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Comparing risk stratification criteria for predicting lymphatic dissemination in endometrial cancer☆,☆☆

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HIGHLIGHTS

- Mayo Criteria is more accurate for identifying patients who may safely omit lymph node dissection in endometrial cancer.
- Tumor diameter >2 cm has an unacceptable false negative rate of predicting lymphatic dissemination.
- Preoperative endometrial sampling can be used to assist with risk stratification in endometrioid endometrial cancer.

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ABSTRACT

Objective. To compare two published risk stratification models (Milwaukee Model vs. Mayo Criteria) to predict lymphatic dissemination (LD) in endometrioid endometrial cancer (EC).

Methods. Patients with stage I-III EC undergoing surgery from 1/1/2004–9/30/2013 were retrospectively reviewed and classified as low-risk vs at-risk for LD using two independent risk models. LD was defined as positive nodes at surgery or lymph node recurrence within 2 years of surgery after negative lymph node dissection (LND) or when LND was not performed. False positive (FP) and false negative (FN) rates for each risk model were calculated.

Results. Among 1103 patients, 81 (7.3%) had LD (72 positive LN and 9 LN recurrences), and most (90.2%) had stage I EC. The Milwaukee Model yielded a low at-risk rate for LD (38.1%) but a high FN rate (13.6%, 95% CI 7.0–23.0). The traditional Mayo Criteria using a cut-off of 2 cm for tumor diameter (TD) had a higher at-risk rate for LD (69.5%) but a FN rate of 0% (95% CI, 0–4.5). Modifying the Mayo Criteria using a TD cutoff of ≤3 cm identified fewer women at-risk (56.8% vs. 69.5%) and had a lower FP rate (53.6% vs. 67.1%), but had a higher FN rate (3.7%, 95% CI, 0.8–10.4).

Conclusions. The Milwaukee Model had the lowest at-risk rate of LD but an unacceptable FN rate. Modifying the Mayo Criteria by increasing the TD cutoff from the traditional ≤2 cm to ≤3 cm would spare an estimated 13.5% of patients LND, but the accompanying FN rate is unacceptably high. The traditional Mayo Criteria for low-risk EC remains the most sensitive in determining which patients LND can be omitted.

1. Introduction

Endometrial cancer (EC) is a heterogeneous disease and management should be tailored based on each individual woman's risk-assessment. Those at highest risk of death from disease will present with extrauterine spread of disease at time of diagnosis, but a subset of women, approximately 27% [1], will be low-risk for lymphatic dissemination (LD), and nearly all will be cured with simple hysterectomy and bilateral salpingo-oophorectomy alone [1]. Those meeting low-risk criteria may not benefit from additional surgical interventions given

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that the incidence of lymphatic dissemination in low-risk EC is 0.0 to 1.3% [1,2]. The implementation of sentinel lymph node (SLN) assessment has changed practice patterns, but it has not eliminated the need for pre-operative and intra-operative risk assessment given the 10–20% rate of SLN mapping failure [3], institutional variability in frozen section pathology and availability of SLN detection technology, and in situations of occult malignancy when pre-incision cervical dye injection for SLN mapping may not have been done.

Several preoperative and intraoperative tumor characteristics (tumor grade, depth of invasion, and tumor diameter) [2,4] have been identified to aid in stratification of patients deemed to be low-risk or at-risk of lymphatic dissemination. The Mayo Criteria, which defines low-risk as having either a) tumor diameter ≤2 cm with International Federation of Gynecology and Obstetrics (FIGO) grade 1 or 2 disease, and < 50% myometrial invasion or b) any tumor diameter with any grade and 0% myometrial invasion [2], has been assessed prospectively and can be used to guide the omission of lymph node assessment in low-risk patients without compromising cause-specific survival (99% at 5 years) among low-risk patients [1]. Other risk stratification criteria have been developed with the goals of better refining the definition of low-risk EC and further decreasing the proportion of women requiring lymphadenectomy but without sacrificing diagnostic accuracy with an acceptable low false negative rate.

One risk stratification criteria published by Cox Bauer and colleagues [5] was developed using combinations of continuous and categorical predictors that were evaluated in a series of logistic regression models for predictive power and best fit [5]. The best fit model determined by the lowest false negative rate, defined low-risk as having a maximum tumor diameter ≤ 5 cm and myometrial invasion ≤33% (regardless of grade). Based on these criteria, they identified nearly 43% of women with endometrioid EC to be at low-risk for LD compared to the historical 24% that meet low-risk criteria using Mayo Criteria [2,6] and approximately 19% more women in their cohort would be spared from undergoing lymphadenectomy.

The primary objective of this study was to compare the false negative rates between two published risk stratification criteria (Milwaukee Model vs. Mayo Criteria) to predict LD in endometrioid EC. A secondary goal was to test the impact of modifications to the current Mayo Criteria on the false negative rates.

Box 1
Description of risk stratification criteria.

Mayo Criteria [2]
Low-risk

- TD ≤2 cm, grade 1 or 2, MI <50%
- MI 0%, any TD or grade

Low-intermediate risk

- TD >2 cm or unknown, grade 1 or 2, MI <50%

High-intermediate risk

- Grade 1 or 2, 50% ≤ MI < 66%
- Grade 3, MI <50%

High risk

- Grade 1 or 2, MI ≥66%
- Grade 3, MI ≥50%
- Adnexal metastasis

Milwaukee Model [4]
Low-risk

- TD ≤5 cm, any grade, MI ≤33%

Low-intermediate risk

- TD >5 cm, any grade, MI ≤33%
- TD ≤5 cm, any grade 33% < MI ≤66%
- TD ≤5 cm, grade 1, MI >66%

High-intermediate risk

- TD >5 cm, grade 1, 33% < MI ≤66%
- TD ≤5 cm, grade 2 or 3, MI >66%

High risk

- TD >5 cm, any grade, MI>66%
- TD >5 cm, grade 2 or 3, 33% < MI ≤66%

Abbreviations: TD, Tumor diameter; MI, myometrial invasion.

2. Materials and methods

Patients with newly diagnosed endometrioid EC who underwent surgery from 1/1/2004–09/30/2013, prior to introduction of sentinel lymph node biopsy, at Mayo Clinic, Rochester, Minnesota, were included in this study. Patients were subsequently excluded if any of the following were present: stage IV disease, non-endometrioid histology, receipt of neoadjuvant therapy, and/or synchronous invasive cancers. Patients were also excluded if they had incomplete tumor data required for the risk stratification criteria (i.e. preoperative sampling grade, tumor diameter, and percent of myometrial invasion) or insufficient follow-up (i.e. <2 years) among those without positive nodes at the time of surgery or without a lymph node recurrence within two years of surgery. During the study time period, lymphadenectomy was omitted in patients at low-risk for LD based on the previously published Mayo Criteria [2]. All lymph node assessments in the study period were performed using lymphadenectomy (pelvic ± paraaortic lymphadenectomy); none of the patients had a sentinel lymph node biopsy. Prior to study initiation Mayo Clinic Institutional Review Board approval was obtained and patients were screened for research authorization.

Data were obtained from a comprehensive EC surgical database which has been previously described [7,8]. Collected variables included those utilized in the two preexisting risk stratification schemes for predicting LD, denoted as Mayo Criteria [2,9] and Milwaukee Model [5] (Box 1). LD was defined as either 1) positive lymph nodes at the time of surgical staging or 2) lymph node recurrence within 2 years of surgery after negative lymph node dissection (LND) or in the setting of no LND.

Statistical analyses were performed using the SAS version 9.4 software package. To evaluate the comparability of the Milwaukee Model patient cohort [5] used to develop the Milwaukee Model with the current Mayo Clinic study cohort, we used the two-sample *t*-test to compare continuously-scaled characteristics and the chi-square test to compare categorical characteristics between the Milwaukee Model cohort from the Cox Bauer publication [5] and the Mayo Clinic cohort. Using the Mayo Clinic cohort only, we evaluated the following risk stratification schemes: the Milwaukee Model, the original Mayo Criteria, and modifications of the Mayo Criteria using different cutoffs for tumor diameter. For each risk stratification scheme, patients in the Mayo Clinic cohort were classified as "at-risk" if they met any criteria greater than low-risk (i.e. either low-intermediate, high-intermediate or high risk). Among the patients with LD, the false negative rate is the proportion of patients who met criteria for low-risk. Among the patients without LD, the false positive rate is the proportion of patients who did *not* met criteria for low-risk. Ninety-five percent confidence intervals (95% CI) for these rates were constructed using the Clopper-Pearson method based on the exact binomial distribution. The false negative rates were compared between risk stratification schemes using a two-sided exact McNemar's test for comparing correlated proportions. In the primary analyses, the risk stratification schemes were applied using the grade from the preoperative sampling and tumor diameter and myometrial invasion from the final pathology report. A secondary analysis was

performed using the grade from the final pathology report or the centralized final pathology grade by a single gynecologic pathologist.

3. Results

3.1. Patient demographics

We identified 1817 women who had surgery for EC from 1/1/2004–09/30/2013. A total of 1103 patients met inclusion criteria, had complete data for defining the risk stratification criteria and were included in the Mayo Clinic cohort (Fig. 1). Among the 1103 patients, 749 (67.9%) patients underwent pelvic and/or paraaortic lymphadenectomy and 354 patients had nodal dissection omitted per institution protocol (Mayo Criteria). Lymphatic dissemination was identified in 81 (7.3%) patients, 72 patients had positive lymph nodes at time of surgery and 9 patients had a lymph node recurrence within 2 years from surgery after negative LND or when LND was not performed in the Mayo Clinic cohort. The median time to recurrence for these 9 patients was 1 year (interquartile range (IQR), 0.8, 1.1 years) and 6 of the 9 died due to disease.

Comparability of Milwaukee Model Development Cohort with Mayo Clinic Validation Cohort.

The Milwaukee Model development cohort in the publication by Cox Bauer [5] included 737 patients all of whom underwent pelvic and/or paraaortic lymphadenectomy (institutional standard of care) at time of surgery [5] and LD was present in 68 (9.2%) patients. There was no difference in the proportion of patients with LD between the two cohorts (7.3% vs. 9.2%, $p = 0.15$). The two cohorts were similar with respect to age at surgery, and race/ethnicity with the exception that Milwaukee cohort excluded racial ethnic groups other than white non-Hispanic and African American non-Hispanic due to low numbers. The percentage of patients with FIGO stage I disease (90.2% vs. 80.1%, $p < 0.001$) or FIGO grade 1 (57.9% vs. 49.0%, $p < 0.001$) was significantly higher in the Mayo Clinic cohort compared to the Milwaukee cohort and the average tumor diameter (35.5 vs. 45.5 mm, $p < 0.001$) and average percent of myometrial invasion (25.1 vs 38.3%, $p < 0.001$) were significantly lower in the Mayo Clinic cohort compared to the Milwaukee cohort. Furthermore the percentage of patients with cervical stromal invasion (3.4% vs. 5.6%, $p = 0.027$) and lymphovascular space invasion (6.3% vs. 16.8%, $p < 0.001$) were significantly lower in the Mayo Clinic cohort (Table 1).

3.2. Performance of Milwaukee Model and Mayo Criteria to correctly identify low-risk EC in the Mayo Clinic cohort

Utilizing FIGO grade from the preoperative sampling and TD and myometrial invasion from the final pathology report, we applied the

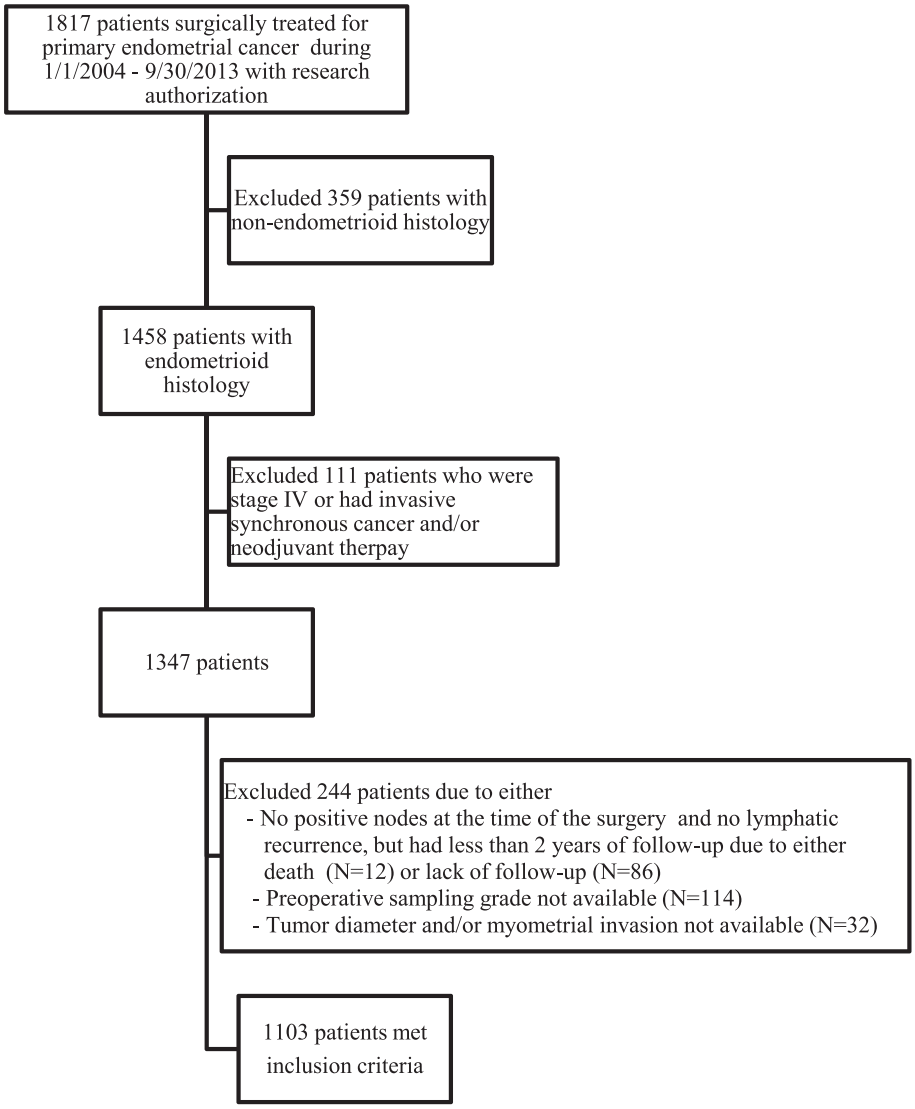

Fig. 1. Flow diagram of included patients in the Mayo Clinic Cohort.

Table 1
Summary of patient characteristics in the two cohorts.

Characteristic	Milwaukee Model cohort [4][a] (January 2003–December 2013), $N = 737$	Mayo Clinic cohort (January 2004–September 2013), $N = 1103$	P
Age at surgery (years), mean (SD)	63.3 (10.5)	63.5 (10.5)	0.69
Race, N (%)			<0.001
White	707 (95.9)	1031 (93.5)	
Black	30 (4.1)	2 (0.2)	
All others	–	20 (1.8)	
Unknown/chose not to disclose	–	50 (4.5)	
BMI (kg/m^2), mean (SD)	34.4 (9.4)	35.4 (9.7)	0.03
Preoperative sampling grade, N (%)			–
1	Not reported	689 (62.5)	
2		309 (28.0)	
3		105 (9.5)	
Final Pathology			
FIGO stage, N (%)			<0.001
I	590 (80.1)	995 (90.2)	
II	34 (4.6)	21 (1.9)	
III	113 (15.3)	87 (7.9)	
FIGO grade, N (%)			<0.001
1	361 (49.0)	639 (57.9)	
2	253 (34.3)	343 (31.1)	
3	123 (16.7)	121 (11.0)	
Tumor diameter (mm), mean (SD)	45.5 (26.9)	35.5 (22.2)	<0.001
Myometrial invasion (%), mean (SD)	38.3 (30.3)	25.1 (27.2)	<0.001
Cervical stromal invasion, N (%)	41/734 (5.6)	38 (3.4)	0.03
Lymphovascular space invasion, N (%)	115/683 (16.8)	70 (6.3)	<0.001
Lymphatic dissemination, N (%)	68 (9.2)	81 (7.3)	0.15

Abbreviations: BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; LD, lymphatic dissemination; SD, standard deviation.
[a] These patient and tumor characteristics were obtained from the original publication by Cox Bauer et al. [4].

Milwaukee Model and the Mayo Criteria to the patients in the Mayo Clinic cohort. In addition to the traditional Mayo Criteria which uses a cutoff of ≤2 cm for TD, alternative criteria were explored using cutoffs of ≤3, ≤4, and ≤5 cm. Table 2 summarizes the performance of the "at-risk" categorization of each risk stratification criteria to correctly identify patients with LD (additional detail is presented in Supplemental Table 1). Upon applying the Milwaukee Model, 61.9% of patients were classified as low-risk and 38.1% were classified as "at-risk" for LD (Table 2). In contrast, 30.5% of patients were classified as low-risk and 69.5% were classified as "at-risk" using the traditional Mayo Criteria with the TD ≤2 cm cutoff. Utilizing the Milwaukee Model would result in 32.9% fewer lymphadenectomies compared to traditional Mayo Criteria, based on comparing the false positive (FP) rates of 34.2% and 67.1%, respectively. The FP rate decreased to 53.6%, 39.4%, and 30.0% as the cutoff for TD increased to 3, 4, or 5 cm, resulting in 13.5%, 27.7%, and 37.1% fewer lymphadenectomies, respectively, compared to the traditional Mayo Criteria. Although the Milwaukee Model had a low "at-risk" rate for LD of 38.1%, it had a high false negative (FN) rate of 13.6% (95% CI, 7.0–23.0). While modifying the Mayo Criteria using a TD ≤3 cm cutoff yielded a lower FN rate of 3.7% (95% CI, 0.8–10.4), the lowest FN rate (0.0%, 95% CI, 0–4.5) was observed using the traditional Mayo Criteria with the TD ≤2 cm cutoff. The FN rate was significantly lower using the traditional Mayo Criteria compared to the Milwaukee model (0% vs. 13.6%, $p < 0.001$). Characteristics of the 11 patients falsely deemed 'low-risk' by the Milwaukee Model but not by the traditional Mayo Criteria are presented in Table 3. Among these 11 patients, TD ranged from 2.2 to 5.0 cm, 8 patients had grade 2 disease on preoperative sampling, and all had myometrial invasion <50%.

Similar diagnostic indices were obtained utilizing final pathology FIGO grade from each patient's tumor to define the risk stratification criteria (Supplemental Table 2). The FN rate for the Milwaukee Model and the traditional Mayo Criteria were 12.6% (95% CI, 6.5–21.5) and 0% (95% CI, 0–4.2), respectively.

4. Discussion

In a well-annotated cohort of 1103 patients, we found that utilizing the Milwaukee Model's criteria to define low-risk for LD (maximum tumor diameter ≤ 5 cm and myometrial invasion ≤33%), would allow more women to avoid surgical LND and risks associated with the LND procedures; however, this model's criteria resulted in an unacceptable false negative rate of 13.6%, sacrificing the diagnostic and potential therapeutic implications of verifying lymph node status [10–12]. Using the Milwaukee Model in our cohort, 11 patients with LD would *not* have been identified as "at-risk" and would not have received appropriate adjuvant treatment. Additionally, patients with positive lymph nodes at surgical staging are at high risk of recurrence which is also associated with an increase in cancer-specific mortality [13]. Upon applying the

Table 2
Performance of the "at-risk"[a] categorization of each risk stratification criteria utilizing preoperative sampling grade to identify patients in the Mayo Clinic cohort with lymphatic dissemination.

Risk stratification criteria	"At-risk"[a] N (% of 1103)	Sensitivity (95% CI)	False negative rate (95% CI)	Specificity (95% CI)	False positive rate (95% CI)
Milwaukee Model	420 (38.1%)	86.4% (77.0–93.0)	13.6% (7.0–23.0)	65.8% (62.8–68.7)	34.2% (31.3–37.2)
Mayo Criteria[b]					
Utilizing TD ≤2 vs. >2 cm cutoff	767 (69.5%)	100% (95.5–100)	0% (0–4.5)	32.9% (30.0–35.9)	67.1% (64.1–70.0)
Utilizing TD ≤3 vs. >3 cm cutoff	626 (56.8%)	96.3% (89.6–99.2)	3.7% (0.8–10.4)	46.4% (43.3–49.5)	53.6% (50.5–56.7)
Utilizing TD ≤4 vs. >4 cm cutoff	479 (43.4%)	93.8% (86.2–98.0)	6.2% (2.0–13.8)	60.6% (57.5–63.6)	39.4% (36.4–42.5)
Utilizing TD ≤5 vs. >5 cm cutoff	378 (34.3%)	87.7% (78.5–93.9)	12.3% (6.1–21.5)	70.0% (67.0–72.8)	30.0% (27.2–33.0)

Abbreviations: CI, confidence interval; TD, tumor diameter.
[a] Patients classified "at-risk" are those who met criteria for greater than low-risk (i.e. either low-intermediate, high-intermediate or high risk) based on each of the different risk stratification scheme.
[b] Utilizing the Mayo Criteria with different cutoffs for TD defining those low-risk and > low-risk ("at-risk").

Table 3
Characteristics of the 11 patients with lymphatic dissemination in the Mayo Clinic cohort identified as being low-risk by the Milwaukee Model.

Patient	FIGO stage	Preoperative sampling FIGO grade	Tumor diameter (mm)	Myometrial invasion (%)	Cervical stromal invasion	Lympho-vascular space invasion	Adnexal involvement
1	III	2	22	25	No	No	No
2	III	2	30	25	No	No	No
3	III	2	30	30	No	No	No
4	III	2	31	23.5	No	No	No
5	III	2	32	21.4	Yes	No	Yes
6	III	2	41	3.7	No	No	No
7	III	1	47	11.11	No	No	No
8	III	1	47	6.45	No	No	Yes
9	III	1	47	13	No	No	No
10	III	2	50	16.67	No	No	No
11	III	2	50	10	No	No	No

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics.

Milwaukee Model, 38.1% were classified as "at-risk" for LD compared to 69.5% using the Mayo Criteria. In an attempt to decrease the number of women requiring lymph node assessment, we explored a 'modified' Mayo Criteria that increased the maximal TD cutoff to ≤3 cm but this also resulted in an unacceptable false negative rate of 3.7%, given that it could be as high as 10.4% based on the upper limit of the 95% confidence interval. A false negative rate of <5% has been well accepted for other tumor types and utilized to change clinical practice [14,15]. Therefore traditional Mayo Criteria for defining low-risk, using a ≤ 2 cm cutoff, with a 95% CI upper limit for the false negative rate that is <5%, appears to remain the optimal cutoff guiding omission of lymph node assessment in women with grade 1 and 2 endometrioid EC with <50% myometrial invasion.

Other LD risk stratification systems in EC have been proposed, such as a model developed by Tuomi and colleagues in Helsinki, Finland [16]. This model uses a combination of circulating markers (serum CA-125, leukocytosis, thrombocytosis), preoperative tumor characteristics (grade 3 endometrioid, clear cell, serous, undifferentiated, neuroendocrine histology) to predict the probability of patients having advanced disease at time of diagnosis [17]. Comparing the Helsinki Model, the, Mayo Criteria, and the Milwaukee Model in a Finnish cohort, the expected lymphadenectomy rate (at-risk rate) was 71.5% using Mayo Criteria, 62.4% using Helsinki Model and 48.8% using the Milwaukee Model. The false negative rates in their investigation were similar among the models: 2.3% using Mayo Criteria, 0% using Helsinki Model, and 2.0% using Milwaukee Model. However, generalizability may be limited as there are notable differences between cohorts such as lower mean BMI in the Finnish cohort (28.7 kg/m^2) compared to this present study's cohort (35.4 kg/m^2) and environmental exposures may be different in Finland compared to the Midwest United States. Additionally, the Helsinki Model uses serum CA-125 which is rarely elevated in low grade, early stage EC and is usually elevated in advanced stage and/or type II ECs [18]. The Helsinki Model was also developed considering all histologic types and was designed to be more inclusive of the spectrum of EC. Current practice guidelines indicate that all women with apparent early stage type II EC should undergo lymph node assessment. Therefore, incorporating type II histologies into a lymph node metastasis prediction model is not necessary for surgical planning and obscures the applicability of the resultant performance statistics [19]. For these reasons, the Helsinki Model is less clinically applicable in the setting of determining which women with EC are low-risk and can have LN assessment omitted.

LND in the setting of EC staging has evolved over the past 3 decades and continues to evolve. Recognizing that patients undergoing comprehensive lymphadenectomy are also at increased risk of postoperative complications (i.e. surgical site infections, nerve and vascular injuries, etc. [10,11,20]), the introduction of sentinel lymph node biopsy has allowed for more targeted surgical assessment of LN status. Sentinel lymph node (SLN) biopsy has been demonstrated to have positive LN detection rate comparable to comprehensive lymphadenectomy [21] with a fraction of the leg lymphedema risk. However, technology to perform SLN may not be available at some centers and as SLN safety data builds, we will undoubtedly better define the risks of pelvic sidewall structure injury and cost-effectiveness of SLN in each EC risk stratum [12]. Also, at present 10–20% of patients will not have a SLN identified at the time of surgery and Mayo Criteria can safely be used to omit full lymphadenectomy in those at low-risk who do not map [3,6].

Additionally, women determined to have low-risk EC may be candidates for curative intent simple total vaginal hysterectomy (TVH). The Society of Gynecologic Oncology (SGO) and American College of Obstetricians and Gynecologists (ACOG) jointly state that minimally-invasive surgical (MIS) staging of endometrial cancer should be standard of care and since 2015 Commission on Cancer has used MIS as a quality metric [22,23]. While SGO and ACOG have been reserved in their statements on TVH in the treatment of EC [22] and prospective studies to date have only assessed the diagnostic accuracy of SLN performed prior to hysterectomy, [24–26] based on this present study, nearly 31% of women with a new diagnosis of endometrioid EC do not benefit from LND (using Mayo Criteria) and, as TVH reduces the rates of surgical site infection, vaginal cuff dehiscence, operating time, and cost of surgical care by up to 40% over other MIS approaches [27–29] without negatively impacting oncologic outcomes [27,30], Mayo Criteria can guide appropriate selection of women that are candidates for curative intent TVH.

One argument against the use of the Mayo Criteria to identify patients who are able to forego the use of lymphadenectomy at time of surgery is the dependence on availability of intraoperative frozen section analysis. Our group [7] previously published that preoperative biopsy and intraoperative TD can effectively identify low-risk patients, with <1% having positive nodes [7]. In our study, the percent of patients at-risk for LD were not significantly different whether using preoperative endometrial tumor grade compared to final pathology tumor grade (69.5% vs.68.1%). This is an important finding as this makes our criteria applicable to all settings, including those in which intraoperative frozen section is not available. Additionally, this information, along with our previously published nomogram [31], may be most useful in counseling patients who present for recommendations on the utility for surgical LND following an incidental diagnosis of EC at the time of hysterectomy for presumed benign disease [31].

This study's main strengths are its large sample size and the standardized approach to LND utilized among the clinical practice during the study period. The limitations to this study include those inherent to its retrospective nature and that 146 patients were excluded because of incomplete variables needed to apply the risk stratification criteria.

In conclusion, the traditional Mayo Criteria for low-risk EC remains the most accurate model in predicting patients who can safely forgo LND. The combined utilization of the Mayo Criteria to identify women at an acceptably low-risk of LD and application of SLN biopsy has the potential to improve the safety and value of EC care.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.08.005.

Author contributions

Drs. Kilts, Bakkum-Gamez, Glaser, Langstraat, Kumar, Gostout, Podratz, Dowdy, Cliby, and Mariani developed the original concept and study design. Dr. Kilts performed data abstraction; Ms. Weaver and Ms. McGree performed data analyses. Drs. Kilts and Bakkum-Gamez generated the initial drafted manuscript; finally, all co-authors (Drs. Bakkum-Gamez, Glaser, Langstraat, Kumar, Gostout, Podratz, Dowdy, Cliby, and Mariani; Ms. Weaver, Ms. McGree) performed interpretation of the data, critically reviewed and edited the manuscript, and approved the final submitted version.

Declaration of competing interest

The authors have no conflicts of interest.

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