Total Mesorectal Excision with Intraoperative Assessment of Internal Anal Sphincter Innervation Provides New Insights into Neurogenic Incontinence

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BACKGROUND: The aim of this prospective study was to assess internal anal sphincter (IAS) innervation in patients undergoing total mesorectal excision (TME) by intraoperative neuromonitoring (IONM).

STUDY DESIGN: Fourteen patients underwent TME. IONM was carried out through pelvic splanchnic nerve stimulation under continuous electromyography of the IAS. Anorectal function was assessed with the digital rectal examination scoring system and a standardized questionnaire.

RESULTS: Nine of 11 patients who underwent low anterior resection had positive IONM results, with stimulation-induced increased IAS electromyographic amplitudes (median 0.23 µV [interquartile range [IQR] 0.05, 0.56] vs median 0.89 µV [IQR 0.64, 1.88], p < 0.001) after TME. The patients with the positive IONM results were continent after stoma closure. Of 2 patients with negative IONM results, 1 had fecal incontinence after closure of the defunctioning stoma and received a permanent sigmoidostomy. In the other patient the defunctioning stoma was deemed permanent due to decreased anal sphincter function. In 3 patients who underwent abdominoperineal excision, IONM assessed denervation of the IAS after performance of the abdominal part.

CONCLUSIONS: This study demonstrated that IONM of IAS innervation in rectal cancer patients is feasible and may predict neurogenic fecal incontinence. (J Am Coll Surg 2012;214:306–312. © 2012 by the American College of Surgeons)

Sphincter-saving surgery has increasingly been used in patients with low rectal cancer without compromising oncologic results. However, low anterior resection (LAR) can result in persistent dysfunctional symptoms, which, in about one-third of patients, mainly influence postoperative quality of life. Studies revealed that the so-called anterior resection syndrome diminishes quality of life more than a permanent stoma after abdominoperineal excision (APE).1-3 One characteristic factor of this syndrome is fecal incontinence, which might occur after damage of sphincter muscle fibers or its autonomic innervations.4-6 Actual anatomic studies based on conventional macroscopic and computer-assisted anatomic dissections have demonstrated that posterosuperior branches rising from the inferior edge of the inferior hypogastric plexus form a secondary plexus that gives branches to the internal anal sphincter (IAS).7-8 Consequently, neurogenic fecal incontinence could be reduced by a nerve-sparing operation. However, there are only inconsistent classifications or categorizations of the quality of pelvic autonomic nerve preservation on the basis of intraoperative macroscopic assessment, functional outcomes, and postoperative diagnostic testing. The superior hypogastric plexus and the hypogastric nerves can be macroscopically identified and preserved in most TME procedures. More challenging is preservation of the inferior hypogastric plexus and its branches.9,10 Currently, several types of neuromonitoring systems are available and are used in almost all surgical centers. Intraoper-
In recent experimental studies, a practicable method for intraoperative monitoring of IAS innervation has been established. Autonomic nerve stimulation was performed under continuous electromyography (EMG) of the smooth anal sphincter muscle.13-15 The aim of this study was to prove the feasibility of this newly developed method in patients undergoing total mesorectal excision (TME) for rectal cancer. Technical and functional results were compared.

**METHODS**

A total of 14 rectal cancer patients, 11 men and 3 women, with a median age of 67 years (range 50 to 89 years), were investigated. Written informed consent was obtained from all patients. The study was approved by the local board of ethics (Ethics Committee of the Medical Association of Rhineland-Palatinate, Germany).

Median tumor distance from the anal verge, measured with rigid rectoscopy, was 7.5 cm (range 1.0 to 11.5 cm). The tumor included the anterior quadrant in 10 patients.

Two patients had a history of pelvic surgery (prostatectomy and nephrectomy; cystoprostatectomy and orthotopic urinary reconstruction with an ileum neobladder), and 2 patients had received radiotherapy for carcinoma of the prostate.

After discussion of treatment plans in a multidisciplinary tumor board, 6 patients underwent neoadjuvant radiochemotherapy. One patient with synchronous liver metastasis received neoadjuvant chemotherapy. In 5 of 6 patients with neoadjuvant radiochemotherapy adjuvant chemotherapy was performed. One patient underwent adjuvant chemotherapy only.

**Assessment of anorectal function**

All patients underwent physical examination and anorectal endosonography. Anorectal function was determined on the basis of the Wexner score.16 Results of the digital rectal examination for resting and squeezing pressure were adapted to the digital rectal examination scoring system (DRESS).17 Anorectal function was assessed before neoadjuvant therapy, preoperatively, before stoma closure, and during follow-up (at 3, 6, 9, and 12 months).

**Anesthesia**

After oral premedication, general anesthesia was performed either with balanced sevoflurane and sufentanil in 6 patients or total intravenous anesthesia (TIVA) with propofol and remifentanil in 8 patients. A thoracic epidural catheter was inserted in 12 patients. Intraoperative epidural analgesia with sufentanil was given only in 3 patients, who underwent balanced anesthesia. Muscle relaxation was maintained with atracurium until the peritoneum was closed.

**Operative procedure and IONM of internal anal sphincter innervation**

Total mesorectal dissection was carried out with monopolar diathermy by a colorectal surgeon. Anterior dissection was performed in the extramesorectal plane anteriorly of Denovilliers’ fascia. The IONM setup enabled electrical neurostimulation and online processing of electromyographic signals of the IAS (Nemo, inomed Medizintechnik GmbH). The processing was carried out with a newly developed neuromonitoring software (NeuroExplorer version 4.3, inomed Medizintechnik GmbH), which enabled suppression of the nonrelevant frequency parts.14

**Neurostimulation**

Electrical stimulation of the pelvic splanchnic nerves (PSN—synonym for erectile nerves/nervi erigentes) was carried out with a handheld bipolar microfork probe (inomed Medizintechnik GmbH) sequentially on both pelvic sides (Fig. 1). Additional nerve mapping was carried out if PSN could not be clearly identified macroscopically. IONM was performed after rectal resection in patients undergoing LAR, and after mesorectal dissection before perineal excision in patients undergoing APE. Currents of 6 to 15 mA, frequency of 30 Hz, and monophasic rectangular pulses with pulse duration of 200 μs were chosen.

**Electromyography of the internal anal sphincter**

EMG of the IAS was performed with a bipolar needle electrode (inomed Medizintechnik GmbH) inserted transanally.

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**Abbreviations and Acronyms**

- APE = abdominoperineal excision
- DRESS = digital rectal examination scoring system
- EMG = electromyography
- IAS = internal anal sphincter
- IONM = intraoperative neuromonitoring
- IQR = interquartile range
- LAR = low anterior rectal resection
- PSN = pelvic splanchnic nerves
- TME = total mesorectal excision
under endosonographic guidance as described by Sorensen and associates. Impedance measurement verified correct placement. The reference electrode was placed at the left gluteal muscle. The electrode application and connection to the neuromonitoring device takes approximately 4 minutes. Neurostimulation with consecutive increase in EMG amplitude (in V) was considered as positive IONM result. The IONM signal was continuously visualized on the monitor of the device.

### Acquisition of data and analysis

Evaluation of the recorded IONM signals was carried out intraoperatively. For postoperative verification of IAS activity, the acquired data were additionally analyzed in MATLAB (Version 7.7.0.471, The Math Works, Inc) under supervision of an electrophysiologist.

All data were transferred into SPSS version 18.0 (Statistical Package for Social Sciences program). Statistical analysis was carried out using the Wilcoxon’s signed rank test. Results were expressed as median and interquartile range. A value of $p < 0.05$ was considered statistically significant. Because this was a feasibility study, no formal power or sample size calculation was performed.

### RESULTS

#### Preoperative anorectal function

Preoperative digital rectal examination determined decreased anal sphincter function in 4 patients. After neoadjuvant radiochemotherapy, sphincter tonus was decreased in 2 patients (Table 1). Endoanal ultrasound demonstrated a tumor infiltration of the IAS in 1 female patient. In the other patients, IAS was without defect. Severe fecal incontinence associated with liquid and solid stool leakage and significant reduction in quality of life was noted in 3 patients (Wexner score > 14).

#### Surgery

Eleven patients underwent a sphincter-saving procedure with side-to-end coloanal (n = 1), side-to-end colorectal (n = 2), and straight colorectal anastomosis (n = 8). In each patient, the splenic flexur was mobilized, except in one 83-year-old patient. All anastomoses were less than 5 cm above the anal verge and were performed with a gently inserted 29-mm or 33-mm circular stapler. Each patient received a temporary defunctioning stoma. No anastomotic leakage occurred. Three patients underwent APE without coning. In 1 patient a rather unilateral excision of the levator muscle was necessary because of sphincter infiltration. Two patients required en bloc resection of adjacent organs (seminal vesicles and vagina) due to a locally advanced tumor. In 1 patient, MRI showed 2 suspect extramesorectal lymph nodes, which were intraoperatively identified and dissected.

Local R0 resection was successfully performed in all patients. Thirteen specimens demonstrated a complete mesorectum. One specimen showed good bulk of mesorectum, but some small irregularities on the surface.

#### IONM and functional outcomes

Nine of 11 patients undergoing LAR had positive IONM results (Table 2). Two patients had unilateral positive IONM results on the right pelvic side. PSN stimulation resulted in significant increased amplitudes of the time-based electromyographic signal, confirming intact innervation of the IAS (Figs. 2, 3).

Stoma closure was performed in 10 patients at a median interval of 3.5 months (range 1 to 7 months) after LAR. In 2 patients, IONM failed to demonstrate activation of the IAS. One of these patients had no noticeable resting tone 6 months after operation, a reduced squeezing tone, and a flaccid anal canal at digital rectal examination. At this stage, the patient preferred a permanent stoma. The other patient with the observed negative IONM result developed severe perineal inflammation due to newly developed major fecal incontinence after stoma closure. The DRESS scores were diminished, so a permanent stoma was created.

In the 2 patients with unilateral positive IONM results, latest follow-up after stoma closure demonstrated normal resting and squeezing scores, perfect continence, and only mild symptoms. After stoma closure, the 7 patients with bilateral positive IONM results had DRESS scores as good as they were preoperatively. In 4 of these patients continence was perfect for gas, liquid, and solid stool. Three patients (nos. 4, 5, and 11 in Table 2) reported only minor incontinence, which was attributed to rare loss of control of...
gas, and occasional liquid stool soiling in one of them. In 3 patients undergoing APE, IONM performed after circumferential mesorectal dissection resulted in absence of increasing EMG amplitudes of the IAS.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Sex</th>
<th>Age, y</th>
<th>Tumor localization above anal verge, cm</th>
<th>Endoanal ultrasound (IAS)</th>
<th>Patient history</th>
<th>T-category</th>
<th>Comment</th>
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<td>60</td>
<td>2.5</td>
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<td>RT for prostate cancer</td>
<td>pTis</td>
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<td>2</td>
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<td>54</td>
<td>10</td>
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<td></td>
</tr>
<tr>
<td>3</td>
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<td>73</td>
<td>10</td>
<td>Normal</td>
<td>ypT2</td>
<td></td>
<td></td>
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<tr>
<td>4</td>
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<td>54</td>
<td>11.5</td>
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<td>Normal</td>
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<td>83</td>
<td>6</td>
<td>Normal</td>
<td>pT3</td>
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<tr>
<td>7</td>
<td>Male</td>
<td>69</td>
<td>5</td>
<td>Normal</td>
<td>Orthotopic neobladder after cystoprostatectomy for bladder cancer</td>
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<td></td>
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<td>Partial resection of vagina</td>
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</table>

IAS, internal anal sphincter; RT, radiation therapy.

DISCUSSION

Because sphincter-saving surgery has been increasingly used, the postoperative functional integrity of the IAS has gained a much greater emphasis on preserving fecal incon-

Table 2. Intraoperative Neuromonitoring and Functional Results after Total Mesorectal Excision

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Operation</th>
<th>Anastomosis</th>
<th>Anesthesia</th>
<th>EDC</th>
<th>DRESS score (preop)</th>
<th>Preoperative wexner-score</th>
<th>IONM</th>
<th>FU, mo</th>
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<th>Wexner-score</th>
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<td>INH</td>
<td>Regular</td>
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<td>Positive</td>
<td>12 3 3 3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>LAR</td>
<td>Coloanal end-to-end</td>
<td>INH</td>
<td>Regular</td>
<td>(3) 3 (0) 0</td>
<td>Positive*</td>
<td>9 3 3 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
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<td>TIVA</td>
<td>Inserted</td>
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<tr>
<td>4</td>
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<td>TIVA</td>
<td>Inserted</td>
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<td>Positive</td>
<td>6 3 3 7</td>
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<tr>
<td>5</td>
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<td>TIVA</td>
<td>Inserted</td>
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<td>Positive</td>
<td>6 3 3 2</td>
<td></td>
<td></td>
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<tr>
<td>6</td>
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<td>TIVA</td>
<td>Inserted</td>
<td>1 2</td>
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<td>6 1 1</td>
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<td>Coloanal end-to-end</td>
<td>TIVA</td>
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<td>Negative</td>
<td>2 1</td>
<td>19</td>
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<tr>
<td>8</td>
<td>LAR</td>
<td>Coloanal end-to-end</td>
<td>TIVA</td>
<td>Inserted</td>
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<td>Positive</td>
<td>9 3 3</td>
<td>1</td>
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<tr>
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<td>LAR</td>
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<td>TIVA</td>
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<td>3 3 0</td>
<td>Positive*</td>
<td>3 3 3</td>
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<td>INH</td>
<td>Regular</td>
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<td>—</td>
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<td>—</td>
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</table>

Numbers in parentheses indicate results before neoadjuvant therapy.

*Unilateral.

1Received permanent stoma.

APE, abdomino-perineal excision; DRESS, digital rectal examination scoring system (resting score: 3, normal; 2, mildly decreased tone; 1, very low tone; 0, no discernable tone at rest, an open or patulous anal canal; squeeze score: 3, normal; 2, fair increase but below normal; 1, slight increase in tone; 0, no discernable increase in tone with squeezing effort); EDC, epidural catheter; FU, follow-up after stoma closure (month); INH, inhalative anesthesia; IONM, intraoperative neuromonitoring; LAR, low anterior resection; LN, lymph node; TIVA, total intravenous anesthesia.
Anal continence is impaired if IAS activity is decreased, either by direct trauma or by damage to its innervations. The extrinsic nerves of sympathetic and parasympathetic origin provide significant excitatory and inhibitory modulation. In case of LAR, the extrinsic system is at risk during mesorectal dissection.

Confirming our experimental studies, results of this study demonstrated that the change in IAS activity in response to intraoperative electrical stimulation of PSN is accomplished in male and female rectal cancer patients by EMG amplitude increases. The manometrically measured IAS response to intraoperative electrical stimulation of the sympathetic nerves depends on experimental setup, stimulation parameters, neuroanatomy, and anesthesia at the point of stimulation. This seems to be similar in terms of parasympathetic stimulation. The PSNs are variable in diameter and give dorsal input to the inferior hypogastric plexus mainly at the level of S3 and S4. In this region electrical stimulation was carried out after the initial posterior mesorectal dissection. At the level of S2, where most of the sacral splanchnic nerves (sympathetic ganglion) originate, neurostimulation did not result in IONM responses.

Recent anatomic and immunohistochemical studies revealed that the hypogastric nerves and the PSN are not purely sympathetic and parasympathetic. The coexistence of cholinergic and adrenergic fibers and the potential stimulation of efferent and afferent nerve pathways may lead to excitatory and inhibitory effects on the IAS activity with complex neuromodulatory responses.

Horgan and associates could not demonstrate an inhibition of the resting anal sphincter tone during presacral nerve stimulation after mesorectal dissection in 2 of 6 patients. Resting pressures were similar to those of others in their study. However, compared with neurostimulation results observed with intraoperative anal manometry, continuous EMG of the IAS seems to be less vulnerable to surgical intervention during TME. Moreover, it has been demonstrated that the value of anal manometry in assessing sphincter function and continence control is questionable. The neuromonitoring technique presented here has a short learning curve for setup. For first time use, it is important that an experienced surgeon or electrophysiologist gives a briefing on how to interpret the electromyographic signals.

Focusing on stimulation results after rectal resection, the influence of the intrinsic autonomic innervation, which is cut by circumferential rectal myotomy, could be excluded. In this study, 9 of 11 patients undergoing LAR had positive IONM results, confirming intact extrinsic innervation of the IAS and good anorectal function at follow-up. One of the 2 patients with the negative IONM results developed major fecal incontinence 8 weeks after closure of the initial defunctioning stoma and received a permanent sigmoiodostomy. In the other patient, the defunctioning stoma was deemed permanent at 6 month after LAR with low side-to-end colorectal anastomosis. At follow-up, there was no discernable tone at rest on rectal digital examination. After pulling out the finger, the anal canal remained open even with squeezing effort, which is a clinical sign of IAS palsy after LAR, as described by Stelzner and coworkers.

Lindgren and colleagues found that the risk of ending up with a permanent stoma because of bad anorectal function was 11% (20 of 188 patients) in patients without occurrence of anastomotic leakage after LAR. However, the rate presented in this study is higher. Primary incontinence, former radiotherapy for cancer of the prostate gland, and en bloc resection of seminal vesicles may contribute to the observed negative IONM results, and therefore increase the risk of postoperative neurogenic fecal incontinence after LAR. The IAS accounts for up to 80% of resting pressure. Anal continence is impaired if IAS activity is decreased, either by direct trauma or by damage to its innervations. The extrinsic nerves of sympathetic and parasympathetic origin provide significant excitatory and inhibitory modulation. In case of LAR, the extrinsic system is at risk during mesorectal dissection.

Figure 2. Electromyography of the internal anal sphincter (IAS) before and during electrical stimulation of the pelvic splanchnic nerves.

Figure 3. Comparison between the electromyographic amplitudes of the internal anal sphincter (IAS) before and during electrical stimulation of the pelvic splanchnic nerves (Wilcoxon’s signed rank test).
continenct. Four patients showed an increased stool frequency, which had improved at follow-up. However, these patients had positive IONM results. Interestingly, in the group of patients undergoing APE, no increasing EMG amplitudes of the IAS could be observed after mesorectal dissection, before the perineal excision was performed.

Considering the neurostimulations during mesorectal dissection (not presented here), 3 of 5 patients with negative IONM results after LAR or full mobilization of the rectum for APE had previous positive stimulation results. Therefore, the negative IONM results in these 3 patients could be attributed to sphincter damage or damage to the inferior hypogastric plexus or its branches to the IAS. In the other 2 patients (nos. 13 and 14 in Table 2), no positive IONM results could be observed during the whole procedure, which might be explained by preoperative neurogenic fecal incontinence.

Limitations of this study are the small sample size of patients with heterogeneous basic demographics, and the lack of a standardized anesthetic regimen with regard to IONM.

CONCLUSIONS

In conclusion, this prospective study demonstrated for the first time that intraoperative electrical stimulation of PSN performed under EMG of the IAS is feasible in rectal cancer patients. The method has the potential to identify autonomic nerve damage intraoperatively and may predict neurogenic fecal incontinence. However, to draw intraoperative consequences from neuromonitoring, data from controlled clinical trials are needed.

Author Contributions

Study conception and design: Kneist, Koch, Lang

Acquisition of data: Kneist, Kauff, Huppert, Lang

Analysis and interpretation of data: Kneist, Kauff, Gockel, Huppert, Koch, Hoffmann

Drafting of manuscript: Kneist, Kauff, Gockel

Critical revision: Kneist, Lang, Hoffmann, Koch

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