.555
Type of resection (n)			0.474
LAR	30	32	
APE	12	11	
Open/laparoscopic	32/10	32/11	0.525
Stapled anastomosis (n)			0.389
Colorectal	25	22	
Coloanal	5	10	
Intraoperative blood loss, ml	500 (150, 650)	500 (100, 700)	0.714
Blood transfusion, units	0 (0, 0)	0 (0, 0)	0.658
Anastomotic leakage (n)[a]	2	3	0.881
pR0, pR2 (n)	34, 8	35, 8	0.589
pCRM negative, >1 mm (n)	40	39	0.349
M.E.R.C.U.R.Y. Graduation (n)			0.261
I°, complete	39	38	
II°, nearly complete	3	3	
III°, incomplete	0	2	
Local recurrence	0	1	0.506

Values are reported as median (interquartile range) or the number of patients

M Male, *F* Female, *ASA* American Society of Anesthesiologists, *UICC* Union Internationale Contre le Cancer, *LAR* Low anterior resection, *APE* Abdomino-perineal excision, *pIONM* Pelvic intraoperative neuromonitoring, *CRM* Circumferential resection margin involvement

[a] Two patients in the non-pIONM group underwent reoperation and three were managed conservatively

or Mann-Whitney *U* test was used. Statistical significance was defined as $p < 0.05$.

Results

Patients

Patients' demographic, clinical, and histopathological details are shown in Table 1. Baseline data on urogenital function of the non-pIONM and pIONM group are summarized in Table 2.

No deaths occurred within 30 days following surgery. During the further follow-ups, tumor-related death occurred in two patients with stage IV and in two patients with stage III rectal cancer. Another two patients died of progressive heart failure. Seven patients had a history of pelvic surgery (transurethral resection of the prostate ($n = 3$); hysterectomy ($n = 4$)).

Urinary Dysfunction

Of 85 patients, 25 (29%) reported new onset of UD according to the IPSS and Qol after the first follow-up (FU1: 3 months after stoma closure or 6 months after surgery in those with a permanent stoma). Minor UD was reported by 22 patients (26%) and major dysfunction with need for long-term catheterization by 3 (4%) of these. At the second follow-up (FU2: 6 months after stoma closure or 9 months after surgery in those with a permanent stoma), 27 of 84 patients (32%) had newly developed UD, 26 patients (31%) with minor dysfunction, and one (1%) with major dysfunction. At the third follow-up (FU3: 12 months after surgery), 26 of 81 patients (32%) reported new onset of UD with major dysfunction in one (1%) of them. After 2 years (FU4: 24 months after surgery) still 27 of 79 patients (34%) suffered from minor UD and one from major dysfunction.

In the univariate analysis, increased risk for new onset of UD after short-term follow-up was associated with tumor involving the anterior quadrant, tumor location in the middle rectal third, excessive intraoperative blood loss (≥1000 ml), non-performance of pIONM, and a voluminous mesorectum (≥6 cm). At the second follow-up non-performance of pIONM and a voluminous mesorectum remained significant risk factors. At the 1- and 2-year follow-up, neoadjuvant CRT and absence of pIONM were found to significantly increase the risk for new onset of UD (Table 3). In the multivariable logistic regression analysis, all identified factors, except for excessive blood loss and tumor involving the anterior quadrant, remained significant predictors (Table 4). During the follow-ups, the pIONM group had significantly lower rates of newly developed UD than the non-pIONM group (Fig. 1). After the first follow-up, 6 of 43 patients (14%) had newly developed UD in the pIONM group and 23 of 42 (55%) in the non-pIONM group ($p = 0.002$) and at the second follow-up, 7 of 43 patients (16%) in the pIONM group and 20 of 41 (49%) in the non-pIONM group ($p = 0.001$). After 1 and 2 years, 6 of 41 (15%) and 8 of 40 patients (20%) undergoing pIONM reported new onset of UD while 20 of 40 (50%) and 20 of 39 patients (51%) undergoing surgery without pIONM had newly developed UD ($p = 0.001$ and $p = 0.004$).

Table 2 Patients' baseline data of urogenital function

	Non-pIONM group	pIONM group	*p*
Urinary function	($n = 42$)	($n = 43$)	
IPSS	2 (0, 5)	3 (1, 4)	0.134
Qol	1 (1, 1)	1 (0, 1)	0.228
Male sexual function*	($n = 17$)	($n = 25$)	
IIEF total	68 (48, 72)	61 (54, 70)	0.271
Erectile function	27 (25, 30)	24 (22, 29)	0.387
Orgasm	10 (6, 10)	10 (6, 10)	0.967
Sexual desire	8 (6, 10)	7 (5, 9)	0.279
Intercourse satisfaction	13 (9, 14)	11 (8, 14)	0.279
Overall satisfaction	9 (7, 10)	9 (7, 10)	0.652
Female sexual function*	($n = 5$)	($n = 1$)	
FSFI total	33.0 (31.0, 35.0)	31.0	
Desire	6.0 (4.1, 6.0)	4.0	
Arousal	6.0 (5.2, 6.0)	6.0	
Lubrication	5.1 (4.2, 6.0)	5.4	
Orgasm	6.0 (5.1, 6.0)	5.6	
Satisfaction	5.6 (5.4, 6.0)	5.0	
Pain	6.0 (4.6, 6.0)	5.0	

Values are reported as median (interquartile range)

IPSS, International Prostate Symptom Score, *Qol* Quality of life due to urinary symptoms, *IIEF* International Index of Erectile Function, *FSFI* Female Sexual Function Index

* In sexually active patients

Sexual Dysfunction

Of 85 patients, 48 (56%) were sexually active (7 females and 41 males). Of those, 25 (52%) reported new onset of SD after the first follow-up (FU1). Eleven patients (44%) had mild to moderate dysfunction and 14 (56%) severe SD. At the second follow-up (FU2), 30 patients (63%) developed SD. Fifteen of those (50%) reported mild to moderate dysfunction and 15 patients (50%) severe dysfunction. Twelve months after surgery (FU3), 34 of 47 patients (72%) suffered from new onset of SD, 18 patients (53%) with mild to moderate dysfunction, and 16 (47%) with severe dysfunction. After 2 years (FU4), still 33 of the remaining 46 patients (72%) reported of disturbed sexual function with mild to moderate dysfunction in

Table 3 Univariate analysis with new onset of urinary dysfunction after total mesorectal excision for rectal cancer

Potential	3 months		6 months		12 months		24 months	
risk factors	after SC	*p*	after SC	*p*	post-OP	*p*	post-OP	*p*
Sex								
F	9 of 26		10 of 25		9 of 24		8 of 23	
M	16 of 59	0.326	17 of 59	0.226	17 of 57	0.335	20 of 56	0.575
Age (years)								
≤75	22 of 69		23 of 69		24 of 68		26 of 66	
>75	3 of 16	0.236	4 of 15	0.432	2 of 13	0.138	2 of 13	0.087
Tumor site								
Lower rectal third	6 of 43		12 of 43		12 of 42		13 of 41	
Middle rectal third	19 of 42	*0.002**	15 of 41	0.269	14 of 39	0.320	15 of 38	0.314
Ant. quadrant involvement								
No	3 of 22		6 of 22		6 of 22		6 of 22	
Yes	22 of 63	*0.049**	21 of 62	0.386	20 of 59	0.387	22 of 57	0.250
Neoadjuvant CRT								
No	17 of 53		14 of 52		11 of 50		13 of 49	
Yes	8 of 32	0.330	13 of 32	0.144	15 of 31	*0.013**	15 of 30	*0.031**
Type of resection								
LAR	21 of 62		22 of 61		21 of 59		21 of 58	
APE	4 of 23	0.111	5 of 23	0.161	5 of 22	0.203	7 of 21	0.517
Approach								
Open	21 of 64		22 of 64		21 of 62		22 of 61	
Laparoscopic	4 of 21	0.178	5 of 20	0.310	5 of 19	0.375	6 of 18	0.533
Intraoperative blood loss (ml)								
≤1000	18 of 72		23 of 71		22 of 68		24 of 66	
>1000	7 of 13	*0.042**	4 of 13	0.592	4 of 13	0.594	4 of 13	0.481
pIONM								
Yes	6 of 43		7 of 43		6 of 41		8 of 40	
No	23 of 42	*0.002**	20 of 41	*0.001**	20 of 40	*0.001**	20 of 39	*0.004**
pCRM positive (≤1 mm)								
No	23 of 79		25 of 78		24 of 76		26 of 74	
Yes	2 of 6	0.573	2 of 6	0.488	2 of 5	0.518	2 of 5	0.585
Mesorectal thickness (cm)[a]								
<6	15 of 65		17 of 64		18 of 62		19 of 60	
≥6	10 of 20	*0.023**	10 of 20	*0.048**	8 of 19	0.214	9 of 19	0.165
Tumor size								
≤4 cm	16 of 57		19 of 56		18 of 53		18 of 52	
>4 cm	9 of 28	0.442	8 of 28	0.406	8 of 28	0.407	10 of 27	0.511
pT-category								
(y)pT 0–2	11 of 40		13 of 40		13 of 39		14 of 38	
(y)pT3	14 of 45	0.451	24 of 44	0.566	13 of 42	0.503	14 of 41	0.494
UICC IV								
No	19 of 69		20 of 68		19 of 65		21 of 65	
Yes	6 of 16	0.308	7 of 16	0.208	7 of 16	0.205	7 of 14	0.171
Anastomotic leakage								
No	18 of 57		19 of 56		19 of 54		19 of 53	
Yes	3 of 5	0.210	3 of 5	0.244	2 of 5	0.590	2 of 5	0.602

SC stoma closure, *F* Female, *M* Male, *CRT* Chemoradiotherapy, *APE* Abdomino-perineal excision, *LAR* Low anterior resection, *pIONM* Pelvic intraoperative neuromonitoring, *CRM* Circumferential resection margin involvement, *UICC* Union Internationale Contre le Cancer

[a] Largest cross-section diameter measured by the pathologist on the fixed specimen

* Statistical significance was defined as $p < 0.05$

18 patients (55%) and severe dysfunction in 15 patients (45%).

In the univariate analysis, non-performance of pIONM and a voluminous mesorectum (≥6 cm) were associated with an increased risk for new onset of SD at short-term follow-up. Again at the 1- and 2-year follow-up, neoadjuvant CRT and absence of pIONM were found to significantly increase the risk for SD (Table 5). In the logistic regression analysis, all identified risk factors remained significant predictors (Table 6). At each follow-up, the pIONM group was found to have significantly lower rates of newly developed SD than the non-pIONM group (Fig. 2).

After the first follow-up, 10 of 26 patients (38%) had newly developed SD in the pIONM group and 15 of 22 (68%) in the non-pIONM group ($p = 0.038$). At the second follow-up, 12 of 26 patients (46%) had new onset of SD in the pIONM group and 18 of 22 (82%) in the non-pIONM group ($p = 0.011$). After 1 and

Table 4 Independent risk factors for postoperative new onset of urinary dysfunction assessed by logistic regression analysis

	Relative risk[a]		Relative risk[a]		Relative risk[a]		Relative risk[a]	
	3 months		6 months		12 months		24 months	
	After SC	*p*	After SC	*p*	Post-OP	*p*	Post-OP	*p*
Tumor located in the middle rectal third	5.9 (1.7; 20.1)	*0.005**	–	–	–	–	–	–
Ant. quadrant involvement	3.4 (0.8; 14.9)	0.106	–	–	–	–	–	–
Neoadjuvant CRT	–	–	–	–	3.9 (1.3; 11.5)	*0.014**	3.1 (1.1; 8.8)	*0.031**
Excessive blood loss	3.7 (0.7; 18.6)	0.119	–	–	–	–	–	–
Non-performed pIONM	8.6 (2.3; 32.0)	*0.001**	5.8 (2.0; 17.2)	*0.001**	6.6 (2.1; 20.4)	*0.001**	4.6 (1.6; 13.1)	*0.004**
Voluminous mesorectum	5.5 (1.4; 21.4)	*0.015**	3.7 (1.1; 11.8)	*0.029**	–	–	–	–

CRT Chemoradiotherapy, *pIONM* Pelvic intraoperative neuromonitoring

[a] 95% confidence intervals

* Statistical significance was defined as $p < 0.05$

2 years, 15 of 26 (58%) and 14 of 25 patients (56%) undergoing pIONM reported new onset of SD while in the non-pIONM group 19 of 21 patients (90%) had newly developed SD for both follow-ups ($p = 0.013$ and $p = 0.010$).

Discussion

The present prospective study demonstrated that a majority of patients suffered at least from minor/mild to moderate newly developed urogenital dysfunction after TME. New onset of minor UD was reported by 26% and slightly increased to 34% during the further course, while major UD was present in 4% and dropped to 1% after 2 years. New onset of mild to moderate SD occurred in 44% and increased to 55%. Severe SD was present in 56% and decreased to 45%. Studies based on non-validated instruments, however, generally underestimate the dysfunction rates. This is likely to be attributed to the simple format of questions, which do not allow one to distinguish between the varying levels of disturbances. The inconsistency of data is further enhanced by investigating heterogeneous study populations, lack of documentation of preoperative function, and the inclusion of patients who already suffered from severe dysfunction prior to any rectal cancer therapy. In the context of multimodal rectal cancer therapy, the actual results further highlight that even after 2 years a considerable amount of patients still report UD and SD.

In previous studies, several predictors for postoperative urogenital dysfunction were identified on the basis of quantitative surveys. Hendren and colleagues used highly sensitive validated instruments to evaluate sexual function in over 200 rectal cancer patients and demonstrated in a retrospective design that up to approximately 70% of those reported abnormal functional results following treatment.[3] According to their multivariate analysis, pelvic radiation was found to have a negative impact on sexual

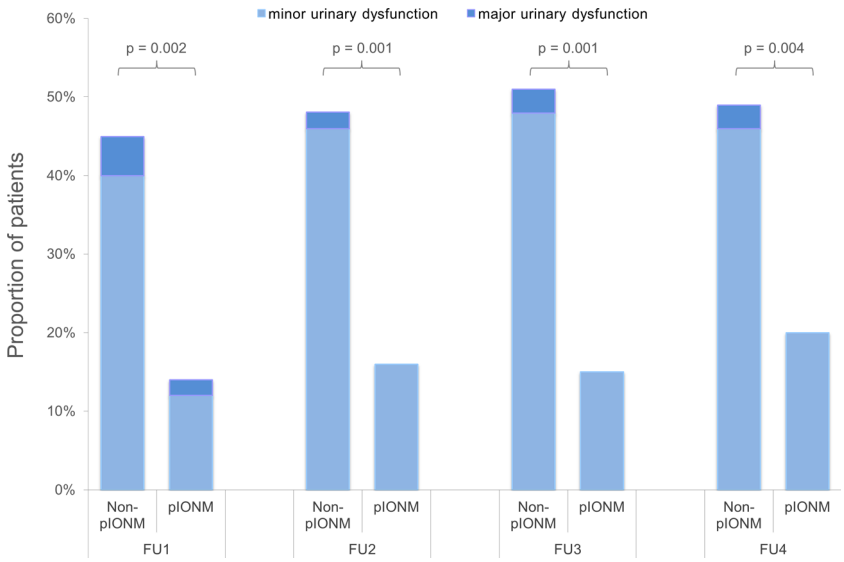

Fig. 1 New onset of urinary dysfunction after total mesorectal excision with and without pelvic intraoperative neuromonitoring (pIONM). Urinary functional outcome (minor and major dysfunction) was prospectively assessed at 3 and 6 months after stoma closure or at 6 and 9 months after surgery in patients with a permanent stoma (follow-up (FU) 1 and FU2). Further follow-ups were performed at 12 and 24 months after surgery (FU3 and FU4)

Table 5 Univariate analysis with new onset of sexual dysfunction after total mesorectal excision for rectal cancer

Potential	3 months		6 months		12 months		24 months	
risk factors	after SC	*p*	after SC	*p*	post-OP	*p*	post-OP	*p*
Sex								
F	3 of 6		4 of 6		4 of 6		4 of 6	
M	22 of 42	0.625	26 of 42	0.599	30 of 41	0.538	29 of 40	0.552
Age (years)								
≤ 75	24 of 46		29 of 46		32 of 45		32 of 45	
> 75	1 of 2	0.734	1 of 2	0.614	2 of 2	0.519	1 of 1	0.717
Tumor site								
Lower rectal third	11 of 21		15 of 21		16 of 21		16 of 21	
Middle rectal third	14 of 27	0.601	15 of 27	0.205	18 of 26	0.422	17 of 25	0.389
Ant. quadrant involvement								
No	6 of 13		9 of 13		9 of 13		9 of 13	
Yes	19 of 35	0.430	21 of 35	0.406	25 of 34	0.518	24 of 33	0.541
Neoadjuvant CRT								
No	15 of 28		15 of 28		16 of 27		16 of 27	
Yes	10 of 20	0.519	15 of 20	0.113	18 of 20	*0.020**	17 of 19	*0.025**
Type of resection								
LAR	22 of 38		24 of 38		27 of 37		26 of 36	
APE	3 of 10	0.112	6 of 10	0.565	7 of 10	0.569	7 of 10	0.589
Approach								
Open	22 of 39		25 of 39		29 of 28		28 of 37	
Laparoscopic	3 of 9	0.190	5 of 9	0.454	5 of 9	0.198	5 of 9	0.211
Intraoperative blood loss (ml)								
≤1000	18 of 39		23 of 39		27 of 38		26 of 37	
>1000	7 of 9	0.089	7 of 9	0.257	7 of 9	0.520	7 of 9	0.501
pIONM								
Yes	10 of 26		12 of 26		15 of 26		14 of 25	
No	15 of 22	*0.038**	18 of 22	*0.011**	19 of 21	*0.013**	19 of 21	*0.010**
pCRM positive (≤1 mm)								
No	25 of 47		30 of 47		34 of 46		33 of 45	
Yes	0 of 1	0.479	0 of 1	0.375	0 of 1	0.277	0 of 1	0.283
Mesorectal thickness (cm)[a]								
<6	14 of 34		19 of 34		23 of 33		22 of 32	
≥6	11 of 14	*0.019**	11 of 14	0.125	11 of 14	0.404	11 of 14	0.381
Tumor size								
≤4 cm	18 of 35		21 of 35		25 of 34		24 of 33	
>4 cm	7 of 13	0.570	9 of 13	0.406	9 of 13	0.518	9 of 13	0.541
pT-category								
(y)pT 0–2	13 of 24		14 of 24		16 of 24		15 of 23	
(y)pT3	12 of 24	0.500	16 of 24	0.383	18 of 23	0.288	18 of 23	0.257
UICC IV								
No	19 of 36		23 of 36		26 of 35		25 of 34	
Yes	6 of 12	0.565	7 of 12	0.494	8 of 12	0.435	8 of 12	0.457
Anastomotic leakage								
No	19 of 35		21 of 35		24 of 34		23 of 33	
Yes	3 of 3	0.183	3 of 3	0.240	3 of 3	0.376	3 of 3	0.364

SC stoma closure, *F* Female, *M* Male, *CRT* Chemoradiotherapy, *APE* Abdomino-perineal excision, *LAR* Low anterior resection, *pIONM* Pelvic intraoperative neuromonitoring, *CRM* Circumferential resection margin involvement, *UICC* Union Internationale Contre le Cancer

[a] Largest cross-section diameter measured by a pathologist on the fixed specimen

* Statistical significance was defined as $p < 0.05$

life. This was further supported by the findings of a prospective randomized trial in patients undergoing TME with and without neoadjuvant short-term radiation. On the basis of non-validated questionnaires, the investigators of the Dutch TME Trial revealed preoperative radiotherapy to be an independent predictor for SD.[7, 10] The present study demonstrated that the negative effect of preoperative radiation on sexual function is not evident at short course but becomes initially significant 1 year after surgery and remains an independent predictor even after 2 years. According to a previous randomized controlled study, these results might also hold true for patients undergoing preoperative short-term CRT. McLachlan and colleagues compared the effect of neoadjuvant short- and long-term CRT for T3 rectal cancer and showed within a 1-year follow-up that both groups worsened substantially in the postoperative period to the same degree.[18]

UD after TME was thought to be mainly caused by surgery. The data of the Dutch TME trial demonstrated in a cohort of approximately 800 patients within a 5-year follow-up period

Table 6 Independent risk factors for postoperative new onset of sexual dysfunction assessed by logistic regression analysis

	Relative risk[a]		Relative risk[a]		Relative risk[a]		Relative risk[a]	
	3 months		6 months		12 months		24 months	
	After SC	*p*	After SC	*p*	Post-OP	*p*	Post-OP	*p*
Neoadjuvant CRT	–	–	–	–	10.2 (1.7; 62.0)	*0.012**	9.3 (1.5; 56.8)	*0.016**
Non-performed pIONM	3.7 (1.0; 13.4)	*0.045**	5.3 (1.4; 19.8)	*0.015**	11.2 (1.8; 67.7)	*0.009**	11.3 (1.9; 68.1)	*0.008**
Voluminous mesorectum	9.7 (1.2; 25.9)	*0.025**	–	–	–	–	–	–

CRT Chemoradiotherapy, *pIONM* pelvic intraoperative neuromonitoring

[a] 95% confidence intervals

* Statistical significance was defined as $p < 0.05$

that damage to the pelvic autonomic nerves was a significant risk factor for UD, whereas preoperative radiation was not found to be an independent predictor.[7] Conversely, Adam and colleagues observed temporary UD in men in relation to neoadjuvant CRT without impact of surgery in a fairly large collective of 169 rectal cancer patients including also T4 cancer and partial mesorectal excision. Their survey was based on validated instruments limited to 1 year.[6] The present study further demonstrated, similarly to the results concerning new onset of SD, that pelvic irradiation has a negative impact on UD in the long run, even after 2 years without any significance in the short-term. This is supported by the data of the Stockholm I and II trial, which showed based on non-validated questionnaires that the 65 patients who were randomized to preoperative radiotherapy had significantly worse UD within a mean follow-up of 15 years than those undergoing TME alone.[19]

The assessment of pelvic autonomic nerve preservation in the Dutch TME trial was carried out based on the surgeons' intraoperative visual impression. This should be treated with caution and may be a weakness of this study. As stated by the authors themselves, even with accurate neuroanatomical knowledge sparing of this complex neural network is difficult, which suggests that its identification is at least equally difficult. Previous studies based on electrophysiological nerve testing demonstrated that visual assessment of pelvic autonomic nerves is less meaningful.[20] A recently published work based on this novel method showed that identification rates of the inferior hypogastric plexus were almost twice as high under electrophysiological assessment compared to those under visual assessment (~80% vs. 45%).[21] Thus, early electrophysiological detection of iatrogenic nerve damage may lead to more effective personalized initiation of urologic and proctologic therapies. The pIONM was found to be a reliable tool for quality control of nerve-sparing and could be used for clarification of functional and surgical topography in the minor pelvis in order to guide nerve-sparing.[12, 22] A case control study further demonstrated that pIONM is associated with significant lower ano-vesical dysfunctions and a trend towards lower sexual functional disturbances following TME.[23] Fang and

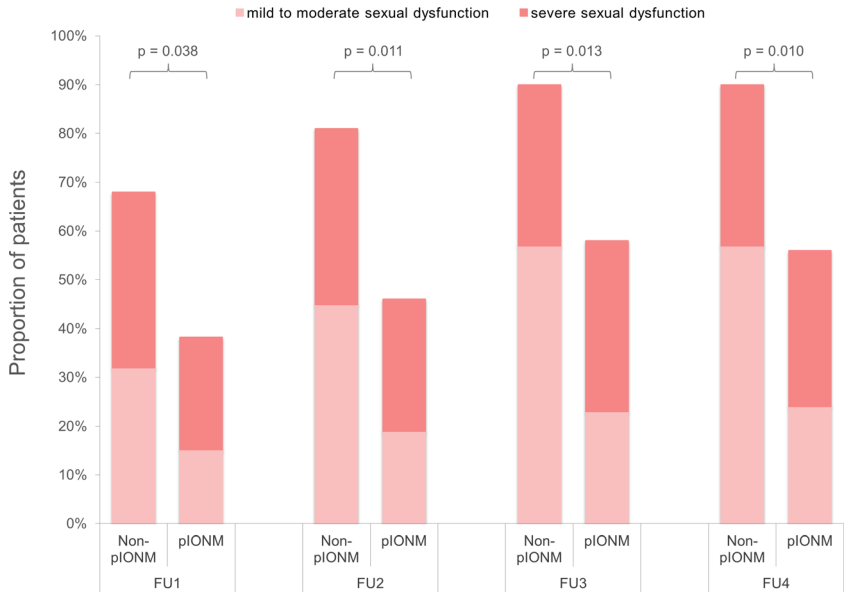

Fig. 2 New onset of sexual dysfunction after total mesorectal excision with and without pelvic intraoperative neuromonitoring (pIONM). Sexual functional outcome (mild to moderate and severe dysfunction) was prospectively assessed at 3 and 6 months after stoma closure or at 6 and 9 months after surgery in patients with a permanent stoma (follow-up (FU) 1 and FU2). Further follow-ups were performed at 12 and 24 months after surgery (FU3 and FU4)

colleagues reported in a collective of 189 rectal cancer patients that those undergoing rectal excision with electrophysiological nerve testing had significantly lower rates of UD and erectile dysfunction within a follow-up of 6 months after surgery.[24] The present study confirmed these results by identifying non-performance of pIONM to be a significant risk factor for UD at any follow-up, even after 2 years. Similarly, nerve-sparing without pIONM was found to be an independent predictor for SD. This is further highlighted by the subgroup analysis, which showed significantly higher rates of newly developed UD and SD in the non-pIONM group (Figs. 1 and 2). In accordance to this, the domains covered by the IIEF and FSFI were also lower.

An expert group of surgeons outlined that surgery is especially challenging in a narrow, deep pelvis and is further complicated in obese males, patients with bulky tumors located less than 12 cm from the anal verge and distorted tissue planes due to neoadjuvant radiotherapy.[25] Our multivariate analysis revealed that an excessive volume of mesorectum interferes with the transabdominal nerve-sparing technique by possibly leading to additional narrowness in the minor pelvis. Similarly, a bulky tumor located in the middle rectal third was found to have a negative impact resulting in worse functional outcome. However, these findings do only hold true in the short run.

Based on validated surveys, Duran and colleagues identified in a small collective of 56 rectal cancer patients that either localization of tumor in the middle or lower rectal third is a significant risk factor for new onset of UD, while for SD only the tumor in the distal part was determined to be an effective cause.[26] These differences are probably attributed to the small study population and the fact that only patients without neoadjuvant CRT were included for the risk factor analysis. Adam and colleagues further confirmed that a low-lying tumor compared to one in the upper part is a predictive factor for erectile dysfunction, while no significant difference was found for the comparison of tumor location in the middle and lower rectal third.[6]

The present study is limited to the relatively small sample size, especially with regard to the risk factor analysis. The results of this analysis are of an exploratory nature and thus should be verified in bigger datasets. The strength, however, lies in the prospective design with evaluation of function based on validated instruments at specific time intervals. A selection bias cannot be ruled out, as performance of pIONM was not randomized in this cohort. Furthermore, the patients and the pIONM team were not blinded.

Conclusion

The performance of pIONM during TME was found to be one of the most effective factors reducing the incidence of postoperative UD and SD. When applying this method, the surgeon needs to additionally focus on the detection of pelvic nervous tissue, which probably supports his or her ability to identify nerve branches and thereby preserve function. The negative impact of neoadjuvant CRT is initially evident 1 year after surgery and remains an independent predictor in the long run. Therefore, in order to maintain function, any doctors treating rectal cancer patients should particularly consider the importance of intraoperative protection of the pelvic autonomic nerves and restriction of indication for neoadjuvant CRT where appropriate without compromising oncological result. This is rounded off by better educating patients about posttreatment functional disturbances in order to channel expectations into realistic perspective.

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References

1. Havenga K, Enker WE, McDermott K, Cohen AM, Minsky BD, Guillem J. Male and female sexual and urinary function after total mesorectal excision with autonomic nerve preservation for carcinoma of the rectum J Am Coll Surg 1996;182:495–502.
2. Lange MM, van deVelde CJ. Urinary and sexual dysfunction after rectal cancer treatment. Nat Rev Urol 2011;8:51–57.
3. Hendren SK, O'Connor BI, Liu M, Asano T, Cohen Z, Swallow CJ, Macrae HM, Gryfe R, McLeod RS. Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer. Ann Surg 2005;242:212–223.
4. Attaallah, W, Ertekin C, Tinay I, Yegen C. High rate of sexual dysfunction following surgery for rectal cancer. Ann Coloproctol 2014;30:210–215.
5. Bregendahl S, Emmertsen KJ, Lindegaard JC, Laurberg S. Urinary and sexual dysfunction in women after resection with and without preoperative radiotherapy for rectal cancer: a population-based cross-sectional study. Colorectal Dis 2015;17:26–37.
6. Adam JP, Denost Q, Capdepont M, van Geluwe B, Rullier E. Prospective and longitudinal study of urogenital dysfunction after proctectomy for rectal cancer Dis *Colon rectum* 2016;59:822–830.
7. Lange MM, Maas CP, Marijnen CA, Wiggers T, Rutten HJ, Kranenbarg EK, van de Velde CJ; Cooperative Clinical Investigators of the Dutch Total Mesorectal Excision Trial. Urinary dysfunction after rectal cancer treatment is mainly caused by surgery. Br J Surg 2008;95:1020–1028.
8. Wallner C, Lange MM, Bonsing BA, Maas CP, Wallace CN, Dabhoiwala NF, Rutten HJ, Lamers WH, Deruiter MC, van de Velde CJ; Cooperative Clinical Investigators of the Dutch Total Mesorectal Excision Trial. Causes of fecal and urinary incontinence after total mesorectal excision for rectal cancer based on cadaveric surgery: a study from the Cooperative Clinical Investigators of the Dutch total mesorectal excision trial. J Clin Oncol 2008;26:4466–4472.

9. Tekkis, PP, Cornish JA, Remzi FH, Tilney HS, Strong SA, Church JM, Lavery IC, Fazio VW. Measuring sexual and urinary outcomes in women after rectal cancer excision. Dis *Colon rectum* 2009;52: 46–54.
10. Marijnen CA, van de Velde CJ, Putter H, van den Brink M, Maas CP, Martijn H, Rutten HJ, Wiggers T, Kranenbarg EK, Leer JW, Stiggelbout AM. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 2005; 23: 1847–1858.
11. Scheer AS, O'Connor AM, Chan BP, Moloo H, Poulin EC, Mamazza J, Auer RC, Boushey RP. The myth of informed consent in rectal cancer surgery: what do patients retain? Dis *Colon rectum* 2012;55:970–975.
12. Kauff DW, Koch KP, Somerlik KH, Hoffmann KP, Lang H, Kneist W. Evaluation of two-dimensional intraoperative neuromonitoring for predicting urinary and anorectal function after rectal cancer surgery. Int J Colorectal Dis 2013;28:659–664.
13. Denis L, Griffiths K, Khoury S. Measuring the symptom and health impact of benign prostatic hyperplasia and its treatment. In: Denis L, Griffiths K, Khoury S, et al, eds. 4th International consultation on benign prostatic hyperplasia. Paris: Health Publication; 1998:265–280.
14. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Peña BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 1999;11:319–326.
15. Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. Urology 1999;54:346–351.
16. Wiegel M, Meston C, Rosen R. The Female Sexual Function Index (FSFI): cross-validation and development of clinical cutoff scores J Sex Marital Ther 2005;31:1–20.
17. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Agostino R Jr. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000;26:191–208.
18. McLachlan SA, Fisher RJ, Zalcberg J, Solomon M, Burmeister B, Goldstein D, Leong T, Ackland SP, McKendrick J, McClure B, Mackay J, Ngan SY. The impact on health-related quality of life in the first 12 months: a randomised comparison of preoperative short-course radiation versus long-course chemoradiation for T3 rectal cancer (Trans-Tasman Radiation Oncology Group Trial 01.04) Eur J Cancer 2016;55:15–26.
19. Pollack J, Holm T, Cedermark B, Altma, D, Holmström B, Glimelius B, Mellgren A. Late adverse effects of short-course preoperative radiotherapy in rectal cancer. Br J Surg 2006;93:1519–1525.
20. Kneist W, Junginger T. Intraoperative electrostimulation objectifies the assessment of functional nerve preservation after mesorectal excision. Int J Colorectal Dis 2007;22:675–682.
21. Kneist W, Hanke L, Kauff DW, Lang, H. Surgeons' assessment of internal anal sphincter nerve supply during TaTME—inbetween expectations and reality Minim Invasive Ther Allied Technol 2016;25:241–246.
22. Kauff DW, Wachter N, Bettzieche R, Lang H, Kneist W. Electrophysiology-based quality assurance of nerve-sparing in laparoscopic rectal cancer surgery: Is it worth the effort? Surg Endosc 2016;30:4525–4532.
23. Kneist W, Kauff DW, Juhre V, Hoffmann KP, Lang H. Is intraoperative neuromonitoring associated with better functional outcome in patients undergoing open TME? Results of a case-control study. Eur J Surg Oncol 2013;39:994–999.
24. Fang JF, Wei B, Zheng ZH, Chen TF, Huang Y, Huang JL, Lei PR, Wei HB. Effect of intra-operative autonomic nerve stimulation on pelvic nerve preservation during radical laparoscopic proctectomy. Colorectal Dis 2015;17:268–276.
25. Motson RW, Whiteford MH, Hompes R, Albert M, Miles WF; Expert Group. Current status of trans-anal total mesorectal excision (TaTME) following the Second International Consensus Conference Colorectal Dis 2016;18:13–8.
26. Duran E, Tanriseven M, Ersoz N, Oztas M, Ozerhan IH, Kilbas Z, Demirbas S. Urinary and sexual dysfunction rates and risk factors following rectal cancer surgery Int J Colorectal Dis 2015;30:1547–1555.