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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.

Table 2
Comparison of myometrial invasion between intraoperative frozen section and postoperative paraffin section [*n* (%)].

Paraffin section			
Frozen section	<1/2	≥1/2	Total
<1/2	144 (99.3)	3 (8.1)	147 (80.8)
≥1/2	1 (0.7)	34 (91.9)	35 (19.2)
Total	145 (100.0)	37 (100.0)	182 (100.0)

Table 3
Correlation of tumor grade and myometrial invasion [*n* (%)].

Tumor grade	Myometrial invasion		
	<1/2	≥1/2	Total
G1	114 (44.2)	18 (24.7)	132 (39.9)
G2	117 (45.3)	32 (43.8)	149 (45.0)
G3	27 (10.5)	23 (31.5)	50 (15.1)
Total	262 (100.0)	74 (100.0)	336 (100.0)

Clinical factors affecting the accuracy of FS

According to concordance of histologic grade and depth of myometrial invasion between FS and PS, patients were divided into concordance and discordance groups. More than 50 clinical factors were compared, and some with clinical significance are shown in Table 4. The presence of postmenopausal bleeding was related to higher concordance between FS and PS for myometrial invasion ($p = 0.018$). In the comparison of histologic grades between FS and PS results, the mean age at menopause was 51.7 ± 3.3 years in the concordance group and 49.3 ± 7.3 years in the discordance group, which reached a statistical difference ($p = 0.011$). The systolic/diastolic ratio of endometrial blood flow was 2.0 ± 0.5 in the concordance group, which was significantly lower than that of 2.3 ± 0.5 in the discordance group ($p = 0.015$). Apparently, later age at menopause and a lower systolic/diastolic ratio of endometrial blood flow were associated with the higher concordance of FS in tumor grade. Age at menarche, delivery number, endometrial thickness, and dimension of neoplasm had no effect on the accuracy of FS in determining both tumor grade and myometrial invasion.

Role of FS in predicting lymph node metastasis

Depending on the presence of high-risk factors for lymph node involvement at intraoperative FS, lymphadenectomy was performed. According to FS results, no positive lymph nodes were found in patients with atypia. Three (4.8%) of 62 patients with Grade 1, two (6.9%) of 29 patients with Grade 2, and two (10%) of 20 patients with Grade 3 had nodal metastasis. The incidence of lymph node metastases was 3.6% (3/81) in patients with <1/2 myometrial invasion and 12% (3/22) in patients with 50% or more (≥1/2) myometrial invasion.

Grade 3 tumor and ≥1/2 myometrial invasion are considered to be indicative of a high risk of lymph nodal involvement. The results of using these two variables, based on FS assessment, to predict lymph node metastasis are shown in Table 5. The sensitivity was 29.4% for G3 and 15.8% for ≥1/2 myometrial invasion, with the corresponding specificity being 85.8% and 80.5%, respectively.

Intraoperative predictors combining FS assessment of histologic grade and depth of myometrial invasion were established. Four models were designed to predict lymph node metastasis, excluding patients with Grade 3 tumors and ≥1/2 myometrial invasion. The incidence of lymph node metastasis by those models is shown in

Table 4
Comparison of clinical factors between concordance and discordance groups (%).

	Tumor grade		Myometrial invasion	
	Concordance	Discordance	Concordance	Discordance
Age (y)				
<70	133 (67.9)	63 (32.1)	155 (96.9)	5 (3.1)
≥70	19 (82.6)	4 (17.4)	22 (100.0)	0 (0.0)
p	0.230		0.521	
Postmenopausal bleeding				
Yes	87 (73.7)	31 (26.3)	99 (100.0)	0 (0.0)
No	65 (64.4)	36 (35.6)	78 (94.0)	5 (6.0)
p	0.144		0.018	
Lower abdominal pain				
Yes	17 (68.0)	8 (32.0)	19 (86.4)	3 (13.6)
No	135 (69.6)	59 (30.4)	158 (98.8)	2 (1.2)
p	0.518		0.013	
Vaginal discharge				
Yes	136 (69.7)	59 (30.3)	155 (98.1)	3 (1.9)
No	16 (66.7)	8 (33.3)	22 (91.7)	2 (8.3)
p	0.815		0.130	
Neoplasm dimension				
<25 mm	34 (65.4)	18 (34.6)	42 (95.5)	2 (4.5)
≥25 mm	21 (77.8)	6 (22.2)	24 (96.0)	1 (4.0)
p	0.309		0.704	
RI				
<0.5	24 (80.0)	6 (20.0)	24 (88.9)	3 (11.1)
≥0.5	20 (60.6)	13 (39.4)	31 (96.9)	1 (3.1)
p	0.108		0.323	
Histologic type				
I	142 (71.4)	57 (28.6)	161 (97.0)	5 (3.0)
II	9 (50.0)	9 (50.0)	15 (100.0)	0 (0.0)
p	0.067		0.646	
Cervical involvement				
Yes	24 (77.4)	7 (22.6)	29 (96.7)	1 (3.3)
No	127 (67.9)	60 (32.1)	148 (97.4)	4 (3.6)
p	0.401		0.598	
Lymph node number				
<20	61 (74.4)	21 (25.6)	72 (94.7)	4 (5.3)
≥20	46 (70.8)	19 (29.2)	56 (98.2)	1 (1.8)
p	0.710		0.391	
Gross depth of invasion				
No	3 (33.3)	6 (66.7)	8 (100.0)	0 (0.0)
<1/2	13 (76.5)	4 (23.5)	13 (92.9)	1 (7.1)
≥1/2	12 (92.3)	1 (7.7)	12 (100.0)	0 (0.0)
p	0.013*		>0.99	
Tumor grade				
Atypia	6 (46.2)	7 (53.8)	4 (100.0)	0 (0.0)
G1	75 (78.1)	21 (21.9)	83 (98.8)	1 (1.2)
G2	42 (60.0)	28 (40.0)	66 (98.5)	1 (1.5)
G3	19 (82.6)	4 (17.4)	17 (85.0)	3 (15.0)
p	0.008*		0.027	
Myometrial invasion				
<1/2	98 (76.0)	31 (24.0)	143 (98.6)	2 (1.4)
≥1/2	30 (76.9)	9 (23.1)	34 (91.9)	3 (8.1)
p	0.002*		0.058	
ER				
Positive	39 (69.6)	17 (30.4)	52 (100.0)	0 (0.0)
Negative	11 (78.6)	3 (21.4)	11 (91.7)	1 (8.3)
p	0.742		0.187	
PR				
Positive	33 (66.0)	17 (34.0)	46 (97.9)	1 (2.1)
Negative	17 (85.0)	3 (15.0)	17 (100.0)	0 (0.0)
p	0.263		1.000	
P53				
Positive	17 (73.9)	6 (6.1)	21 (100.0)	0 (0.0)
Negative	31 (70.5)	13 (29.5)	38 (97.4)	1 (2.6)
p	>0.99		0.650	
Outcome				
Live	85 (85.9)	32 (82.1)	96 (83.5)	2 (50.0)
Dead	14 (14.1)	7 (17.9)	19 (16.5)	2 (50.0)
P	0.696		0.004	

ER = estrogen receptor; PR = progestrone receptor; RI = resistance index.

Table 5
Predictive result on FS.

	TP	FP	TN	FN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Grade 3 tumor	5	22	133	12	29.4	85.8	18.5	91.7
≥1/2 myometrial invasion	3	32	132	16	15.8	80.5	9.4	89.2

FN = false negative; FP = false positive; FS = frozen section; NPV = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive.

Table 6
Incidence of lymph node metastases by modeled predictor.

	Case	PLN (+)	PALN (+)
G1 + no invasion	4	0	0
G2 + no invasion	0	0	0
G1 + <1/2 myometrial invasion	42	1 (2.4%)	1 (2.4%)
G2 + <1/2 myometrial invasion	21	1 (4.8%)	0

G = grade; PALN = para-aortic lymph node; PLN = pelvic lymph node.

Table 6. G1 + no myometrial invasion and G2 + no myometrial invasion predictors had no metastases, G1 + <1/2 myometrial invasion had a 2.4% risk of both pelvic lymph node and para-aortic lymph node metastasis, and G2 + <1/2 myometrial invasion had a 4.8% risk of pelvic lymph node metastasis. Although G1 or G2 and no myometrial invasion on FS were factors suggesting that lymphadenectomy was not necessary, a few of these patients exhibited lymph node metastasis, emphasizing the necessity of lymph node dissection.

Survival outcome of patients with or without lymph node dissection

At a median of 412 weeks of follow-up, 196 cases were analyzed. Nineteen of the 79 patients who did not undergo lymph node resection died of endometrial cancer, with an overall survival rate of 75.9%. Twenty-four of the 117 patients who underwent lymphadenectomy died as a result of disease progression, with an overall survival rate of 79.5% (Figure 1). Although there was no statistically significant difference in overall survival between the two groups ($p = 0.086$), overall survival was relatively higher in patients who had undergone lymphadenectomy.

Discussion

The accuracy of intraoperative FS has been discussed extensively in the literature, and the results are varied. Reported concordance rates between FS and PS range from 68% to 95% for tumor grade,[9–13] and from 72% to 95% for depth of myometrial invasion.[9,11,12]

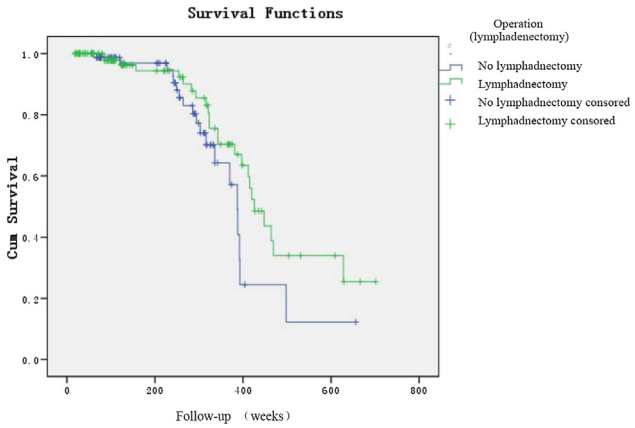

Figure 1. Kaplan–Meier analysis of overall survival of patients with or without lymph node dissection. Cum = cumulative.

However, other studies did not find high concordance between FS and PS. Case et al[14] carried out a prospective blinded evaluation and found an accuracy rate of 58% in tumor grade and 67% in depth of myometrial invasion for FS, which correlated poorly with the final pathology. Papadia et al[15] reported that in 16% of 174 cases, FS underestimated the risk status for lymph node metastasis when compared with permanent section. Kumar et al[8] found that FS results disagreed with PS results in 35% of cases for the tumor grade, in 28% for the depth of myometrial invasion, in 13% for cervical involvement, and in 32% for lymphovascular invasion. In 2009, our study in 218 patients showed that the concordance rates between FS for tumor grade and depth of myometrial invasion were 69% and 87%, respectively.[3] In the present study, we reviewed more cases in order to investigate the accuracy of FS and the clinical factors affecting it.

In this study, FS was highly accurate for determining the depth of myometrial invasion that the overall concordance rate was 97.8%, which is higher than those reported in previous studies. This finding might be due to processing of more FSs in our pathology department. Nowadays, pathologists always make two to four sections for FS diagnosis. It was reported that with a minimum of four transverse sections, the accuracy of FS for myometrial invasion was 95%,[10,16] while with only one to two sections, the accuracy was 72%.[11,17] When tumor infiltration into the myometrium was obvious to the pathologists, the deepest invasive site could be identified. If not, FSs were made at random, thus increasing the possibility of missing the area of myometrial invasion.

Intraoperative FS was correlated with PS for tumor grade in 78.6% of cases in our study. Some authors feel that determining whether solid nonsquamous growth comprises less than or greater than 5% of the tumor is often problematic and arbitrary.[18] In a retrospective review, Scholten et al[19] found a shift from Grade 2 to Grade 1 in 78% of cases that were originally Grade 2. Similarly, lower concordance of Grade 2 was observed in our study when compared with Grades 1 and 3. In an environment cold enough for FS, a cell may be enlarged or damaged as a result of ice formation inside the cell, making it difficult for a pathologist to determine the exact tumor grade. We found that the concordance rate for Grade 3 disease was highest, partly because Grade 3 tumor could contain Grade 1 and 2 tumor tissue. When Grade 3 tissue was identified, the diagnosis of Grade 3 disease was definitive; when Grade 3 tissue was not obtained, the patient could be downgraded on the basis of FS assessment. In our study, 32 (17.1%) patients were upgraded on the final pathology, while only eight (4.3%) were downgraded. In the 32 cases diagnosed with normal, simple hyperplasia, or complex hyperplasia on FS, the histologic grade rose in 20 cases, of which 12 were found to have endometrial carcinoma on the final pathology.

Postmenopausal bleeding is the most common primary symptom in endometrial cancer. In our study, more patients with postmenopausal bleeding and later age at menopause increased the accuracy of FS in determining the depth of myometrial invasion. Higher rates of concordance for tumor grade and myometrial invasion were seen in patients aged ≥70 years; however, the number of patients in this age group was small and the results were not statistically significant. Age is believed to be a prognostic factor in endometrial cancer,[20] so older patients and those with later

menopause should receive more attention. Ultrasound scanning can detect the size of the uterus and neoplasm, and the thickness and blood flow of the endometrium. We found that the size of the uterus or neoplasm, and the thickness of the endometrium were not associated with concordance of tumor grade in endometrial carcinoma. However, a lower systolic/diastolic ratio of blood flow correlated with a higher concordance rate for tumor grade between FS and PS. It has been reported that blood flow rates correspond with increased angiogenesis in endometrial cancers, and might potentially be used as a good factor for predicting tumor progression and metastasis in affected women.[21,22]

In 2006, the American College of Obstetricians and Gynecologists recommended surgical staging for women with endometrial cancer, except for those who are young or perimenopausal with Grade 1 endometrioidal adenocarcinoma associated with atypical endometrial hyperplasia, and those at an increased risk of mortality secondary to comorbidities.[23] Despite the recommendations of American College of Obstetricians and Gynecologists, there is still controversy within our field, specifically with regard to those patients with the disease appearing to be confined to the uterus.[24–26] In the GOG-33 study, patients with Clinical Stage I endometrial cancer were stratified into three risk categories. High-risk patients, defined as having deep myometrial invasion, had an 18% risk of pelvic node metastasis and a 15% risk of para-aortic lymph node metastasis. Intermediate-risk patients, defined as having Grade 2 or 3 histology and/or intermediate myometrial invasion, had a 2–6% risk of nodal metastasis. Low-risk patients with Grade 1 histology and endometrial involvement only had no lymph node metastasis in this study.[6] Mariani et al[27] have suggested that patients with Grade 1 or 2 endometrioid tumors, with <50% depth of invasion and <2 cm tumor diameter, or patients with no myometrial invasion regardless of the grade and diameter should not undergo lymphadenectomy in Mayo clinic practice. In our study, predicting lymph node metastases at tumor Grade 3 and $\geq$1/2 myometrial invasion as independent factors achieved relatively high specificity of 85.8% and 80.8%, respectively. Examinations with high specificity are always used to ascertain the diagnosis. Thus, we concluded that the risk of lymph node metastases is related to a poorly differentiated grade of tumor and deep invasion into the myometrium.

In many institutions, the risk of lymph node metastasis is modeled from the information obtained by intraoperative FS combined histologic grade and depth of myometrial invasion, and then the institutional guidelines regarding surgical management are established. Patients with Grade 1 or 2, and <1/2 myometrial invasion are not generally regarded as being in the high-risk subgroup. Is it reliable to omit lymphadenectomy solely depending on FS assessment? In our study, for patients who had both an intraoperative FS revealing Grade 1 or 2 endometrial cancer, and <1/2 myometrial invasion, we constructed four models to predict lymph node metastasis. Model G1 + <1/2 myometrial invasion had a 2.4% risk of both pelvic lymph node and para-aortic lymph node metastasis, and G2 + <1/2 myometrial invasion had a 4.8% risk of pelvic lymph node metastasis. Although the incidence is not high, based on FS assessment, a percentage of patients will have high-risk findings on the final pathology that increase their risk of nodal involvement, but will not have had a lymph node dissection, and postoperative adjuvant treatment will not be administered appropriately. These four models were derived from the data reported by Frumovitz et al in 2004.[28] They demonstrated that the G1 + no invasion predictor had only a 1–2% chance of nodal metastasis and probably was the only predictor for which one might decide to forgo lymph node sampling. However, the risk of lymph node spread of the other three predictors ranged from 2% to 6%. These data indicated that surgeons who use these variables as the foundation for their decision on whether to sample lymph nodes should perhaps reconsider this approach.[28] Papadia et al[15] performed a retrospective review in early-stage endometrial cancer patients classified as those with low, intermediate, and high risk for lymph nodal involvement. In 16% of the cases, FS underestimated the risk when compared with the permanent section. They suggested that relying on intraoperative FS to assess the risk status for lymph node involvement led to suboptimal management in a substantial number of cases.[15]

A key issue in deciding whether or not to perform a routine lymphadenectomy is whether lymphadenectomy improves outcomes. In our study, after a median follow-up period of 412 weeks, no statistically significant difference was found in overall survival between patients who underwent lymph node resection and those who did not ($p = 0.086$). However, overall survival in patients with lymphadenectomy was relatively longer than in patients without lymphadenectomy. Multiple studies evaluating this issue have reported contradictory results. Some authors have reported that among patients with intermediate- or high-risk disease characteristics, there was a survival advantage in those who underwent lymph node resection.[29–32] In contrast, others concluded that there was no statistically significant difference in disease-free and overall survival between patients who underwent lymphadenectomy and who did not,[33] and only a small portion of patients would have benefited from routine lymphadenectomy.[34–36] It is difficult to make any definitive conclusion about the therapeutic role of lymphadenectomy from retrospective studies.

In summary, it was concluded that the determination of depth of myometrial invasion by FS was highly accurate; however, the accuracy of FS in determining tumor grade was less reliable. Relying on FS to tailor lymphadenectomy might lead to suboptimal management. Therefore, gynecologic oncologists have to be cautious when using FS assessment to determine the extent of operation. This is the reason we support full staging for all patients with endometrial cancer until a better method for predicting lymph node metastasis can be validated.

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References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin*. 2010;60:277–300.
2. Mikuta JJ. International Federation of Gynecology and Obstetrics staging of endometrial cancer 1988. *Cancer*. 1993;71:1460–1463.
3. Wang X, Zhang H, Di W, Li W. Clinical factors affecting the diagnostic accuracy of assessing dilation and curettage vs frozen section specimens for histologic grade and depth of myometrial invasion in endometrial carcinoma. *Am J Obstet Gynecol*. 2009;201:194e1–194e10.
4. Goudge C, Bernhard S, Cloven NG, Morris P. The impact of complete surgical staging on adjuvant treatment decisions in endometrial cancer. *Gynecol Oncol*. 2004;93:536–539.
5. Ben-Shachar I, Pavelka J, Cohn DE, et al. Surgical staging for patients presenting with grade 1 endometrial carcinoma. *Obstet Gynecol*. 2005;105:487–493.
6. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. *Cancer*. 1987;60:2035–2041.
7. Morrow CP, Bundy BN, Kurman RJ, et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1991;40:55–65.
8. Kumar S, Bandyopadhyay S, Semaan A, et al. The role of frozen section in surgical staging of low risk endometrial cancer. *PLoS One*. 2011;6:e21912.
9. Malviya VK, Deppe G, Malone Jr JM, Sundareson AS, Lawrence WD. Reliability of frozen section examination in identifying poor prognostic

indicators in stage I endometrial adenocarcinoma. *Gynecol Oncol*. 1989;34:299–304.
10. Fanning J, Tsukada Y, Piver MS. Intraoperative frozen section diagnosis of depth of myometrial invasion in endometrial adenocarcinoma. *Gynecol Oncol*. 1990;37:47–50.
11. Noumoff JS, Menzin A, Mikuta J, Lusk EJ, Morgan M, LiVoisi VA. The ability to evaluate prognostic variables on frozen section in hysterectomies performed for endometrial carcinoma. *Gynecol Oncol*. 1991;42:202–208.
12. Kucera E, Kainz C, Reinthaller A, et al. Accuracy of intraoperative frozen-section diagnosis in stage I endometrial adenocarcinoma. *Gynecol Obstet Invest*. 2000;49:62–66.
13. Shim JU, Rose PG, Reale FR, Soto H, Tak WK, Hunter RE. Accuracy of frozen-section diagnosis at surgery in clinical stage I and II endometrial carcinoma. *Am J Obstet Gynecol*. 1992;166:1335–1338.
14. Case AS, Rocconi RP, Straughn Jr JM, et al. A prospective blinded evaluation of the accuracy of frozen section for the surgical management of endometrial cancer. *Obstet Gynecol*. 2006;108:1375–1379.
15. Papadia A, Azioni G, Brusaca B, et al. Frozen section underestimates the need for surgical staging in endometrial cancer patients. *Int J Gynecol Cancer*. 2009;19:1570–1573.
16. Stephan JM, Hansen J, Samuelson M, et al. Intra-operative frozen section results reliably predict final pathology in endometrial cancer. *Gynecol Oncol*. 2014;133:499–505.
17. Zaino RJ. FIGO staging of endometrial adenocarcinoma: a critical review and proposal. *Int J Gynecol Pathol*. 2009;28:1–9.
18. Lax SF, Kurman RJ, Pizer ES, Wu L, Ronnett BM. A binary architectural grading system for uterine endometrial endometrioid carcinoma has superior reproducibility compared with FIGO grading and identifies subsets of advance-stage tumors with favorable and unfavorable prognosis. *Am J Surg Pathol*. 2000;24:1201–1208.
19. Scholten AN, Creutzberg CL, Noordijk EM, Smit VTHBM. Long-term outcome in endometrial carcinoma favors a two- instead of a three-tiered grading system. *Int J Radiat Oncol Biol Phys*. 2002;52:1067–1074.
20. Jolly S, Vargas C, Kumar T, et al. Vaginal brachytherapy alone: an alternative to adjuvant whole pelvis radiation for early stage endometrial cancer. *Gynecol Oncol*. 2005;97:887–892.
21. Kupesic-Urek S, Shalan H, Kurjak A. Early detection of endometrial cancer by transvaginal color Doppler. *Eur J Obstet Gynecol Reprod Biol*. 1993;49:46–49.
22. Sawicki V, Spiewankiewicz B, Stelmachow J, Cendrowski K. Color Doppler assessment of blood flow in endometrial cancer. *Eur J Gynaecol Oncol*. 2005;26:279–284.
23. American College of Obstetricians and Gynecologists. ACOG practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. *Obstet Gynecol*. 2005;106:413–425.
24. Sala P, Morotti M, Menada MV, et al. Intraoperative frozen section risk assessment accurately tailors the surgical staging in patients affected by early-stage endometrial cancer: the application of 2 different risk algorithms. *Int J Gynecol Cancer*. 2014;24:1021–1026.
25. Koskas M, Rouzier R, Amant F. Staging for endometrial cancer: the controversy around lymphadenectomy—can this be resolved? *Best Pract Res Clin Obstet Gynaecol*. 2015. http://dx.doi.org/10.1016/j.bpobgyn.2015.02.007. pii:S1521-6934(15)00026-7. [Epub ahead of print].
26. Abdullan NA, Huang KG, Casanova J, et al. Sentinel lymph node in endometrial cancer: a systematic review on laparoscopic detection. *Gynecol Minim Invasive Ther*. 2013;2:75–78.
27. Mariani A, Dowdy SC, Cliby WA, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. *Gynecol Oncol*. 2008;109:11–18.
28. Frumovitz M, Slomovitz BM, Singh DK, et al. Frozen section analyses as predictors of lymphatic spread in patients with early-stage uterine cancer. *J Am Coll Surg*. 2004;199:388–393.
29. Chan JK, Cheung MK, Huh WK, et al. Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients. *Cancer*. 2006;107:1823–1830.
30. Kilgore LC, Partridge EE, Alvarez RD, et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. *Gynecol Oncol*. 1995;56:29–33.
31. Cragun JM, Havrilesky LJ, Calingaert B, et al. Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. *J Clin Oncol*. 2005;23:3668–3675.
32. Trimble EL, Kosary C, Park RC. Lymph node sampling and survival in endometrial cancer. *Gynecol Oncol*. 1998;71:340–343.
33. Hidaka T, Kato K, Yonezawa R, et al. Omission of lymphadenectomy is possible for low-risk corpus cancer. *Eur J Surg Oncol*. 2007;33:86–90.
34. Belinson JL, Lee KR, Badger GJ, Pretorius RG, Jarrell MA. Clinical stage I adenocarcinoma of the endometrium—analysis of recurrences and the potential benefit of staging lymphadenectomy. *Gynecol Oncol*. 1992;44:17–23.
35. ASTEC study group, Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet*. 2009;373:125–136.
36. ASTEC/EN.5 Study Group, Blake P, Swart AM, et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. *Lancet*. 2009;373:137–146.