Incidence of sentinel lymph node metastases in apparent early-stage endometrial cancer: a multicenter observational study

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ABSTRACT

Objective Ultrastaging is accurate in detecting nodal metastases, but increases costs and may not be necessary in certain low-risk subgroups. In this study we examined the risk of nodal involvement detected by sentinel lymph node (SLN) biopsy in a large population of apparent early-stage endometrial cancer and stratified by histopathologic characteristics. Furthermore, we aimed to identify a subgroup in which ultrastaging may be omitted.

Methods We retrospectively included patients who underwent SLN (with bilateral mapping and no empty nodal packets on final pathology) ± systematic lymphadenectomy for apparent early-stage endometrial cancer at two referral cancer centers. Lymph node status was determined by SLN only, regardless of non-SLN findings. The incidence of macrometastasis, micrometastasis, and isolated tumor cells (ITC) was measured in the overall population and after stratification by histotype (endometrioid vs serous), myometrial invasion (none, <50%, ≥50%), and grade (G1, G2, G3).

Results Bilateral SLN mapping was accomplished in 1570 patients: 1359 endometrioid and 211 non-endometrioid, of which 117 were serous. The incidence of macrometastasis, micrometastasis, and ITC was 3.8%, 3.4%, and 4.8%, respectively. In patients with endometrioid histology (n=1359) there were 2.9% macrometastases, 3.2% micrometastases, and 5.3% ITC. No macro/micrometastases and only one ITC were found in a subset of 274 patients with low-grade (G1-G2) endometrioid endometrial cancer without myometrial invasion (all <1%). The incidence of micro/macrometastasis was higher, 2.8%, in 708 patients with low-grade endometrioid endometrial cancer invading <50% of the myometrium. In patients with serous histology (n=117), the incidence of macrometastases, micrometastasis, and ITC was 11.1%, 6.0%, and 1.7%, respectively. For serous carcinoma without myometrial invasion (n=36), two patients had micrometastases for an incidence of 5.6%.

Conclusions Ultrastaging may be safely omitted in patients with low-grade endometrioid endometrial cancer without myometrial invasion. No other subgroups with a risk of nodal metastasis of less than 1% have been identified.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Sentinel lymph node biopsy and ultrastaging are accurate in detecting nodal metastases in endometrial cancer, especially low-volume disease. However, this increases costs and may not be useful in certain subgroups. In fact, it has already been shown that the risk of nodal involvement in patients with non-invasive, low-grade (grade 1 and 2) endometrioid endometrial cancer is extremely low.

WHAT THIS STUDY ADDS

⇒ In low-grade, non-invasive endometrioid endometrial cancer the risk of nodal metastasis is extremely low (<1%). In serous histotype, high-grade endometrioid, or low-grade endometrioid with myometrial invasion, the risk of micro/macrometastases ranges from 1.5% to 43.5%.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Ultrastaging might be safely omitted in low-grade, non-invasive endometrial cancers.

INTRODUCTION

Endometrial cancer is the fourth most common cancer diagnosed in women in the United States, with 66 200 new cases and 13 030 deaths expected in 2023.[1] The prognosis is excellent in early-stage disease, with a 5-year overall survival rate of more than 80%; however, spread to the pelvic lymph nodes results in a less than 60% survival rate.[2] Hence, surgical management of early-stage endometrial cancer includes pelvic lymph node dissection, with or without para-aortic lymph node evaluation.[3 4] Sentinel lymph node (SLN) biopsy is an accepted alternative to systematic lymphadenectomy, as several studies have demonstrated the accuracy and safety of this technique.[5–8]

The introduction of SLN biopsy and ultrastaging (deeper serial sections and immunohistochemical staining of SLN) has increased the detection of isolated tumor cells (ITC) and micrometastases, often

referred to as low-volume metastases. It is controversial whether all patients benefit from SLN biopsy and ultrastaging, as the risk of nodal involvement may be low in certain subgroups. Following previous studies that did not include SLN staging, Mueller et al investigated the frequency of nodal metastases after stratifying patients by histotype, myometrial invasion, and tumor grade.[9 10] Their large retrospective study showed no micro- or macrometastases and <1% ITC in 510 patients with non-invasive, low-grade (grades 1 and 2) endometrioid endometrial cancer. Therefore, they suggest omitting ultrastaging in this subset of patients.

Based on previous studies, we hypothesized that the risk of any type of nodal metastasis in certain subgroups of endometrial cancer may be low enough to omit ultrastaging. In an attempt to confirm the findings of Mueller et al,[9] our primary objective was to report the incidence of SLN metastases in apparent early-stage endometrial cancer after stratification by histologic subtype, myometrial invasion, and grade. In addition, we aimed to identify a subgroup in whom ultrastaging may be omitted.

METHODS

This was a multicenter, retrospective, observational study conducted at two referral cancer centers: the Mayo Clinic, Rochester, USA and the European Institute of Oncology, Milan, Italy. Patients were screened for the following eligibility criteria using existing databases: (1) surgical staging including lymph node evaluation; (2) age greater ≥18 years; (3) apparent early stage, defined as endometrial cancer considered to be International Federation of Gynecology and Obstetrics (FIGO) 2009 stage I-II prior to surgical staging; (4) any histotype or grade on the final pathology report; and (5) surgical treatment performed at Mayo Clinic from October 2013 to December 2020 or at the European Institute of Oncology from January 2010 to December 2022. We excluded patients who declined consent to research or who had invasive synchronous cancers.

The existing retrospective databases are intended for research purposes and contain de-identified data on endometrial cancer patients undergoing surgical staging at both centers. Surgical staging was performed according to existing guidelines at the time of surgery. In general, a minimally invasive approach was preferred, and the procedure included hysterectomy with bilateral salpingoophorectomy and SLN biopsy (in cases of failed SLN mapping, re-injection of the cervix was considered, but reflex side-specific nodal dissection was performed if multiple mapping failures occurred). Omental biopsy was performed in the case of serous histology.

For the purposes of this study, lymph node status was determined by SLN biopsy only, regardless of non-SLN findings when systematic lymph node dissection was performed. In addition, we only selected patients who underwent successful staging with bilateral SLN mapping, and no empty nodal packets on final pathology. At both centers, ultrastaging of SLN was performed according to standard clinical protocol after confirmation of negative hematoxylin and eosin (H&E) staining. Four 5 µm sections were cut from paraffin-embedded blocks at approximately 50 µm intervals. For each pelvic lymph node, three sections were stained with H&E and one with anti-cytokeratin AE1/AE3 antibodies for immunohistochemistry. Nodal metastases were classified based on their size[11 12]: macrometastasis if >2.0 mm, micrometastasis >0.2 to ≤2.0 mm, and ITC ≤0.2 mm or <200 cells. Cytokeratin-positive staining without positive H&E was not considered as ITC.

Since the presence of either micrometastases or macrometastases upstages the disease and influences the choice of adjuvant treatment, we reported these as "positive nodes". The risk of these metastases is reported as both separate and aggregate values.[13] The incidence of ITC was reported separately. Histologic subtypes and grading were defined according to the fifth edition of the WHO Classification of Female Genital Tumors.[14] According to the binary approach proposed by several international organizations, grade 1 and 2 tumors were considered as low-grade and grade 3 as high-grade.[13–15] Myometrial invasion was categorized as absent, less than half of the myometrium, or equal to or more than half of the myometrium.

The study was approved by the Mayo Clinic Institutional Review Board (ID#19–0 04 650) and European Institute of Oncology Ethics Committee (UID2418). In accordance with the Journal's guidelines, we will make our data available for independent analysis by a team selected by the editorial team for the purpose of additional data analysis or reproducibility of this study in other centers, if requested. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[16]

Statistical Analyses

Descriptive statistics were calculated and reported as mean (SD) for continuous variables and frequency (percentage) for categorical variables. They were used to compare patient characteristics by SLN mapping with or without lymphadenectomy and then by site. Descriptive statistics were also used to evaluate lymph node involvement stratified by myometrial invasion and grade in endometrioid endometrial cancer and then lymph node involvement stratified by myometrial invasion in serous endometrial cancer. The same statistics were used to evaluate lymph node involvement, stratified according to myometrial invasion and grade, after the data from a previous study by Mueller et al[9] were combined to our cohort. A threshold of 1% nodal involvement was used to determine whether ultrastaging could be omitted, based on the findings of Mueller et al.[9] Forest plots with effect-size estimate and 95% CI were used to summarize previous studies. All statistical analyses were performed using the SAS version 9.4 software package (SAS Institute, Cary, North Carolina, USA).

RESULTS

During the study period, 2442 patients underwent pelvic nodal assessment: 633 with systematic lymphadenectomy only and 1809 through SLN biopsy with (n=292) or without (n=1517) systematic lymphadenectomy (the patient flow diagram is provided in Online supplemental figure 1). Bilateral SLN mapping was successful in 1574 patients, while unilateral mapping failed in 235 patients. Four additional patients with bilateral SLN mapping were excluded because the grade or the nodal metastases size were unknown. In total, 1570 patients (1359 endometrioid and 211 non-endometrioid, of which 117 were serous) were included in the final analysis. A description of the clinicopathologic characteristics of the included patients is provided in Table 1 for the entire cohort and Online supplemental table 1 after stratification by center. Online

Table 1 Clinical, surgical, and pathological characteristics of endometrial cancer patients who underwent bilateral sentinel lymph node mapping with or without lymphadenectomy at the participating centers during the study period

Characteristic	Total (n=1570)	SLN removal only (n=1416)	SLN removal and LND (n=154)
Age at surgery (years), mean (SD)	63.3 (10.4)	63.5 (10.6)	62.2 (8.9)
BMI (kg/m^2)			
N	1524	1372	152
Mean (SD)	32.4 (8.6)	32.4 (8.5)	32.8 (9.0)
Surgical approach			
Laparotomy	45 (2.9)	31 (2.2)	14 (9.1)
Vaginal	50 (3.2)	44 (3.1)	6 (3.9)
Robotic	1411 (89.9)	1280 (90.4)	131 (85.1)
Laparoscopy	64 (4.1)	61 (4.3)	3 (1.9)
Histology			
Endometrioid	1335 (85.0)	1214 (85.7)	121 (78.6)
Serous	117 (7.5)	98 (6.9)	19 (12.3)
Clear cell	32 (2.0)	26 (1.8)	6 (3.9)
Undifferentiated	6 (0.4)	6 (0.4)	0
Carcinosarcoma	24 (1.5)	22 (1.6)	2 (1.3)
Mixed	45 (2.9)	39 (2.8)	6 (3.9)
Other	11 (0.7)	11 (0.8)	0
Histology			
Non-endometrioid	211 (13.4)	180 (12.7)	31 (20.1)
Endometrioid*	1359 (86.6)	1236 (87.3)	123 (79.9)
FIGO 2009 stage			
IA	1143 (72.8)	1066 (75.3)	77 (50.0)
IB	200 (12.7)	174 (12.3)	26 (16.9)
II	49 (3.1)	41 (2.9)	8 (5.2)
IIIA/B	54 (3.4)	47 (3.3)	7 (4.5)
IIIC1	100 (6.4)	76 (5.4)	24 (15.6)
IIIC2	12 (0.8)	4 (0.3)	8 (5.2)
IV	12 (0.8)	8 (0.6)	4 (2.6)
FIGO grade			
1	776 (49.4)	737 (52.0)	39 (25.3)
2	430 (27.4)	378 (26.7)	52 (33.8)
3	364 (23.2)	301 (21.3)	63 (40.9)
Myometrial invasion			
None	366 (23.3)	348 (24.6)	18 (11.7)
<50%	877 (55.9)	799 (56.4)	78 (50.6)
≥50%	327 (20.8)	269 (19.0)	58 (37.7)
LVSI			
Absent	1308 (83.3)	1203 (85.0)	105 (68.2)
Present	256 (16.3)	209 (14.8)	47 (30.5)
Unknown	6 (0.4)	4 (0.3)	2 (1.3)
Pelvic lymph nodes			
Negative	1383 (88.1)	1268 (89.5)	115 (74.7)
ITC	75 (4.8)	66 (4.7)	9 (5.8)

Continued

Table 1 Continued

Characteristic	Total (n=1570)	SLN removal only (n=1416)	SLN removal and LND (n=154)
Micrometastases	53 (3.4)	42 (3.0)	11 (7.1)
Macrometastases	59 (3.8)	40 (2.8)	19 (12.3)
Tumor size (mm)			
N	1406	1260	146
Mean (SD)	37.1 (21.5)	36.1 (20.9)	46.0 (24.4)
Tumor diameter			
≤2 cm	284 (18.1)	269 (19.0)	15 (9.7)
>2 cm	1122 (71.5)	991 (70.0)	131 (85.1)
Unknown	164 (10.4)	156 (11.0)	8 (5.2)
Number of lymph nodes removed†, median (IQR)			
SLN	3 (2, 4)	3 (2, 4)	3 (2, 4)
Pelvic LND	12 (4, 21)	–	12 (4, 21)
Para-aortic LND	7 (3, 15)	4 (2, 7)	10 (5, 16)
Total (SLN and pelvic LND)	3 (2, 5)	3 (2, 4)	15 (9, 24)
Total (SLN, pelvic LND, and para-aortic LND)	3 (2, 5)	3 (2, 4)	17 (9, 28)

Variables are reported for the entire population and stratified by type of lymph node evaluation.
Results presented are number (N) and percentage (%) unless otherwise specified.
*Includes 24 mixed or other histotypes that were reclassified as endometrioid after review of the electronic medical record (22 sentinel lymph node (SLN) removal only, 2 SLN removal and lymphadenectomy).
†Among those with listed lymph node assessment.
BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; ITC, isolated tumor cells; LAVH, laparoscopic assisted-vaginal hysterectomy; LND, lymphadenectomy; LVSI, lymphovascular space invasion; SD, standard deviation; SLN, sentinel lymph node.

supplemental table 2 describes patients who underwent unilateral SLN mapping and were excluded from the main analysis.

First, we evaluated the risk of nodal involvement in the entire study population of 1570 patients. A total of 59 (3.8%) macrometastases, 53 (3.4%) micrometastases, and 75 (4.8%) ITC were detected. As a result, SLN plus ultrastaging identified 112 patients with positive nodes (micro/macrometastases), leading to upstaging in 7.1% of endometrial cancers.

Endometrioid Histology

We then focused our attention on endometrioid histotypes. In 1359 patients, SLN biopsy and ultrastaging identified 39 (2.9%) macrometastases, 43 (3.2%) micrometastases, and 72 (5.3%) ITC. The resulting risk of positive nodal involvement (micro/macrometastasis) was 6.0%. The population was stratified by grade and myometrial invasion to identify groups at low risk of lymph node involvement (Table 2). Among 274 low-grade

Table 2 Lymph node involvement stratified by myometrial invasion and grade in endometrioid endometrial cancer

	Grade 1 (n=775)			Grade 2 (n=428)			Grade 3 (n=156)			Total (n=1359)		
Parameter	ITC	Micro	Macro	ITC	Micro	Macro	ITC	Micro	Macro	ITC	Micro	Macro
No MI invasion	0/227 (0.0)	0/227 (0.0)	0/227 (0.0)	1/47 (2.1)	0/47 (0.0)	0/47 (0.0)	0/22 (0.0)	0/22 (0.0)	1/22 (4.5)	1/296 (0.3)	0/296 (0.0)	1/296 (0.3)
<50% MI	18/453 (4.0)	5/453 (1.1)	2/453 (0.4)	13/255 (5.1)	9/255 (3.5)	4/255 (1.6)	3/65 (4.6)	3/65 (4.6)	1/65 (1.5)	34/773 (4.4)	17/773 (2.2)	7/773 (0.9)
≥50% MI	14/95 (14.7)	8/95 (8.4)	7/95 (7.4)	14/126 (11.1)	16/126 (12.7)	14/126 (11.1)	9/69 (13.0)	2/69 (2.9)	10/69 (14.5)	37/290 (12.8)	26/290 (9.0)	31/290 (10.7)
Column total	32/775 (4.1)	13/775 (1.7)	9/775 (1.2)	28/428 (6.5)	25/428 (5.8)	18/428 (4.2)	12/156 (7.7)	5/156 (3.2)	12/156 (7.7)	72/1359 (5.3)	43/1359 (3.2)	39/1359 (2.9)

Notes: Each cell reports the number of patients with nodal involvement/total number of patients in the cell (cell percentage). For patients who underwent both sentinel lymph node (SLN) biopsy and systematic lymphadenectomy (LND), only data regarding sentinel nodes are reported. It should be noted that 2/1359 (0.1%) with negative SLN had a positive lymph node at systematic LND (both "positive unknown type" at pelvic and/or para-aortic LND, grade 2 with <50% myometrial invasion).
ITC, isolated tumor cells; Macro, macrometastases; MI, myometrial invasion; Micro, micrometastases.

Table 3 Lymph node involvement stratified by myometrial invasion in serous endometrial cancer (n=117)

Parameter	SLN metastases		
	ITC	Micro	Macro
No MI invasion	0/36 (0.0)	2/36 (5.6)	0/36 (0.0)
<50% MI	2/58 (3.4)	4/58 (6.9)	4/58 (6.9)
≥50% MI	0/23 (0.0)	1/23 (4.3)	9/23 (39.1)
Column total	2/117 (1.7)	7/117 (6.0)	13/117 (11.1)

Notes: Each cell reports the number of patients with nodal involvement/total number of patients in the cell (cell percentage). For patients who underwent both sentinel lymph node (SLN) biopsy and systematic lymphadenectomy (LND), only data regarding SLN are reported. It should be noted that 1/117 (0.9%) with negative SLN had a positive lymph node at systematic LND (macrometastases at pelvic LND, grade 3 with ≥50% myometrial invasion)
ITC, isolated tumor cells; Macro, macrometastases; MI, myometrial invasion; Micro, micrometastases; SLN, sentinel lymph node.

(G1-G2) endometrioid endometrial cancers without myometrial invasion, SLN biopsy and ultrastaging identified one ITC (0.4%) and no micro/macrometastases. In contrast, 20 patients with positive nodes (14 micrometastases and 6 macrometastases) were found in 708 low-grade endometrioid endometrial cancers invading the inner half of the myometrium, accounting for a risk of 2.8%. Additionally, 31 (4.4%) ITC were detected in the last group. In all the other subgroups involving either high-grade or ≥50% myometrial invasion, the risk of positive nodes (micro/macrometastases) was always higher, ranging from 4.5% (endometrioid G3 without myometrial invasion) to 23.8% (endometrioid G2 with ≥50% myometrial invasion). The risk of ITC ranged from 4.6% to 14.7%, except for 22 patients with high-grade endometrioid endometrial cancers without myometrial invasion, in which no ITC were found.

Serous Histology

We then focused on the 211 patients with non-endometrioid histologic subtypes. Clear cell, undifferentiated, carcinosarcoma, mixed, and rare histologic subtypes accounted for 94 cases (Online supplemental table 3). Due to the high heterogeneity of this group, further analysis was not carried out. Serous histology was present in 117 cases (Table 3), including 13 (11.1%) with macrometastases, 7 (6.0%) with micrometastases, and 2 (1.7%) with ITC. In total, the risk of positive nodes was 17.1%.

We identified 36 patients with serous endometrial cancer and no myometrial invasion. In this group, we identified two micrometastases and no macrometastases leading to a risk of positive nodes of 5.6%. No ITC were found in this subgroup. In the 58 patients with serous carcinoma and ≤50% myometrial invasion, 13.8% had positive nodes (4 micrometastases, 4 macrometastases). In 23 patients with ≥50% myometrial invasion, risk of nodal metastasis exceeded 40%. Only two ITC were found which were in tumors that invaded the inner half of the myometrium.

Additional Analyses

Although excluded from the primary analyses, we also examined the risk of nodal involvement in patients undergoing unilateral SLN mapping. In this population there were also no nodal metastases in endometrioid tumors without myometrial invasion (n=36) (Online supplemental table 4).

We also combined our cohort with the cohort from Memorial Sloan Kettering Cancer Center described by Mueller et al.[9] After pooling the results of both studies, in low-grade endometrioid endometrial cancer without myometrial invasion (n=784) there were no micro/macrometastases and only 3 (0.4%) ITC, whereas high-grade endometrioid endometrial cancer (n=42) had 2 (4.8%) micro/macrometastases and no ITC (Table 4).

Table 4 Lymph node involvement in endometrioid (A) and serous (B) endometrial cancer, after combining Mayo Clinic, European Institute of Oncology, and Memorial Sloan Kettering Cancer Center (Mueller et al.[9] 2020) cohorts

(A)

Parameter	Grade 1 (n=1488)		Grade 2 (n=606)		Grade 3 (n=224)		Total (n=2318)	
	ITC	Micro/Macro	ITC	Micro/Macro	ITC	Micro/Macro	ITC	Micro/Macro
No MI invasion	2/676 (0.3)	0/676 (0.0)	1/108 (0.9)	0/108 (0.0)	0/42 (0.0)	2/42 (4.8)	3/826 (0.4)	2/826 (0.2)
<50% MI	38/655 (5.8)	16/655 (2.4)	17/331 (5.1)	16/331 (4.8)	5/96 (5.2)	5/96 (5.2)	60/1082 (5.5)	37/1082 (3.4)
≥50% MI	33/157 (21.0)	21/157 (13.4)	21/167 (12.6)	38/167 (22.8)	12/86 (14.0)	16/86 (18.6)	66/410 (16.1)	75/410 (18.3)
Column total	73/1488 (4.9)	37/1488 (2.5)	39/606 (6.4)	54/606 (8.9)	17/224 (7.6)	23/224 (10.3)	129/2318 (5.6)	114/2318 (4.9)

(B)

	ITC	Micro/Macro
No MI invasion	2/77 (2.6)	4/77 (5.2)
<50% MI	2/81 (2.5)	12/81 (14.8)
≥50% MI	2/44 (4.5)	17/44 (38.6)
Column total	6/202 (3.0)	33/202 (16.3)

Notes: Each cell reports the number of patients with nodal involvement/total number of patients in the cell (cell percentage). For patients who underwent both sentinel lymph node (SLN) biopsy and systematic lymphadenectomy, only data regarding SLN are reported.
ITC, isolated tumor cells; Macro, macrometastases; MI, myometrial invasion; Micro, micrometastases.

DISCUSSION

Summary of Main Results

In our cohort, patients with apparent early-stage endometrial cancers had a 7% combined risk of micro/macrometastasis, regardless of histotype, myometrial invasion, and grade. In a subgroup of patients with endometrioid histotype, the risk of positive nodes was 6%. However, in 274 low-grade endometrioid endometrial cancer without myometrial invasion, no nodal metastases and only one ITC were found. The presence of either myometrial invasion or a higher grade increased the risk of micro/macrometastasis or ITC to above 1%.

Serous endometrial cancers were approximately three times more likely to have micro/macrometastases compared with endometrioid histologic subtypes. The absence of myometrial invasion decreased the incidence of nodal involvement, but the risk was still almost 6%.

Results in the Context of Published Literature

FIGO has recently published a new staging system for endometrial cancer.[13] Among the innovations introduced, non-aggressive histotypes (ie, low-grade endometrioid) confined to a polyp or the endometrium are now assigned to stage IA1, a category which is expected to have the best prognosis. Our findings of no positive lymph nodes in this subgroup suggest a very low risk of recurrence and therefore support this classification in a separate category.

We conducted a literature review on the incidence of nodal metastases in apparent early-stage endometrial cancer. Online supplemental table 5 and Online supplemental figure 2 summarize studies with more than 100 patients.[5 7–9 17–25] The risk of macrometastasis exhibited substantial variability, with 6 of 13 studies reporting an incidence higher than ours,[7 19–23] as shown in Online supplemental figure 2. We hypothesize that the higher intrinsic risk of their study populations and the inclusion of fewer patients may have caused this discrepancy. It should be noted that Holloway et al[19] and Kennard et al[22] had a common subset of patients, Persson et al[7] considered macro- and micrometastases as the same entity, and most of these studies included fewer than 500 patients.[7 19 21–23] Conversely, the incidence of micrometastasis and ITC was more homogeneous, since only three studies[17 19 22] reported a higher frequency of low-volume metastases. Overall, we can conclude that the estimates provided by our study are likely to be representative of the apparent early-stage endometrial cancer population.

We compared our results with those reported by Mueller et al[9] whose patient stratification was similar to ours. First, the risk of any lymph node involvement in low-grade tumors without myometrial invasion was comparable, as they found no micro/macrometastases and only 2 (0.4%) ITC in 510 cases. Although the risk of micro/macrometastasis in low-grade endometrioid cancer with <50% myometrial invasion is lower in our study (2.8% vs 4.3%), it is estimated to be greater than 1% in both reports, favoring the use of ultrastaging. In addition, both studies agree on the high risk of nodal involvement, either macrometastases or low-volume metastases, in serous endometrial cancer, even after stratification by myometrial invasion.

High-grade endometrioid endometrial cancer is a heterogeneous group of tumors that warrants separate discussion. In our cohort of endometrioid endometrial cancer, high-grade tumors showed the highest incidence of any size of nodal metastases in the entire population and after stratification by myometrial invasion. In fact, the only macrometastasis found in tumors without myometrial invasion was in a high-grade endometrial cancer. The new FIGO staging system classified them as "aggressive", similar to the non-endometrioid histotype, to emphasize the need for more intensive treatment.[13] Although molecular classification seems to recognize groups of high-grade endometrioid endometrial cancer with different clinical behaviors and may guide adjuvant treatment in the future, the role of surgical nodal assessment is still essential, at least for *POLE*-mutated, mismatch repair deficient (MMRd), and no specific molecular profile (NSMP) tumors.[26 27] In the future, surgical nodal staging may be omitted in p53 abnormal endometrial cancer, but supporting evidence is needed.

There is still debate regarding the best technique for nodal assessment in high-risk endometrial cancer - lymphadenectomy versus SLN with ultrastaging.[28] This issue was beyond the scope of our study, but it should be noted that 3% of high-grade endometrioid and 6% of serous endometrial cancers harbored micrometastases, which are likely to be missed if ultrastaging is not performed. We also found that grade 2 tumors had an apparently higher risk of nodal involvement compared with grade 1 tumors (Table 2). Although a binary approach to grading has been adopted by many organizations, including WHO and FIGO,[13 14] it should at least be recognized that grade 2 may be associated with more aggressive histologic features and further studies should clarify its prognostic role.

Strengths and Weaknesses

To our knowledge, the current study is the largest to estimate the risk of nodal metastases in apparent early-stage endometrial cancer, since we included more than 1500 endometrial cancers staged at referral institutions, using a standardized surgical and pathological approach.

We also recognize several limitations. We did not provide a comprehensive evaluation of oncologic outcomes in patients with low-volume metastases, which was beyond the scope of this study. A significant confounder that we did not control for was lymphovascular space invasion, which should be considered when interpreting these results. Furthermore, molecular subtypes may be an unmeasured and critical confounder. Indeed, p53 abnormal endometrial cancer has been reported to have a higher risk of nodal metastasis, even after adjustment for pre-operative grade, histotype, and CA125.[29] Although the role of molecular classification in surgical planning is promising and intriguing, its widespread use is hampered by its high cost. Therefore, our results are still valid until a definitive paradigm shift in this direction occurs, especially in resource-limited settings.

Implications for Practice and Future Research

As the risk of nodal metastases is low or absent in patients with non-invasive endometrioid endometrial cancer, ultrastaging could be omitted in this subpopulation. This strategy could benefit the healthcare system by reducing costs, estimated at about US$500 per patient, with no effect on oncologic outcomes.[30] Notably, the European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology (ESGO/ESTRO/ESP) 2020[4] guidelines suggest that even lymph node evaluation, not only SLN, could be omitted in low-grade, non-invasive

endometrioid endometrial cancers. Conversely, in the case of serous histology and no myometrial invasion, ultrastaging is critical as the risk of nodal metastases is high. Although ultrastaging in low-grade endometrioid cancer with <50% myometrial invasion is controversial, we believe it is reasonable to use this technique because the incidence of micro- and macrometastasis is approximately 3%. The use of ultrastaging in G1 endometrioid cancer with <50% myometrial invasion is even more debatable, as the risk of positive nodes is only 1.5%, yet the incidence of ITC in this subgroup is 4%. Therefore, ultrastaging should be performed unless the impact of ITC is clearly considered to be irrelevant.

The threshold for omitting ultrastaging (1%) is based on the findings of Mueller et al and is further supported by the ESGO/ESTRO/ESP 2020 guidelines.[4 9] Although we recognize that each center may use a different benchmark, we do not feel that a higher risk is negligible. In addition, some endometrial cancers are not always fully staged with SLN since they are treated in low-resource settings or are diagnosed after surgery. In these cases, our study, along with the results of Mueller et al,[9] could improve patient counseling and help to decide whether a second-look lymph node evaluation is warranted.

No definite protocol for ultrastaging has been universally accepted. Hence, the risk of nodal metastases may vary between institutions. A consensus on the definition of nodal metastases, particularly for low-volume disease, and a standard protocol for ultrastaging are warranted to increase the generalizability and reproducibility of the studies on this topic.

CONCLUSIONS

Ultrastaging may be safely omitted in patients with low-grade endometrioid endometrial cancer without myometrial invasion. No other subgroups with a risk of nodal metastasis of less than 1% have been identified.

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