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Prospective validation of an intraoperative algorithm to guide surgical staging in early endometrial cancer

Jason R. Lefringhouse [a,*], Jeffrey W. Elder [a,1], Lauren A. Baldwin [a], Rachel W. Miller [a], Chris P. DeSimone [a], John R. van Nagell Jr [a], Luis M. Samoyoa [b], Dava S. West [b], Emily V. Dressler [c], Meng Liu [c], Frederick R. Ueland [a]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Kentucky, Markey Cancer Center, Lexington, KY, United States
[b] Department of Pathology, University of Kentucky, Markey Cancer Center, Lexington, KY, United States
[c] Division of Cancer Biostatistics, University of Kentucky, Markey Cancer Center, Lexington, KY, United States

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ABSTRACT

Objectives. Prospectively validate an intraoperative surgical staging algorithm to stratify patients with early endometrial cancer by risk of lymph node metastasis.

Methods. Subjects with endometrial cancer clinically confined to the uterus were prospectively enrolled at an academic cancer center between Jan 2012 and Jun 2015. Study participants were stratified intraoperatively into two groups based on risk of nodal involvement using cell type, tumor grade, myometrial invasion, and tumor size in accordance with an established protocol from the Mayo Clinic. Low risk (LR) subjects received extrafascial hysterectomy with bilateral salpingo-oophorectomy; high risk (HR) patients received complete surgical staging including bilateral pelvic and para-aortic lymphadenectomy.

Results. Of the 200 subjects enrolled, 194 were eligible for analysis. The algorithm identified 132 (68%) HR and 62 (32%) LR cancers. Of the HR subjects, 126 had lymphadenectomy performed with 14 (11%) positive for nodal metastases. Five HR subjects experienced disease recurrence. Of the 62 LR cancers, two patients developed disease recurrence. Ten LR cancers were upgraded to HR on final pathology due to lesion size (6) and grade (4). None of these patients experienced disease recurrence. The algorithm demonstrated 90% sensitivity (18/20) and 36% specificity (62/174) as determined by positive lymph nodes and/or disease recurrence.

Conclusions. Intraoperative assessment of early endometrial cancer can be used to determine the extent of surgical staging. The studied algorithm has low specificity and modifications are necessary to better match the surgical procedure to the risk of metastatic cancer.

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1. Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in the United States, and the incidence continues to rise. In 2016, there are expected be 60,050 new cases of EC with an estimated 10,470 deaths [1]. The majority of women with EC present with early stage disease where survival rates exceed 80% following primary surgery [2]. In the United States, standard surgical staging for women with EC includes extrafascial hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy. In 2014, the Society of Gynecologic Oncology Clinical Practice Endometrial Cancer Working Group reported: 1) patients with grade 1–2 endometrioid tumors, <50% myometrial invasion, and tumor of 2 cm or less are at low risk for recurrence and may not require a pelvic and para-aortic lymphadenectomy, and 2) lymphadenectomy may alter or eliminate the need for adjuvant therapy and its associated morbidity [3]. Today, there remains disagreement among specialists both on the necessity and extent of surgical staging for women with early EC [2,4–6].

The Mayo Clinic has published extensively on the surgical management of early EC, defining a subgroup of women at very low risk for lymph nodal involvement in which lymphadenectomy can be omitted. The authors developed an institutional algorithm that directs surgical treatment based on pathologic intraoperative consultation (IOC). Intraoperative stratification is based on the risk of nodal involvement: *low risk* (confined to corpus, grade 1 or 2 endometrioid type, myometrial invasion ≤50%, tumor diameter ≤ 2 cm), or *high risk* (does not meet low risk criteria). The low risk (LR) group is not required to undergo lymph node sampling or lymphadenectomy, while the high risk (HR) group receives bilateral pelvic and para-aortic lymphadenectomy [5,7]. In 2008,

* Corresponding author at: Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Kentucky, Markey Cancer Center, 800 Rose Street, Lexington, KY 40536, United States.
E-mail address: jlefringhouse@gmail.com (J.R. Lefringhouse).
[1] Current affiliation: Division of Gynecologic Oncology, Greenville Hospital System Cancer Institute, Greenville, SC.

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the authors published results on 422 women treated with this algorithm. Of the 112 in the LR group not requiring lymphadenectomy, 22 (20%) had lymphadenectomy and all nodes were negative for metastases. In the HR group, 22% had metastatic nodal involvement identified by lymphadenectomy. The investigators determined that the five-year recurrence-free survival was 98% in low risk women and 54% in high risk patients ($p < 0.001$) [8]. Despite these encouraging reports, further study is needed to determine how the intraoperative algorithm performs outside the unique Mayo Clinic setting where the intraoperative pathology processing differs substantially from other institutions.

This prospective investigation of women with early endometrial cancer was undertaken to evaluate the performance of the Mayo Clinic algorithm and its concordance with final pathology when using targeted intraoperative frozen section analysis.

2. Materials and methods

Study participants who met eligibility criteria were consecutively enrolled and underwent surgical treatment at the University of Kentucky between January 2012 and June 2015. Institutional review board approval was obtained and the trial was registered on ClinicalTrials.gov (NCT01512810). Eligible participants had histologically confirmed EC clinically confined to the uterus. The use of preoperative imaging was not required but could be used at the discretion of the treating physician. Eligible subjects had a GOG performance status of 0, 1, or 2, and were surgical candidates for a complete hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy. Subjects were included if a previous diagnosis of invasive cancer or chemotherapy was >5 years prior to enrollment; those with prior vaginal, pelvic or abdominal irradiation were excluded.

The treating surgeon and patient collectively determined whether the operation was via laparotomy or a robotic-assisted laparoscopic approach. Laparoscopy alone was not offered because the participating surgeons prefer to perform lymphadenectomy with robotic-assistance. When surgically removed, the uterus and cervix were promptly sent to surgical pathology for intraoperative evaluation according to the IOC algorithm. The uterus was bivalved in the coronal axis. Visible endometrial lesions were measured in three dimensions with the longest dimension defined as the primary tumor diameter. At least one representative frozen section of the tumor was performed and a systematic intraoperative risk assessment was completed. If multiple lesions were noted, the largest lesion was measured and recorded. Histologic type was classified according to World Health Organization criteria. Architectural grading was based on degree of glandular differentiation according the FIGO guidelines and assignment of stage utilized the 2009 FIGO staging system [9].

In accordance with the Mayo Clinic criteria, the LR group was defined by the presence of all of the following criteria: endometrioid cell type with disease confined to the uterine corpus, any grade without myometrial invasion, grade 1 or 2 tumors with myometrial invasion less than or equal to 50%, and primary tumor diameter ≤ 2 cm. Low risk subjects underwent hysterectomy with bilateral salpingo-oophorectomy, but were not required to have pelvic and para-aortic lymphadenectomy. The remaining subjects were classified as HR and were surgically staged with bilateral pelvic (right and left external iliac, internal iliac, obturator, common iliac) and bilateral para-aortic lymphadenectomy to the level of the inferior mesenteric artery.

The study employed a prospective non-randomized stratified observational design to estimate 2-year recurrence-free survival (RFS) rates. Sample size was determined a priori, using retrospective data from the University of Kentucky Endometrial Cancer Database; we predicted 2-year RFS rates to be 92% in the low-risk and 82% in the high-risk subgroup. With the assumption that 60% of subjects would be categorized as low risk during IOC, 167 eligible patients would provide 80% power to estimate the 2-year RFS rate within ±5.8% for low risk and ±9.8% for high risk based on a two-sided exact 95% binomial confidence interval for a single proportion. If low-risk subgroup rates of 55% or 50% were observed, the total sample size would be increased to 182 or 200 respectively to maintain similar precision. Thus, the final sample size was 200. Once subjects were classified as LR or HR, statistical analysis included Fisher's exact test and 2-sample *t*-tests to assess for differences between risk statuses for categorical and continuous variables respectively. Discordance between IOC and final path reports were calculated with corresponding Kappa statistics. Differences were considered statistically significant at $p < 0.05$. Statistical analyses were conducted using the SAS version 9.4 software package (SAS Institute, Inc.: Cary, NC).

3. Results

A total of 200 subjects with EC were consecutively enrolled and 194 were eligible for analysis. Of the six ineligible subjects, three did not meet inclusion criteria, two declined surgery, and one had surgery at another facility (Fig. 1). The mean lymph node count for the 126 high risk patients who had lymph nodes removed was 15.4 (range 0–44). The mean lymph node count for the patients who had a completed pelvic and para-aortic lymphadenectomy was 17.7 (range 6–44).

3.1. Findings related to risk groups

Based on intraoperative evaluation, 32% (62/194) were LR and 68% (132/194) were HR. The clinical and pathological characteristics are shown in Table 1. Five subjects in the LR group not requiring lymphadenectomy by protocol received at least partial lymphadenectomy. All lymph nodes were negative on final pathology, but one patient developed disease recurrence at 18 months after surgery. In all, two subjects (3%) in the LR group developed recurrent disease. They were the only patients in the LR group to receive additional therapy following surgery.

Fourteen of 132 (10%) subjects in the HR group had positive lymph nodal metastases on final pathology. Intraoperatively, all were grade 2 or 3 tumors or had a lesion size >3 cm. Three patients had a lesion size of 2–3 cm. There were no lymph node metastases identified for grade 1 tumors with a lesion size ≤3 cm. Five of 14 (36%) had cervical involvement (Table 2). Of the 132 subjects in the HR group, 32% received either adjuvant radiation (11%), chemotherapy (14%), or both (7%). All HR subjects with lymph node metastases received adjuvant therapy.

Of the seven subjects who developed disease recurrence, five were HR including one with positive lymph nodes and two with cervical involvement on final pathology. Two subjects with recurrence were in the LR cohort (Table 3). One LR subject was initially classified as HR by tumor size because the lesion grossly appeared to replace the entire surface of the endometrium. Lymph node dissection was initiated (seven negative para-aortic nodes), but a representative frozen section identified only complex atypical hyperplasia and the lymph node dissection was discontinued. The final pathology revealed a grade 1, endometrioid adenocarcinoma with a single focus of invasive disease confined to the endometrium. She developed a pelvic recurrence at two years and was treated with pelvic radiation; a supra-clavicular lymph node recurrence 10 months later was treated with chemotherapy; the patient is alive 29 months after completion of therapy. The second subject with a LR recurrence had a 1.5 cm, grade 1 endometrioid adenocarcinoma with 10% myometrial invasion on final pathology. A vaginal cuff recurrence at seven months was treated with whole pelvic radiation and vaginal cuff brachytherapy. The patient is alive and without definitive progression 26 months after her recurrence.

During the mean follow up of 15.3 months (range 1–43), six subjects died: four were disease related and two were from causes unrelated to their cancer diagnosis. At this time, there is no difference in recurrence-free survival between the HR and LR groups on Kaplan-Meier analysis.

3.2. Findings related to individual algorithm components

The discordance by risk group between IOC and final pathology was 5.7% (11/194, $K = 0.861$, $p < 0.0001$). Sixteen percent (10/62) of subjects

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