ORIGINAL ARTICLE

The accuracy of intraoperative assessment of myometrial invasion in early-stage endometrial cancer and its association with lymph nodes metastasis

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ABSTRACT

Introduction: Assessment of the depth of myometrial invasion is important for optimal surgical strategies and treatments. This study aims to assess the accuracy of intraoperative evaluation of myometrial invasion in FIGO early-stage endometrial cancer and its association with lymph node metastasis, impacting treatment decisions and patient outcomes.

Materials and Methods: This is a retrospective study analysis of 150 patients diagnosed preoperatively with early-stage endometrial cancer who underwent surgical staging in Institut Kanser Negara (IKN), Putrajaya from January 2018 until December 2022. After the hysterectomy procedure, all uterine specimens will be opened for intraoperative assessment of the depth of myometrial invasion by a gynae oncology surgeon. According to FIGO classification, the depth was assessed to be either greater or less than 50% of myometrial thickness. Gross estimation during operation will be compared with the final histopathological result. This study aims to evaluate the accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of intraoperative myometrial invasion compared to the final histology. Secondly, this research aims to explore the association between depth of myometrial invasion and lymph nodes involvement.

Results: A total of 150 patients were recruited, the sensitivity and specificity of intraoperative assessment in detecting depth of myometrial invasion were 42% and 94%, respectively and the PPV and NPV were 78% and 76%. The overall accuracy was 77%. The sensitivity of only 42% in this study suggested that intraoperative myometrial assessment missed as many as 58% of patients who had deep myometrial invasion. A total of 9 (6%) patients were found to have lymph nodes involvement with 5 of them showing deeper myometrial invasion. Although there was a higher number of lymph node involvement observed in cases with deeper myometrial invasion, the difference was not statistically significant (p > 0.05).

Conclusion: We conclude that intraoperative assessment of myometrial invasion is still reliable and inexpensive method to practice. Accuracy of assessment can be improved in integrate MRI and transvaginal ultrasound in preoperative assessment.

KEYWORDS:
Endometrial Carcinoma, Intraoperative assessment, Myometrial Invasion, Lymph Nodes Metastasis

INTRODUCTION

Endometrial cancer ranks as the sixth most common cancer globally among women, with a notable surge in its incidence observed over the last two decades.[1] According to the summary Malaysia National Cancer Report 2017 – 2021, endometrial cancer stands as the fourth most prevalent malignancy among women in Malaysia.[2] The incidence rate in Malaysia shown an upward trend, increasing from 3.8 to 4.6 cases per 100 000 population, highlighting the growing concern surrounding this form of cancer among women.[2]

Approximately 48.6 % of women in Malaysia were diagnosed with Stage 1 endometrial cancer at presentation.[2] The mainstay of treatment for early-stage endometrial cancer is hysterectomy and bilateral salpingo-oophorectomy with or without systematic lymphadenectomy.[3] Lymphadenectomy has been associated with several postoperative complications such as lymphoedema, deep vein thrombosis (DVT), and paralytic ileus due to autonomic nerve injuries. In more extensive procedures, it can even result in life-threatening conditions such as major vessels injuries.[4]

According to European Society of Gynecology Oncology (ESGO) guideline, Grade 1 and Grade 2 endometrioid tumors and myometrial invasion less than 50% is considered as low-risk endometrial cancer and the risk of lymph node involvement is less than 5%.5 Based on the European Society for Medical Oncology (ESMO) guideline, in low-risk endometrioid Adenocarcinoma FIGO Stage 1A, lymphadenectomy can be omitted.[3] Several studies also showed that there is no benefit of systematic lymphadenectomy in Stage 1a endometrial cancer.[6,7] It is also widely opinion that systematic lymphadenectomy is recommended for cases involving Grade 2 to Grade 3 endometrioid tumors that infiltrate over half of the myometrial thickness and non-endometrioid histological types.[3,5]

Several methods available for evaluation of myometrial invasion either preoperative or intraoperative assessment. Preoperatively, magnetic resonance imaging (MRI) and

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transvaginal sonography (TVS) had been widely used to assess myometrial invasion.[8] However, not all centers can provide ultrasound experts and some limitation in medical imaging such as MRI, include challenges in securing timely appointments. Therefore, not all centers especially in Malaysia government hospital settings are able to offer early MRI appointment, which can potentially impact the scheduling surgeries.[8,9] Intraoperative frozen section is one of the accurate methods for evaluation of myometrial invasion and consider as high accuracy.[8] Unfortunately, not all centers can provide trained pathologist specifically experts in gynecologic oncology that can interpret intraoperative frozen section specimen.[10] Therefore, the accuracy of assessment of myometrial invasion is important to avoid unnecessary lymphadenectomy and overtreatment in patient diagnosed with early endometrial cancer.

Our hospital at the Institut Kanser Negara (IKN), Putrajaya serves as a prominent referral center, handling a substantial volume of endometrial cancer cases per year. The primary objective of this study is to measure the accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of our routine practice of gross intraoperative assessment of myometrial invasion compared to the final histology in early stage of endometrial cancer. Our secondary objective is to assess and compare the association between superficial and deep myometrial invasion with lymph node metastasis.

MATERIALS AND METHODS

Approval from the Medical Research and Ethics Committee (MREC) was obtained prior to the commencement of this study (NMRR ID-24-00793-OOS).

Study Design and Participants

This retrospective study involved 150 patients with pre-operative histopathological diagnosis of endometrial carcinoma based on either dilatation and curettage or hysteroscopic specimens. All the newly diagnosed patients with endometrial cancer FIGO Stage 1 were operated and continued treatment and follow up in IKN between January 2018 to December 2022. All the detailed information were reviewed from IKN's Hospital Information System 'Fisicien' such as patient characteristics, histology, treatment, intraoperative gross examination results of the uterine specimens and final histopathological report.

The eligible patients were aged 18 and older with newly diagnosed preoperatively Endometrial Cancer (FIGO) Stage 1 that underwent surgical procedures and continued follow up in IKN. Exclusion criteria encompassed patients with Endometrial Cancer Stage 2 and above diagnosed preoperatively, synchronous tumour or more than one primary cancer and those with incomplete medical record.

There is no routine preoperative assessment in IKN Hospital for preoperative staging of early endometrial cancer. Diagnostic imaging such as transvaginal ultrasound, computed tomography, or magnetic resonance imaging are used differently depending in the physician's decision and option of treatment. All patients decided and agreed for operation will undergo comprehensive surgical staging including hysterectomy and bilateral salpingo-oophorectomy either by abdominal approach or laparoscopy. Pelvic lymphadenectomy was performed in all patients. Intraoperatively, after the hysterectomy procedure, anterior wall of uterus was incised using scalpel or Mayo Scissor and opened vertically along the uterine fundus to cervix to assess the depth of myometrial invasion. Full thickness incisions were made through the tumour, myometrium and cervix. The assessment process is shown in Fig. 1. Intraoperative gross assessment of depth of myometrial invasion was carried out by the gynaecologic oncologist in each case, which were noted to be less than or equal to 50% or more than 50% involvement of myometrial invasion. All the parameters were described in the operative notes and were compared with the final histopathology report.

Statistical Analysis

The data analysis will be done using the SPSS version 27. Accuracy, sensitivity, specificity, positive predictive value and negative predictive value were calculated. Descriptive statistics were done for qualitative data as number and percentage. Analysis for independent variables were done using the Chi Square test or Fisher's exact test as appropriate. The p-value of <0.05 was considered significant.

RESULTS

A total of 330 patients newly diagnosed with endometrial cancer between January 2018 until December 2022. Out of these, 180 patients were excluded due to Stage 2 and above (n=71), patients with synchronous tumour or with more than one primary cancer (n=21), patients with incomplete operative findings (n=11), and another 36 patients were also excluded, in view of during COVID-19 period, the patients underwent surgery at IKN and subsequently received postoperative follow-up at their respective hospitals for review of the final histopathology results. As a result, 150 patients were recruited in the study (Fig.1).

The baseline characteristics of patients are summarized in Table 1. The mean age was 55 ⌖ 11.7 years old and majority of them are among the postmenopausal group (60%). Mean body mass index was 31 ⌖ 6.56 kg/m2. Low parity among the highest risk in early endometrial cancer (46%). Majority of them had multiple comorbidities, which comprised 43% of the patients.

The procedure and histologic information are summarized in Table II. Majority of the patients had endometrioid histology (97.3%) and grade 1 tumour (54%). 97 patients underwent open laparotomy (64.7%), and others had minimally invasive surgical approach (35.3%).

Intraoperative assessment of depth of myometrial invasion was correctly correspond with final histopathological report in 115 (76.7%) out of 150 patients. Table 3 compare the intraoperative myometrial assessment to final histopathology results. The sensitivity in detecting myometrial invasion was only 42% and specificity was 94% (Table IV). The PPV and NPV was 77.7 % and 76.4 % respectively. False gross intraoperative assessment was found

Table I: Baseline characteristics of patients

	n	%
Age (years; mean ± SD)	55 ± 11.7	
Body Mass Index	31 ± 6.56	
Menopausal State		
- Pre-menopause	60	40%
- Post-menopause	90	60%
Parity		
- Low parity	69	46%
- Para 2 – 4	60	40%
- More than 4	21	14%
Comorbidities		
- Diabetes Mellitus	8	5.3%
- Hypertension	23	15%
- Multiple	65	43%
- Others	6	4%
- No medical illness	48	32%

Table II: Procedure and histopathologic information

Characteristic	n	%
Pre-operative Endometrial Sampling		
- Office endometrial sampling	72	48%
- Hysteroscopy and curettage	78	54%
Operation mode		
- Laparotomy	97	64.7%
- Laparoscopy	53	35.3%
Histological Cell type		
- Endometrioid	146	97.3%
- Non-endometrioid	4	2.7%
Tumor grading (preop)		
- Grade 1	81	54%
- Grade 2	61	40.7%
- Grade 3	8	5.3%

Table III: Comparison of Intraoperative Assessment of Myometrial Invasion versus Final Histopathologic Results

Intraoperative gross assessment	Final Histopathology Result	
	Less than 50% invasion	More than 50% invasion
Myometrial invasion < 50 %	94 (94%)	29 (58%)
Myometrial invasion > 50 %	6 (6%)	21 (42%)

Table IV: Diagnostic test related to intraoperative gross assessment of depth of myometrial invasion in endometrial cance

Sensitivity	42%
Specificity	94%
Negative predictive value	76.4%
Positive predictive value	77.7%
Accuracy	76.7%

in 35 patients (23.3%). The depth of myometrial invasion was underestimated in 29 patients, and it was overestimated in 6 patients.

Regarding relation between myometrial invasion and positive lymph nodes metastasis, it was found that there was no significant relation between lymph nodes metastasis and the depth of myometrial invasion. A total of 9 (6%) patients were found to have lymph nodes involvement with 5 of them showing deeper myometrial invasion based on final histopathology report. Although there was a higher number of lymph node involvement observed in cases with deeper myometrial invasion, the difference was not statistically significant ($p > 0.05$).

DISCUSSION

According to the World Health Organization (WHO), the increasing prevalence of overweight is a concerning issue in many countries, including middle and lower-income countries such as Malaysia.[11] Based on the data collected from the National Health and Morbidity Survey (NHMS) 2019, the prevalence of overweight among adults in Malaysia was reported to be 50.1% and it was significantly higher among females.[11] As the prevalence of obesity among women in Malaysia continues to rise, it serves as one of the contributing factors to the increasing trend of endometrial cancer within Malaysian population.[2]

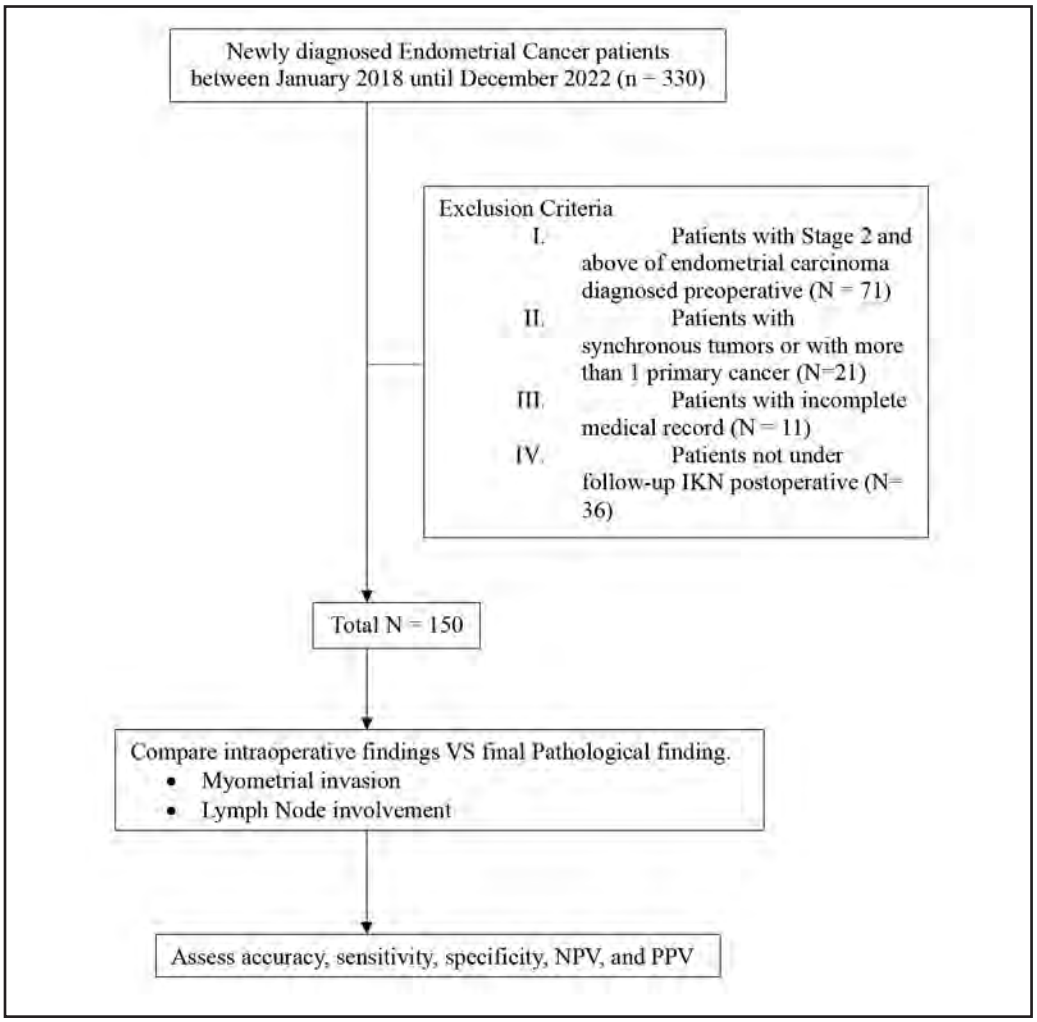

Fig. 1: Flow chart

Majority of women diagnosed with early-stage endometrial cancer are obese and have multiple comorbidities such as diabetes mellitus and hypertension.[12] Obese women undergoing prolong and extensive surgery such as systematic lymphadenectomy may be at increased risk of perioperative complications.[12] Certainly, lymphadenectomy is deemed important for comprehensive staging in endometrial cancer due to its significance in postoperative adjuvant therapy and prognosis.[13] Based on the latest FIGO staging of endometrial cancer 2023, lymph node staging should be performed in intermediate or high-risk endometrial cancer.[14] Hence, a selective approach of lymphadenectomy should be considered in low-risk early stage endometrial cancer, to balance between benefits of complete staging and the risks associated with the surgical procedure.[13]

Apart from tumor grading and histological type, depth of myometrial invasion is one of the most important risk factors for lymph node metastases.[15] Deeper myometrial invasion has been found to be associated with lymph nodes involvement.[15,24] There are several preoperative and intraoperative tools for surgical staging to identify the depth of myometrial invasion such as transvaginal ultrasound, magnetic resonance imaging (MRI), intraoperative gross assessment and intraoperative frozen section.[15] Each method exhibited varying levels of accuracy in identifying the depth of myometrial invasion.[16-18,22] Predictive value of transvaginal ultrasound in determination of depth of myometrial invasion is 80-87%.[15]

The sensitivity and specificity of MRI in detecting depth of myometrial invasion were 65.6% and 88.5%, respectively.[18] Unfortunately, not all government hospital were equipped with MRI facilities offering early appointment availability.[16] Intraoperative gross examination has been proposed as simple and inexpensive tools to visualize the depth of myometrial invasion.[16] Studies have shown that myometrial invasion is a strong predictor of node metastasis, with a sensitivity rate reaching up to 86%.[19] Various methods, whether used individually or in combination, preoperatively or intraoperatively are used to categorize patients into low or high-risk groups of endometrial cancer for complete surgical staging.[22]

Based on our study, we found that intraoperative gross assessment had good specificity (94%) and accuracy (76.7%) but relatively poor sensitivity (42%). Compared to previous meta-analysis, the pooled sensitivity and specificity of intraoperative gross examination compared with final histology were 71% and 91% respectively.[17] The study

conducted by Cem Yagmur Ozdemir et al, demonstrated a low sensitivity of 34 % and a specificity of 100% in predicting deep myometrial invasion.[20] Differences in the expertise and abilities of the surgeons could be a potential explanation for the comparatively reduced sensitivity observed during intraoperative macroscopic examinations in their research.[20]

The sensitivity of only 42% in our study showed that intraoperative myometrial assessment missed as many as 58% of patients who had deep myometrial invasion. The detection of myometrial invasion by gross examination exhibits poor sensitivity, which can be attributed to several factors. These factors include the experience of the surgeon, the infiltrative pattern and grading of the disease, as well as retrospective design method employed.

Nowadays, intraoperative frozen section analysis serves as a valuable tool in assessing the depth of myometrial invasion.[21] Based on the systemic review, intraoperative frozen section had higher accuracy in detecting the depth of myometrial invasion.[21] In contrast, ESGO guideline did not agree frozen section analysis due to poor reproducibility.[5] Apart from that, it is also not widely available in all facilities in view of inadequate specialized, skilled and available gynae pathologist to interpret the frozen section specimen.[21]

Many studies shown correlation between deeper myometrial invasion and lymph nodes metastasis.[4,23] In low-risk endometrial cancer cases, comprising superficial myometrial invasion and low-grade endometrioid histology, lymph node involvement was observed in 6% of patients.[5] This figure closely aligns with our study population, where 6% of the 150 recruited patients had lymph node metastasis.

Our institute is considered to have one of the largest numbers of cancer cases per year in Peninsular Malaysia, highlighting the strength of our study. In addition, our institute has appropriate human resources, including skilled oncologists, a resident training system and pathologists. Our limitation of this study was data collection. Some of the cases were continue follow-up postoperatively in other institution. Another limitation was the study was retrospective in nature. Lastly, for the best results, a change of study design to a prospective data collection approach and the level of operator who examined the uterine specimen each case, might be more suitable to achieve higher accuracy of intraoperative gross assessment in this study.

CONCLUSION

Intraoperative myometrial assessment during surgical staging showed good specificity and accuracy but limited sensitivity. These findings suggest that it remains a valuable clinical tool to guide surgeon to decide the best surgical treatment for each individual. However, combination of other modalities such as transvaginal ultrasound and MRI should be implemented accordingly to maximize the diagnostic accuracy.

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