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Original Article

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Is an Intraoperative Frozen Section Useful for Judging the Necessity of Lymphadenectomy in Patients With Endometrial Cancer?

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Abstract

Background: We evaluated whether an intraoperative frozen section is useful for judging the necessity of lymphadenectomy for treating endometrial cancer.

Methods: We examined 106 patients with endometrial cancer in whom histological grade and uterine muscle layer invasion were evaluated using an intraoperative frozen section at our institution between 2012 and 2016. We compared the intraoperative frozen-section diagnosis with a preoperative evaluation regarding the accuracy of determining histological grade and uterine muscular invasion, which are considered risk factors for lymph-node metastasis.

Results: The preoperative evaluation and intraoperative frozen section had 55% and 75% diagnostic accuracies, respectively (P = 0.002). The frozen-section diagnosis was superior to preoperative evaluation, particularly for detecting the presence of uterine muscular invasion.

Conclusions: A frozen section is useful if the presence of muscular invasion is included in the criteria for determining whether lymphadenectomy should be performed.

Keywords: Endometrial neoplasms; Lymph-node excision; Frozen sections

Introduction

The basic procedures to treat endometrial cancer are hysterectomy and bilateral salpingo-oophorectomy. Additional options are pelvic node lymphadenectomy, para-aortic lymphadenectomy and partial omentectomy.

Pelvic node lymphadenectomy is necessary to accurately determine the stage of and postoperative therapy for endometrial cancer [1-3]. However, when the histological grade is endometrioid G1 or G2 and muscular invasion is absent or shallow, the probability of pelvic node metastasis is very low and pelvic node lymphadenectomy is considered unnecessary [4-6].

Para-aortic lymphadenectomy and omentectomy are also used to determine the stages of and postoperative therapy for endometrial cancer. However, like the pelvic nodes, if the histological grade is endometrioid G1 or G2 and muscular invasion is shallow, the probability of metastasis is very low and the benefit of para-aortic lymphadenectomy and omentectomy is small [1, 7-13].

The degree of muscular invasion and histological grade indicates whether lymphadenectomy and omentectomy should be performed. In previous studies, the accuracy of diagnosing muscular invasion using magnetic resonance imaging (MRI), transvaginal sonography and intraoperative macroscopic observation was 54-90%, 73-87% and 74-91%, respectively [14-36]. The accuracy of determining histological grade using preoperative endometrial biopsy has been reported to be between 35% and 97% [14, 17, 18, 20, 23, 25, 35, 37, 38]. Diagnoses made by evaluating muscular invasion and histological grade using preoperative MRI and biopsy may overestimate or underestimate the risk of lymph-node metastasis. Overestimation leads to unnecessary lymphadenectomy, which increases the surgical time and complications that are associated with the procedure. Underestimation increases the risk of lymph node recurrence after surgery and may omit necessary postoperative treatment.

Diagnosis using an intraoperative frozen section may decrease unnecessary lymphadenectomy and may also increase lymphadenectomy that should have been performed. Many studies have shown that an intraoperative frozen section was useful because it has a significantly higher accuracy for determining the histological grade and muscular invasion than a preoperative evaluation. In this study, we retrospectively examined patients seen at our institution and assessed the accuracy of intraoperative frozen sections for determining the risk of lymph-node metastasis and indicating the need for lymphadenectomy in patients with endometrial cancer.

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Materials and Methods

Patients

A total of 106 patients with endometrial cancer for which histological grade and muscular invasion were evaluated using an intraoperative frozen section at our institution between January 2012 and December 2016 were enrolled in this study. Preoperative biopsy specimens were taken using endometrial curettage in an outpatient setting or under anesthesia in the operating room. Preoperative muscular invasion was evaluated with MRI.

The uterus was removed and incised longitudinally at the anterior wall from the cervix to the fundus. We prepared one or two specimens of the entire muscular layer vertically to the uterine cavity surface at the sites that were considered to have the deepest invasion based on preoperative MRI findings and intraoperative macroscopic observation.

Histological grading

With respect to histological grade, the patients were classified into three groups: endometrioid G1, endometrioid G2 and high-grade malignancy (endometrioid G3, serous, clear cell), and the accuracy of the preoperative evaluation and frozen-section diagnosis were calculated. Next, we classified the patients into two groups: G1 and G2 + high-grade and into two groups: G1 + G2 and high-grade, and calculated the accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the preoperative evaluation and frozen-section diagnosis.

Muscular invasion

With respect to muscular invasion, the patients were classified into three groups: no muscular invasion, < 1/2 invasion and ≥ 1/2 invasion, and the accuracy of the preoperative evaluation and frozen-section diagnosis were calculated. Next, we classified the patients into two groups: with invasion and without invasion and into two groups: < 1/2 invasion and ≥ 1/2 invasion, and calculated the accuracy, sensitivity, specificity, PPV and NPV of the preoperative evaluation and frozen-section diagnosis.

Risk for lymph node metastasis

At our institution, if there is no muscular invasion and the histological grade is G1 or G2, we perform a hysterectomy and bilateral salpingo-oophorectomy alone. If muscular invasion is present, pelvic node dissection is added. If muscular invasion is ≥ 1/2 or the histology is high-grade, para-aortic lymph node dissection and partial omentectomy are also added. Based on this, we classified the patients into three risk groups (low, intermediate and high) according to the risk for lymph-node metastasis. Patients in the low-risk group had no muscular invasion and the histological grade was G1 or G2. Patients in the intermediate-risk group had < 1/2 muscular invasion and the histological grade was G1 or G2. Patients in the high-risk group had ≥ 1/2 invasion or a histologically high grade. Then, we classified the patients into three groups: a low-, intermediate- and high-risk group and into two groups: a low + intermediate-risk group and high-risk group, and calculated the accuracy of the preoperative evaluation and frozen-section diagnosis.

Table 1. Characteristics of the 106 Patients With Endometrial Carcinoma

Age	56 (51 - 64)
Stage (n)	
IA	64
IB	24
II	1
IIIA	6
IIIB	1
IIIC1	3
IIIC2	7
Grade (n)	
G1	63
G2	32
Risk classification (n)	
High-grade	11
Low-risk	34
Intermediate-risk	34
High-risk	38

G1: endometrioid G1; G2: endometrioid G2; High-grade: endometrioid G3, clear cell, serous; Low-risk: G1 or G2, no muscular invasion; Intermediate-risk: G1 or G2, < 1/2 invasion; High-risk: high-grade or ≥ 1/2 invasion.

Statistical analyses

McNemar's test was used to compare the accuracies of the preoperative evaluation and frozen-section diagnoses. It tests the difference between the proportions of two paired samples using Chi-square distribution. EZR version 1.25 was used for statistical analysis [39].

This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as the Helsinki Declaration. This study was approved by Institutional Review Board.

Results

Histological grading

Table 1 shows the characteristics of the 106 patients with en-

Table 2. Comparison of the Tumor Grade Between the Preoperative and Permanent-Section Diagnoses in the 106 Patients With Endometrial Carcinoma

Permanent-section diagnosis	Preoperative diagnosis					Total	Accuracy
	Unknown	No tumor	G1	G2	High- grade		
G1	5	3	52	3	0	63	83%
G2	6	2	14	10	0	32	44%
High-grade	1	1	3	1	5	11	45%
Total	12	6	69	14	5	106	63%

Table 3. Comparison of the Tumor Grade Between the Frozen-Section and Permanent-Section Diagnoses in the 106 Patients With Endometrial Carcinoma

Permanent-section diagnosis	Frozen-section diagnosis					Total	Accuracy
	Unknown	No tumor	G1	G2	High- grade		
G1	1	4	54	4	0	63	86%
G2	1	0	15	15	1	32	47%
High-grade	0	0	3	4	4	11	36%
Total	2	4	72	23	5	106	69%

G1: endometrioid G1; G2: endometrioid G2; High-grade: endometrioid G3, clear cell, serous. There was not a significant difference between the frozen-section and preoperative diagnoses (P = 0.391).

dometrial cancer enrolled in this study. When the patients were classified into three groups based on the histological grade, the preoperative evaluation and intraoperative frozen-section accuracies were 63% and 69%, respectively (P = 0.391) (Tables 2 and 3). When the patients were classified into the two groups: G1 and G2 + high-grade, the accuracies were 67% and 77%, respectively (P = 0.054) (Table 4). When the patients were classified into the two groups: G1 + G2 and high-grade, the accuracies were 84% and 91%, respectively (P = 0.070) (Table 4).

Muscular invasion

When the patients were classified into the three groups: no invasion, < 1/2 invasion and ≥ 1/2 invasion, the preoperative and frozen-section diagnostic accuracies were 63% and 76%, respectively (P = 0.018) (Tables 5 and 6). When the patients were classified into the two groups: with invasion and without invasion, the diagnostic accuracies were 75% and 89%, respectively (P = 0.007) (Table 4). When the patients were classified into the two groups: < 1/2 invasion and ≥ 1/2 invasion, the diagnostic accuracies were 81% and 85%, respectively (P = 0.522) (Table 4).

Risk for lymph-node metastasis

When the patients were classified into the three groups: low-risk, intermediate-risk and high-risk groups according to the risk for lymph-node metastasis, the preoperative and frozen-section diagnostic accuracies were 55% and 75%, respectively (P = 0.002) (Tables 7 and 8). When the patients were classified into

Table 4. Comparison of the Grade and Muscular Invasion Between the Preoperative and Frozen-Section Diagnoses in the 106 Patients With Endometrial Carcinoma

DiagnoaAsis	Test target	Accuracy	Sensitivity	Specificity	PPV	NPV	P value
Preoperative	G2 and high-grade	67%	37%	87%	84%	73%	
Frozen-section	G2 and high-grade	77%	56%	92%	86%	76%	0.054
Preoperative	High-grade	84%	45%	88%	100%	94%	
Frozen-section	High-grade	91%	36%	97%	80%	93%	0.070
Preoperative	Invasion present	75%	81%	65%	83%	67%	
Frozen-section	Invasion present	89%	88%	91%	97%	78%	0.007
Preoperative	≥ 1/2 invasion	81%	67%	89%	89%	89%	
Frozen-section	≥ 1/2 invasion	85%	61%	97%	96%	84%	0.522

PPV: positive predictive value; NNP: negative predictive value.

Table 5. Comparison of Muscular Invasion Between the Preoperative (MRI) and Permanent-Section Diagnoses in the 106 Patients With Endometrial Carcinoma

Permanent-section diagnosis	Preoperative (MRI) diagnosis					Total	Accuracy
	Unknown	Invasion present (depth unknown)	No invasion	< 1/2	≥ 1/2		
No invasion	0	1	22	10	1	34	65%
< 1/2 invasion	1	3	9	21	2	36	58%
≥ 1/2 invasion	2	2	2	6	24	36	67%
Total	3	6	33	37	27	106	63%

Table 6. Comparison of Muscular Invasion Between the Frozen-Section and Permanent-Section Diagnoses in the 106 Patients With Endometrial Carcinoma

Permanent-section diagnosis	Frozen-section diagnosis					Total	Accuracy
	Unknown	Invasion present (depth unknown)	No invasion	< 1/2	≥ 1/2		
No invasion	1	0	31	2	0	34	91%
< 1/2 invasion	0	0	7	28	1	36	78%
≥ 1/2 invasion	0	1	2	11	22	36	61%
Total	1	1	40	41	23	106	76%

There was a significant difference between the frozen-section and preoperative diagnoses (P = 0.018).

two groups: low-risk + intermediate-risk group and high-risk group, the diagnostic accuracies were 71% and 84%, respectively (P = 0.006) (Supplementary Tables 1 and 2, www.jcgo.org).

Discussion

For the diagnosis of histological grade, the accuracy of frozen-section diagnosis is slightly higher than that of a preoperative evaluation. However, the differences between the two techniques were not significant in any comparisons. For preoperative evaluation, the frequency of unknown histological grade was higher than that in frozen-section diagnosis, which seemed to lower the accuracy of the preoperative evaluation. Main reason for unknown histological grades in preoperative evaluation was that tissue could not be collected because of

Table 7. Comparison of the Risk of Lymph-Node Metastasis Between the Preoperative and Permanent-Section Diagnoses in the 106 Patients With Endometrial Carcinoma

Permanent-section diagnosis	Preoperative diagnosis				Total	Accuracy
	Unknown	Low-risk	Intermediate-risk	High-risk		
Low-risk	3	18	8	1	30	60%
Intermediate-risk	7	9	20	3	39	51%
High-risk	8	5	4	20	37	54%
Total	18	32	32	24	106	55%

Table 8. Comparison of the Risk of Lymph-Node Metastasis Between the Frozen-Section and Permanent-Section Diagnoses in the 106 Patients With Endometrial Carcinoma

Permanent-section diagnosis	Frozen-section diagnosis				Total	Accuracy
	Unknown	Low-risk	Intermediate-risk	High-risk		
Low-risk	1	27	2	0	30	90%
Intermediate-risk	0	8	29	2	39	74%
High-risk	2	2	10	23	37	62%
Total	3	37	41	25	106	75%

Low-risk: G1 or G2, no muscular invasion; Intermediate-risk: G1 or G2, < 1/2 invasion; High-risk: high grade or ≥ 1/2 invasion; High-grade: endometrioid G3, clear cell, serous. There was a significant difference between the preoperative diagnosis and the frozen-section diagnosis (P = 0.002).

Table 9. Accuracy of the Grade and Muscular Invasion Using Frozen-Section Diagnosis According to Past Studies

Paper	Year	Number of cases	Accuracy of grade (three groups)	Accuracy of grade (two groups)	Accuracy of invasion (three groups)	Accuracy of invasion (two groups)	Conclusion of the paper
This study		106	69	91	76	85	Useful
Wang et al [40]	2016	112	89	-	-	97	Useful
Acikalin et al [41]	2015	291	84	-	92	-	Useful
Karabagli et al [42]	2015	79	90	-	89	-	Useful
Gallego et al [22]	2014	51	-	-	-	90	Unuseful
Stephan et al [43]	2014	116	88	-	-	98	Useful
Turan et al [44]	2013	756	89	-	85	-	Useful
Kisu et al [21]	2013	111	-	-	-	94	Useful
Kumar et al [45]	2012	784	99	-	99	-	Useful
Ozturk et al [25]	2012	220	-	90	-	92	Useful
Savelli et al [26]	2012	131	-	-	-	92	Useful
Ugaki et al [20]	2011	303	71	-	77	87	Useful
Kumar et al [46]	2011	146	65	-	72	-	Unuseful
Furukawa et al [18]	2010	168	85	-	86	-	Useful
Ozdemir et al [16]	2009	64	-	-	-	91	Useful
Kucera et al [47]	2009	63	86	-	87	-	Useful
Wang et al [37]	2009	218	69	-	-	87	-
Maneschi et al [34]	2008	78	-	-	-	95	-
Montalto et al [48]	2008	87	84	-	94	-	Useful
Sanjuan et al [14]	2006	89	-	87	-	89	Useful
Case et al [49]	2006	77	58	-	-	67	Unuseful
Quilivan et al [50]	2001	209	89	-	-	95	Useful
Kucera et al [51]	2000	70	84	-	80	-	Useful
Shim et al [52]	1992	199	-	-	-	91	Useful
Fanning et al [38]	1990	216	-	96	-	95	Useful

Accuracy of grade (three groups): endometrioid G1, endometrioid G2, high-grade. Accuracy of grade (two groups): endometrioid G1 or G2, high-grade. Accuracy of invasion (three groups): no invasion, < 1/2 invasion, ≥ 1/2 invasion. Accuracy of invasion (two groups): no invasion or < 1/2 invasion, ≥ 1/2 invasion.

cervical stenosis or that collected tissue was small amount.

For the diagnosis of muscular invasion, an intraoperative frozen-section diagnosis was more accurate than a preoperative evaluation, which was due to the frozen-section diagnosis of the presence or absence of muscular invasion being superior to the preoperative evaluation. It is very difficult to judge the presence of muscular invasion using MRI when the invasion is very shallow. For the diagnosis of ≥ 1/2 muscular invasion, the frozen-section diagnosis was slightly more accurate than the preoperative evaluation, but the difference was not significant.

For determining the risk of lymph-node metastasis, the accuracy of the three-group comparison was 55% for the preoperative evaluation and 75% for the frozen-section diagnosis, which was a significant difference. In the two-group comparison, the presence or absence of muscular invasion did not need to be determined, and the accuracy was 71% for the preoperative comparison and 84% for the frozen-section diagnosis. This was a significant difference; however, the superiority of frozen-section diagnosis was less than that in the three-group comparison. Judgement of the presence or absence of muscular invasion contributed to the superiority of the intraoperative frozen section to determine the risk of lymph-node metastasis. If the presence or absence of muscular invasion is not considered in the determination to perform lymphadenectomy, an intraoperative frozen section may be less meaningful.

Table 9 shows the accuracies of intraoperative frozen section for histological grade and muscular invasion that were reported in the past [14, 16, 18, 20-22, 25, 26, 34, 37, 38, 40-52]. It is not unusual that the accuracy obtained by classifying the patients into two groups is higher than that obtained by classifying them into three groups. Many reports concluded that intraoperative frozen sections are useful because of their high accuracy in diagnosing histological grade and muscular invasion of endometrial cancer. The accuracies reported in our study are not higher than those of other studies. In many other studies, after removal, the uterus was longitudinally opened and

transversely incised at millimeter intervals for several layers. Then, a frozen section was made from the part of the uterus that was determined, using macroscopic findings, to have the deepest invasion. After removal, we opened the uterus longitudinally and cut it once in the location that was considered to have the deepest invasion as seen on MRI and in macroscopic findings. The method used to create an intraoperative frozen section may affect its accuracy for determining muscular invasion. Other studies showed that a diagnosis made using a frozen section was superior to that of a preoperative evaluation, particularly for determining the presence or absence of muscular invasion [20, 21].

This study has some limitations. This was a retrospective study with a small number of patients, and there was no uniformity in the methods of preoperatively determining the histological grade. A cost-effective analysis is necessary to determine the true value of a frozen section for assessing the risk of metastasis.

Conclusion

A frozen section is useful for making the diagnosis of endometrial cancer if the absence or presence of muscular invasion is a criterion for determining the need for lymphadenectomy.

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We had neither fund nor needed financial disclosure.

Conflict of Interest

We declare no conflict of interest associated with this study.

Informed Consent

We obtained no informed consent from the patients because this study was observational study.

Author Contributions

All authors have participated in the work and assume responsibility for the manuscript.

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