

Transperitoneal vs extraperitoneal approach for aortic sentinel node detection in endometrial cancer



Mikel Gorostidi, MD, MS; Ruben Ruiz, MD; Claudia Galan, MD; Ibon Jaunarena, MD; Paloma Cobas, MD; Arantxa Lekuona, MD; Irene Diez-Itza, MD, PhD

BACKGROUND: Although the sentinel lymph node technique in endometrial cancer is currently replacing pelvic and aortic lymphadenectomy for the evaluation of lymph node status in endometrial cancer, its performance is not yet standardized.

OBJECTIVE: This study aimed to describe the detection rates and locations of aortic sentinel lymph node detection after dual cervical and fundal indocyanine green injection in patients with endometrial cancer, using the transperitoneal and extraperitoneal approaches.

STUDY DESIGN: Between June 26, 2014 and December 31, 2019, 278 patients underwent laparoscopic surgery for endometrial cancer at our institution. In all cases, we performed sentinel lymph node biopsy with dual cervical and fundal indocyanine green injection, and back-up lymphadenectomy in high-risk cases. A post hoc analysis was performed to evaluate differences between the transperitoneal and extraperitoneal approach to aortic sentinel lymph nodes.

RESULTS: The detection rates were as follows: overall detection rate: 93.2% (259/278); pelvic detection rate: 90.3% (251/278); bilateral pelvic detection rate: 68.0% (189/278); aortic detection rate: 66.9% (186/278); and isolated aortic detection rate: 2.88% (8/278). Transperitoneal and extraperitoneal aortic detection rates were similar (65.0% and 69.6%, respectively), with no significant differences ($P=.441$). Isolated aortic metastases were similar in both groups (2% vs 4.7%, respectively; $P=.185$). The laterality of aortic sentinel lymph node detection was influenced by the surgical approach ($P=.002$), but not its location above or below the inferior mesenteric artery ($P=.166$ and $P=.556$, respectively).

CONCLUSION: The detection rates at the aortic level were similar between the transperitoneal and extraperitoneal approaches, with no impact on subsequent pelvic detection. The transperitoneal approach detected more laterocaval, precaval, and interaortocaval nodes, whereas the extraperitoneal approach detected more preaortic and left lateroaortic nodes.

Keywords: endometrial neoplasms, laparoscopies, lymphatic system, operative, sentinel lymph node, surgical procedures

From the Obstetrics & Gynecology department, Hospital Universitario Donostia, San Sebastián, Spain (Drs Gorostidi, Ruiz, Galan, Jaunarena, Cobas, Lekuona, and Diez-Itza); Biodonostia Health Research Institute, San Sebastián, Spain (Drs Gorostidi, Jaunarena, Lekuona, and Diez-Itza).

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Corresponding author: Mikel Gorostidi, MD, MS. mgorostidi@sego.es

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Introduction

Endometrial cancer (EC) is the most frequent malignant tumor of the female genital tract in developed countries, and its incidence has been increasing in recent years.¹ It is estimated that approximately 320,000 cases are diagnosed each year, with an incidence of 5.9% in developed countries.² However, the vast majority of patients (67%) have low-grade tumors confined to the uterus at diagnosis, with a 5-year survival rate of 90%.

Knowledge of lymph node involvement is one of the most important factors determining prognosis and the need for adjunctive treatment in these patients.³ The overall risks of metastasis to the pelvic and aortic nodes are 9% and 6%, respectively. In the case of well-differentiated tumors, these risks drop to 3% and 2%, and in tumors restricted to the endometrium to as low as 1%.⁴

Sentinel lymph node (SLN) detection in EC is now considered a standard alternative that can safely replace lymphadenectomy in women with tumors confined to the uterus.⁵ In the assessment of the SLN in the paraaortic area, access can be either transperitoneal or extraperitoneal. Although in the case of lymphadenectomy at this level both routes have been compared in terms of lymph node yield and perioperative results,⁶ there have been no studies to date comparing these 2 access approaches in the case of the paraaortic SLN.

The aim of this study is to analyze the differences found in terms of detection rate (DR) and location depending on the surgical approach to the aortocaval space.

Materials and Methods

In April 2014, the Donostia University Hospital Ethics Committee approved a prospective interventional clinical trial

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Why was this study conducted?

This study was performed to evaluate whether the approach to the aortic nodes could modify the identification of the aortic sentinel node in endometrial cancer.

Key findings

Extraperitoneal access identifies more aortic sentinel nodes in the left latero-aortic and preaortic locations.

What does this add to what is known?

The selection of the sentinel node in locations where it is more difficult to identify the afferent pathways of the lymphatic drainage chains is influenced by the visualization of a fluorescence node per se, “green” or true sentinel, making it more difficult to identify it unequivocally and may cause false negatives of the technique.

(ref. RRS-ECG-2014) titled “Evaluation of SLN Biopsy for Management of Endometrial Adenocarcinoma.” Between June 26, 2014 and December 31, 2019, 278 patients underwent laparoscopic surgery for EC at our hospital. All patients gave written consent for SLN biopsy. Data were obtained prospectively. Descriptions of the methods, the technique of dual transcervical and cervical superficial and deep fundal injection of the indocyanine green (ICG) tracer, and inclusion and exclusion criteria have been published previously.⁷

Women with low-risk preoperative stratification according to the European Society for Medical Oncology guidelines⁸ (<50% myometrial invasion assessed by magnetic resonance imaging, histologic grade G1–2 endometrioid disease assessed by endometrial biopsy) underwent transperitoneal SLN biopsy of the pelvic and paraaortic area, followed by hysterectomy and bilateral salpingo-oophorectomy and uterine frozen section, with subsequent pelvic and aortic lymphadenectomy if deep myometrial invasion was detected. Patients with high-risk EC also underwent SLN biopsy of the pelvic and paraaortic area, but in these cases an extraperitoneal approach was followed, and then full pelvic and paraaortic lymphadenectomy and hysterectomy and bilateral salpingo-oophorectomy were completed. In cases of type II histology, omentectomy and peritoneal biopsies were also performed.

The SLN at the pelvic level is defined as the first lymph node that receives the

afferent drainage via the upper and lower parametrial pathways visualized with fluorescence uptake using the tracer. In case of doubt as to which is the first station of lymph node drainage or division of the afferent pathways, >1 SLN can be removed. At the aortic level, it is complex to follow the infundibulopelvic afferent pathways of lymphatic drainage. The SLN is defined as the lymph node that has the most evident tracer uptake, and an additional lymph node may be removed in case of doubt as to which one corresponds to the true SLN.

The tracer was injected after pneumoperitoneum, trocar placement, peritoneal washings, and tubal sealing. As soon as the tracer was injected, the aortic SLN was searched for and dissected. First, the aortic SLN was removed, and afterward the pelvic SLNs were detected. When an extraperitoneal approach was selected, detection of the pelvic SLNs was done after completion of aortocaval lymphadenectomy. In cases of type II histology, omentectomy and peritoneal biopsies were also performed.

The surgeries were performed by 3 surgeons: 2 senior surgeons and a fellow supervised by one of the senior surgeons, using the same methodology.

All cases were treated according to their stage, as indicated by information provided by lymph node ultrastaging and knowledge of low-volume disease.

The results were analyzed with Stata 15 statistical software (StataCorp LLC, College Station, TX), describing means and standard deviation, or medians and

interquartiles (25–75) for quantitative variables and proportions for categorical variables. Means were compared using the Student *t* test, and proportions were compared using the Fisher exact 2-tailed test. Confidence intervals (CIs) were calculated using the Newcombe method. The significance level was set at $P < .05$. A diagnostic test was also performed using lymphadenectomy as the gold standard.

Results

A total of 278 patients were studied: 163 (58.6%) of them were operated using a transperitoneal approach and 115 (41.4%) using a retroperitoneal approach; 97.4% of the women in the extraperitoneal group had high-risk EC and 90.2% in the transperitoneal group had low-risk EC. The demographic characteristics of the population and the distribution of the different variables studied are summarized in [Table 1](#).

The SLN was detected in 259 patients, representing an overall DR of 93.2%. The aortic, pelvic, and bilateral pelvic DRs were 66.9%, 90.3%, and 68.0%, respectively. The DRs and the specific rates for each group can be seen in [Table 2](#). There were no significant differences in DR (including aortic detection) between the 2 groups (Fisher exact test).

The location of the aortic nodes was also studied. There were more women with SLNs (laterocaval, precaval, and interaortocaval) located on the right in the transperitoneal approach: 84 (54.9%) vs 32 (30.2%), and this difference was significant (Fisher exact test $P = .002$). There were also more women with SLNs (preaortic and latero-aortic) located on the left in the extraperitoneal approach: 69 (65.1%) vs 67 (43.8%), and this difference was also significant (Fisher exact test $P = .002$) ([Table 3](#)).

There was no difference between approaches in the location above or below the inferior mesenteric artery (IMA). The Fisher exact test for number of women with SLNs resulted in $P = .556$ for SLNs below the IMA, and $P = .166$ for SLNs above the IMA ([Table 4](#)).

A median of 1 aortic node (Interquartile range [IQR], 25–75; 0–3

TABLE 1
Characteristics of the population

Characteristics	Transperitoneal	Extraperitoneal	P value
Age (y)	61.0 (SD, 10.4)	66.2 (SD, 9.9)	<.0001 ^a
BMI (kg/m ²)	27.9 (SD, 5.8)	29.1 (SD, 5.8)	.0811
Inpatient stay (d)	2.1 (SD, 1.6)	2.6 (SD, 1.5)	.0039 ^a
Uterus weight (g)	120 (SD, 60.5)	138 (SD, 99.4)	.1053
Tumor size (mm)	29 (SD, 12.7)	38 (SD, 17.4)	.0001 ^a
Tumor grade			
• G1	104 (63.8%)	35 (30.4%)	<.001
• G2	41 (25.2%)	33(28.7%)	
• G3	18 (11.0%)	47 (40.9%)	
LVSI	28 (17.2%)	36 (31.3%)	.005 ^a
Myometrial invasion			
• No invasion	19 (11.7%)	5 (4.4%)	.001 ^a
• <50%	128 (78.5%)	48 (42.1%)	
• ≥50%	16 (9.8%)	61 (53.5%)	
Preoperative risk			
• Low risk	147 (90.2%)	3 (2.6%)	<.001 ^a
• High risk	16 (9.8%)	112 (97.4%)	
Lymphadenectomy node cont			
• Pelvic	11.8 (SD, 6.4)	15.1 (SD, 6.7)	.0264 ^a
• Aortic	13.3 (SD, 6.6)	14.3 (SD, 6.3)	.4643
FIGO stage			
• IA	154 (94.5%)	93 (80.9%)	.001 ^a
• IB	2 (1.2%)	5 (4.4%)	
• II	7 (4.3%)	17 (14.8%)	
Histology			
• Endometrial cancer	152 (93.3%)	86 (74.8%)	.001 ^a
• Serous cancer	3 (1.8%)	21 (18.3%)	
• Carcinosarcoma	0 (0%)	5 (4.4%)	
• Clear-cell carcinoma	4 (2.5%)	1 (0.9%)	
• Mixed	4 (2.5%)	2 (1.9%)	

Data are presented as median (±SD) or percentage in case of categories. Significance level was calculated with the *t* test for continuous data and Fisher exact test for categorical variables.

BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; SD, standard deviation.

^a Statistically significant result.

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SLNs) was removed with both approaches; a median of 2 (IQR, 25–75; 2–3 SLNs) aortic nodes were removed with the transperitoneal approach and a median of 3 (IQR, 25–75; 2–3 SLNs)

with the extraperitoneal approach. The global median of removed SLNs (pelvic and aortic) was 4 in both approaches (IQR, 25–75; 3–5 SLNs by transperitoneal approach; and IQR, 25–75; 3–6

SLNs by extraperitoneal approach). No significant differences were identified.

A positive SLN was detected in isolation in the aortic area in 11 patients, representing 4.3% of the sample and

TABLE 2**Global, aortic, pelvic, and bilateral pelvic detection rates in the transperitoneal, extraperitoneal, and combined groups**

DR	EC DR	Transperitoneal	Extraperitoneal	Fisher exact test
Global	93.2%	93.9%	92.2%	$P=.634$ (ns)
Aortic	66.9%	65.0%	69.6%	$P=.441$ (ns)
Pelvic	90.3%	92.0%	87.0%	$P=.224$ (ns)
Pelvic bilateral	68.0%	71.2%	63.5%	$P=.193$ (ns)

DR, detection rate; EC, endometrial cancer; ns, nonsignificant.

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24.4% of the total number of patients with positive nodes (Table 5).

The results of the diagnostic test for the transperitoneal approach were sensitivity (Se) of 100% (95% CI, 81.6–100), specificity (Sp) of 100% (95% CI, 96.2–100), negative predictive value (NPV) of 100% (95% CI, 96.2–100), and positive predictive value (PPV) of 100% (95% CI, 81.6–100). For the extraperitoneal approach, these were Se of 96.6% (95% CI, 82.8–99.4), Sp of

100% (95% CI, 97.2–100), NPV of 99.3% (95% CI, 96.0–99.9), and PPV of 100% (95% CI, 87.9–100).

Discussion

This study evaluated the differences between the transperitoneal and retroperitoneal approaches in the detection of SLNs at the paraaortic level in terms of DR and the anatomic location of the nodes. Detection was similar in both cases: 65% and 69.6%, respectively;

however, the location varied according to the access approach.

This study is a post hoc analysis of the original prospective study conducted at our center for the evaluation of the SLN technique by dual injection with the aim of identifying the 3 main uterine drainage pathways: high parametrial, low parametrial, and infundibulopelvic pathways.⁹ With regard to identification of the infundibulopelvic pathway, we indicate the advantages of

TABLE 3**Location and number of aortic sentinel lymph nodes by surgical approach**

Right SLNs	Transperitoneal	Retroperitoneal	Total
0	69 (45.1%)	74 (69.8%)	143 (55.2%)
1	50 (32.7%)	21 (19.8%)	71 (27.4%)
2	27 (17.6%)	9 (8.5%)	36 (13.9%)
3	5 (3.3%)	2 (1.9%)	7 (2.7%)
4	1 (0.7%)	0 (0%)	1 (0.4%)
5	1 (0.7%)	0 (0%)	1 (0.4%)
Total	153	106	259
Left SLNs			
0	86 (56.2%)	37 (34.9%)	123 (47.5%)
1	41 (26.8%)	28 (26.4%)	69 (26.6%)
2	17 (11.1%)	26 (24.5%)	43 (16.6%)
3	5 (3.3%)	12 (11.3%)	17 (6.6%)
4	2 (1.3%)	2 (1.9%)	4 (1.5%)
5	2 (1.3%)	1 (0.9%)	3 (1.2%)
Total	153	106	259

Right SLNs: laterocaval, precaval, and interaortocaval SLNs neg/isolated tumoral cells/micromets and macromets. Left SLNs: preaortic and lateroaortic SLNs neg/isolated tumoral cells/micromets and macromets.

SLN, sentinel lymph node.

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TABLE 4**Location and number of aortic sentinel lymph nodes with respect to the inferior mesenteric artery by surgical approach**

Inframesenteric SLNs	Transperitoneal	Retroperitoneal	Total
0	54 (35.3%)	37 (34.9%)	91 (35.1%)
1	53 (34.6%)	45 (42.5%)	98 (37.8%)
2	35 (12.9%)	19 (17.9%)	54 (20.9%)
3	8 (5.2%)	2 (1.9%)	10 (3.9%)
4	2 (1.3%)	2 (1.9%)	4 (1.5%)
5	1 (0.7%)	1 (0.9%)	2 (0.8%)
Total	153	106	259
Supramesenteric SLNs			
0	96 (62.8%)	54 (50.9%)	150 (57.9%)
1	42 (27.5%)	34 (32.1%)	76 (29.3%)
2	12 (7.8%)	16 (15.1%)	28 (10.8%)
3	2 (1.3%)	2 (1.9%)	4 (1.5%)
4	1 (0.7%)	0 (0%)	1 (0.4%)
Total	153	106	259

SLN, sentinel lymph node.

Gorostidi. Transperitoneal vs extraperitoneal approach for aortic sentinel node detection in endometrial cancer. *Am J Obstet Gynecol Glob Rep* 2022.**TABLE 5****Isolated aortic, pelvic, and pelvic and aortic sentinel lymph node metastases by surgical approach**

SLN metastasis	Total EC n (% , % of N+)	Transperitoneal approach n (% , % of N+)	Extraperitoneal approach n (% , % of N+)	P value
Total				
• Isolated aortic metastasis	11 (4.3%, 24.4%)	5 (3.3%, 29.4%)	6 (5.7%, 20.6%)	.365
• Isolated pelvic metastasis	26 (10.0%, 57.8%)	8 (5.2%, 47.1%)	18 (17.0%, 61.7%)	.003 ^a
• Pelvic and aortic metastases	8 (3.1%, 17.8%)	4 (2.6%, 23.5)	4 (3.8%, 13.7%)	.720
Total SLN metastases	45 (17.4%)^a	17 (11.1%)^a	28 (26.5%)^a	

EC, endometrial cancer; SLN, sentinel lymph node.

^a Statistically significant resultGorostidi. Transperitoneal vs extraperitoneal approach for aortic sentinel node detection in endometrial cancer. *Am J Obstet Gynecol Glob Rep* 2022.

cervical injection, with excellent drainage in the high and low parametrial pathways, over fundic injection.

The 2 analyzed groups were not homogeneous, which is explained by the different preoperative risk stratification of their tumors; this could have led to biases in the evaluation of the results because our approach differed according to this stratification. For this reason, differences between the 2 populations were to be expected, although it was not

expected that this would influence the anatomic location of the aortic SLN.

The reason for the difference in the selection of surgical approach is that the extraperitoneal approach is traditionally performed in our center for aortocaval lymphadenectomy because it facilitates the approach to the infrarenal lymph node areas considered particularly important in high-risk EC¹⁰ and allows moving the intestinal loops (which hinder surgery, especially in obese women

in whom this type of cancer is characteristic) away from the field.¹¹ Conversely, we consider that women who do not have an indication for aortocaval lymphadenectomy because of lack of risk factors should not undergo the greater dissection applied with this approach, nor the required placement of 2 additional trocars. In this regard, it should be noted that the aortic DRs were similar.

The search for the SLN at the pelvic level is performed immediately after

identification of the aortic SLN in the transperitoneal approach, but completing the aortocaval lymphadenectomy needs to be delayed if extraperitoneal access is used. This fact could have influenced both the DRs at this level and the number of SLNs obtained; however, transperitoneal and extraperitoneal pelvic DRs were 92.0% and 87.0%, respectively, with no significant differences. Although there was an increase in bilateral pelvic detection in the transperitoneal approach (71.2% vs 63.5%), this was not statistically significant, and thus we are not able to conclude whether the delay in the search for the pelvic SLN owing to the performance of an extraperitoneal aortic lymphadenectomy, can contribute to a lower rate of pelvic detection. Despite this, the detection figures are within the standard of most published studies,^{12–14} without reaching the excellent and desirable bilateral pelvic DRs obtained in the SHREC study.¹⁵ SLN detection can be maximized, with maximum interest in high-risk group, grade 3, and nonendometrioid histologies following specific algorithms, such as the one described by Bollino et al.¹⁶ The figures for Se, NPV, and false negatives in high-risk cases are in line with the latest published studies.^{13,15,17}

The number of aortocaval nodes obtained by the extraperitoneal approach is reported to be higher,^{18,19} especially in higher-body mass index patients,¹¹ although there are studies where no significant differences are found.⁶ There is no reason to expect the number of SLNs obtained at this level to vary, which is what we found in our study: 1 SLN was found in most cases, although occasionally we identified >1 node, with the 75th percentile of our study showing 3 aortic SLNs.

The greater localization of “right” nodes (laterocaval, precaval, and interaortocaval SLNs) in the transperitoneal approach (54.9% vs 30.2%) is striking. This is probably because of a better visualization of the anterior aspect of the great vessels, especially the laterocaval and interaortocaval SLNs, and vice versa, the greater localization of “left” nodes (preaortic and lateroaortic

SLNs) in the retroperitoneal approach (65.1% vs 43.8%). Both differences were statistically significant, undoubtedly because of better access to the lateroaortic and infrarenal region by retroperitoneal approach, and the subsequent performance of lymphadenectomy. The SLN detection technique does not allow us to easily identify the drainage pathways at the aortic level, which complicates the identification of the first lymph node, consequently raising doubts on whether the true SLN and not a “green node” has been identified. The difficulty of identifying and following the drainage pathways with precision is undoubtable in the aortocaval region, as opposed to the pelvis, where it is easier to follow the drainage pathway and identify the first and secondary stations. It is a fact that aortocaval lymph node drainage involves a more complex network compared with pelvic drainage, and is anatomically more complicated to follow.²⁰ This disadvantage could lead to the identification of false aortic SLNs.

Nevertheless, in our study we demonstrated that we correctly identified aortic lymph node disease (even in cases of microscopic or isolated disease), with only 1 false-negative case, which supports the validity of our technique.

Although ICG as a tracer allows excellent visualization of nodal drainage, it migrates rapidly throughout the nodal chain, ultimately revealing a complete nodal lymphogram (unlike other tracers such as technetium), and the use of combined tracers may be justified to improve these results.

We found no significant differences in identifying SLNs above or below the IMA, nor in the DR of isolated aortic metastasis between the transperitoneal and retroperitoneal approach (5.7% and 3.3%, respectively, corresponding to 20.6% and 29.4%, respectively, of the total number of women with positive nodes). The higher percentage of isolated pelvic metastases found with the extraperitoneal approach is striking, with no adequate explanation for this finding other than the greater probability of lymph node involvement because of the higher preoperative risk.

The number of isolated aortic metastases found was similar with both approaches. Although the percentage of patients with nodal involvement in the low-risk group was lower (7.3% vs 26.7% after ultrastaging in our series), the percentage of isolated aortic involvement was similar in low- and high-risk groups. Similar findings have been reported in a retrospective analysis of 2767 patients with nodal involvement from the Surveillance, Epidemiology, and End Results database (or the SEER database).²¹ With some groups, as with ours, efforts were made to detect direct drainage pathways to the aortocaval region, with good results at this level^{22,23}; however, the relevance of aortic SLN detection in different risk groups is a controversial issue.²⁰ We also detected a higher percentage of isolated pelvic metastases with the extraperitoneal approach, with the only explanation being the higher detection of isolated pelvic ITC in high-risk EC.

This study has the limitation of being a post hoc study, not designed to resolve the differences between the 2 routes, and exposed to bias owing to a nonhomogeneous population. However, it is not expected that the DR or anatomic location of the nodes would necessarily be different for this reason. In fact, the main limitation of this study was the dilemma on the definition of aortic SLN used methodologically and whether it should be considered a true SLN, given that although we can clearly observe the infundibulopelvic dissemination pathway, we cannot differentiate whether the afferent channel reaching the aortic SLN comes from the pelvic pathway and results in second-echelon green nodes (false SLNs) or from lymphatics in the infundibulopelvic ligament (potentially true SLNs) or both (impossible-to-define true SLNs). In fact, delaying the removal of the aortic SLN may cause the tracer to eventually produce a lymphography of the entire lymph node chain. For this reason, it is important to selectively remove the first node of the drainage chain as defined in the SLN concept, which for obvious reasons is more difficult to perform at the aortic level. This could have increased our false-negative

rate after the detection of the pelvic SLN because its search was delayed in the extraperitoneal vs transperitoneal technique; however, the rate was not altered. The strength of this study is its prospective, consecutive-patient design and the high number of patients collected and assessed over 5.5 years. Another fact to highlight is that this study improved on the existing evidence on the differences between the extraperitoneal and transperitoneal approach.

Although our results at the aortic level have been excellent, documenting no false negatives in the detection of isolated aortic metastases, and additionally detecting aortic lymph node metastases that are very difficult to detect by cervical injection, we could not methodologically ensure that every defined aortic SLN was a true SLN. In fact, although isolated aortic involvement in patients with lymph node involvement is as high as 1 in 4 patients, the overall number of patients with positive nodes is relatively low in EC, and it is possible that the removed aortic SLNs do not always correspond to the true SLNs. The differences found between the 2 approaches support this hypothesis. We could have defined these nodes as green nodes, but this does not correspond either to the purpose of this investigation or to the results obtained in this study.

Exclusive injection in the infundibulopelvic ligament could solve the problem, but it would obviate the main drainage pathway to the pelvic nodes and the objective of this technique, which is to add drainage pathways and obtain the most realistic information on lymph node involvement.

Future studies should primarily evaluate the correct demonstration of the identification of the true aortic SLN (perhaps using a tracer that does not migrate to successive nodal stations or dual tracers), and the rate of aortic SLN detection and localization by both approaches and their impact on morbidity and other perioperative outcomes in homogeneous populations with EC.

Conclusion

The rates of detection of aortic SLNs by transperitoneal and extraperitoneal

approaches are similar, with no impact on subsequent pelvic detection. The transperitoneal route detects more latero-caval, precaval, and interaortocaval SLNs, whereas the extraperitoneal route detects more preaortic and left latero-aortic SLNs. ■

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Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.xagr.2022.100120](https://doi.org/10.1016/j.xagr.2022.100120).

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