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Predictors of extensive lymphatic dissemination and recurrences in node-positive endometrial cancer

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HIGHLIGHTS

- Lymph node metastasis size in FIGO stage IIIC EC correlates with extent of lymphatic dissemination.
- Traditional primary tumor prognostic factors do not predict occurrence of high-volume metastases in FIGO stage IIIC EC.
- Lymphovascular space invasion is the strongest predictor of nonvaginal relapses in FIGO stage IIIC EC.

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ABSTRACT

Objective. To identify predictors of extensive lymphatic dissemination and distant recurrences in node-positive endometrial cancer (EC).

Methods. Clinicopathologic data were collected of patients who had fully staged EC with at least 1 positive lymph node. Permanent sections of metastatic lymph nodes were reviewed; metastases were characterized according to size (≤2 mm and >2 mm) and location in the lymph node (intra- vs extracapsular). Risk of occurrence of multiple pelvic and para-aortic lymph node dissemination was calculated by combining risk factors identified at multivariate analysis.

Results. Of 96 patients, 85 had positive pelvic nodes, of whom 71 (83.5%) had high-volume metastases. In the presence of both macrometastasis in the pelvic basin (odds ratio [OR], 13.42; [95% CI, 2.44–73.83]) and uterine serosal involvement of the tumor at final pathologic evaluation (OR, 11.84 [95% CI, 1.22–115.11]), multiple pelvic node dissemination occurred in 91.7% of cases (vs 7.7% in the absence of both). Concomitant presence of pelvic macrometastasis, lymphovascular space invasion (LVSI), and extracapsular invasion led to 85.7% occurrence of para-aortic involvement (vs 11.1% if no factors present). LVSI was independently associated with nonvaginal recurrences (hazard ratio, 2.62 [95% CI, 1.33–5.16]).

Conclusions. Presence of high-volume metastases in the pelvic lymph nodes is associated with concomitant presence of multiple positive pelvic nodes, as well as para-aortic node involvement. LVSI is associated with both para-aortic node involvement and occurrence of nonvaginal relapses. In this era of sentinel lymph node mapping, these factors may help predict the extent of lymphatic dissemination in EC.

1. Introduction

The cornerstone for treatment of endometrial cancer (EC) consists of surgical removal of the uterus, fallopian tubes, and ovaries, complemented by pelvic and para-aortic lymphadenectomy [1]. Because of the lack of consensus regarding the performance of retroperitoneal staging, different institutions have adopted various approaches [2], ranging from complete pelvic and para-aortic lymphadenectomy

Abbreviations: EBRT, external beam radiation therapy; EC, endometrial cancer; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; IQR, interquartile range; ITC, isolated tumor cells; LVSI, lymphovascular space invasion; OR, odds ratio; SLN, sentinel lymph node; VB, vaginal brachytherapy.

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routinely performed for all patients to the complete omission of lymphadenectomy in selected cases. Most centers rely on preoperative or intraoperative characteristics of the primary tumor to decide whether to perform lymphadenectomy. These characteristics include histologic type and grade of differentiation determined with preoperative biopsy, depth of myometrial invasion reported through imaging or frozen section analysis, and tumor diameter [3–6]. In addition to assessment of primary tumor characteristics and a pelvic and para-aortic lymphadenectomy, another method to determine lymphatic dissemination is sentinel lymph node (SLN) mapping with ultrastaging. The high detection rate, sensitivity, and negative predictive values of SLN mapping with ultrastaging [7–10] have highlighted its role as a reliable strategy to identify patients who may require adjuvant therapy.

Despite a great utility otherwise, neither primary tumor features nor SLN procedure is able to predict the number or the histologic characteristics of additional positive pelvic lymph nodes, or the likelihood of positivity in the para-aortic basin. Some investigators have tried to address these limitations through the identification of risk factors. They have found that the presence of high-volume metastasis in the SLN was associated with further non-SLN involvement [11] and that grossly positive pelvic nodes, lymphovascular space invasion (LVSI), and the number (n > 2) of positive pelvic nodes were independently associated with para-aortic node involvement [12–14].

A recent classification and regression tree analysis showed that neither the total number of excised lymph nodes nor the assessment of para-aortic lymph node status was an important predictor of overall survival [15]. However, other authors sustain that surgical locoregional treatment of the para-aortic area can improve survival for patients with intermediate- or high-risk EC and can ameliorate the prognosis of patients with FIGO (International Federation of Gynecology and Obstetrics) stage IIIC disease [16,17]. Generally, identification of disease harbored in the lymphatic system is used as a prognostic factor, and it potentially can drive clinical decisions toward postoperative treatment Therefore, especially in the SLN mapping era, gathering information about further non-SLN involvement may help in the postoperative setting of treatment discussion.

An improved characterization of lymph node metastases of patients with positive pelvic and para-aortic nodes may lead to further insights about disease management. The choice of adjuvant treatment (eg, brachytherapy, external beam radiotherapy, chemotherapy, hormonal therapy) might be driven by the characteristics of the lymph nodes when associated with other prognostic factors. Thus, we performed a comprehensive characterization of node-positive ECs, correlating the characteristics of the positive lymph nodes with the primary tumor characteristics, the risk of multiple pelvic and para-aortic disseminations, and the occurrence of nonvaginal relapses.

2. Methods

This study used a retrospectively identified cohort of patients with the diagnosis of EC who underwent surgery between January 1, 1999, and December 31, 2008, at Mayo Clinic in Rochester, Minnesota. To be included in this study, patients needed to have a pelvic and para-aortic lymphadenectomy performed with at least 1 positive node (pelvic or para-aortic, or both) identified and at least 5 para-aortic nodes removed. Endometrioid and nonendometrioid histologic assessments were included. Exclusion criteria were defined as absence of research authorization, presence of synchronous malignancies, previous neoadjuvant therapies, FIGO stage IV disease, and slides not available for pathologic review. The Mayo Clinic Institutional Review Board approved this study.

Clinicopathologic information was collected retrospectively. The information was: histologic subtype of the endometrial tumor, FIGO stage, FIGO grade, peritoneal cytologic characteristics, presence of LVSI, myometrial invasion (none, ≤50%, or >50% of myometrial wall); cervical stromal, uterine serosal, adnexal and low uterine segment invasion; and tumor diameter (≤2 cm or >2 cm, measured during gross inspection of the sample). The considered adjuvant treatment types were adjuvant systemic chemotherapy, external beam radiation therapy (EBRT), and vaginal brachytherapy (VB). Recurrence was reported as *isolated vaginal* or *nonvaginal* (peritoneal [carcinomatosis], lymphatic [retroperitoneal or isolated nodal disease], and hematogenous [brain, lungs, liver, bone]), as previously described [13,18].

Permanent sections of metastatic lymph nodes were reexamined by a gynecologic pathologist (Y.H.); metastases were categorized according to size, as defined by the American Joint Committee on Cancer (isolated tumor cells [ITC], ≤0.2 mm and ≤200 cells), micrometastases (>0.2 mm to ≤2 mm or >200 cells, or both), and macrometastases (>2 mm) [19] and their location within the lymph node (intra- vs extracapsular). Positive pelvic nodes were subcategorized as *single positive* (n = 1) and *multiple positive* (n > 1). The number of positive pelvic lymph nodes was further divided into 4 groups: 1 positive node, 2 or 3 positive nodes, 4 or 5 positive nodes, and >5 positive nodes.

Statistical analyses were performed with the SAS version 9.4 software package (SAS Institute Inc). Demographic and clinicopathologic characteristics were compared among patients with high- vs low-volume metastases (macrometastases vs micrometastases or ITC) with χ^2 test or Fisher exact test for categorical variables and the Wilcoxon rank sum test for age.

Associations of the demographic and clinicopathologic characteristics with presence of multiple positive pelvic nodes and of positive para-aortic nodes, respectively, were evaluated univariately with χ^2 test or Fisher exact test, and multivariable models were fit with logistic regression to estimate adjusted odds ratio (OR) and corresponding 95% CI. Duration of follow-up was calculated from the date of surgery to the date of documented recurrence; the follow-up for patients without a recurrence was censored at the date of their last relevant clinical follow-up. Univariate and multivariate Cox proportional hazards models were fit to evaluate factors for an association of a nonvaginal recurrence; associations were summarized as the hazard ratio (HR) and corresponding 95% CI. Factors with a $P < .20$ based on the univariate analyses were considered in the multivariate model building through backwards and stepwise modeling. All calculated P values were 2 sided, and $P < .05$ was considered statistically significant.

3. Results

3.1. Study cohort

A total of 1415 patients underwent surgery for EC between January 1999 and December 2008 at Mayo Clinic in Rochester, Minnesota. Patients with FIGO stage IIIC disease (n = 102) met the inclusion criteria, but 6 of them were excluded because they did not have slides available for review (n = 3) or had an inadequate negative para-aortic lymphadenectomy with <5 nodes removed (n = 3). A final number of 96 cases met the inclusion criteria. Endometrioid tumors were the most represented among the cohort (n = 61 [63.5%]) vs nonendometrioid (n = 35 [36.5%]).

3.2. Lymph node metastasis characterization

The median numbers of pelvic and para-aortic nodes removed during the primary operation were 31 and 15. In total, 533 nodes were reviewed by a pathologist. Isolated positive para-aortic nodes were found in 11 patients, and 85 patients had positive pelvic nodes. Data of these 85 patients were used for analysis in the present study and are presented herein; descriptive data for the 11 patients with isolated para-aortic metastasis are presented in Supplementary Table 1. After classifying the nodal metastasis according to the largest metastasis in the pelvic lymph nodes, we found 71 cases (83.5%) with macrometastasis, 7 (8.2%) with micrometastasis, and 7 (8.2%) with ITC (Fig. 1).

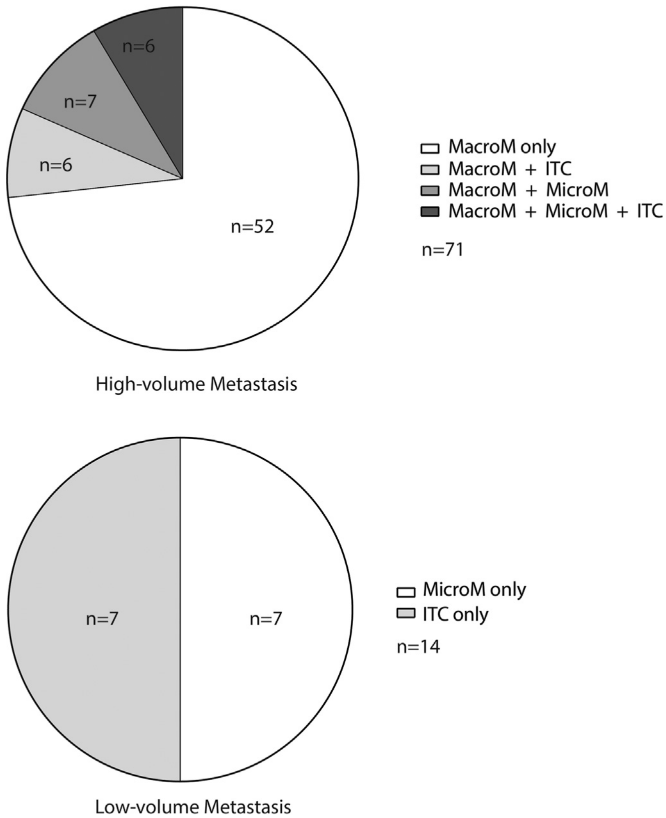

Fig. 1. Histologic Characterization of the Pelvic Lymph Node Metastasis. Nodal metastases were classified in accordance with the largest metastasis found in the pelvic lymph nodes. Among patients with MacroM, 73% presented with MacroM only, whereas the other 27% had MacroM, MicroM, or ITC, or a combination. Of patients for whom the bigger metastasis was a MicroM or ITC, no other type of metastasis was found among their surgically removed lymph nodes. ITC indicates isolated tumor cells; MacroM, macrometastasis; MicroM, micrometastasis.

3.3. High- vs low-volume metastasis

Clinicopathologic characteristics were collected for the 85 patients with positive pelvic nodes (Table 1). Comparison of high-volume metastasis (macrometastasis) with low-volume metastasis (micrometastasis or ITC) showed that none of the primary tumor characteristics were significantly associated with the presence of high-volume metastasis. However, para-aortic lymph node involvement was associated with high-volume metastasis ($P = .002$).

3.4. Involvement of multiple pelvic nodes

Among the 85 patients, 50 had involved multiple pelvic nodes, of whom 19 had >5 positive nodes. None of the traditional primary tumor characteristics were associated with multiple positive pelvic node involvement (Table 2). However, these nodes were more prevalent among patients with pelvic macrometastasis than patients with pelvic micrometastasis or ITC (67.6% [48/71] vs 14.3% [2/14]; $P < .001$); extracapsular involvement vs intracapsular involvement (86.7% [13/15] vs 52.9% [37/70]; $P = .02$), with vs without adnexal involvement (92.3% [12/13] vs 52.8% [38/72]; $P = .008$), and with vs without serosal involvement (92.3% [12/13] vs 52.8% [38/72]; $P = .008$). In multivariate analysis, the same 2 variables were identified separately through both stepwise and backwards variable selection methods; the adjusted OR (95% CI) was 13.42 (2.44–73.83) for pelvic macrometastasis and 11.84 (1.22–115.11) for serosal involvement. The risk of occurrence of multiple pelvic node involvement was

Table 1
Clinical and histopathologic characteristics of patients with stage IIIC endometrial cancer, overall and stratified by size of pelvic nodal metastasis.

Characteristic[a]	Overall (N = 85)	Pelvic metastasis characterization		P value[b]
		Macrometastasis (n = 71)	Micrometastasis or ITC (n = 14)	
Age at surgery, mean (SD), y	64.4 (12.0)	64.3 (12.5)	64.5 (9.6)	0.86
Histologic evaluation				0.79
Nonendometrioid	33 (38.8)	28 (39.4)	5 (35.7)	
Endometrioid	52 (61.2)	43 (60.6)	9 (64.3)	
FIGO grade				0.20
1	15 (17.6)	11 (15.5)	4 (28.6)	
2	21 (24.7)	20 (28.2)	1 (7.1)	
3	49 (57.6)	40 (56.3)	9 (64.3)	
LVSI				0.40
No	46 (54.1)	37 (52.1)	9 (64.3)	
Yes	39 (45.9)	34 (47.9)	5 (35.7)	
Myometrial invasion, %				0.87
≤50	32 (37.6)	27 (38.0)	5 (35.7)	
>50	53 (62.4)	44 (62.0)	9 (64.3)	
Cervical stromal invasion				0.73
No	68 (80.0)	56 (78.9)	12 (85.7)	
Yes	17 (20.0)	15 (21.1)	2 (14.3)	
Peritoneal cytologic evaluation				0.08
Negative	56 (65.9)	44 (62.0)	12 (85.7)	
Positive	25 (29.4)	24 (33.8)	1 (7.1)	
Not sampled	4 (4.7)	3 (4.2)	1 (7.1)	
Adnexal involvement				0.11
No	72 (84.7)	58 (81.7)	14 (100.0)	
Yes	13 (15.3)	13 (18.3)	0 (0.0)	
Serosal involvement				0.68
No	72 (84.7)	59 (83.1)	13 (92.9)	
Yes	13 (15.3)	12 (16.9)	1 (7.1)	
Vaginal invasion				0.99
No	82 (96.5)	68 (95.8)	14 (100.0)	
Yes	3 (3.5)	3 (4.2)	0 (0.0)	
Low uterine segment invasion				.99[c]
No	34 (40.0)	29 (40.8)	5 (35.7)	
Yes	33 (38.8)	29 (40.8)	4 (28.6)	
Unknown	18 (21.2)	13 (18.3)	5 (35.7)	
Tumor diameter, cm				0.67
≤2	4 (4.7)	3 (4.2)	1 (7.1)	
>2	79 (92.9)	66 (93.0)	13 (92.9)	
Unknown	2 (2.4)	2 (2.8)	0 (0.0)	
Positive para-aortic nodes	45 (52.9)	43 (60.6)	2 (14.3)	0.002

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; ITC, isolated tumor cells; LVSI, lymphovascular space invasion.
[a] Values are presented as number (percentage) of patients unless specified otherwise.
[b] χ^2 or Fisher exact for categorical variables and Wilcoxon rank sum for age.
[c] Determined on the basis of 67 patients with known information.

Table 2
Univariate analysis of associations with multiple positive pelvic nodes of 85 patients who had stage IIIC endometrial cancer.

Characteristic	Multiple positive pelvic nodes, no. (%)	P Value[a]
Age at surgery, y		0.18
Quartile 1: 39.2–54.2 (n = 21)	15 (71.4)	
Quartile 2: 54.3–63.5 (n = 21)	12 (57.1)	
Quartile 3: 63.6–72.3 (n = 21)	14 (66.7)	
Quartile 4: 72.4–92.0 (n = 22)	9 (40.9)	
Histologic evaluation		0.79
Nonendometrioid (n = 33)	20 (60.6)	
Endometrioid (n = 52)	30 (57.7)	
FIGO grade		0.60
1 or 2 (n = 36)	20 (55.6)	
3 (n = 49)	30 (61.2)	
LVSI		0.36
No (n = 46)	25 (54.3)	
Yes (n = 39)	25 (64.1)	
Myometrial invasion		0.71
≤50% (n = 32)	18 (56.3)	
>50% (n = 53)	32 (60.4)	
Cervical stromal invasion		0.27
No (n = 68)	38 (55.9)	
Yes (n = 17)	12 (70.6)	
Peritoneal cytologic evaluation		0.29
Negative (n = 56)	30 (53.6)	
Positive (n = 25)	18 (72.0)	
Not sampled (n = 4)	2 (50.0)	
Adnexal involvement		0.008
No (n = 72)	38 (52.8)	
Yes (n = 13)	12 (92.3)	
Serosal involvement		0.008
No (n = 72)	38 (52.8)	
Yes (n = 13)	12 (92.3)	
Vaginal invasion		0.26
No (n = 82)	47 (57.3)	
Yes (n = 3)	3 (100.0)	
Low uterine segment invasion		0.05[b]
No (n = 34)	18 (52.9)	
Yes (n = 33)	25 (75.8)	
Unknown (n = 18)	7 (38.9)	
Tumor diameter, cm		0.66
≤2 (n = 4)	2 (50.0)	
>2 (n = 79)	46 (58.2)	
Unknown (n = 2)	2 (100.0)	
Pelvic metastasis type		<0.001
ITC or micrometastasis (n = 14)	2 (14.3)	
Macrometastasis (n = 71)	48 (67.6)	
Location of the pelvic metastasis		0.02
Intracapsular (n = 70)	37 (52.9)	
Extracapsular (n = 15)	13 (86.7)	

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; ITC, isolated tumor cells; LVSI, lymphovascular space invasion.
[a] χ^2 or Fisher exact test.
[b] Determined on the basis of 67 patients with known information.

calculated according to the presence or absence of the identified risk factors at multivariate analysis (Table 3).

3.5. Para-aortic lymph node involvement

Para-aortic metastases were found in 45 patients (52.9%) with positive pelvic nodes. Among several prognostic factors, 5 were associated with para-aortic lymph node involvement on the basis of univariate analysis (Table 4). Patients with LVSI were more likely to have positive para-aortic nodes than patients without LVSI (66.7% [26/39] vs 41.3% [19/46]; $P = .02$). Patients with adnexal involvement were more likely to have positive para-aortic nodes than patients without adnexal involvement (84.6% [11/13] vs 47.2% [34/72]; $P = .01$). Additionally, patients with pelvic macrometastasis were more likely to have positive para-aortic nodes than those with either pelvic micrometastasis or ITC (60.6% [43/71] vs 14.3% [2/14]; $P = .002$). Patients with extracapsular metastasis were more likely to have positive para-aortic nodes than those with intracapsular metastasis (86.7% [13/15] vs 45.7% [32/70]; $P = .004$), and patients with >5 positive pelvic nodes were more likely to have positive para-aortic nodes than those with 1 positive pelvic lymph node (84.2% [16/19] vs 28.6% [10/35]; $P < .001$).

In a multivariable logistic analysis, no factor attained statistical significance after the inclusion of the strongest predictor, the number of positive pelvic nodes. However, if we ignore this predictor, the same 3 variables were identified separately with both stepwise and backwards variable selection methods: adjusted OR (95% CI) was 3.11 (1.16–8.36) for LVSI, 6.78 (1.34–34.44) for pelvic macrometastasis, and 6.35 (1.26–32.02) for extracapsular metastasis. The risk of occurrence of para-aortic involvement was calculated according to the presence or absence of the identified risk factors (Table 5).

3.6. Nonvaginal recurrence

Complete information about the type and schedule of adjuvant treatment was available for 69 patients. EBRT ± VB was administered to 25 patients (36.2%), systemic chemotherapy ±VB to 13 (18.8%), and EBRT and systemic chemotherapy ±VB to 31 (44.9%). The other 16 patients either had no adjuvant treatment (n = 12) or the administration of adjuvant treatment was unknown (n = 4).

Almost one-half of the 85 patients had a recurrence (n = 39, 45.9%). Among them, 32 patients had a nonvaginal recurrence (lymphatic [n = 11], hematogenous [n = 8], peritoneal [n = 3], or a combination [n = 10]) or had no documented route (n = 5), while only 2 patients had a local (vaginal) recurrence. For these 37 patients, median (interquartile range [IQR]) time to recurrence was 13.0 (5.5–24.3 months). Among the other 48 patients, the median duration of follow-up was 61.0 (IQR, 18.0–81.5 months). Among the 45 patients with positive para-aortic nodes, 23 (51.1%) had a documented recurrence, of which 22 were nonvaginal relapses (lymphatic [n = 8], hematogenous [n = 2], peritoneal [n = 1], or a combination [n = 7]) or the route was not documented (n = 4).

With consideration of the limitations related to the relatively small sample number, the univariate analysis of all patients showed that the type of metastasis was not significantly associated with increased risk of nonvaginal recurrence (Table 6). However, a statistically significant association with high-grade histologic characteristics, LVSI, and multiple positive pelvic nodes was observed. On multivariable analysis, the presence of >5 positive pelvic nodes (adjusted HR [95% CI], 3.43 [1.70–6.95]; $P < .001$) and LVSI (adjusted HR [95% CI], 2.89 [1.45–5.75]; $P = .003$) were independently associated with nonvaginal recurrence. However, if the number of positive pelvic nodes as a predictor was ignored, none of the other variables attained statistical significance after LVSI was included in the model.

Table 3
Occurrence of multiple pelvic nodes involvement according to presence or absence of risk factors identified at multivariate analysis of the 85 patients with FIGO stage IIIC endometrial cancer.

Pelvic metastasis	Serosal involvement	No. of patients	Multiple positive pelvic nodes, no. (%)
ITC or micrometastasis	No	13	1 (7.7)
ITC or micrometastasis	Yes	1	1 (100.0)
Macrometastasis	No	59	37 (62.7)
Macrometastasis	Yes	12	11 (91.7)

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; ITC, isolated tumor cells.

Table 4
univariate analysis of associations with positive PA nodes in the 85 patients with FIGO stage IIIC endometrial cancer.

Characteristic	Positive PA nodes, No. (%)	*P* value[a]
Age at surgery, y		0.29
Quartile 1: 39.2–54.2 (n = 21)	13 (61.9)	
Quartile 2: 54.3–63.5 (n = 21)	13 (61.9)	
Quartile 3: 63.6–72.3 (n = 21)	11 (52.4)	
Quartile 4: 72.4–92.0 (n = 22)	8 (36.4)	
Histologic evaluation		0.81
Nonendometrioid (n = 33)	18 (54.5)	
Endometrioid (n = 52)	27 (51.9)	
FIGO grade		0.98
1 or 2 (n = 36)	19 (52.8)	
3 (n = 49)	26 (53.1)	
LVSI		0.02
No (n = 46)	19 (41.3)	
Yes (n = 39)	26 (66.7)	
Myometrial invasion		0.67
≤50% (n = 32)	16 (50.0)	
>50% (n = 53)	29 (54.7)	
Cervical stromal invasion		0.99
No (n = 68)	36 (52.9)	
Yes (n = 17)	9 (52.9)	
Peritoneal cytologic evaluation		0.86
Negative (n = 56)	31 (55.4)	
Positive (n = 25)	12 (48.0)	
Not sampled (n = 4)	2 (50.0)	
Adnexal involvement		0.01
No (n = 72)	34 (47.2)	
Yes (n = 13)	11 (84.6)	
Serosal involvement		0.50
No (n = 72)	37 (51.4)	
Yes (n = 13)	8 (61.5)	
Vaginal invasion		0.24
No (n = 82)	42 (51.2)	
Yes (n = 3)	3 (100.0)	
Low uterine segment invasion		0.27[b]
No (n = 34)	16 (47.1)	
Yes (n = 33)	20 (60.6)	
Unknown (n = 18)	9 (50.0)	
Tumor diameter, cm		0.56
≤2 (n = 4)	2 (50.0)	
>2 (n = 79)	41 (51.9)	
Unknown (n = 2)	2 (100.0)	
Pelvic metastasis type		0.002
ITC or micrometastasis (n = 14)	2 (14.3)	
Macrometastasis (n = 71)	43 (60.6)	
Location of metastasis		0.004
Intracapsular (n = 70)	32 (45.7)	
Extracapsular (n = 15)	13 (86.7)	
Positive pelvic nodes, No.[c]		<0.001
1 (n = 35)	10 (28.6)	
2 (n = 16)	8 (50.0)	
3–5 (n = 14)	10 (71.4)	
>5 (n = 19)	16 (84.2)	

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; ITC, isolated tumor cells; LVSI, lymphovascular space invasion; PA, para-aortic.
[a] χ^2 or Fisher exact test.
[b] Determined on the basis of 67 patients with known information.
[c] One patient with unknown number of pelvic nodes removed.

Table 5
Occurrence of PA involvement according to presence or absence of risk factors identified at multivariate analysis among the 85 patients with FIGO stage IIIC endometrial cancer.

Pelvic macrometastasis	LVSI	Extracapsular metastasis	Patients, No.	Positive PA, no. (%)
Yes	Yes	Yes	7	85.7 (6)
Yes	No	Yes	8	87.5 (7)
Yes	Yes	No	27	70.4 (19)
Yes	No	No	29	37.9 (11)
No	Yes	No	5	20.0 (1)
No	No	No	9	11.1 (1)

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; PA, para-aortic.

Table 6
Univariate analysis of associations with nonvaginal recurrence in 85 patients with FIGO stage IIIC endometrial cancer[a].

Characteristic	Nonvaginal Recurrence-Free Survival at 2 y, (95% CI)	HR (95% CI)	*P* Value
Age at surgery, y			0.65
Quartile 1: 39.2–54.2 (n = 21)	64.0	Reference	
Quartile 2: 54.3–63.5 (n = 21)	70.2	0.64 (0.26–1.61)	
Quartile 3: 63.6–72.3 (n = 21)	47.8	1.16 (0.48–2.81)	
Quartile 4: 72.4–92.0 (n = 22)	70.2	0.82 (0.34–1.98)	
Histologic evaluation			0.18
Nonendometrioid (n = 33)	51.9	Reference	
Endometrioid (n = 52)	73.6	0.64 (0.34–1.23)	
FIGO grade			0.046
1 or 2 (n = 36)	77.4	Reference	
3 (n = 49)	55.8	2.10 (1.02–4.35)	
LVSI			0.01
No (n = 46)	77.2	Reference	
Yes (n = 39)	49.6	2.62 (1.33–5.16)	
Myometrial invasion, %			0.35
≤50 (n = 32)	68.1	Reference	
>50 (n = 53)	61.6	1.39 (0.70–2.77)	
Cervical stromal invasion			0.11
No (n = 68)	67.2	Reference	
Yes (n = 17)	52.1	1.80 (0.87–3.73)	
Peritoneal cytologic evaluation			0.49
Negative (n = 56)	67.3	Reference	
Positive (n = 25)	58.9	1.54 (0.76–3.09)	
Not sampled (n = 4)	50.0	1.11 (0.26–4.72)	
Adnexal involvement			0.45
No (n = 72)	67.1	Reference	
Yes (n = 13)	46.9	1.40 (0.58–3.37)	
Serosal involvement			0.95
No (n = 72)	66.8	Reference	
Yes (n = 13)	51.9	1.03 (0.43–2.46)	
Vaginal invasion			0.66
No (n = 82)	64.1	Reference	
Yes (n = 3)	66.7	0.64 (0.09–4.67)	
Low uterine segment invasion			0.39[b]
No (n = 34)	66.7	Reference	
Yes (n = 33)	60.3	1.36 (0.65–2.87)	
Unknown (n = 18)	64.7	1.27 (0.54–2.99)	
Tumor diameter, cm			0.63
≤2 (n = 4)	75.0	Reference[c]	
>2 (n = 79)	62.5	1.67 (0.32–8.87)	
Unknown (n = 2)	100.0	0.54 (0.02–14.36)	
Pelvic metastasis type			0.52
ITC or micrometastasis (n = 14)	77.9	Reference	
Macrometastasis (n = 71)	61.5	1.36 (0.53–3.50)	
Location of metastasis			0.21
Intracapsular (n = 70)	69.5	Reference	
Extracapsular (n = 15)	40.2	1.65 (0.75–3.61)	
Positive pelvic nodes, No.[d]			0.01
1 (n = 35)	76.0	Reference	
2 (n = 16)	62.5	1.33 (0.53–3.31)	

Table 6 (*continued*)

Characteristic	Nonvaginal Recurrence-Free Survival at 2 y, (95% CI)	HR (95% CI)	*P* Value
3–5 (n = 14)	83.3	0.87 (0.30–2.51)	
>5 (n = 19)	29.9	3.39 (1.51–7.65)	
Adjuvant treatment			0.08
None (n = 12)	56.6	Reference	
EBRT ± VB (n = 25)	66.8	0.86 (0.28–2.62)	
Systemic chemotherapy ± VB (n = 13)	35.2	1.61 (0.48–5.35)	
Systemic chemotherapy + EBRT ± VB (n = 31)	75.6	0.42 (0.13–1.36)	
Unknown (n = 4)	66.7	0.41 (0.05–3.70)	

Abbreviations: EBRT, external beam radiation therapy; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; ITC, isolated tumor cells; LVSI, lymphovascular space invasion; VB, vaginal brachytherapy.

[a] Of the 85 patients, 37 had a nonvaginal recurrence with median (interquartile range) time to recurrence of 13 (5.5–24.3) months. Among the other 48 patients, median (interquartile range) of follow-up was 61.0 (18.0–81.5) months.

[b] Determined on the basis of 67 patients with known information.

[c] Firth bias correction applied because of zero cell issue.

[d] One patient with unknown number of pelvic nodes removed.

Furthermore, we analyzed the data, comparing patients with a regional recurrence (lymphatic, n = 11) vs patients with distant recurrence (hematogenous, peritoneal, or a combination; n = 21). On the comparison of the patient and tumor characteristics, a greater proportion of patients with a regional recurrence were observed to have LVSI (81.8% [9/11] vs 52.4% [11/21]), low uterine segment invasion (88.9% [8/9] vs 33.3% [6/18]), and pelvic macrometastasis (100% [1/11] vs 76.2% [16/21]).

In the group of patients with low-volume metastasis (n = 14), none of the 7 patients with ITC died of disease (median [range] follow-up, 4.8 [1.6–6.8] years), and all of them received adjuvant treatment (EBRT without VB, n = 3; systemic chemotherapy and EBRT with VB, n = 3; systemic chemotherapy, n = 1). Among the 7 patients with micrometastasis (median [range] follow-up, 2.8 [0.5–8.5] years), 2 died of disease after receiving adjuvant treatment of systemic chemotherapy and EBRT ± VB. One patient had a grade 3, stage IIIC endometrioid adenocarcinoma and had bone and hilar metastasis during adjuvant treatment; the other patient had serous stage III EC and had a relapse 2 years after completion of adjuvant treatment in the pelvis and the lungs. Among the other 5 patients, 2 received no form of adjuvant treatment, 2 received systemic chemotherapy and EBRT ± VB, and 1 received EBRT only.

3.7. Risk factors of interest

After multivariate analysis, we selected pelvic macrometastasis, LVSI, and serosal involvement as risk factors of interest and further evaluated their association with the concomitant presence of multiple positive pelvic nodes, positive para-aortic nodes, and the occurrence of nonvaginal recurrences within 3 years (ie, outcomes). At least 1 of these factors was present in 77 of 85 patients. In 9 cases, all 3 risk factors of interest were present; 28 and 40 patients had 2 of 3 and 1 of 3, respectively.

A consistent dose-response effect was observed in the relationship between the number of risk factors present and the occurrence of multiple pelvic lymph nodes. However, the same effect was not observed for the occurrence of para-aortic involvement or the 3-year rates for survival free of nonvaginal recurrence (Supplementary Table 2).

4. Discussion

Lymph nodes generally represent the first site of extrauterine disease among women with EC. Gathering information about the lymph nodes status is useful not only from a prognostic point of view but also for directing adjuvant treatment. Use of SLN mapping is a rational alternative to complete lymphadenectomy for staging purposes. However, the prediction of the exact extent of lymphatic involvement has been challenging. Hence, identification of predictors of non-SLN involvement is needed.

In the present study, we provided important information regarding metastasis characterization and predictors of lymphatic dissemination in a patient cohort with positive lymph nodes detected after complete lymphadenectomy. We interrogated both the dimension of the metastasis and the established primary tumor prognostic factors for risk assessment of involvement of multiple pelvic nodes, para-aortic involvement, and nonvaginal recurrences.

We found that, as a first observation, large-volume metastases were more frequently observed than low-volume metastases (83.5% vs 16.5%) in our cohort. Immunohistochemical staining was not performed in negative lymph nodes, thus possibly leading to an underestimation of the frequency of low-volume metastases compared with other data available (49.4%) [20]. Nevertheless, these results highlight the changes in endometrial cancer clinical care that have occurred in the past 20 years. If in the pre–sentinel lymph node era, patients with low-volume metastasis were treated as aggressively as patients with high-volume metastasis with extensive pelvic and para-aortic lymphadenectomy. Today an active debate is ongoing about the prognosis carried by low-volume metastasis and the risk of overtreatment for patients with disease that is limited to the uterus.

Subsequently, we interrogated well-established primary tumor prognostic factors for their association with the occurrence of low- vs high- volume metastasis. Recent data have shown that for patients with metastatic lymph nodes, the presence of macrometastasis was more likely associated with predictive features of more advanced disease (grade 2 or grade 3 tumors, nonendometrioid histologic subtypes, and >50% myometrial invasion) [21]. However, in our cohort, none of the well-recognized prognostic factors adequately predicted the occurrence of low- vs high- volume metastasis, possibly because of the small sample number.

The occurrence of multiple pelvic node involvement was associated with the presence of macrometastasis in the pelvic basin and serosal involvement of the tumor at final histologic analysis. When both factors were present, the risk of multiple pelvic involvement reached 91.7%, yet the risk of multiple pelvic involvement due to the presence of a macrometastasis only was 62.7%. Similarly, in a recent retrospective study on SLN mapping, 60.8% of the patients with SLN metastasis measuring >2 mm were found to have non-SLN involvement [11].

Focusing on the risk of occurrence of para-aortic involvement, we identified 3 predictive factors at multivariate analysis: pelvic macrometastasis, extracapsular metastasis, and LVSI. Among these factors, presence of pelvic macrometastasis attained highest statistical significance with an adjusted OR (95% CI) of 6.78 (1.34–34.44). Our group previously focused on metastasis diameter as a risk factor for para-aortic involvement and showed that its correlation with para-aortic lymph node invasion was not statistically significant [22]. These data conflict with our current findings, but the previous study involved fewer patients with positive pelvic nodes and used a more lenient criterion for definition of para-aortic assessment. The contemporary presence of the 3 risk factors for para-aortic involvement led to an 85.7% risk of finding positive para-aortic nodes (although the number of patients was limited at 7); in the absence of all 3 factors, the risk decreased to 11.1%. Although the presence of macrometastasis without LVSI or extracapsular involvement led to a 37.9% risk of finding para-aortic positive nodes, the diameter of the metastasis should not be considered alone. Instead, it should be considered in association with the primary tumor and lymph node characteristics since LVSI and extracapsular involvement together led to a higher risk of para-aortic involvement (87.5%).

When analyzing the type of recurrences, we found the presence of LVSI as the single predictor of nonvaginal recurrence at multivariate analysis. Despite the limitation of a relatively small sample size, these data reflect the well-known association of LVSI with poor prognosis and the consequent role of adjuvant treatment of patients with LVSI-positive tumors [23]. In our cohort, most patients with low-volume metastasis received a form of adjuvant treatment after surgery, and only 2 of them died of disease. Although focused on SLN data, a study from the Memorial Sloan Kettering Cancer Center group has similarly shown that for patients with SLN low-volume metastasis who received a form of adjuvant treatment after surgery, the 3-year recurrence-free survival significantly improved compared with patients who had macrometastasis in the SLN [24].

The strengths of our study include the strict inclusion criteria for the high number of lymph nodes surgically removed and the complete review of slides by a gynecologic pathologist. Limitations include the retrospective design, the single-institution setting with a limited sample size that met the strict inclusion criteria, and the lack of immunohistochemical staining for negative lymph nodes.

5. Conclusion

The volume of lymph node metastasis in the pelvic basin of patients with node-positive EC is associated with both the extent of pelvic involvement and the existence of para-aortic invasion but not with the occurrence of nonvaginal recurrences. Indeed, the presence of LVSI was associated with both para-aortic invasion and nonvaginal relapse occurrence. In the era of SLN mapping, characterization of nodal metastases, as well as definition of predictors able to identify additional positive pelvic or para-aortic nodes, is crucial. The information provided herein could be used to better define the treatment algorithm for candidates of SLN mapping, such as the inclusion of high-volume metastasis among the negative prognostic factors, and proceed with more aggressive treatment in those cases while sparing the patients with low-volume metastasis from the unnecessary adverse effects. Prospective studies are needed to validate our data, and questions remain about the role of low-volume metastasis on oncologic outcomes and the benefits of adjuvant therapy in this subgroup of patients.

Author contributions

All authors contributed to the manuscript. V.Z., A.F., A.M., and G.E.G. conceived and designed the study. V.Z., J.C., F.M., and S.C. collected and organized patients' data. Y.H. reviewed the pathologic biospecimen. M.E.M.G. and A.L.W. conducted the statistical analysis. All authors have read and approved the final version of the manuscript.pt?>

Declaration of Competing Interest

The authors have no conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.07.006.

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