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Original article

Accuracy of frozen section in management and prediction of lymph node metastasis in endometrial carcinoma

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ABSTRACT

Objective: This study aimed to investigate clinical factors affecting the concordance between frozen section (FS) and paraffin section (PS) findings in endometrial cancer, and evaluate the role of FS in predicting lymph node (LN) metastases.

Methods: Tumor grade and depth of myometrial invasion based on FS and PS findings were compared in 376 patients. Clinical factors affecting the accuracy of FS in predicting LN metastasis were evaluated. Overall survival was compared between patients who underwent lymphadenectomy and those who did not.

Results: Overall concordance of tumor grade was 78.6% (147/187). Later age at menopause ($p = 0.011$) and a lower systolic/diastolic ratio of endometrial blood flow ($p = 0.015$) were associated with high concordance between FS and PS for tumor grade. Overall concordance for the depth of myometrial invasion was 97.8% (178/182). There was greater concordance between FS and PS for myometrial invasion in patients with postmenopausal bleeding ($p = 0.018$) and lower abdominal pain ($p = 0.013$). G1 and G2 + no myometrial invasion predicted no metastasis; G1 + <1/2 myometrial invasion predicted a 2.4% risk of both pelvic LN and para-aortic LN metastasis. G2 + <1/2 myometrial invasion predicted a 4.8% risk of pelvic LN metastasis. Patients undergoing lymphadenectomy showed relatively longer survival than those without lymphadenectomy ($p = 0.086$).

Conclusion: The accuracy of FS in determining tumor grade and myometrial invasion appears to be reliable. LN metastases cannot be predicted adequately by intraoperative FS. We recommend complete surgical staging for all patients with endometrial cancer.

Introduction

Endometrial cancer is one of the most common malignancies of the female genital tract, and its incidence in China is similar to that reported in the United States.[1] Comprehensive surgical staging is the cornerstone of management in endometrial cancer.[2] Pathology results, including preoperative endometrial biopsy, intraoperative frozen section (FS), and postoperative paraffin section (PS), are used to determine the management of endometrial cancer at three stages. Preoperative assessments consist of endometrial biopsy, fractional dilation and curettage (D&C), and hysteroscopy, and provide an initial diagnosis to clinicians. However, pathologic findings obtained from preoperative intervention often differ from the final pathology.[3–5] Our previous study showed that the overall concordance between D&C and final pathology was only 35.2% (62/176) for tumor grade.[3] Intraoperative FS can detect the tumor grade, depth of myometrial invasion, histologic subtype, and cervical extension of the tumor. During surgery, FS is the only way to identify the subgroup of patients who have a high risk of extrauterine metastases and to direct comprehensive surgical staging.

Postmenopausal bleeding is the initial symptom in most endometrial cancer patients. Thus, approximately 75% of all cases undergoing endometrial biopsy are diagnosed at early Stage I and have an excellent prognosis. The overall 5-year survival rate is 80–90%.[6,7] The Gynecologic Oncology Group (GOG-33) study verified that the incidence of lymph node metastasis is very low in most of the early-stage endometrial cancers.[6] Although lymph node involvement has been proved to be the most significant prognostic factor, the role of lymphadenectomy in the surgical

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management of early-stage endometrial cancer remains controversial.[8] The issue is whether or not lymph node invasion can be predicted pre- or intraoperatively. When a "high risk" of lymph node metastases is detected, comprehensive surgical staging should be performed; otherwise, lymphadenectomy may be omitted. The risk of lymph node metastasis is directly related to high grade of tumor and deeper invasion into the myometrium.

In this study, we retrospectively compared the results of intraoperative FS and postoperative PS, and explored clinical factors affecting the concordance between FS and final pathology. The role of FS in predicting lymph node metastases was also evaluated.

Materials and methods

Medical documents for 389 patients with abnormal uterine bleeding, who underwent D&C or hysteroscopy from July 1996 to January 2008 at Renji Hospital affiliated to Shanghai Jiao Tong University ($n = 170$) and from September 2008 to September 2011 at Shanghai First Maternity & Infant Hospital affiliated to Tongji University ($n = 219$), were reviewed retrospectively. Patients who had undergone previous pelvic radiation or had clinically advanced disease, coexisting second malignancy, and uterine sarcoma were excluded. This study was approved by the institutional review board of both the universities.

The indication for surgical treatment was endometrial cancer or complex endometrial hyperplasia with atypia. A total of 376 patients were managed by surgery, and FS was performed in 220 of them. The primary surgical procedure was total or radical hysterectomy and bilateral salpingo-oophorectomy. When the uterus was removed, the surgeons observed the dimension of foci and depth of myometrial invasion, and then the uterus was submitted to the Department of Pathology for FS assessment. The uterus was bivalved, and the endomyometrium was sliced transversely at 4–5 mm intervals. One full-thickness section of the endometrial wall at the point of deepest invasion was submitted for microscopic examination. Sections of 5 μm were cut by a Cryotome E (Artmoor, Runcorn, UK), mounted on a glass slide, stained with hematoxylin–eosin, and dehydrated. Full thickness was evaluated on one slide, and cervical involvement was evaluated on another slide. The sections were microscopically evaluated by two pathologists within 30 minutes.

Based on FS results, patients considered to be at risk of metastatic disease, such as Grade 3 tumor or >1/2 myometrial invasion, underwent lymph node dissection.

Statistical analysis

The Mann–Whitney test and χ^2 tests were used for categorical variables and the likelihood ratio calculation, respectively. A two-tailed Student t test was used to calculate the means of continuous variables. A value of $p < 0.05$ was considered statistically significant. Kaplan–Meier survival analysis was used to measure overall survival of patients with or without lymph node dissection. Those statistical analyses were processed with SPSS statistical software version 15.0 (SPSS, Inc., Chicago, IL, USA).

Results

Among 389 patients, 327 were diagnosed to have endometrial cancer or complex atypical endometrial hyperplasia by D&C and 50 were diagnosed by hysteroscopy preoperatively. The mean age of the 389 patients was 57.74 ± 9.52 years (range 26–85 years), the mean age of menarche was 14.99 ± 1.59 years, and 232 had undergone menopause at a mean age of 51.06 ± 4.16 years. The presenting symptoms in these 389 patients were as follows: postmenopausal bleeding in 232 patients (59.6%), which occurred at a median time of 108.4 months after menopause; abnormal perimenopausal bleeding in 11 patients (2.8%); menstrual disorders, including irregular menstrual cycle, prolonged bleeding, and menorrhagia in 95 patients (24.4%); and profuse vaginal discharge in 60 patients (15.4%). The other 51 patients (13.1%) were asymptomatic, but endometrial thickening and intrauterine neoplasm were detected by B ultrasound.

A total of 376 patients underwent radical hysterectomy and bilateral salpingo-oophorectomy, with pelvic lymph node dissection in 197 patients or simultaneously with para-aortic lymph node dissection in 41 (43) patients. It was found that 266 patients (70.7%) in IA, 39 patients (10.4%) in IB, 22 patients (5.9%) in IIA, six patients (1.6%) in IIB, 10 patients (2.7%) in IIIA, two patients (0.5%) in IIIB, 17 patients (4.5%) in IIIC, one patient (0.3%) in IVA, and 13 patients (3.5%) in IVB were based on FIGO 2009 surgical staging system. In all, 345 (90.3%) patients had type I adenocarcinoma; the other 37 patients had type II endometrial carcinoma, including 24 patients with papillary serous carcinoma, six with clear cell carcinoma, five with adenosquamous carcinoma, and two with squamous carcinoma. Among 197 patients undergoing lymph node resection, 22 (11.3%) presented with pelvic lymph node metastasis and five (12.2%) with para-aortic lymph node metastasis.

Comparison of tumor grade between FS and PS

Table 1 summarizes the results of histologic grade concordance between FS and PS. Among the patients in whom the final pathologic diagnosis was endometrial cancer or atypia, the overall concordance rate of tumor grade was 78.6% (147/187). Accuracy was highest for Grade 3 (95.2%) and lowest for Grade 2 (60.6%). Based on the final pathology, a total of 32 patients (17.1%) were upgraded and eight (4.3%) downgraded.

Comparison of depth of myometrial invasion between FS and PS

Myometrial invasion was assessed in 182 patients (Table 2). The overall concordance between intraoperative FS and PS was 97.8% (178/182). Among the 182 cases, only four showed discordance. These findings suggest that FS was reliable for the assessment of tumor invasion.

Histologic grade and depth of myometrial invasion were believed to be the most important prognostic factors for lymph node metastasis. Table 3 shows the correlation between tumor grade and depth of myometrial invasion. Among the patients with ≥1/2 myometrial invasion, the total percentage of Grade 2 and 3 tumors was 75.3%, and the percentage of Grade 1 was 24.7%. In cases with <1/2 invasion, the percentage of Grade 3 was only 10.5%. Thus, a poorly differentiated tumor grade implied aggressive tumor invasion into the myometrium.

Table 1
Comparison of tumor grade between intraoperative frozen section and postoperative paraffin section [n (%)].

Frozen section	Paraffin section				
	Atypia	G1	G2	G3	Total
Atypia	6 (85.7)	8 (9.1)	3 (4.2)	0	17 (9.1)
G1	0	78 (88.6)	20 (28.2)	0	98 (52.4)
G2	0	1 (1.1)	43 (60.6)	1 (4.8)	45 (24.1)
G3	1 (14.3)	1 (1.1)	5 (7.0)	20 (95.2)	27 (14.4)
Total	7 (100.0)	88 (100.0)	71 (100.0)	21 (100.0)	187 (100.0)

G = grade; n = number of patients.