Self-Reported Long-Term Autonomic Function After Laparoscopic Total Mesometrial Resection for Early-Stage Cervical Cancer

A Multicentric Study

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Objectives: This multicentric retrospective study investigates the early and long-term self-reported urinary, bowel, and sexual dysfunctions in early-stage cervical cancer patients who submitted to laparoscopic total mesometrial resection (L-TMMR), total laparoscopic radical hysterectomy, vaginal-assisted laparoscopic radical hysterectomy, and laparoscopic-assisted radical vaginal hysterectomy.

Methods: Cervical cancer patients, FIGO (International Federation of Gynecology and Obstetrics) stage IA2–IB1/IIA1 who submitted to nerve-sparing radical hysterectomy were recruited. Pelvic functions were assessed within 30 days (early outcome) and 12 months after surgery (long-term outcome).

Results: Two hundred thirteen subjects receiving nerve-sparing radical hysterectomy were enrolled. Laparoscopic total mesometrial resection was performed in 46 patients (21.6%), total laparoscopic radical hysterectomy in 65 patients (30.5%), vaginal-assisted laparoscopic radical hysterectomy in 54 patients (25.4%), and laparoscopic-assisted radical vaginal hysterectomy in 48 women (22.5%). Operative time was significantly lower in the L-TMMR group (240 minutes; range, 120–670 minutes; $P = 0.001$). The overall perioperative complication rate was 11.3%, with no statistically significant differences among the 4 groups. Stress incontinence and sensation of bladder incomplete emptying were detected, respectively, in 54 patients (25.6%) and 65 patients (30.7%) with a significantly lower prevalence among those in the L-TMMR group, which resulted, respectively, in 11.1% ($P = 0.022$) and 13.3% ($P = 0.036$). The prevalence rates of constipation, sensation of incomplete bowel emptying, and effort during evacuation were significantly higher among those in the L-TMMR group, resulting in, respectively, 37% ($P = 0.001$), 42.3% ($P = 0.012$), and 50% ($P = 0.039$). One hundred forty-nine patients (70%) were sexually active. Fifty-eight women (38.9%) reported low enjoyment, 83 women (55.7%) medium enjoyment, and 8 women (5.4%) reported high enjoyment, without statistically significant differences among the 4 groups.

Conclusions: Laparoscopic total mesometrial resection is associated with improved long-term urinary autonomic functions and worse gastrointestinal autonomic outcome. Further larger prospective trials are needed to evaluate both the oncological and functional outcomes in order to establish the most appropriate surgical approach for early-stage cervical cancer patients.

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Radical surgery is the recommended treatment for patients with early-stage cervical cancer (ECC), and several different techniques have been developed to properly achieve an adequate surgical disease control,[1] reducing morbidities related to radical hysterectomy (RH).

In particular, the damage to pelvic autonomic innervation during RH represents a frequent cause of major long-term urologic, gastrointestinal, and sexual dysfunctions; therefore, techniques of nerve-sparing RH (NSRH) are currently considered as the best approach to balance surgical radicality and postoperative morbidity.[2,3]

At the same time, in the last decade, several pieces of evidence have supported the safety and feasibility of minimally invasive surgical approaches to perform NSRH. Among these endoscopic techniques, total laparoscopic RH (TLRH), laparoscopic-assisted radical vaginal hysterectomy (LARVH), and vaginal-assisted laparoscopic RH (VALRH) represent the most defined surgical approaches to ensure a wide resection of the disease with a metrically defined radial margin of tumor-free tissue, preserving the autonomic functions.

On the other hand, laparoscopic total mesometrial resection (L-TMMR) recently emerged as an innovative and effective strategy to increase locoregional control, removing the tumor along with the entire embryologically defined uterovaginal (müllerian) compartment, despite metric-defined free margins,[4,5] even if TMMR remains an investigational procedure.

However, despite the large number of studies evaluating pelvic organ dysfunctions in ECC patients who submitted to NSRH,[6] no data are available regarding the impact of L-TMMR on functional outcome in comparison with the other minimally invasive strategies.

For these reasons, we analyze in the present multicentric retrospective study early and long-term self-reported urinary, bowel, and sexual dysfunctions in a large series of ECC patients who submitted to L-TMMR, TLRH, VALRH, and LARVH.

MATERIALS AND METHODS

Study Design

This is a multicentric retrospective study conducted in a large series of patients with ECC admitted to our institutions: the Charitè University of Berlin (Germany) and the Catholic University of the Sacred Heart of Rome and Campobasso (Italy). The local ethics committees approved the study. All patients submitted to mini-invasive NSRH according to 4 different, previously described surgical approaches: L-TMMR, TLRH, VALRH, LARVH.[5,7–10] The radicality of surgical approach for TLRH, VALRH, and LARVH has been classified according to Querleu-Morrow[11] classification. No specific criteria were adopted in order to choose which of these mini-invasive NSRH had to be performed, and the final decision about the approach was made directly by the surgeon based on his experience. All patients admitted at our institutions between January 2012 and April 2015 and who submitted to NSRH were recruited in presence of the following inclusion criteria: histological diagnosis of cervical cancer, International Federation of Gynecology and Obstetrics (FIGO) stage IA2–IB1/IIA1, age between 18 and 75 years, and written informed consent. Exclusion criteria were as follows: metachronous or synchronous neoplasia; history of preoperative urinary, intestinal, or sexual dysfunctions; and psychiatric disorders. All women with recurrent disease were excluded from the final analysis. For all patients, final stage was clinically assigned after investigation under anaesthesia, preoperative pelvic magnetic resonance imaging, cystoscopy, and rectoscopy if required.[12] Adjuvant radiotherapy or chemoradiation was administered in presence of positive lymph nodes, parametrial or/and vaginal involvement, positive surgical resection margins (<5 mm), and large tumor diameter. Lymph vascular space invasion alone was not a criterion for adjuvant therapy. The same schedule of adjuvant radiation/chemoradiation has been administered to all women with a dosage of 45-Gy cisplatin-containing external beam radiation therapy.

For all patients, clinicopathological data and perioperative outcomes were retrospectively collected and analyzed for the study purpose. Pelvic dysfunctions were classified as urinary, gastrointestinal, and sexual.

For all patients, pelvic functions were assessed within 30 days (early outcome) and 12 months after surgery (long-term outcome). In particular, long-term outcome was evaluated through a validated questionnaire recording patients' self-reported pelvic functions.[13] Complaints were considered as moderate/severe when referred by patients as "often" or "daily."

Perioperative Outcomes

Estimated blood loss during surgery, operative time, postoperative hospital stay, and perioperative complications were recorded and classified according to the Franco-Italian Glossary.[14] Early postoperative complications were defined as any adverse event occurring within 30 days and were classified as follows: urological (bladder or urethral injury or fistula), gastrointestinal (intraoperative injury), vascular, and neurological, based on the type of adverse effect.

Urinary Functional Outcome

We analyzed early postoperative bladder dysfunction evaluating the average time to achieve residual urine of less than 50 mL (postvoid residual [PVR]), the average time of postoperative catheterization, and the necessity of recatheterization.

Late urinary dysfunction was evaluated as the presence of dysuria, stress incontinence, urge incontinence, sensation of bladder incomplete emptying, recurrent urinary tract infection, micturition frequency (>8 times per day), and nycturia (>2 times per night).

Bowel Functional Outcome

Early postoperative bowel dysfunction was evaluated analyzing the average time of canalization (time of first flatus) and the use of prokinetics agents during hospitalization. Regarding late postoperative dysfunction, we reported the prevalence of several complaints such as constipation, defecation urgency, fecal incontinence, sensation of incomplete bowel emptying, and effort during evacuation.

Sexual Functional Outcome

Sexual sphere was evaluated 12 months from surgery using the validated questionnaire mentioned previously.[13]

Statistical Analysis

Differences among the 4 groups in term of clinicopathological features at diagnosis, perioperative outcomes, and early/long-term pelvic functions were analyzed using the Pearson χ^2 exact test and Kruskal-Wallis test, as appropriate. All statistical calculations were performed using Stata software version 11.0 (Stata Corp, College Station, TX).

RESULTS

Between January 2012 and April 2015, 276 early-stage cervical cancer patients received nerve-sparing mini-invasive RH in our institutions. Fifteen patients (5.4%) presented disease recurrence, and among these, 9 women (3.2%) died of disease. We attempted to contact all the remaining 261 patients with a telephone call in order to program the follow-up visit at 12 months. Forty-eight women (18.3%) refused the control or did not respond to phone call. Therefore, the final analysis was conducted on a study population of 213 subjects. Laparoscopic total mesometrial resection was performed in 46 patients (21.6%), TLRH in 65 patients (30.5%), VALRH in 54 patients (25.4%), and LARVH in the remaining 48 women (22.5%).

Laparoscopic total mesometrial resections were performed in the 3 institutions as follows: 25 cases were treated at Charite University of Berlin, and 21 patients at the Catholic University of the Sacred Heart of Rome and Campobasso. Each procedure was performed among the 3 centers, as shown in detail in Table 6 (Supplemental Digital Content, http://links.lww.com/IGC/A506).

TABLE 1. Clinicopathological characteristics of the study population

Characteristics	All Cases	VALRH, n (%)	LARVH, n (%)	TLRH, n (%)	TMMR, n (%)	P*
All cases	213	54 (25.4)	48 (22.5)	65 (30.5)	46 (21.6)	—
Age, median (range)†	45 (24–75)	46 (27–75)	43 (25–73)	45 (27–67)	49 (28–74)	0.455
Body mass index, median (range),† kg/m^2	24 (13–38)	25 (18–38)	24 (18–38)	23 (13–38)	24 (18–33)	0.402
Tumor grade						
G1	21 (9.9)	5 (9.3)	6 (12.5)	5 (7.7)	5 (10.9)	
G2	117 (54.9)	30 (55.6)	29 (60.4)	39 (60.0)	19 (41.3)	
G3	75 (35.2)	19 (35.1)	13 (27.1)	21 (32.3)	22 (47.8)	0.426
FIGO stage						
IA2	33 (15.5)	6 (11.1)	6 (12.5)	14 (21.5)	7 (15.2)	
IB1/IIA1	180 (84.5)	48 (88.9)	42 (87.5)	51 (78.5)	39 (84.8)	0.401
Tumor histotype						
Squamous cell	134 (62.9)	33 (61.1)	25 (52.1)	46 (70.8)	30 (65.2)	
Adenocarcinoma	70 (32.9)	20 (37.0)	18 (37.5)	17 (26.2)	15 (32.6)	
Adenosquamous/glassy cell	9 (4.2)	1 (1.9)	5 (10.4)	2 (3.0)	1 (2.2)	0.184
Type of RH (Querleu-Morrow)						
B1–2	92 (55.1)	31 (57.4)	29 (60.4)	32 (49.2)		
C1	75 (44.9)	23 (42.6)	19 (39.6)	33 (50.8)	n.a.	0.456
Adjuvant treatment						
No	117 (54.9)	31 (57.4)	26 (54.2)	34 (52.3)	26 (56.5)	
Radiation alone	10 (4.7)	2 (3.7)	2 (4.2)	5 (7.7)	1 (2.2)	
Chemoradiation	86 (40.4)	21 (38.9)	20 (41.7)	26 (40.0)	19 (41.3)	0.897

*Calculated using χ^2 exact test.
†Calculated using Kruskal-Wallis test.

TABLE 2. Perioperative outcomes in the study population according to surgical approach

Characteristics	All Cases, n (%)	VALRH, n (%)	LARVH, n (%)	TLRH, n (%)	TMMR, n (%)	P*
Perioperative complications						
Yes	24 (11.3)	6 (11.1)	5 (10.4)	10 (15.4)	3 (6.5)	
No	189 (88.7)	48 (88.9)	43 (89.6)	55 (84.6)	43 (93.5)	0.537
Type of complication						
Urinary	13 (6.1)	4 (7.4)	4 (8.3)	3 (4.6)	2 (4.3)	0.783
Gastrointestinal	3 (1.4)	2 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.277
Neurological	3 (1.4)	0 (0.0)	0 (0.0)	3 (4.3)	0 (0.0)	0.074
Vascular	6 (2.8)	1 (1.9)	1 (2.1)	4 (6.2)	0 (0.0)	0.235
Median operative time† (range), min	280 (50–680)	260 (120–390)	310 (180–490)	280 (50–550)	240 (120–670)	**0.001**
Median estimated blood loss† (range), mL	150 (0–800)	100 (0–400)	250 (0–800)	150 (0–500)	200 (0–800)	0.187
Median hospital stay† (range), d	7 (2–28)	9 (3–23)	11 (4–19)	6 (2–15)	7 (3–28)	0.098

Data in bold means statistically significant.
*Calculated using χ^2 exact test.
†Calculated using Kruskal-Wallis test.

Perioperative Outcomes

The clinicopathological characteristics of our study population are presented in Table 1, and no preoperative statistically significant differences were observed.

The median age of the overall population was 45 years (range, 24–75 years), and the median body mass index was 24 kg/m^2 (range, 13–38 kg/m^2). No differences among the 4 groups were observed in term of tumor histotype, grading, and FIGO stage.

No preoperative statistically significant differences were observed among the groups, as shown in Table 2, except for mean operative time, which is significantly lower in the L-TMMR group (240 minutes; range, 120–670 minutes; $P = 0.001$). The overall perioperative complication rate was 11.3%, with no statistically significant differences among the 4 groups.

Urinary Functional Outcomes

The median time to achieve residual urine of less than 50 mL (PVR) was 2 days (range, 0–50 days), and the median time of catheterization was 4 days (range, 1–35 days), which resulted significantly lower in the L-TMMR group (1 day [range, 0–15 days; $P = 0.032$] and 2 days [range, 1–35 days; $P = 0.001$], respectively).

TABLE 3. Early and long-term urinary functions according to surgical approach

Characteristics	All Cases, n (%)	VALRH, n (%)	LARVH, n (%)	TLRH, n (%)	TMMR, n (%)	P*
Early urinary functions						
Median time to normal PVR (range),† d	2 (0–50)	2 (1–3)	2 (1–3)	2 (0–50)	1 (0–15)	0.032
Median time of catheterization (range),† d	4 (1–35)	5 (1–20)	6 (1–14)	4 (1–30)	2 (1–35)	0.001
Necessity of recatheterization	44 (20.7)	10 (18.5)	11 (22.9)	10 (15.4)	13 (28.3)	0.388
Long-term urinary functions						
Dysuria (moderate/severe)	11 (5.2)	4 (7.4)	0 (0.0)	5 (7.7)	2 (4.3)	0.553
Stress incontinence (moderate/severe)	54 (25.6)	20 (37.7)	14 (29.2)	15 (23.1)	5 (11.1)	0.022
Urge incontinence (moderate/severe)	20 (9.4)	5 (9.3)	5 (10.4)	6 (9.2)	4 (8.9)	0.995
Sensation of bladder incomplete emptying (often/daily)	65 (30.7)	20 (37.0)	18 (37.5)	21 (32.3)	6 (13.3)	0.036
Recurrent urinary tract infection (>4 times/y)	8 (3.8)	2 (3.7)	2 (4.2)	3 (4.7)	1 (2.2)	0.927
Mintional frequency (>8 times/d)	20 (9.5)	6 (11.1)	2 (4.3)	9 (13.8)	3 (6.7)	0.318
Nycturia (>2 times/night)	17 (8.0)	6 (11.1)	2 (4.2)	6 (9.2)	3 (6.7)	0.592

*Calculated using χ^2 exact test.
†Calculated using Kruskal-Wallis test.

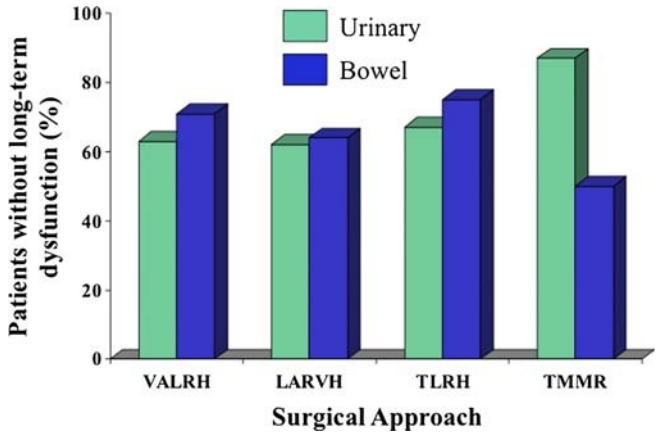

FIGURE 1. Long-term urinary and bowel functions.

In regard to long-term urinary function, the most relevant complaints were stress incontinence and sensation of bladder incomplete emptying detected, respectively, in 54 patients (25.6%) and 65 patients (30.7%) with a significantly lower prevalence among those in the L-TMMR group, which resulted in, respectively, 11.1% ($P = 0.022$) and 13.3% ($P = 0.036$).

No statistically significant differences among the 4 groups were observed for the other reported complaints, as shown in Table 3.

Patients without long-term urinary dysfunctions, as shown in Figure 1, were 87% of those who underwent TMMR, 67% of TLRH, 64% of LARVH, and 63% of those who underwent VALRH.

Interestingly, no differences were documented in term of urinary dysfunction between women receiving TMMR and those who underwent class B or class C NSRH.

Bowel Functional Outcomes

No differences among the 4 groups were detected as early postoperative bowel dysfunctions. The median time of canalization was 3 days (range, 0–16 days), and the use of prokinetic agents during hospitalization has been reported in 85 cases (40.9%).

In regard to long-term bowel function, the most relevant complaints were constipation (38 cases [17.9%]), sensation of incomplete bowel emptying (50 cases [23.7%]), and effort during evacuation reported by 72 patients (34%), with a significantly higher prevalence of these complaints among those in the L-TMMR group, which resulted in, respectively, 37% ($P = 0.001$), 42.3% ($P = 0.012$), and 50% ($P = 0.039$).

No statistically significant differences among the 4 groups were observed for the other reported complaints, as shown in Table 4.

Patients without long-term bowel dysfunctions, as shown in Figure 1, were 50% of those who underwent TMMR, 75% of TLRH, 64% of LARVH, and 71% of those who underwent VALRH.

Sexual Functional Outcome

One hundred forty-nine patients (70%) declared to have been sexually active during the past 4 weeks. Among these, 58 women (38.9%) reported low enjoyment, 83 (55.7%) medium enjoyment, and 8 (5.4%) reported high enjoyment, without

TABLE 4. Early and long-term gastrointestinal functions according to surgical approach

Characteristics	All Cases, n (%)	VALRH, n (%)	LARVH, n (%)	TLRH, n (%)	TMMR, n (%)	P*
Early gastrointestinal functions						
Median canalization time (range),† d	3 (0–16)	3 (1–7)	4 (2–8)	3 (0–16)	3 (0–9)	0.496
Use of prokinetic agents during hospitalization	85 (40.9)	21 (39.6)	19 (39.3)	24 (39.3)	21 (45.7)	0.905
Late gastrointestinal functions						
Constipation (moderate/severe)	38 (17.9)	5 (9.3)	4 (8.5)	12 (18.5)	17 (37.0)	**0.001**
Defecation urgency (moderate/severe)	15 (7.1)	7 (13.0)	1 (2.1)	2 (3.1)	5 (10.9)	0.066
Fecal incontinence (moderate/severe)	6 (2.8)	2 (3.7)	0 (0.0)	1 (1.5)	3 (6.5)	0.241
Sensation of incomplete bowel emptying (moderate/severe)	50 (23.7)	9 (16.7)	11 (23.9)	11 (16.9)	19 (42.3)	**0.012**
Effort during evacuation	72 (34.0)	16 (29.6)	17 (36.2)	16 (24.6)	23 (50.0)	**0.039**

*Calculated using χ^2 exact test.
†Calculated using Kruskal-Wallis test.

TABLE 5. Sexual functions according to surgical approach in the study population

Characteristics	All Cases, n (%)	VALRH, n (%)	LARVH, n (%)	TLRH, n (%)	TMMR, n (%)	P*
Sexual activity						0.838
Yes	149 (70.0)	39 (72.0)	32 (66.7)	44 (67.7)	34 (73.9)	
No	64 (30.0)	15 (27.8)	16 (33.3)	21 (32.3)	12 (26.1)	
Sexual enjoyment						0.996
Low	58 (38.9)	14 (35.9)	12 (37.5)	19 (43.2)	13 (38.2)	
Medium	83 (55.7)	23 (59.0)	18 (56.3)	23 (52.3)	19 (55.9)	
High	8 (5.4)	2 (5.1)	2 (6.2)	2 (4.5)	2 (5.9)	

*Calculated using χ^2 exact test.
†Calculated using Kruskal-Wallis test.

statistically significant differences among the 4 groups, as shown in Table 5.

DISCUSSION

After its first description by M. Höckel,[15] TMMR has been progressively introduced in the surgical management of ECC in several institutions. The diffusion of this approach through the scientific community has been associated with a continuous improvement of the technique, so that TMMR can be now safely performed through minimally invasive laparoscopic[5] and robotic routes.[15] Furthermore, recently published data demonstrated encouraging results in term of perioperative outcome in patients receiving laparoscopic or robotic TMMR, without differences between the 2 groups.[16] On the other hand, it is well known that impairment of pelvic functions, particularly in term of urinary outcome, represents the most relevant issue of standard minimally invasive RH,[17,18] even when nerve-sparing technique is adopted.[19]

Furthermore, we underline that there are no differences among the groups in term of adjuvant radiation treatment; therefore, the results of our study appear particularly relevant considering that we first compared the pelvic organ functions of L-TMMR with standard surgical approaches, including VALRH, LARVH, and TLRH.

For instance, no differences were reported in our study in term of surgical complication rate among the 4 groups. Similarly, blood loss and duration of hospital stay were superimposable in ECC patients receiving L-TMMR, VARLH, LARVH, and TLRH. On the other hand, the length of operative time was slightly in favor of L-TMMR technique, thus confirming the safety and reliability of this approach in the context of the current surgical state of the art for ECC patients.

However, the most relevant finding of our study is represented by the comparison of early and long-term pelvic functions among the 4 surgical approaches. In particular, focusing on the early urinary outcome, L-TMMR showed a reduced time to normal PVR and as consequence a shorter median time of catheterization, compared with VARLH, LARVH, and TLRH. Similarly, at long-term evaluation, urinary stress incontinence and sensation of incomplete bladder emptying occurred in 10% to 15% of cases treated with L-TMMR compared with approximately 30% in patients who submitted to other surgical approaches. Looking carefully at these data, 2 relevant findings clearly emerge: (1) VALRH, LARVH, and TLRH have a similar impact on urinary functional outcome, with impaired bladder emptying and stress urinary incontinence in approximately 30% of cases; (2) L-TMMR is associated with an approximately 2 times' lower rate of long-term urinary dysfunctions, compared with the other approaches.

On the other hand, L-TMMR was associated with worse long-term gastrointestinal functions compared with VALRH, LARVH, and TLRH, with a higher rate of constipation, sensation of incomplete bowel emptying, and effort during evacuation.

Taken together, these results emphasize for the first time that L-TMMR and standard NSRH are associated with 2 different patterns of pelvic dysfunctions, with L-TMMR exerting a more relevant impairment of rectal emptying, and VARLH, LARVH, and TLRH being more frequently associated with impairment of urinary functions.

A potential explanation to these findings could be found in the specific surgical techniques: L-TMMR is characterized by a reduced radicality on the ventral compartment as the suburethral part of the anterior parametrium, where normally the autonomic hypogastric fibers are allocated, is respected. On the other hand, the increased resection needed to remove the posterior mesometrium in the L-TMMR approach to achieve the complete resection of the müllerian embryologic compartment may lead to impairment of autonomic nerves involved in the control of rectal functions.[20,21] As a further potential explanation to these findings, it should be acknowledged that in laparotomic TMMR[4] the adequate rectal traction allows the development of presacral fossa and posterior mesometrium resection preserving hypogastric nerve fibers. On the other hand, this surgical step may be less appropriate through the laparoscopic approach because of an increased difficulty in achieving adequate tractions with an impairment of sympathetic nerve fibers directed to the rectum.

Finally, we also analyzed long-term sexual functions. Interestingly, no differences were observed among the groups in term of sexual activity and sexual enjoyment, thus suggesting that the choice of surgical approach does not impact long-term sexual outcome in ECC patients.

We acknowledge that the retrospective nature of the study and the enrolment over 2 centers represent relevant biases;

however, to our knowledge, this is the first study evaluating the autonomic function after L-TMMR comparing this technique with the other minimally invasive strategies. In addition, the homogeneity of the surgical team and of clinicopathological characteristics at diagnosis and adjuvant treatments in the 4 investigated groups support the reliability of our findings.

In conclusion, we confirm that VARLH, LARVH, and TLRH are associated with similar perioperative outcomes and superimposable early and long-term pelvic functions; furthermore, we demonstrated for the first time that L-TMMR is associated with improved long-term urinary functions and worse gastrointestinal functional outcome. Far from drawing definitive explanations to these conclusions, it clearly emerges the need to prospectively assess both the oncological and functional outcome related to the different techniques of pelvic radical surgery in patients with ECC, in order to establish the most appropriate surgical approach.

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