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RESEARCH ARTICLE

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# Para-aortic lymphadenectomy can be omitted in most endometrial cancer patients at risk of lymph node metastasis

Glauco Baiocchi MD, PhD[1] | Carlos Chaves Faloppa MD[1] | Henrique Mantoan MD[1] | Willian Ricardo Camarço MD[1] | Levon Badiglian-Filho MD, PhD[1] | Lillian Yuri Kumagai MD[1] | Louise De Brot MD, PhD[2] | Alexandre Andre Balieiro Anastacio da Costa MD, PhD[3]

[1] Department of Gynecologic Oncology, AC Camargo Cancer Center, Sao Paulo, Brazil

[2] Department of Anatomic Pathology, AC Camargo Cancer Center, Sao Paulo, Brazil

[3] Department of Medical Oncology, AC Camargo Cancer Center, Sao Paulo, Brazil

**Correspondence**
Glauco Baiocchi, MD, PhD, Departamento de Ginecologia Oncológica, AC Camargo Cancer Center, Rua Antonio Prudente, 211, 01509–010, São Paulo, Brazil.
Email: glbaiocchi@yahoo.com.br; glauco.baiocchi@accamargo.org.br

**Objectives:** To determine the predictive factors of para-aortic lymph node (PALN) metastasis in endometrial cancer (EC) and recommend a subgroup of patients who can safely forgo PALN dissection.

**Methods:** We analyzed a series of 255 patients who were at risk of lymph node metastasis and treated from June 2007 to June 2015. All patients underwent systematic pelvic and para-aortic lymphadenectomy.

**Results:** The median number of pelvic lymph nodes (PLN) and PALNs that were resected was 33 and 15, respectively. Fifty (19.6%) patients had LN metastasis—43 (16.9%) pelvic, 28 (11%) para-aortic, 21 (8.2%) pelvic and para-aortic, and 7 (2.7%) isolated PALN metastasis. PALN metastasis was significantly associated with PLN metastasis, the presence of lymphovascular space invasion, deep myometrial invasion (MI), and histological grade 3. In the multivariate analysis, only pelvic LN metastasis and deep MI remained independent risk factors of PALN metastasis. For patients without LN enlargement ± adnexal metastasis, when deep MI and PLN metastasis were absent, the risk of PALM was 0.8%.

**Conclusions:** Our series supports that PALN metastasis is a rare event in the absence of PLN metastasis and that most patients can safely forego PALN dissection. This subgroup can be identified by the combined absence of PLN metastasis and deep MI.

KEYWORDS

endometrial cancer, lymph node metastasis, para-aortic lymphadenectomy

## 1 | INTRODUCTION

The value of lymph node dissection (LND) in endometrial cancer (EC) remains one of the most controversial topics in gynecological oncology. Although lymph node (LN) involvement is well recognized as an important prognostic factor, the impact of LND in survival continues to be debated.[1] Further, two randomized clinical trials have addressed the therapeutic benefit of pelvic LND in low-risk EC but found no survival benefit.[2,3]

In 2009, the revised staging system recognized para-aortic node (PALN) dissemination as a commonly affected site and stratified tumors by regional nodal status.[4] However, PALN metastases are found in less than 10% of patients,[5] and systematic PALN might be associated with significant morbidity.[6]

Although LN status remains an essential part of EC staging and determines the adjuvant therapy, the routine addition of PALN dissection might only add morbidity, without having an impact on survival in most patients; further, it does not allow adjuvant treatments to be tailored.[6]

The low prevalence of PALN metastasis complicates the identification of a subgroup of patients who are at risk of PALN involvement and who might benefit from PALN dissection. Our aim was to determine the predictive factors of PALN metastasis and recommend a subgroup of patients who can safely forgo PALN

  

dissection. The identification of this subgroup, who is at true risk of PALN, might be spared useless surgeries, lower costs, and diminish morbidity without sacrificing important clinical data. We also compared our data with the best evidence and the current recommendations for PALN dissection.[7]

## 2 | METHODS

We analyzed a series of 434 patients who were treated for endometrial cancer from June 2007 to June 2015 at AC Camargo Cancer Center by the same gynecological oncology team. Of these subjects, 373 underwent lymphadenectomy as part of the surgical staging, and 267 received both pelvic and para-aortic lymphadenectomies. We excluded 12 patients with peritoneal metastasis and ultimately evaluated 255 patients. Thirty-three (12.9%) underwent para-aortic lymphadenectomy up to the inferior mesenteric artery, versus 222 (87.1%) up to the renal vessels.

The criteria for pelvic and para-aortic lymphadenectomies were the presence of 1 of the following: endometrioid histology larger than 2 cm in size and superficial myometrial invasion (<50%) (MI); deep MI (≥50%); grade 3 endometrioid tumors; serous or clear cell histologies; the presence of lymphovascular space invasion (LVSI); and the presence of adnexal metastasis.

We performed frozen section for all patients to determine tumor size and myometrial invasion. Suspicious adnexal mass was also confirmed by frozen section. However, LVSI was not routinely assessed by frozen section. Of the 42 patients with LVSI, eight had superficial myometrial invasion and further three had non-endometrioid histologies. The remaining five patients with LVSI and superficial myometrial invasion had endometrioid grades 1 or 2 and tumor larger than 2 cm. The diagnosis of LVSI was done mainly in the final pathology. Slides of positive pelvic nodes were retrieved and reviewed for the size of the metastasis.

A database was constructed using SPSS, version 20.0 for Mac (SPSS, Inc., Chicago, IL). Chi-square and Fisher's exact were used to analyze the correlations between categories and clinicopathological variables. Multivariate analysis was performed by logistic regression. For all tests, an alpha error of up to 5% ($P < 0.05$) was considered to be significant.

## 3 | RESULTS

The median age was 60.3 years (range, 29-85), and the median tumor size was 3.7 cm (range, 0.3-16). Of 208 endometrioid tumors, 81 (38.9%) were histological FIGO grade 3, and 47 (18.4%) had serous or clear cell histologies. Forty-two (16.7%) patients had LVSI, 121 (47.5%) had deep MI (≥50%), and 26 (10.4%) had adnexal involvement. The clinical and pathological variables are summarized in Table 1.

The median number of pelvic LNs and PALNs that were resected was 33 (range, 5-90) and 15 (range, 2-45), respectively. Fifty (19.6%) patients had LN metastasis: 43 (16.9%) pelvic, 28 (11%) para-aortic, 21 (8.2%) pelvic, and para-aortic, and 7 (2.7%) isolated PALN metastasis. Table 2 summarizes the presence of LN involvement in endometrioid and non-endometrioid histologies.

Notably, of 50 patients with positive LNs, 13 (26%) had suspicious pelvic ± para-aortic LN enlargement. When we excluded three

**TABLE 1** Clinical and pathological characteristics of the 255 patients with endometrial cancer submitted to pelvic and para-aortic lymphadenectomy

| Variable | No. of patients | (%) |
|---|---|---|
| Adnexal metastasis | | |
| No | 224 | 89.6 |
| Yes | 26 | 10.4 |
| Missing | 5 | 2 |
| Histologic type | | |
| Endometrioid | 208 | 81.6 |
| Serous | 25 | 9.8 |
| Clear cell | 18 | 7.1 |
| Mixed[a] | 4 | 1.5 |
| LVSI[b] | | |
| No | 210 | 83.3 |
| Yes | 42 | 16.7 |
| Missing | 3 | 1.2 |
| Myometrial invasion | | |
| <50% | 134 | 52.5 |
| ≥50% | 121 | 47.5 |
| Pelvic LNM[c] | | |
| No | 212 | 83.1 |
| Yes | 43 | 16.9 |
| Number of pelvic LNM[c] | | |
| 1 | 16 | 37.2 |
| ≥2 | 27 | 62.8 |
| Size of pelvic LNM[c] | | |
| Micro | 6 | 21.4 |
| Macro | 22 | 78.6 |
| Missing | 15 | 34.8 |
| Para-aortic LNM[c] | | |
| No | 227 | 89 |
| Yes | 28 | 11 |
| Histologic grade | | |
| Grade 1 + 2 | 127 | 49.8 |
| Grade 3[d] | 128 | 50.2 |
| Tumor size | | |
| ≤2 cm | 45 | 20.9 |
| >2 cm | 170 | 79.1 |
| Missing | 40 | 15.7 |

[a]Mixed: clear cell + serous histologies.
[b]LVSI: Lymphovascular space invasion.
[c]LNM: Lymph node metastasis.
[d]Includes endometrioid G3, clear cell and serous histologies.

**TABLE 2** Correlation between histological type and site of lymph node metastasis for 255 patients with endometrial cancer

| Histology | Pelvic LNM[a] *n* (%) | Para-aortic *n* (%) | Pelvic and Para-aortic *n* (%) | Isolated para-aortic *n* (%) | Any LNM[a] *n* (%) | Total *n* |
|---|---|---|---|---|---|---|
| Endometrioid | 31 (14.9%) | 21 (10.1%) | 15 (7.2%) | 6 (2.9%) | 37 (17.8%) | 208 |
| Serous and Clear Cell | 12 (25.5%) | 7 (14.9%) | 6 (12.8%) | 1 (2.1%) | 13 (27.7%) | 47 |
| All histologies | 43 (16.9%) | 28 (11%) | 21 (8.2%) | 7 (2.7%) | 50 (19.6%) | 255 |

[a]LNM: Lymph node metastasis.

patients with LN enlargement ± adnexal metastasis, only 4 (1.6%) had PALN metastasis without pelvic LN metastasis.

The median number of PLN and PALN metastases was 2 (range, 1-29) and 2 (range, 1-18), respectively. Sixteen patients (37.2%) had one positive PLN, and 27 (62.8%) had ≥2. Of 43 patients with PLN metastasis, the size of the metastasis was measured in 28, the median of which was 4.5 mm (range, 0.5-30).

PALN metastasis was associated with PLN metastasis (48.8% vs 3.3%; $P < 0.001$), presence of LVSI (33.3% vs 6.7%; $P < 0.001$), deep MI (20.7% vs 2.2%; $P < 0.001$), and histological grade 3 (14.8% vs 7.1%; $P = 0.048$). The presence of pelvic node metastasis and the number of positive pelvic nodes (63% ≥2 LN vs 25% 1 LN; $P = 0.016$) correlated with the presence of PALN metastasis (Table 3).

By multivariate analysis, only pelvic LN metastasis (HR 14.7, 5.13-42.3; 95%CI: $P < 0.001$) and deep myometrial invasion (HR 4.28, 1.10-16.5; 95%CI: $P = 0.035$) remained independent risk factors of PALN metastasis (Table 4).

Patients with clear cell and serous histologies were more likely to have adnexal metastasis or suspicious LNs compared with endometrioid tumors (25.5% vs 13.5%; $P = 0.04$). However, clear cell and serous histologies were unrelated to PALN metastasis versus endometrioid histology (14.9% vs 10.1%; $P = 0.34$). Notably, when patients with adnexal or suspicious LNs were excluded, no subject with clear cell and serous tumors had PALN metastasis, compared with 4.4% for endometrioid histology ($P = 0.35$).

Next, we evaluated the 215 patients without suspicious LN enlargement or adnexal metastasis and stratified them by depth of invasion. For patients with superficial MI, 1 of 125 (0.8%) had PALN metastasis without PLN metastasis, but this patient had a grade 3 endometrioid tumor. For patients with deep MI, 3 of 73 (4.1%) had isolated PALN metastasis—with an endometrioid grade 3 tumor with negative LVSI, an endometrioid grade 2 tumor and positive LVSI, and an endometrioid grade 2 tumor with negative LVSI, respectively (Table 5).

**TABLE 3** Association between clinical-pathological variables and para-aortic metastasis for the 255 patients with endometrial cancer

| | Para-aortic lymph node (no. of patients) | | | |
|---|---|---|---|---|
| Variable | Category | Negative | Positive | *P* |
| Adnexal metastasis | No | 204 | 20 | 0.004 |
| | Yes | 18 | 8 | |
| Histologic type | Endometrioid | 187 | 21 | 0.34 |
| | Serous and clear cell | 40 | 7 | |
| LVSI[a] | No | 196 | 14 | <0.001 |
| | Yes | 28 | 14 | |
| Myometrial invasion | <50% | 131 | 3 | <0.001 |
| | ≥50% | 96 | 25 | |
| Pelvic LNM[b] | No | 205 | 7 | <0.001 |
| | Yes | 22 | 21 | |
| Size of pelvic LNM[b] | Micro | 3 | 3 | 0.63 |
| | Macro | 15 | 7 | |
| Number of pelvic LNM[b] | 1 | 12 | 4 | 0.016 |
| | ≥2 | 10 | 17 | |
| Histologic grade | Grade 1 + 2 | 118 | 9 | 0.048 |
| | Grade 3[c] | 109 | 19 | |
| Tumor size | ≤2 cm | 42 | 3 | 0.20 |
| | >2 cm | 147 | 23 | |

[a]LVSI: Lymphovascular space invasion.
[b]LNM: Lymph node metastasis.
[c]Includes endometrioid G3, clear cell and serous histologies.

**TABLE 4** Multivariate analysis (Logistic Regression) for risk of para-aortic lymph node metastasis

| | | Risk of para-aortic LN metastasis | | | |
|---|---|---|---|---|---|
| **Variable** | **Category** | ***n*** | **HR** | **CI** | ***P*** |
| Pelvic LN metastasis | No | 205 | 1.0 | Reference | <0.001 |
| | Yes | 42 | 14.7 | 5.13-42.3 | |
| Myometrial invasion | <50% | 132 | 1.0 | Reference | 0.035 |
| | ≥50% | 115 | 4.28 | 1.10-16.5 | |
| Hystologic grade | Grades 1+2 | 121 | 1.0 | Reference | 0.874 |
| | Grade 3[a] | 126 | 1.09 | 0.37-3.19 | |
| LVSI | Absent | 206 | 1.0 | Reference | 0.075 |
| | Present | 41 | 2.57 | 0.91-7.28 | |
| Adnexal metastasis | No | 221 | 1.0 | Reference | 0.242 |
| | Yes | 26 | 2.11 | 0.60-7.41 | |

HR, Hazard ratio; CI95%, Confidence interval, 95%; LN, Lymph node; LVSI, lymphovascular space invasion.
[a]Includes clear cell and serous histologies.

Further, for patients without adnexal metastasis or LN enlargement, when the two independent factors (deep MI and LN metastasis) were absent—representing 120 of 215 (55.8%) patients—the risk of PALM was 0.8%. For grades 1 and 2, no PALN metastasis was observed. Omitting PALN dissection for all patients with superficial MI (125/215 patients), 0.8% of PALN metastases would have been overlooked. But, for deep MI, the overall prevalence of PALN metastasis was 7/90 (7.8%). When deep MI and PLN metastasis were copresent, the prevalence of PALN metastasis increased to 23.5% (4/17).

## 4 | DISCUSSION

Surgical staging procedures that include regional lymph node dissection are essential for adequate staging and triage to determine the adjuvant therapy in endometrial cancer.[8] Because the significance of the extension of lymphadenectomy, lymph node counts, and anatomic templates continues to be debated by gynecological oncologists, there is no consensus with regard to what an "adequate lymphadenectomy" is. Conversely, it is clear that the potential benefit of lymphadenectomy must outweigh the morbidity, obviating the need for all patients to undergo lymph node dissection. Patients with low-risk tumors should safely have a hysterectomy and salpingo-oophorectomy alone.[9–11]

Several findings highlight the importance of identifying patients for whom PALN dissection can be omitted. First, para-aortic LN metastasis is less prevalent compared with pelvic LN metastasis.[5,12–17] Also, most patients with PALN metastasis also have PLN metastasis.[5,12–17] Finally, systematic PA lymphadenectomy up to the renal vessels, as suggested by certain groups, might add considerable operation times and increase surgical morbidities, such as blood

**TABLE 5** Correlation between myometrial invasion and site of lymph node metastasis for the 215 patients with neither lymph node enlargement or adnexal metastasis

| **Myometrial invasion** | **Pelvic LNM[a]** | **Grade** | **Para-aortic LNM[a]** | **Total** |
|---|---|---|---|---|
| <50% | No: 120 | G1+2: 71 | Yes: 0 | 125 |
| | | G3: 49 | Yes: 1 (0.8%)[b] | |
| | Yes: 5 | G1+2: 1 | Yes: 0 | |
| | | G3: 4 | Yes: 0 | |
| | | | | |
| ≥50% | No: 73 | G1+2: 35 | Yes: 2 (2.2%)[c] | 90 |
| | | G3: 38 | Yes: 1 (1.1%)[d] | |
| | Yes: 17 | G1+2: 7 | Yes: 3 | |
| | | G3:10 | Yes: 1 | |
| Total | | | | 125 |

[a]LNM: Lymph node metastasis.
[b]1/125 patients with <50% depth of invasion.
[c]2/90 patients with ≥50% depth of invasion (1 case had LVSI).
[d]1/90 patients with ≥50% depth of invasion.

**TABLE 6** The prevalence of isolated para-aortic node metastasis with negative pelvic nodes in published series

| Study | Year | *n* | Isolated paraaortic node metastasis | % |
|---|---|---|---|---|
| Chen et al[24] | 1983 | 74 | 3 | 4 |
| Creasman et al[5] | 1987 | 621 | 12 | 1.9 |
| Morrow et al[1] | 1991 | 895 | 18 | 1.7 |
| Larson et al[25] | 1993 | 50 | 0 | 0 |
| Ayhan et al[26] | 1995 | 209 | 6 | 2.9 |
| Fanning et al[27] | 1996 | 60 | 0 | 0 |
| Yokoyama et al[28] | 1997 | 63 | 4 | 6.3 |
| Onda et al[14] | 0997 | 173 | 2 | 1.2 |
| Hirahatake et al[29] | 1997 | 200 | 2 | 1.0 |
| McMeekin et al[13] | 2001 | 607 | 8 | 1.3 |
| Mariani et al[16] | 2004 | 566 | 5 | 0.9 |
| Nomura et al[31] | 2006 | 155 | 4 | 2.6 |
| Mariani et al[32] | 2008 | 281 | 6 | 2.4 |
| Hoekstra et al[30] | 2009 | 1487 | 7 | 0.5 |
| Lee et al[33] | 2009 | 349 | 7 | 2.0 |
| Fujimoto et al[17] | | 355 | 7 | 1.9 |
| Abu-Rustum et al[23] | 2009 | 847 | 12 | 1.4 |
| Chiang et al[23] | 2011 | 171 | 2 | 1.2 |
| Dogan et al[26] | 2012 | 145 | 2 | 1.4 |
| Milam et al[11] | 2012 | 532 | 12 | 2.2 |
| Odagiri et al[41]2014 | 2014 | 266 | 7 | 2.6 |
| Tomisato et al[42] 2014 | 2014 | 260 | 9 | 3.5 |
| Numanoglu et al[43] 2014 | 2014 | 157 | 4 | 2.5 |
| Sueoka et al[44] | 2015 | 502 | 15 | 3.0 |
| Sautua et al[45] | 2015 | 90 | 6 | 6.6 |
| Todo et al[46] 2016 | 2016 | 307 | 6 | 1.9 |
| Present study | 2017 | 255 | 7 | 2.7 |
| Total | | 9677 | 173 | 1.8 |

transfusion, postoperative ileus, and hospital stay length.[9,18,19] Patients who undergo PALN dissection are twice as likely to have a grade ≥2 complication.[9]

Nevertheless, the diagnostic and therapeutic significance of para-aortic LN dissection remains unknown. No phase 3 trial has addressed the prognostic value of PALN dissection. The retrospective Survival Effect of Para-Aortic Lymphadenectomy (SEPAL) study in endometrial cancer reported an impact on overall survival for intermediate- and high-risk patients who were undergoing pelvic and para-aortic LN dissection compared with only pelvic dissection.[20] However, it was difficult to determine whether the improvement in survival was attributed to adjuvant chemotherapy rather than PALN dissection.

In a recent study, by CART analysis, Barlin et al[21] found that para-aortic nodal assessment and node counts did not influence survival. Only two factors affected overall survival: stage I compared with stage > I and a binary grading system (grades 1 and 2 [low-grade] vs grade 3, serous, clear cell, and carcinosarcoma [high-grade]).

Our series included non-endometrioid histologies, and we noted overall PALN metastasis in 11% of patients. However, only 2.7% of patients had PA without PLN metastasis. In the landmark GOG study, Creasman et al[5] reported a similar PA dissemination rate, wherein 2.1% (12/563) of patients had isolated para-aortic nodal metastasis. Since then, many groups have corroborated these findings. In 2011, Chiang et al[22] reviewed 18 series, in which 103 (1.7%) of 6024 patients had isolated para-aortic nodal metastasis with negative pelvic nodes. It is now clear that pelvic LNs are the most common sites of nodal dissemination and that if the pelvic LNs are not involved, there is a small likelihood (<3%) of overlooking para-aortic nodal metastasis. Table 6 summarizes the published series.

Isolated para-aortic nodal recurrence is also an uncommon event. Abu-Rustum et al[23] showed that 6% of all recurrences occur solely in para-aortic nodes and that no isolated para-aortic recurrences develop in grade 1 tumors.

After excluding patients with suspicious adnexal or lymph node enlargement, we analyzed 2 pathological factors—myometrial invasion and histologic grade—and identified a subgroup of patients who could safely forego PALND. No patient with superficial myometrial invasion and grades 1 and 2 had PALN metastasis, regardless of PLN status. Moreover, when the two independent predictive factors of PALN metastasis (deep MI and LN metastasis) were absent, representing 55.8% (120/215) of patients, the risk of PALM was 0.8%. Notably, the number of positive pelvic nodes (63% with ≥2 LNs vs 25% with 1 LN; $P = 0.016$) correlated with the presence of PALN metastasis. However, the size of the PLNM was not predictive of PA node dissemination.

Several independent predictors of PALN metastasis, such as PLN metastasis and LVSI, have been reported,[15,24–26] and many groups recommend selecting patients for PALN dissection, based on intraoperative findings.[14] In a recent large series on endometrioid endometrial cancer patients who were at risk of node dissemination, Kumar et al[27] identified three independent predictors of PALN dissemination—PLN metastasis, deep myometrial invasion, and LVSI—and proposed the use of frozen sections in making intraoperative decisions. Moreover, when these three factors were absent, the risk of PALN metastasis was 0.6%. Of note, the Mayo Clinic and others have reported excellent results on using frozen sections, with a high level of agreement with the final pathology.[28–30]

However, a reliable frozen section is not always available at most centers, especially for LVSI.[27,31–33] The most reliable variable in frozen sections is likely to be MI, and in Kumar et al series,[27] omitting PA lymphadenectomy from all endometrioid ECs with ≤50% MI represented a 1.1% risk of missing PALN metastasis. Similarly, in our series, if all patients with <50% MI forewent PALN dissection, only 0.8% of PALN metastases would have failed to have been diagnosed. Moreover, as we analyzed a subgroup of patients at risk of node metastasis, the risk of isolated para-aortic metastasis is even lower if we consider all patients treated for endometrial cancer.

Our series included patients with clear cell and serous histologies. Although they were more likely to have adnexal metastasis or suspicious LNs compared with endometrioid types, these tumors were not associated with significantly higher PALN metastasis rates. Tumor grade (including grade three endometrioid and non-endometrioid tumors) was also predictive of PALN dissemination in the multivariate analysis. Kumar et al[27] also failed to identify grade 3 (endometrioid) as an independent prognostic factor and suggested that such patients can omit PALN dissection if the other independent criteria are absent. However, they continue to advocate systematic PALN dissection for all serous and clear cell histologies. They argue that omitting PALN dissection in serous tumors with ≤50% MI and negative pelvic nodes is linked to a higher risk of isolated PA metastasis (5%).[34]

Conversely, in our series, when patients with adnexal or suspicious LNs were excluded, no patient with serous or clear cell tumors had PALN metastasis. One can argue that these findings were attributed to the small number of patients with non-endometrioid tumors ($n = 47$), but in another study from the Mayo Clinic, Ayeni et al[35] claimed that after controlling for disease stage, outcomes did not differ between high-risk histologic subtypes and lymphadenectomy status and that extensive surgery did not provide a survival benefit in patients with advanced-stage disease. Further, we did not exclude patients with adnexal metastasis from the primary analysis, because this diagnosis is not usually suspected before the final pathology. Notably, most clinicians recommend adjuvant chemotherapy for non-endometrioid tumors in their daily practice, regardless of node status,[36,37] but the therapeutic and diagnostic value of node dissection for these patients remains unknown.

Whether the low prevalence of isolated para-aortic nodal metastasis (1-3%) declines further when ultrastaging of pelvic sentinel nodes is routinely performed remains undetermined, because investigators have noted an increase in the detection rate of up to 7-8% in sentinel protocols.[38,39] In summary, if pelvic nodes are subjected to more detailed pathological analysis (serial sections and immunohistochemistry), micrometastases can be detected, and the presence of isolated para-aortic nodal metastases might decrease.[40]

Overall, our series is comparable in size with the most significant studies on this topic and contributes valuable data. Moreover, our findings can help stratify patients with regard to PA lymphadenectomy. The strength of our study was the high median node counts, suggesting reliable systematic LN dissection and a uniform surgical approach. Unfortunately, it suffers from the inherent biases of a retrospective, single-institution study design.

In conclusion, most patients with endometrial cancer can safely forego PALN dissection, regardless of histological type. This subset can be identified by the combined absence of pelvic node metastasis and deep MI. Our data confirm that when only MI can be reliably diagnosed in frozen sections, the omission of PA lymphadenectomy in patients with superficial MI is associated with a <1% risk of PALN metastasis.

## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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## SYNOPSIS

Patients with combined absence of pelvic node metastasis and deep myometrial invasion can safely forego para-aortic node dissection in endometrial cancer.