

Original Article



Laparoscopic vs. robotic-assisted laparoscopy in endometrial cancer staging: large retrospective single-institution study

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OPEN ACCESS

Received: Nov 6, 2020
Revised: Jan 9, 2021
Accepted: Jan 29, 2021

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ABSTRACT

Objective: The aim of this study is to analyze and draw the potential differences between the robotic-assisted surgery (RS) and the laparoscopy (LPS) in endometrial cancer staging.

Methods: In this single-institution retrospective study we enrolled 1,221 consecutive clinical stage I–III endometrial cancer patients undergone minimally invasive surgical staging. We compared patients treated by LPS and by RS, on the basis of perioperative and oncological outcomes (disease-free survival [DFS] and overall survival [OS]). A sub-analysis of the high-risk endometrial cancer population was performed in the 2 cohorts.

Results: The 2 cohorts (766 treated by LPS and 455 by RS) were homogeneous in terms of perioperative and pathological data. We recorded differences in number of relapse/progression (11.7% in LPS vs. 7% in RS, $p=0.008$) and in number of deaths (9.8% in LPS vs. 4.8% in RS, $p=0.002$). Whereas, univariate and multivariate analyses according to DFS and OS confirmed that the surgical approach did not influence the DFS or the OS. In the multivariable analysis the association of the age and grading was significant for DFS and OS. In the sub-analysis of the 426 high risk EC patients (280 in LPS and 146 in RS) the univariate and the multivariate confirmed the influence of the age in DFS and OS, independently of the minimally invasive approach.

Conclusions: In our large retrospective analysis, we confirmed that the RS and LPS have similar efficacy and safety for endometrial cancer staging also for the high-risk endometrial cancer patients.

Keywords: Endometrial Cancer; Laparoscopy; Robotic Surgical Procedures; Gynecologic Neoplasms

INTRODUCTION

Endometrial cancer (EC) is the fourth most common malignancy in developed countries, and with over 60,000 cases diagnosed each year represents the most diffuse gynecological cancer

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Presentation

This study was presented in September at 2020 International Gynecologic Cancer Society (IGCS) xDigital Annual Global Meeting, as oral poster presentation for original research. We confirm have the permission to reuse the material in this manuscript.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: P.E., F.F.; Data curation: P.E., R.S., C.I., P.T., G.A.; Investigation: P.E., C.I., G.A.S., R.S.; Methodology: P.E., P.T., G.A.; Software: P.T., R.S.; Supervision: S.G., F.F.; Validation: G.A.S., S.G.; Visualization: G.A.S.; Writing - original draft: P.E.; Writing - review & editing: P.E.

in the United States [1]. Approximately in the 80% of cases, the EC is diagnosed when the disease is still confined to the uterus. For this reason, in the early-stage EC the 5-year survival rate reaches approximately 90% and the surgical treatment is not only essential for the cancer comprehensive staging, but potentially represents the principal curative management [2].

Total hysterectomy and bilateral salpingo-oophorectomy with the lymph-nodal assessment is commonly recognized as the first line management for most of the newly diagnosed EC cases [3]. Over the last 30 years, the surgical approach has evolved rapidly. Several studies demonstrated that laparoscopic approach has become the gold standard to perform the EC staging. In fact, laparoscopy (LPS) is superior rather the laparotomic approach in terms of perioperative outcomes, such as lower intraoperative blood loss and postoperative complications rate, demonstrating to be superimposable in terms of oncological outcomes [4-8].

In minimally invasive surgery (MIS) world, besides the standard LPS, nowadays the robotic-assisted laparoscopy (RS) portrays a full-studied and commonly applied surgical alternative approach in EC staging. Its safety and feasibility were deeply investigated in retrospective and prospective analysis, and its main advantages were recognized in the 3-dimensional view, a shorter learning curve and the better dexterity of the robotic arms compared to standard LPS [9]. This last aspect results to be very important in reducing the technical challenges of complex surgical steps, such as in EC obese patients [10,11]. According to some reports, the RS seems to be superior to LPS in terms of perioperative outcome, but results in the literature, even if widely studied, are still controversial about this topic [12-14]. For what concerns the oncological outcome few studies compared RS to LPS and limited and inconclusive results are available in the literature [12,15-17].

Of note, most studies focused on the use of MIS only on women with low and intermediate risk and usually the high-risk EC patients represented only a small portion population in previous studies [8,18].

The aim of this large retrospective and single-institution study is to analyze and draw the potential differences between the RS and the LPS in EC staging, in terms of oncological and perioperative outcomes. Moreover, we further investigated the 2 MIS approaches in the high-risk EC population, to try to give some answers to an unsolved question about this specific sub-set of patients.

METHODS

In this retrospective analysis we enrolled all clinical uterus-confined EC patients undergone MIS surgery at the Gynecologic Oncology Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, between 2009 and 2019. This study was approved by the Institutional Reviewer Board (N° PROT. APROV. IST CICOG-30-10-19/46), and all the participants gave their consent to the use of medical records for research purposes. Study data were collected using REDCap electronic data capture tool and were managed by the Statistics Technology Archiving Research (STAR) Center of our institution. Collected variables included baseline demographic characteristics, perioperative data, final pathology report, adjuvant treatment, surgery related complications up to 6 months and oncological outcomes.

Intraoperative complications were described as any bowel, urinary tract, nerves, vessels injury, and an estimated blood loss (EBL) ≥ 500 mL occurred during the surgical procedure. The postoperative complications were classified according to the Clavien-Dindo classification. All patients received a follow-up examination according to the European Society for Medical Oncology (ESMO)-European Society of Gynaecological Oncology (ESGO)-European Society for Radiotherapy & Oncology (ESTRO) guidelines [19].

The inclusion criteria were: 1) pathological diagnosis of stage I–III EC, 2) International Federation of Gynecology and Obstetrics (FIGO) grading G1–G3, 3) endometrioid and non-endometrioid, 4) staged with MIS approach hysterectomy and bilateral salpingo-oophorectomy, and 5) age over 18 years and American Society of Anaesthesiologist (ASA) score 1–3. Patients were excluded from the study: 1) if they had incomplete medical records, 2) lack of documentation, 3) advanced clinical FIGO stage (IV), 4) positive nodes at preoperative work-up, 5) neoadjuvant therapy, 6) EC staging performed by laparotomy or any other MIS technique (i.e., single-port, mini-laparoscopy, etc.), and 7) synchronous ovarian-EC diagnosis. In case of the intraoperative detection of pelvic or aortic bulky lymph nodes, the carcinomatosis or intrabdominal parenchymal metastasis during the endoscopic exploration, patients were excluded from the study.

The final pathology report was performed by a dedicated pathologist.

Patients suitable for MIS were divided into 2 cohorts: patients undergone standard laparoscopic approach and whom approached by robotic-assisted laparoscopy.

All patients underwent total hysterectomy, bilateral salpingo-oophorectomy plus lymph-nodal assessment. This latter step was conducted by performing the sentinel lymph nodes mapping or the systematic pelvic lymphadenectomy, depending on the evolution in technology and concept of EC staging in the last years [3]. The paraaortic node dissection was performed only in case of positive nodes at the frozen section analysis.

The surgical procedure was conducted by LPS or RS. No specific preoperative data (i.e., age, cancer stage at preoperative imaging, non-endometrioid histology, etc.) influenced the platform choice, except for patients with a body mass index (BMI) >30 kg/m², who had been preferably selected for the robotic approach.

After the final pathological report, each patient was stratified using the ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer, 2016, EC risk groups classification to guide adjuvant therapy in clinical practice [19].

1. Statistical analysis

Oncological data were collected using last institutional follow up, time and location of recurrence and death, in order to calculate the disease-free survival (DFS) and the overall survival (OS). The two cohorts were compared in terms of perioperative, pathological and oncological outcomes (DFS and OS). A sub-analysis of the two cohorts was performed considering only the high-risk EC cases.

Patient's characteristics were described as absolute frequency and percentage for nominal variables and as median (min–max) for continuous variables. Comparisons between the LPS and RS groups were made with Mann-Whitney test or Student's t-test for continuous

variables and χ^2 or Fisher exact test for nominal variables, as appropriate. The normality of continuous variables was assessed with Shapiro-Francia test.

Survival analysis was performed both in terms of DFS and OS. DFS was defined as the time elapsed from first diagnosis to recurrence or last follow-up while OS was defined as the time from first diagnosis to death or last follow-up. Median follow-up was calculated according to the inverted Kaplan-Meier technique. OS and DFS curves were estimated by Kaplan-Meier product limit method and compared by log-rank test. Univariate and multivariate Cox proportional hazards models were applied to evaluate the impact on DFS and OS of surgical approach (LPS vs. RS), age (under vs. equal or over 65 years), BMI (≤ 30 vs. >30 kg/m²), histotype (endometrioid vs. non-endometrioid), grading, lymph vascular space invasion (LVSI), FIGO stage, class risk, post-operative management and pattern of recurrence (only for OS). A subgroup analysis was also performed for high-risk class patients. The parameters were selected according to their clinical relevance and only those with a $p < 0.05$ at univariate analysis were included in the multivariable analysis (except for surgical approach). LVSI was evaluated both as dichotomous variable (in terms of presence/absence of lymph vascular invasion) and as ordinal variable (in terms of absence, focal and diffused). In order to avoid collinearity, only presence/absence of LVSI was evaluated at multivariable analysis. All estimates were presented with two-sided 95% confidence intervals (CIs).

Statistical analysis had been performed using STATA software (STATA/IC 13.0 for Windows; StataCorp LP, College Station, TX, USA). Two-sided tests were used, and the significance level was set at $p < 0.05$. No imputation was carried-out for missing data.

RESULTS

Initially, medical records of 1880 patients were retrospectively reviewed from the RED Cap electronic data capture tool. After applying the aforementioned inclusion criteria, we obtained a population of 1,221 women diagnosed with a final histological report of stage I–III EC patients. Of them, 766 patients (62.7%) were treated by LPS and 455 (37.2%) by RS.

The **Table 1** reports patient's demographic, intra-operative, pathological and oncological characteristics according to the type of surgery. No differences were detected for the age and, as expected, a significant difference was reported for BMI between LPS (median, 26.4; range, 15.8–66.1) and RS (median, 33.6; range, 17.3–75.3) group ($p < 0.001$). While the 2 study groups were similar in terms of EBL, they were significantly different in the operative time. In fact, the LPS procedures resulted to be shorter with a median of 160 mins (range=32–680 minutes) compared with and a median of 180 mins (range, 50–545 minutes) for the RS procedures ($p < 0.001$). The lymph nodal assessment was performed more often in the RS (85.5% vs. 67.0%; $p < 0.001$), whereas the number of pelvic lymph nodes removed was similar in the 2 groups. No significant differences in terms of rate intraoperative complications were detected between the two groups ($p = 0.133$). Overall, we recorded 39 intraoperative complications: 6 accidental vessel injuries, 6 bladder and 5 ureteral lesions, 6 bowel injuries, 4 EBL > 500 mL, 7 vaginal lacerations during the use of uterine manipulator or uterine extraction, 1 obturator nerve damage and 4 anesthesiologist complications. Similarly, we observed early and late postoperative complications between the groups ($p = 0.102$ and $p = 0.734$ for early and late complications, respectively). In detail, we recorded 64 early surgery related complications: 24 class I (2 small wound dehiscences, 3 non-specific short-term and

Endometrial cancer: laparoscopy vs. robotic surgery
Table 1. Patients' demographic, intra-operative, pathological and oncological characteristics according to the type of surgery of 1,221 women with endometrial cancer

Characteristics	All (n=1,221)	LPS (n=766)	RS (n=455)	p-value
Age (yr)	62 (25–93)	62 (27–93)	63 (25–87)	0.275
BMI (kg/m ²) [†]	28.5 (15.8–75.3)	26.4 (15.8–66.1)	33.6 (17.3–75.3)	<0.001
Operative time (min) [‡]	170 (32–680)	160 (32–680)	180 (50–545)	<0.001
Estimated blood loss >100 mL	307 (25.1)	182 (23.8)	125 (27.5)	0.148
Lymph nodal assessment	902 (73.9)	513 (67.0)	389 (85.5)	<0.001
Sentinel lymph node	581 (47.6)	299 (39.0)	282 (62.0)	<0.001
Lymphadenectomy	321 (26.3)	214 (30.0)	107 (23.5)	0.089
Intra-operative complications	39 (3.2)	20 (2.6)	19 (4.2)	0.133
Surgery related complications				
Up to 30 days (early)	64 (5.2)	34 (4.4)	30 (6.6)	0.102
Up to 6 months (late)	35 (2.9)	21 (2.7)	14 (3.1)	0.734
Histotype				0.074
Endometrioid	1,022 (83.7)	630 (82.2)	392 (86.2)	
No endometrioid	199 (16.3)	136 (17.8)	63 (13.8)	
Serous	87 (7.1)	58 (7.6)	29 (6.4)	0.230*
Clear cells	10 (0.8)	7 (0.9)	3 (0.7)	
Undifferentiated	8 (0.7)	8 (1)	0 (0)	
Carcinosarcoma	7 (0.6)	5 (0.7)	2 (0.4)	
Mixed	87 (7.1)	58 (7.6)	29 (6.4)	
Grading				<0.001
1	161 (13.2)	111 (14.5)	50 (11)	
2	698 (57.2)	401 (52.3)	297 (65.3)	
3	362 (29.6)	254 (33.2)	108 (23.7)	
LVSI [§]	394/1,221 (32.3)	251/766 (32.8)	143/455 (31.4)	0.628
Focal	153/352 (43.5)	96/226 (42.5)	57/126 (45.2)	0.616
Diffused	199/352 (56.5)	130/226 (57.5)	69/126 (54.8)	
No. of pelvic lymph nodes removed	13 (1–49)	12 (1–49)	13 (1–47)	0.120
Stage				0.448
IA	717 (58.7)	451 (58.9)	266 (58.5)	
IB	266 (21.8)	173 (22.6)	93 (20.4)	
II	81 (6.6)	45 (5.9)	36 (7.9)	
IIIA–IIIB	36 (2.9)	25 (3.3)	11 (2.4)	
IIIC1–IIIC2	121 (9.9)	72 (9.4)	49 (10.8)	
Risk class group				0.376
Low	495 (40.5)	298 (38.9)	197 (43.3)	
Intermediate	93 (7.6)	57 (7.4)	36 (7.9)	
High-intermediate	207 (17)	131 (17.1)	76 (16.7)	
High	426 (34.9)	280 (36.6)	146 (32.1)	
Post-operative management				0.292
Follow up	566 (46.4)	354 (46.2)	212 (46.6)	
Chemotherapy	380 (31.1)	250 (32.6)	130 (28.6)	
Radiotherapy–brachytherapy	23 (1.9)	12 (1.6)	11 (2.4)	
Chemotherapy+radiotherapy	252 (20.6)	150 (19.6)	102 (22.4)	
Relapse/progression	122 (10.0)	90 (11.7)	32 (7.0)	0.008
Pattern of disease				0.297
Centro-pelvic	33 (27)	24 (26.7)	9 (28.1)	
Lymphatic	20 (16.4)	16 (17.8)	4 (12.5)	
Hematogenous	22 (18)	17 (18.9)	5 (15.6)	
Mesothelial	9 (7.4)	7 (7.8)	2 (6.3)	
Mixed	38 (31.1)	26 (28.9)	12 (37.5)	
Death	97 (7.9)	75 (9.8)	22 (4.8)	0.002

Results are presented as number (%) or median (min–max) as appropriate. Bold font highlights statistically significant value.

BMI, body mass index; LPS, laparoscopy; LVSI, lymph vascular space invasion; RS, robotic-assisted surgery.

*Endometrioid vs. serous vs. clear cells vs. undifferentiated vs. carcinosarcoma vs. mixed. †Information available for 1,186/1,221 patients. ‡Information available for 1,126/1,221 patients. §Information available for 352/394 patients. ||Information available for 524/534 patients who underwent to pelvic lymphadenectomy.

self-limited electrocardiographic anomalies, 1 small lymphocele, 3 postoperative fever, 15 other self-limited respiratory or neurological or physical alterations); 27 class II (3 wound

infective dehiscences, 4 cardiac fibrillations, 2 postoperative diarrhea, 7 postoperative blood transfusions, 2 sepsis, 2 urinary infections, 4 deep vein thrombosis, 2 pelvic abscess, 1 oxygen desaturation attack); 12 class IIIa/IIIb (4 vaginal cuff dehiscences, 2 drained plural effusions, 1 drained septic lymphocele, 1 urinary sepsis, 2 vesico-vaginal fistulas, 1 pneumothorax, 1 ureteral reimplantation) and 1 class V post-operative complication. Comparable data were reported in terms of histotype, risk group type, LVSI rate, FIGO stage after surgical staging. The only significant difference was reported in cancer grading, with more G3 were detected at the definitive diagnosis in LPS group ($p < 0.001$).

In the LPS group more relapses rather than in the RS group were registered (11.7% vs. 7.0%; $p = 0.008$), though no differences were reported in the pattern of recurrent disease. Accordingly, more deaths occurred in LPS group (9.8% vs. 4.8%; $p = 0.002$). Nevertheless, with a median follow up of 17.7 months (95% CI=16.4–18.8), analyzing the Kaplan-Meier survival curves (**Fig. 1**), no statistically significant differences were appreciable between the LPS and the RS, both in terms of DFS ($p = 0.080$) and OS ($p = 0.070$) (**Fig. 1A and B**). The 3-years OS in the LPS patients was 88.4% versus 92.9% of RS patients, while 5 years after diagnosis, the overall survival probability was 81.4% for LPS versus 85.2% for RS. Univariate and multivariate analyses conducted on the overall study population according to DFS and OS confirmed that the surgical approach did not influence the DFS or the OS (**Table 2**). At the multivariate analysis, the age > 65 years (hazard ratio [HR]=1.45; $p = 0.048$) and the grading G3 (HR=3.08; $p = 0.047$) have had remarkable influence in DFS, and only the age > 65 years in OS (HR=3.43; $p < 0.001$). Moreover, the different pattern of relapse was an independent factor for OS: centro-pelvic HR 3.15, lymphatic HR 6.17, hematogenous HR 8.05, mesothelial 32.64 and mixed recurrence HR 12.39.

In addition, as reported in the methods, we performed a sub-analysis in the 426 high-risk EC patients: 280 in the LPS and 146 in the RS group.

As reported in **Fig. 2**, the surgical approach did not afflict the Kaplan-Meier curves, both in terms of DFS and OS (HR=0.66; $p = 0.143$ and HR=0.74; $p = 0.333$, respectively). In this subgroup, the 3-years OS in the LPS was 77.4% versus 82.3% of RS patients, while 5 years after diagnosis, the OS probability was 66.9% for LPS versus 72.8% for RS.

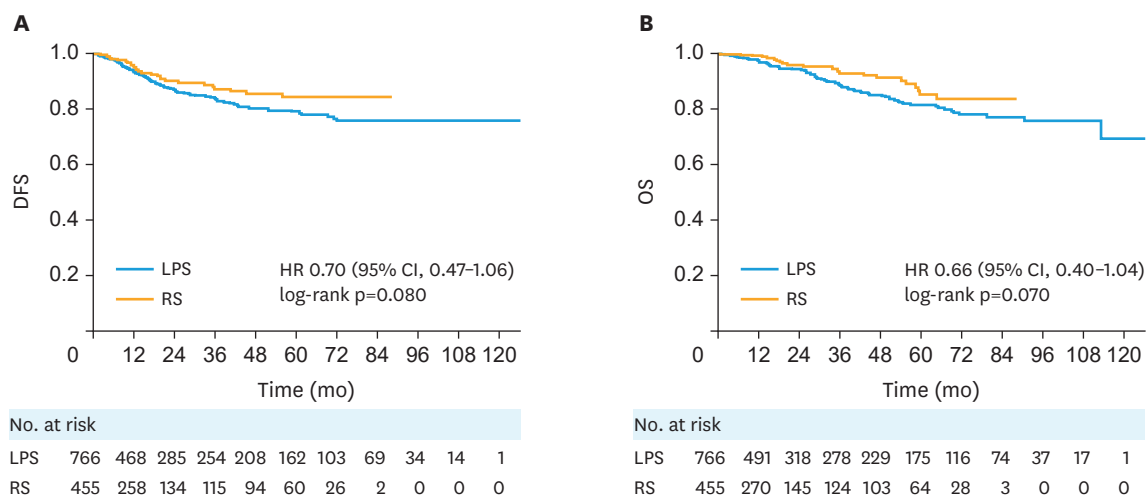


Fig. 1. Survival curves showing the DFS and the OS trends of LPS and RS approaches in overall study population. DFS, disease-free survival; LPS, laparoscopy; OS, overall survival; RS, robotic-assisted laparoscopy.

Endometrial cancer: laparoscopy vs. robotic surgery
Table 2. Univariate and multivariate analysis of patients characteristics according to disease free and OS

Characteristic	Patients at risk	No. of events	DFS				No. of events	OS			
			Univariate		Multivariate			Univariate		Multivariate	
			HR (95% CI)	p-value	HR (95% CI)	p-value		HR (95% CI)	p-value	HR (95% CI)	p-value
Surgical approach											
LPS	766	90	1.00		1.00		75	1.00		1.00	
RS	455	32	0.7 (0.47–1.05)	0.081	0.7 (0.46–1.05)	0.086	22	0.64 (0.4–1.04)	0.072	0.9 (0.54–1.5)	0.687
Age											
≤65 years	753	62	1.00		1.00		33	1.00		1.00	
>65 years	648	60	1.75 (1.23–2.5)	0.002	1.45 (1–2.11)	0.048	64	3.82 (2.5–5.83)	<0.001	3.43 (2.15–5.49)	<0.001
BMI (n=1,186)											
≤30 Kg/m ²	965	73	1.00		NI		52	1.00		NI	
>30 kg/m ²	491	44	0.89 (0.61–1.3)	0.545			41	1.22 (0.81–1.83)	0.351		
Histotype											
Endometrioid	1,022	91	1.00		1.00		65	1.00		1.00	
No endometrioid	199	31	2.5 (1.66–3.77)	<0.001	1.38 (0.78–2.47)	0.271	32	3.83 (2.5–5.86)	<0.001	1.24 (0.66–2.36)	0.504
Grading											
1	161	5	1.00		1.00		5	1.00		1.00	
2	698	65	2.81 (1.12–7.01)	0.027	1.78 (0.68–4.69)	0.242	36	1.87 (0.73–4.76)	0.191	1.19 (0.43–3.31)	0.740
3	362	52	6.94 (2.79–17.28)	<0.001	3.08 (1.01–9.37)	0.047	56	6.18 (2.48–15.44)	<0.001	1.45 (0.42–4.97)	0.555
LVSI											
No	827	62	1.00		1.00		51	1.00		1.00	
Yes	294	60	2.30 (1.61–3.28)	<0.001	1.57 (0.95–2.57)	0.076	46	2.12 (1.42–3.15)	<0.001	1.23 (0.65–2.35)	0.529
LVSI (n=1,779)											
No	827	62	1.00		NI		55	1.00		NI	
Focal	153	18	1.33 (0.79–2.24)	0.290			11	0.96 (0.5–1.84)	0.903		
Diffused	159	30	3.02 (1.95–4.67)	<0.001			32	3.86 (2.48–6.02)	<0.001		
Stage											
IA	717	50	1.00		1.00		40	1.00		1.00	
IB	266	31	1.6 (1.02–2.51)	0.039	0.85 (0.44–1.63)	0.622	26	1.65 (1.01–2.7)	0.047	0.88 (0.39–1.99)	0.758
II	81	14	2.98 (1.64–5.39)	<0.001	1.98 (0.83–4.71)	0.123	7	1.87 (0.84–4.18)	0.126	0.9 (0.29–2.76)	0.854
IIIA–IIIB	36	5	2.07 (0.83–5.19)	0.121	0.92 (0.32–2.67)	0.882	5	2.62 (1.03–6.65)	0.042	1.59 (0.47–5.34)	0.451
IIIC1–IIIC2	121	22	3.69 (2.23–6.11)	<0.001	1.88 (0.87–4.07)	0.107	19	3.96 (2.29–6.85)	<0.001	1.06 (0.4–2.85)	0.903
Risk group											
Low	495	21	1.00		1.00		15	1.00		1.00	
Intermediate	93	9	2.09 (0.96–4.56)	0.065	1.84 (0.64–5.32)	0.261	6	1.85 (0.72–4.76)	0.204	0.75 (0.2–2.75)	0.663
High-intermediate	207	26	2.89 (1.63–5.14)	<0.001	1.41 (0.61–3.25)	0.423	19	2.74 (1.39–5.39)	0.004	1.22 (0.45–3.32)	0.695
High	426	66	4.66 (2.85–7.63)	<0.001	1.27 (0.46–3.55)	0.647	57	5.68 (3.21–10.03)	<0.001	1.73 (0.52–5.73)	0.369
Post-operative management											
Follow up	566	33	1.00		1.00		30	1.00		1.00	
Chemotherapy	380	55	2.49 (1.62–3.84)	<0.001	1.11 (0.61–2.04)	0.730	48	2.36 (1.5–3.73)	<0.001	1.09 (0.55–2.18)	0.806
Radiotherapy-brachytherapy	23	1	1.05 (0.14–7.7)	0.960	0.59 (0.08–4.52)	0.611	0	NE		NE	
Chemotherapy+radiotherapy	252	33	3.09 (1.91–5.02)	<0.001	0.98 (0.48–2.03)	0.959	19	1.98 (1.12–3.53)	0.020	0.59 (0.27–1.28)	0.182
Pattern of disease											
None	1,099	0	NI		NI		37	1.00		1.00	
Centro-pelvic	33	33					7	4.54 (2.02–10.2)	<0.001	3.15 (1.37–7.23)	0.007
Lymphatic	20	20					8	8.33 (3.87–17.9)	<0.001	6.17 (2.71–14.03)	<0.001
Hematogenous	22	22					14	12.21 (6.58–22.65)	<0.001	8.05 (4.03–16.08)	<0.001
Mesothelial	9	9					9	38.78 (18.45–81.51)	<0.001	32.64 (13.21–80.67)	<0.001
Mixed	38	38					22	12.62 (7.43–21.43)	<0.001	12.39 (6.79–22.6)	<0.001

BMI, body mass index; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; LPS, laparoscopy; LPT, laparotomy; LVSI, lymph vascular space invasion; NE, not evaluable; NI, not included in the analysis; OS, overall survival; RS, robotic-assisted surgery.

The univariate and multivariate analyses show that only the age >65 years (p=0.003 and p=0.002) and the grading class G3 (p<0.001) impacted in DFS and OS, respectively. Furthermore, these analyses showed that the centro-pelvic recurrence did not influence significantly the OS, whereas the lymphatic (HR=3.56), hematogenous (HR=5.98),

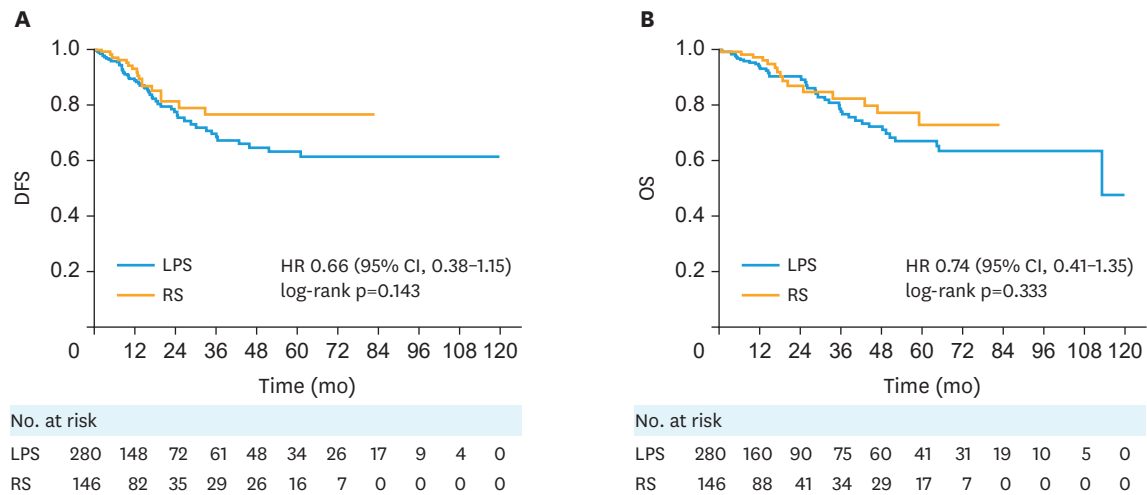


Fig. 2. Survival curves showing DFS and OS trends of LPS and RS approaches in high-risk endometrial cancer population. DFS, disease-free survival; LPS, laparoscopy; OS, overall survival; RS, robotic-assisted laparoscopy.

mesothelial (HR=13.06), and mixed recurrences (HR=8.79) afflicted the survival in univariate and multivariate analysis (**Table 3**).

Off note, we further analyze only the IIIC stages and the non-endometrioid EC in the two population. Again, we did not detect any statistically significant difference between the two approaches in the DFS and OS (HR=0.62; p=0.318 and HR=1.93, p=0.176 for IIIC EC stages and HR=0.50; p=0.103 and HR=0.62; p=0.238 for non-endometrioid EC patients, respectively) (**Supplementary Figs. 1 and 2**).

DISCUSSION

After the LACC study [20], which questioned the role of MIS in early-stage cervical cancer, further large and focused evaluations also for MIS in EC may be mandatory. Moreover, in the literature, the data available about the differences in oncological effectiveness of the two principal MIS approaches (i.e., LPS and RS) are still limited and further analyses are requested.

On these bases, in this large retrospective single-institution study, we extensively investigated the role of LPS and RS in EC staging in terms of perioperative and oncological outcomes. Our results confirm that the RS is almost superimposable to LPS for what concerns the perioperative and the oncological outcomes. These findings were confirmed also in the high-risk EC population, showing that the surgical approaches could be considered equally adequate and reliable in the staging of this subset of patients.

In the last years, several studies have investigated the perioperative outcomes in MIS staging in EC. For what concerns the operative time, in our series the RS was longer than the standard LPS, confirming the assumptions of the vast majority of the literature [12,14,15]. In opposite, Maenpaa et al. [9], reported in a randomized study a different tendency, concluding that RS surgery is faster in EC staging. This difference may be explained by 2 principal aspects in our series: 1) the operative time may have been influenced by the “physiological” single-institution learning curve occurred in 10 years-experience in RS and 2) the prevised different BMI between the 2 populations, whereas similar in the cited trial,

Endometrial cancer: laparoscopy vs. robotic surgery
Table 3. Univariate and multivariate analysis of high-risk patients characteristics according to disease free and OS

Characteristic	Patients at risk	No. of events	DFS				No. of events	OS			
			Univariate		Multivariate			Univariate		Multivariate	
			HR (95% CI)	p-value	HR (95% CI)	p-value		HR (95% CI)	p-value	HR (95% CI)	p-value
Surgical approach											
LPS	280	49	1.00		1.00		42	1.00		1.00	
RS	146	17	0.66 (0.38–1.15)	0.146	0.67 (0.38–1.16)	0.155	15	0.75 (0.41–1.35)	0.335	1.30 (0.68–2.48)	0.421
Age											
≤65 years	222	25	1.00		1.00		16	1.00		1.00	
>65 years	204	41	2.13 (1.29–3.54)	0.002	2.20 (1.33–3.62)	0.003	41	3.95 (2.18–7.17)	<0.001	2.72 (1.44–5.15)	0.002
BMI (n=1,186)											
≤30 kg/m ²	262	40	1.00		NI		28	1.00		NI	
>30 kg/m ²	154	24	1.09 (0.66–1.8)	0.745			26	1.7 (0.99–2.91)	0.055		
Histotype											
Endometrioid	227	35	1.00		NI		25	1.00		1.00	
No endometrioid	199	31	1.27 (0.78–2.06)	0.330			32	1.89 (1.12–3.19)	0.017	1.09 (0.58–2.04)	0.785
Grading											
1	3	0	1.00		1.00		0	1.00		1.00	
2	118	15	3.39E+07	NE	6.04E+07	NE	7	3.09E+07	NE	1.16E+07	NE
3	305	51	7.22E+07 (4.06E+07- 1.28E+08)	<0.001	7.15E+07 (4.00E+07- 1.28E+08)	<0.001	50	8.64E+07 (3.92E+07- 1.91E+08)	<0.001	2.02E+07 (0.81E+07- 5.03E+07)	<0.001
LVSI											
No	222	26	1.00		NI		24	1.00		NI	
Yes	204	40	1.48 (0.91–2.43)	0.117			33	1.32 (0.78–2.24)	0.298		
LVSI (n=399)											
No	202	26	1.00		NI		24	1.00		NI	
Focal	59	11	1.12 (0.55–2.26)	0.759			6	0.64 (0.26–1.57)	0.329		
Diffused	138	22	1.61 (0.91–2.84)	0.101			26	2.02 (1.16–3.54)	0.013		
Stage											
IA	92	9	1.00		NI		11	1.00		NI	
IB	96	16	1.45 (0.64–3.27)	0.377			15	1.03 (0.47–2.24)	0.948		
II	81	14	1.61 (0.69–3.71)	0.268			7	0.61 (0.24–1.58)	0.308		
IIIA–IIIB	36	5	1.13 (0.38–3.36)	0.832			5	0.87 (0.3–2.5)	0.793		
IIIC1–IIIC2	121	22	1.98 (0.91–4.31)	0.084			19	1.27 (0.60–2.66)	0.534		
Post-operative management											
Follow up	55	10	1.00		NI		11	1.00		1.00	
Chemotherapy	139	29	1.06 (0.52–2.17)	0.876			30	1.01 (0.51–2.03)	0.967	0.87 (0.38–2.01)	0.747
Radiotherapy-brachytherapy	3	1	1.64 (0.21–12.9)	0.638			0	NE		3.552E+19 (NE)	NE
Chemotherapy+radiotherapy	229	26	0.70 (0.34–1.46)	0.347			16	0.42 (0.19–0.9)	0.026	0.45 (0.18–1.14)	0.092
Pattern of disease											
None	360	0	NI		NI		21	1.00		1.00	
Centro-pelvic	14	14					2	1.43 (0.34–6.13)	0.626	0.96 (0.22–4.15)	0.959
Lymphatic	13	13					5	3.92 (1.48–10.41)	0.006	3.56 (1.32–9.6)	0.012
Hematogenous	13	13					10	6.65 (3.1–14.26)	<0.001	5.98 (2.65–13.48)	<0.001
Mesothelial	5	5					5	23.28 (8.4–64.54)	<0.001	13.06 (4.19–40.7)	<0.001
Mixed	21	21					14	8.67 (4.36–17.27)	<0.001	8.79 (4.15–18.64)	<0.001

BMI, body mass index; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; LPS, laparoscopy; LPT, laparotomy; LVSI, lymph vascular space invasion; NE, not evaluable; NI, not included in the analysis; OS, overall survival; RS, robotic-assisted surgery.

that may have probably afflicted our results. Based on the results of several studies that have shown specific advantages of RS compared to LPS in obese patients, in our daily practice we generally allocated the RS to the BMI >30 kg/m² patients [10,21]. Moreover, the number of lymph nodal assessment procedures was higher in RS group and this aspect may have been prolonged the operative time in the cohort. Despite these differences, we reported similar perioperative complications rate and EBL between the 2 study groups, confirming the results reported by the aforementioned randomized trial [9]. Corrado et al. [10] previously reported an advantage for the RS compared to LPS in reducing the number of complications in EC

staging. These conflicted conclusions reflect the results in the literature: complications rate is a very heterogeneous outcome in the previous published retrospective studies [22].

To date, the vast majority of published studies mostly investigated the perioperative outcomes in EC staging, and limited data are properly focused on the oncological adequacy and potential differences between the LPS and RS. In this large 10-year single-institution experience we demonstrated that the 2 approaches are similar for this topic. Even if we found a significant difference in number of relapses and consequentially in deaths between the two study groups, this result was demonstrated to be not linked to the surgical platform. Whereas, the multivariate analysis demonstrated that the age > 65 years, the grading and the presence of recurrence influenced the DFS and OS in overall enrolled patients. Furthermore, these findings were confirmed also in a sub-set population of 426 high-risk EC, suggesting that RS and LPS could be considered valid alternatives also in this sub-group of EC patients. In this study, we confirmed the recent findings of Legge et al. [23], demonstrating that the presence of relapse represents a risk factor in reducing the OS, independently of the pattern of recurrence. We did not observe association between different patterns of recurrence and survival in all the study population, but found that, in the high-risk population, the centro-pelvic recurrence was not statistically linked to the OS, confirming the potential curative role of secondary surgery in selected patients.

Classically, previous studies described no differences between MIS and laparotomy in terms of oncological outcomes [8,18,24-26]. The LAP-2 randomized study confirmed that the LPS is comparable to laparotomy in EC staging for both DFS and OS [8]. After this, further investigations reported similar results in robotic EC surgical staging compared to laparotomy [16,17,27]. Following the technological innovation, also the ultra-MIS techniques were demonstrated to be safe and adequate in EC surgery [28-30]. Besides this, the RS and LPS remains worldwide the most diffuse MIS approaches for EC staging [31] and, prior to this study, comparative analysis of RS and LPS are limited. In 2014, Cardenas-Goicoechea et al. [15] reported in 415 EC patients, 14.8% of recurrences in robotic procedures and 12.1% in laparoscopic ones and no significant differences in terms of OS and DFS between RS and LPS (3-years OS, 93.3% vs. 93.6%; 3-years DFS, 83.3% vs. 88.4% in RS and LPS, respectively). Similarly, Corrado et al. [10], in a retrospective matched cohort study including 526 EC patients, reported no differences in survival outcomes among patients who underwent to LPS, RS and laparotomy [9]. In another recent single-institution, retrospective cohort study, Chambers et al. [32], enrolled 1,150 EC patients treated by LPS, single-port and RS. The authors concluded that the surgical platform did not influence the survival in EC patients. Our results are comparable to what reported by these previous studies. Differently by the cited cohort studies, we initially excluded all IV stage EC patients and the oncological results reported in our series were not afflicted by the advanced stages. So, the results of this study provide further evidences that RS and LPS are equivalent alternatives in clinically uterus-confined EC patients.

For what concern the high-risk EC, limited data support the oncological efficacy and safety of MIS in this sub-set of patients and most studies reported merely the non-inferiority of endoscopic approach respect to the laparotomy [33,34]. Theoretically, the use of MIS in high-risk EC could have some concerns. This type of tumors is usually larger and with higher risk for lymphatic dissemination, port-site metastasis and tumor spillage during uterine manipulation [35,36]. In the LAP2 trial, 492 non-endometrioid tumors were included and the MIS resulted to be not inferior to laparotomy in this sub-set of patients [8]. Bilimoria et al.

[37], in a population-based analysis of the National Cancer Database, examined the impact of MIS in stage I–III non-endometrioid EC staging. Again, the authors concluded asserting that the use of MIS in this sub-type EC did not affect survival outcomes. Differently by the previous reports, in our series we focused the investigation on the specific impact of LPS and RS in survival outcomes, not only in non-endometrioid cancers but in all stage I–III high-risk EC sub-types.

The main strength of this retrospective study is the large number of enrolled patients and the specific sub-set EC population studied. To our knowledge, this is the largest study, including 1,221 I–III stage EC patients overall and among them 426 high-risk EC, that extensively investigated perioperative and oncological outcomes of the strongholds of MIS in EC staging. Furthermore, confirming that the MIS is feasible and safe in high-risk EC patients, our findings suggest that RS and LPS have similar safety and efficacy and do not influence the survival outcome in this specific population. Limitations are represented by the retrospective design and the 17.7 months median follow-up time. A limit in our analyses may be represented by the initial “learning curve” of the involved surgeons in RS, at the beginning of our experience. This aspect may have afflicted mostly the perioperative outcomes (i.e., the OT or the complication rate, etc.). Another limitation, linked to the retrospective nature of the study, is represented by unequal distribution of G3 EC cases between the two groups. The higher number of G3 in LPS group may be explained by the consistent presence of BMI <30 kg/m² patients, more likely with high-grade and not hormone-dependent tumors. This aspect may have influenced the number of relapses and consequentially the deaths occurred. Building on the multivariate analysis results, in which the grading was an independent risk factor for DFS, this aspect may have afflicted our data. Nevertheless, the two population were homogeneous for risk groups and for the number of patients with >65 years.

In conclusion, this study demonstrated that RS and LPS are equally adequate for EC staging, not only in overall population, but also in high-risk EC patients. Based on our experience, there should be continued balanced support for choice of gynecological surgeons and learning regarding the use of RS and LPS for EC surgical staging. These assumptions suggest the design of further prospective investigations to definitely confirm that RS and LPS are equally reliable in EC surgical management.

SUPPLEMENTARY MATERIALS

Supplementary Fig. 1

Survival curves showing the DFS and the OS trends of LPS and RS approaches in stage IIIC1–IIIC2 EC patients.

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Supplementary Fig. 2

Survival curves showing the DFS and the OS trends of LPS and RS approaches in non-endometrioid EC patients.

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