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Original Article

Is presumed clinical stage I endometrial cancer using PET-CT and MRI accurate in predicting surgical staging?

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ABSTRACT

Objective: To evaluate upstaging, lymph node (LN) metastasis, and recurrence in patients with presumed stage I endometrial cancer using preoperative magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT).
Methods: Retrospective review of 422 patients with presumed clinical stage I endometrial cancer diagnosed via MRI and PET-CT (July 2014–June 2023). Surgical staging included pelvic lymph nodes (PLNs) and para-aortic lymph nodes (PALNs), classifying patients as low/intermediate- or high-risk groups.
Results: Post-operative upstaging rate was 14.5% (8.8% low/intermediate-risk vs. 22.8% high-risk, p<0.001). LN metastasis occurred in 5.5% of patients (2.0% low/intermediate-risk vs. 10.5% high-risk, p<0.001), with a dual imaging negative predictive value of 0.945. PLN metastasis was 4.5% (2.0% low/intermediate vs. 8.2% high-risk, p=0.003), and PALN metastasis was 2.6% (0.4% low/intermediate-risk vs. 5.8% high-risk, p=0.001). In low/intermediate-risk group: tumors ≤2cm had 1.1% LN metastasis rate, endometrium-limited 0.8%, and ≤2cm with endometrium-limited 0.9%. Deep myometrial invasion (odds ratio [OR]=4.4; 95% confidence intervals [CIs]=1.6–12.4) and tumor size >2 cm on MRI (OR=2.9; 95% CI=0.8–9.9) increased LN metastasis risk. Median 48.5-month follow-up showed an 8.1% overall recurrence rate (4.0% low/intermediate-risk vs. 14.0% high-risk, p<0.001), with 2.4% nodal recurrences (1.2% low/intermediate-risk vs. 4.1% high-risk).
Conclusion: High-risk patients had significant upstaging, LN metastasis, and recurrence rates. Even in low/intermediate-risk groups, some patients exhibited LN metastasis and nodal recurrence, underscoring the importance of comprehensive surgical staging, including PALN evaluation, for precise diagnosis and treatment.

Keywords: Endometrial Cancer; Neoplasm Staging; Lymph Node Metastasis; Neoplasm Recurrence, Local

Synopsis

In patients with presumed stage I endometrial cancer based on preoperative imaging, 14.5% were upstaged. Lymph node (LN) metastasis occurred in 5.5%, with 8.1% recurrence. The high-risk group showed higher rates of upstaging, LN metastasis, and recurrence. Thorough surgical staging with LN evaluation is essential for precise diagnosis and treatment.

Presentation
The original manuscript has not been presented or published previously. The abstract was submitted to the 2023 IGCS Annual Global Meeting.

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: K.S.W.; Data curation: S.K.E., S.Y., L.J.Y., N.E.J., K.S., K.Y.T., K.S.W.; Formal analysis: S.K.E., K.S.W.; Methodology: K.S.W.; Supervision: K.S.W.; Validation: K.S.W.; Visualization: S.K.E.; Writing - original draft: S.K.E.; Writing - review & editing: S.K.E., K.S.W.

INTRODUCTION

Endometrial cancer ranks as the sixth most common cancer in women, with 417,000 cases reported in 2020 [1]. Notably, early detection enables surgical intervention, resulting in a 5-year survival rate of approximately 95% [2]. In the diagnostic landscape of endometrial cancer, dynamic contrast-enhanced magnetic resonance imaging (MRI) can accurately assess myometrial invasion, cervical involvement, and lymph node (LN) metastasis [3,4]. Additionally, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) serves as a valuable tool for detecting occult metastatic lesions [5]. Consequently, the utilization of both MRI and PET-CT in the preoperative radiologic assessment of endometrial cancer is on the rise, underscoring the increasing preference for these imaging modalities.

The necessity and extent of LN assessment during the surgical staging of endometrial cancer were determined based on the results of these evaluations. However, in patients with LN-negative early-stage endometrial cancer identified using these imaging techniques, uncertainty persists regarding the extent of LN assessment—whether to limit it to pelvic lymph nodes (PLNs) or include the para-aortic lymph nodes (PALNs) [6,7]. To guide the LN assessment in clinical stage I endometrial cancer, understanding which patients are more likely to have LN metastasis and determining the incidence of metastasis in the PLN and PALN regions are crucial. Current studies on LN metastasis are limited and outdated, often relying on old data that do not reflect current practices. Particularly, the number of studies investigating the LN metastasis rates in patients with negative findings on MRI and PET-CT scans is limited.

Hence, our study aimed to investigate the actual rates of upstaging, LN metastasis, and recurrence in patients with clinical stage I uterine confined cancer, excluding those with cervical invasion or LN metastasis, as confirmed by preoperative MRI and PET-CT. We also aimed to analyze our results based on preoperative risk categories.

MATERIALS AND METHODS

1. Patient

This retrospective study was conducted at Yonsei University (Seoul, Korea). It included patients with endometrial cancer classified as stage I according to the MRI and FDG PET-CT findings, following the International Federation of Gynecology and Obstetrics (FIGO) staging system. The study spanned from July 2014 to June 2023 and was approved by the Institutional Review Board of the Yonsei University Health System, Severance Hospital (4-2023-0718, dated July 27, 2023), and the requirement for informed consent was waived. It involved both PLN and PALN assessments during surgical staging at the Yonsei Cancer Center. Patients with preoperative clinical stages II–IV on MRI or PET-CT scans, who did not undergo both PLN and PALN assessments during surgical staging, with other malignancies, with a history of radiation therapy, or who underwent surgical staging following a hysterectomy for benign disease but were incidentally found to have endometrial malignancy were excluded.

Among the 1,348 patients, 422 met the inclusion criteria (**Fig. 1**). A retrospective analysis was conducted using clinical variables (age, body mass index [BMI], gravidity, parity, and menopausal status) and operational data (surgical approaches, LN assessment methods, and

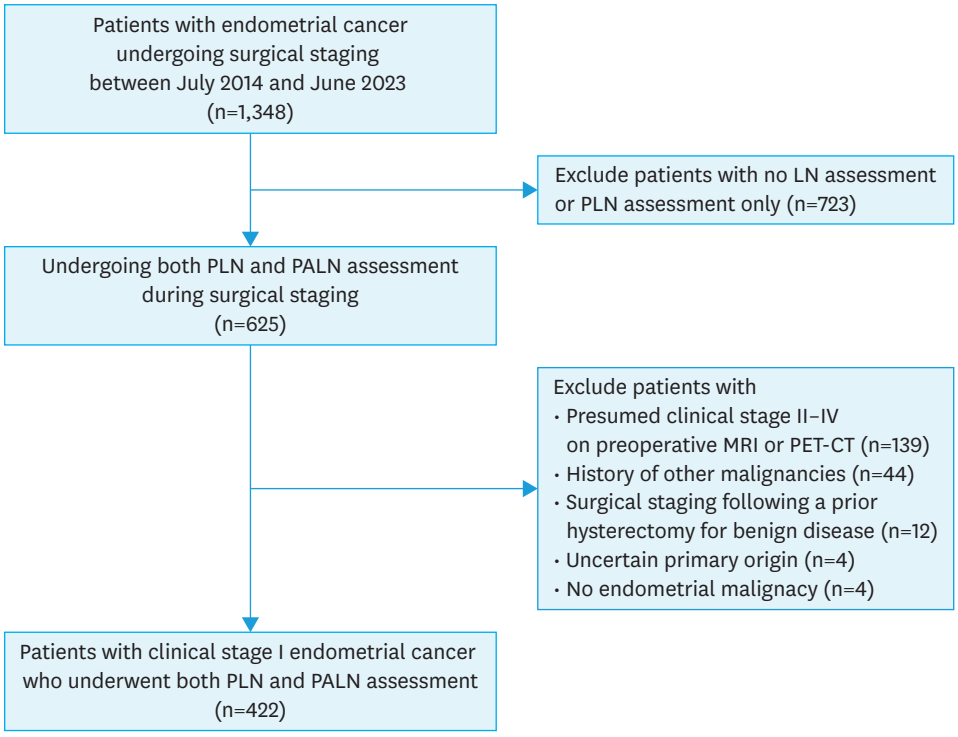

Fig. 1. Flowchart illustrating the process of selecting patients with endometrial cancer.
LN, lymph node; MRI, magnetic resonance imaging; PALN, para-aortic lymph node; PET-CT, positron emission tomography-computed tomography; PLN, pelvic lymph node.

levels). Specifically, we investigated whether surgeons assessed the PALN only up to the area between the aortic bifurcation and the inferior mesenteric artery (IMA), known as the "lower PALN," or extended their evaluation up to the area between the IMA and the renal vein, known as the "upper PALN."

Histopathological variables included histological type and grade, tumor size, myometrial invasion, lymphovascular space involvement (LVSI), and LN metastasis. The entire patient cohort was stratified into preoperative risk groups based on myometrial invasion depth (myometrial invasion ≥1/2 on MRI) and high-grade histology (encompassing endometrioid grade 3, serous papillary, clear cell, undifferentiated, dedifferentiated, mesonephric adenocarcinoma, mesonephric-like adenocarcinoma, carcinosarcoma, and mixed types with high-grade histology as shown preoperative biopsy). Consequently, patients were categorized into low/intermediate-risk (n=251; endometrioid adenocarcinoma G1/2, myometrial invasion <1/2, and no cervical involvement) and high-risk groups (n=171; endometrioid adenocarcinoma G3, or non-endometrioid types, or myometrial invasion ≥1/2). Data on adjuvant treatment, overall response, recurrence status, and survival rates were collected until September 2023.

Postoperatively, the patients underwent routine evaluations 1 week after discharge. Based on the final pathology results and tumor board recommendations, some patients underwent adjuvant chemotherapy and/or radiotherapy, while others followed regular surveillance schedules: quarterly for 2 years, biannually for 3 years, and annually thereafter.

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2. Surgical procedures

Surgical staging was conducted by 7 experienced gynecologic oncology surgeons at a tertiary referral center, where over 180 patients with endometrial cancer undergo surgical staging annually. The surgical methods employed encompass laparotomy, laparoscopy, and robotic approaches. The surgical method is predominantly at the discretion of the surgeon, taking into account the patient's medical history and comorbidities. The surgical staging procedure involved a total hysterectomy, salpingo-oophorectomy, and assessment of both PLN and PALN. In selected premenopausal women with disease limited to less than half of the endometrium, preservation of one or both ovaries was considered. The method used for assessing the LNs, whether conventional LN dissection (LND) or sentinel LN (SLN) biopsy, was determined based on the histologic type and grade derived from the preoperative endometrial biopsy results, as well as the surgeon's discretion. Indocyanine green served as a fluorescent tracer for SLN mapping, utilizing either a one-step technique (cervical injection) or a 2-step technique (bilateral uterine cornus and cervical injection), as previously described by our study group [8].

3. Statistical analysis

The statistical analyses were conducted using SPSS Statistics for Windows (version 26.0; SPSS Inc., Chicago, IL, USA). Student's t-test was employed for comparing continuous variables with normal distributions, while Pearson's χ^2 and Fisher's exact tests were used for evaluating categorical variables. To ascertain the risk factors for LN metastasis, variables with a p-value of <0.05 in the univariate analysis were subjected to further assessment in the multivariate logistic regression model. A p-value of <0.05 was considered significant.

RESULTS

1. Overall study population

The demographic and clinicopathological characteristics of the 422 patients are presented in **Table 1**. Surgical staging was performed using minimally invasive surgery methods, such as laparoscopy or robot-assisted procedures, in 84.6% of the patients. SLN mapping was conducted in 73.5% (310/422) of the patients, and 60% (187/310) of them underwent SLN mapping with LND for validation.

In terms of preoperative clinical stage, 73.5% and 26.5% of the patients had stages IA and IB, respectively. After surgical staging, 14.5% (61/422) of the patients were upstaged compared with their initial estimates (**Table 2**). Among the 310 patients initially diagnosed with stage IA disease, 32 (10.3%) were upstaged (IB=13, II=11, IIIA=1, and IIIC=7). Among the 112 patients with stage IB disease, 39 (34.8%) were down-staged to IA, 44 (39.3%) remained at IB, and 29 (25.9%) were upstaged (II=7, IIIA=4, IIIC=14, and IVB=4).

The median number of total harvested LNs was 13, with an interquartile range (IQR) of 8–22. Specifically, the median number of PLN was 8 (IQR: 5–14), while that of PALN was 4 (IQR: 2–8). LN metastasis was identified in 23 (5.5%) patients, demonstrating a negative predictive value of 0.945 for double-negative findings on preoperative MRI and PET-CT in detecting nodal metastasis (**Table 3**). Of these, 19 (4.5%) patients had PLN metastases, while 11 (2.6%) had PALN metastases. Metastases in the pelvic area alone, para-aortic area alone, and both pelvic and paraaortic areas were detected in 12 (2.8%), 4 (0.9%), and 7 (1.7%) patients, respectively.

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Table 1. Demographic and clinicopathologic characteristics of all patients (n=422)

Characteristics	Values
Age (yr)	54.5±10.7
BMI (kg/m^2)	24.8±4.4
Gravidity	3 (1–4)
Parity	2 (1–2)
Menopause	256 (60.7)
Surgical method	
Laparotomy	65 (15.4)
Laparoscopy	229 (54.3)
Robot	128 (30.3)
LN assessment method	
LND	112 (26.5)
SLN	310 (73.5)
Clinical stage (FIGO, 2014)	
IA	310 (73.5)
IB	112 (26.5)
Surgical stage (FIGO, 2014)	
IA	317 (75.1)
IB	57 (13.5)
II	18 (4.3)
IIIA	5 (1.2)
IIIB	-
IIIC1	11 (2.6)
IIIC2	10 (2.4)
IVA	-
IVB	4 (0.9)
Histology*	
Endometrioid	367 (87.0)
Malignant mixed mullerian tumor	14 (3.3)
Serous	12 (2.8)
Clear cell	9 (2.1)
Endometrial stromal sarcoma	6 (1.4)
Mesonephric	6 (1.4)
Mucinous	1 (0.2)
Others	7 (1.7)
Grade*	
1	184 (43.6)
2	139 (32.9)
3	70 (16.6)
Others	29 (6.9)
Preoperative risk group	
Low/Intermediate	251 (59.5)
High	171 (40.5)
Myometrial invasion depth*	
<½	340 (80.6)
≥½	82 (19.4)
Tumor size (cm)*	
≤2	185 (43.8)
>2	237 (56.2)
Lymphovascular space invasion	
Negative	329 (78.0)
Positive	93 (22.0)
Focal	46 (10.9)
Substantial/Frequent/Diffuse	15 (3.5)
NA	32 (7.6)
Peritoneal cytology	
Negative	283 (67.0)
Atypical cells	59 (14.0)
Positive	21 (5.0)
NA	59 (14.0)

Values are presented as mean ± standard deviation, median (interquartile range), or number (%).
BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; LND, lymph node dissection; NA, not available; SLN, sentinel lymph node.
*The measurement was determined based on the permanent pathologic report.

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Table 2. Postoperative FIGO stage in clinical stage I endometrial cancer on magnetic resonance imaging and positron emission tomography-computed tomography

Postoperative FIGO stage	Initial clinical stage		
	IA (n=310)	IB (n=112)	Total (n=422)
IA	278 (89.7)	39 (34.8)	317 (75.1)
IB	13 (4.2)	44 (39.3)	57 (13.5)
II	11 (3.5)	7 (6.3)	18 (4.3)
IIIA	1 (0.3)	4 (3.6)	5 (1.2)
IIIB	-	-	-
IIIC1	5 (1.6)	6 (5.4)	11 (2.6)
IIIC2	2 (0.6)	8 (7.1)	10 (2.4)
IVA	-	-	-
IVB	-	4 (3.6)	4 (0.9)
Upstaged cases	32 (10.3)	29 (25.9)	61 (14.5)

Values are presented as number (%).
FIGO, International Federation of Gynecology and Obstetrics.

Table 3. Comparison of upstaging rate, LN metastasis, and recurrence between preoperative low/intermediate-risk (n=251) and high-risk (n=171) groups

Variables	All patient (n=422)	Low/Intermediate-risk group (n=251)	High-risk group (n=171)	p-value
Up-staging rate and causes*	61 (14.5)	22 (8.8)	39 (22.8)	<0.001
More than half MI	13 (3.1)	7 (2.8)	6 (3.5)	
Cervical invasion	18 (4.3)	10 (4.0)	8 (4.7)	
Uterine serosa and/or adnexal invasion	5 (1.2)	-	5 (2.9)	
LN metastasis	21 (5.0)	5 (2.0)	16 (9.4)	
Distant metastasis	4 (0.9)	-	4 (2.3)	
LN metastasis	23 (5.5)	5 (2.0)	18 (10.5)	<0.001
PLN	19 (4.5)	5 (2.0)	14 (8.2)	0.003
PALN	11 (2.6)	1 (0.4)	10 (5.8)	0.001
PLN only	12 (2.8)	4 (1.6)	8 (4.7)	0.076
PALN only	4 (0.9)	-	4 (2.3)	0.026
Both PLN and PALN	7 (1.7)	1 (0.4)	6 (3.5)	0.019
Recurrence	34 (8.1)	10 (4.0)	24 (14.0)	<0.001
Distant organ	16 (3.8)	3 (1.2)	13 (7.6)	0.001
Vagina	11 (2.6)	5 (2.0)	6 (3.5)	0.365
LN	10 (2.4)	3 (1.2)	7 (4.1)	0.098
Peritoneum	9 (2.1)	1 (0.4)	8 (4.7)	0.004

Values are presented as number (%).
LN, lymph node; MI, myometrial invasion; PALN, para-aortic lymph node; PLN, pelvic lymph node.
*Causes affecting the final surgical stage in cases of upstaging.

2. Upstaging rates in low/intermediate-risk and high-risk groups

Of the 422 patients, 61 (14.5%) exhibited upstaging (**Table 3**). The primary factors contributing to upstaging included LN metastasis (5.0%), cervical invasion (4.3%), more than half myometrial invasion (3.1%), uterine serosa and/or adnexal invasion (1.2%), and distant metastasis (0.9%). When stratified based on preoperative risk, 22 patients (8.8%) in the low/intermediate-risk group were upstaged compared with the 39 patients (22.8%) in the high-risk group, indicating a significantly higher incidence of upstaging in the latter group ($p<0.001$).

In the high-risk group, LN metastasis (9.4%) and cervical invasion (4.7%) were the most common causes of upstaging. Conversely, cervical invasion (4.0%) and deep myometrial invasion (2.8%) were predominant in the low/intermediate-risk group, respectively.

Within the low/intermediate-risk group, when the tumor was limited to the endometrium as shown on preoperative MRI, upstaging occurred in 5 patients (3.9%), of whom 4 had cervical invasion and one had LN metastasis (**Table S1**). Among those with invasion in less than half

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of the myometrium on preoperative MRI, 17 (13.9%) were upstaged (7 with deep myometrial invasion, 6 with cervical invasion, and 4 with LN metastasis). Significantly, the rate of upstaging was lower in patients whose tumors were confined to the endometrium than in those with invasion in less than half of the myometrium (p=0.005).

3. LN metastasis in low/intermediate-risk and high-risk groups

Among all patients, 23 (5.5%) exhibited LN metastasis (**Table 3**). LN metastasis occurred in 5 (2.0%) low/intermediate-risk patients and 18 (10.5%) high-risk patients (p<0.001). The incidence of LN metastasis was significantly higher in the high-risk group than in the low/intermediate-risk group (PLN, p=0.003; PALN, p=0.001; PALN only, p=0.026; both PLN and PALN, p=0.019).

In the low/intermediate-risk group with LN metastasis, one patient (0.8%) had an endometrium-limited tumor detected on preoperative MRI, while 4 patients (3.3%) exhibited invasion in less than half of the myometrium (**Table S1**). Notably, the patient with an endometrium-limited tumor and LN metastasis had a tumor size of >2 cm detected on permanent pathological examination (although preoperative MRI measured it as <2 cm) with metastasis to the PLN. Among those with invasion in less than half of the myometrium and LN metastasis, all 4 patients had a tumor of >2 cm (although one was measured as <2 cm on preoperative MRI), with 3 showing metastasis to the PLN alone and one showing metastasis to the PLN and lower PALN.

No significant differences were noted in age, BMI, menopausal status, or surgical approach between the LN metastasis (LN positive) group and no LN metastasis (LN negative) group (**Table S2**). However, the incidence of clinical stage IB on preoperative MRI (69.6% in the LN-positive group vs. 24.1% in the LN-negative group), non-endometrioid histology (26.1% vs. 12.3%), deep myometrial invasion (69.6% vs. 16.5%), tumor size >2 cm (87.0% vs. 53.1%), and LVSI (78.3% vs. 18.8%) was relatively high in the LN-positive cohort.

The study patients were stratified according to the following 5 preoperative variables: preoperative risk, myometrial invasion depth on MRI, tumor size on MRI, preoperative histology, and PALN evaluation level (**Table 4**). We examined the prevalence of LN metastasis in each nodal area across stratified groups. A higher prevalence of LN metastasis was noted in the high-risk group (10.5% vs. 2.0% in the low/intermediate-risk group, p<0.001), in patients with a myometrial invasion depth of ≥1/2 on MRI (14.3% vs. 2.3%, p<0.001), and in patients with a tumor of >2 cm on MRI (9.8% vs. 1.8%, p<0.001). However, no significant differences were found in the prevalence or patterns of LN metastases based on the results of preoperative histology or PALN evaluation level.

In our study, we also assessed the preoperative risk factors associated with LN metastasis in patients with presumed clinical stage I endometrial cancer (**Table 5**). Univariate analysis revealed that LN metastasis was associated with the depth of myometrial invasion and tumor size on MRI (p<0.001 each). Specifically, in patients with deep myometrial invasion (>1/2 depth), 14.3% (16/112) experienced LN metastasis, compared to 2.3% (7/310) with less invasion (<1/2 depth). For larger tumors (>2 cm), the metastasis rate was 9.8% (19/194), while it was 1.8% (4/228) for smaller tumors (≤2 cm). Multivariable analysis further confirmed the deep myometrial invasion (odds ratio [OR]=4.4; 95% confidence interval [CI]=1.6–12.4) and tumor size of >2 cm on MRI (OR=2.9; 95% CI=0.8–9.9) as significant risk factors for LN metastasis.

Table 4. Prevalence of LN metastasis in presumed clinical stage I endometrial cancer: stratified analysis according to the preoperative risk factors (n=422)

Variables	Metastatic LN sites					
	Any LN	PLN	PALN	PLN only	PALN only	PLN and PALN
Preoperative risk group						
Low/Intermediate (n=251)	5 (2.0)	5 (2.0)	1 (0.4)	4 (1.6)	0 (0.0)	1 (0.4)
High (n=171)	18 (10.5)	14 (8.2)	10 (5.8)	8 (4.7)	4 (2.3)	6 (3.5)
p-value	<0.001	0.003	0.001	0.076	0.026	0.019
Myometrial invasion depth on MRI						
<½ (n=310)	7 (2.3)	6 (1.9)	2 (0.6)	5 (1.6)	1 (0.3)	1 (0.3)
≥½ (n=112)	16 (14.3)	13 (11.6)	9 (8.0)	7 (6.3)	3 (2.7)	6 (5.4)
p-value	<0.001	<0.001	<0.001	0.018	0.059	0.002
Tumor size on MRI (cm)						
≤2 (n=228)	4 (1.8)	4 (1.8)	0 (0.0)	4 (1.8)	0 (0.0)	0 (0.0)
>2 (n=194)	19 (9.8)	15 (7.7)	11 (5.7)	8 (4.1)	4 (2.1)	7 (3.6)
p-value	<0.001	0.003	<0.001	0.144	0.044	0.004
Preoperative histology						
Endometrioid G1, G2 (n=334)	16 (4.8)	13 (3.9)	7 (2.1)	9 (2.7)	3 (0.9)	4 (1.2)
Endometrioid G3 and non-endometrioid (n=88)	7 (8.0)	6 (6.8)	4 (4.5)	3 (3.4)	1 (1.1)	3 (3.4)
p-value	0.288	0.250	0.252	0.720	ns	0.161
PALN evaluation level*						
Up to lower PALN area (n=239)	13 (5.4)	12 (5.0)	4 (1.7)	9 (3.8)	1 (0.4)	3 (1.3)
Up to upper PALN area (n=183)	10 (5.5)	7 (3.8)	7 (3.8)	3 (1.6)	3 (1.6)	4 (2.2)
p-value	0.991	0.557	0.221	0.193	0.321	0.473

Values are presented as number (%).
LN, lymph node; MRI, magnetic resonance imaging; ns, not significant; PALN, para-aortic lymph node; PLN, pelvic lymph node.
*The "lower PALN area" refers to the region between the aortic bifurcation and the inferior mesenteric artery, while the "upper PALN area" refers to the region between the inferior mesenteric artery and the renal vein.

Table 5. Univariate and multivariate analyses assessing the preoperative risk factors for LN metastasis in presumed clinical stage I endometrial cancer (n=422)

Variables	Univariate analysis		Multivariate analysis
	No. of patients with LN metastasis (%)	p-value	OR (95% CI)
Age (yr)		0.748	
<60 (n=288)	15 (5.2)		
≥60 (n=134)	8 (6.0)		
BMI (kg/m^2)		0.066	
<25 (n=243)	9 (3.7)		
≥25 (n=179)	14 (7.8)		
Gravidity		0.765	
Nulligravida (n=64)	4 (6.3)		
Primi/Multigravida (n=358)	19 (5.3)		
Parity		0.417	
Nulliparous (n=82)	6 (7.3)		
Primi/Multiparous (n=340)	17 (5.0)		
Menopausal status		0.646	
Pre-menopause (n=166)	8 (4.8)		
Menopause (n=256)	15 (5.9)		
Myometrial invasion depth on MRI		<0.001	4.4 (1.6–12.4)
<½ (n=310)	7 (2.3)		
≥½ (n=112)	16 (14.3)		
Tumor size on MRI (cm)		<0.001	2.9 (0.8–9.9)
≤2 (n=228)	4 (1.8)		
>2 (n=194)	19 (9.8)		
Preoperative histology		0.288	
Endometrioid G1, G2 (n=334)	16 (4.8)		
Endometrioid G3 and non-endometrioid (n=88)	7 (8.0)		

BMI, body mass index; CI, confidence interval; LN, lymph node; MRI, magnetic resonance imaging; OR, odds ratio.

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4. PALN metastasis

The incidence of PALN metastasis was significantly higher in preoperative high-risk patients, those with deep myometrial invasion, and those with a tumor size of >2 cm on MRI (**Table 4**). Additionally, although not considered significant, patients with high-grade preoperative histology or those who underwent extended PALN evaluation up to the upper para-aortic area had a 2-fold higher rate of PALN metastasis.

Among the 11 patients with PALN metastasis, 7 showed involvement in the lower PALN area, 3 in the upper area, and one in both areas (**Table S3**).

A significant correlation was noted between PLN and PALN metastases, with PALN metastasis rates of 36.8% in patients with PLN metastasis and 1.0% in those without PLN metastasis ($p<0.001$). Furthermore, we explored the relationship between PALN and bilateral PLN metastases, with common iliac LN involvement (**Table S4**). Approximately 75% (3/4) of the patients with bilateral PLN metastasis and 26.7% (4/15) with unilateral metastasis showed PALN involvement. However, statistical analysis revealed no significant correlations between PLN bilaterality and PALN metastasis ($p=0.117$) or between common iliac LN and PALN metastasis in patients with PLN involvement ($p=0.603$).

5. Recurrence

The median follow-up duration was 48.5 months (range: 0.4–106.8 months), with a disease-free survival of 46.1 months. Among the 422 patients, 34 (8.1%) experienced disease recurrence and 5 died (3 from disease progression, one from pneumonia, and one from anaphylactic shock following the administration of contrast media).

The types of recurrence were categorized as distant organ, vaginal, LN, and peritoneal (**Table 3**). Distant organ recurrence was the most common (3.8%), followed by vaginal recurrence (2.6%), LN recurrence (2.4%), and peritoneal recurrence (2.1%). The recurrence rates differed significantly between the risk groups: 4.0% in the low/intermediate-risk and 14.0% in the high-risk groups ($p<0.001$), with the high-risk group showing higher rates across all recurrence types. Univariate analysis indicated higher recurrence rates in older patients (≥60 years), menopausal women, those with deeper myometrial invasion (≥1/2), larger tumors (>2 cm), high-grade histology (endometrioid G3 or non-endometrioid), positive LVSI, and nodal involvement (**Table S5**). Multivariate analysis revealed that myometrial invasion depth and histology are risk factors for recurrence (OR=4.4; 95% CI=2.1–9.3 and OR=2.6; 95% CI=1.2–5.5, respectively).

6. Tumor size and LN metastasis/recurrence patterns

In the low/intermediate-risk group (n=251), we stratified patients based on tumor size detected on preoperative MRI to assess for LN metastasis and recurrence types (**Table S6**).

For patients with tumors of ≤2 cm (n=179), LN metastasis occurred in 1.1% (2/179), all involving the PLNs alone. The overall recurrence rates were 3.4% (6/177) in the LN group and 0% (0/2) in the LN-positive group (vaginal recurrence, 4; LN recurrence, 2; and distant organ recurrence, 2). One patient with LN recurrence died due to disease progression.

In the cohort with a tumor of >2 cm (n=72), LN metastasis was observed in 4.2% (3/72; 2 PLN metastasis alone and one with both PLN and PALN metastases). However, no recurrence was noted in 3 patients with LN metastasis. Among those without LN metastasis (n=69), the recurrence rate was 5.8% (4/69) across various sites: one with LN recurrence, one with

vaginal recurrence, one with peritoneal recurrence, and one with distant organ recurrence. Meanwhile, one patient with distant organ recurrence died due to disease progression.

DISCUSSION

In this single-institution retrospective study, we analyzed actual upstaging, LN metastasis, and recurrence rates in patients initially diagnosed with clinical stage I endometrial cancer using MRI and PET-CT.

A previous study investigating the LN metastasis rates in clinical stage I endometrial cancer, namely, the Gynecologic Oncology Group (GOG) 33 study reported LN metastasis rates of 11% for both PLN and PALN, 9% for PLN alone, and 5% for PALN alone [9]. Consistently, our study highlighted deep myometrial invasion as a significant risk factor for LN metastasis, aligning with GOG 33's findings. Subsequent to these discoveries, the shift from clinical to surgical-pathologic staging in the FIGO system in 1988, and its 2009 update, underscores the importance of surgical staging over pre-surgical clinical assessments [10,11].

A Japanese study on clinical stage I endometrial cancer revealed a 12% PLN metastasis rate (8.6% for stage IA, 18.7% for stage IB) and a 5% PALN metastasis rate (2.5% for stage IA, 8.5% for stage IB). Both our and the Japanese study identified deep myometrial invasion and PLN metastasis as risk factors for PALN metastasis, with no significant correlation between the bilaterality of PLN and PALN metastases. While our study didn't find a significant link between common iliac LN involvement and PALN metastasis, the Japanese study did, though both had small sample sizes [12]. Both preceding studies, not using advanced radiologic tools like MRI or FDG PET-CT, might have included more patients at risk of upstaging, suggesting a higher incidence of occult LN metastases.

Our study revealed that the high-risk group, based on preoperative risk categorization, had a significantly higher metastasis rate than the low/intermediate-risk group. Additionally, among low/intermediate-risk patients with tumors ≤2 cm, 1.1% had LN metastasis (**Table S6**). This rate rose to 4.2% for those with tumors larger than 2 cm. A previous study reported a 0.8% metastasis rate (3/389) in the low-risk group with tumors <2 cm, whereas the high-risk group had a 6.3-fold higher risk [13]. Several studies have emphasized the correlation between tumor size and LN metastasis rates [14,15]. In patients with early-stage endometrioid-type endometrial cancer, LN metastasis rates were 11.5% in high-risk patients (endometrioid grades 3 or 4, or invasion depth ≥50%) and 2.0% in low-risk patients (grades 1 or 2, no or <50% invasion). For low-risk patients with tumors ≤2 cm, the rate was 1.0%; for tumors >2 cm but ≤5 cm, it was 2.3%; and for tumors >5 cm, 3.5% [16].

However, in the low/intermediate-risk group, 2 patients with tumors <2 cm developed LN metastasis, and 2 instances of nodal recurrence occurred, leading to one patient's death. Thus, despite low prevalence in this group, surgical staging remains crucial for detecting LN metastasis.

Our study also noted a higher tendency for PALN metastasis in the high-risk group, those with deep myometrial invasion, tumor size exceeding 2 cm, high-grade histology, and whose PALN evaluation extended to the upper PALN area. Among patients with PALN metastasis, 36.4% (4/11) had metastases in the upper PALN area, indicating potential LN metastases in both lower and upper PALN areas, even with negative double-imaging studies.

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Previous studies show that among patients with PALN metastasis, 77% had metastasis to the upper PALN, and 63% with lower PALN metastases also had positive nodes in the upper region [17,18]. Other studies have reinforced these findings, indicating that among high-risk patients with early or advanced endometrial cancer, approximately 50% with LN metastasis and 88% with PALN metastasis demonstrated evidence of upper PALN involvement [6,19].

Considering these findings, our study investigated the extent of PALN evaluation, determining the adequacy of this assessment and comparing LN metastasis rates accordingly. While no statistically significant differences were found in LN metastasis rates based on evaluation extent, PALN metastasis detection was approximately twice as high when evaluation included the upper PALN area (1.7% vs. 3.8% for evaluations "up to lower PALN area" vs. "up to upper PALN area").

Despite ongoing debates regarding the survival benefits of extensive PALN evaluation in early-stage endometrial cancer, our findings underscore significant rates of upstaging and PALN metastasis in high-risk preoperative groups, highlighting the importance of thorough LN assessment up to the upper PALN area in surgical staging [20].

In our study, 8.1% of patients initially diagnosed with clinical stage I endometrial cancer based on dual-imaging studies experienced disease recurrence. The high-risk group generally exhibited higher recurrence rates across all sites compared to the low-risk group. We identified deep myometrial invasion and histology as significant risk factors for recurrence. A previous retrospective study found a 9.6% recurrence rate in the low-risk group and 29.3% in the intermediate- to high-risk group, emphasizing the significance of myometrial invasion depth and histology as critical factors in recurrence rates [21].

Our study reflects contemporary practices, including surgical staging, adjuvant treatments according to current guidelines, and advanced radiological tools, such as MRI and FDG PET-CT. It also highlights modern surgical methods such as minimally invasive surgery and SLN mapping. In contrast to earlier studies on surgical stage I endometrial cancer, this study was conducted in a real-world clinical setting, presumed to have stage I disease as indicated by radiological evaluations. This approach offers a realistic perspective on potential upstaging, LN metastasis, and recurrence rates in these patients. However, it has limitations, including a small sample size, a single-institution design, and a retrospective nature. Owing to its retrospective nature, ultra-staging was not conducted, and not all patients underwent molecular profiling, hindering the integration of recent molecular classifications in the updated 2023 FIGO staging system. Future research, incorporating comprehensive molecular profiling, may elucidate LN metastasis rates and survival outcomes based on molecular classification subtypes within this patient cohort. This approach could significantly enhance patient stratification, inform personalized treatment strategies, and improve prognosis.

In conclusion, within the cohort of patients presumed to have stage I endometrial cancer based on the results of MRI and PET-CT, the high-risk group demonstrated significant rates of upstaging, PLN, and PALN metastasis, along with increased recurrence rates. Notably, even patients in the low/intermediate-risk group experienced LN metastasis and nodal recurrence. These findings underscore the critical importance of comprehensive surgical staging, including PALN evaluation, for achieving a precise diagnosis and treatment.

SUPPLEMENTARY MATERIALS

Table S1

Comparison of up-staging rate, LN metastasis, and recurrence in low/intermediate-risk group: stratified with myometrial invasion depth determined by preoperative magnetic resonance imaging (n=251)

Table S2

Demographics and clinicopathologic characteristics of patients according to LN metastasis (n=422)

Table S3

The distribution of PALN metastasis according to the site of metastasis (n=11)

Table S4

PALN metastasis in relation to PLN bilaterality and common iliac LN involvement

Table S5

Univariate and multivariate analysis assessing risk factors for recurrence in presumed clinical stage I endometrial cancer (n=422)

Table S6

Correlation of tumor size on preoperative MRI with LN metastasis and recurrence patterns in low/intermediate-risk group patients (n=251)

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