RESEARCH COMMUNICATION

Accuracy of Frozen Sections for Intraoperative Diagnosis of Complex Atypical Endometrial Hyperplasia

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Abstract

Objective: The purpose of this study was to correlate the histological diagnosis made during intraoperative frozen section (FS) examination of hysterectomy samples with complex atypical endometrial hyperplasia (CAEH) diagnosed with definitive paraffin block histology. Methods: FS pathology results of 125 patients with a pre-operative biopsy showing CAEH were compared retrospectively with paraffin block pathology findings. Results: Paraffin block results were consistent with FS in 78 of 125 patients (62.4%). The FS sensitivity and specificity of detecting cancer were 81.1% and 97.9%, with negative and positive predictive values of 76.7%, and 98.4%, respectively. Paraffin block results were reported as endometrial cancer in 77 of 125 (61.6%) patients. Final pathology was endometrial cancer in 45.3% patients diagnosed at our center and 76.9% for patients who had their diagnosis at other clinics (p=0.018). Paraffin block results were consistent with FS in 62.4% of all cases Consistence was 98.4% in patients who had endometrial cancer in FS. Conclusion: FS does not exclude the possibility of endometrial cancer in patients with the preoperative diagnosis of CAEH. In addition, sufficient endometrial sampling is important for an accurate diagnosis

Keywords: Complex atypical endometrial hyperplasia - endometrial cancer - frozen section

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Introduction

Adenocarcinoma of the endometrium is the most common gynecological cancer (Jemal et al., 2003). The disease is staged surgically and this includes total hysterectomy, bilateral salphingo-oophorectomy, pelvic and para-aortic lymphadenectomy and peritoneal cytology (Larson et al., 1992).

Endometrial hyperplasia is classified into four different categories; simple hyperplasia with or without cytological atypia and complex hyperplasia with or without cytological atypia. The rate of progression to endometrial carcinoma has been estimated to be 0-3% in patients without atypia, 0-8% in patients with simple atypical hyperplasia, and 9-29% in patients with complex atypical endometrial hyperplasia (CAEH) (Kurman et al., 1985; Tabata et al., 2001). The risk of concomitant endometrial carcinoma has been reported to be 20-59% in CAEH (Lambert et al., 1994; Kimura et al., 2003; Valenzuela et al., 2003; Antonsen et al., 2012; Morotti et al., 2012). In addition to, the distinction between atypical endometrial hyperplasia and well differentiated adenocarcinoma of the endometrium is one of the more difficult differential diagnoses in gynecologic pathology (Mills & Longacre, 2011).

Frozen section (FS) is used to identify patients at high risk, including poorly differentiated tumor grade, deep myometrial invasion, and cervical extension of the tumor. In the literature studies about the accuracy of FS are limited. Some studies reported low accuracy rate of FS (Bilgin et al., 2004; Indermaur et al., 2007).

The aim of this study was to evaluate the accuracy of FS in comparison with final pathology to determine reliability of FS for directing the surgical management of endometrial cancer.

Materials and Methods

This study was retrospectively performed between 1993 and 2010 at our Gynecologic Oncology Department. The study was approved by our institutional review board. Medical data were collected from 125 patients treated in our clinic and evaluated retrospectively. Clinical and pathological information was obtained from patient charts. The patients were staged according to 2009 FIGO criteria.

Preoperative Analysis

Diagnosis of the patients was carried out by pipelle biopsy in five patients (4%) while the remaining patients were diagnosed by fractional dilation and curettage (D&C). Pathologic specimens which were identified as complex atypical hyperplasia by other centers were examined again and the diagnosis was confirmed. All cases diagnosed using WHO criteria as endometrial

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hyperplasia or endometrial carcinoma were scored for degree of glandular crowding, architectural complexity and cytological atypia.

Frozen Section Analysis

The uterus was opened and the cavity was inspected for irregularities of counter and color. Then 2-5 full-thickness slices were made through the wall of the uterus. The area of deepest myometrial invasion was selected for FS examination. If no tumor was apparent on gross examination, at least 5 random sections were performed. All of the samples were frozen at -25ºC, were cut to 8μ in thickness and stained with hematoxylin and eosin manually. In the cancer cases, samples were evaluated in terms of grade, the depth of myometrial invasion, lymphovascular space invasion and the size of tumor. Any suspicious lesions were detected grossly in cervix and adnexia were sampled for FS analysis.

After FS the remaining tissue was formalin fixed and paraffin embedded for further histopathological analyses. Bilateral pelvic and para-aortic lymphadenectomy was performed for staging the patients according the results of FS. The staging criteria were as follows: high tumor grade, deep myometrial invasion (≥½), cervical extension, primary tumor diameter >2cm, non-endometrioid histological type.

Statistical Analysis

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated with 95% confidence intervals (CIs) for each parameter. The correlation between FS and final pathology was calculated as $\varkappa$ coefficient. The data were analyzed by using SPSS (Statistical Package for Social Sciences) 17.0 for Windows and differences were considered as significant when $P < 0.05$.

Results

A total of 125 consecutive patients with CAEH were included in this study. The mean age of the patients was 54.4 years with a range of 32 to 83 years. Sixty-five patients were menopausal. D&C was performed to 86 patients in our hospital and 39 patients in other clinics and all of these patients' diagnosis was confirmed by our pathologists. The characteristics of all cases and cancer cases are shown in Table 1. The median time interval between D&C and operation was 20 days (5-152 days) (Table 1).

Paraffin block results were reported as endometrial cancer in 77 of 125 (61.6%) patients. Final pathology was endometrial cancer in 47 of 86 (45.3%) patients who diagnosed at our hospital while 30 of 39 (76.9%) patients who had their diagnosis at other clinics (p=0.018). Histopathologic diagnosis was endometrioid type in 74 of 77 patients and mixed type in three of 77 patients. Seventy-four patients had grade 1 and three patients had grade 2 endometrial tumor. Myometrial invasion was detected in 44 patients and seven of these patients had ≥½ myometrial invasion. Thirteen patients (10.4%) were staged surgically according to the results of FS and only one patient had pelvic lymph node metastases. After surgical staging 69 patients had stage IA, seven patients had stage IB and one patient had stage $IIIC_2$ tumor, histopathologic diagnosis was endometrioid type of this stage $IIIC_2$ tumor and external radiotherapy was given as adjuvant treatment to this patient. But the disease was recurred in pelvic, upper abdominal region and in lung after nine months from surgery. Paclitaxel + carboplatin combination was given to the patient as salvage chemotherapy. However, the disease showed progression and the patient died after 21 months from the operation.

Table 1. General Features of All Patients and Cancer Patients

Parameters		All patients		Cancer patients	
		Mean/ n	(%)	Mean/ n	(%)
Age (years):		54.4	32-83	57.6	32-83
Operation time interval between dilatation & curettage and operation (days)		24.3	5-152	19.2	5-127
Menopausal status:					
	Not in menopause	60	48.0	27	35.1
	Menopausal	65	52.0	50	64.9
Paraffin blocks result:					
	Benign	48	38.4		
	Malignant	77	61.6	77	100
Cell Type:	Endometrioid	74	59.2	74	96.1
	Mixed type	3	2.4	3	3.9
The depth of myometrial invasion:					
	Only the endometrium	33	26.4	33	42.9
	<½	37	29.6	37	48.1
	≥½	7	5.6	7	9.1
Grade:	1	74	59.2	74	96.1
	2	3	2.4	3	3.9
Stage:	IA	69	55.2	69	89.6
	IB	7	5.6	7	9.1
	IIIC2	1	0.8	1	1.3
Surgery:	TAH+BSO	112	89.6	64	83.1
	Staging procedure	13	10.4	13	16.9

From 48 paraffin block results that not considered as endometrial cancer, 10 of them classified as normal endometrium, 13 as simple atypical hyperplasia, three as complex non-atypical hyperplasia and 22 as complex atypical hyperplasia.

Paraffin block results were consisted with FS in 78 patients (62.4%) (Table 2). Consistence was highest in patients who had endometrial cancer in FS. Paraffin block results were reported as cancer in 60 of 61 (98.4%) patients which was considered as cancer in FS. Other patients' paraffin block results were complex atypical hyperplasia. Paraffin block was resulted as cancer; in one patient from 27 patients (3.7%) which had no malignancy (normal or simple hyperplasia) in FS, in 12 patients from 29 patients (41.4%) which had CAEH in FS, in three patients from four patients which the pathologist could not distinguish between endometrial cancer and FS. Also paraffin block was reported as cancer in one patient which had complex hyperplasia without atypia in FS.

The sensitivity and specificity of detecting cancer in FS were 81.1%, 97.9% and NPV and PPV were 76.7%, 98.4% respectively.

Diagnosis of endometrial cancer was missed in 14 patients with FS. All of these patients had grade

Table 2. The Results of Frozen/Section and Paraffin Blocks

Frozen	Paraffin block results				
	Normal	Hyperplasia without atypia		Complex hyperplasia with atypia	Cancer
		Simple	Complex		
Normal	7 (26%)	11 (41%)	1 (4%)	7 (26%)	1 (4%)
Simple hyperplasia (atypia)					
without	1 (50%)	0	0	1 (50%)	0
with	0	0	0	1 (100%)	0
Complex hyperplasia (atypia)					
without	0	0	0	0	1 (100%)
with	2 (7%)	2 (7%)	2 (7%)	11 (38%)	12 (41%)
Cancer	0	0	0	1 (2%)	60 (98%)
Cannot rule out Endometrial Cancer					
	0	0	0	1 (25%)	3 (75%)
Total	10 (8%)	13 (10%)	3 (2%)	22 (18%)	77 (62%)

1 endometrioid type cancer, 12 of 14 patients had no myometrial invasion and the other two patients had <½ myometrial invasion so staging surgery did not performed to these patients.

Discussion

The distinction of atypical hyperplasia from well-differentiated endometrioid carcinoma is important for clinical management, both for consideration of maintaining fertility in reproductive-age patients and for planning appropriate surgical therapy when preservation of fertility is not an issue.

The risk of concomitant endometrial carcinoma has been reported to be 20-59% in CAEH (Janicek & Rosenheim, 1994; Trimble et al., 2006; Antonsen et al., 2012). FS identifies the patients who are at high risk for extrauterine spread and often surgical management of patients with preoperative diagnosis of endometrial CAEH is influenced by intraoperative FS. Decisions such as a need for surgical staging can be determined by the presence or absence of invasive disease on FS. Certainly defining the limitations of FS is very important. In our study, the underlying adenocarcinoma rate was 61.6% in patients with preoperatively diagnosed as CAEH. Final pathology was endometrial cancer in 45.3% of patients which had diagnosed in our clinic while 76.9% patients which had diagnosed in other clinics. We are not performed second D&C to these types of patients because we routinely use FS analysis to all CAEH in our clinic. Endometrial sampling should be sufficient for an accurate diagnosis. Also the diagnosis of CAEH has trouble in itself. Current WHO classification of endometrial hyperplasia is problematic because of poor diagnostic reproducibility. The wide range of histomorphologic presentation of endometrial hyperplasia is accompanied by high intra and interobserver variability in diagnostic classification. In a study complete diagnostic agreement of CAEH was achieved by three pathologists in only 40% of cases (Zaino et al., 2006).

Twenty-six patients' final pathology was downgraded to complex non-atypical hyperplasia, simple hyperplasia or normal endometrium. These results suggest that the lesion was taken totally by D&C in these 26 patients.

In this study, the compatibility between frozen section and paraffin block results was 62.4% for histopathological diagnosis. NPV was %76.7 and PPV was %98.4. In our study tumor could not be determined with high rates by FS.

In our study 14 patients with endometrial cancer were missed with FS and all of these patients had grade 1 endometrioid type cancer and 12 of 14 patients had no myometrial invasion. Endometrial cancer often shows well differentiated and superficial infiltration in CAEH so lesions are usually not observed grossly in FS. Therefore in this group of patients sections were taken randomly in FS. This is one of the factors leading to the insufficiency of FS and may be an explanation for 14 missed endometrial cancer diagnosis in our study. Dankwa and Davies (1985) states that focal tumor focus constitutes the inevitable error group in FS. In the cases where the gross tumor can't be seen in the limited number of sections, tumor may be overlooked. This condition explains the high rate of inconsistency and underestimates in FS. The size of specimen, insufficient time for examination, problematic transfer of specimen to the pathology laboratory (like the ambient temperature), the bleeding time of uterus, the presence of atrophic endometrium, the cell type and grade level, the number of sections received and the presence of experienced pathologists are the limitations of FS. Moreover, it is very difficult to evaluate myometrial invasion if the tumor is located at cornual area or adenomyotic lesions (Fanning et al., 1990).

In conclusion; on CAEH three points of major consequence were found. The first, FS examination is a necessity to avoid from incomplete surgery in CAEH, although it is not a good predictor to rule out endometrial cancer in CAEH. Secondly, another result of our study was sufficient endometrial sampling is needed for an accurate diagnosis. And the last, because of the risk of concomitant endometrial carcinoma is very high; patients with atypical hyperplasia of the endometrium should be treated in oncological centers.

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The authors declare no conflict of interest

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