



Intra-operative frozen section results reliably predict final pathology in endometrial cancer



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HIGHLIGHTS

- Correlation between frozen section and paraffin section for histology, grade, and depth of invasion was 97.5%, 88%, and 98.2% respectively.
- Our results support frozen section analysis as a means to guide intra-operative decision-making regarding the necessity of a lymphadenectomy.
- Frozen section is a reasonable alternative to the “all or none” approach regarding lymphadenectomy for low-risk endometrial cancer patients.

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ABSTRACT

Objectives. Typically, complete surgical staging is necessary for patients with high-risk endometrial cancer. However, patients with low-risk disease may be able to avoid lymphadenectomy and its associated morbidity. We sought to evaluate the agreement rates between the intra-operative frozen sections (FSs) and the final paraffin sections (PSs) at our institution, and to determine if this was a reliable method for guiding our intra-operative decision-making with regard to the necessity of lymphadenectomy.

Materials and methods. 116 patients with a pre-operative diagnosis of endometrioid adenocarcinoma of the uterus or complex atypical hyperplasia (CAH) underwent surgery at our institution. Demographic data, as well as information on stage, grade, histology and depth of invasion determined at FS and on PS were collected. Cohen's kappa statistic was used to assess the agreement rate between FS and final PS with regard to depth of invasion, grade, and histology.

Results. Our correlation rate between FS and final PS for histologic subtype, grade, and depth of myometrial invasion was 97.5%, 88%, and 98.2% respectively. Seven cases identified as complex atypical hyperplasia on FS were later determined to be cancerous on final PS, resulting in two patients being undertreated.

Conclusions. Our results support the use of FS analysis as a means to guide intra-operative decisions regarding lymphadenectomy. Determination of histologic subtype, depth of invasion and grade is reliable at our institution, and demonstrates high concordance rates between FS and PS. These factors should be used to guide intra-operative decision-making regarding the necessity of a lymphadenectomy in patients with endometrial cancer.

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Introduction

With an estimated incidence of 49,560 new cases in 2013, endometrial cancer is the most common gynecologic malignancy in the United States [1]. More than 70% of women present with disease confined to the uterus, with the remainder having more advanced disease [2]. The cornerstone of treatment for endometrial cancer involves a hysterectomy and bilateral salpingo-oophorectomy. The indication and extent of lymph

node dissection in the surgical management of endometrial cancer remain highly controversial [3–5]. In fact, whereas there is general agreement about the necessity of complete surgical staging for high-risk endometrial cancer patients [6], this is less clear in patients with apparent low-risk disease. The identification of those patients with low-risk disease who also have a high probability of nodal involvement, and therefore might benefit from a lymphadenectomy is a current clinical question that remains unanswered.

One common approach is the use of intra-operative frozen section (FS) to identify pathologic high-risk features, such as deep myometrial invasion, tumor size and/or high-grade disease, to guide intra-operative decision-making. However, because the correlation between those

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high-risk factors and lymph node involvement is derived from studies examining paraffin sections (PSs), the accuracy of intra-operative FS is key in the guidance of intra-operative decision-making. There have been conflicting reports in the literature about the accuracy and reliability of findings based upon intra-operative frozen sections in endometrial cancer tissue specimens. In some centers it was found to be a useful tool for guiding intra-operative decision-making [7–9], whereas in others it was found to be inconsistent [10,11]. At our institution, a lymphadenectomy is usually performed on all patients with grade 2 and 3 endometrial cancers independent of the histology or depth of tumor invasion, as well as on all patients with grade 1 endometrioid adenocarcinoma with more than 50% myometrial invasion. We sought to evaluate the reliability and agreement rates between the intra-operative FS and the final PS at our institution, and to determine if this was a reliable method for guiding our intra-operative decision-making with regard to the necessity of lymphadenectomy.

Material and methods

This study was approved by the Institutional Review Board of the University of Iowa Hospitals and Clinics (UIHC). Between January and December 2012, one hundred and sixteen patients with a pre-operative diagnosis of endometrioid adenocarcinoma of the uterus, complex atypical hyperplasia (CAH) or a suspicion of endometrial carcinoma underwent surgery at our institution as part of their treatment. All patients had had pre-operative endometrial sampling performed locally, and the slides were reviewed by one of twelve attending pathologists at UIHC. In only 3/116, the same surgical pathologist who verified the pre-operative sample results also verified the FS report, while the rest of the cases were determined by different staff pathologists. In addition, in only 9/116, the same surgical pathologist who verified the pre-operative sample results also verified the final report. During surgery, the uterus was submitted to the pathology laboratory for frozen section examination, and resulting information was then used to guide intra-operative decision-making. A lymphadenectomy was performed on all patients with grade 1 endometrioid adenocarcinomas of the uterus with more than 50% myometrial invasion, as well as on all patients with findings of grade 2 or 3 tumors. The practice at our institution until early 2010 was to perform comprehensive surgical staging with both bilateral pelvic and para-aortic lymph node dissection on all patients diagnosed with endometrial cancer regardless of their histology or grade of disease. Starting in 2010, there was a paradigm shift adopted by most of the surgeons at our institution, wherein lymph node dissection was omitted on patients with grade 1 disease and less than 50% invasion, as determined intraoperatively. However, lymphadenectomy was still routinely performed on any patient with a grade 2 or 3 tumor as determined by pre-operative biopsy.

Frozen section analysis was performed in the following manner. Upon receipt of a hysterectomy specimen in the gross pathology laboratory, the uterus was inked and measured, followed by sectioning first through the cervical canal and endometrial cavity longitudinally (“bivalving”), then sectioning horizontally from fundus to cervix (“bread-loafing”) to assess the deepest point of invasion. This task was routinely performed by resident physicians or pathology assistants. Oversight for selection of sections for freezing was performed by surgical pathology fellow physicians or faculty. One full-thickness section of endometrial tumor, grossly assessed to be the deepest point of invasion, with underlying myometrium and serosa was frozen in Optimal Cutting Temperature media and sectioned on the cryostat into 5 μ m slices. Three different levels were cut, separated by approximately 25–50 μ m, which were then stained with a rapid hematoxylin and eosin stain for microscopy. Both microscopic depth of myometrial invasion as well as tumor subtype and grade were carried out on the single frozen section. Occasionally an additional section was frozen if the first slides showed equivocal findings or the sections were of particularly poor quality. Microscopy was performed by surgical pathology fellow

physicians, with the final assessment at frozen section made by any one of twelve different attending surgical pathologists. In most cases, the frozen section remnant was then submitted for permanent histology, and several additional sections of tumor were paraffin-embedded and used for the final microscopic analysis. In 45% of the cases (52/116), the same surgical pathologist who verified the FS results also verified the final pathology report, while the rest of the cases had different pathologists for FS and permanent section analyses. A blinded central review of all the cases was performed by an experienced gynecologic pathologist at UIHC. Our cancer center biostatistician then compared the central review of both the frozen section and the final paraffin section with those used in our manuscript. There was no statistical difference seen between the two groups with respect to cell type, grade, or depth of invasion.

A retrospective review of the electronic medical record was performed to gather demographic data, and Cohen's kappa statistic was used to assess the agreement rate between FS and final PS with regard to depth of invasion, grade, and histologic subtype. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were calculated with 95% confidence intervals for each parameter. The data analysis for this paper was generated using SAS software, Version 9.3 (Cary, NC).

Results

A total of 116 patients underwent surgery and were treated at our institution during the study period. Patient characteristics are shown in Table 1. As shown in Table 2, there were 94 patients with a pre-operative diagnosis of endometrial carcinoma, 20 patients with complex atypical hyperplasia (CAH), and two patients with suspicion for carcinoma. All patients were evaluated initially by intra-operative FS, and then by a definitive PS to determine the degree of concordance between FS and PS. A total of thirty one patients underwent a lymphadenectomy. Four of them were found to have metastatic disease in their pelvic lymph nodes, and one in both the pelvic and para-aortic lymph nodes. Table 2 shows the breakdown of patients stratified by their pre-operative, intra-operative (frozen section) and post-operative (paraffin section) diagnoses.

Table 1
Patient characteristics (N = 116).

Characteristic	Number (%)
Age, mean	60.1
Range	34–93
BMI, mean	37.7
Range	20.1–71.2
Race	
White	102 (88%)
African American	11 (9.5%)
Others	3 (2.5%)
FIGO stage	
I	93 (80.1%)
II	3 (2.6%)
III	4 (3.4%)
IV	1 (0.8%)
Unstaged	15 (12.9%)
Grade	
1	83 (71.4%)
2	13 (11.2%)
3	5 (4.3%)
Not graded	15 (12.9%)
Lymphadenectomy	
Yes	31 (26.7%)
No	85 (73.3%)

Age in years.

BMI: Body mass index (kg/m²).

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