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Does Preoperative Diagnosis of Endometrial Hyperplasia Necessitate Intraoperative Frozen Section Consultation?

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Background: In women with endometrial hyperplasia, there is a risk for co-existent endometrial cancer when patients are subjected to immediate surgical treatment.

Aims: The aim of this study was to investigate the frequency of endometrial cancer and the accuracy of frozen section analysis at the time of hysterectomy among patients with endometrial hyperplasia, to reveal whether or not a preoperative diagnosis of endometrial hyperplasia necessitates frozen section consultation.

Study Design: Retrospective cross-sectional study.

Methods: A department database review was performed to identify patients who were subjected to hysterectomy with a preoperative diagnosis of endometrial hyperplasia, during the period from 2007 to 2014.

Results: The study group included 189 cases. The final pathological examination revealed endometrial cancer in 16 women (8.4%). The risk of cancer in patients with endometrial hyperplasia was 1 of 125 (0.8%) in simple hyperplasia without atypia, 1 of 21 (4.8%) in complex hyperplasia without atypia and 14 of 43 (32.5%) in atypical hyperplasia. Of women with cancer, 2 of 16 (12.5%) had high-risk features. Frozen section analysis was requested in 46 cases. Frozen sections helped to identify six out of 11 cases of endometrial cancer (54.5%). The sensitivity, specificity and positive and negative predictive values of frozen section analysis for the detection of endometrial cancer among women with endometrial hyperplasia were 54.4%, 97.2%, 85.7% and 87.5%, respectively.

Conclusion: Although a significant proportion of patients with atypical endometrial hyperplasia are diagnosed with endometrial cancer following hysterectomy, most of these cases have low-risk features and do not require surgical staging. Additionally, intraoperative frozen section analysis if not helpful for diagnosing concurrent endometrial cancer in patients with endometrial hyperplasia. Therefore, it seems that patients with endometrial hyperplasia can be operated upon in settings with no available method for obtaining frozen sections intraoperatively.

Keywords: Endometrial hyperplasia, endometrial cancer, frozen sections

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries and the most common histologic type of endometrial cancer is endometrioid type adenocarcinoma (1). The precursor lesion for endometrioid type endometrial adenocarcinoma endometrial hyperplasia which is defined as the proliferation of endometrial glands resulting in increased gland to stroma ratio (2). Endometrial hyperplasia is classified into four categories by World Health Organization (WHO) classification system which was introduced in 1994 and currently it is the most widely used classification system. The WHO classes of endometrial hyperplasia are simple hyperplasia with or without cytologic atypia and complex hyperplasia with or without cytologic atypia. Simple or complex hyperplasia refers to the relationship between glandular and stromal tissue architectural patterns; atypia refers to nuclear abnormalities. The risk of progression from hyperplasia to endometrioid type carcinoma is mostly related to the presence of atypia and therefore the

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risk for progression to carcinoma is highest in complex endometrial hyperplasia with atypia (3). In women with endometrial hyperplasia, there is also a risk for co-existent endometrial cancer when patients are subjected to immediate surgical treatment. The risk of co-existent endometrial cancer in atypical endometrial hyperplasia was reported to be as high as 43% in the Gynecologic Oncology Group study (4). Hence, use of intraoperative frozen section evaluation may be considered during surgical treatment of patients with endometrial hyperplasia since diagnosis of endometrial cancer necessitates surgical staging. Conventional surgical staging procedure includes total hysterectomy with bilateral salpingo-oophorectomy and bilateral pelvic and para-aortic lymph node dissection (5). However, approximately 75% of patients with endometrioid type adenocarcinoma of endometrium is confined to the uterus at the time of diagnosis and a more conservative surgery may be considered for those (6,7). Patients with certain well-defined pathologic features are classified as low-risk for extrauterine disease and lymph node spread. Therefore, for these patients, systematic retroperitoneal lymphadenectomy may be omitted to avoid over-treatment and related complications (8). As a result, it may also be considered that most of the patients with endometrial hyperplasia who are diagnosed to have co-existent endometrial cancer via intraoperative frozen section analysis will not require a full staging procedure. Therefore, we aimed to investigate the frequency of endometrial cancer in cases preoperatively diagnosed as endometrial hyperplasia, and to evaluate the accuracy of frozen section analysis in discriminating endometrium cancer cases intraoperatively.

MATERIALS AND METHODS

This study included patients with a preoperative diagnosis of endometrial hyperplasia who underwent surgical treatment between 2007 and 2014. All patients underwent total abdominal hysterectomy with or without bilateral salpingo-oophorectomy according to age and menopausal status. Patients with endometrial carcinoma was staged using the revised 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system. Clinical and pathological characteristics including patient age, preoperative WHO class of endometrial hyperplasia, intraoperative frozen section results and permanent pathology were evaluated. For microscopic evaluation in frozen section, most suspicious areas for invasive disease were sampled. If there was no visible macroscopic lesion one section was evaluated. In women with co-existent endometrial cancer, the invasive disease was classified as low-risk or high-risk based on grade, depth of invasion, tumor size, and cervical involvement. In our department, patients with non-endometrioid type histology or endometrioid type histology with grade 3 disease, deep myometrial invasion, tumor diameter is >2 cm with myometrial invasion and cervical involvement are considered for comprehensive surgical staging with retroperitoneal lymph node dissection according to Mayo criteria. Conversely, in patients with endometrioid type grade 1 or 2 disease with no or superficial myometrial invasion when the tumor diameter is 2 cm or less lymphadenectomy is not performed.

This study was approved by the Institutional Ethics Committee. Individual medical records of the patients with endometrial hyperplasia who underwent surgical treatment were reviewed retrospectively. Informed consent was not obtained from the patients.

Statistical Package for the Social Sciences software version 17.0. (SPSS Inc.; Chicago, IL, USA) was used to record and manage the data. Frozen section and permanent paraffin section results were compared and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated with 95% confidence intervals (CIs) for each parameter. For the purposes of this study, the permanent pathological diagnoses were assumed to be the gold standard. Cross tabulations were analyzed using chi-square or Fisher's exact test, as appropriate. P values less than 0.05 were considered to be statistically significant.

RESULTS

The study group consisted of 189 consecutive patients with a mean age of 50.4 years (range: 34-82 years). Among them, 122 women (59.2%) were premenopausal while and 77 (40.8%) were postmenopausal. Of the patients, 33 had (17.5%) complex atypical, 10 had (5.3%) simple atypical endometrial hyperplasia, 21 had (11.1%) complex endometrial hyperplasia with no atypia, 125 had (66.1%) simple endometrial hyperplasia without atypia (Table 1). The presenting symptom was menorrhagia in 56 (29.6%) women, menometrorrhagia in 52 (27.5%) women, metrorrhagia in 4 (2.11%) women and postmenopausal bleeding in the remaining 77 (40.7%) women.

Of the 189 cases reviewed, final pathological examination revealed endometrial cancer in 16 cases (8.5%). Risk of endometrial cancer was 1 of 125 (0.8%) in simple hyperplasia without atypia, 1 of 21 (4.8%) in complex hyperplasia without atypia, and 14 of 33 (42.4%) in complex endometrial hyperplasia with atypia. (Table 1). When only the presence and absence of atypia was considered, endometrial cancer was diagnosed in final pathology in 2 out of 146 cases (1.4%) of endometrial hyperplasia without atypia and in 14 out of 43 cases (32.6%) of endometrial hyperplasia with atypia ($p<0.001$) (Table 2). Among 16 patients with endometrial cancer, all had endometrioid type adenocarcinoma. All but one had grade 1 disease. Only 2 (12.5%) had tumor measuring more than 2 cm in diameter and only 2 had deep (more than 50%) myometrial invasion. Of cases with cancer, 14 (87.5%) had stage 1a disease mostly according to the pathologic evaluation of hysterectomy

TABLE 1. Preoperative diagnoses and final pathology results in terms of the presence and absence of endometrial cancer

	Presence of endometrial cancer in final pathology		
	No	Yes	Total
Preoperative diagnosis	n (%)	n (%)	(n)
Complex EH with atypia	19 (57.6%)	14 (42.4%)	33
Simple EH with atypia	10 (100.0%)	0 (0.0%)	10
Complex EH without atypia	20 (95.2%)	1 (4.8%)	21
Simple EH without atypia	124 (99.2%)	1 (0.8%)	125
Total n (%)	173 (91.5%)	16 (8.5%)	189 (100%)

EH: endometrial hyperplasia

TABLE 2. Presence of atypia and the presence or absence of endometrial cancer in final pathology

	Presence of endometrial cancer in final pathology		
	No	Yes	Total
Preoperative diagnosis	n (%)	n (%)	(n)
EH with atypia	29 (67.4%)	14 (32.6%)	43
EH without atypia	144 (98.6%)	2 (1.4%)	146
Total (n)	173 (91.5%)	16 (8.5%)	189

EH: endometrial hyperplasia

with adnexectomy specimen and among two surgically staged patients, one had stage 1b (>50% myometrial invasion) and the other had stage 3a (adnexal involvement) disease (Table 3).

Among the women with endometrial cancer, only 2 (12.5%) had high-risk features necessitating comprehensive surgical staging. For those patients, deep myometrial invasion in one and deep myometrial invasion with large tumor in the other led the disease to be designated as high risk. One of these two patients was detected by frozen section. High-risk features were revealed by permanent pathology in other patient and re-laparotomy was performed for staging surgery.

Of the 16 patients with endometrial cancer, 10 (62.5%) were postmenopausal, and 6 (37.5%) were premenopausal. There was no significant correlation between menopausal status and the diagnosis of endometrial cancer on permanent sections (p=0.068).

During the operation, frozen section consultation was requested for 46 of 189 patients (24.3%). Of these 46 cases, cancer was discovered in paraffin sections from 11. Frozen section successfully identified endometrial cancer in 6 cases and only one of those 6 cases had high-risk features requiring a full staging procedure. The sensitivity, specificity, positive and negative predictive values of frozen section analysis for the detection of EC among women with endometrial hyperplasia were 54.4% (95% CI: 23.4-83.3), 97.2% (95% CI: 85.1-99.9), 85.7% (95% CI: 42.1-99.6), and 87.5% (95% CI: 72.6-95.7), respectively.

DISCUSSION

The mode of treatment mainly depends on the presence or absence of atypia for women with endometrial hyperplasia. When endometrial hyperplasia with atypia is diagnosed, hysterectomy is considered as definitive treatment by most of the clinicians when future fertility is not an issue since such disease is much more associated with co-existent endometrial cancer. Previous studies have shown that patients with atypical endometrial hyperplasia have a 20-52% risk of co-existent endometrial cancer (4,9-15). Our data are consistent with the literature and we found that the risk of co-existent endometrial cancer was 32.6% in patients with atypical endometrial hyperplasia. For this reason, some of the women with endometrial hyperplasia may need more extensive surgery due to the risk for extra-uterine spread of co-existent endometrial adenocarcinoma. The problem is how to determine those patients. Although standard treatment for women with endometrial cancer included a comprehensive staging surgery consisting of total abdominal hysterectomy and bilateral salpingo-oophorectomy with pelvic and para-aortic lymph node dissection, several studies published over the past several years have questioned the necessity of such a comprehensive surgery for most of the patients with endometrial cancer (7,8,16-19). Mariani and coworkers demonstrated that patients with endometrioid type Grade 1 or 2 disease with no or superficial myometrial invasion have a negligible risk for lymphatic metastasis when the tumor diameter is 2 cm or less. Therefore, tumor diameter, depth of myometrial invasion, histologic subtype and grade of tumor are important pathologic features which determine the risk of extra-uterine disease and lymph node involvement. Thus, these parameters may be used to guide the decision of performing a lymphadenectomy in endometrial cancer (7,17-19). Frozen section evaluation is helpful in the determination of these parameters.

Same principle may be applied to women with endometrial hyperplasia because a full staging procedure with systematic lymph node dissection will not be required for most of the patients with co-existent endometrial cancer. Therefore, frozen section may be required to make an intraoperative decision about the extent of surgery in patients who were scheduled for surgical treatment of endometrial hyperplasia. In the literature, numerous studies have been published which specifically focused on the accuracy of frozen section analysis in women with endometrial hyperplasia. Bilgin et al. (20) reported that frozen section analysis detected 50% of endometrial cancer in patients with endometrial hyperplasia. Morotti et al. (21) have found that the sensitivity of frozen section analysis for the detection of endometrial cancer among women with endometrial hyperplasia was 73%. Salman et al. (22) reported that 75% of patients with endometrial cancer were successfully detected by frozen section analysis. In another study, Indermaur et al.

TABLE 3. Clinicopathological features of the malignant cases

Cases	Preoperative diagnosis	Age	FS result	High-risk or low-risk according to FS	Grade	Myometrial invasion	Stage*	Tumor size	Surgery
1	Simple EH without atypia	51	Not requested	NA	1	<1/2	IA	<2 cm	TAH+BSO
2	Complex EH without atypia	46	Not requested	NA	1	<1/2	IA	<2 cm	TAH+BSO
3	Complex EH with atypia	55	Endometrial cancer	Low risk	1	<1/2	IA	<2 cm	TAH+BSO
4	Complex EH with atypia	48	Deferred for paraffin section	NA	1	<1/2	IA	<2 cm	TAH+BSO
5	Complex EH with atypia	50	Endometrial cancer	Low risk	1	<1/2	IA	<2 cm	TAH+BSO
6	Complex EH with atypia	62	Endometrial cancer	Low risk	1	<1/2	IA	<2 cm	TAH+BSO
7	Complex EH with atypia	72	Endometrial cancer	Low risk	1	<1/2	IA	<2 cm	TAH+BSO
8	Complex EH with atypia	67	Endometrial cancer	Not specified	2	>1/2	IIIA	<2 cm	TAH+BSO+LND
9	Complex EH with atypia	77	Endometrial cancer	Not specified	1	<1/2	IA	<2 cm	TAH+BSO
10	Complex EH with atypia	44	Benign	NA	1	<1/2	IA	<2 cm	TAH+BSO
11	Complex EH with atypia	70	Benign	NA	1	<1/2	IA	<2 cm	TAH+BSO
12	Complex EH with atypia	53	Benign	NA	1	<1/2	IA	<2 cm	TAH+BSO
13	Complex EH with atypia	49	Benign	NA	1	<1/2	IA	<2 cm	TAH+BSO
14	Complex EH with atypia	66	Not requested	NA	1	<1/2	IA	>2 cm**	TAH+BSO
15	Complex EH with atypia	70	Not requested	NA	1	>1/2	IB	>2 cm	TAH+BSO+LND
16	Complex EH with atypia	47	Not requested	NA	1	<1/2	IA	<2 cm	TAH+BSO

*According to pathologic evaluation of the total abdominal hysterectomy+bilateral salpingo-oophorectomy specimen in 14 patients
**Tumor limited to endometrium
FS: frozen section; NA: not applicable; EH: endometrial hyperplasia; TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oophorectomy; LND: lymph node dissection

(10) reported that the sensitivity of frozen section analysis for the detection of endometrial cancer among women with atypical hyperplasia was as low as 27%. The present study showed that the sensitivity of frozen section analysis for the detection of co-existent endometrial carcinoma in women with endometrial hyperplasia was 54.4% which means frozen section missed 5 out of 11 cancers. Our study found that the negative predictive value of frozen section analysis for the detection of EC in women with endometrial hyperplasia was 87.5% and therefore use of frozen section evaluation could not completely rule out the presence of co-existent endometrial cancer. Similarly, Turan et al. (23) found that negative predictive value for co-existent endometrial cancer in patients with complex atypical endometrial hyperplasia was only 76.7%.

On the other hand, in the current study, of the six patients who have been diagnosed to have co-existent endometrial cancer on frozen section analysis, only one had high-risk features and required surgical staging. In the study of Indermaur et al. (10), none of the patients with co-existent endometrial cancer diagnosed by frozen section analysis had high-risk features. Similarly, Merisio et al. (12) reported that of the patients with atypical endometrial hyperplasia, in only 2 out of 30 with co-existent endometrial carcinoma had deep myometrial invasion. Therefore, in women with endometrial hyperplasia, the co-existence of endometrial cancer is mostly occult and commonly has low-risk features. Accordingly, these patients rarely require comprehensive surgical staging.

These facts render the routine use of frozen section evaluation questionable because frozen section analysis may miss certain co-existent cancers. Furthermore, the information from frozen section analysis rarely affects the extent of surgery. According to our study, only 2 of the 189 patients (1.05%) had high-risk features necessitating comprehensive surgical staging. Therefore, performing staging to only 2 patients may be more feasible than requesting frozen section consultation for 189 patients. However, our study has some limitations include its retrospective design and small sample size.

In conclusion, a significant proportion of patients with atypical endometrial hyperplasia are diagnosed to have endometrial cancer following hysterectomy. However, most of these cases had low-risk features and did not require surgical staging. In addition, our study detected a low sensitivity levels of frozen section analysis for the detection of endometrial cancer among women with endometrial hyperplasia. Therefore, the role of intraoperative frozen section analysis is limited in the surgical management of patients with endometrial hyperplasia and these patients may be operated in settings where routine intraoperative frozen section is unavailable.

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