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Total laparoscopic vs. conventional open abdominal nerve-sparing radical hysterectomy: clinical, surgical, oncological and functional outcomes in 301 patients with cervical cancer

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ABSTRACT

Objective: Total laparoscopic nerve-sparing radical hysterectomy (TL-NSRH) has been considered a promising approach, however, surgical, clinical, oncological and functional outcomes have not been systematically addressed. We present a large retrospective multi-center experience comparing TL-NSRH vs. open abdominal NSRH (OA-NSRH) for early and locally-advanced cervical cancer, with particular emphasis on post-surgical pelvic function.
Methods: All consecutive patients who underwent class C1-NSRH plus bilateral pelvic + para-aortic lymphadenectomy for stage IA2–IIB cervical cancer at 4 Italian gynecologic oncologic centers (Negrar, Varese, Bologna, Avellino) were enrolled. Patients were divided into TL-NSRH and OA-NSRH groups and were investigated with preoperative questionnaires on urinary, rectal and sexual function. Postoperatively, patients filled a questionnaire assessing quality of life, taking into account sexual function and psychological status. Oncological outcomes were analyzed using Kaplan-Meyer method.
Results: 301 consecutive patients were included in this study: 170 in the TL-NSRH group and 131 in the OA-NSRH group. Patients in the OA-NSRH group were more likely to experience urinary incontinence and (after 12-months follow-up) urinary retention. No patient in the TL-NSRH group vs. 5 (5.5%) in the OA-NSRH group had complete urinary retention (at the >24-month follow-up [p=0.02]). A total of 20 (11.8%) in the TL-NSRH and 11 (8.4%) patients in the OA-NSRH had recurrence of disease (p=0.44) and 14 (8.2%) and 9 (6.9%) died of disease during follow-up, respectively (p=0.83).
Conclusion: Our study shows that TL-NSRH is feasible, safe and effective and conjugates adequate radicality and improvement in post-operative functional outcomes. Oncological outcomes of laparoscopic procedures deserve further investigation.

Keywords: Hysterectomy; Laparoscopy; Laparotomy; Cervical Cancer; Treatment Outcome

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INTRODUCTION

Despite the wide spread of screening programs, cervical cancer still represents the fourth most common malignancy in women worldwide (being the second in developing countries) and the second most common cause of cancer-related deaths among women between 20 and 39 years old [1]. Surgery represents one of the mainstays of treatment in early-stage disease and radical hysterectomy (RH) with nodal dissection provides very good results in patients with International Federation of Gynecology and Obstetrics (FIGO) stage IA2–IIA node-negative disease, with 5-year survival rates >90% [2].

RH is a challenging procedure and it has been traditionally related to a high incidence of peri-operative complications [3]. In addition, relevant long-term functional sequelae are associated with the procedure [4-6]. Iatrogenic denervation during radical surgery seriously interferes with pelvic function and results in considerable patients' distress and impaired quality of life (QoL), particularly in young women. In recent years, nerve-sparing RH (NSRH) has been proposed to reduce postoperative morbidity, without compromising oncological radicality [7-9]. The nerve-sparing concept was originally described by Kobayashi in 1960 [10], and subsequently described in different techniques by several authors [5,11-13]. The results of the available series show that NSRH is equivalent to conventional RH in terms of survival, but it allows the preservation of pelvic function [14].

The advent of minimally invasive techniques has significantly improved the short-term outcomes of patients undergoing major gynecologic surgery, including RH, by enhancing recovery and decreasing pain and post-operative complications [15,16]. However, recent publications (and particularly the Laparoscopic Approach to Cervical Cancer [LACC] trial) have raised serious concerns regarding the oncological safety of endoscopic surgery in cervical cancer [17,18], describing a significant and alarming increase in the rate of recurrence. Despite the deep rethinking of the role of endoscopy in this setting, total laparoscopic RH has been adopted for years with the potential to increase the possibility to spare autonomic neural structures during the procedure: the image magnification offered by the laparoscope has markedly improved the possibility to identify and visualize thin structures, such as the pelvic autonomic nerves. Some studies have reported the outcomes of total laparoscopic NSRH (TL-NSRH), but a recent review on this issue has identified only 7 non-randomized series on a limited number of patients, comparing nerve-sparing vs. conventional procedures [14]. In addition, the authors of the review acknowledged that functional outcomes have been seldom described in depth in the available literature [14].

The aim of this study is to report our multi-center experience in terms of clinical outcomes and prognosis, comparing TL-NSRH vs. conventional open abdominal NSRH for early-stage or locally-advanced cervical carcinoma, performed before the publication of the LACC trial. A particular attention was paid to the description of functional results and patients' QoL.

MATERIALS AND METHODS

The present analysis is a multi-institutional, retrospective series of consecutive patients who underwent class C1 (Querleu-Morrow classification) NSRH (performed by laparoscopy or by open abdominal surgery) [19] and systematic bilateral pelvic ± additional para-aortic lymphadenectomy for the treatment of carcinoma of the uterine cervix. The study involved

patients from 4 Italian Institutions: Gynecologic Oncology and Minimally-Invasive Pelvic Surgery Unit of the IRCCS (Scientific Institute for Research, Hospitalization and Healthcare)— Sacro Cuore Don Calabria Hospital, Negrar di Valpolicella (Verona), Endoscopica Malzoni, Center for Advanced Endoscopic Gynecologic Surgery, Avellino, Department of Obstetrics and Gynecology, DIMEC, S. Orsola Hospital, University of Bologna, and the Department of Obstetrics and Gynecology, University of Insubria, Varese. The protocol for this study was in line with the Strengthening the Reporting of Observational Studies in Epidemiology statement. From January 2007 to December 2012, all consecutive patients with early stage or locally advanced cervical cancer who underwent NSRH were enrolled. Inclusion criteria were: age >18 years, stage IA2–IIB, provision of written informed consent. Patients with positive history of malignancy and those with absolute contraindication to surgery were excluded. At the time of informed consent before surgery, each patient agreed to the use of her data in future clinical retrospective studies. Data on patient characteristics, tumor classification, pathology, surgical factors and follow-up were analyzed. Clinical staging of cervical carcinoma and preoperative evaluation were based on complete physical and rectovaginal examination, routine blood and urine analysis, chest radiography, transvaginal ultrasound. Cystoscopy and rectoscopy were performed only on specific indication; magnetic resonance imaging (MRI), or computed tomography (CT) were performed in the vast majority of cases (when clinical examination was ambiguous or inconclusive). The stage of the disease was determined by using the FIGO 2009 staging system. Patients were divided into TL-NSRH group and open abdominal (OA-NSRH) group, according to the type of surgical approach adopted. The surgical approach was chosen according to the availability or not of a surgical team with extensive experience in laparoscopic surgery.

1. Operative technique

The procedures were performed by surgeons with extensive experience in gynecologic oncology and (for the TL-NSRH group) in advanced minimally-invasive radical surgery (>50 laparoscopic type C radical hysterectomies performed). Bipolar coagulation ± a ultrasonic device was used. Regarding the radicality of parametrial resection, the surgical steps of type C1 RH, as per the Querleu-Morrow classification system were followed [19]. The intervention was performed according to the technique previously reported by Malzoni et al. [20] (for laparoscopic NSRH) and Raspagliesi et al. [13] (for open abdominal NSRH) with technical modifications in parametrial dissection for the nerve-sparing approach, as recently published by our group (**Supplementary Data 1**) [21]. Ovarian preservation was performed in patients <40 years of age and with squamous histology. The indwelling urethral catheter was removed 3 days after the intervention. Intermittent catheterization was performed by patients 3 times a day until residual urine volumes less than 100 ml were obtained at least 3 consecutive times.

2. Clinical outcomes and QoL

All patients were investigated with pre-operative questionnaires on urinary, rectal and sexual function (**Supplementary Data 2**). Post-operative complications were divided into 2 groups according to the timing of their occurrence (i.e. within or after 7 days). Postoperative bladder function was assessed by means of post-voiding residual (PVR), evaluated by ultrasound or catheterization after voiding. According to the principles by Asimakopoulos et al. [22], bladder function was classified normal when PVR was ≤100 mL and the patient voided spontaneously; on the contrary it was classified abnormal when PVR was >100 mL and self-catheterization was necessary after the first month of follow-up. In the latter case, the time of spontaneous voiding recovery after self-catheterization was evaluated. Patients performed self-intermittent catheterization at home if they experienced voiding difficulty or urinary

retention of >100 mL at the time of discharge. The number of days of self-catheterization from discharge until resolution were recorded and calculated. Rectal manometry was planned only for patients with severe rectal dysfunction referred pre-operatively. In the study plan, every patient with severe bladder and rectal dysfunction after 18 months was considered as "denervated". For these patients, long-term urodynamic studies and ano-rectal manometry were planned, in order to assess the neurologic impairment. During the follow-up period (6, 12, and 18 months after the operation), patients were asked to fill a questionnaire regarding pelvic function and QoL. The questionnaire was modified from the Bergmark's series [23] and assessed QoL using a score based on 54 items which take into account sexual function (according to DSM-IV criteria) and psychological status according to the short World Health Organization QoL scores [24]. All patients provided a written informed consent to participate in the survey. For bowel and bladder dysfunction, a confirmation was obtained by urodynamic tests and anorectal manometry.

3. Neoadjuvant/adjuvant treatment and follow-up

All the patients classified as FIGO stage IB2–IIB as well as those with stage IIA >4 cm, at pre-operative clinical and radiological examination, were administered 3 cycles of neo-adjuvant chemotherapy (NACT) with associated cisplatin/carboplatin and paclitaxel +/− iphosphamide prior to surgery: in case of progressive or stable disease after NACT, surgery was not accomplished and patients were submitted to chemoradiation. Adjuvant pelvic/para-aortic radiotherapy was administered in patients with detection of positive pelvic/para-aortic nodes, parametrial/lympho-vascular spread of disease detected at definitive histology and G3 histotypes, and in case of involved surgical resection margins (<5 mm), as per the Sedlis criteria [25]. Adjuvant chemotherapy with cisplatin was added in case of positive nodes. The follow-up period lasted from the date of surgery until January 2017. Follow-up consisted of a pelvic examination every 3 month during the first 2 years, twice a year from the third to the fifth year, then yearly. Pap smear and thoraco-abdominal CT scan were planned every year. Pelvic recurrences were detected by clinical examination and confirmed, as far as retroperitoneal recurrences, on CT and/or MRI scans. Disease-free survival (DFS) and overall survival (OS) were calculated. DFS was defined as the period from the surgical intervention to the evidence of recurrent disease. OS was defined as the time from date of operation to death.

4. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA). The Students' t-test and Mann-Whitney U test were used for comparison of continuous variables as appropriate. The Fisher's exact test and the χ^2 test were used for categorical variables. All the tests were 2-sided and statistical significance was assigned at the level of $p < 0.05$. Survival rates were calculated according to the Kaplan-Meier method. The corresponding p-value was computed using the log-rank (Mantel-Cox) test.

RESULTS

1. Patients group, pre-operative and operative data

A total of 301 consecutive patients were included in this study: 170 in the TL-NSRH group and 131 in the OA-NSRH group. Preoperatively, 2 (1.2%) and 1 (0.8%) patients had urodynamically proven detrusor overactivity and 1 (0.6%) and 0 patient had mixed urinary incontinence in the TL-NSRH and OA-NSRH groups, respectively. Seven patients were

excluded from the analysis because of stable/progressive disease after NACT. Three patients (1.8%) in the TL-NSRH group and 3 (2.3%) in the OA-NSRH group reported mild/moderate difficulty to empty the bladder (with partial Valsalva maneuver) but at urodynamic studies, no neurologic impairment of detrusor muscle was detected. This impairment was related to urethral stenosis, confirmed by cystoscopy, and elderly age: 5 of these 6 patients were ≥70 years. No patient reported severe impairment of rectal function.

All the 301 patients underwent type C1 NSRH with systematic pelvic lymphadenectomy for invasive cervical cancer. Fifty-six of them, were submitted to additional para-aortic lymphadenectomy: 27 and 39 in the TL-NSRH and OA-NSRH groups, respectively. No conversion to laparotomy was registered in the TL-NSRH group. No differences were found in terms of demographic and pathological characteristics between groups, although a tendency towards a higher stage and a lower rate of adenocarcinomas in the OA-NSRH was noted (**Table 1**). No difference was noted in terms of the proportion of patients who underwent neoadjuvant chemotherapy.

Seventy-two (42.4%) patients in the TL-NSRH and 69 (52.6%) in the OA-NSRH group received adjuvant treatment (p=0.09). Namely, in the TL-NSRH 24 (14.1%) patients underwent radiation therapy only, 44 (25.9%) had chemotherapy + radiotherapy and 4 (2.3%) patients received chemotherapy only; in the OA-NSRH 25 (19.1%) and 44 (33.6%) patients received radiation therapy only and chemo-radiation, respectively, in the post-operative period.

Table 1. Baseline characteristics of the patients included and peri-operative/histological details

Characteristic	TL-NSRH (n=170)	OA-NSRH (n=131)	p-value
Age (yr)	48 (26–78)	50 (26–79)	0.259
BMI (kg/m^2)	22.6 (17.5–40)	22.9 (17.1–39)	0.653
Stage			0.085
IA2	34 (20)	18 (13.7)	
IB1	78 (45.9)	56 (42.7)	
IB2	17 (10)	24 (18.3)	
IIA	18 (10.6)	23 (17.6)	
IIB	17 (10)	10 (7.6)	
Grading			0.654
1	16 (9.4)	10 (7.6)	
2	107 (62.9)	89 (67.9)	
3	47 (27.6)	32 (24.4)	
Histology			0.066
Squamous	122 (71.8)	109 (83.2)	
Adenocarcinoma	40 (23.5)	18 (13.7)	
Others	8 (4.7)	4 (3.1)	
Lymphovascular space involvement	42 (24.7)	29 (22.1)	>0.999
Neoadjuvant chemotherapy	51 (30)	50 (38.2)	0.137
Operative time (min)	208 (95–350)	220 (100–400)	0.453
Blood loss (mL)	200 (20–1,400)	400 (50–1,400)	0.009
Hospital stay (days)	3 (2–31)	5 (4–28)	0.007
Pelvic lymphadenectomy	170 (100)	131 (100)	>0.999
No. of pelvic nodes removed	22 (1–65)	21 (8–70)	0.723
Patients with positive pelvic nodes	33 (20.9)	30 (22.9)	0.476
Para-aortic lymphadenectomy	27 (15.9)	29 (22.1)	0.179
No. of para-aortic nodes removed	18 (4–40)	13 (1–40)	0.338
Patients with positive para-aortic nodes	9 (5.5)	10 (7.6)	0.480
Adjuvant therapy	72 (42.4)	69 (52.6)	0.076
Recurrence	20 (11.8)	11 (8.4)	0.341
Dead of disease	14 (8.2)	9 (6.9)	0.825

Values are presented as median (interquartile range) or number (%).
OA-NSRH, open abdominal; TL-NSRH, total laparoscopic nerve-sparing radical hysterectomy.

Table 2. Post-operative complications within 7 days

Type of early post-operative complication (within 7 days)	TL-NSRH (n=170)	OA-NSRH (n=131)	p-value
Hemoperitoneum	2 (1.2)	0	0.507
Post-operative anemia	1 (0.6)	10 (7.6)	0.014
Urinary retention	13 (7.6)	20 (15.2)	0.041
Urinary incontinence	1 (0.6)	1 (0.8)	>0.999
Urinary tract infection	2 (1.2)	2 (1.5)	>0.999
Sepsis	1 (0.6)	0	>0.999
Pelvic collection	1 (0.6)	0	>0.999
Dynamic ileum	0	1 (0.8)	0.435
Pyrexia	2 (1.2)	1 (0.8)	>0.999
Bowel subocclusion	0	1 (0.8)	0.435
Lower limb hyposthenia	1 (0.6)	5 (3.8)	0.089

Values are presented as number (%).
OA-NSRH, open abdominal; TL-NSRH, total laparoscopic nerve-sparing radical hysterectomy.

2. Clinical and functional outcomes and QoL

Intra-operative complications included 7 vs. 34 cases of intra-operative blood loss >500 mL in the TL-NSRH vs. OA-NSRH, respectively (p<0.01). Two organ injuries in the TL-NSRH group and 4 in the OA-NSRH group were observed (p=0.25): 2 case of bladder lesions (successfully repaired laparoscopically) in the TL-NSRH group, 2 cases of ureteral injury repaired intraoperatively with positioning of a stent, one vena cava injury and one bowel lesion in the OA-NSRH group. Post-operative complications within the first 7 days after intervention are summarized in **Table 2**. Two patients (1.2%) in the TL-NSRH group presented hemoperitoneum and required reoperation the day after RH. Both the re-operations were completed laparoscopically. The site of bleeding was at the level of the residual parametrium in both cases. Thirty-three cases of post-operative urinary retention occurred within 7 days in the overall population; the rate of immediate post-operative urinary retention was higher in the OA-NSRH group. All these cases resolved within 21 supplementary days of bladder self-catheterization.

Post-operative complications occurring >7 days after the operation are listed in **Table 3**. Regarding urologic complications, hydronephrosis occurred in 4 patients (2.4%) in the TL-NSRH group and in 5 (3.8%) patients in the OA-NSRH group, due to post-operative ureteral stenosis (p=0.51). All cases were treated with cystoscopic double-J stent placement and they had spontaneous resolution after 3 months. Four patients (4.7%) in the TL-NSRH

Table 3. Post-operative complications after >7days

Type of post-operative complication after >7 days	TL-NSRH (n=170)	OA-NSRH (n=131)	p-value
Dysuria	5 (2.9)	7 (5.3)	0.376
Lymphocele	10 (5.8)	15 (11.5)	0.094
Lymphedema	10 (5.8)	8 (6.1)	>0.999
Lymphorrhea	13 (7.6)	0	<0.001
Ureteral fistula	4 (2.3)	6 (4.6)	0.340
Vesico-vaginal fistula	1 (0.6)	1 (0.8)	>0.999
Ureteral stenosis	4 (2.3)	5 (3.8)	0.509
Hydronephrosis	4 (2.3)	5 (3.8)	0.509
Thrombophlebitis	0	1 (0.8)	0.435
Vaginal cuff dehiscence	4 (2.3)	0	0.135
Abdominal wound dehiscence	0	1 (0.8)	0.435
Self-catheterization at discharge	24 (14.1)	34 (25.9)	0.012

Values are presented as number (%).
OA-NSRH, open abdominal; TL-NSRH, total laparoscopic nerve-sparing radical hysterectomy.

group and 6 patients (4.6%) in the OA-NSRH group presented ureteral fistula within 22 days after surgery. In all cases stent placement for 3 months was sufficient to restore the ureteral integrity. In 2 of these patients a laparoscopic uretero-neocystostomy with psoas-hitch was necessary, due to fibrotic ureteral stenosis after the healing of the fistula. One patient in each group had a vesico-vaginal fistula, which was treated conservatively, with an indwelling Foley catheter in the bladder for 2 months. After catheter removal, resolution of the fistula was observed in the patient in the TL-NSRH group, whereas the patient in the OA-NSRH underwent re-laparotomy, fistula repair and omental flap.

The rate of lymphorrhea was higher in the TL-NSRH group, whereas the rate of self-catheterization at discharge was higher in the OA-NSRH group. The days of self-catheterization were <3 in all cases but one (6 days in the TL-NSRH group). One (0.6%) patient in the TLNSRH group died 27 days after surgery due to encephalitis caused by sudden deterioration of her HIV infection. Of the remaining patients, 132 (78.1%) vs. 126 (96%) gave their consent to complete the study questionnaire at the 1-month follow-up in the TL-NSRH vs. OA-NSRH groups respectively. At 6, 12, 24 and 36 months, 116 vs. 98, 111 vs. 97, 100 vs. 91, and 82 vs. 69 patients completed the questionnaire, in the TL-NSRH vs. OA-NSRH, respectively. The questionnaire was divided into 3 sections.

Data about urinary, bowel and fecal function are provided in **Table 4**. The patients with pre-operative urinary incontinence did not show significant worsening post-operatively. Patients in the OA-NSRH group were more likely to experience urinary incontinence and, after 12 months follow-up, urinary retention. No patient in the TL-NSRH group vs. 5 (5.5%) in the OA-NSRH group had complete urinary retention at the >24-month follow-up (p=0.02).

Anal incontinence was uncommon, and its percentage was comparable between TL-NSRH and OA-NSRH groups. All the patients experiencing anal incontinence defined their condition as "rare". Fecal constipation was similar between groups up to the 2-year follow-up, but at the last checkpoint it was more common in the OA-NSRH group.

Seventy-one patients (41.7%) and 65 (49.6%) who were sexually active before the operation in the TL-NSRH and OA-NSRH groups, respectively, accepted to complete the questionnaire about sexual activity at the 12-month follow-up. Of them, 62 (87.3%) and 57 (87.7%) recovered sexual activity after surgery in the TL-NSRH and OA-NSRH groups, respectively. Forty-eight (77.4%) and 39 (68.4%) of the women who recovered sexual activity after surgery considered their sexual life as "satisfactory" in 2 groups, respectively (p=0.30). Of them, only 10 (20.8%)

Table 4. Data regarding urinary and fecal continence and sexual function

Postoperative elapsed time	Urinary incontinence		p-value	Voiding difficulties		p-value	Anal incontinence		p-value	Fecal constipation		p-value
	TL-NSRH	OA-NSRH		TL-NSRH	OA-NSRH		TL-NSRH	OA-NSRH		TL-NSRH	OA-NSRH	
Within 1 mo (TL vs. OA 132 vs. 126)	16 (12.1)	25 (19.0)	0.090	24 (18.2)	34 (27.0)	0.101	2 (1.5)	4 (3.2)	0.438	21 (15.9)	21 (16.7)	>0.999
1–6 mo (TL vs. OA 116 vs. 98)	14 (12.1)	25 (25.5)	0.013	21 (18.1)	27 (27.6)	0.103	3 (2.6)	4 (4.1)	0.705	18 (15.5)	21 (21.4)	0.290
6–12 mo (TL vs. OA 111 vs. 97)	14 (12.7)	25 (25.8)	0.009	15 (13.5)	24 (24.7)	0.050	3 (2.7)	4 (4.1)	0.707	15 (13.5)	20 (20.6)	0.196
12–24 mo (TL vs. OA 100 vs. 91)	14 (14.0)	24 (26.4)	0.010	10 (10.0)	23 (25.3)	0.007	3 (3.0)	3 (3.3)	>0.999	13 (13.0)	20 (21.9)	0.126
>24 mo (TL vs. OA 82 vs. 69)	11 (13.5)	22 (31.9)	0.009	3 (3.7)	18 (26.1)	<0.001	3 (3.7)	3 (4.3)	>0.999	8 (9.8)	17 (24.6)	0.017

Values are presented as number (%).
OA-NSRH, open abdominal; TL-NSRH, total laparoscopic nerve-sparing radical hysterectomy.

Table 5. Sexual dysfunction after 12 months

| Type of sexual dysfunction	TL-NSRH (n=71)	OA-NSRH (n=65)
Reduction of frequency of intercourses	20 (28.2)	28 (43.1)
Dyspareunia	14 (19.7)	17 (26.2)
Vaginal dryness	24 (33.8)	35 (53.8)
Use of lubricants	22 (31.0)	27 (41.5)
Postcoital bleeding	4 (5.6)	3 (4.6)
Reduced libido	16 (22.5)	29 (44.6)

Values are presented as number (%).
OA-NSRH, open abdominal; TL-NSRH, total laparoscopic nerve-sparing radical hysterectomy.

in the TL-NSRH group and 5 (12.8%) in the OA-NSRH group had received radiation therapy; of the 14 and 18 patients in the TL- and OA-NSRH group with an unsatisfactory quality of sexual life, 11 (78.5%) and 15 (83.3%) had received adjuvant radiation therapy in the 2 groups, respectively (p<0.001 for both groups). **Table 5** summarizes data regarding sexual function at 12 months post-operatively.

The performance or not of para-aortic lymphadenectomy did not affect functional outcomes.

3. Survival and follow-up

The median follow-up was 30 (6-88) and 39 (8-85) months in the TL-NSRH and OA-NSRH groups, respectively. Twenty (11.8%) in the TL-NSRH and 11 (8.4%) patients in the OA-NSRH had a recurrence of disease (p=0.44) and 14 (8.2%) and 9 (6.9%) died of disease during follow-up, respectively (p=0.83). No patient was lost to follow-up. Three deaths in the TL-NSRH group were unrelated to cervical cancer (1 cerebral stroke, 1 encephalitis due to HIV progression and 1 myocardial infarction). The first relapse of disease was in the pelvis in 14 patients (70%) and at distant sites in 6 (30%) patients in the TL-NSRH. In the OA-NSRH group the first location of recurrence was the pelvis in 7 (63.6%) cases and distant sites in 4 (36.4%) cases. Cumulative DFS was 88.2%. Stage-specific DFS was 100% for stage IA2 (0 recurrences out of 34 patients) in both groups, 91.1% vs. 94.7% for IB1, 88.2% vs. 87.5% for IB2, 73.3% vs. 73.6% for IIA, 70.6% vs. 90% for IIB disease in the TL-NSRH vs. OA-NSRH groups, respectively. Stage-specific OS rates were 100% for stage IA2 in both groups, 91.1% vs. 94.6% for IB1, 88.2% vs. 87.5% for IB2, 67.7% vs. 91.3% for IIA and 93.3% vs. 90% for IIB disease in TL-NSRH vs. OA-NSRH groups, respectively. Kaplan-Meyer curves of disease-free (Log-rank Mantel-Cox test p=0.15) and OS (p=0.66) for the overall population are reported in **Figs. 1** and **2**. A tendency towards earlier recurrences was noted in the laparoscopic group, but
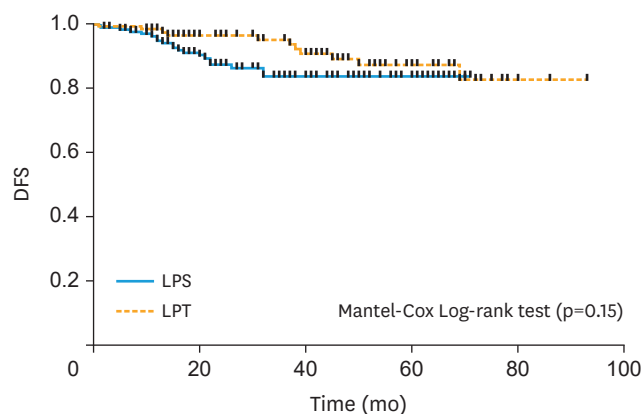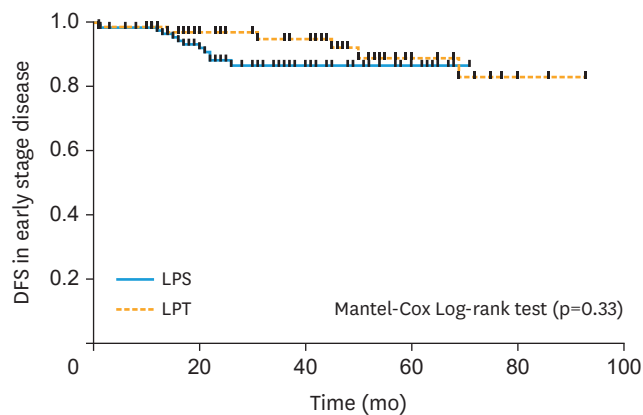

Fig. 1. DFS of the study cohort according to the surgical approach.
DFS, disease-free survival; LPS, laparoscopic surgery; LPT, laparotomy.
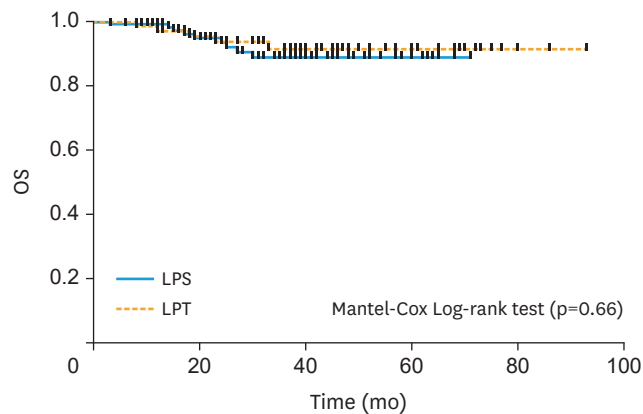
Fig. 2. OS of the study cohort according to the surgical approach.
LPS, laparoscopic surgery; LPT, laparotomy; OS, overall survival.

Fig. 3. DFS in early stage disease.
DFS, disease-free survival; LPS, laparoscopic surgery; LPT, laparotomy.

in the long-term the DFS curves were superimposable. **Fig. 3** reports the DFS for early stage-disease in the 2 groups (p=0.33).

DISCUSSION

A recent review and meta-analysis of studies comparing outcomes of nerve-sparing laparoscopic RH to those of standard minimally-invasive RH reported a total of 325 nerve-sparing procedures from 7 independent series [14]. The authors concluded that NSRH is more time-consuming but may be associated with similar oncological outcomes compared to non-nerve sparing radical procedures. The evaluation of functional outcomes in the included series was extremely poor and the level of evidence was low [14]. In this context, the recommendation of performing type C1 RH whenever possible, relies more on anatomical and logical considerations, rather than on scientific evidence.

The present study represents one of the largest available series of nerve-sparing laparoscopic vs. open abdominal radical hysterectomies for cervical cancer and it includes an extremely detailed and thorough evaluation of peri-operative surgical outcomes and post-operative pelvic function.

The main findings of our study are: first, the risk of surgical complications of this technically-challenging procedure is acceptable; we observed 25 (8.3%) cases of intra-/post-operative urinary tract lesions in the overall population, although our cohort included patients with locally-advanced disease, submitted to NACT [4,26]. Second, we provide a large amount of data showing that the rate of pelvic dysfunction after this type of radical surgery is low, thus demonstrating that preservation of the neural autonomic fibers has actually a positive effect on patients' post-operative wellbeing and QoL. Third, the rate of pelvic dysfunction is lower when laparoscopic surgery is accomplished, rather than traditional open abdominal surgery. Fourth, the oncological outcomes and the survival rates of TL-NSRH well compare with the available series of non-nerve-sparing laparoscopic procedures [27]. Similar to the LACC trial [17], we observed a tendency towards earlier recurrences in the group of patients submitted to laparoscopic surgery. However, with extended follow-up, the DFS curves of laparoscopic and open abdominal procedures move closer and finally overlap. On the other hand, OS was quite similar between the 2 groups in our series.

In the era post-LACC trial, the presentation of series of laparoscopic radical hysterectomies for cervical cancer, may be unpopular. However, some considerations have spurred us to publish the present article: 1) one of the main criticisms against the LACC trial is the inclusion of many centers with not renowned experience in minimally invasive techniques for cervical cancer; the criterion for including a center in that trial was the evaluation by a central committee of 2 unedited videos of endoscopic RH. The operators involved in laparoscopic procedures have a solid background in advanced minimally-invasive surgery. 2) The data presented have been collected before the publication of the LACC study. 3) Our oncological data well compare with an important historical series by Landoni et al. [2] describing the use of open surgery in cervical cancer, and including more favorable cases. The very good results of open surgery in the LACC trial appear unprecedented and difficult to be replicated. 4) Our thorough analysis of the outcomes of nerve-sparing surgery performed on a considerable number of patients may be helpful for pre- and post-operative counseling and could be at least partly independent of the type of surgical approach used. 5) The observation that urinary incontinence, voiding difficulties and fecal constipation, although generally low, were more common among patients submitted to OA-NSRH may imply an important finding, i.e. that the magnified view of the laparoscope may allow a more subtle and precise identification of the pelvic autonomic fibers, with a more efficient sparing of nerves and function.

It is well accepted that bladder, colorectal and sexual dysfunction affect the long-term recovery of patients undergoing RH for cervical cancer. This type of outcome depends on the disruption of the pelvic autonomic nerves during resection of the lateral and posterior parametria. Specific steps of RH may cause surgical neuro-ablation of autonomic fibers leading to or belonging to the pelvic plexus (PP). The injured neural structures during RH are: the superior hypogastric plexus (ortho-sympathetic) during presacral and para-aortic lymph-node dissection; the hypogastric nerves (HNs - ortho-sympathetic) during resection of uterosacral and rectovaginal ligaments; the pelvic splanchnic nerves (PSNs; parasympathetic) and the PP (mixed ortho- and parasympathetic) during resection of the cardinal ligament in the lateral part of the parametrium and during resection of the vesicovaginal ligaments and paracolpia in the caudad anterior part of the parametrium [28].

Thanks to the enhanced view of the laparoscopes, the performance of nerve-sparing surgery using a minimally-invasive approach appears extremely precise and allows a careful and respectful dissection of the "*pars vasculosa*" from the "*pars nervosa*" of the parametrium [29,30],

which can be resected with an adequate oncological radicality but at the same time sparing the visceral efferent branches of the PP and finally resulting in lower bladder, ano-rectal and sexual dysfunction.

In our experience, the first step for a safe NSRH is the knowledge of the anatomy of the female pelvis and pelvic ligaments. To better identify neural fibers and surgical landmarks, avascular spaces are routinely developed: typically, the medial and lateral (Latzko's space) pararectal spaces are dissected, in order to achieve different dissection planes, leading to the Deep Uterine Vein and to the origin of the parasympathetic PSN at the sacral roots [26]. According to the series by Ercoli et al. [30], it is anatomically possible to identify 3 main groups of visceral efferent fibers, leaving the PP, directed to the target viscera:

a) The medial efferent bundle: a group of thin fibers directed medially toward the rectum running through the mesorectum
b) The cranial efferent bundle: a group of thin fibers directed cranially toward the uterus running through the parametrium
c) The anterior efferent bundle: a group formed by 3 or four main fibers directed anteriorly towards the bladder and the vagina, running through the paracervix

Regardless of the surgical approach, the accomplishment of an adequate NSRH mandates to reveal the PP with its efferent groups of fibers and to transect only the uterine branches arising from the cranial efferent bundle. In this way, bilateral preservation of HN, PSN and medial and anterior efferent bundles from the PP, is achieved [6,30,31].

In recent years, the importance of NSRH in cervical cancer has become even more evident, considering that more than 54% of women diagnosed are younger than 50 years of age [1]. Since 5-year survival has been reported between 88%–97% after RH for early stage node-negative cervical cancer [2,17,32], the definition of procedures with a lower impact on post-operative QoL appears crucial. Unfortunately, the main limitation of the available studies on this issue is the lack of adequate analysis of the post-operative pelvic dysfunction and the short follow-up period, particularly in terms of QoL and functional outcomes.

Concerning bladder function, our study shows that 12–24 months after the operation no patients in the laparoscopic group and only 5 in the overall cohort complained of complete urinary retention: a prolonged period of follow-up is therefore essential to detect the real bladder dysfunction rates after RH [33]. This aspect may reflect the fact that nerve-sparing radical procedure actually spare at least some visceral fibers of the PP, even in cases in which denervation seems evident. However, in case of partial neural damage, a long time may be required by the "survivor" visceral fibers of the PP for sprouting and increasing their connections with the target viscera.

As previously described, rectal dysfunctions can occur after laparoscopic RH [34]. Internal and external sphincters contract by coordination of parasympathetic and sympathetic fibers, while defecation involves the interaction of voluntary and involuntary pathways. It is not easy to quantify the grade of the most common bowel functional complaints, such as constipation, incomplete evacuation, tenesmus, or diarrhoea. However, some studies show a negative effect of RH on bowel function (higher volumes of rectal distension to elicit the anorectal inhibitory reflex, slow transit constipation, tenesmus, diarrhoea, faecal leakage, and flatus incontinence) [35]. Non-adequate radical mobilization of the rectum and radical resection of the dorsal and lateral paracervix can result in partial damage to the

autonomic innervations of the rectum [31]. Long et al. [36] identified a total of 17 clinical trials in a recent systematic review and meta-analysis on NSRH. They reported only 2 studies that evaluated data about the time of recovery of the anorectal function: the time to first defecation was significantly shorter in the NSRH group in comparison with RH group [37,38]. However, that review does not take into account the rate of incontinence, constipation and soiling, after RH [36]. Our results analyze in detail these aspects and show no case of "frequent" fecal incontinence at the last follow-up; 16.6% of patients complained of moderate constipation, with no impact on QoL after surgery. Of note, the majority of these patients reported constipation even before RH.

Considering sexual function, it is well known that after RH, women experience changes in their vaginal anatomy and function, resulting in sexual dysfunction for many patients. These changes include shortening and inelasticity of the vagina, resection of the paracolpia, and loss of ovarian function [7]. Of course, radiotherapy is a contributing factor to sexual dysfunction, with the associated loss of elasticity, vaginal dryness, shortening and consequent dyspareunia, due to fibrosis and vascular reaction of the irradiated tissues. Moreover, we must take into account also the psychological impact of a diagnosis of cervical cancer. In our series, only a small proportion of the women included were sexually active. This may be due in part to the fact that approximately one third of patients was >60 years and in part to the fact that the diagnosis of cervical disease had a detrimental impact on the sexuality of the women included. Overall, our data show good results in terms of sexual function and >70% of patients reported a satisfactory sexual life and unchanged libido. A recent study by Pieterse et al. [34] on a series of 229 patients (123 NSRH; 106 conventional RH) evaluated with a validated questionnaire) showed a significant sexual deterioration both at 12 and 24 months after surgery for the total study group (nerve sparing and classic RH). The complaints included absence of sexual activity, narrow or short vagina, pain during intercourse, little or no lubrication during sexual activity, and an overall unsatisfactory for sexual life. However, sexual activity increased significantly after 12 and 24 months of follow-up compared with the situation before the treatment. The authors concluded that there was not a clear difference in self-reported sexual life between groups of women treated with different surgical procedure (nerve sparing versus non nerve-sparing technique). Conversely, a previous study by our group shows that NSRH is associated with significantly better sexual outcomes, compared with the "classical" RH technique [7].

Regarding oncologic outcomes, we acknowledge that the concerns regarding minimally invasive surgery in cervical cancer represent nowadays a major barrier about its use in this malignancy. However, we believe that this argument deserves a thorough reconsideration and new data are needed to confirm or deny the detrimental effect of endoscopic techniques. In any case, our survival data are comparable with the majority of the available reports on cervical cancer and therefore we believe that they can be considered encouraging [2,25,39,40]. In our opinion, final words on the role of minimally invasive surgery in cervical cancer are still to be pronounced.

Among the limitations of the present study we mention the retrospective design, the relatively small number of patients included and the inclusion of both early and locally-advanced stages submitted to neoadjuvant chemotherapy. The detailed collection of pre-, intra- and post-operative data, and the specific assessment of functional outcomes mitigate the possible reporting bias due to the retrospective nature of our analysis and represent the major strengths of this study. Regarding the inclusion of patients submitted to neoadjuvant

treatment, a large, multicentre propensity-matched analysis by Ghezzi et al. [39] has shown that the use of laparoscopic surgery in this specific setting is adequate and provides optimal oncological results. Another possible limitation is the inherent selection bias: we noticed a higher proportion of patients with larger tumors in the open abdominal group; this raises the problem of a possible imbalance between the 2 groups both in terms of oncologic and functional outcomes. Moreover, the exclusion of the 7 patients who were refractory to NACT may have biased our survival analysis regarding locally-advanced disease. We also acknowledge that several factors, apart from the type of surgical approach, affect post-operative urinary and bowel function following NSRH, such as tumor size, urinary tract infection as well as individual surgeon's technique. To possibly correct for at least a part of these factors, it would be interesting to perform a study comparing pelvic function following NSRH with vs. without NACT. In conclusion, our study shows that TL-NSRH is a feasible, safe and effective procedure that conjugates adequate radicality with an improvement in post-operative functional outcomes. Irrespective of the surgical approach chosen (minimally-invasive or open) and outside of the aseptic setting of clinical trials, our data provide a reliable picture of the everyday clinical scenario in patients affected by early-stage as well as locally advanced cervical cancer. These data may serve as the basis for clinical counselling and future discussions on this relevant topic.

SUPPLEMENTARY MATERIALS

Supplementary Data 1
Operative technique

Click here to view

Supplementary Data 2
Questionnaire

Click here to view

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