Intraoperative Frozen Section Versus Intraoperative Gross Examination in the Assessment of Myometrial Invasion in Clinical Stage I Endometrial Cancer

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Objective: To evaluate the accuracy of frozen section and gross examination in assessing myometrial invasion in endometrial cancer with respect to definitive histological examination.
Methods: A retrospective study of women who underwent surgical treatment for clinical stage I endometrial cancer at the Pamela Youde Nethersole Eastern Hospital between 1 July 2003 and 30 June 2013 was conducted. The women underwent intraoperative gross examination or frozen section for assessment of myometrial invasion. Deep myometrial invasion was defined as involvement of ≥50% of the thickness of the myometrium. The final histopathology was considered the reference standard. The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value for both modalities were analysed.
Results: Of 115 women included in the study, 49 had gross examination and 66 had frozen section. Gross examination correctly identified (accuracy) the depth of myometrial invasion in 67.3% of cases with sensitivity, specificity, and positive and negative predictive values of 33.4%, 78.4%, 33.3%, and 78.4%, respectively. Frozen section correctly identified (accuracy) 95.5% of cases with sensitivity, specificity, and positive and negative predictive values of 92.3%, 96.2%, 85.7%, and 98.1%, respectively.
Conclusion: Frozen section appeared to be more effective than gross examination in assessing myometrial invasion and hence should be preferred as a basis for selective lymphadenectomy for clinical stage I endometrial cancer.
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Introduction

Endometrial cancer is the sixth most common cancer in women worldwide, and the twelfth most common cancer overall[1]. In 2012, endometrial cancer occurred in 320,000 women and caused 76,000 deaths. In 2011, carcinoma of the corpus was the fourth leading cancer for women in Hong Kong, with an incidence of 685 cases and a relative frequency of 5.3%[2]. Fortunately, most patients with carcinoma of the uterus present early with abnormal bleeding and therefore approximately 70% to 75% of patients are diagnosed with stage I disease, with high 5-year survival rates of 88% and 75% for stage IA and 1B, respectively[3].

In 1988, the International Federation of Gynaecology and Obstetrics (FIGO) Cancer Committee changed the staging of endometrial carcinoma from a clinical to a surgicopathological system[4]. While there

is general agreement about the necessity of complete surgical staging for high-risk endometrial carcinoma as the risk of nodal metastasis is high, the management of low-risk endometrial cancer is controversial. There has been an emerging dichotomy between European and North American treatment protocols for the management of low-risk endometrial cancer. Some authors advocate only hysterectomy and bilateral salpingo-oophorectomy without lymphadenectomy, while others suggest comprehensive surgical staging for all patients with low-risk disease[5,6].

Data have shown that the risk of lymph node metastasis is directly related to the depth of myometrial invasion[7]. Patients with more than 50% gross myometrial invasion had a 6.4-fold higher prevalence of pelvic

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lymph node metastases, a 6.9-fold higher prevalence of para-aortic lymph node metastases, and a 6.7-fold higher prevalence of advanced surgical stage than those with less than 50% myometrial invasion[7]. In what can be considered as early-stage carcinomas, i.e. when there is superficial myometrial invasion of less than 50% of the thickness of the myometrium, no invasion of the cervical stroma, tumour measurement <2 cm, and a less aggressive histological type (grades 1 and 2), it has been demonstrated that patients do not benefit from lymphadenectomy in terms of recurrence and survival[5]. Assessment of the degree of myometrial invasion is therefore essential to avoid under- or over-treatment.

Gross visual examination of the tumour cut surface during the operation is a common method to evaluate the depth of myometrial invasion. Several studies have proposed that intraoperative gross examination is comparable to the final histological evaluation[7-9]. Intraoperative frozen section (FS) was shown to be more accurate in assessing depth of myometrial invasion and enabling the tumour grade and cell type to be assessed; however, marked variability in reported accuracy has been found among institutions that used this method[10]. Frozen section has the disadvantage of prolonging operative time and requires a skilled histologist, thereby increasing the overall cost of the procedure. Since the introduction of selective pelvic lymphadenectomy for low-risk endometrial carcinoma in our unit, FS is preferred to gross examination for assessment of the depth of myometrial invasion. This study aimed to compare the validity of intraoperative FS compared with gross examination in predicting the depth of myometrial invasion.

Methods

This was a retrospective consecutive case note review of all patients who were diagnosed with endometrial cancer on curettage or office endometrial biopsy and were surgically treated at Pamela Youde Nethersole Eastern Hospital (PYNEH) from 1 July 2003 to 30 June 2013.

Only patients with clinical stage I disease with preoperative histological diagnosis of grade 1 or 2 endometrial cancer of low-risk cell types were included in this cohort. Clinical stage I disease was defined as tumour confined to the uterus on preoperative clinical examination, imaging, and intraoperative gross examination prior to hysterectomy. Women with clinical stage 2 or above or with synchronous ovarian cancer were excluded from this study as the extent of surgery would depend on factors other than grading or myometrial invasion. All patients

with preoperative diagnosis of grade 3 endometrial cancer or demonstrated clear cell, serous papillary differentiation, or carcinosarcoma were classified as high-risk cell types and were excluded from the study. Any patients without a definite preoperative tumour grade were also excluded from the study. Detailed patient demographics, operation details, and histology results were retrieved from the clinical records. The primary treatment for all recruited patients was hysterectomy and bilateral salpingo-oophorectomy done via open surgery, laparoscopy, or robot-assisted laparoscopy.

In the gross examination group, almost all patients were operated in or before 2009 and had routine pelvic lymphadenectomy regardless of the myometrial invasion. All the gross examinations were performed by one of the consultant gynaecologists who had a special interest in oncology. After removal of the uterus, its anterior wall was incised and opened along the uterine fundus to the cervix using a scalpel. At gross inspection of the uterine cavity and wall, the depth of myometrial invasion was noted as less or greater than 50% after a full-thickness incision was made through the tumour. The estimated depth of myometrial invasion was noted in the patient's operative record. These operative findings were compared with the final histological report.

In the FS group, the uterus, fallopian tubes, and ovaries were removed and submitted fresh for FS evaluation intraoperatively. The level of expertise for FS evaluation varied from fellow to senior consultant pathologists. The pathologist reporting the FS had the presenting pathology grade available for reference. The uterus was sliced at 3 to 5 mm intervals to look for possible myometrial invasion foci; the deepest focus was sampled. One to three blocks were taken for FS depending on the distribution and macroscopic appearance of the tumour. With myometrial invasion ≥50% on the FS, the decision of whether to perform lymph node dissection was taken by the surgeon.

Accurate FS pathology was defined as complete concordance between FS reporting and definitive reporting of paraffin sections with regard to the depth of myometrial invasion (<50% or ≥50%). Any degree of discordance between the FS and final histopathology was defined as inaccurate FS pathology. The same comparison was made between gross examination and paraffin sections on depth of myometrial invasion for degree of concordance.

The study was approved by the Cluster Research Ethics Committee of Hong Kong East Cluster under the

Hospital Authority. Statistical analysis was carried out by Predictive Analytics Software 18 (formerly the Statistical Package for the Social Sciences; SPSS, Inc., Chicago [IL], US) and Statistical Analysis System version 9.1 (SAS Institute, Inc., Cary [NC], US). For the association of categorical data, Chi-squared test and Fisher's exact test were used according to the data pattern. For continuous data with a highly skewed distribution, a non-parametric test (i.e. Mann-Whitney U test) was used. A p value of <0.05 was considered statistically significant.

Results

A total of 203 women were diagnosed with uterine cancer and underwent hysterectomy at PYNEH during the study period, of whom 196 were diagnosed with endometrial cancer. Only 115 patients fulfilled the criteria of clinical stage I disease with low-grade tumour on preoperative histology; 49 had gross examination and 66 had frozen section. The general baseline epidemiological data were similar in both groups (Table 1).

Gross examination only correctly identified (accuracy) the depth of myometrial invasion in 67.3% of the 49 patients. A positive test was defined as deep myometrial invasion with involvement of ≥50% of the thickness of the myometrium.

The false-negative and false-positive rates were 66.7% (8/12) and 21.6% (8/37), respectively (Table 2). The sensitivity, specificity, positive predictive value, and negative predictive value were 33.3%, 78.4%, 33.3%, and 78.4%, respectively.

Table 1. Demographics and surgicopathological factors*

	Gross examination (n=49)	Frozen section (n=66)	Total (n=115)	p Value
Age at operation (years)	58 (52.5-73.5)	56 (52-65.25)	58 (52-68)	0.19
Body weight (kg)†	60.75 (51.63-65.93)	58.75 (51-66.63)	60.3 (51.25-66.35)	0.82
Menopausal status				
Premenopausal	16 (32.7)	22 (33.3)	38 (33.0)	0.94
Postmenopausal	33 (67.3)	44 (66.7)	77 (67.0)	
Postmenopausal age (years)	50 (47-54)	51 (50-53)	50 (50-54)	0.21
Hypertension	27 (55.1)	28 (42.4)	55 (47.8)	0.18
Diabetes mellitus	6 (12.2)	11 (16.7)	17 (14.8)	0.51
Tamoxifen	3 (6.1)	2 (3.0)	5 (4.3)	0.65
Polycystic ovarian syndrome	0	2 (3.0)	2 (1.7)	0.51
Hereditary non-polyposis colorectal cancer gene carrier	1 (2.0)	3 (4.5)	4 (3.5)	0.64
Unopposed hormone replacement therapy	1 (2.0)	0	1 (0.9)	0.43
Preoperative tumour grade				0.71
1	40 (81.6)	52 (78.8)	92 (80.0)	
2	9 (18.4)	14 (21.2)	23 (20.0)	

* Data are shown as median (interquartile range) or No. (%)
† Missing data of 1 patient in the gross examination group

Table 2. Depth of myometrial invasion in gross examination and frozen section compared with final histopathology

Final histopathology	Gross examination (n=49)		Frozen section diagnosis (n=66)	
	<50%	≥50%	<50%	≥50%
<50%	29/37 (78%)	8/37 (22%)	51/53 (96%)	2/53 (4%)
≥50%	8/12 (67%)	4/12 (33%)	1/13 (8%)	12/13 (92%)

The FS correctly identified (accuracy) the depth of myometrial invasion in 95.5% of the 66 patients. The false-negative rate was 7.7% (1/13) and false-positive rate was 3.8% (2/53) [Table 2]. The sensitivity, specificity, positive predictive value, and negative predictive value were 92.3%, 96.2%, 85.7%, and 98.1%, respectively.

Discussion

Because of the prognostic importance of intraoperative findings, FIGO adopted a surgicopathological system for the staging of endometrial carcinoma in 1988[11]. The incidence of lymph node metastasis increases with grade of tumour, depth of myometrial invasion, cervical or adnexal involvement, lymphovascular invasion, and poor histological type[4].

The role of lymphadenectomy in the management of early endometrial cancer has been discussed extensively since the introduction of surgicopathological staging. A significant number of women with clinical early-stage disease have extrauterine disease within the pelvic or para-aortic lymph nodes[4]. However, routine lymphadenectomy increases morbidity, such as bleeding, lymphocyst formation, and lymphoedema[12-14]. Also, addition of lymphadenectomy to the staging surgery of early-stage endometrial cancer has been shown not to improve the survival[5] despite earlier data that demonstrated survival benefits[15]. In order to avoid morbidity due to overtreatment, identification of the risk factors that can accurately predict pelvic lymph node involvement and therefore guide the need for selective lymphadenectomy in high-risk patients is indicated.

The key finding from our study was that FS analysed by general anatomic pathologists appeared to be much more accurate than gross examination by experienced surgeons in the assessment of myometrial invasion in endometrial cancer, with accuracies of 95.5% and 67.3%, respectively.

Unlike previous studies of FS and gross examination, which included all cases of endometrial cancer, this study is clinically relevant as it concentrated on the subgroup of patients for whom the decision to perform full surgical staging is made during surgery.

Gross examination of the depth of myometrial invasion is an inexpensive, fast and, in some studies, accurate method for identifying patients at increased risk for extrauterine metastases. The accuracy of intraoperative gross examination of myometrial invasion has been evaluated in several studies with controversial results.

Several studies[7,8,16] found the procedure to be highly accurate (>86%). However, Larson et al[7] and Franchi et al[8] both did prospective studies of larger sample sizes that included endometrial cancer of all cell types, grades, and stages. The uteri were incised along the lateral walls along the course of the uterine vessels for examination instead of being cut on the anterior wall along the uterine fundus to the cervix as in our study. Doering et al[16] conducted a study limited to patients with clinical stage I endometrial cancer, but all cell types and grades of tumour were included. Noumoff et al[17] found that the depth of myometrial invasion by gross evaluation was in accordance with the final specimen in only 67.7% of cases, which corresponds to our findings of 67.3% accuracy.

In this study, we found that FS assessment of the depth of myometrial invasion in patients with endometrial cancer was considerably higher than gross examination, with accuracy of 95.5%. Other studies evaluating the accuracy of FS support our findings. A retrospective analysis of 209 patients in which presenting histology of grade 3 or high-risk cell types were excluded also demonstrated accuracy of 94.7%[18]. An older study of 204 patients also demonstrated accuracy of 95%[19]. However, other prospective studies have reported accuracy as low as 67%[20]. Since the sample for FS is taken from the point of deepest macroscopically visible invasion, sampling error is possible. It has been commented that it would be particularly difficult to determine the best spot for sampling if the tumour macroscopically appeared to be confined to the endometrium and showed no signs of discrimination such as change of colour or consistency[21].

The discrepancies between the different studies described above could lie with the expertise of the surgeons who performed gross examination or of the pathologists who performed FS. In the present study, all the gross examinations were performed by the few consultant gynaecologists who had a special interest in oncology, whereas FSs were performed by pathologists who had obtained their fellowship, albeit with varying levels of experience. Interobserver and intraobserver errors could be present, and further prospective studies to evaluate the impact of such errors and to correlate with the experience of individual observers would be worthwhile.

With FS, the duration of operation is prolonged resulting in longer exposure to general anaesthesia and higher risk of infection for the patient. In addition, since the extent of the operation will be dictated by the result of the FS, the exact time allocated for each operation will be difficult

to estimate beforehand, thus creating problems in resource management. In order to avoid these shortcomings, other imaging techniques such as ultrasonography, computed tomography, and magnetic resonance imaging (MRI) have also been employed to evaluate the depth of myometrial invasion with different degrees of reliability[7]. Among these methods, MRI is currently seen as the best technique for myometrial assessment. However, Furukawa et al[10] reported the diagnostic accuracy with MRI to be as low as 54.8% whereas Manfredi et al[22] reported diagnostic accuracy of 89%. Further studies have yet to be performed to compare the diagnostic accuracy of FS or gross examination with MRI in predicting the degree of myometrial invasion. Apart from accuracy, there could also be concerns about the cost-effectiveness and availability of such expensive imaging technology, especially in developing countries.

Our study have several limitations. First, this retrospective study could be subjected to data bias, as only records with complete data were included for analysis. Second, despite the fact that the study period spanned more than 10 years, the number of cases that satisfied the preset inclusion criteria of clinical low-risk stage I endometrial cancer and could therefore be analysed was limited. Third, there could be interobserver and intraobserver errors as surgeons and pathologists with varying experience were performing the gross examinations and FSs.

Nevertheless, we believe this local study still provides valuable information for other centres in Hong Kong, which may still be relying purely on gross examination to decide which subgroup of patients require lymphadenectomy in clinical stage I endometrial cancer.

Although MRI may provide better preoperative planning of the indicated surgical procedure and time allocated for each operation, as well as allowing more precise preoperative counselling to the patient, its accuracy for myometrial invasion assessment is still controversial and requires further evaluation. To date, there is still no consensus on a gold standard for preoperative or intraoperative assessment of myometrial invasion in clinical stage I endometrial cancer. According to our data, FS is highly accurate and so, in terms of decision-making, it should be valuable and effective. Moreover, FS has benefit over MRI and gross examination in providing assessment of tumour grade. This is particularly important as some studies have suggested that correlation between presenting tumour grade and final histopathology is often poor[23,24].

In conclusion, this study suggests that FS is more accurate than gross examination in the assessment of myometrial invasion in early-stage endometrial cancer, so the decision on the need for selective lymphadenectomy should be based on FS findings.

Declaration

The authors declared no conflicts of interest in connection with this article.

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