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Surgical Complications Comparing Extraperitoneal vs Transperitoneal Laparoscopic Aortic Staging in Early Stage Ovarian and Endometrial Cancer

The STELLA-2 Randomized Clinical Trial

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Highlights

- Paraaortic lymphadenectomy is performed for surgical staging in early stage ovarian and endometrial cancer.
- The transperitoneal or the extraperitoneal approach can be used for minimally invasive surgery.
- Both routes did not show differences in complications and oncological outcome.
- The extraperitoneal approach provided a higher nodal retrieval.

Abstract

Objective. To determine whether the extraperitoneal approach for paraaortic staging lymphadenectomy results in a lower rate of surgical complications compared to the transperitoneal approach, without compromising oncological outcomes.

Methods. Prospective randomized multicenter study of patients with early endometrial or ovarian cancer undergoing paraaortic lymphadenectomy in 2010-2019. Patients were randomized to minimally invasive surgery (laparoscopy or robotic-assisted) using an extraperitoneal or a transperitoneal approach. The primary end point measure was a composite outcome that included developing one or more of the following surgical complications: bleeding during paraaortic lymphadenectomy ≥ 500 mL, any intraoperative complication related to paraaortic lymphadenectomy, severe postoperative complication (Dindo ≥ IIIA), impossibility to complete the procedure, or conversion to laparotomy.

Results. There were 103 patients in the extraperitoneal group and 100 in the transperitoneal group. Differences in the composite outcome (transperitoneal 26.0% vs, extraperitoneal 18.4%; *P* = 0.195) were not found. Differences in the operative time, conversion to laparotomy, intraoperative bleeding, or survival were not observed. A higher number of lymph nodes were retrieved through the extraperitoneal approached (median, interquartile range [IQR] 12 [7-17] vs, 14 [10-19]: *P* = 0.026). Older age and greater body mass index (BMI) or waist-to-hip ratio (WHR) increased the risk for surgical complications independently of the laparoscopic approach.

Conclusions. The extraperitoneal approach did not show differences regarding surgical and oncological parameters compared with the transperitoneal approach, although the number of aortic nodes retrieved was higher. The decision to use one or another laparoscopic route is a matter of the surgeon preference.

Trial registration ClinicalTrials.gov.identifier: NCT02676726

Keywords: Early stage endometrial cancer, early stage ovarian cancer, laparoscopic extraperitoneal paraaortic staging, transperitoneal paraaortic staging, complications, robotic surgery, survival, disease-free survival.

1. Introduction

Lymphatic staging is the gold standard in the management of intermediate and high risk endometrial malignancies [1] and early stage of epithelial ovarian cancer [2-4]. The International Federation of Gynecology and Obstetrics (FIGO) considers lymphatic spread as an independent prognostic factor in endometrial [5] and epithelial ovarian cancer [6], while most international guidelines continue to recommend lymphatic staging as part of the diagnostic surgical management of these patients [7,8]. Paraaortic lymph node involvement occurs in 14% to 21% of women with early stage epithelial ovarian cancer [9,10], and in about 8% of women with endometrial cancer [11]. Minimally invasive techniques [12,13] have shown similar nodal yields as compared with laparotomy, but with lower perioperative morbidity and cost, reducing the delay between surgical staging and adjuvant chemotherapy when needed [14].

Paraaortic lymph node dissection (PALND) during minimally invasive procedures is performed either through the transperitoneal or the extraperitoneal approach. Retrospective studies have compared these techniques regarding surgical morbidity and oncologic outcome with controversial results [14-18]. In the first randomized prospective trial (STELLA trial) [18] of 60 patients with endometrial or ovarian cancer requiring PALND, significant differences between both routes in operative time and collected lymph nodes were not found, although severe complications (Clavien- Dindo grade III or higher) related to the aortic procedure were observed in 10.3% of patients in the transperitoneal group and in 3.2% in the extraperitoneal group (P = 0.25). Therefore, a potential increased risk of complications with that surgical route required to be assessed in a larger randomized trial. The

primary objective of the STELLA-2 trial was to assess whether the extraperitoneal approach for PALND was associated with decreased surgical morbidity vs the transperitoneal approach. Secondary objectives were to assess differences in nodal yield, operative time, length of stay, and oncologic outcome. Results of the study would provide sound evidence as a basis for decisions about the technique for surgical staging in women undergoing PALND in clinical practice.

2. Materials and methods

2.1. Study design and participants

This was a prospective randomized open-label multicenter trial conducted at the Departments of Gynecology of three Spanish reference centers in Gynecologic Oncology between June 2012 and January 2019. The study was approved by the Clinical Research Ethics Committee of Hospital Universitari Vall d'Hebron (study protocol PR(AMI) 168/2015) as the reference center and by the institutional review boards of the participating hospitals. The trial was performed in accordance with the Declaration of Helsinki (7th revision) and the principles of good clinical practice. All eligible patients provided written informed consent at the time of hospital admission before randomization. The trial protocol is available as supplementary material. The study was registered at ClinicalTrials.gov (identifier NCT02676726).

Patients diagnosed with either primary early stage endometrial or ovarian carcinoma requiring PALND as part of the surgical staging process were eligible. Eligibility criteria for endometrial cancer were deep myometrial invasion (≥ 50% as elicited by magnetic resonance imaging [MRI] and/or transvaginal ultrasound) or

stromal cervical involvement, grade 3 endometrial tumors, or non-endometrioid tumors. Ovarian cancer patients eligible for the study had previous histologic diagnosis of ovarian cancer and clinical stage I or II disease, requiring a surgical staging and completion of surgical therapy. Tumors were staged according to FIGO (2009) for endometrial cancer [19] and FIGO (2014) [20] for ovarian cancer. Patients diagnosed with advanced endometrial cancer based on findings of imaging techniques (computed tomography [CT], MRI, and/or positron emission tomography [PET]) or advanced endometrial or ovarian cancer based on intraoperative findings (e.g. peritoneal carcinomatosis at starting laparoscopy) were excluded from the study. Other exclusion criteria were 136 previous aortic lymphadenectomy and pelvic and/or aortic radiotherapy.

2.2. Randomization and procedures

Patients were randomized to the extraperitoneal or transperitoneal approach for PALND, with the remaining additional surgical procedures completed by the transperitoneal route. Laparoscopic or robot-assisted PALND was not randomized and there were no specific selection criteria for the laparoscopy or robotic procedures, the last of which was used according to availability of the da Vinci surgical system (IntuitiveInc., Sunnyvale, CA, USA). The da Vinci Xi system was used in all hospitals except in one center in which the da Vinci S was used before January 2018. Randomization was performed centrally by an independent biostatistics unit of Vall d'Hebron Research Institute, using random block sizes of 2, 4, and 6, and stratified according to center. Randomly generated sealed opaque envelopes were opened after

the participant has given written informed consent. Blinding was not feasible due to ethical reasons and the surgical nature of treatment.

All operations were performed by four staff surgeons who were proficient in robotic-assisted laparoscopy. The laparoscopic conventional and robot-assisted technique for PALND both by the extraperitoneal and the transperitoneal route has been previously described in detail by our group [12,13,18]. Surgery was started by the PALND first in all patients. In transperitoneal PALND, when performing pelvic procedures, extra ancillary trocars were placed. Aortic lymph nodes were classified into supra- and inframesenteric in reference to their location relative to the inferior mesenteric artery, were placed without fragmentation in endoscopic bags, and were submitted separately for histopathologic examination. Adjuvant chemotherapy, radiotherapy or both was indicated according to treatment protocols for endometrial or ovarian cancer used at each center.

For each patient the following data were prospectively recorded: age at the time of surgery; anthropometric variables including body mass index (BMI), waist-to hip ratio (WHR) (calculated by dividing the waist circumference at the level of the floating rib by the hip circumference), abdominal circumference, and sagittal abdominal diameter (SAD) (calculated as the distance between the skin of the abdomen and the back at the umbilical level, taking advantage of the cross sections obtained radiologically for the diagnosis); age-adjusted Charlson comorbidity index (ACCI) [21]; intraoperative blood loss (estimated by the surgical team according to the irrigation-suction balance); intraoperative complications (categorized as individual

events); operative time (calculated as skin to skin time for the whole procedure and skin to completion for PALND); and early (within ≤ 30 days after surgery) and late (between > 30 days and 6 months after surgery) postoperative complications, which were assessed according to the Clavien-Dindo classification system [22]. Severe complications were defined as grade IIIA or higher. Patients were followed according to protocols of each participating hospital based on final postoperative staging. Overall survival (OS) was defined as the time from surgery to the date of death from any cause, and disease-free survival (DFS) as the time from surgery to the date of first recurrence.

2.3. Outcomes

The primary end point of the study was the occurrence of surgical complications defined by a composite variable according to which a surgical complication was recorded in the presence of at least one of the following events: bleeding during PALND ≥ 500 mL, any intraoperative complication related to PALND, severe postoperative complication (Dindo ≥ IIIA), impossibility to complete the procedure, or conversion to laparotomy. In patients with more than one postoperative complication, that with the highest Clavien-Dindo grade was selected. The secondary end points included the number of lymph nodes retrieved, the operative time, the length of hospital stay, and oncologic outcome (OS and DFS).

2.4. Statistical analysis

The sample size calculation was based on a previously published randomized trial (the

STELLA trial) [18] reporting an overall rate of complications of 24% for the transperitoneal approach and 10% for the extraperitoneal approach. With the significance threshold at 0.05, power set at 80%, and losses at 5%, a total of 210 patients (105 in each group) was calculated. Continuous variables were expressed as mean and (SD) values or as median values with interquartile range (IQR) and were compared using the Student's *t* test, the Welch's t test, or the Mann-Whitney test, as appropriate. Categorical variables were expressed as frequencies with percentages and compared using the χ^2 test or the Fisher exact test. All tests were 2-tailed. Imputation of missing values was not performed. Oncologic outcome was analyzed with the Kaplan-Meier method, whereas the log-rank test and univariate and multivariate adjusted Cox regression models were used for the comparison between groups. In the univariate model, odds ratio (OR) for continuous variables (age, BMI) measured the effect of 1 unit increase. The variable SAD was divided by 10 and WHR was standardized, so that 1 unit change in the OR was associated with a change of 10 units in SAD and of 1 SD in WHR. For the construction of the multivariate model, a selection method based on maximum likelihood estimation and Akaike information criterion (AIC) was used, considering all relevant variables related to the primary end point. The STATA statistical program (version 15.0) was used for the analysis of data.

3. Results

A total of 209 patients (transperitoneal group, n = 104; extraperitoneal group, n = 105) were randomized of which 203 received the allocated intervention (transperitoneal group, n = 100; extraperitoneal group, n = 103). In the transperitoneal group, 2

patients refused the operation after randomization, 1 patient had a previously undiagnosed peritoneal carcinomatosis confirmed at the beginning of the procedure, and 1 patient had a suspicious adnexal mass, the malignancy of which was not confirmed before randomization. In the extraperitoneal group, 2 patients with a previously undiagnosed peritoneal carcinomatosis did not receive the intervention. The CONSORT flow chart shows that 2 patients in the extraperitoneal group and 4 patients in the transperitoneal group did not receive the allocated intervention and were excluded from the analysis (Figure 1).

Baseline characteristics and intraoperative and pathologic details (Table 1) were comparable between groups. The use of conventional laparotomy or robotic-assisted laparotomy, duration of operation, and intraoperative blood loss was similar. In patients undergoing the extraperitoneal approach as compared to the transperitoneal approach, the median number of total aortic lymph nodes (14 [IQR 10-219 19] vs. 12 [7-17]; P = 0.026) and supramesenteric nodes (6 [4-9] vs. 5 [3-8]; P = 0.039) retrieved was significantly higher. However, there were no differences between both laparoscopic approaches in the median number of inframesenteric lymph nodes retrieved. The median length of stay was 3 days for both study groups.

Differences between the transperitoneal and the extraperitoneal groups in relation to the primary end point were not found (26.0% vs. 18.4%, P = 0.195).

Complications associated with PALND are shown in Table 2. Intraoperative complications occurred in 7 (7%) patients in the transperitoneal group and in 2 (1.9%) in the extraperitoneal group (P = 0.642). In the transperitoneal group, there were 2 serosal intestinal injuries, 2 ureteral injuries, and 3 vascular injuries (inferior

mesenteric artery, vena cava, and left renal artery), whereas 2 vascular injuries (vena cava) occurred in the extraperitoneal group. Severe (Dindo ≥ IIIA) early postoperative complications occurred in 1 patient in each group (chylous ascites that resolved with conservative measures). Among PALND-associated late complications, 2 patients in the extraperitoneal group developed lower limb lymphedema.

PALND could not be completed in 13 (13%) patients in the transperitoneal approach (poor exposure in Trendelenburg position due to fatty mesentery) and in 9 (8.7%) patients in the extraperitoneal group (P = 0.328), which included peritoneal rupture and a poor surgical field in 4, anesthesia-related hypercapnia in 3 and vena cava injury irreparable by the extraperitoneal route in 2. Conversion to laparotomy was necessary in 6 (6%) patients in the transperitoneal group (suspicion of possible peritoneal metastatic nodules intraoperatively in 2, visceral obesity preventing Trendelenburg position in 2, severe adhesions in 1, and accidental ureteral section in 1) and in 9 (8.7%) patients in the extraperitoneal group (P = 0.456). Reasons for conversion in the extraperitoneal group were large uterine size in 3 multiparous women with high vaginal compliance preoperatively, poor exposure in Trendelenburg position due to visceral obesity in 2, vascular lesions in 2, laparoscopically unresectable conglomerate lymph nodes in 1, and severe adhesions in 1. Also, 8 (7.8%) patients randomized to the extraperitoneal approach required conversion to the transperitoneal route mainly due to rupture of the peritoneum and intraperitoneal gas leak.

Complications associated with the laparoscopy staging procedure are shown in Table 3. There were no statistically significant differences between the transperitoneal

and extraperitoneal routes in intraoperative, early, and late complications. Intraoperative and early postoperative intestinal-related complications were more frequent in the transperitoneal group than in the extraperitoneal group (4% vs. 0%, *P* = 0.057 and 5% vs. 1%, *P* = 0.115, respectively). Early postoperative severe complications (Dindo ≥ IIIA) were also more frequent in the transperitoneal group (11% vs. 3.9%, *P* = 0.052).

In the multivariable analysis, age, BMI, and WHR were significant independent variables that increased the risk of surgical complications. The laparoscopic approach (transperitoneal or extraperitoneal) was not statistically significant either at univariate or multivariate testing (Figure 2) (see Table 1 in Supplement). The laparoscopic approach was unrelated to oncologic outcome, both in endometrial and ovarian cancer 261 patients. At 30 months, the OS in endometrial cancer patients was 95.6% (95% CI 86.9-98.6) for the transperitoneal approach and 96.2% (95% CI 88.5-98.8) for the extraperitoneal approach, while in ovarian cancer patients was 100% for both arms. Results of OS and DFS for endometrial and ovarian cancer according to laparoscopic approach and OS stratified by FIGO stage are shown in the Supplement. Significant differences in oncological outcome by laparoscopic approach for either endometrial or ovarian cancer were not found, but OS in endometrial cancer showed significant differences when patients were stratified by FIGO stage (*P* = 0.004).

4. Discussion

The present study shows that transperitoneal or extraperitoneal approach used for surgical staging in early ovarian and endometrial cancer did not affect surgical

morbidity and oncologic outcome. However, the extraperitoneal approach was associated with the possibility of retrieving a higher number of supramesenteric nodes, which would be a clinically relevant finding in the presence of isolated infrarenal nodal involvement. Older age and increased BMI and WHR were risk factors for surgical morbidity independently of the laparoscopic access technique.

To our knowledge, a direct comparison of surgical complications associated with transperitoneal and extraperitoneal laparoscopic lymphadenectomy for early stage ovarian and endometrial cancer in a prospective randomized study has not been previously reported. The selection of the most appropriate laparoscopic approach is still controversial. A systematic review and meta-analysis of seven studies with a total of 608 women with advanced cervical, ovarian and high-risk endometrial cancer reported a longer operative time (35 min) and higher rate of intraoperative complications (OR 2.4, 95% CI 1.02-5.63) in the transperitoneal group as compared to the extraperitoneal route [23]. In this meta-analysis, however, pooled data of all patients undergoing paraaortic transperitoneal vs extraperitoneal lymphadenectomy were analyzed, in contrast to our study in which surgical complications were disaggregated by those specifically associated with PALND and those associated with the overall laparoscopic procedure.

In relation to intraoperative complications, one of the advantages of the extraperitoneal approach is the absence of bowel loops interposition in the surgical field and visualization of ureters. In a retrospective chart review of 36 transperitoneal approaches and 79 extraperitoneal approaches of infrarenal lymphadenectomy for gynecological malignancies, O'Hanlan et al. [16] registered 1 left renal artery

297 transection only. In a series of 173 patients with locally advanced cervical carcinoma
298 undergoing extraperitoneal PALND reported by Leblanc et al. [24], four patients (2.3%)
299 developed intraoperative complications, including 1 partial ureteral transection, 3
300 vascular injuries, and no intestinal lesions. These findings are consistent with our
301 study, in which intestinal and ureteral lesions associated with PALND occurred in 4
302 patients in the transperitoneal group and in none of the extraperitoneal group.
303 Postoperatively, intestinal lesions were also more frequent in the transperitoneal
304 approach (Table 4).

305 Lymphocele is the most common complication related to extraperitoneal
306 PALND [15,25], particularly when preventive peritoneal marsupialization has not been
307 performed. In 120 patients with locally advanced cervical cancer reported by Köhler et
308 al. [26], surgical approach for staging was transperitoneal in 93.4% of patients and
309 early postoperative complications in 9 patients included symptomatic lymphocele in 4,
310 thrombosis in 1, ileus in 1, nerve irritation in 1, and relaparoscopy in 2 because of
311 omental prolapse after removal of a drain in 1 and chylous ascites in 1. In the present
312 study, significant differences in the distribution of early complications according to the
313 laparoscopy approach were not observed but severe events (Dindo ≥ IIIA) not
314 specifically related to PALND occurred more frequently in the transperitoneal group.

315 Technical difficulties of the extraperitoneal approach include reconversion to
316 the transperitoneal route by accidental rupture of the peritoneum or greater
317 difficulties to solve an intraoperative lesion. In a retrospective review of paraaortic
318 lymphadenectomy for gynecologic malignancies using the transperitoneal approach in
319 51 patients and the extraperitoneal approach in 21, Akladios et al. [14] reported only 1

(1.3%) conversion to laparotomy in the transperitoneal group and 3 conversions from extraperitoneal to transperitoneal PALND (14.2%). Pakish et al. [17] in a comparison of extraperitoneal vs. transperitoneal PALND for staging endometrial carcinoma, 3 patients (8.8%) in the extraperitoneal group required conversion to transperitoneal laparoscopic lymphadenectomy due to peritoneal entry during the extraperitoneal dissection in 2 and suboptimal visualization in 1, which are consistent with a rate of conversion of 7.7% found in our study. On the other hand, the rate of conversion to an open procedure was 9.6% for the extraperitoneal approach and 6.0% for the transperitoneal approach. The previous study of Pakish et al. [17] limited to patients with endometrial cancer showed a conversion rate of 8.8% for the extraperitoneal approach and 15.7% for the transperitoneal route. It should be noted that patients with locally advanced cervical cancer were not included. In patients with endometrial or ovarian malignancy, conversion to open surgery may be related to the need of performing other surgical procedures as part of the management of the disease (e.g. hysterectomy) rather than exclusively related to the PALND procedure.

PALND procedures through any approach has been associated with operative times between 155 and 190 min [15,24]. Our median operative times were 150 min and 110 min in the extraperitoneal and transperitoneal groups, but operative times of PALND were 15 and 20 min, respectively. Differences may be attributed to the notable surgeons' experience with both laparoscopic routes, so that cases attributable to the learning curve could be excluded. Endoscopic extraperitoneal lymphadenectomy has a steep learning curve similar to that for transperitoneal laparoscopy [27].

342 The mean number of lymph nodes retrieved reported by other authors for the
343 transperitoneal approach (between 4.5 and 19) or the extraperitoneal approach
344 (between 10.5 and 20.8) [14,15-17,24] is similar to findings of our study. A higher
345 number of lymph nodes were retrieved by the extraperitoneal route (median 14 vs.
346 12), which is also consistent with previous reports [16,17,28]. In women with
347 endometrial carcinoma, Abu-Rustum et al. [29] using the Classification and Regression
348 Tree (CART) method showed that the removal of 10 or more lymph nodes was a
349 predictor of survival in endometrial stage I-IIIA patients, emphasizing the importance
350 of accurate surgical staging as the most important prognostic factor. Given the
351 relevance of intraoperative detection of the sentinel lymph node in lymphatic staging
352 of endometrial cancer [30,31], cervical cancer [32,33], or vulvar cancer [34-36], the
353 future role of PALND will be probably restricted to specific indications (e.g. tumors
354 with high risk of lymphatic dissemination).

355 Despite the strengths of a prospective randomized trial the study failed to
356 demonstrate superiority of the extraperitoneal approach vs the conventional
357 transperitoneal approach for the primary end point. This finding might have been
358 influenced by difficulties in differentiating specific complications associated with
359 PALND from the remaining complications associated with surgical procedures.

360 In summary, laparoscopic staging through the extraperitoneal approach is a
361 safe procedure for LAPND in patients with early ovarian and endometrial cancer, with
362 an acceptable surgical morbidity, without compromising oncologic outcome, and
363 offering higher nodal yield as compared with the transperitoneal approach.

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Conflict of interests

None of the authors reported any conflict of interest.

Author contributions

Dr Díaz-Feijoo and Gil-Moreno had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Díaz-Feijoo, Bebia, and Gil-Moreno.

Acquisition, analysis, or interpretation of data: Díaz-Feijoo, Bebia, Hernández, Gilabert-Estalles, Franco-Camps, de la Torre, Segrist, Chipiriliu, Cabrera, Perez-Benavente, and Gil-Moreno.

Drafting of the manuscript: Díaz-Feijoo, Bebia, Gil-Moreno.

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Statistical analysis: Bebia.

Obtained funding: Díaz-Feijoo.

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Data Sharing

Data of this study are available from the corresponding author upon request.

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This study contains supplementary data

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514 biopsy in women with squamous cell carcinoma of the vulva: a gynecologic
515 oncology group study. J Clin Oncol. 2012;30(31):3786-3791.
516 doi:10.1200/JCO.2011.41.2528
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519

520 **Table 1.** Baseline Characteristics and Surgical and Pathologic Findings

Characteristic	Laparoscopic approach		*P* Value
	Extraperitoneal (N = 103)	Transperitoneal (N = 100)	
Age, years, mean (SD)	63.7 (10.2)	63.0 (11.0)	
Body mass index, kg/m^2, mean (SD)	29.6 (6.6)	29.1 (6.7)	
Waist-to-hip ratio, median (IQR)	0.90 (0.85-0.98)	0.91 (0.83-0.98)	
Abdominal circumference, cm, mean (SD)	104.9 (17.5)	102.2 (16.6)	
Sagittal abdominal diameter, cm, mean (SD)	193.6 (94.6)	193.4 (100.2)	
ACCI, median (IQR)	2 (2-4)	2 (1-3)	
Previous abdominal surgery, N (%)	31 (30.1)	33 (33.0)	
FIGO stage (2009) endometrial cancer, N (%)	87 (84.4)	79 (79.0)	0.370
IA	25 (28.7)	26 (32.9)	
IB	20 (23.0)	22 (27.8)	
II	18 (20.7)	22 (27.8)	
IIIA	6 (6.9)	2 (2.5)	
IIIB	1 (1.1)	1 (1.3)	
IIIC1	5 (5.7)	1 (1.3)	
IIIC2	10 (11.5)	5 (6.3)	
IVA	1 (1.1)	0	
IVB	1 (1.1)	0	
FIGO stage (2014) ovarian cancer, N (%)	16 (15.6)	21 (21.0)	
IA	2 (12.5)	3 (14.3)	0.840
IC1	3 (18.8)	7 (33.3)	
IC2	4 (25.0)	4 (19.0)	
IC3	1 (6.3)	1 (4.8)	
IIA	3 (18.8)	3 (14.3)	
IIB	0	2 (9.5)	
IIIA2	1 (6.3)	0	
IIIB	1 (6.3)	0	
IIIC	1 (6.3)	1 (4.8)	
Histologic subtype, N (%)			
Endometrial cancer			
Endometrioid	47 (54.0)	45 (57.0)	0.881
Non-endometrioid	40 (46.0)	34 (43.0)	
Ovarian cancer			
Serous	8 (50)	7 (33.3)	0.260
Endometrioid	6 (37.5)	6 (28.6)	
Mucinous	0	4 (19.0)	
Clear cell	2 (12.5)	4 (19.0)	
Tumor grade, N (%)			
Grade 1 well differentiated	8 (7.8)	12 (12.0)	0.594
Grade 2 moderately differentiated	42 (40.8)	38 (38.0)	
Grade 3 poorly differentiated	53 (51.5)	50 (50.0)	
Type of laparoscopy, N (%)			
Conventional laparoscopy	68 (66.0)	62 (62)	0.551
Robotic-assisted laparoscopy	35 (34.0)	38 (38)	
Operative time, min, median (IQR)			
Skin to skin	275 (225-320)	270 (240-300)	0.996
PALND procedure	90 (72-120)	90 (70-120)	0.735

521

522

Table 1. Baseline Characteristics and Surgical and Pathologic Findings (continued)

Characteristic	Laparoscopic approach		*P* Value
	Extraperitoneal (N = 103)	Transperitoneal (N = 100)	
Blood loss, mL, median (IQR)			
Skin to skin	150 (55-200)	110 (50-200)	0.660
PALND procedure	15 (5-50)	20 (5-50)	0.942
Blood transfusion, N (%)	3 (2.9)	4 (4)	0.718
Aortic lymph nodes retrieved, median (IQR)	14 (10-19)	12 (7-17)	0.026
Supramesenteric	6 (4-9)	5 (3-8)	0.039
Inframesenteric	7 (5-10)	7 (4-10)	0.246
Patients with positive aortic nodes*			
Endometrial cancer	15 (17.2)	7 (8.9)	0.112
Ovarian cancer	1(6.3)	0	0.432
Length of stay, days, median (IQR)	3 (2-4)	3 (2-4)	0.281
Other procedures, N (%)			
Hysterectomy	93 (90.3)	90 (90.0)	0.945
Bilateral adnexectomy	81 (78.6)	74 (74.0)	0.437
Unilateral adnexectomy	6 (5.8)	6 (6.0)	0.960
Pelvic lymphadenectomy	99 (96.1)	100 (100.0)	0.781
Omentectomy	31 (30.1)	46 (46.0)	0.019
Appendectomy	2 (1.9)	3 (3.0)	0.237
Sentinel lymph node biopsy	8 (7.8)	10 (10.0)	0.576

*Percentages related to the total of patients affected of endometrial or ovarian cancer in each treatment branch.

Abbreviations: SD, standard deviation; IQR: interquartile range; ACCI: age-adjusted Charlson comorbidity index: PALND: paraaortic lymph node dissection.

537 **Table 2.** Intraoperative, Early, and Late Complications Associated with Paraaortic Lymph Node
538 Dissection (PALND)

539

Complication	Laparoscopic approach		*P* Value
	Extraperitoneal (N = 103)	Transperitoneal (N = 100)	
Intraoperative, N (%)	2 (1.9)	7 (7.0)	0.642
Vascular injury	2 (1.9)	3 (3.0)	
Inferior mesenteric artery		1	
Vena cava	2	1	
Left renal vein		1	
Intestinal serosal lesion		2 (2.0)	
Ureteral lesion		2 (2.0)	
Incomplete PALND, N (%)	9 (8.7)	13 (13.0)	0.330
Conversion to transperitoneal approach, N (%)	8 (7.8)	NA	
Conversion to laparotomy, N (%)	9 (8.7)	6 (6.0)	0.456
Early postoperative (≤ 30 days), N (%)	1 (1.0)	1 (1.0)	1.00
Chylous ascites (Dindo ≥ IIIA)	1 (1.0)	1 (1.0)	
Late postoperative (> 30 days until 6 months), N (%)	2 (1.9)	0	0.506
Lymphedema left lower limb	2 (1.9)		

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541

542 **Table 3.** Intraoperative, Early, and Late Complications Associated with the Laparoscopy Staging
543 Procedure Including Paraaortic Lymph Node Dissection (PALND)

544

Complication	Laparoscopic approach		*P* Value
	Extraperitoneal (N = 103)	Transperitoneal (N = 100)	
Intraoperative, N (%)	7 (6.8)	14 (14.0)	0.092
Vascular	3 (2.9)	4 (4.0)	
Intestinal	0	4 (4.0)	
Urinary	1 (1.0)	3 (3.0)	
Other (anesthesia, laparoscopic access)	3 (2.9)	3 (3.0)	
Early postoperative (≤ 30 days), N (%)	29 (28.2)	24 (24.0)	0.500
Abdominal wall	8 (7.8)	6 (6.0)	
Vascular	4 (3.9)	4 (4.0)	
Intestinal	1 (1.0)	5 (5.0)	
Urinary	4 (3.9)	1 (1.0)	
Lymphatic	7 (6.8)	6 (6.0)	
Other	5 (4.8)	2 (2.0)	
One or more Dindo ≥ IIIA complication	4 (3.9)	11 (11.0)	0.052
Late postoperative (> 30 days until 6 months), N (%)	21 (20.4)	14 (14.0)	0.241
Abdominal wall	6 (5.8)	3 (3.0)	
Vascular	3 (2.9)	0	
Intestinal	1 (1.0)	1 (1.0)	
Urinary	0	2 (2.0)	
Lymphatic	12 (11.7)	8 (8.0)	
One or more Dindo ≥ IIIA complication	11 (10.7)	8 (8.0)	0.782

545

546

Table 4. Literature review of perioperative outcomes of extraperitoneal versus transperitoneal minimally invasive paraaortic lymphadenectomy

			Intraoperative complications [No. Injuries]		**Operative time [minutes, mean (SD) or median (range)]**		**Transperitoneal conversion [%]**		**Laparotomy conversion [%]**		**PA Nodes retrieved [mean (SD) or median (range)]**	
			E	T	E	T	E	T	E	T	E	T
Morales, 2013	Retrospective	E=28 T=19	-	2 vascular	150 (35)	185 (27)	-	NA	3.5	2.1	15 (5.9)	17.4 (8.6)
Pakish, 2014	Retrospective	E=34 T=160	1 vascular 1 intestinal	7 vascular	339.5 (242-453)*	286 (101-480)*	8.8	NA	8.8	3.9-15.7	10 (4-22)	5 (1-24)
O'Hanlan, 2015	Retrospective	E=79 T=39	1 vascular	1 nervous	240*	202*	-	NA	1.2	8.3	28 (1-36)	20 (1-37)
Akladios, 2015	Retrospective	E=21 T=51	-	2 vascular 1 ureteral	200 (35-360)*	125.6 (45-180)*	14.2	NA	0	1.3	13 (3-25)	17 (4-37)
Current study	Prospective	E=103 T=100	3 vascular 1 urinary	4 vascular 4 intestinal 3 urinary	90 (72-120)	90 (70-120)	7.8	NA	8.7	6.0	14 (10-19)	12 (7-17)

*Operative times reported for the whole surgery (skin-to-skin, including other procedures than paraaortic lymphadenectomy), Abbreviations: PA: paraaortic. SD: standard deviation. E: Extraperitoneal. T: Transperitoneal

Legends

Figure 1. CONSORT flow chart diagram.

Figure 2. Forest plot of the results of univariate and multivariate analysis. WHR: waist-hip ratio. BMI: body mass index. Odds ratio (OR) for age and BMI measured the effect of 1 unit increase, and 1 unit change in the OR of WHR was associated with a change of 1 SD.

Table 2. Intraoperative, Early, and Late Complications Associated with Paraaortic Lymph Node Dissection (PALND)

Complication	Laparoscopic approach		*P* Value
	Extraperitoneal (N = 103)	Transperitoneal (N = 100)	
Intraoperative, N (%)	2 (1.9)	7 (7.0)	0.642
Vascular injury	2 (1.9)	3 (3.0)	
Inferior mesenteric artery		1	
Vena cava	2	1	
Left renal vein		1	
Intestinal serosal lesion		2 (2.0)	
Ureteral lesion		2 (2.0)	
Incomplete PALND, N (%)	9 (8.7)	13 (13.0)	0.330
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Early postoperative (≤ 30 days), N (%)	1 (1.0)	1 (1.0)	1.00
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Late postoperative (> 30 days until 6 months), N (%)	2 (1.9)	0	0.506
Lymphedema left lower limb	2 (1.9)		

Table 3. Intraoperative, Early, and Late Complications Associated with the Laparoscopy Staging Procedure Including Paraaortic Lymph Node Dissection (PALND)

Complication	Laparoscopic approach		*P* Value
	Extraperitoneal (N = 103)	Transperitoneal (N = 100)	
Intraoperative, N (%)	7 (6.8)	14 (14.0)	0.092
Vascular	3 (2.9)	4 (4.0)	
Intestinal	0	4 (4.0)	
Urinary	1 (1.0)	3 (3.0)	
Other (anesthesia, laparoscopic access)	3 (2.9)	3 (3.0)	
Early postoperative (≤ 30 days), N (%)	29 (28.2)	24 (24.0)	0.500
Abdominal wall	8 (7.8)	6 (6.0)	
Vascular	4 (3.9)	4 (4.0)	
Intestinal	1 (1.0)	5 (5.0)	
Urinary	4 (3.9)	1 (1.0)	
Lymphatic	7 (6.8)	6 (6.0)	
Other	5 (4.8)	2 (2.0)	
One or more Dindo ≥ IIIA complication	4 (3.9)	11 (11.0)	0.052
Late postoperative (> 30 days until 6 months), N (%)	21 (20.4)	14 (14.0)	0.241
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Intestinal	1 (1.0)	1 (1.0)	
Urinary	0	2 (2.0)	

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Table 1. Baseline Characteristics and Surgical and Pathologic Findings

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Previous abdominal surgery, N (%)	31 (30.1)	33 (33.0)	
FIGO stage (2009) endometrial cancer, N (%)	87 (84.4)	79 (79.0)	
IA	25 (28.7)	26 (32.9)	
IB	20 (23.0)	22 (27.8)	
II	18 (20.7)	22 (27.8)	
IIIA	6 (6.9)	2 (2.5)	0.370
IIIB	1 (1.1)	1 (1.3)	
IIIC1	5 (5.7)	1 (1.3)	
IIIC2	10 (11.5)	5 (6.3)	
IVA	1 (1.1)	0	
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IC1	3 (18.8)	7 (33.3)	
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IC3	1 (6.3)	1 (4.8)	
IIA	3 (18.8)	3 (14.3)	0.840
IIB	0	2 (9.5)	
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Histologic subtype, N (%)			
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Endometrioid	47 (54.0)	45 (57.0)	0.881
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Ovarian cancer			
Serous	8 (50)	7 (33.3)	
Endometrioid	6 (37.5)	6 (28.6)	0.260
Mucinous	0	4 (19.0)	
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Grade 1 well differentiated	8 (7.8)	12 (12.0)	
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Conventional laparoscopy	68 (66.0)	62 (62)	0.551
Robotic-assisted laparoscopy	35 (34.0)	38 (38)	
Operative time, min, median (IQR)			
Skin to skin	275 (225-320)	270 (240-300)	0.996
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Characteristic	Laparoscopic approach		*P* Value
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Other procedures, N (%)			
Hysterectomy	93 (90.3)	90 (90.0)	0.945
Bilateral adnexectomy	81 (78.6)	74 (74.0)	0.437
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Pelvic lymphadenectomy	99 (96.1)	100 (100.0)	0.781
Omentectomy	31 (30.1)	46 (46.0)	0.019
Appendectomy	2 (1.9)	3 (3.0)	0.237
Sentinel lymph node biopsy	8 (7.8)	10 (10.0)	0.576

*Percentages related to the total of patients affected of endometrial or ovarian cancer in each treatment branch.
Abbreviations: SD, standard deviation; IQR: interquartile range; ACCI: age-adjusted Charlson comorbidity index: PALND: paraaortic lymph node dissection.

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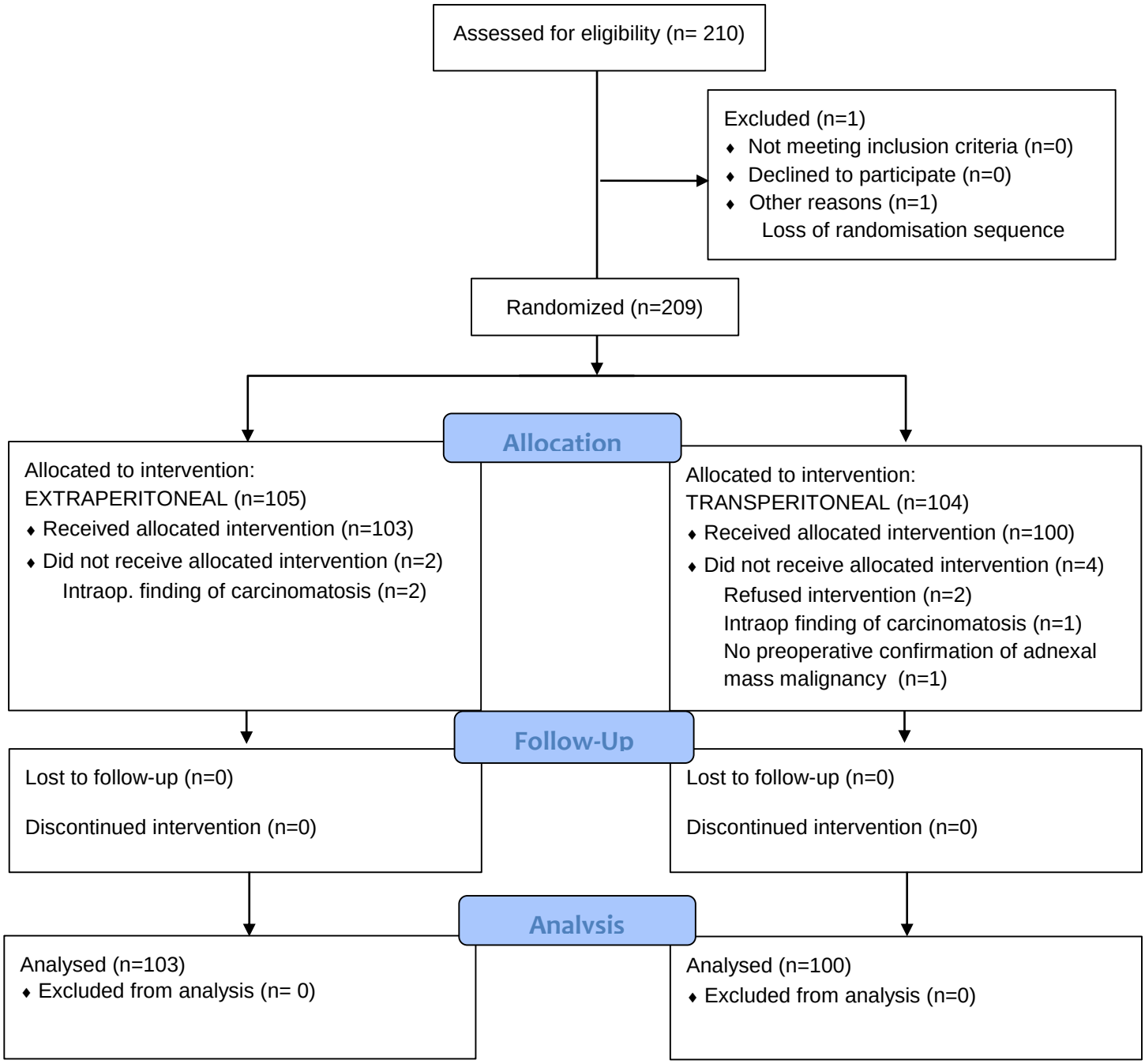
Current study	Prospective	E=103 T=100	3 vascular 1 urinary	4 vascular 4 intestinal 3 urinary	90 (72-120)	90 (70-120)	7.8	NA	8.7	6.0	14 (10-19)	12 (7-17)

*Operative times reported for the whole surgery (skin-to-skin, including other procedures than paraaortic lymphadenectomy), Abbreviations: PA: paraaortic. SD: standard deviation. E: Extraperitoneal. T: Transperitoneal

CONSORT

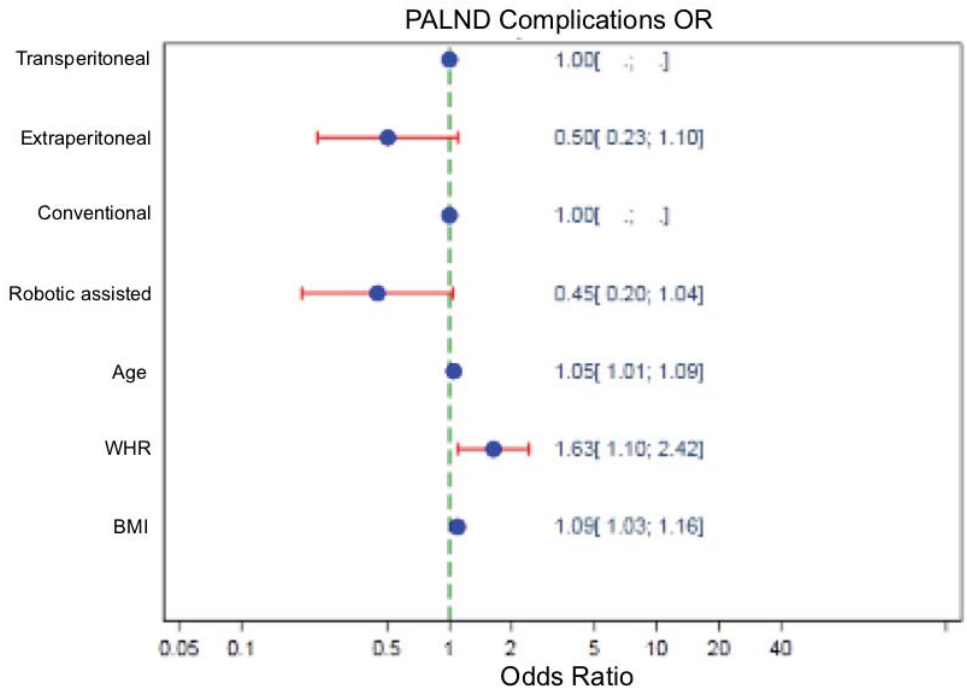
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



5. Figure

Click here to access/download;5. Figure;Figure 2.pdf



Surgical Complications Comparing Extraperitoneal vs Transperitoneal Laparoscopic Aortic Staging in Early Stage Ovarian and Endometrial Cancer

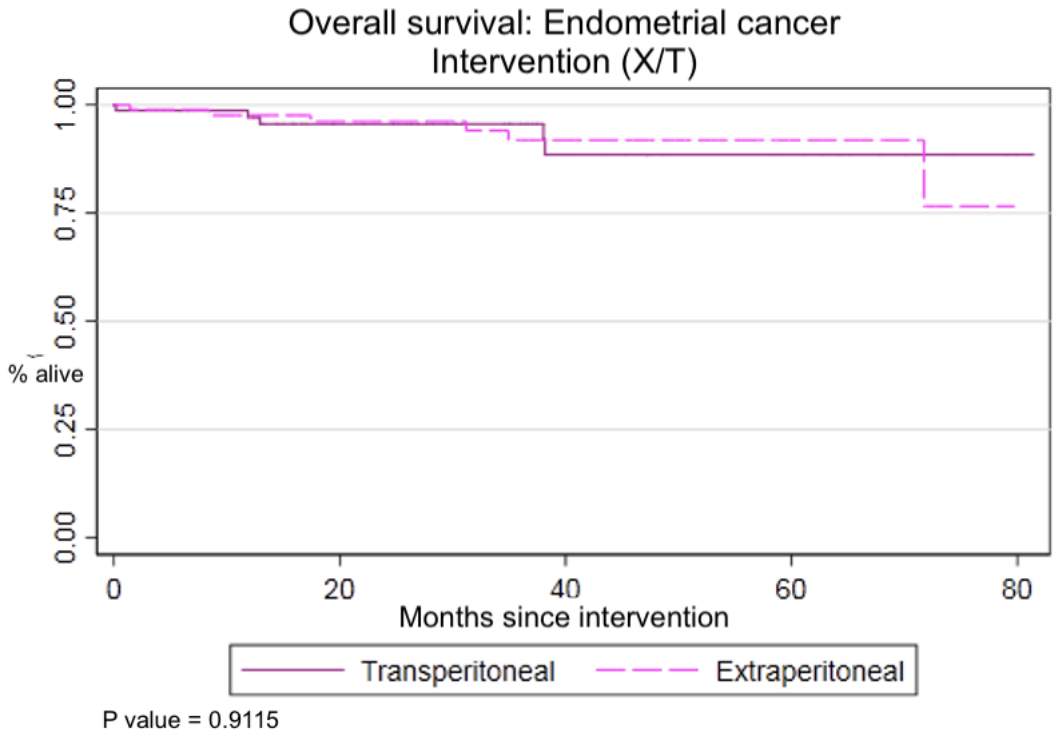
The STELLA-2 Randomized Clinical Trial

Supplementary material

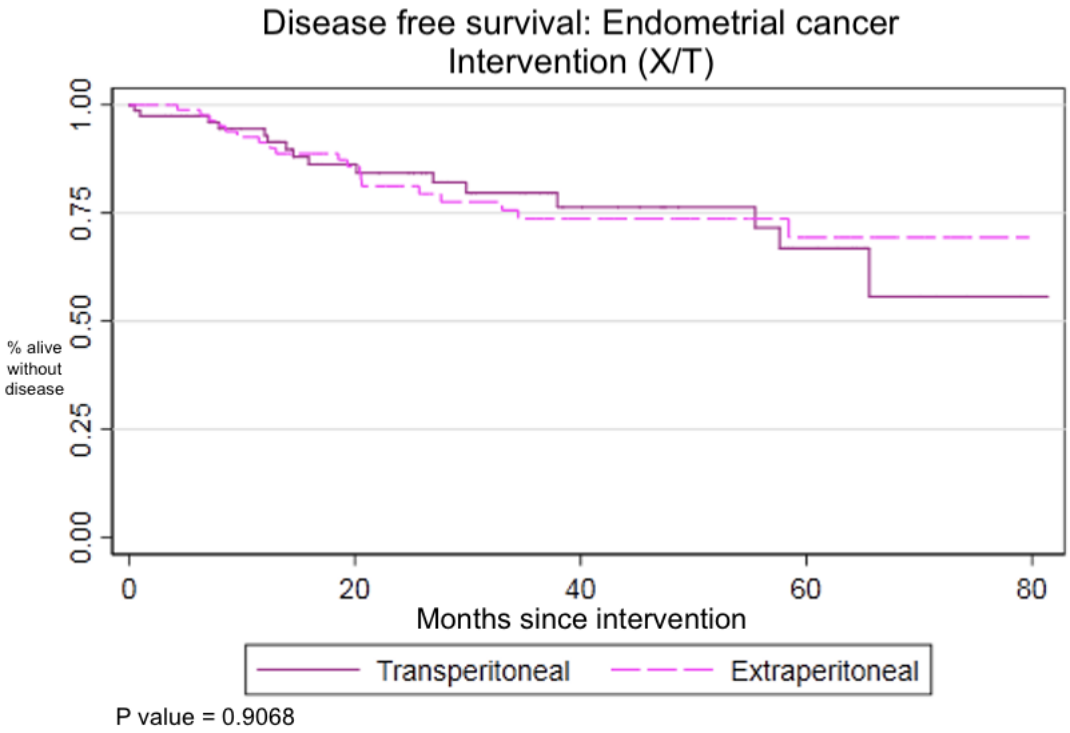
List of contents:

Variables	Univariate model		Multivariate model
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)
Laparoscopic approach		.1970	
Transperitoneal	1 (ref)		1 (ref)
Extraperitoneal	0.64 (0.33-1.26)		0.50 (0.23-1.10)
Body mass index (BMI), kg/m^2	1.09 (1.04-1.15)	.0005	1.09 (1.03-1.16)
Sagittal abdominal diameter (SAD)	1.01 (0.97-1.04)	.6607	
Age, years	1.05 (1.02-1.09)	.00054	1.05 (1.01-1.09)
Waist-to-hip ratio (WHR)	1.68 (1.18-2.40)	.0040	1.64 (1.10-2.42)
Type of cancer			
Endometrial	1 (ref)		
Ovarian	1.16 (0.50-2.68)	.727	
Type of laparoscopy			
Conventional	1 (ref)		1 (ref)
Robotic-assisted	0.66 (0.32-1.36)	.264	0.45 (0.20-1.04)

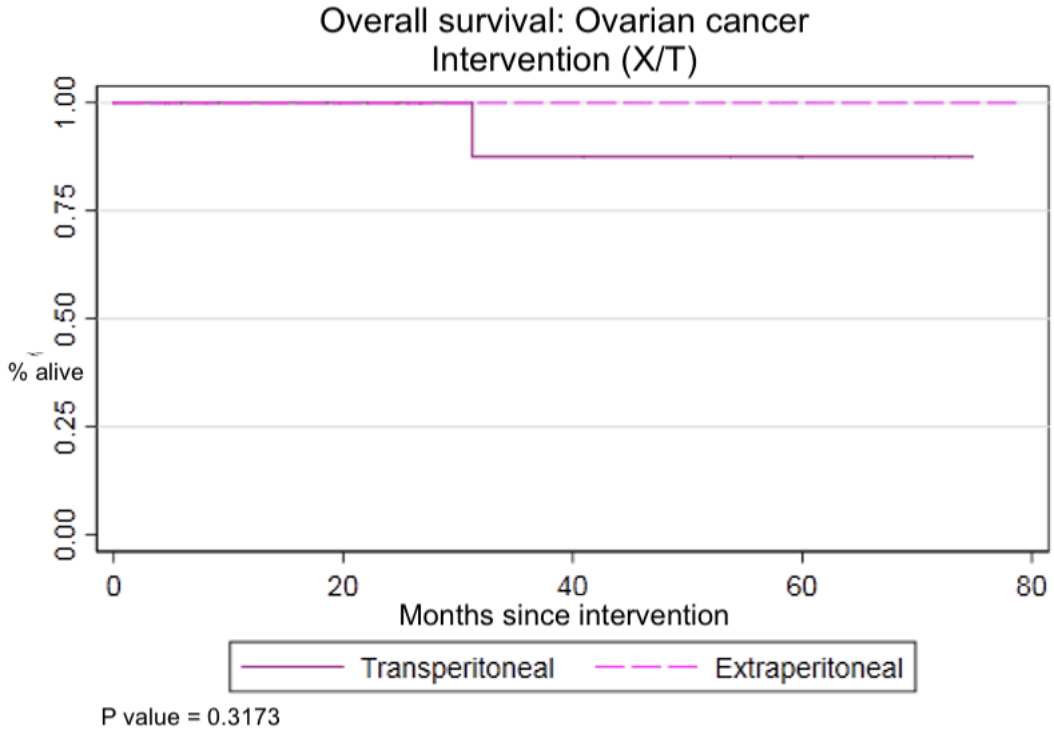
eTable 1.- Univariate and multivariate models.



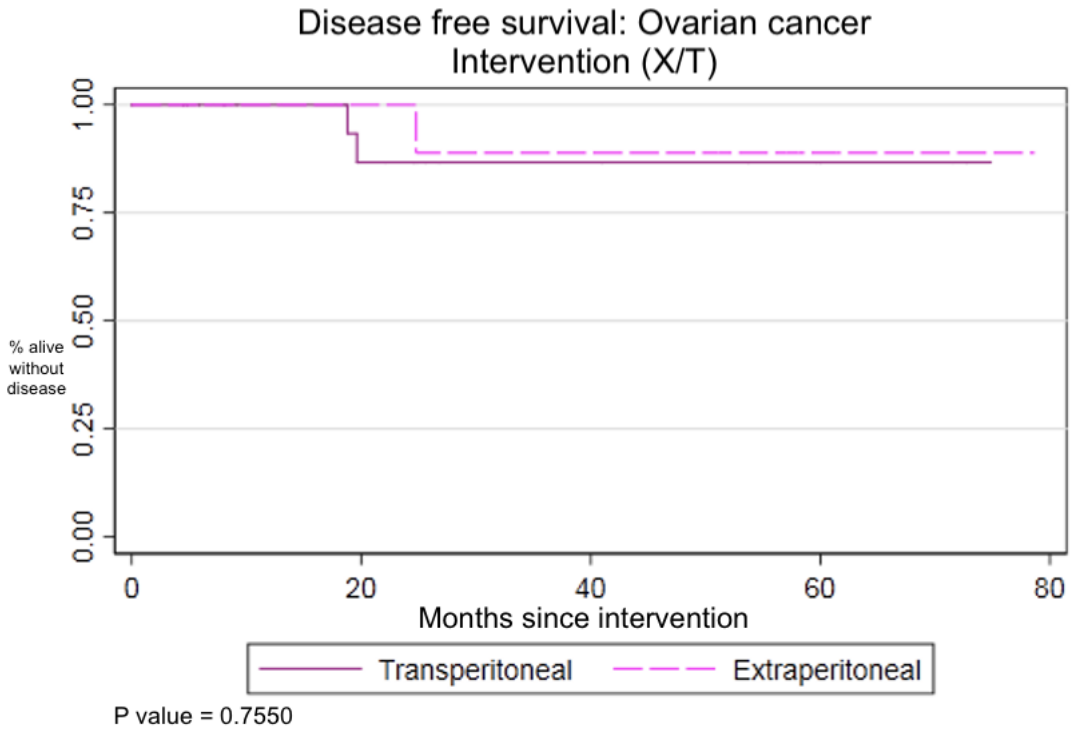
eFigure 1.- Overall survival in Endometrial cancer by Intervention (Transperitoneal “T”, Extraperitoneal “X”)



eFigure 2.- Disease free survival in Endometrial cancer by Intervention (Transperitoneal “T”, Extraperitoneal “X”)



eFigure 3.- Overall survival in Ovarian cancer by Intervention (Transperitoneal "T", Extraperitoneal "X")



eFigure 4.- Disease free survival in Ovarian cancer by Intervention (Transperitoneal “T”, Extraperitoneal “X”)

Type of Article: Research Paper

Surgical Complications Comparing Extraperitoneal vs Transperitoneal Laparoscopic Aortic Staging in Early Stage Ovarian and Endometrial Cancer

The STELLA-2 Randomized Clinical Trial

Highlights

- Paraaortic lymphadenectomy is performed for surgical staging in early stage ovarian and endometrial cancer.
- The transperitoneal or the extraperitoneal approach can be used for minimally invasive surgery.
- Both routes did not show differences in complications and oncological outcome.
- The extraperitoneal approach provided a higher nodal retrieval.