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The Impact of Sentinel Node-Mapping in Staging High-Risk Endometrial Cancer

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ABSTRACT

Background. This study aimed to determine the impact of sentinel lymph node (SLN)-mapping on the staging of high-risk endometrial cancer (endometrioid grade 3, serous, clear cell, carcinosarcoma, deep myometrial invasion, or angiolymphatic invasion).

Methods. The study analyzed a series of 236 patients treated at AC Camargo Cancer Center from June 2007 to February 2017. The compared 75 patients who underwent SLN-mapping (SLN group) with 161 patients who received pelvic ± para-aortic lymphadenectomy (N-SLN group). Patients with adnexal, peritoneal, or suspicious node metastases were excluded from the study.

Results. The groups did not differ in terms of age, histologic type, or presence of deep myometrial invasion. The overall detection rate for SLNs was 85.3%, and bilateral SLNs were observed in 60% of the patients. Of 20 positive SLNs, 8 (40%) were detected only after immunohistochemistry (IHC). The findings showed an overall sensitivity of 90%, a negative predictive value of 95.7%, and a false-negative predictive value of 4.3%. The SLN group had more pelvic node metastases detected than the N-SLN group (26.7 vs 14.3%; $p = 0.02$). However, the rate of para-aortic node metastases did not differ between the two groups (13.5 vs 5.6%; $p = 0.12$). Five patients (3.5%) in the N-SLN group had isolated para-aortic node metastases versus none in the patients with SLN mapped. Additionally, the SLN group received more adjuvant chemotherapy (48 vs 33.5%; $p = 0.03$).

Conclusions. The data suggest that SLN-mapping identifies more pelvic node metastases than lymph node dissection alone and increases the node detection rate by 12.5% after IHC. Furthermore, no isolated para-aortic node metastases are observed when SLN is detected.

Although lymph node (LN) involvement is well recognized as an important prognostic factor in endometrial cancer, the impact of lymph node dissection (LND) on survival continues to be debated. Furthermore, two randomized clinical trials examining the therapeutic value of pelvic LND in presumed uterine-confined disease found no survival benefit.[1,2]

Despite confinement of their disease to the uterus, most patients with endometrial cancer undergo systematic lymphadenectomy for staging purposes, resulting in prolonged operating times, increased costs, and potential morbidity. Consequently, sentinel lymph node (SLN)-mapping has emerged as a viable alternative to complete lymphadenectomy in endometrial cancer.[3]

Although growing evidence supports SLN-mapping in endometrial cancer, with SLN status accurately predicting the status of the regional lymphatic basin, most trials have included patients at low risk for lymph node involvement. Moreover, few studies have compared patients who have undergone SLN-mapping and systematic lymphadenectomy alone.

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This study aimed to compare a series of patients at high risk for lymph node metastasis who received SLN-mapping with patients who underwent systematic lymph node dissection without SLN-mapping. We hypothesized that SLN-mapping could more accurately identify women with positive lymph nodes and increase the detection rate of pelvic node metastasis, thereby lowering the risk of isolated para-aortic metastases.

METHODS

We analyzed a series of 602 patients treated for endometrial cancer from June 2007 to February 2017 at AC Camargo Cancer Center by the same gynecologic oncology team. Of these subjects, 358 underwent systematic lymphadenectomy as part of the surgical staging procedure without SLN-mapping. We excluded 58 patients with peritoneal or adnexal metastasis and 13 patients with suspicious lymph node enlargement. Also, 125 low-risk endometrial cancers were excluded. Ultimately, 161 high-risk patients were included in the nonsentinel lymph node (N-SLN) group.

Separately, 183 patients underwent sentinel node-mapping from November 2012 to February 2017, 88 of whom were high-risk patients. Six of these subjects were excluded due to suspicious lymph node enlargement, as well as seven patients who had not undergone lymph node dissection together with SLN-mapping. Ultimately, 75 patients constituted the sentinel lymph node group (SLN). The patients in the SLN protocol were prospectively assigned after institutional review board approval (#120563). Figure 1 summarizes the enrollment.

The criteria for high-risk tumors required one of the following: high-grade tumor (endometrioid grade 3 and nonendometrioid histologies: serous, clear cell, or carcinosarcoma), deep myometrial invasion (MI) ($\geq$ 50%), or the presence of angiolymphatic invasion (LVSI).

In the sentinel node protocol, all patients received patent blue dye. The following was administered only by cervical injection: a total of 4 ml of patent blue dye [1 ml superficial and 1 ml deep (1 cm)] at 3 and 9 o'clock. All blue nodes were resected, and patients with suspicious enlargements were excluded. After SLN resection, the patients also received a systematic pelvic $\pm$ para-aortic lymphadenectomy.

A gynecologic pathologist prospectively viewed the pathologic specimens. The SLNs were examined by IHC when the hematoxylin-eosin (H&E) stain was negative. Briefly, the SLNs were serially sectioned every 2 mm and stained with H&E at three levels of the tissue block. If the sample was negative, a pan-cytokeratin stain was performed at each of the three levels. The SLNs were classified as macrometastasis (tumor $\geq$ 2.0 mm), micrometastases (tumor cell aggregates between 0.2 and 2 mm), isolated tumor cells (ITCs) (individual tumor cells or aggregates $\leq$ 0.2 mm), or negative.

All lymph nodes with macroscopic, microscopic, and isolated tumor cells were considered to be positive. Non-sentinel lymph nodes were reported as positive or negative for metastases based on routine sectioning and examination of a single H&E-stained slide per a standard protocol.

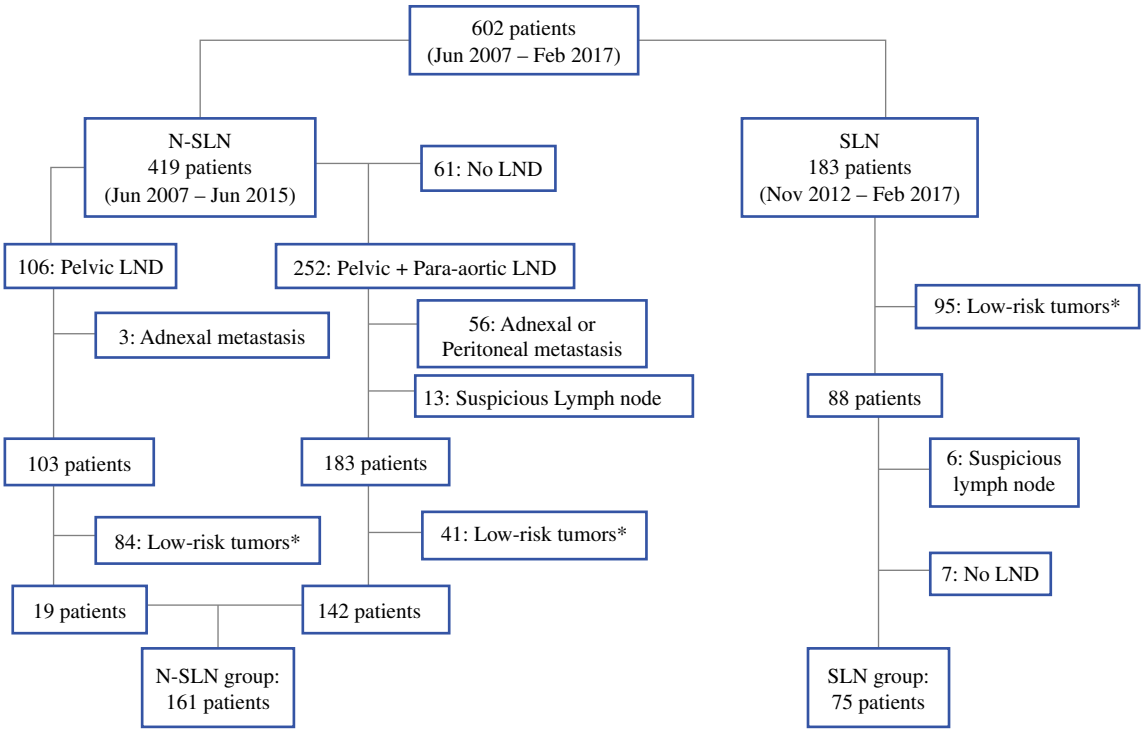
A database was constructed using SPSS, version 20.0 for Mac (SPSS, Inc., Chicago, IL, USA). Chi-square, Fisher's exact, Kruskal–Wallis, and Student *t* tests were used to analyze the correlations between categories and clinicopathologic variables. For all tests, a p value lower than 0.05 was considered to be significant.

RESULTS

This study included 236 high-risk patients (161 in the N-SLN group and 75 in the SLN group). The groups did not differ in terms of age, histologic type, or presence of deep myometrial invasion. Compared with the N-SLN group, the SLN group had more minimally invasive surgeries (68 vs 3.1%; $p < 0.001$) and higher rates of LVSI (42.7 vs 15.5%; $p < 0.001$). The pelvic lymph node counts were higher in the N-SLN group (median, 32 vs 26; $p = 0.02$). The para-aortic node count did not differ between groups (median, 16). Regarding adjuvant treatment, radiotherapy did not differ between the groups. In the SLN group, 48% of the patients received adjuvant chemotherapy compared with 33.5% in the N-SLN group ($p = 0.03$). The clinical and pathologic data are summarized in Table 1.

With regard to the presence of LN metastasis, the SLN group had more pelvic node metastases than the N-SLN group (26.7 vs 14.3%; $p = 0.02$). However, the rates for para-aortic LN metastasis were statistically similar (13.5 vs 5.6%; $p = 0.12$). Five (3.5%) of the N-SLN patients had para-aortic metastasis without pelvic LN metastasis. Conversely, one patient (1.9%) in the SLN group had isolated para-aortic LN metastasis, and this patient had mapping failure in the pelvis, with normal lymph nodes from the completion of pelvic lymphadenectomy (Table 2). The patients whose SLNs were mapped had no isolated para-aortic LN metastasis.

In the SLN group, the overall detection rate was 85.3% (64/75), and bilateral SLNs were observed in 60% (45/75). A total of 133 SLNs were detected, with a median of 2 (range 1–5) and a median positive SLN count of 1.5 (range 1–4). Most SLNs were seen in the external iliac and obturatory areas. However, the SLNs of two patients (1.5%) were detected in the retroperitoneal area, one of



N-SLN: Non-sentinel node mapping; SLN: Sentinel node mapping; LND: Lymph node dissection
*Endometrioid grades 1 or 2, <50% myometrial invasion, absence of lymphovascular space invasion

FIG. 1 Schematic description of patient's enrollment

which was para-caval and intercavo-aortic below the inferior mesenteric artery. Notably, both patients were positive for micrometastases and had no other SLNs in the right hemi-pelvis. The lymphatic trunk leading to the para-aortic nodes clearly emanated from the pre-sacral lymphatics.

We had two false-negatives. The first patient had a unilateral negative SLN with a positive ipsilateral non-SLN positive lymph node, and the second patient had bilateral negative SLNs with positive pelvic non-SLNs.

We recorded an overall sensitivity of 90%, a negative predictive value (NPV) of 95.7%, a false-negative rate of 10% (2/20), and a false-negative predictive value (FNPV) of 4.3% (2/46). In the evaluation per 121 hemi-pelvises, these rates were respectively 92.6, 97.9, 7.4, and 2.1%.

Of the 64 patients who had SLNs detected, 20 (31.3%) were positive. The findings showed four patients (6.3%) with ITCs, six patients (9.4%) with micrometastases, and eight patients (12.5%) with macrometastases. Notably, eight patients (12.5%) had LN metastases detected only after IHC. In 14 patients (70%), the SLN was the only positive node. Five endometrioid tumors (12.5%) had LN metastases detected only after IHC. In the entire SLN group, only IHC detected node metastasis 10.6% (8/75) of the patients and 10.4% (5/48) of all the endometrioid patients (Table 3).

DISCUSSION

Although most patients with endometrial cancer present with early-stage disease, the standard treatment still includes systematic lymph node dissection for staging. Recently, SLN-mapping has emerged as an acceptable surgical strategy for deciding between complete lymphadenectomy and no node dissection. This approach can help to avoid the morbidity associated with a complete lymphadenectomy, such as neurovascular injury, lymphocyst formation, and lymphedema.[4]

A recent meta-analysis that included 55 studies and 4915 patients reported an overall SLN detection rate of 81% (95% confidence interval CI 77–84%) versus a 50% detection rate for bilateral SLNs (95% CI 44–56%). Moreover, the use of indocyanine green increased the bilateral SLN detection rate compared with blue dye (74.6 vs 50.5%).[5] Yet, the studies noted an overall sensitivity of 96% (95% CI 91–98%) and false-negative rates lower than 5% when the analysis was performed per hemipelvis.[5,6] Since 2014, the National Comprehensive Cancer Network (NCCN) guidelines have recommended SLN-mapping as an alternative option for node staging in endometrial cancer.[7]

TABLE 1 Clinical and pathologic characteristics of the 236 high-risk endometrial cancer patients

Variable	N-SLN ($n = 161$)	SLN ($n = 75$)	p value
Median age: years (range)	61 (36–85)	61 (41–83)	0.72
Median BMI: kg/m^2 (range)	26.7 (16.2–58.3)	27.2 (17.9–43.7)	0.58
Minimally invasive surgery	5 (3.1)	51 (68)[a]	<0.001
Type of lymphadenectomy			
Pelvic	19 (11.8)	23 (30.7)	<0.001
Pelvic and para-aortic	142 (88.2)	52 (69.3)	
Median pelvic node count (range)	32 (2–90)	26 (10–69)	0.02
Median para-aortic node count (range)	16 (2–45)	16 (2–68)[b]	0.38
Adjuvant treatment			
External beam radiotherapy	91 (56.5)	44 (58.7)	0.75
Brachytherapy	121 (75.2)	56 (74.7)	0.93
Chemotherapy	54 (33.5)	36 (48)	0.033
Histologic type			
Endometrioid	107 (66.5)	48 (64)	
Serous	22 (13.6)	10 (13.3)	
Clear cell	13 (8.1)	8 (10.7)	
Carcinosarcoma	14 (8.7)	7 (9.3)	
Serous + clear cell	3 (1.9)	2 (2.7)	
Undifferentiated	2 (1.2)	0	
Endometrioid	107 (66.5)	48 (64)	0.71
Non-endometrioid	54 (33.5)	27 (36)	
Histologic grade			
1	21 (13)	7 (9.3)	
2	19 (11.8)	23 (30.7)	
3[a]	121 (75.2)	45 (60)	
Histologic type and grade			
Endometrioid G1 or 2	40 (24.8)	30 (40)	0.012
Endometrioid G3	68 (42.2)	18 (24)	
Non-endometrioid	53 (32.9)	27 (36)	
Presence of LVSI[c]	25 (15.5)	32 (42.7)	<0.001
Myometrial invasion $\geq$ 50%	97 (60.2)	43 (57.3)	0.67

N-SLN nonsentinal lymph node; *SLN* sentinel lymph node; *BMI* body mass index; *MIS* minimally invasive surgery; *LVSI* Lymphovascular space invasion

[a]35 (46.7%) conventional laparoscopies and 16 (21.3%) robotic assisted laparoscopies

[b]Included patients with pelvic and para-aortic node dissection

[c]Included non-endometrioid histologies

We have presented a series of patients with at least one recognized uterine risk factor for node metastasis: high-grade histology and the presence of LVSI or deep myometrial invasion. The SLN group had more cases with LVSI, and this finding may be explained by better identification in recent years by a gynecologic pathologist. Patients with suspicious node enlargement shown on preoperative imaging or found during surgery were excluded. Patients subjected to SLN-mapping have been prospectively enrolled since late 2012 and compared with a series of patients who were treated by the same surgical team and underwent node dissection without SLN-mapping.

During the study period, we also witnessed a paradigm shift in the surgical treatment of high-risk patients from laparotomy to laparoscopy. In the SLN-mapping group, the patients received only blue dye by cervical injection. Nevertheless, the overall detection rate was 85.3%, and the detection rate for bilateral SLNs was 60%, approaching the rates of published series with indocyanine green.[8,9] This finding might prompt centers with low resources in low-middle-income countries to begin an SLN-mapping

TABLE 2 Lymph node metastasis distribution of the 236 high-risk endometrial cancer patients

Lymph node metastasis	All patients ($n = 236$)	N-SLN ($n = 161$)	SLN ($n = 75$)	p
Pelvic *n* (%)	44 (18.2)	23 (14.3)	20 (26.7)	0.02
Para-aortic n (%)	15 (7.7)[a]	8 (5.6)[b]	7 (13.5)[c]	0.12
Any *n* (%)	49 (20.7)	28 (17.4)	21 (28)	0.06
Isolated para-aortic *n* (%)	6 (2.6)[a]	5 (3.5)	1 (1.9)[c]	

N-SLN nonsentinal lymph node; *SLN* sentinel lymph node

[a]194 patients had pelvic and para-aortic lymphadenectomy

[b]142 patients had pelvic and para-aortic lymphadenectomy

[c]52 patients had pelvic and para-aortic lymphadenectomy

TABLE 3 Lymph node metastasis distribution of the 64 patients with sentinel node detected regarding histologic type

	Endometrioid ($n = 40$)	Non-endometrioid ($n = 24$)	All patients ($n = 64$)
Lymph node metastasis			
Pelvic *n* (%)	14 (35)[a]	6 (25)	20 (31.3)
Para-aortic *n* (%)	4 (16)[b]	2 (8.3)[c]	6 (12)[d]
Isolated *n* (%)	-	-	0
Any *n* (%)	14 (35)	6 (25)	20 (31.3)
Median SLN detected	2 (1–5)	2 (1–4)	2 (1–5)
Median positive SLN (range)	1.5 (1–4)	1.5 (1–2)	1.5 (1–4)
SLN metastasis size			
Isolated tumor cells *n* (%)	2 (5)	2 (8.3)	4 (6.3)
Micrometastasis *n* (%)	5 (12.5)	1 (4.2)	6 (9.4)
Macrometastasis *n* (%)	5 (12.5)	3 (12.5)	8 (12.5)
Diagnosis after IHC *n* (%)	5 (12.5)[e]	3 (12.5)[f]	8 (12.5)

SLN sentinel lymph node; *IHC* immunohistochemistry

[a]2 Patients had a negative SLN and positive pelvic nodes

[b]1 Patient had a positive intercavo-aortic sentinel node and a positive sentinel node in the left hemipelvis

[c]1 Patient with carcinosarcoma had a para-caval positive sentinel node and also a bilateral positive pelvic non-sentinel node

[d] 50 Patients had a pelvic and para-aortic lymphadenectomy

[e]5/12 (41.7%) positive SLN

[f]3/6 (50%) positive sentinel node

program because blue dye is an inexpensive marker and can be used in both open and laparoscopic surgeries.

Most studies investigating SLN-mapping have included patients at low risk for lymph node involvement and thus might have underestimated the false-negative rate. Recently, Soliman et al.[10] reported a series of only high-grade and deep invasive endometrial cancers for which patients underwent SLN-mapping followed by pelvic and para-aortic lymph node dissection. An 89% detection rate was reported, suggesting that SLN-mapping accurately identifies node metastases, with an NPV of 98% and an FNPV of 2% when the analysis is performed by hemipelvises. Positive nodes were found in 22.8% of the patients (43% of ITCs and micrometastases), and the SLN was the only positive node in 40% of the patients,. Our data corroborate these findings. In our study, 26.7% of the high-risk patients had positive nodes (50% of ITCs and micrometastases), and when the analysis was performed by hemipelvis, the NPV was 97.9% and the FNPV was 2.1%. In 14 patients (70%), the SLN was the only positive node.

Few publications have compared the results from the addition of SLN-mapping to lymphadenectomy alone. Raimond et al.[11] compared 156 patients who had SLN-mapping with 95 patients who had pelvic node dissection. In their study, SLN-mapping and ultra-staging were performed for low- and intermediate-risk patients, and the former detected a metastatic node three times more often than complete pelvic lymphadenectomy alone (16.2 vs

TABLE 4 Published series of sentinel node-mapping associated with para-aortic lymphadenectomy

Study	*n*	High-grade[a]	Non-endometrioid	Positive node (%)	Isolated PA SLN	Isolated PA positive node[b]
1. Holloway et al.[12]	119	29 (24.4%)	21 (17.6%)	36 (30.3%)	NA	0
2. Rossi et al.[9]	356[c]	102 (28.6%)	64 (18%)	41 (11.5%)	3 (0.8%)	0
3. Soliman et al.[10]	101	101	57 (56.4%)	23 (22.8%)	2 (2%)	0
4. Present series	75[d]	45 (60%)	27 (36%)	20 (26.7%)	2 (2.6%)	0

PA para-aortic; *SLN* sentinel lymph node

[a]High-grade histologies include endometrioid grade 3 and non-endometrioid histologies

[b]Includes only patients with sentinel node mapped

[c]196 Patients had para-aortic lymphadenectomy

[d]52 Patients had para-aortic lymphadenectomy

5.1%; $p = 0.03$). Their study had no false-negatives, and the IHC findings modified the adjuvant therapy in half of all the cases.

Holloway et al.[12] compared a series of 661 patients who had undergone pelvic and para-aortic lymphadenectomy with 119 patients subjected to SLN-mapping plus node dissection, including 68 high intermediate- and high-risk patients in the SLN-mapping group (GOG99 stratification). Despite the similarity in demographics and pathologic risk factors, the SLN group had more LN metastases detected (30.3 vs 16.3%; $p < 0.001$) and received more adjuvant therapy (28.6 vs 16.3%; $p = 0.003$). The SLN was the only positive node in 18 (50%) of the mapped cases, and the false-negative rate was 2.8%.

Colleagues from Memorial Sloan Kettering Cancer Center (MSKCC) compared the performance of an SLN algorithm with systematic lymphadenectomy at the Mayo Clinic for endometrioid adenocarcinoma, with less than 50% myometrial invasion. The detection of pelvic node metastases favored the SLN algorithm (5.1 vs 2.6%; $p = 0.03$), with no difference in para-aortic node metastases.[13]

Our study included only patients with a high risk of nodal metastasis and recorded a higher pelvic node metastasis rate for the SLN-mapping group (26.7 vs 14.3%; $p = 0.02$), but no significant difference in para-aortic node metastases (13.5 vs 5.6%; $p = 0.12$). Notably, when only patients with mapped SLNs were considered, 31.3% had pelvic positive nodes. Despite the differences in uterine risk factors between the groups, 10.6% (8/75) of the patients in the SLN group had node metastasis diagnosed only after IHC. If these patients had been excluded, the SLN group would have had a node positivity rate of 17.3%, similar to the N-SLN group (17.4%), reinforcing the impact of ultra-staging on the detection of node metastases. Moreover, the SLN group received more adjuvant chemotherapy (33.5 vs 48%).

One of the remaining uncertainties in SLN-mapping is the risk of isolated para-aortic node metastasis. Nearly half of all patients with pelvic node metastasis also have para-aortic node metastasis.[14–16] However, isolated para-aortic metastasis is an uncommon event, with rates ranging from 1 to 3%.[14–16] Whether the prevalence of isolated para-aortic nodal metastasis declines further when ultra-staging of pelvic sentinel nodes is routinely performed remains unknown. Theoretically, if pelvic nodes are subjected to a more detailed pathologic analysis, micrometastases can be detected, and the presence of isolated para-aortic nodal metastases might decrease.[3,6,16] However, a major concern remains due to the lower rates of para-aortic SLN detection after cervical dye injection compared with fundal or hysteroscopic injection.[5,6]

However, recent studies have suggested a negligible risk of isolated para-aortic metastasis when SLNs are mapped (Table 4). In the Fluorescence Imaging for Robotic Endometrial Sentinel lymph node biopsy trial,[9] no isolated para-aortic nodal metastases developed among the patients with detected SLNs. In this trial, 58% of the patients underwent para-aortic lymphadenectomy, and 29% ($n = 102$) had high-grade tumors. The para-aortic SLN detection rate was higher than in other studies with cervical injection (23%), but isolated para-aortic SLN-mapping after cervical injection was performed in three cases (< 1%), two of which had SLN metastases. Similarly, Holloway et al.[12] found no isolated para-aortic metastases in patients with mapped SLNs versus 0.9% in the group subjected to LND without SLN-mapping. Finally, in their validation trial of high-risk patients, Soliman et al.[10] found 2% of SLNs only in the para-aortic region and detected one isolated para-aortic node metastasis in an unmapped patient.

Our series had 1.5% of SLNs mapped in the para-aortic region, and one patient in the SLN group had isolated para-aortic metastasis. However, this patient had no SLN mapped. In summary, no isolated para-aortic metastasis was detected in SLN-mapped patients. This finding refutes the value of para-aortic lymphadenectomy in staging for

patients with pelvic negative SLNs, especially if they are detected bilaterally.

Overall, our series was comparable in size with the most recent studies on this topic and contributed valuable data. The strengths of our study were its inclusion of only high-risk patients, the presence of a comparison group, and the high median node counts for both groups, suggesting that the systematic node dissection is reliable and the surgical approach is uniform. Although the sentinel node data were prospectively collected, the study still might suffer from the inherent biases of a retrospective single-institution design because the control group data were retrieved from our databank.

In conclusion, our data suggest that SLN-mapping and ultra-staging for high-risk patients increases the detection of node metastases and influences adjuvant treatment-related decisions. Moreover, patients with negative SLNs that are mapped can safely forgo para-aortic lymphadenectomy.

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