

# Challenges to Intraoperative Evaluation of Endometrial Cancer

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## ABSTRACT

**Background and Objectives:** Intraoperative evaluation of the uterus has been reported to predict risk of lymph node spread in endometrial cancer. Four criteria have been prospectively validated by the Mayo Clinic; histopathology, grade, tumor size, and depth of myometrial invasion. The objective of this study is to assess the accuracy of intraoperative evaluation in a university-affiliated teaching setting.

**Methods:** This study was a retrospective chart review of 105 cases of endometrial cancer who underwent robotic-assisted staging from January 2016 through December 2017.

**Results:** Seventy-five cases were included. The mean age was 65 y and mean body mass index was 33 kg/m<sup>2</sup>. Fifty-eight patients (80.6%) had no change between intraoperative and postoperative grade. This yielded a 19.4% discordance rate with a significant disagreement ( $P = .003$ , Cohen's  $\kappa = 0.705$ ). Fifty-eight patients (82.9%) had no change in depth of invasion. This yielded a 17.1% discordance rate with a significant disagreement ( $P = .0498$ , Cohen's kappa of 0.69 [95% confidence interval, 0.53–0.85]). Average tumor diameter was 3.4 cm. Seven patients (11.7%) were upsized from the low-risk ( $\leq 2$  cm) to the high-risk category ( $> 2$  cm). This led to an 11.7%

discordance rate, with a significant disagreement ( $P = .008$ , Cohen's kappa of 0.69 [95% confidence interval, 0.48–0.89]). In 15 of 75 cases (20%), intraoperative evaluation of the size of the tumor was not possible and deferred to the final pathology report.

**Conclusion:** We conclude the Mayo Clinic Criteria cannot be universally adopted until all four criteria can be validated through a prospective study that includes institutions that have variable resources.

**Key Words:** endometrial cancer, staging, lymph node dissection, frozen section.

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## INTRODUCTION

Endometrial cancer is the most common gynecologic cancer with 60,000 new cases and 10,000 deaths annually in the United States.<sup>1</sup> Most cases (67%) present at an early stage, whereas lymph node metastasis is present in 21% of cases at diagnosis.<sup>2</sup> Spread to lymph nodes negatively influences prognosis and informs adjuvant management decisions.<sup>3,4</sup> Hence, lymph node dissection is a requirement of the International Federation of Gynecology and Obstetrics (FIGO) staging system.<sup>5</sup>

A survey of gynecologic oncologists in the United States in 2010 did not find a standard practice pattern among gynecologic oncologists.<sup>6</sup> Several studies have reported an increased risk of postoperative complications attributable to lymph node dissection.<sup>7,8</sup> Two prospective trials did not show a survival benefit to this procedure.<sup>9,10</sup> Other dimensions to the controversy surrounding lymph node dissection include that neither the anatomic boundaries of the dissection have been standardized, nor can the candidates for the procedure be prospectively identified.<sup>11</sup>

Intraoperative frozen section evaluation of four main variables has been reported to accurately predict a high risk for lymph node spread and the need for lymph node dissection. Those variables, known as the Mayo Clinic Criteria, include histopathology, grade, depth of invasion, and size of the tumor.<sup>12–14</sup> The validity of this algorithm has not been universally accepted at all institutions.<sup>15–17</sup>

The objective of this study was to assess the accuracy of intraoperative frozen section evaluation in a university-affiliated teaching setting.

## MATERIALS AND METHODS

This is a retrospective chart review of patients with endometrial cancer at a university-affiliated teaching hospital who underwent robotic-assisted surgical staging from January 2016 through December 2017. Institutional review board approval was obtained.

Included were patients aged 18–89 y with endometrial intraepithelial neoplasia (EIN), in which invasive carcinoma could not be ruled out on preoperative biopsy or endometrioid adenocarcinoma who underwent intraoperative frozen section evaluation. Exclusion criteria included clear cell carcinoma, serous carcinoma, or carcinosarcoma as well as patients with evidence of cancer outside the uterus.

Intraoperative evaluation was correlated with the final pathology report to assess for concordance/discordance. Variables investigated included histopathology, FIGO grade, depth of myometrial invasion, and tumor size. We recorded the cases in which there was a discrepancy between intraoperative evaluation and the final pathology report as well as cases in which the intraoperative evaluation was deferred to the final sections. A clinically significant discrepancy was defined as one in which intraoperative evaluation of the uterus would have affected lymph node dissection strategy.

Staging and grading were defined according to the 2018 FIGO staging system.<sup>5</sup> Depth of invasion compared tumors with  $\leq 50\%$  to those with  $>50\%$ . EIN that was deemed grade 0. Stage 0 was assigned to cases that were found to have no carcinoma. Size was defined as either high risk, i.e.,  $>2$  cm in greatest diameter, or low risk, i.e.,  $\leq 2$  cm in greatest diameter based on previous publications.<sup>11</sup>

All patients underwent robotic-assisted total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, and assessment of peritoneal cytology. Lymph node dissection was omitted when impractical because of morbid obesity or unsafe because of comorbidities such as chronic cardiopulmonary disorders. Otherwise, lymph node dissection protocol followed Mayo Clinic Criteria for low-risk and high-risk cancer.<sup>11–13</sup> As part of a separate study, sentinel lymph node biopsy was performed in most of this cohort<sup>18</sup>; this included cases with preoperative EIN/cannot rule out carcinoma.

Unfixed hysterectomy specimens received intraoperative pathology evaluation for specimen dimensions, weight, and intactness. Uteri were bisected and grossly visible endometrial tumor was measured. Serial cut sections of the endomyometrium were performed, and gross tumor maximum depth of myometrial invasion was measured. Two to four frozen section samples were obtained from the deepest area of gross invasion or the thickest area of tumor in the absence of grossly evident invasion. In cases without grossly visible tumor, random sections of endomyometrium were submitted for frozen section evaluation. Frozen sections were prepared with hematoxylin-eosin staining and examined microscopically to confirm the presence of endometrial carcinoma. Tumor grade was assigned using FIGO histopathologic criteria.<sup>5</sup> The maximum depth of myometrial invasion was measured microscopically. Size was evaluated grossly and microscopically if feasible or deferred for permanent sections.

After intraoperative consultation, specimens, including remaining frozen section tissue, were fixed in formalin for at least 12 h. Complete gross examination and tissue sampling were performed according to College of American Pathologists (CAP) protocol, and sections from the entire endomyometrium were submitted for permanent histologic slides. The final diagnosis including tumor size, grade and depth of myometrial invasion was based on histopathologic examination of all slides including frozen section tissue. American Joint Committee on Cancer eighth edition TNM and FIGO staging criteria were used.<sup>5</sup> Sentinel lymph nodes were evaluated by ultrastaging using immunohistochemistry as previously described.<sup>18</sup>

Mean and standard deviation were used to summarize the continuous variables. Frequency and percentage were used to summarize the categorical variables. McNemar's test was used to assess the marginal homogeneity between intraoperative and postoperative results with regard to the grade, depth of invasion, and size category. The two-sided *P* values were reported. The Stuart-Maxwell test was used when the number of categories of a variable was more than two. The Cohen's kappa and its 95% confidence interval (CI) was also calculated to quantify the agreement. A value of *P* = .05 or less was considered statistically significant.

## RESULTS

A total of 105 charts were reviewed. Intraoperative evaluation was performed in 78 cases. Three cases were excluded because they had evidence of cancer outside the

uterus. Hence, 75 cases were included in the data analysis. The mean age was 65 y (range 38–89) and mean body mass index was 33 kg/m<sup>2</sup> (range 16–49 kg/m<sup>2</sup>).

Thirty-two patients (42.7%) had postoperative grade 1. Twenty-eight (37.3%) had grade 2. Grade 3 was found in 10 patients (13.3%). Five patients (6.7%) had EIN on final pathology. Stage 1 was found in 56 (74.7%) patients, stage 2 was found in nine (12.0%), and stage 3 was found in five patients (6.7%) (IIIA: one patient; IIIC1: two patients; IIIC2: one patient) (Table 1).

Characteristics	n = 75
Age, y	
Range	38–89
Mean (SD)	64.7 (10.3)
BMI, kg/m <sup>2</sup>	
Range	16–49
Mean (SD)	33.3 (7.9)
Had prior abdominal surgery, n (%)	36 (48.0)
ASA grade, n (%)	
1	2 (2.7)
2	42 (56.0)
3	31 (41.3)
Postoperative grade, n (%)	
0	5 (6.7)
1	32 (42.7)
2	28 (37.3)
3	10 (13.3)
Postoperative stage, n (%)	
0	5 (6.7)
1	56 (74.7)
2	9 (12.0)
3	5 (6.7)
Lymph node dissection, n (%)	
LND not performed	11 (14.7)
Any LND performed	64 (85.3)
Sentinel LND	58 (77.3)
Pelvic LND	38 (50.7)
Paraortic LND	20 (26.7)

BMI, body mass index; ASA, American Society of Anesthesiologists; LND, lymph node dissection.

Lymph node dissection was performed in 64 (85.3%) patients and was positive in four patients (5.3%). Fifty-eight patients (77.3%) had sentinel lymph node biopsy. Thirty-eight patients (50.7%) had systematic pelvic lymph node dissection, and 20 patients (26.7%) had paraortic lymph node dissection. Six patients had no sentinel lymph node dissection, four of whom had pelvic lymph node dissection, and two had both pelvic and paraortic lymph node dissection (Table 1).

### Histopathology

Preoperatively, all patients had endometrioid adenocarcinoma or EIN. Intraoperative evaluation was deferred in three patients (4%). All three had grade 1 endometrioid adenocarcinoma. On final analysis, one patient (1.3%) was found to have clear cell carcinoma and one (1.3%) had serous carcinoma. Both were correctly identified on intraoperative evaluation as high grade. One underwent pelvic and paraortic lymph node dissection, whereas the other did not undergo lymph node dissection secondary to morbid obesity and other comorbidities.

### Grade

Fifty-eight patients (80.6%) had no change between intraoperative and postoperative grade. Fourteen patients (19.4%) had an increase and 0 (0%) had a decrease in grade. In three (4%) patients, the diagnosis was deferred. All three had grade 1 endometrioid adenocarcinoma. This yielded a 19.4% discordance rate, which was found to be a statistically significant disagreement ( $P = .003$ , Cohen's  $\kappa = 0.705$ ) (Table 2). When we included the three deferred cases, the clinical discrepancy became 22.7%. When comparing low grade (0, 1, 2) and high grade (3) tumors, the distributions were not statistically different (Stuart-Maxwell test,  $P = .082$ , Cohen's kappa of 0.80 (95% CI, 0.63–0.97)).

Among a total of 10 grade 3 cases, three (30%) were upgraded from intraoperative grade 2. Among 28 grade 2

Frozen Grade vs Postoperative Grade	n = 72 <sup>a</sup>	P Value
Grade change, n (%)		
Increase	14 (19.4)	.003
Decrease	0 (0)	Stuart-Maxwell test
No change	58 (80.6)	

<sup>a</sup>Statistical analysis excluded deferred cases.

tumors, nine (32.1%) were called grade 1 intraoperatively. For the 32 grade 1 tumors in this study, two (6.3%) were upgraded from an intraoperative assessment of EIN.

**Depth of Invasion**

Fifty-eight patients (82.9%) had no change in depth of myometrial invasion, whereas 10 (14.3%) had an increase in depth of invasion ( $\leq 50\%$  intraoperative vs.  $> 50\%$  postoperative), and two (2.9%) had a decrease. The depth of invasion was deferred in five patients (6.7%). This culminated in a 17.1% discordance rate between the intraoperative and postoperative assessments, with a statistically significant disagreement ( $P = .0498$ , Cohen’s kappa of 0.69 [95% CI, 0.53–0.85]) (Table 3). When we included the deferred cases, the clinical discrepancy became 22.7%.

**Tumor Size**

Average gross tumor diameter was 3.4 cm (range, 0–9.5cm). When comparing the intraoperative and postoperative size categories, seven patients (11.7%) were upsized from the low-risk ( $\geq 2$  cm) to the high-risk category ( $> 2$  cm). This led to a 11.7% discordance rate, with a statistically significant disagreement ( $P = .008$ , Cohen’s kappa of 0.69 [95% CI, 0.48–0.89]) (Table 4). In 15 of 75 cases (20%), intraoperative evaluation of the size of the tumor was not possible and was deferred to the final pathology report. When we included the 15 deferred cases, the clinical discrepancy became 29.3%.

Twelve of the 75 cases (16%) had a clinically significant discrepancy between the intraoperative evaluation and the final pathology report. This was exclusively related to either a discrepancy in size (five of 12) or a deferral of size evaluation (seven of 12). All 12 patients had sentinel lymph node biopsy. One patient had pelvic lymph node dissection and one had both pelvic and paraaortic lymph node dissection. None of the 12 patients had lymph node

Frozen DOI vs Postoperative DOI	n = 70 <sup>a</sup>	P Value
DOI change, n (%)		
Increase	10 (14.3)	.0498
Decrease	2 (2.9)	Stuart-Maxwell test
No change	58 (82.9)	

<sup>a</sup>Statistical analysis excluded deferred cases.

Frozen Size Category vs Postoperative Size Category	n = 60 <sup>a</sup>	P value
Size change, n (%)		
Increase	7 (11.7)	.008
Decrease	0 (0)	McNemar’s test
No change	53 (88.3)	

<sup>a</sup>Statistical analysis excluded deferred cases.

metastasis based on previously described ultrastaging techniques<sup>18</sup> (Table 5).

**CONCLUSION**

We found a significant disagreement between the intraoperative frozen section evaluation and final pathology report regarding tumor size, grade, and depth of myometrial invasion. The clinical discrepancy rate in size evaluation between intraoperative and postoperative assessment was 29.3%. More importantly, there was a 20% deferral rate in size evaluation, and all 12 patients with a clinically significant discrepancy that would have altered operative staging were size related.

These results render intraoperative evaluation of endometrial cancer impractical at our institution unless a dramatic effort in time, resources, and personnel is made to affect a clinically significant change. Tumor size equal to or less than 2 cm in endometrial cancer has been associated with low risk of myometrial invasion, lymph node metastasis, recurrence, and death.<sup>12,19</sup> Intraoperative determination of tumor size is based on measurement of grossly visible tumor. The final pathologic diagnosis incorporates microscopic examination of the entire endomyometrium with gross correlation. In cases of noninvasive or minimally invasive sessile endometrial carcinoma, demarcation of tumor from surrounding benign endometrium may be grossly unapparent. In such cases, intraoperative size measurement may be deferred or underestimated, resulting in discordance with the final diagnosis. It is impractical at our institution to perform more than four frozen sections of endomyometrium in an effort to map the tumor size intraoperatively.

In 2000, Mayo Clinic investigators retrospectively evaluated 328 patients who were treated surgically for grade 1 or 2 tumors,  $\leq 50\%$  myometrial invasion, and no evidence of extrauterine spread. They found that no patient with

**Table 5.**  
Significant Discrepancy

n	Age, y	BMI, kg/m <sup>2</sup>	STAGE	Frozen Grade <sup>a,b</sup>	Postoperative Grade	Frozen DOI	Postoperative DOI	Frozen Size	Postoperative Size	SLNB	PLND	PALND
1	60	38	1A	d	1	d	≤50%	d	4 cm	1	0	0
2	51	36	1A	1	1	d	≤50%	d	3 cm	1	0	0
3	56	43	1A	2	2	≤50%	≤50%	d	11 cm	1	0	0
4	53	26	1A	1	1	≤50%	≤50%	d	2.5 cm	1	0	0
5	69	42	1A	1	1	d	≤50%	d	5 cm	1	0	0
6	74	30	2	2	2	≤50%	≤50%	d	7 cm	1	1	1
7	44	42	1A	1	1	0	≤50%	d	2.8 cm	1	1	0
8	56	41	1A	1	1	≤50%	≤50%	2 cm	2.7 cm	1	0	0
9	49	44	1A	1	1	0	0	2 cm	2.5 cm	1	0	0
10	52	27	1A	1	1	≤50%	≤50%	2 cm	3 cm	1	0	0
11	56	47	1A	1	1	≤50%	≤50%	1.5 cm	2.2 cm	1	0	0
12	38	37	1A	0	1	0	≤50%	0	4 cm	1	0	0

DOI, depth of invasion; BMI, body mass index; d, deferred; SLNB, sentinel lymph node biopsy; PLND, pelvic lymph node dissection; PALND, paraaortic lymph node dissection. Sentinel lymph node dissection was performed in endometrial intraepithelial neoplasia when preoperative biopsy could not rule out carcinoma.

<sup>a</sup>All pathology was endometrioid adenocarcinoma.

<sup>b</sup>FIGO grade.

tumor diameter ≤2 cm had positive lymph nodes or died of disease.<sup>12</sup> The authors concluded that patients with FIGO grade 1 or 2 endometrial cancer, ≤50% myometrial invasion, and ≤2 cm in greatest diameter could safely be treated without lymph node dissection or radiation therapy.<sup>12</sup> Accordingly, what came to be known as the Mayo Clinic Criteria were published in 2004, and, based on intraoperative frozen section evaluation, patients with the above criteria were spared lymph node dissection to avoid the potential complications associated with the procedure without compromising outcome.<sup>20</sup>

It was not until 2012 that the same group published a prospective validation of this strategy in a study that evaluated 784 consecutive patients with endometrial cancer treated over a 4-y period.<sup>13</sup> They found a 4% discordance between intraoperative frozen section and the permanent paraffin section. In an additional 7% of cases, frozen section analysis could not render a definitive diagnosis. The authors concluded that a clinically significant discordance between intraoperative frozen section and paraffin section occurred in only 1.3% of cases, confirming the validity of the Mayo Clinic Criteria in the intraoperative evaluation of endometrial cancer at that institution, when using all four parameters; histology, grade, myometrial invasion, and maximum tumor diameter.<sup>13</sup>

Several studies have been published using some of the parameters used by the Mayo Clinic with varying results.<sup>14–17,21,22</sup> In a prospective blinded study, Case et al.<sup>21</sup> reported a 67% correlation (95% CI, 55–79%) in depth of invasion between intraoperative and postoperative evaluation as well as a 58% correlation (95% CI, 46–70%) in tumor grade. With a clinically relevant upstaging in 18% (95% CI, 8–28%), the authors concluded that frozen section for histologic grade and depth of myometrial invasion correlates poorly with final pathology.<sup>21</sup> On the other hand, Stephan et al.<sup>22</sup> retrospectively evaluated 116 patients who underwent intraoperative evaluation and found a correlation with the final report in 97.5%, 88%, and 98.2% in histologic subtype, grade, and depth of myometrial invasion, respectively. These authors concluded that this supported the use of intraoperative frozen section analysis in guiding staging decisions.<sup>22</sup>

Historic risk factors for lymph node metastasis are based on final pathology for patients undergoing surgical staging for endometrial cancer. The only prospective published validated method is that of the Mayo Clinic. Duplication of the Mayo Clinic results require the following: 1) strict use of all four Mayo clinic variables, including size, and (2) systematic pelvic and infrarenal paraaortic lymph node

dissection, which may be required in up to 75% of patients.

We conclude the Mayo Clinic Criteria cannot be universally adopted until all four criteria can be validated through a prospective study that includes institutions that have variable resources.

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