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The reliability of intra-operative assessment on predicting tumor size, myometrial invasion, and cervical involvement in patients with a pre-operative diagnosis of complex atypical hyperplasia or (clinical Stage I) endometrial cancer: A prospective cohort study*.

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Abstract

Objectives: The objective of this study is to assess the reliability of intraoperative uterine assessment compared to final pathologic evaluation in patients with EC and whether assessment improves with experience.

Methods: Following IRB approval, a prospective cohort study of women surgically managed with biopsy proven complex atypical hyperplasia (CAH) or EC between March 2015 and December 2016 was performed. Demographics, preoperative biopsy results, procedure, intraoperative and final pathologic evaluation of lesion size, myometrial invasion, and lower uterine segment/cervical involvement were abstracted. Agreement between intraoperative and final pathologic evaluation of tumor involvement of the uterus was determined using the kappa statistic and the intraclass correlation coefficient (ICC).

Results: 264 patients with a preoperative diagnosis of CAH or EC were included - 71 (26.9%) with CAH and 193 (73.1%) with EC. Mean age was 62.6 ± 11.5 , and mean BMI was 37.2 ± 10.1 . The majority of women were Caucasian (67%). 227 (85.9%) patients underwent a laparoscopic or robotic hysterectomy, while 36 (13.6%) underwent an abdominal hysterectomy. 233 (88.3%) patients had EC and 21 (7.9%) patients had CAH on final pathology. There was fair agreement between intraoperative estimation of myometrial invasion ($\kappa=0.37$). Moderate agreement

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exists between intraoperative estimation of lower uterine segment/cervical involvement ($\kappa=0.57$). There was a strong agreement between intraoperative tumor size assessment and final path ($\text{ICC}=0.74$). Intraoperative correlation of tumor size was similar for the first half of the cohort ($\kappa=0.50$) and the second half ($\kappa=0.46$) chronologically.

Conclusions: Despite only fair correlation in myometrial invasion, intraoperative assessment of cervical involvement and especially tumor size is more readily identified and overall accurate. Therefore, intraoperative evaluation is an additional tool to use when making the decision to proceed with surgical staging.

Keywords

Intraoperative assessment; endometrial cancer; tumor size

Introduction

Endometrial carcinoma is the most common gynecologic cancer in the United States, with a 2.8% lifetime risk of diagnosis, and 61,380 new cases estimated for 2017.(1) The majority of patients are diagnosed with stage I or II disease and have excellent outcomes, but for the smaller proportion of women with advanced stage disease, prognosis is significantly worse. (2) The initial treatment of endometrial cancer consists of a hysterectomy, bilateral salpingo-oophorectomy, and surgical staging. Comprehensive surgical staging includes both pelvic and para-aortic lymphadenectomies which carry their own potential morbidity.

Lymphadenectomy has been associated with various postoperative complications including lymphedema, vascular injury, deep vein thrombosis, pulmonary embolism, and nerve injury. (3–5) Franchi and colleagues reported a postoperative complication rate of 26.7% in a study where patients underwent a lymphadenectomy at time of total abdominal hysterectomy. Of note, the overall rate of complications was almost 3 times higher when the lymph node dissection contained 14 or more lymph nodes and almost 10 times higher when more than 19 lymph nodes were removed.(3) Lymphadenectomy and the total number of lymph nodes removed demonstrated a strong association with lymphedema, and lymphedema was associated with a negative impact on quality of life scores based on questionnaires and survey responses from nine different studies.(4) Researchers have also found a lack of benefit in overall survival in patients with early stage disease undergoing lymphadenectomy, so there is continued debate over the need for lymphadenectomy in those patients at low risk for lymph node metastasis.(6–10)

Techniques developed and evaluated to predict myometrial invasion and lymph node positivity include transvaginal ultrasound, magnetic resonance imaging, and intraoperative gross evaluation.(11–15) Unfortunately, none of these techniques have been shown to determine which patients need surgical staging at the time of hysterectomy.(11–14) When intraoperative gross tumor evaluation was studied, Marcickiewicz and Sundfeldt concluded that evaluation of myometrial invasion was accurate only with Grade 1 tumors and that final histological evaluation should remain the gold standard for tumor involvement of the uterus. (15)

Mariani et al. developed a set of criteria known as the Mayo criteria to determine those patients at risk of lymphatic spread.(10) They found that patients with a grade 1 or 2 tumor that is less than or equal to 2cm in size with less than 50% myometrial invasion showed no evidence of macroscopic disease spread outside the uterus. They concluded that these patients can be managed without lymphadenectomy as there was no difference in recurrence-free survival seen in those patients who underwent lymphadenectomy compared to those who did not.(10) These criteria have also been validated for use at other institutions with similar outcomes.(16)

The Mayo criteria have proven to be a reproducible algorithm to determine who is at risk for metastasis and thus appears to be a reasonable tool to use when determining the need for lymphadenectomy intraoperatively. In this study, gynecologic oncology trained pathologists performed intraoperative frozen section analysis, but, unfortunately, many clinical practices across the United States do not have dedicated pathologists who are trained specifically in gynecologic oncology that routinely assess or interpret intraoperative frozen section specimens.(10) This may make intraoperative decisions based on frozen section pathology difficult and in some cases unreliable for many gynecologic oncologists. Given this known limitation, the objective of this study was to assess the reliability of intraoperative uterine assessment compared to final pathologic evaluation in patients with EC and whether assessment improves with experience.

Methods

IRB approval was obtained and a prospective observational cohort study was performed from March 2015 through December 2016. All patients who were surgically managed by a gynecologic oncologist with preoperative biopsy proven complex atypical hyperplasia (CAH) or presumed stage I endometrial cancer (EC) were included. Patients with non-endometrial pathology or those who did not undergo primary surgical intervention were excluded from this analysis. Demographics, pre-operative biopsy results, procedure performed, and intraoperative and final pathologic evaluation of lesion size, myometrial invasion, and lower uterine segment/cervical involvement were abstracted.

Once the uterus was removed, it was opened using either a knife or surgical scissors making an incision either anteriorly, posteriorly, or at the three or six o'clock position with the decision of which method and location to open the specimen left to the discretion of the primary surgeon. Data sheets were intra-operatively completed by the attending surgeon for each patient noting the surgical procedure, instrument used to open specimen and how the specimen was opened, estimated size of lesion, estimated myometrial invasion, and estimated lower uterine segment/cervical involvement. Tumor size estimation was based on greatest tumor diameter. All uterine evaluations performed by the attending surgeon in this study were gross evaluations and these were compared to the microscopic evaluations performed by a board-certified pathologist at our institution. Prior to this study, faculty at our institution did not routinely perform intraoperative uterine assessment.

The decision to perform a lymph node dissection was also left to the discretion of the primary surgeon. The decision was made for the attending surgeon to evaluate the uterus

grossly as opposed to the pathologist for two reasons. First, a comparison of gross inspection to microscopic evaluation by pathologists has already been performed; in this study, Goff et al found that pathologist over-estimated depth of invasion in well-differentiated tumors ~63% of the time but under-estimated moderately-to-poorly differentiated tumors ~69% and ~78% of the time respectively. (17, 18) Second, we sought to improve the external validity of the study as not all surgeons have the benefit of gynecologic-specific pathologists readily available for frozen section analysis.

Information regarding patient demographics, preoperative histology, final pathologic evaluation including final histology, tumor grade, myometrial invasion, tumor size, and lower uterine segment or cervical involvement, and surgical stage were abstracted and entered into a secure database. Sample size calculations demonstrated that 230 patients were required to detect a kappa coefficient of 0.70 with $\beta=0.20$ and $\alpha=0.05$. The level of agreement between intraoperative and final pathologic evaluation of tumor size, myometrial involvement, and lower uterine segment/cervical involvement was determined using kappa coefficients and intraclass correlation coefficients (ICC), where relevant. Kappa coefficients and ICC were used as they are the standard statistics for comparisons such as these. The Kappa coefficient was initially described by Jacob Cohen in order to compare inter-observer agreement.(19) In order to make the Kappa coefficient more descriptive, Landis and Koch described ranges of Kappa coefficients that would generally relate to a degree of inter-observer agreement.(20) Ranges of Kappa coefficient with the corresponding strength of inter-observer agreement are as follows: <0.00 poor, 0.00 to 0.20 slight, 0.21 to 0.40 fair, 0.41 to 0.60 moderate, 0.61 to 0.80 substantial, and 0.81 to 1.00 almost perfect.(20) Kappa coefficients have been reported in numerous clinical studies including those comparing final pathology to frozen section analysis in endometrial cancer.(21–23)

Results

Between March 2015 and December 2016, 270 patients with biopsy proven EC or CAH underwent primary surgical management with intraoperative evaluation by a gynecologic oncologist at our institution. Of these, three patients were excluded after being diagnosed with cervical cancer and three others because the size of the intrauterine tumor was unable to be adequately measured on final pathology. A total of 264 patients were included for comparison.

Patient demographics are depicted in Table 1. The mean BMI was 37.16 kg/m² (median 35.7, range 17.5 to 78.4). The majority of patients were white (66.7%). 48.9% of patients had an office endometrial biopsy and 44.3% underwent a dilation and curettage for preoperative evaluation. The majority of patients also had their initial evaluation at an external hospital system (77.3%). 198 (88%) of patients were diagnosed with stage IA or IB disease. On final pathology the majority of tumors were grade 2 (65.0%). 60.2% (159) of patients underwent a lymph node dissection and 14 (5.3%) had node positive disease.

Pre- and postoperative histology is compared in Table 2. Of 71 patients who had a preoperative biopsy of CAH, only 17 had CAH on final pathology whereas 46 patients had a malignancy noted on final pathology. Overall, only 21 out of 264 patients had CAH on final

pathology. Thirty-one (11.7%) patients had benign histology on final pathologic evaluation. The most common histology was endometrioid (62.5%) followed by uterine papillary serous carcinoma (10.9%) followed by non-endometrioid adenocarcinoma (8.3%).

Of the 264 patients included in this study, 240 patients had both intraoperative assessment and final pathologic evaluation of myometrial involvement and LUS/cervical involvement. Intraoperative evaluation of myometrial invasion compared to the gold standard of final pathologic evaluation was fair ($\kappa=0.38$) (Table 3). Of the 180 patients who were identified as having less than 50% myometrial invasion, 30 were found to have actually greater than 50% invasion (16.7%). Only 33 of 60 patients (55%) were correctly identified intra-operatively as having greater than 50% myometrial invasion. There was moderate agreement between intraoperative and final pathologic evaluation of lower uterine segment (LUS) or cervical involvement ($\kappa=0.57$) (Table 4). There was also moderate agreement in comparison of estimation of tumor size in relation to size less than or equal to 2 cm or greater than 2 cm ($\kappa=0.45$) (Table 5). When considering tumor size as a continuous variable there was a strong correlation between intraoperative and final pathologic evaluation ($\text{ICC}=0.74$).

Given that this study occurred over a time period of greater than 12 months we compared the evaluation of tumor size, myometrial invasion, and LUS/cervical involvement in the first half of the study period to that of the second half in an effort to determine if surgeon experience over time would improve the correlation between intraoperative and final pathologic evaluation. The agreement for myometrial invasion over the 1st and 2nd halves of the study was fair ($\kappa=0.34$ and $\kappa=0.38$, respectively). Regarding LUS/cervical involvement, there was moderate agreement during both halves of the study ($\kappa=0.54$ and $\kappa=0.58$, respectively). Finally, with respect to the comparison of size related to 2cm there was moderate agreement during both halves of the study ($\kappa=0.50$ and $\kappa=0.41$ for the respective halves).

Discussion

Given the ongoing debate regarding the benefit of lymphadenectomy for patients with early stage disease at low risk of recurrence, a reliable and widely applicable method for determining which patients in this population should or should not undergo lymph node dissection could help surgeons more effectively evaluate and treat patients while minimizing their exposure to surgical complications. We sought to determine whether intraoperative evaluation of the uterine specimen in endometrial cancer patients correlates with final pathologic assessment in an effort to identify a reliable method for determining which patients should undergo surgical staging with lymph node dissection.

In regards to evaluation of myometrial involvement, correlation with final pathologic assessment was moderate at best. The difficulty in accurately assessing tumor involvement of the myometrium is not surprising given prior attempts to evaluate myometrial invasion with preoperative and intraoperative magnetic resonance imaging (MRI) or ultrasound. Imaging does not provide reliable results as some studies show equivalence (13) while many others only a moderate ability to adequately detect the level of myometrial invasion.(11, 12,

14, 24) There has been at least one other study which showed that intraoperative visual inspection of myometrial invasion is reliable; however, this was not reproduced in our study. (15)

For our comparison of LUS/cervical involvement, our intraoperative assessment was again moderate. However, these results may be somewhat skewed by the realization that during the comparison of final pathologic evaluation it was determined that lower uterine segment involvement was not routinely specified or evaluated in the final pathologic evaluation. Therefore, the determination of LUS involvement was very difficult to ascertain based on the final pathology report and could be a source of significant variation in these results. Cervical involvement, on the other hand, was consistently reported and in only 6 cases, out of 240, was cervical involvement not appreciated intraoperatively. The overall rarity of cervical involvement can explain the lack of correlation in this regard.

The last element of the Mayo criteria which we compared was tumor size in relation to 2cm. When we compared the intraoperative assessment of gross tumor size (i.e. actual estimated size in centimeters) to largest size measured on final pathology, we found a strong correlation. Although we found a strong correlation with assessment of gross tumor size, our ability to accurately determine tumor size related to 2cm was moderate at best. When further evaluating the size estimation, the mean size on final pathology was 3.61cm with a standard deviation of 2.69cm. Thus, the majority of tumors were approximately 2cm in size and determining the difference between greater than and less than 2cm proved to be difficult intraoperatively. Although size estimation as a continuous variable showed a strong correlation, tumor size of 2cm remains clinically significant in relation to risk of lymph node metastasis.(10)

Finally, we were unable to show any improvement in tumor assessment over the first and second halves of this study period. There could be several reasons that we did not see an improvement over time in spite of our large sample size. Although we had a relatively large number of patients in this study, the number of patients per primary surgeon was variable; three surgeons contributed less than 10 patients apiece while three other surgeons contributed more than 40 patients each to the study. This variation could explain a lack of an improvement for all surgeons over time. Also, there was some surgeon turnover during the study period and we are not able to ascertain an improvement if a particular surgeon was not part of the study in one of the two halves being evaluated.

There are several strengths of our study, namely the prospective nature and relatively large number of patients. We did not standardize the method each surgeon used for intraoperative assessment, which may make this study more generalizable and applicable outside of our institution. Also, our rates of lymph node positivity were in line with published and reproduced data.(9, 10, 16) Interestingly, our rate of endometrial cancer with a pre-operative diagnosis of CAH was 64.8%. Thus, 45 of 71 patients with a pre-operative pathologic diagnosis of CAH had endometrial cancer on final path. Of the remaining 25 patients, 17 had CAH on final path, 4 had benign disease with no evidence of hyperplasia at all, 2 patients had simple hyperplasia without atypia, one patient had complex hyperplasia without atypia, and one patient had adenoma malignum on final pathology. Thus, our rate of

endometrial cancer in the setting of CAH is much higher than the 42.6% reported in a recent Gynecologic Oncology Group study. (25)

As we mentioned, our rate of cancer on final pathologic evaluation with a preoperative diagnosis of CAH is much higher than reported in the literature. One possible explanation for this is based on the large referral base which makes up our patient population. More than 75% of patients in this study were referred from outside providers and we found that a large majority of these patients also had documentation by the referring provider or pathologist of their suspicion for an underlying cancer. This concern resulted in referral to our practice but may also represent a patient population at a higher baseline risk of underlying malignancy causing the discrepancy that we see in our cohort.

This study also has some limitations. One of these is that it was performed at a single institution. Also, the number of patients per surgeon varied and thus the unequal weight could have affected the final statistics. Although a uniform technique for uterine evaluation was not established in an attempt to make the study more generalizable, this could have negatively impacted the study in several ways. If a standardized method of intraoperative uterine evaluation could be established, this might reduce intra-surgeon variability and make the comparison of improvement between the first and second halves of the study more reliable.

When this study was conceived and planned, sentinel lymph node mapping was not routinely used at our institution; however, over the last several years sentinel lymph node mapping for endometrial cancer has gained increasing traction, especially with improvements that have been made in laparoscopic camera optics and the technique for successful sentinel lymph node mapping. One of the initial techniques injected dye directly into the uterine serosa, but the results were inconsistent and not reliable. (26, 27) Currently, injecting fluorescent dye into the cervix has shown increased sensitivity and reproducibility for mapping the pelvic sentinel lymph nodes. (28, 29) A multicenter, prospective, cohort study of 385 patients, the FIRES trial, was recently published which demonstrated a 97% sensitivity for detecting the sentinel lymph node and only a 3% chance of missing lymph node metastases.(30) The recent data on sentinel lymph node mapping now allows for a relatively low-risk alternative to complete lymphadenectomy in a select patient population.

Frozen section pathologic evaluation has been evaluated, and used, as a means to identify patients who may require a lymphadenectomy at the time of hysterectomy. Several retrospective studies have reported on the accurate correlation of myometrial invasion and histologic grade on intra-operative frozen section to the final pathologic evaluation. (21, 23, 31) These results seem reassuring in regards to the utility of frozen section analysis in operative decision making. However, these reviews did not all consist of pathologic review by a gynecologic pathologist; in many cases the same pathologist who evaluated in the frozen section also performed the final evaluation, and in the case of Desouki et al, the results are based on a database from several different institutions. (21, 23, 31)

Case et al reported on a blinded prospective comparison between frozen section analysis and final pathologic evaluation that histologic grade and myometrial invasion correlated poorly.

They obtained intra-operative frozen section specimens on 60 patients with either endometrial adenocarcinoma or complex atypical hyperplasia. The pathologists who evaluated the final pathology were blinded as to the interpretation of the frozen section analysis and all pathologic evaluation was performed by a gynecologic pathologist. Case and colleagues demonstrated that 28% of patients were upstaged from their frozen section to final pathology with 11% being clinically relevant. Further, myometrial invasion correctly correlated from frozen to final pathology in 67% of cases and histologic grade correctly correlated in only 58% of cases.(32) Other retrospective analyses also echo this prospective evaluation. Kumar et al demonstrated that final pathology resulted in an upstaging in 26% of patients compared to frozen pathology and that, if frozen section alone were to be used for intra-operative decision making, this would have resulted in suboptimal surgical management in ~9% of patients.(22) In this retrospective review, all frozen section and final pathology evaluations were performed by gynecologic pathologists.

In conclusion, assessment of myometrial invasion has been attempted by many different approaches and unfortunately gross evaluation appears to be equally as poor and unreliable. Cervical involvement and tumor size assessment, however, can be more accurately assessed. As a whole, intraoperative uterine assessment does not appear to offer an advantage over sentinel lymph node biopsy in patients at low-risk for metastatic spread to the lymph nodes. Sentinel lymph node biopsy may in fact become the standard of care in the future resulting in the use of intraoperative uterine assessment of tumor involvement to determine the need for surgical staging only when sentinel lymph node mapping is not an option or successful and intraoperative frozen section is not available.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA: A Cancer Journal for Clinicians. 2017;67(1):7–30. [PubMed: 28055103]
2. Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, et al. Carcinoma of the Corpus Uteri. International Journal of Gynecology and Obstetrics.95:S105–S43.
3. Franchi M, Ghezzi F, Riva C, Miglierina M, Buttarelli M, Bolis P. Postoperative complications after pelvic lymphadenectomy for the surgical staging of endometrial cancer. Journal of Surgical Oncology. 2001;78(4):232–40. [PubMed: 11745815]
4. Lindqvist E, Wedin M, Fredrikson M, Kjølhede P. Lymphedema after treatment for endometrial cancer – A review of prevalence and risk factors. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2017;211:112–21. [PubMed: 28242470]
5. AlHilli MM, Mariani A. The role of para-aortic lymphadenectomy in endometrial cancer. International Journal of Clinical Oncology. 2013;18(2):193–9. [PubMed: 23412768]
6. Calais G, Descamps P, Vitu L, Body G, Lansac J, Bournoux P, et al. Is lymphadenectomy useful in the treatment of endometrial carcinoma? Gynecologic Oncology. 1990;38(1):71–5. [PubMed: 2354829]
7. Dowdy SC, Borah BJ, Bakkum-Gamez JN, Weaver AL, McGree ME, Haas LR, et al. Prospective assessment of survival, morbidity, and cost associated with lymphadenectomy in low-risk endometrial cancer. Gynecologic Oncology.127(1):5–10. [PubMed: 22771890]

8. Eltabbakh GH, Piver MS, Hempling RE, Shin KH. Excellent long-term survival and absence of vaginal recurrences in 332 patients with low-risk stage I endometrial adenocarcinoma treated with hysterectomy and vaginal brachytherapy without formal staging lymph node sampling: Report of a prospective trial. *International Journal of Radiation Oncology • Biology • Physics*.38(2):373–80.
9. Mariani A, Dowdy SC, Cliby WA, Gostout BS, Jones MB, Wilson TO, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: A paradigm shift in surgical staging. *Gynecologic Oncology*.109(1):11–8. [PubMed: 18304622]
10. Mariani A, Webb MJ, Keeney GL, Haddock MG, Calori G, Podratz KC. Low-risk corpus cancer: Is lymphadenectomy or radiotherapy necessary? *American Journal of Obstetrics & Gynecology*. 182(6):1506–19.
11. Alcázar JL, Orozco R, Martínez-Astorquiza Corral T, Juez L, Utrilla-Layna J, Mínguez JA, et al. Transvaginal ultrasound for preoperative assessment of myometrial invasion in patients with endometrial cancer: a systematic review and meta-analysis. *Ultrasound in Obstetrics & Gynecology*. 2015;46(4):405–13. [PubMed: 26011665]
12. Christensen JW, Dueholm M, Hansen ES, Marinovskij E, Lundorf E, Ørtoft G. Assessment of myometrial invasion in endometrial cancer using three-dimensional ultrasound and magnetic resonance imaging. *Acta Obstetrica et Gynecologica Scandinavica*. 2016;95(1):55–64. [PubMed: 26485119]
13. Gallego JC, Porta A, Pardo MC, Fernández C. Evaluation of myometrial invasion in endometrial cancer: comparison of diffusion-weighted magnetic resonance and intraoperative frozen sections. *Abdominal Imaging*. 2014;39(5):1021–6. [PubMed: 24699937]
14. Kisu I, Banno K, Lin L-Y, Ueno A, Abe T, Kouyama K, et al. Preoperative and intraoperative assessment of myometrial invasion in endometrial cancer: comparison of magnetic resonance imaging and frozen sections. *Acta Obstetrica et Gynecologica Scandinavica*. 2013;92(5):525–35. [PubMed: 23163480]
15. Marcickiewicz J, Sundfeldt K. Accuracy of intraoperative gross visual assessment of myometrial invasion in endometrial cancer. *Acta Obstetrica et Gynecologica Scandinavica*. 2011;90(8):846–51. [PubMed: 21534933]
16. Convery PA, Cantrell LA, Di Santo N, Broadwater G, Modesitt SC, Secord AA, et al. Retrospective review of an intraoperative algorithm to predict lymph node metastasis in low-grade endometrial adenocarcinoma. *Gynecologic Oncology*.123(1):65–70. [PubMed: 21742369]
17. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer: A gynecologic oncology group study. *Cancer*. 1987;60(S8):2035–41. [PubMed: 3652025]
18. Goff BA, Rice LW. Assessment of Depth of Myometrial Invasion in Endometrial Adenocarcinoma. *Gynecologic Oncology*. 1990;36(1):46–8.
19. Cohen J A Coefficient of Agreement for Nominal Scales. *Education and Psychological Measurement*. 1960;20(1):37–46.
20. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33(1):159–74. [PubMed: 843571]
21. Desouki MM, Li Z, Hameed O, Fadare O. Intraoperative Pathologic Consultation on Hysterectomy Specimens for Endometrial Cancer: An Assessment of the Accuracy of Frozen Sections, “Gross-Only” Evaluations, and Obtaining Random Sections of a Grossly “Normal” Endometrium. *American journal of clinical pathology*. 2017;148(4):345–53. [PubMed: 28967955]
22. Kumar S, Bandyopadhyay S, Semaan A, Shah JP, Mahdi H, Morris R, et al. The role of frozen section in surgical staging of low risk endometrial cancer. *PLoS One*. 2011;6(9):e21912.
23. Stephan JM, Hansen J, Samuelson M, McDonald M, Chin Y, Bender D, et al. Intra-operative frozen section results reliably predict final pathology in endometrial cancer. *Gynecol Oncol*. 2014;133(3):499–505. [PubMed: 24699308]
24. Taufiq M, Masroor I, Hussain Z. Diagnostic accuracy of diffusion weighted magnetic resonance imaging in the detection of myometrial invasion in endometrial carcinoma. *Journal of the College of Physicians and Surgeons Pakistan*. 2016;26:13+. [PubMed: 26787024]

25. Trimble CL, Kauderer J, Zaino R, Silverberg S, Lim PC, Burke JJ, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia. *Cancer*. 2006;106(4):812–9. [PubMed: 16400639]
26. Burke TW, Levenback C, Tornos C, Morris M, Wharton JT, Gershenson DM. Intraabdominal lymphatic mapping to direct selective pelvic and paraaortic lymphadenectomy in women with high-risk endometrial cancer: results of a pilot study. *Gynecol Oncol*. 1996;62(2):169–73. [PubMed: 8751545]
27. Frumovitz M, Bodurka DC, Broaddus RR, Coleman RL, Sood AK, Gershenson DM, et al. Lymphatic mapping and sentinel node biopsy in women with high-risk endometrial cancer. *Gynecol Oncol*. 2007;104(1):100–3. [PubMed: 16963111]
28. Barranger E, Cortez A, Grahek D, Callard P, Uzan S, Darai E. Laparoscopic sentinel node procedure using a combination of patent blue and radiocolloid in women with endometrial cancer. *Annals of surgical oncology*. 2004;11(3):344–9. [PubMed: 14993032]
29. Holub Z, Jabor A, Lukac J, Kliment L. Laparoscopic detection of sentinel lymph nodes using blue dye in women with cervical and endometrial cancer. *Medical science monitor : international medical journal of experimental and clinical research*. 2004;10(10):Cr587–91.
30. Rossi EC, Kowalski LD, Scalici J, Cantrell L, Schuler K, Hanna RK, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. *The Lancet Oncology*. 2017;18(3):384–92. [PubMed: 28159465]
31. Gitas G, Proppe L, Alkatout I, Rody A, Kotanidis C, Tsolakidis D, et al. Accuracy of frozen section at early clinical stage of endometrioid endometrial cancer: a retrospective analysis in Germany. *Archives of gynecology and obstetrics*. 2019;300(1):169–74. [PubMed: 31006842]
32. Case AS, Rocconi RP, Straughn JM Jr., Conner M, Novak L, Wang W, et al. A prospective blinded evaluation of the accuracy of frozen section for the surgical management of endometrial cancer. *Obstetrics and gynecology*. 2006;108(6):1375–9. [PubMed: 17138769]

Table 1.**Patient Demographics**

Mean BMI ($\pm$ St. Dev)	37.2 $\pm$ 10.1
Mean Age ($\pm$ St. Dev)	62.6 $\pm$ 11.5
Procedure	
TVH/BSO	1 (0.4%)
TLH/BSO	1 (0.4%)
TLH/BSO/LND	1 (0.4%)
RA-TLH	4 (1.5%)
RA-TLH/BSO	81 (30.7%)
RA-TLH/BSO/LND	140 (53.0%)
TAH	2 (0.8%)
TAH/BSO	14 (5.3%)
TAH/BSO/LND	20 (7.6%)
Race	
Caucasian	176 (66.7%)
African American	87 (32.9%)
Other	1 (0.4%)
Pre-operative Grade	
Grade 1	65 (69.9%)
Grade 1–2	6 (3.1%)
Grade 2	41 (21.2%)
Grade 2–3	28 (14.5%)
Grade 3	19 (9.8%)
Unknown	34 (17.6%)
Pre-Op Biopsy	
D&C	117 (44.3%)
EMBx	129 (48.9%)
Other	18 (6.8%)
Biopsy Location	
External	204 (77.3%)
Internal	60 (22.7%)
Final Stage	
IA	155 (66.5%)
IB	43 (18.5%)
II	10 (4.3%)
IIIA	7 (3.0%)
IIIB	2 (0.9%)
IIIC1	1 (0.4%)
IIIC2	4 (1.7%)
IVB	3 (1.3%)
Grade (final path)	

	Grade 1	42 (18.6%)
	Grade 2	147 (65.0%)
	Grade 2–3	5 (2.2%)
	Grade 3	32 (14.2%)
Node Status		
	Positive	14 (5.3%)
	Negative	145 (54.9%)
	Not Done	105 (39.8%)

TVH = total vaginal hysterectomy. BSO = bilateral salpingo-oophorectomy. TLH = total laparoscopic hysterectomy. LND = lymph node dissection. RA-TLH = robotic assisted laparoscopic hysterectomy. X = exploratory laparotomy. TAH = total abdominal hysterectomy. D&C = Dilation and Curettage. EMBx = endometrial biopsy. External = referring provider outside of home institution. Internal = University of Alabama at Birmingham.

Table 2.

Pathologic Evaluation

POST-OP HISTOLOGY → PRE-OP HISTOLOGY ↓	CAH	Adenocarcinoma	Endometrioid	UPSC	Clear Cell	Sarcoma	Other	
CAH	17	1	44	1	0	0	8	71
Adenocarcinoma	0	4	3	4	1	0	2	14
Endometrioid	3	15	112	11	1	0	4	146
UPSC	0	2	0	11	1	0	1	15
Clear Cell	0	0	0	0	1	0	0	1
Sarcoma	0	0	0	0	0	1	2	3
Other	1	0	6	2	0	1	4	14
	21	22	165	29	4	2	21	264

UPSC = uterine papillary serous carcinoma.

Table 3.

Comparison of myometrial invasion

Final Pathology Evaluation → Intra-operative Evaluation ↓	1/2	> 1/2	Total
1/2	150	30	180
> 1/2	27	33	60
Total	177	63	240

Only 240 patients either met criteria for this comparison or had evaluation of myometrial invasion both on intra-operative evaluation form and final pathologic evaluation. The Kappa for this comparison was $k=0.377$.

Table 4.

Comparison of Lower Uterine Segment/Cervical Involvement

Final Pathology Evaluation → Intra-operative Evaluation ↓	None	LUS	Cervix	Both	Total
None	179	7	2	1	189
LUS	12	17	3	5	37
Cervix	1	0	2	0	3
Both	1	2	2	6	11
Total	193	26	9	12	240

LUS = lower uterine segment. Only 240 patients either met criteria for this comparison or had evaluation of LUS/cervical involvement both on intra-operative evaluation form and final pathologic evaluation. The kappa for this comparison was $k=0.568$.

Table 5.

Comparison of tumor size in relation to 2cm

Final Pathology Evaluation → Intra-operative Evaluation ↓	2cm	> 2cm	Total
2cm	57	41	98
> 2cm	21	120	141
Total	78	161	239

Only 239 patients either met criteria for comparison of size in relation to 2cm or had estimation of size in relation to 2cm both on intra-operative evaluation form and final pathologic evaluation. The kappa for this comparison was $k=0.447$.