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ORIGINAL CONTRIBUTION

Sacral Neuromodulation in Patients With Low Anterior Resection Syndrome: The SANLARS Randomized Clinical Trial

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BACKGROUND: Sacral neuromodulation might be effective to palliate low anterior resection syndrome after rectal cancer surgery, but robust evidence is not available.

OBJECTIVE: To assess the impact of sacral neuromodulation on low anterior resection syndrome symptoms as measured by validated scores and bowel diaries.

DESIGN: Randomized, double-blind, 2-phased, controlled, multicenter crossover trial (NCT02517853).

SETTINGS: Three tertiary hospitals.

PATIENTS: Patients with major low anterior resection syndrome 12 months after transit reconstruction after rectal resection who had failed conservative treatment.

INTERVENTIONS: Patients underwent an advanced test phase by stimulation for 3 weeks and received the pulse generator implant if a 50% reduction in low anterior resection syndrome score was achieved. These patients entered the randomized phase in which the generator was left active or inactive for 4 weeks. After a 2-week washout, the sequence was changed. After the crossover, all generators were left activated.

MAIN OUTCOME MEASURES: The primary outcome was low anterior resection syndrome score reduction. Secondary outcomes included continence and bowel symptoms.

RESULTS: After testing, 35 of 46 patients (78%) had a 50% or greater reduction in low anterior resection syndrome score. During the crossover phase, all patients showed a reduction in scores and improved symptoms, with better performance if the generator was active. At 6- and 12-month follow-up, the mean reduction in low anterior resection syndrome score was –6.2 (95% CI –8.97 to –3.43; $p < 0.001$) and –6.97 (95% CI –9.74 to –4.2; $p < 0.001$), with St. Mark's continence score –7.57 (95% CI –9.19 to –5.95, $p < 0.001$) and –8.29 (95% CI –9.91 to –6.66; $p < 0.001$). Urgency, bowel emptiness sensation, and clustering episodes decreased in association with quality-of-life improvement at 6- and 12-month follow-up.

LIMITATIONS: The decrease in low anterior resection syndrome score with neuromodulation was

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SANLARS (The SAcral Neuromodulation in Low Anterior Resection Syndrome trial) NCT02517853.

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underestimated because of an unspecific measuring instrument. There was a possible carryover effect in sham stimulation sequence.

CONCLUSIONS: Neuromodulation provides symptoms and quality-of-life amelioration, supporting its use in low anterior resection syndrome. See **Video Abstract**.

NEUROMODULACIÓN SACRA EN PACIENTES CON SÍNDROME DE RESECCIÓN ANTERIOR BAJA: ENSAYO CLÍNICO ALEATORIZADO SANLARS

ANTECEDENTES: La neuromodulación sacra podría ser eficaz para paliar el síndrome de resección anterior baja después de la cirugía de cáncer de recto, pero no hay pruebas sólidas disponibles.

OBJETIVO: Evaluar el impacto de la neuromodulación sacra en los síntomas del síndrome de resección anterior baja, medido mediante puntuaciones validadas y diarios intestinales.

DISEÑO: Ensayo cruzado multicéntrico, controlado, aleatorizado, doble ciego, de dos fases (NCT02517853).

LUGARES: Tres hospitales terciarios.

PACIENTES: Pacientes con puntuación de resección anterior baja importante, 12 meses después de la reconstrucción del tránsito después de la resección rectal en quienes había fracasado el tratamiento conservador.

INTERVENCIONES: Los pacientes se sometieron a una fase de prueba avanzada mediante estimulación durante tres semanas y se les implantó el generador de impulsos si se lograba una reducción del 50% en la puntuación del síndrome de resección anterior baja, ingresando a la fase aleatorizada en la que el generador se dejaba activo o inactivo durante cuatro semanas. Después de observar por 2 semanas, se cambió la secuencia. Después del cruce, todos los generadores quedaron activados.

PRINCIPALES MEDIDAS DE RESULTADO: El resultado primario fue la reducción de la puntuación del síndrome de resección anterior baja. Los resultados secundarios incluyeron continencia y síntomas intestinales.

RESULTADOS: Después de las pruebas, 35 de 46 pacientes (78%) tuvieron una reducción ≥50% en la puntuación del síndrome de resección anterior baja. Durante el cruce, todos los pacientes mostraron una reducción en las puntuaciones y una mejora de los síntomas, con un mejor rendimiento si el generador estaba activo. A los 6 y 12 meses de seguimiento, la reducción media en la puntuación del síndrome de resección anterior baja fue -6,2 (-8,97; -3,43; $p < 0,001$) y -6,97 (-9,74; -4,2; $p < 0,001$), con Puntuación de continencia de St. Mark's -7,57 (-9,19; -5,95, $p < 0,001$) y -8,29 (-9,91; -6,66; $p < 0,001$). La urgencia, la sensación de vacío intestinal y los episodios de agrupamiento disminuyeron en asociación con una mejora en la calidad de vida a los 6 y 12 meses de seguimiento.

LIMITACIONES: La disminución en la puntuación del síndrome de resección anterior baja con neuromodulación se subestimó debido a un instrumento de medición no específico. Posible efecto de arrastre en la secuencia de estimulación simulada.

CONCLUSIONES: La neuromodulación mejora los síntomas y la calidad de vida, lo que respalda su uso en el síndrome de resección anterior baja. *(Traducción—Dr. Mauricio Santamaria)*

KEY WORDS: Fecal incontinence; Low anterior resection syndrome; Postoperative dysfunction; Rectal cancer; Sacral neuromodulation.

Over the past few decades, multimodal treatment together with standardized minimally invasive total mesorectal excision have improved oncological outcomes for locally advanced rectal cancer.[1–3] This has led to increased rates of anal sphincter preservation, but, in turn, it has resulted in a higher incidence of functional disorders.

Low anterior resection syndrome (LARS) covers all alterations of bowel function determined by resection of the rectum that can lead to worse quality of life, including fecal incontinence, urgency, and increased number of stools and fragmentation.[4] The score can grade the severity of LARS (eg, major or minor LARS).[5] The cause of LARS is multifactorial, including direct lesion of the anal sphincters, damage to the nerves involved in the defecation, decrease of the distensibility and denervation of colonic plasty, preoperative radiotherapy, and diverting ileostomy.[6–8]

No specific treatment is available for LARS. Therapeutic options range from conservative measures to tibial nerve stimulation.[9,10] Sacral neuromodulation (SNM) has been proposed to palliate LARS symptoms after the optimal results reported for fecal incontinence after failed conservative treatment.[11] SNM is a 2-stage procedure, consisting of a test phase and subsequent generator implantation in patients with clinical improvement. The mechanism of action of SNM is poorly understood, with multiple nerve pathways activated at the medullary level and the brain.[12,13] Recent systematic reviews and meta-analyses of retrospective studies and case series have shown successful results for SNM on LARS symptoms with an implantation rate between 74% and 83% with fecal incontinence scores and episodes reduction and quality-of-life improvement.[14–16]

This randomized study aimed to prospectively assess the efficacy of SNM in patients with LARS.

MATERIALS AND METHODS

Study Design

The SAcral Neuromodulation in Low Anterior Resection Syndrome study (NCT02517853) was designed as a multicentric, prospective, randomized, double-blind, 2-phased, controlled, crossover trial to assess the clinical effect of SNM in patients with LARS symptoms. SNM was performed at 3 tertiary Spanish hospitals. This study followed the principles of the Declaration of Helsinki and was reported according to the Consolidated Standards of Reporting Trials guidelines for crossover trials.[17]

Before undergoing any procedure required for the study, patients who met inclusion criteria were asked to provide written informed consent. The protocol was approved by the ethical committees of participating hospitals.

Inclusion and Exclusion Criteria

The following inclusion criteria were adopted: patients older than 18 years and younger than 80 years who had undergone sphincter-preserving rectal resection for rectal cancer by any approach, who had undergone definitive colorectal transit reconstruction surgery at least 1 year before, and who presented with major LARS (LARS score more than 29). Patients were invited to participate after failure of conservative measures and noninvasive therapies.

Patients were excluded if they had had resections of bowel segments other than the rectum or if they were diagnosed with irritable bowel syndrome, IBD, metastatic disease at rectal surgery, or recurrence during follow-up. Those patients not suitable for SNM were also excluded.

Interventions

This study was designed on the basis of the usual clinical practice for SNM. During the initial visit, a full medical history was collected, and patients completed questionnaires and assessments before the start of treatment. Patients who met the eligibility criteria underwent an advanced test phase for 3 weeks with a tined quadripolar electrode. Insertion was usually performed as outpatient surgery under local anesthesia with sedation. The electrode (Electrode 3889-28, Interstim; Medtronic, Minneapolis, MN) was inserted at the S3 or S4 foramen under radioscopic control. The stimulated sacral nerve root providing the best perineal and/or ipsilateral plantar motor response with midline sensation at the lowest amplitude was chosen. Once the implantation was completed, the lead was connected to an external battery (Medtronic 353101 Interstim), leaving a maximum subsensorial threshold amplitude programmed for 3 weeks with standard parameters (frequency 14 Hz, pulse width 210 μs). The patient was monitored by a nurse who was specialized in programming neuromodulation devices every week to detect wound complications and adverse effects. Changes in modulation electrical parameters were permitted within these weeks.

The investigators visited the patients after 3 weeks of temporary stimulation to evaluate symptom improvement. If a decrease of 50% in LARS score compared to baseline was achieved, the patient was offered definitive implantable pulse generator (IPG) placement. If there was no evidence of clinical improvement or the patient declined to continue the therapy, the electrode was removed and the patient was withdrawn from the study.

Implantation was performed under local anesthesia with sedation on an outpatient basis. The electrode was connected to a stimulator (Stimulator 3058, Interstim) and implanted subcutaneously in the low lateral lumbar region, ipsilateral to the stimulation electrode. Prophylactic antibiotics were given before implantation of the electrode and stimulator.

Immediately after IPG implantation, patients entered the double-blinded, crossover randomized phase to receive either 4 weeks of active modulation (generator "ON") or sham stimulation (generator "OFF"). After a washout period of 2 weeks, the sequence was changed and the generator was turned ON or OFF for 4 additional weeks. The group with a first phase of active modulation was named group ON→OFF, and the group with a first sequence of sham stimulation was named group OFF→ON.

After permanent generator implantation, the unblind nurses used the latest electrical configuration in the test phase for the ON period of the crossover interval. The test and ON phases were programmed at the highest subsensory level for patient comfort. Modulation parameters were allowed to be changed after the crossover period. Adverse events or complications were recorded at each visit (study design detailed in Fig. 1).

Outcomes

The primary end point was the clinical response with SNM to LARS symptoms as measured by the LARS scale.[5,18] A 50% or more reduction in LARS score was expected after the test phase, and a 40% reduction was expected at 12 months after permanent generator implantation compared to baseline.

Secondary end points included assessment of fecal incontinence, Health-Related Quality of Life (HRQoL), and bowel assessment. Fecal continence was assessed with the St. Mark's fecal incontinence score,[19] and HRQoL was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30.[20] Details regarding the tools used in the present study are available in Supplemental Material at http://links.lww.com/DCR/C279.

Patients were also asked to complete a diary that included the mean number of fecal urgency episodes with

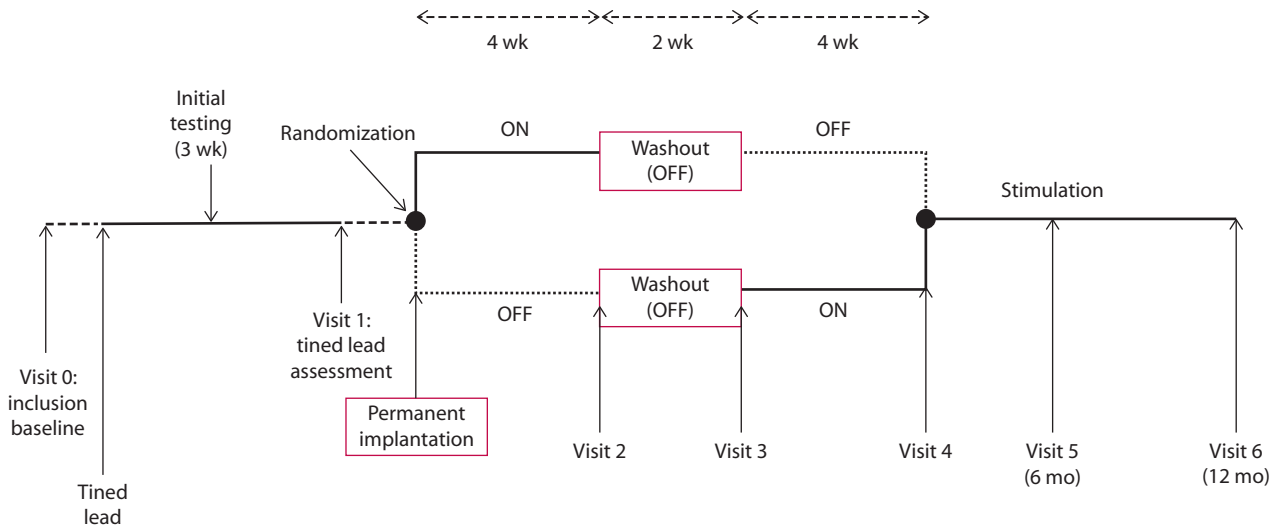

FIGURE 1. Study design. Patients who responded to advanced electrodes (tined-lead stimulation) had permanent generator implantation and were randomized to a crossover intervention (OFF→ON and ON→OFF modulation therapy). All patients had active modulation from the crossover period until the 12-mo visit.

or without incontinence, percentage of full evacuation sensation, and mean number of daily clustering episodes.

For control visits, patients graded satisfaction with therapy using a visual analog scale, ranging from 0 (least satisfaction) to 10 (maximum satisfaction). Satisfaction with treatment was defined as a visual analog scale score of 7/10 or more.

All outcome measures were assessed from baseline to the last visit 12 months after permanent implantation, except for HRQoL and patient's satisfaction with the therapy, which were not assessed during the crossover phase.

Randomization and Masking

On enrollment, patients were randomly allocated 1:1 in one of the 2 groups for "ON" or "OFF" intervals in the crossover intervention phase. A centralized computer system was used for randomization, using balanced blocks of variable size to ensure equal assignment to treatment. Center-specific randomization vectors were assigned. Patient allocation to each sequence was randomized and double-blinded. The patient and the principal investigator did not know the sequence. The nurse responsible for programming was unblinded and knew the assignment groups.

Statistical Analysis

For qualitative variables, frequencies, percentages, and CIs are presented. Quantitative variables are presented as means ± SD or median with interquartile ranges (IQRs).

To compare the values of the categorical variables, the χ^2 test or Fisher exact probability test was used as appropriate. To compare the quantitative variables, the Student *t* test for independent samples or the Mann-Whitney *U* test were used according to the distribution.

Comparisons of change in different scales at the different measurement points were made by comparing repeated measures with ANOVA of respected means or the adjustment of a mixed linear model in which the changes were evaluated throughout the period according to the analysis strategy. The intention-to-treat approach was used for the analyses. A p value of <0.050 was considered statistically significant.

For the calculation of the sample size, a type I error of 5% and a power of 80% were considered. The mean of the LARS score was estimated in the group without treatment at 35 points, and a desired reduction of at least 5 points in the LARS scale was anticipated. Given the nonsymmetry of the variable, data were transformed into a logarithmic scale. Therefore, the difference between the groups to be detected was log (35) – log (30) = 0.15 ± 0.29. The sample size was 30 patients. A meta-analysis estimated that 20% of patients with LARS do not respond to the first phase of percutaneous nerve stimulation;[16] therefore, the total sample size was adjusted to 36 patients. Analyses and sample calculation were performed using STATA version 15.1 (StataCorp LLC, TX).

RESULTS

Between February 2019 and May 2022, 46 of 54 patients entered the study protocol and underwent advanced electrode stimulation placement. The mean age for the crossover study population was 63.66 (±7.46) years. After the

TABLE 1. Patient demographics and basic clinical characteristics

Variable	IPG implantation: No (N = 11)	IPG implantation: Yes (N = 35)	p
Age, y, median (IQR)	59.00 (49.00–72.00)	64.00 (59.00–68.00)	0.211[a]
Sex, n (%)			
Female	3 (27.3%)	11 (31.4%)	>0.99[b]
Male	8 (72.7%)	24 (68.6%)	
BMI, kg/m^2, median (IQR)	28.07 (23.34–28.73)	27.10 (24.80–29.03)	0.642[a]
ASA, n (%)			
1	1 (9.1%)	3 (8.6%)	>0.99[b]
2	8 (72.7%)	23 (65.7%)	
3	2 (18.2%)	9 (25.7%)	
Preoperative tumor distance from anal verge, cm, median (IQR)	7.00 (6.00–13.00)	7.00 (5.00–10.00)	0.385[a]
Neoadjuvant chemotherapy, n (%)			
No	3 (27.3%)	4 (11.4%)	0.332[b]
Yes	8 (72.7%)	31 (88.6%)	
Neoadjuvant radiotherapy, n (%)			
No	3 (27.3%)	5 (14.3%)	0.374[b]
Yes	8 (72.7%)	30 (85.7%)	
Radiotherapy course, n (%)			
Short course	3 (42.9%)	5 (20%)	0.326[b]
Long course	4 (57.1%)	20 (80%)	
Adjuvant chemotherapy, n (%)			
No	5 (45.5%)	5 (14.3%)	0.043[b]
Yes	6 (54.5%)	30 (85.7%)	
Tumor approach, n (%)			
Open	4 (36.4%)	4 (11.4%)	0.16[b]
Laparoscopic	6 (54.5%)	28 (80%)	
Robotic	1 (9.1%)	3 (8.6%)	
TaTME, n (%)			
No	9 (81.8%)	30 (85.7%)	>0.99[b]
Yes	2 (18.2%)	5 (14.3%)	
TME, n (%)			
No	2 (18.2%)	3 (8.6%)	0.579[b]
Yes	9 (81.8%)	32 (91.4%)	
PME, n (%)			
No	10 (90.9%)	32 (91.4%)	>0.99[b]
Yes	1 (9.1%)	3 (8.6%)	
Anastomosis type, n (%)			
Handsewn	3 (27.3%)	10 (29.4%)	>0.99[b]
Mechanic side-to-end	2 (18.2%)	6 (17.6%)	
Mechanic end-to-end	6 (54.5%)	18 (52.9%)	
Derivate stoma at rectal surgery, n (%)			
No	4 (36.4%)	6 (17.1%)	0.219[b]
Yes	7 (63.6%)	29 (82.9%)	
Colorectal anastomosis leakage, n (%)			
No	7 (63.6%)	34 (97.1%)	0.008[b]
Yes	4 (36.4%)	1 (2.9%)	
pT, n (%)			
0	2 (18.2%)	11 (31.4%)	0.592[b]
1	0 (0%)	4 (11.4%)	
2	2 (18.2%)	4 (11.4%)	
3	7 (63.6%)	16 (45.7%)	
pN, n (%)			
0	6 (54.5%)	30 (85.7%)	0.049[b]
1	4 (36.4%)	3 (8.6%)	
2	1 (9.1%)	2 (5.7%)	
Previous treatment for LARS, n (%)			
No	6 (54.5%)	23 (65.7%)	0.721[b]
Yes	5 (45.5%)	12 (34.3%)	

BMI = body mass index; IPG = implantable pulse generator; IQR = interquartile range; LARS = low anterior resection syndrome; PME = partial mesorectal excision; TaTME = transanal total mesorectal excision.

[a]Mann-Whitney *U* test.

[b]Fisher exact probability test.

TABLE 2. Neuromodulation advanced test characteristics

Variable	IPG implantation: No (n = 11)	IPG implantation: Yes (n = 35)	p
Stimulated root, n (%)			0.086[a]
S3 left	5 (45.5%)	19 (54.3%)	
S3 right	5 (45.5%)	16 (45.7%)	
S4 right	1 (9.1%)	0 (0%)	
Intensity, mA, median (IQR)	1.20 (0.40–1.40)	1.00 (0.80–1.20)	0.897[b]
Frequency, Hz, median (IQR)	14.00 (11.00–14.00)	14.00 (13.00–14.00)	0.437[b]
Pulse width, μs, median (IQR)	220.00 (210.00–220.00)	210.00 (210.00–220.00)	0.121[b]
Perineal contraction, n (%)			0.053[a]
No	2 (18.2%)	0 (0%)	
Yes	9 (81.8%)	35 (100%)	
Plantar contraction, n (%)			0.239[a]
No	1 (9.1%)	0 (0%)	
Yes	10 (90.9%)	35 (100%)	

IPG = implantable pulse generator; IQR = interquartile range.
[a]Fisher exact probability test.
[b]Mann-Whitney *U* test.

3-week testing period, 35 patients (76%) had permanent generator implantation. Demographic and baseline characteristics according to IPG status are summarized in Table 1. The percentage of patients who had had a leak of a colorectal anastomosis was higher in the nonresponder group after testing (36.4% vs 2.9%; $p = 0.008$). All but 1 patient received S3 root stimulation. The median (IQR) sensory threshold was 1 V (0.8–1.2 V) in those who responded to the test (Table 2).

During the first sequence of the crossover experimental part, 18 patients had inactive stimulation (group OFF→ON) and 17 had active stimulation (group ON→OFF), which later changed according to the protocol (Fig. 2).

No patient had tumor recurrence, died, or was lost at follow-up. One patient developed a wound infection at the site of IPG implantation, which was treated with antibiotics. Two other patients underwent abdominal surgery (hernia repair and small rectal prolapse distal to the anastomosis).

Primary Outcome Measure: Changes in the LARS Score

The baseline mean LARS score was 37.94 (±4.05) for the whole study group. After testing, the score showed a 59.12% mean reduction, corresponding to 15.51 (±8.74) points (effect size, −22.43 [95% CI, −25.2 to −19.66] $p < 0.001$).

During the crossover phase, group OFF→ON had a mean LARS score of 32.72 (±6.72) when the generator was disconnected, whereas the score decreased to 29.72 (±10.31) after active stimulation (−1.42; [−7.16 to 1.16]; $p = 0.156$). Group ON→OFF had a mean LARS score of 26.00 (±10.24) in active stimulation, whereas the score increased to 32.88 (±6.63) after the generator was shut down (3.17 [2.6–11.16] $p = 0.002$; Table 3).

At 6- and 12-month follow-up, the LARS score decreased by 16.3% and 18.4%, respectively, compared to baseline ($p < 0.001$; Table 4).

Secondary Outcome Measures

Changes in Fecal Incontinence

The baseline mean St. Marks' continence score was 18.63 (±3.84). After testing, the score decreased by 65.8% to 6.37 (±3.94; effect size, −12.26; [95% CI, −13.88 to −10.63]; $p < 0.001$). During the crossover phase, the score was lower while the generator was active, but the decrease in the score for the OFF→ON sequence was not statistically significant (−0.23 [−2.67 to 2.12] $p = 0.819$). Group ON→OFF had continence score worsening while the generator was disconnected (+2.63 [0.83–5.76] $p = 0.009$; Table 5).

At 6- and 12-month follow-up, the continence score improved by 40.6% and 44.5%, respectively, compared to baseline ($p < 0.001$; Table 6).

Changes in LARS and continence scores are summarized in Figure 3.

Changes in Personal Bowel Assessments

During the crossover phase, when the generator was active, both groups showed better performance in urgency episodes per day, sensation of complete bowel emptying, and clustering episodes within an hour (see Supplemental Table 1 at http://links.lww.com/DCR/C279).

Active modulation after testing reduced urgency episodes per day, sensation of complete bowel emptying, clustering, and discrimination between gas and stool compared to baseline at 6- and 12-month follow-up (Table 7 and Fig. 4).

Satisfaction with treatment was reported by 82.8% of patients after testing and 67.7% and 69.7% after 6 and 12 months.

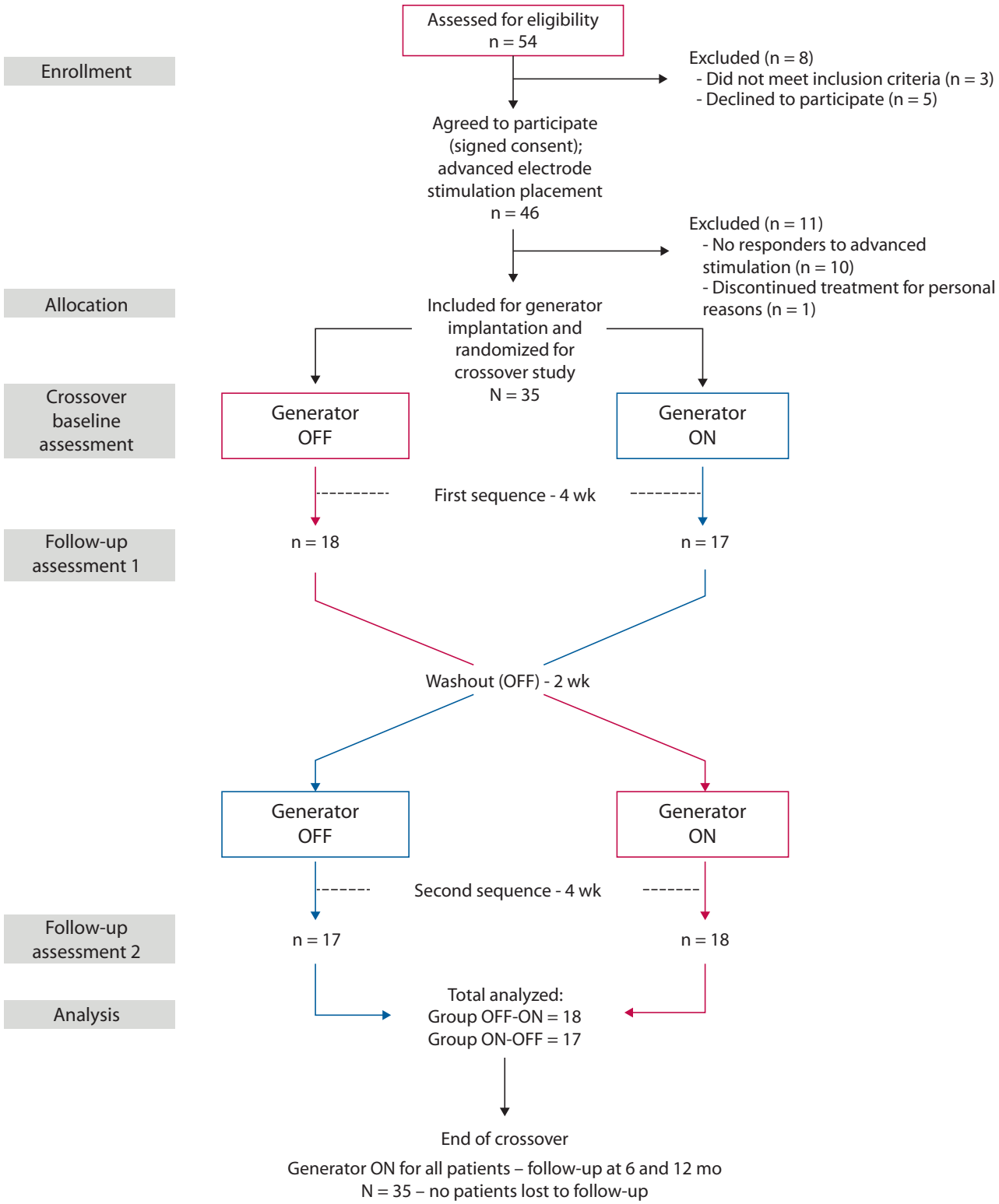

FIGURE 2. Consolidated Standards of Reporting Trials flow diagram for the SAcral Neuromodulation in Low Anterior Resection Syndrome trial, showing participant flow through each stage of the randomized controlled trial (enrollment, intervention allocation, follow-up, and data analysis).

Changes in Quality of Life

At 6- and 12-month follow-up, global health status and functioning spheres (physical, role, emotional, cognitive, and social) increased, whereas fatigue, pain, insomnia, and diarrhea decreased (Fig. 5; Supplemental Table 2 at http://links.lww.com/DCR/C279).

TABLE 3. LARS score evolution (crossover)

Visit	*OFF→ON group (n = 18)*	*Difference (95% CI)*	*ON→OFF group (n = 17)*	*Difference (95% CI)*
Baseline (v0)	38.56 (2.87) 39.00 (37.00–41.00)	v1 vs v0 −10.28 (−25.8 to −17.51) $p < 0.001$	37.29 (5.02) 39.00 (36.00–41.00)	v1 vs v0 −10.71 (−27.51 to −18.96) $p < 0.001$
After advanced test evaluation 3 wk (v1)	16.89 (7.22) 16.00 (13.00–20.00)		14.06 (10.12) 15.00 (6.00–16.00)	
First crossover evaluation 4 wk (v2)	32.72 (6.72) 33.00 (29.00–39.00)		26.00 (10.24) 28.00 (19.00–34.00)	
Washout period 2 wk (v3)	32.83 (7.12) 35.00 (31.00–38.00)	v4 vs v2 (ON vs OFF) −1.42 (−7.16 to 1.16) $p = 0.156$	32.18 (5.56) 33.00 (28.00–35.00)	v4 vs v2 (OFF vs ON) 3.17 (2.6–11.16) $p = 0.002$
Second crossover evaluation 4 wk (v4)	29.72 (10.31) 33.00 (21.00–38.00)		32.88 (6.63) 34.00 (29.00–39.00)	
12-mo evaluation (v6)	30.97 (7.68) 35.00 (27.00–37.00)	v6 vs v0 −6.97 (−9.74 to −4.2) $p < 0.001$ v6 vs v1 10.77 (11.61–19.31) $p < 0.001$		

Data presented as mean (SD) and median (interquartile range).
LARS = low anterior resection syndrome.

TABLE 4. LARS score evolution (active modulation)

Visit	*N = 35*	*Difference (95% CI) Respect to baseline (v0)*	*Difference (95% CI) Respect to test evaluation (v1)*
Baseline (v0)	37.94 (4.05) 39.00 (36.00–41.00)		
After advanced test evaluation 3 wk (v1)	15.51 (8.74) 15.00 (9.00–20.00)	v1 vs v0 −22.43 (−25.2 to −19.66) $p < 0.001$	
6-mo evaluation (v5)	31.74 (7.56) 33.00 (29.00–39.00)	v5 vs v0 −6.2 (−8.97 to −3.43) $p < 0.001$	v5 vs v1 11.31 (12.38–20.08) $p < 0.001$
12-mo evaluation (v6)	30.97 (7.68) 35.00 (27.00–37.00)	v6 vs v0 −6.97 (−9.74 to −4.2) $p < 0.001$	v6 vs v1 10.77 (11.61–19.31) $p < 0.001$

Data presented as mean (SD) and median (interquartile range).
LARS = low anterior resection syndrome.

DISCUSSION

This trial demonstrated that SNM can palliate LARS symptoms. Active modulation had positive effects compared to sham stimulation in terms of improvement in LARS and continence scores, daily fecal urgency and clustering episodes, sensation of complete bowel emptying, and better stool/gas discrimination. These changes implied an important improvement in HRQoL. Seventy-six percent of patients responded to advanced lead stimulation and underwent IPG implantation, in line with those of reviews with case series, whose positive test rates range from 74.4%[14] to 83.3%.[16] During the crossover phase, active modulation showed better performance than sham stimulation. Interestingly, the group of patients who had a first sequence of active stimulation after IPG (ON→OFF) showed better clinical outcomes than those who had the generator disconnected during the first 4 weeks (OFF→ON). This is difficult to explain, but a potential carryover effect after the positive initial test phase might be involved. Those patients who had sham stimulation during the first sequence of the crossover and endured the washout period might have experienced more difficulties in calculating clinical enhancement after the stimulator was activated.

The improvement in LARS score observed after the test phase was not maintained at 6- and 12-month follow-up with active stimulation. These results differ from other series,[21,22] in which the score remained under 21 points at 9- and 20-month follow-up. LARS score has been suggested to be appropriate to screen patients with LARS, but it performs worse when assessing bowel dysfunction with questions about its specificity and sensitivity.[23] Hence, information on continence score variations and a bowel diary including urgency, clustering, bowel emptying, and HRQoL was collected. Even when the LARS score worsened at 6- and 12-month follow-up, HRQoL items dramatically improved with active stimulation, especially

TABLE 5. St. Mark's Continence Score evolution (crossover)

Visit	*OFF→ON group (n = 18)*	*Difference (95% CI)*	*ON→OFF group (n = 17)*	*Difference (95% CI)*
Baseline (v0)	19.67 (2.93) 20.50 (18.00–22.00)	v1 vs v0 −10.06 (−14.62 to −9.83) $p < 0.001$	17.53 (4.43) 18.00 (13.00–22.00)	v1 vs v0 −9.83 (−14.76 to −9.83) $p < 0.001$
After advanced test evaluation 3 wk (v1)	7.44 (3.90) 7.00 (5.00–9.00)		5.24 (3.77) 5.00 (2.00–7.00)	
First crossover evaluation 4 wk (v2)	12.89 (6.24) 12.50 (6.00–18.00)		8.71 (5.27) 8.00 (5.00–11.00)	
Washout period 2 wk (v3)	12.39 (5.08) 11.50 (9.00–16.00)	v4 vs v2 (ON vs OFF) −0.23 (−2.67 to −2.12) $p = 0.819$	10.71 (5.41) 10.00 (6.00–14.00)	v4 vs v2 (OFF vs ON) 2.63 (0.83–5.76) $p = 0.009$
Second crossover evaluation 4 wk (v4)	12.61 (5.23) 12.00 (9.00–16.00)		12.00 (6.27) 13.00 (7.00–17.00)	

Data presented as mean (SD) and median (interquartile range).

TABLE 6. St. Mark's Continence Score evolution (active modulation)

Visit	*N = 35*	*Difference (95% CI) Respect to baseline (v0)*	*Difference (95% CI) Respect to test evaluation (v1)*
Baseline (v0)	18.63 (3.84) 19.00 (16.00–22.00)		
After advanced test evaluation 3 wk (v1)	6.37 (3.94) 6.00 (3.00–9.00)	v1 vs v0 −12.26 (−13.88 to −10.63) $p < 0.001$	
6-mo evaluation (v5)	11.06 (5.54) 11.00 (7.00–15.00)	v5 vs v0 −7.57 (−9.19 to −5.95) $p < 0.001$	v5 vs v1 5.57 (2.43–6.94) $p < 0.001$
12-mo evaluation (v6)	10.34 (5.61) 10.00 (6.00–16.00)	v6 vs v0 −8.29 (−9.91 to −6.66) $p < 0.001$	v6 vs v1 4.72 (1.71–6.23) $p < 0.001$

Data presented as mean (SD) and median (interquartile range).

global health status, physical, role, emotional, and cognitive function. Therefore, the authors believe that the LARS score should not be used alone after any therapeutic procedure for LARS.

Among the constellation of symptoms of LARS, fecal incontinence is one of the most limiting and bothersome. SNM has proven to be effective in patients with fecal incontinence,[11,24,25] but its mechanism of action is still unknown. Recently, the role of the cyclic motor pattern originated in the rectosigmoid junction has gained importance as a contributor to incontinence. This reflex originates from the distal colon and rectosigmoid junction in a retrograde direction after meals, preventing rectal filling.[26,27] SNM upregulates retrograde motility of the sigmoid colon, restoring this physiological brake function in patients with fecal incontinence.[28,29] LARS pathophysiology includes the loss of the recto-anal inhibitory reflex, sphincteric dysfunction, neorectal hyposensitivity, and impaired compliance. SNM could act by upregulating sequences of propagation in the neorectum and remnant colon combined with cycle motor pattern initialization, helping patients normalize distal colonic motility after rectosigmoid resection by retarding the flow of feces into the rectum.[28] Neorectal sensitivity can also improve with SNM, contributing to better function and amelioration of other symptoms (eg, fragmentation).[30] Keane et al[31] identified a reduction in antegrade propagating contractions in LARS, suggesting that the loss of anterograde versus retrograde cyclic motor pattern could underlie different symptom phenotypes, such as clustering or incontinence. Further research in LARS-associated motility disorders can help professionals optimize treatments. In this study, continence score and urgency episodes decreased with active stimulation after the test phase, in the crossover phase, and at 6- and 12-month intervals. Therefore, it is plausible to consider SNM in LARS patients with a fecal incontinence phenotype at an earlier stage, as recommended in cohorts with the native rectum.

SNM has few described complications. The authors have experienced that although lead implantation can be technically demanding because of the fibrosis in the sacral tissues induced by radiotherapy and surgical changes, it is safe in these patients, with only 1 patient who developed a wound infection managed with antibiotics.

Patients who did not experience improvement after test evaluation had a higher incidence of colorectal anastomosis leakage than those who did (36.4% vs 2.9%). Anastomotic and pelvic fibrosis could explain that

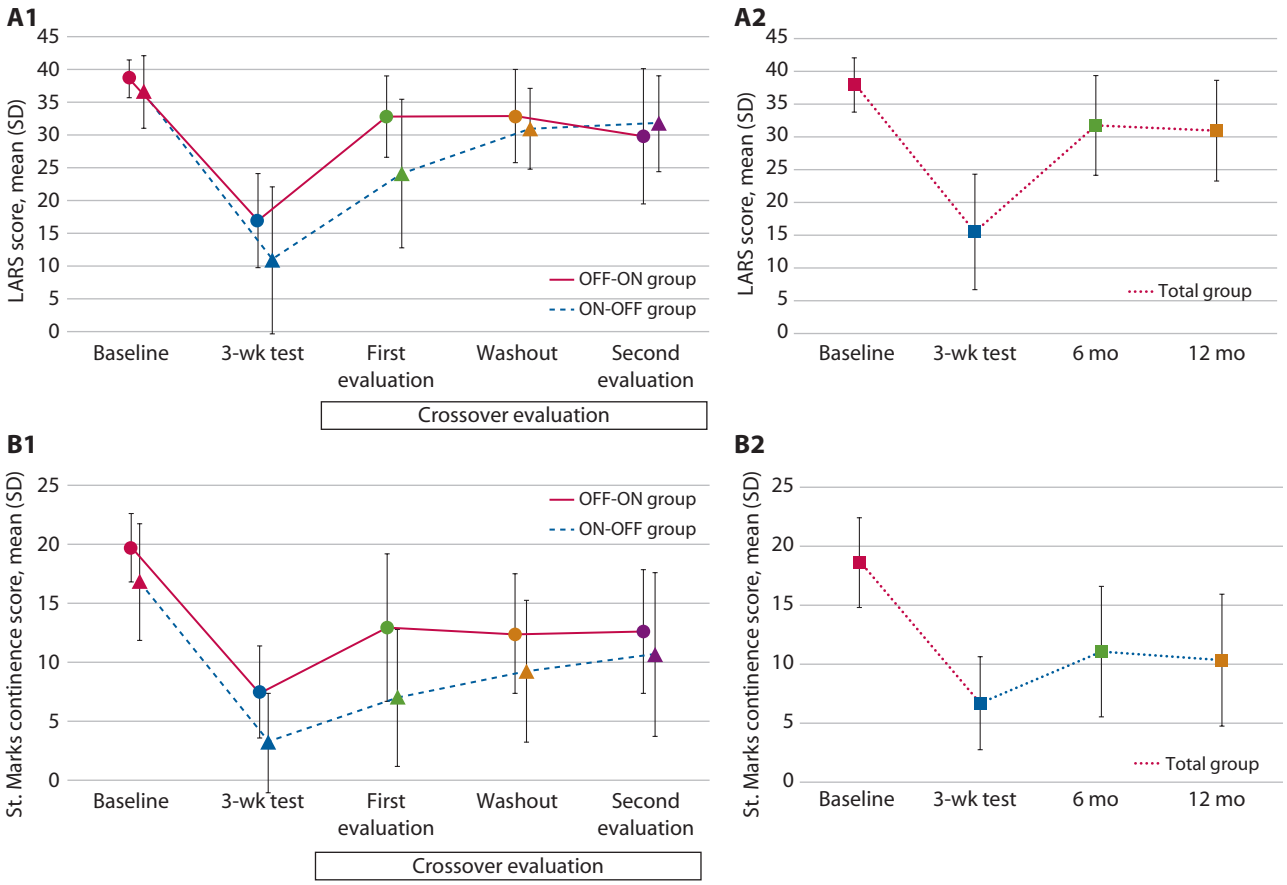

FIGURE 3. LARS and continence scores throughout the study. A1, LARS score during the crossover intervention. A2, LARS score with active modulation. B1, St. Mark's continence score during the crossover intervention. B2, St. Mark's continence score with active modulation. LARS = low anterior resection syndrome.

TABLE 7. Stool and bowel assessment with active modulation

Variable		*Baseline (v0)*	*Advanced test evaluation 3 wk (v1)*	*6-mo evaluation (v5)*	*12-mo evaluation (v6)*	*OR (95% CI); p* *v1 vs v0* *v5 vs v0* *v6 vs v0*
Urgency episodes per day	0–1	44.4% (n = 12)	93.1% (n = 27)	87.1% (n = 27)	90.9% (n = 30)	0.01 (0.001–0.18); 0.001
	>2	55.6% (n = 15)	6.9% (n = 2)	12.9% (n = 4)	9.1% (n = 3)	0.37 (0.12–1.37); 0.002
						0.02 (0.002–0.21); 0.001
Sensation of complete bowel emptying	<50%	85.7% (n = 24)	14.8% (n = 4)	41.9% (n = 13)	33.3% (n = 11)	73 (10.4–512.43); <0.001
	>50%	14.3% (n = 4)	85.2% (n = 23)	58.1% (n = 18)	66.7% (n = 22)	12.93 (2.83–59.19); 0.001
						20.52 (4.19–100.4); 0.000
Clustering episodes within an hour	0–1	14.3% (n = 4)	72.4% (n = 21)	41.9% (n = 13)	48.5% (n = 16)	0.04 (0.01–0.19); <0.001
	>2	85.7% (n = 24)	27.6% (n = 8)	58.1% (n = 18)	51.5% (n = 17)	0.18 (0.04–0.75); 0.018
						0.13 (0.03–0.55); 0.005
Discrimination between stool and gas	No	39.3% (n = 11)	13.8% (n = 4)	9.7% (n = 3)	9.1% (n = 3)	12.51 (1.61–96.92); 0.016
	Yes	60.7% (n = 17)	86.2% (n = 25)	90.3% (n = 28)	90.9% (n = 30)	21.72 (2.32–202.67); 0.007
						23.24 (2.5–215.86); 0.006

modulation inputs given by the electrode could not provide clinically relevant changes. Other known risk factors for LARS did not differ between groups. Because of the lack of evidence regarding indication for SNM in patients with LARS, it is reasonable to avoid SNM in those cases who had anastomotic leakage or to provide those patients with more realistic expectations.

This study has limitations. First, the primary end point was not achieved at 12-month follow-up because a 40% reduction in LARS score was not experienced by

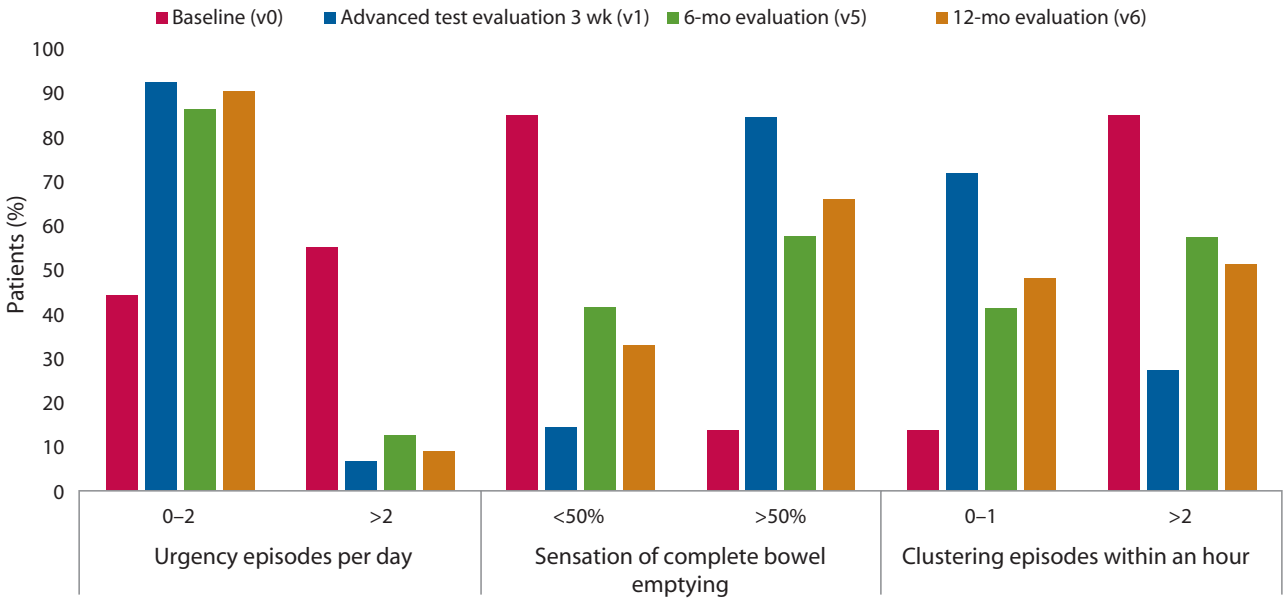

FIGURE 4. Symptoms assessment with active modulation.

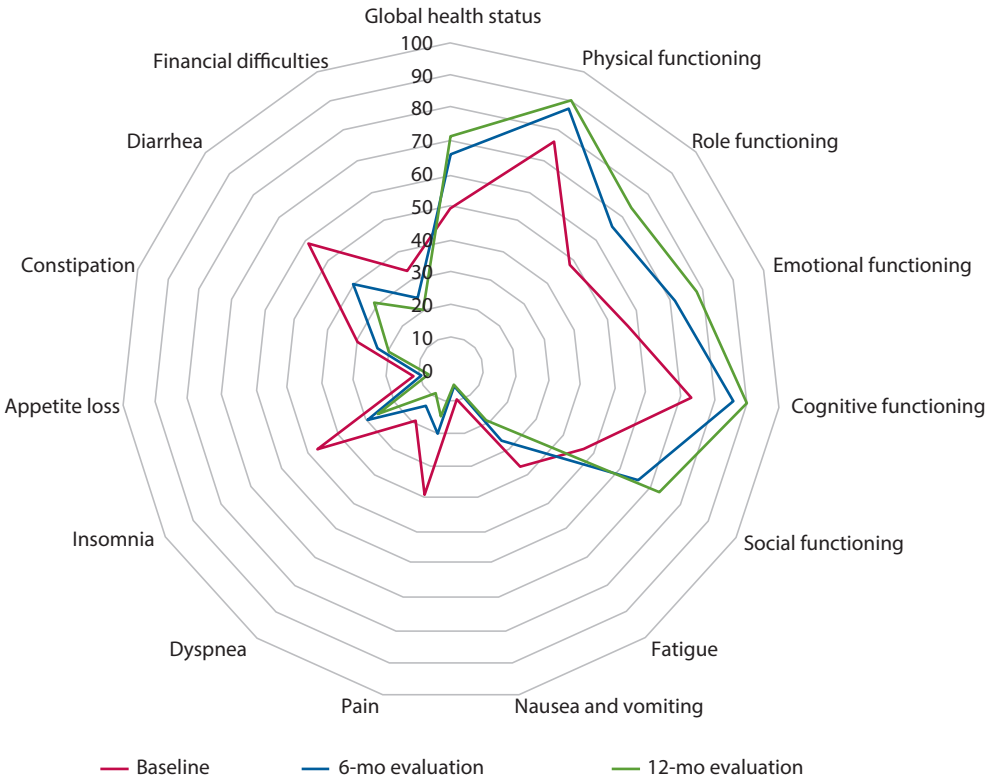

FIGURE 5. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (QLQ–C30) life changes with active modulation.

all patients after active SNM. This could be attributed to the LARS score not being the best assessment of the outcomes of treatments.[23] Second, the time of intervention for crossover active and sham stimulation could have been too short to detect more relevant changes in LARS. Also, there may have been a risk of a carryover effect from one intervention to the next one, and it is difficult to estimate the time required for the intervention to be fully washed out. A 1-year follow-up might not be long enough to validate the use of SNM for LARS. The authors did not consider patients' expectations to discriminate them from actual outcomes, but their satisfaction was excellent in almost 70% of the study sample associated with HRQoL improvement.

This study also has strengths and implications for clinical practice. Being a crossover trial, it has the advantage of minimizing the risk of confounding because it affords comparison between groups in a self-paired manner. It would be unfair to compare a surgical approach for LARS with conservative treatment or other noninvasive treatments. Stringent inclusion criteria were chosen, and follow-up included the use of diaries and HRQoL tools besides the LARS and continence scores, which could undermine therapy results.

LARS management is currently empirical and based on expert-opinion recommendations. SNM is often recommended as the last resource before stoma creation.[8,32] This study, originally presented at the annual meeting of the American Society of Colon and Rectal Surgeons,[33] demonstrated that SNM benefits patients with LARS symptoms. Comprehensive counseling with patients should be considered before offering SNM at an earlier stage in the treatment algorithm of LARS or association with other therapies. The SAcral Neuromodulation in Low Anterior Resection Syndrome RCT provided information that should be discussed with patients, facilitating patient empowerment and shared decision-making.

REFERENCES

1. Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. *Arch Surg*. 1998;133:894–899.
2. Kapiteijn E, Marijnen CAM, Nagtegaal ID, et al; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. 2001;345:638–646.
3. Wibe A, Syse A, Andersen E, Tretli S, Myrvold HE, Søreide O; Norwegian Rectal Cancer Group. Oncological outcomes after total mesorectal excision for cure for cancer of the lower rectum: anterior vs abdominoperineal resection. *Dis Colon Rectum*. 2004;47:48–58.
4. Bryant CLC, Lunniss PJ, Knowles CH, Thaha MA, Chan CLH. Anterior resection syndrome. *Lancet Oncol*. 2012;13: e403–e408.
5. Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. *Ann Surg*. 2012;255:922–928.
6. Lee WY, Takahashi T, Pappas T, Mantyh CR, Ludwig KA. Surgical autonomic denervation results in altered colonic motility: an explanation for low anterior resection syndrome? *Surgery*. 2008;143:778–783.
7. Keane C, Sharma P, Yuan L, Bissett I, O'Grady G. Impact of temporary ileostomy on long-term quality of life and bowel function: a systematic review and meta-analysis. *ANZ J Surg*. 2020;90:687–692.
8. Marinello F, Pellino G, Espín-Basany E. Low anterior resection syndrome: an unavoidable price to pay to preserve the rectum? *Front Oncol*. 2022;12:994720.
9. Marinello FG, Jiménez LM, Talavera E, et al. Percutaneous tibial nerve stimulation in patients with severe low anterior resection syndrome: randomized clinical trial. *Br J Surg*. 2021;108:380–387.
10. Dulskas A, Smolskas E, Kildusiene I, Samalavicius NE. Treatment possibilities for low anterior resection syndrome: a review of the literature. *Int J Colorectal Dis*. 2018;33:251–260.
11. Hollingshead JRF, Dudding TC, Vaizey CJ. Sacral nerve stimulation for faecal incontinence: results from a single centre over a 10-year period. *Colorectal Dis*. 2011;13:1030–1034.
12. Janssen PTJ, Komen N, Melenhorst J, et al. Sacral neuromodulation for fecal incontinence: a review of the central mechanisms of action. *J Clin Gastroenterol*. 2017;51:669–676.
13. Carrington E, Evers J, Grossi U, et al. A systematic review of sacral nerve stimulation mechanisms in the treatment of fecal incontinence and constipation. *Neurogastroenterol Motil*. 2014;26:1222–1237.
14. Ramage L, Qiu S, Kontovounisios C, Tekkis P, Rasheed S, Tan E. A systematic review of sacral nerve stimulation for low anterior resection syndrome. *Colorectal Dis*. 2015;17:762–771.
15. Huang Y, Koh CE. Sacral nerve stimulation for bowel dysfunction following low anterior resection: a systematic review and meta-analysis. *Colorectal Dis*. 2019;21:1240–1248.
16. Ram E, Meyer R, Carter D, Gutman M, Rosin D, Horesh N. The efficacy of sacral neuromodulation in the treatment of low anterior resection syndrome: a systematic review and meta-analysis. *Tech Coloproctol*. 2020;24:803–815.
17. Dwan K, Li T, Altman DG, Elbourne D. CONSORT 2010 statement: extension to randomised crossover trials. *BMJ*. 2019;366:I4378.
18. Juul T, Ahlberg M, Biondo S, et al. International validation of the low anterior resection syndrome score. *Ann Surg*. 2014;259:728–734.
19. Vaizey CJ, Carapeti E, Cahill JA, Kamm MA. Prospective comparison of faecal incontinence grading systems. *Gut*. 1999;44:77–80.
20. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85: 365–376.
21. D'Hondt M, Nuytens F, Kinget L, Decaestecker M, Borgers B, Parmentier I. Sacral neurostimulation for low anterior resection syndrome after radical resection for rectal cancer: evaluation of treatment with the LARS score. *Tech Coloproctol*. 2017;21:301–307.
22. Eftaiha SM, Balachandran B, Marecik SJ, et al. Sacral nerve stimulation can be an effective treatment for low anterior resection syndrome. *Colorectal Dis*. 2017;19:927–933.
23. Ribas Y, Muñoz-Duyos A. How useful is the LARS score in the evaluation and treatment of LARS? *Tech Coloproctol*. 2019;23:195–196.
24. Altomare DF, Giuratrabocchetta S, Knowles CH, Duyos AM, Robert-Yap J, Matzel KE. Long-term outcomes of sacral nerve stimulation for faecal incontinence. *Br J Surg*. 2015;102: 407–415.
25. Mellgren A, Wexner SD, Coller JA, et al; SNS Study Group. Long-term efficacy and safety of sacral nerve stimulation for fecal incontinence. *Dis Colon Rectum*. 2011;54: 1065–1075.

26. Lin AY, Dinning PG, Milne T, Bissett IP, O'Grady G. The "rectosigmoid brake": review of an emerging neuromodulation target for colorectal functional disorders. *Clin Exp Pharmacol Physiol*. 2017;44:719–728.
27. Lin AY, Varghese C, Paskaranandavadivel N, et al. Faecal incontinence is associated with an impaired rectosigmoid brake and improved by sacral neuromodulation. *Colorectal Dis*. 2022;24:1556–1566.
28. Patton V, Wiklendt L, Arkwright JW, Lubowski DZ, Dinning PG. The effect of sacral nerve stimulation on distal colonic motility in patients with faecal incontinence. *Br J Surg*. 2013;100:959–968.
29. Michelsen HB, Christensen P, Krogh K, et al. Sacral nerve stimulation for faecal incontinence alters colorectal transport. *Br J Surg*. 2008;95:779–784.
30. Croese AD, Whiting S, Vangaveti VN, Ho YH. Using sacral nerve modulation to improve continence and quality of life in patients suffering from low anterior resection syndrome. *ANZ J Surg*. 2018;88:E787–E791.
31. Keane C, Paskaranandavadivel N, Vather R, et al. Altered colonic motility is associated with low anterior resection syndrome. *Colorectal Dis*. 2021;23:415–423.
32. Christensen PIM, Baeten C, Espín-Basany E, et al. Management guidelines for low anterior resection syndrome—the MANUEL project. *Colorectal Dis*. 2021;23:461–475.
33. Marinello F, Fraccalvieri D, Planellas P, et al. Treatment of low anterior resection syndrome symptoms with sacral neuromodulation: preliminary results of a randomized, multicentric, crossover trial [ASCRS abstract S25]. *Dis Colon Rectum*. 2023;66:e367.