

The accuracy of frozen section analysis at hysterectomy in patients with atypical endometrial hyperplasia

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Summary

Purpose of investigation: To evaluate the accuracy of frozen section analysis in patients with atypical endometrial hyperplasia. **Methods:** Women who underwent hysterectomy with frozen section analysis for atypical endometrial hyperplasia were identified. Frozen section evaluation aimed to give information about the presence of malignancy. Also, myometrial or cervical involvement was assessed in cases with malignancy to reveal the need for staging. Final pathological evaluation results were compared with intraoperative frozen section analyses. **Results:** Twelve patients (34.3%) had endometrial cancer on final pathologic examination and eight required a staging procedure due to either myometrial invasion or cervical involvement; 75% of patients with endometrial cancer were successfully detected by frozen section analysis. Moreover, among women with cancer, frozen section examination revealed 75% of cases who required surgical staging. **Conclusion:** Frozen section analysis of hysterectomy specimens in patients with atypical endometrial hyperplasia is necessary to determine the presence of cancer and the need for surgical staging.

Key words: Frozen section; Endometrial hyperplasia; Atypical endometrial hyperplasia; Endometrial cancer; Surgical staging.

Introduction

Endometrial cancer (EC) is the most common gynaecological malignancy in developed countries [1]. Of the two major forms of EC with different clinicopathologic and prognostic characteristics, type I tumours are estrogen-related and are preceded by endometrial hyperplasia (EH) [2, 3].

EH is characterized by the nonphysiological proliferation of the endometrium that results in irregular shaped glands of varying sizes [4]. The diagnosis of EH is usually achieved through diagnostic evaluation of women with abnormal uterine bleeding by endometrial biopsy [5]. EH is categorized according to the architectural disruption and the presence or absence of cytological atypia. Thus, there are four types of EH in the World Health Organization classification including simple or complex hyperplasia with or without atypia [6]. The risk of progression of EH to EC is closely related to the presence of cytological atypia and to architectural crowding; 1.6% of patients with EH without atypia develop EC in a mean duration of nearly ten years while 23% of patients with atypical EH develop EC in four years [7]. Moreover, up to 50% of patients with atypical EH were reported to have coexistent EC with considerable rates of invasion beyond the endometrium [8]. Therefore, both preoperative pathological identification and intraoperative frozen section analysis are important since they closely guide clinical management which may be quite different depending on the presence of atypia and presence or absence of coexistent EC [9, 10].

The aim of this study was to retrospectively evaluate the accuracy of frozen section diagnoses of patients treated with total abdominal hysterectomy who had a preoperative diagnosis of atypical EH.

Materials and Methods

A review of the Hacettepe University Faculty of Medicine Gynaecology and Pathology database was performed to identify patients diagnosed with EH between January 2002 and June 2008.

Among 92 women with a preoperative diagnosis of atypical EH, 35 patients who subsequently underwent hysterectomy with frozen section analysis at our institution within four weeks following diagnosis were identified. The clinicopathologic characteristics of these patients were obtained using medical records.

All patients had undergone endometrial sampling via Karman aspiration or curettage with a diagnosis of abnormal uterine bleeding. After diagnosis, all patients initially underwent total abdominal hysterectomy with or without salpingo-oophorectomy and the specimen was sent for frozen section evaluation. The pathologist evaluated the specimen grossly and sampled abnormal endometrial areas for microscopic evaluation. During the frozen section examination, it was reported whether the specimen contained any areas consistent with EC or not. In cases detected with EC, it was also reported whether myometrial invasion greater than 50% or cervical involvement was present or not to guide the extent of surgery. In patients with myometrial invasion and/or cervical involvement, surgery was extended to include bilateral pelvic and paraaortic lymph node dissection and infracolic omentectomy in order to determine the surgical stage of disease. Further surgery was not performed in cases in whom endometrial cancer was reported to be confined only to the endometrium.

The results of final pathological evaluation were compared with intraoperative frozen section analyses to document the success of frozen section examination in diagnosing endometrial cancer in patients with atypical EH and in detecting the patients who required comprehensive surgical staging procedure.

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Table 1. — *Clinical and pathological characteristics of patients with atypical endometrial hyperplasia.*

Characteristic	
Age (mean, range):	
All patients	51.4 (35-77)
Patients without EC	48.5 (35-75)
Patients with EC	56.8 (42-77)
Presenting symptoms (n, %):	
PMB	13 (37.1)
Heavy and/or irregular menses	22 (62.9)
Preoperative diagnoses (n, %):	
Simple EH with atypia	2 (5, 7)
Complex EH with atypia	33 (94.3)
Surgery (n, %):	
TAH	3 (8.6)
TAH + BSO	26 (74.3)
Staging	6 (17.1)
EC at frozen (n, %):	
Present	9 (25.7)
Absent	26 (74.3)
EC at final pathology (n, %):	
Present	12 (34.3)
Absent	23 (65.7)

EC: Endometrial carcinoma; PMB: postmenopausal bleeding; EH: endometrial hyperplasia; TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oophorectomy; Staging: total abdominal hysterectomy + bilateral salpingo-oophorectomy + bilateral pelvic and paraaortic lymph node dissection + infracolic omentectomy.

Results

The mean age of the study group was 51.4 years (range 35-77). Endometrial sampling was performed for postmenopausal bleeding in 13 patients and for heavy and/or irregular menstrual bleeding in 22 premenopausal patients. The preoperative diagnoses were simple hyperplasia with atypia in two patients (5.7%) and complex hyperplasia with atypia in remaining 33 patients (94.3%) (Table 1).

Initially, 32 patients in the study group underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy and three underwent total abdominal hysterectomy. After frozen section evaluation, 29 patients (82.9%) did not undergo further surgical intervention while six (17.1%) were subjected to a comprehensive surgical staging procedure including bilateral pelvic and paraaortic lymph node dissection in addition to total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Twelve patients (34.3%) had EC on final pathologic examination. All EC cases were diagnosed as having complex hyperplasia with atypia preoperatively. Therefore, 36.4% of patients with a biopsy diagnosis of complex hyperplasia with atypia had EC at final pathology. Of patients with EC, eight were postmenopausal. EC was more common in postmenopausal patients (61.5% vs 18.2%, $p = 0.024$). Additionally, mean age of patients with EC was significantly higher compared with patients without EC (56.8 vs 48.5, $p = 0.014$).

Thirty-two of 35 frozen section diagnoses were consistent with final pathological diagnoses in detecting the presence of EC in patients with a preoperative diagnosis

of atypical EH. In this respect, the accuracy of frozen section examination was 91.4%.

On the other hand, among 12 patients with EC, nine were successfully detected by frozen section analysis with an accuracy of 75.0%. Six of these nine patients underwent staging surgery following EC diagnosis at frozen section. Interestingly, in two of these cases the tumour was found to involve the whole myometrium and uterine serosal surface which meant FIGO Stage 3a tumour, and therefore they were given adjuvant radiation. One patient in this group also had cervical stromal involvement and was given radiotherapy as well. The remaining three patients had well-differentiated EC with only superficial myometrial invasion and they were not given adjuvant therapy (Table 2).

Three patients who had a frozen section diagnosis of EC were not subjected to staging surgery because all were reported to have well differentiated EC confined only to the endometrium without apparent myometrial invasion on frozen section examination. Final pathologic examination also confirmed the frozen section diagnosis in two of these patients. However, one patient was diagnosed as having cervical stromal involvement and was given adjuvant radiotherapy since a restaging procedure was rejected by the patient (Table 2).

Table 2. — *Clinical and pathologic characteristics of patients with endometrial carcinoma.*

Patients	Age	EC at Frozen Section	Details Frozen Section Analysis	Operation	Final Stage	Final Grade	Additional Therapy
Case 1	46	Absent	No EC	TAH+BSO	2a*	1	RT
Case 2	62	Absent	No EC	TAH+BSO	1a*	1	None
Case 3	64	Absent	No EC	TAH+BSO	1a*	1	None
Case 4	48	Present	G1 EC confined to endometrium	TAH+BSO	2b*	2	RT
Case 5	52	Present	G1 EC confined to endometrium	TAH+BSO	1a*	1	None
Case 6	42	Present	G1 EC confined to endometrium	TAH+BSO	1a*	1	None
Case 7	57	Present	G1 EC with DMI	Staging	3a	1	RT
Case 8	67	Present	G1 EC with DMI	Staging	3a	2	RT
Case 9	55	Present	G1 EC with MI	Staging	1b	1	None
Case 10	62	Present	G1 EC with cervical involvement	Staging	2b	2	RT
Case 11	77	Present	G1 EC with MI	Staging	1b	1	None
Case 12	50	Present	G1 EC with MI	Staging	1b	1	None

*According to findings in hysterectomy specimen without a comprehensive surgical staging procedure.

G: grade; EC: endometrial carcinoma; MI: myometrial invasion; SMI: superficial myometrial invasion; DMI: deep myometrial invasion; TAH + BSO: total abdominal hysterectomy + bilateral salpingo-oophorectomy; Staging: total abdominal hysterectomy + bilateral salpingo-oophorectomy + bilateral pelvic and paraaortic lymph node dissection + infracolic omentectomy; RT: radiotherapy.

Frozen section analysis failed to diagnose EC in three of 35 cases (8.6%). The endometrium was reported to be free of malignancy at frozen section examination. However, well differentiated ECs were diagnosed at final pathologic examination. The disease was confined to endometrium in two patients who did not receive adjuvant treatment. The third patient had EC with cervical glandular involvement and received adjuvant radiotherapy because the patient was a poor candidate for a restaging procedure due to uncontrolled medical problems (Table 2).

In 12 patients with EC at final pathology, a staging procedure was required in eight due to either myometrial invasion or cervical involvement. Frozen section successfully documented six of them. In this respect, the success of frozen section examination was 75%. One of the missed cases had cervical glandular involvement and the other had cervical stromal involvement.

Discussion

EH is the precursor lesion of EC which is the most commonly seen malignancy of the female genital tract [1-3]. The management of women with EH is mostly influenced by the age and fertility desire of the patient and presence or absence of cytological atypia. Nevertheless, the principal concern in these patients is the risk of having a coexistent EC or progression to EC [11]. Cytological atypia is the most important feature in EH for the development or coexistence of EC [12]. Up to 50% of patients with atypical EH were reported to have coexistent EC [8]. Given the noteworthy risk of detecting a coexistent EC in women with atypical EH, some may consider a routine staging surgical procedure for all of these patients. However, it is estimated that routine surgical staging in all patients with atypical EH would be associated with a 20% complication rate and a 6% rate of serious complications which is a higher percentage than the risk of lymph node involvement [13]. In our series, 34.3% of patients with atypical EH and 36.4% of patients with complex atypical EH had EC at final pathology. Therefore, although the surgical approach is the more commonly preferred treatment method when atypical EH is diagnosed, surgical management of women, namely the extent of surgery, is frequently influenced by intraoperative frozen section analysis. The decision to perform a comprehensive surgical staging including bilateral salpingo-oophorectomy and lymph node dissection can only be determined by the presence or absence of malignant endometrial disease on frozen section analysis [10, 11]. Otherwise, the surgeon might be obliged to perform a restaging surgery exposing the patient to the risk of a second invasive procedure. Also, some legal and ethical issues related with the over-treatment or under-treatment of patients may arise.

The limitations of frozen section appear to be highly important from this point of view but in the current literature the data on the accuracy of frozen section at time of hysterectomy is limited. In one series of 46 women who

underwent hysterectomy for atypical EH, frozen section failed to diagnose 50% of EC [14]. In another series, the accuracy of frozen section diagnosis for endometrial adenocarcinoma in patients with complex atypical EH was 65%. According to their results, the authors characterised frozen section as an unreliable tool in determining the definitive decision of management [10]. Nevertheless, the availability of a pathologist specifically experienced in gynaecological pathology is an important issue in frozen section analysis due to the fact that there are a range of abnormalities seen in hyperplastic endometrium and differentiation between them may be quite difficult [11]. There is considerable interobserver and intraobserver variation in the diagnosis of EH even in biopsy specimens [15-17]. Only pathologists with frequent exposure to such specimens are likely to be proficient in reporting results of these specimens [11]. In the current study, the accuracy of frozen section diagnoses was 91.4% in detecting the presence or absence of EC. Moreover, frozen section examination detected 75% of cases with EC. To the best of our knowledge, such a high detection rate has not been reported in the English literature up to date. The frozen section analysis in our study group was performed by a gynaecological pathologist studying specifically specimens originating from gynaecology clinics who is often exposed to such specimens. The high detection rate of EC in our series of patients with atypical EH may essentially be attributed to the proficiency of the pathologist.

It was reported that EC confined to the endometrium may be missed during frozen section [13]. However, gross evaluation of hysterectomy specimens was reported to accurately predict myometrial invasion in 88.2% of patients [18]. Two of four cases with grade 1 EC confined only to the endometrium were missed in our series. However, neither restaging nor adjuvant therapy is required in such patients. Therefore missing these women during frozen section analysis may be acceptable since lymph node involvement was detected in less than 1% of patients. Nonetheless, detecting the presence of myometrial invasion at frozen section is much more important because lymphatic spread is considerable in this situation. In cases with myometrial invasion, the risk of lymphatic involvement is 5% or higher and a staging surgery including lymph node dissection should be performed [19]. Myometrial invasion was detected in 75% and 89% of patients with atypical EH having coexistent EC in two different studies [8, 20]. In the current series, all five patients with myometrial invasion of different degrees were successfully diagnosed at frozen examination.

Eight cases with EC in our series required surgical staging due to either myometrial invasion or cervical involvement. Frozen section successfully detected six of them. In this respect, the success of frozen section examination was 75%. Both the missed cases had cervical involvement. In fact, two of three cases with cervical involvement could not be detected. Therefore, in addition to the myometrium, the uterine cervix should also be inspected carefully in such cases during frozen analysis.

Also, in patients with abnormal uterine bleeding, endocervical sampling should be performed in addition to endometrial sampling to detect cervical invasion of an endometrial tumour. When cervical involvement is documented preoperatively, the patient should undergo radical hysterectomy to eliminate the necessity of postoperative adjuvant radiotherapy.

Moreover, the missed cases in the current study were under-diagnosed on frozen examination; none of the cases were over-diagnosed. Therefore, the surgeon may safely make a decision of performing a staging procedure when the frozen section diagnosis is EC with myometrial or cervical spread.

In patients with a preoperative diagnosis of atypical EH, the clinician should also remember that some patients will have tumors with higher grades. Janicek *et al.* reported grade 2 or 3 lesions in 21% of patients [20]. In our study group, although none of the cases had grade 3 lesions, three (25%) had grade 2 tumours. Thus, advanced stages and higher grades may be expected frequently in patients with atypical EH.

Conclusion

The diagnosis of atypical EH carries a considerable risk of a coexistent EC. Therefore, frozen section analysis of hysterectomy specimens in such patients is necessary to determine cases having EC and cases with EC requiring surgical staging. The accurate detection of EC may be possible especially in the presence of a pathologist specifically experienced in gynaecological pathology. Thus, at least, cases with myometrial invasion who have a risk of extrauterine spread are detected and staging surgery is completed in the same setting. Additionally, it should always be kept in mind that advanced stage and high grade diseases may be detected more than expected in patients with a biopsy diagnosis of atypical EH. Therefore, the patients should undergo surgery in centers where a gynaecological oncologist is available and a staging surgery can be completed. This approach can prevent morbidities resulting from over-treatment and medico-legal issues resulting from under-treatment.

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