The accuracy of frozen section of uterine lesions in the practice of gynecologic surgery. A retrospective assessment study in a tertiary government training hospital

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ABSTRACT

Objective. This study aimed to determine the accuracy, sensitivity and specificity of frozen section (FS) in the diagnosis of uterine neoplasm in a tertiary government training hospital.

Methodology. This is a retrospective validation study from 2004-2015 involving cases of uterine lesions from gynecologic surgeries. All histopathologic results of frozen and paraffin sections were retrieved and reviewed. Chi square test with 2x2 Fischer Exact test adjustment was used to check for associations. Accuracy indices of FS tool were estimated such as sensitivity, specificity, likelihood ratios, negative and positive predictive values, and overall accuracy. A p-value of < 0.05 alpha is considered significant.

Results. A total of 143 uterine specimens were submitted for frozen section analysis. The utilization rate of FS is 1% per year. The FS results were correlated with the final histopathologic diagnosis with 96% agreement rate. Utilizing a median number of 3 sections per specimen provides an overall accuracy rate of 97%. The accuracy rate of FS is equal between combined benign-premalignant and malignant cases at 96%. The accuracy rate is not statistically affected by the procedure by which the specimen was taken, as well as the source and gross morphology of the specimen. Moreover, a minimum of 11 sections per specimen is needed to obtain an accuracy rate of 99-100%. The accuracy rate particularly for endometrial lesions is between 94 and 100%.

Conclusion. Accuracy rates of frozen section on uterine lesions are high regardless of the sampling procedure and source of the specimen. Increasing the number of sections during FS parallels that of the final histopathologic diagnosis. FS for uterine lesions is a vital and cost-effective intraoperative decision tool to maximize care of patients.

Keywords: Accuracy rate, Frozen section, Uterine lesion

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in the female pelvis worldwide.[1,2] In the Philippines, uterine cancer has been identified as the 9th leading site of cancer among women, with an incidence of 3.2%. There is an estimated 4.3 new cancer cases per 100,000 women in 2005. About 546 Filipino women afflicted with this disease died in 2005.[3] In 75% of cases, the tumor is confined to the uterine corpus at the time of diagnosis, and overall survival at 5 years is 80-90%.[4]

Preoperative endometrial sampling either by curettage or hysteroscopic-guided biopsy is a standard approach to detect malignant disease, histologic type and tumor grade.[5,6] Because its accuracy rate is 90%, then 10% of endometrial lesions may not be correctly diagnosed preoperatively.[7] Hence, intraoperative assessment is recommended for equivocal and/or suspicious lesions. Furthermore, endometrial and uterine lesions should be assessed preoperatively and intraoperatively to plan the appropriate surgical management. Evaluation of malignant status and extent of the uterine malignancy may be done preoperatively using imaging techniques but with limitations.[1,3]

Endometrial hyperplasia is known to be a precursor lesion for endometrial carcinoma. It has been reported that atypical endometrial hyperplasia coexists with endometrial adenocarcinoma in as high as 43% of cases.[7,8] The latest 2015 Clinical Practice Guidelines of the Society of Gynecologic Oncologists of the Philippines recommends frozen section evaluation for equivocal and/or suspicious lesions in patients with a preoperative diagnosis of atypical complex hyperplasia to rule out coexisting adenocarcinoma.[7]

Myoma uteri is the most frequent indication for hysterectomies performed for benign conditions. Preoperative endometrial sampling has not been proven

to be of any benefit in this condition. The malignancy risk of myoma uteri is 13.4% and 1.1% for postmenopausal and premenopausal women, respectively. It was reported that endometrial carcinoma was 5.5 times more common in postmenopausal patients with myoma and uterine bleeding in comparison to the analogous group of patients in the reproductive period.[9,10]

Prevalence of sarcomas after surgery for presumed leiomyoma is a more recent concern in the practice of gynecology. The incidence of unexpected sarcoma for patients with presumed benign leiomyoma was around 0.1 to 0.5%, with majority of patients being postmenopausal.[11,12] A preoperative assessment of the risk of malignancy of a myoma is very challenging. Clinical characteristics of the two entities are indistinguishable. Preoperative imaging and even endometrial sampling could not distinguish between the two.[13] Hence, intraoperative histopathologic assessment is of great importance to tailor appropriate procedure.

Surgical therapy for endometrial cancer and uterine sarcoma includes hysterectomy, bilateral salpingooophorectomy and lymphadenectomy.[3,7] Particularly for endometrial stromal sarcoma and mixed mullerian sarcoma, surgical procedure includes total hysterectomy with bilateral salpingooophorectomy, lymphadenectomy with or without omentectomy and peritoneal biopsies.[7] However, for leiomyosarcoma, bilateral salpingooophorectomy and pelvic and para-aortic lymphadenectomy are not recommended since lymph node involvement is seen in only <3%.[9]

In cases where a uterine lesion is suspicious for malignancy intraoperatively, frozen section of the lesion should be requested. Likewise, intraoperative frozen section of endometrial tumors is utilized to determine the tumor grade, myometrial invasion and presence of extrauterine spread. Appropriate and definitive surgery must be performed for malignant lesions. Moreover, such procedures entail special skills to prevent morbidity. A referral to a Gynecologic Oncologist is recommended at the initial exploration.

In the local setting, there were only two published reports on this topic, both of which dealt primarily on the endometrium. They were limited by the short duration of the study and inadequate sample size. Hence, this investigation was conducted to determine the accuracy rate of frozen section on various uterine lesions in a tertiary government training hospital where a significant number of samples were evaluated. Results of this study would provide supplementary and vital evidence that support the use of procedures that could offer optimal and cost-effective care for patients.

OBJECTIVES

This study aimed to determine the concordance between frozen section and final paraffin histopathologic diagnoses of uterine lesions in a tertiary government training hospital. Specifically, this investigation aimed:

1. To determine the accuracy of frozen section in terms of sensitivity, specificity, positive predictive value and negative predictive value in the diagnosis of various uterine neoplasms.

2. To determine if the following factors affect concordance between the frozen section and final paraffin histopathologic diagnoses:
   a. age of the patients
   b. method of sampling (curettages, biopsies or hysterectomy)
   c. source of lesion (cervix, endometrium, myometrium)
   d. number of sections processed
   e. gross morphology of lesions
   f. histologic category (benign, premalignant and malignant)

3. To review whether the appropriate surgical procedure was altered by the result of the frozen section diagnosis.

4. To assess the importance of frozen section in relation to the preoperative diagnosis.

METHODOLOGY

Study Design and Population

This is a retrospective validation study of all gynecologic surgeries for uterine neoplasms done at the Department of Obstetrics and Gynecology from 2004 to 2015 submitted for histopathologic examination. This was approved by the Institution's Ethical and Technical Review Board.

A frozen section would yield a baseline accuracy of 85% sensitivity and 85% specificity. This study needed a minimum of 136 cases assuming such accuracy values with precision +/- 6% CI at 95% (Figure 1). This study primarily utilized logbooks, computerized database and compiled results of histopathologic diagnosis of the patients who underwent procedure and/or surgery for uterine neoplasms. Selection bias may result from incomplete data, missing logbooks and/or pathologic results.

Description of Study Procedure

A review of all submitted specimens pertaining to uterine neoplasms submitted for paraffin histopathologic diagnosis with or without frozen section at the Section of Surgical Pathology from January 2004

Proportion - Infinite N	
N (Population size)	Infinite
p (expected proportion)	**0.85**
d (precision)	**0.06**
z alpha/2 (95% CI)	1.96
n - num	0.4898
n - den	0.0036
Sample size, n	**136**

Figure 1. Sample size computation

through June 2015 was performed to identify cases to be included in the study. This corresponds to the number of procedures performed by the department since it is the protocol of the hospital to submit all surgical specimens for histopathologic examination.

Cases of uterine tumors submitted for frozen section were retrieved from the surgical pathology logbooks, computerized database and compiled files of results. All histopathologic results of frozen and paraffin sections were retrieved and reviewed. The following data were collected and recorded using the data extraction form: age of the patient, gravidity and parity, sampling procedure, source of the specimen, gross description of the specimen, frozen section result, number of sections taken for FS analysis, and final paraffin diagnosis.

Data Processing and Statistical Analysis

Data were encoded in Microsoft Excel Spreadsheet and analyzed with SPSS version 21. Normally distributed continuous variables were expressed as mean ± SD, while those profiles which were categorical types were expressed using frequency and percentages. Moreover, in testing associations between FS and final histopathologic findings, Chi square test with 2x2 Fischer Exact test adjustment was used. After performing test of association, accuracy indices of FS tool were estimated such as sensitivity, specificity, likelihood ratios, negative and positive predictive values, and overall accuracy. A p-value of < 0.05 alpha is considered significant.

RESULTS

Utilization rate of frozen section

Between 2004 and 2015, the Department of Anatomic Pathology received an average of 1500 specimens involving uterine lesions per year for histopathologic examination, and an average of 12 uterine specimens per year were submitted for frozen section analysis. The utilization rate is only 1% annually. During this 12-year period, there were 143 specimens from uterine lesions submitted for frozen section diagnosis.

Table 1 presents the demographic and clinical characteristics of the cases submitted for frozen section analysis. The median age of patients was 43 years, median gravidity of G2.5, and parity of P2. Almost 95% of the lesions subjected for FS were from the uterus, with 48% accounting for the endometrium, and 47% for the myometrium.

Concordance and Accuracy Rates

The FS results such as benign, premalignant, and malignant were associated with the final histopathologic results with 96% agreement rate. A total of 4 cases were signed out as benign and 2 cases as premalignant on frozen section, but turned out to be malignant on final histopathologic diagnosis. There was 1 case of deferred FS diagnosis. For the 12-year period of this study, the accuracy rates of FS in the diagnosis of uterine tumors ranged from 90 to 100%. The overall accuracy of frozen section was 97%.

Table 2 presents the performance of frozen section in the three categories of diagnosis. It showed that frozen section has the highest sensitivity on premalignant and benign uterine lesions, but with the lowest specificity if these 2 categories were combined. The overall accuracy is highest for benign lesions compared to premalignant and malignant lesions, with rates of 97%, 90.9% and 95.7% respectively. The accuracy rate becomes equal between malignant lesions and benign-premalignant lesions taken as one.

Clinicopathologic variables and concordance rate

Age, gravidity, and parity of patients did not confound the agreement rates of FS and final paraffin diagnoses (p value > 0.05). In addition, the procedure by which the specimens were taken, the source, and the gross description of the specimens did not show significant effect on the concordance rate of frozen section diagnosis. However, specimens obtained by polypectomy, those sampled from the endometrium, and those described as polypoid showed higher trend of discordancy during FS, but the difference is not statistically significant (p value > 0.05) (Table 3).

Size of the uterine specimen and number of sections

The mean largest diameter of the uterine lesions subjected for FS was 9 cm (median: 7 cm), and the mean number of sections per specimen was 3. Analysis showed that the number of sections in relation to the size of the specimen has no impact in the concordance of FS and the final histopathologic results. Nevertheless, by utilizing the One Proportion Power Analysis, eleven sections per specimen would ensure a 99-100% accuracy rate for FS diagnosis.

Clinical impact of frozen diagnosis on surgical management

There were 6 cases signed out as benign and/or premalignant on FS but turned out malignant on final histopathologic diagnosis. All patients except one did not undergo appropriate surgical procedure. The surgeons of this case probably had high suspicion of malignancy despite a premalignant intraoperative FS diagnosis. This comprised 23% (5/21) of patients in whom complete surgical staging should have been performed. No patient was overtreated due to frozen section diagnosis.

Preoperative diagnosis and Frozen section results

This study explored on the concordance of the preoperative diagnosis with the result of the frozen section. The preoperative assessment was concordant with the frozen section diagnosis with 61% agreement rate (86/142). Among the discordant cases, 82% (45/55) had a preoperative consideration of malignancy which turned out benign on FS and final diagnosis.

Sample Size - Infinite Population

$$SS = \frac{Z^2 \times (p) \times (1 - p)}{C^2}$$

SS = Sample Size
Z = Z-value[A] (e.g., 1.96 for a 95 percent confidence level)
P = Percentage of population picking choice, expressed as decimal[B]
C = Confidence interval, expressed as decimal (e.g., .04 = +/- 4 percentage points)

A Z-values (Cumulative Normal Probability Table) represent the probability that a sample will fall within a certain distribution

The Z-values for confidence levels are:
1.645 = 90 percent confidence level
1.96 = 95 percent confidence level
2.576 = 99 percent confidence level

DISCUSSION

Intraoperative consultation is primarily performed to confirm the presence and histologic type of malignancy, as well as to determine the adequacy of resection by examining the surgical margins.[14] The confidence on frozen section of uterine lesions in this institution, particularly endometrial curettings, is very low due to previous reports on the low correlation of frozen section with the final histopathologic diagnosis.[15,16] Hence, most gynecologists perform conservative management or a preoperative biopsy prior to the definitive surgery.

Several findings have shown the limitations of frozen section, such as (1) frozen artifacts can produce inferior slides for microscopic examination, and (2) sampling errors can result from the heterogeneity of tumors. Hence, they are more difficult and challenging to interpret than paraffin-embedded sections. The uses of intraoperative frozen section in endometrial tumors are primarily to determine the grade, myometrial invasion and presence of extrauterine spread.[14,17]

The reported concordance rate of this study is 96% with an accuracy rate of 97%. The accuracy rate was not affected by the procedure by which the specimens were taken, the source, and the gross description of the specimens. In other studies, the reported concordance rate of frozen section is 85-96% in both depth of invasion and tumor grade.[4,18] In the prospective report by Kumar et al, there is a 98.7%, 100% and 97% concordance in the frozen section and paraffin diagnoses for histology, tumor size, and grade, respectively. A 7% discordance rate in histologic type, grade and myometrial invasion translated into a potential change in clinical management in 1.3% of patients.[17] Another study cited that evaluation of the depth of myometrial invasion with intraoperative biopsy showed a sensitivity, specificity and accuracy of 86%, 94% and 92%, respectively.[19] The present study however, did not investigate the grade, histologic types and invasion of the lesions that turned out to be malignant.

Ugaki et. al.[20] in their retrospective study, stated that the accuracy rate of intraoperative frozen section for the diagnosis of histology was 71%, whereas the accuracy rate of preoperative prediction by endometrial curettage was 68%. They concluded that the accuracy of frozen section tends to be slightly better than the preoperative procedures of MRI and endometrial surface biopsy. Thus, frozen section diagnosis is still useful for directing primary operative management. A similar investigation of Celim et al.[21] reported that preoperative examination has an accuracy rate of 95.8% for histological type and 90% histological grade. Utilizing frozen section, the accuracies of histological grade and subtype were found to be 92% and 98%, respectively.

In the more recent report of Stephan et.al.22, the correlation rate between frozen section and final paraffin section for histologic subtype, grade, and depth of myometrial invasion was 97.5%, 88%, and 98.2% respectively. Seven cases identified as complex atypical hyperplasia on FS turned out to be malignant on final paraffin section, resulting in two patients being undertreated.

Another scenario where frozen section is important is

Table 1. Demographic and clinical profiles of cases submitted for frozen section diagnosis.		
Patients' Profiles	**No. Of Cases**	**Percent**
Age		
Mean (Sd)	44.5	11.6
Median	43	
<40 Years-Old	59	41%
41-50	50	35%
>51	34	24%
Gravidity		
Mean (SD)	2.85	2.68
Median	2.5	
G0	29	20%
G1-G2	19	13%
G3 =/>	47	33%
Parity		
Mean (SD)	2.50	2.40
Median	2.00	
Po	32	22%
Pi-2	19	13%
P3=/>	45	31%
Sampling /Procedure		
Curettage	5	3.5
Hysterectomy/Myomectomy	126	88.1
Punch Biopsy	6	4.2
Polypectomy	6	4.2
Source of specimen		
Endometrium/ Endometrial mass	69	48.3
Myometrium	67	46.9
Cervix	4	2.8
Serosa	3	2.1
Gross Description		
Necrotic/Friable	8	5.6
Polypoid	31	21.7
Solid	70	49.0
Thickened	27	18.9
Tissue fragments	7	5.9

Table 2. Performance of FS in the three categories of diagnosis				
FZ Section Accuracy	**Benign**	**Pre-Malignant**	**Combined Benign and Pre-malignant**	**Malignant**
Sensitivity	96.7%	100.0%	100.0%	70.0%
Specificity	100.0%	88.2%	71.4%	100.0%
Likelihood Ratio +		8.50	3.50	
Likelihood Ratio -	0.03	0.00	0.00	0.30
Predictive value positive	100.0%	71.4%	95.3%	100.0%
Predictive value negative	78.9%	100.0%	100.0%	95.3%
Overall accuracy**	97.0%	90.9%	95.8%	95.7%

at the time of hysterectomy of patients with a preoperative diagnosis of premalignant lesions or atypical endometrial hyperplasia. In a recent prospective Gynecologic Oncology Group study, 42.6% of women with atypical endometrial hyperplasia on endometrial biopsy was found to have endometrial cancer at final histopathology of the hysterectomy specimen within 12 weeks from the diagnosis.[23] In the report of Toquero et al, the chance that

Table 3. Clinicopathologic variables and concordance of FS									
Profiles	Total		Concordant		Disconcordant		Deferred		
	n=143		n=136		n=6		n=1		p-value
Sampling									
curettage	5	3%	5	4%	0	0%	0	0%	
hysterectomy/myomectomy	126	88%	120	88%	5	83%	1	100%	0.815
punch biopsy	6	4%	6	4%	0	0%	0	0%	
polypectomy	6	4%	5	4%	1	17%	0	0%	
Source of specimen									
endometrium/EM mass	69	48%	63	46%	6	100%	0	0%	
myometrium	67	47%	66	49%	0	0%	1	100%	0.255
cervix	4	3%	4	3%	0	0%	0	0%	
serosa	3	2%	3	2%	0	0%	0	0%	
Gross description									
necrotic/friable	8	6%	8	6%	0	0%	0	0%	
polypoid	31	22%	27	20%	4	67%	0	0%	
solid	49	34%	49	36%	0	0%	0	0%	0.117
solid with cystic/ necrosis	21	15%	20	15%	0	0%	1	100%	
thickened	21	15%	20	15%	1	17%	0	0%	
tissue fragments	13	9%	12	9%	1	17%	0	0%	

atypical endometrial hyperplasia is upgraded to a malignant carcinoma on final histopathologic diagnosis is as high as 74%.[24] Hence, it is very crucial to request for intraoperative frozen section for macroscopically suspicious endometrial lesions with preoperative non-malignant diagnosis. The sensitivity, specificity and accuracy of frozen section are 73%, 93% and 81.8%, respectively in another report.[25]

In the study of Balik et al[10], there is an increased risk of malignancy in post-menopausal women, especially among those with endometrial polyp and complex atypia hyperplasia. Although clinicians rely on endometrial sampling results, diagnoses must be confirmed by frozen section when atypical endometrial hyperplasia and endometrial polyp are discovered among patients in the post-menopausal age group. In their review, the potential malignancy risk of endometrial polyp is 0.8%-4.8%. This risk increases with age and becomes higher in women greater than 65 years old. In the report of Tulandi et. al.[26], they stated that the only reliable preoperative test for determination of the types of myometrial tumors is either frozen section evaluation or paraffin tissue sections of surgical specimens.

There were two local studies on the utilization of frozen section for endometrial specimens. The first was a prospective study involving 43 patients. The overall agreement of frozen section and paraffin section diagnoses was 100%. The study implied that there might be more discrepancies with frozen section in samples from curettage or biopsy.[27] A retrospective study involving 36 patients with abnormal uterine bleeding who underwent hysterectomy with frozen section revealed a 97.2% accuracy rate in determining a benign or malignant lesion.[28]

There is good evidence that complete surgical staging with pelvic lymph node dissection is beneficial in high-risk endometrial cancer. However, patients who are classified as low risk (endometrioid type, grade 1-2, less than 50% myometrial invasion) can be safely treated with hysterectomy without lymphadenectomy.[29,30] Although systematic pelvic lymphadenectomy statistically significantly improved surgical staging, it did not improve disease-free or overall survival among low risk patients.[31] These reports were supported by the review of Vidal et al considering the results of PORTEC I and II.[32] Moreover, addition of lymphadenectomy would entail more related morbidities.[2,33,34] Other reports would still recommend complete surgical staging in all endometrial cancers.[33] In this institution, a complete surgical staging procedure is performed on all cases of endometrial cancer.

Selective surgical staging through intraoperative frozen section has been shown to be associated with decreased morbidity and costs compared to complete surgical staging.[35,36] However, according to Frumovitz et. al.,[37] the combination of intraoperative frozen section analysis for histologic grade and depth of myometrial invasion does not correlate well with final pathologic grade and stage. Data from their models suggest a significant risk of lymph node spread even for patients with seemingly low-risk disease. Until better markers of lymphatic spread become available, they do recommend complete surgical staging of all patients with endometrial cancer. Hence, intraoperative FS is important in order to know at least the extent of malignancy for definitive management.

Histology is considered the definitive diagnosis of uterine sarcomas. To date, the only reliable test for

detecting the types of myometrial tumors is investigation of either frozen sections or permanent formalin-fixed tissue sections of surgical specimens. FS of suspicious lesions might reduce the risk of laparoscopic morcellation of unsuspected leiomyosarcomas while still offering the advantages of a minimally invasive technique.[26] In another review, FS analysis is not reliable for excluding uterine sarcoma. Multiple areas must be sampled to achieve a precise diagnosis, while frozen section analysis typically depends upon a limited tissue sample. Therefore, there is a high possibility of a false-negative outcome even if a sarcoma is present.[38] It is not encouraged to perform FS for immediate diagnosis because generally, it does not allow a complete diagnosis. And when preoperative treatment is an option, radiological imaging may provide additional information to help the clinician evaluate the malignancy status intraopertively.[39] In this study, the agreement rate of FS with the final histopathologic diagnosis on sarcoma is 100% with only 6 cases studied. This shows that FS has a potential use in the diagnosis of sarcoma intraoperatively.

CONCLUSION

Concordance and accuracy rates of frozen section on uterine lesions are high regardless of the sampling procedure and source of the specimen. Increasing the number of sections during frozen section parallels that of the final histopathologic diagnosis. Frozen section for uterine lesions is a vital and cost-effective intraoperative decision to maximize care of patients. With this, under- and over-treatment of patients may be prevented.

Clinical variables such as age, gravidity, and parity of patients did not affect the agreement rates. The procedure by which the specimens were taken, the source and the gross description of the specimens did not show significant effect on the concordance rate of frozen section diagnosis.

An average of three sections for frozen diagnosis will give a considerably high accuracy rate, but increasing to eleven sections would further increase the accuracy rate to 100%.

Specimens taken by polypectomy or curettage, and those obtained from the endometrium showed higher disagreement rate but the difference is not statistically significant. Therefore, increasing the number of sections maybe an option to increase the probability of accurate frozen section result.

The present study provides evidence that contradicts previous reports on the low correlation of FS with the final histopathologic diagnosis. Results of this investigation could increase the confidence of the clinician on the utility of FS of uterine lesions. However, due to the limitations of frozen section, even with a relatively high accuracy rate, clinical decision intraoperatively would still be of utmost importance. Clinical decision would fill up the flaws of frozen section to prevent undertreatment of patients.

LIMITATION AND RECOMMENDATION

The limitation of this study is it being retrospective in nature. Although two local studies have already been conducted, the present investigation attempted to overcome the previous limitations of short study duration and small sample size. Unlike the previous reports, this study analyzed various uterine lesions and specimens, as well as the clinical and histopathologic characteristics of uterine lesions that may affect the performance rates of FS. Additionally, measures on how to overcome these sources of errors were explored, and potential predictors that may help in the intraoperative decision-making were determined. This study added to the limited knowledge on the clinical impacts of FS misdiagnosis on the surgical management of patients. A prospective study on the correlation of frozen section diagnosis with other clinical and sonographic variables is recommended. Tumor grade, histologic types, and myometrial invasion can also be included in the frozen section analysis.

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