Review Article/บทฟื้นฟูวิชาการ

Hysteroscopy in Endometrial Cancer

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Abstract

Endometrial cancer is one of the most common gynecological malignancies. The majority of the patients present with abnormal vaginal bleeding; hence, the disease is diagnosed in the early stages. Usually transvaginal ultrasound and endometrial biopsy are the beneficial investigations, notably with occasional failure to obtain adequate endometrial tissue. Hysteroscopy increases the sensitivity and accuracy to identify endometrial cancer; however, the pressure of fluid distension media should be optimized because of the concern of impaired prognosis from malignant cell spillage. In sentinel lymph node mapping, hysteroscopic injection is considered as a method to potentially increase the detection rate in the para-aortic area. Fertility-sparing treatment of endometrial cancer in early stages is feasible with the combination of hysteroscopic resection and progestin therapy.

Keywords: Endometrial cancer, Hysteroscopy

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Introduction

Endometrial cancer is the second most common gynecologic malignancy globally and in Thailand. The mortality is low, comparing to cervical cancer and ovarian cancer,[1] due to the nature of the disease with early clinical manifestation, abnormal vaginal bleeding. The early diagnosis is undeniably crucial but the appropriate investigation with high accuracy is still disputable. For many decades, fractional curettage has been deemed the gold diagnostic standard for the women presenting with abnormal vaginal bleeding.[2] With the revolution of ambulatory practices and minimally invasive approaches, currently the additional diagnostic options are transvaginal ultrasound (TVS), office-based endometrial biopsy and hysteroscopy.[3]

Hysteroscopy is an ideal method to evaluate lesions or pathology of the uterine cavity. The scope was inserted through a cervix to visually examine the endometrium, with the help of extension media. As a minimally invasive procedure, it can be performed in the office, day surgery unit or operating theatre.

Hysteroscopy in the Diagnosis of Endometrial Cancer

TVS has the distinct advantages of minimal invasion and convenience, with the immediate results. The measured endometrial thickness, exceeding 4 mm in post-menopausal women, is considered a triage for further investigations to obtain the tissue for histopathology.[4] However, the measurement is merely applicable in the post-menopausal group and, at the end of the day, the preoperative histopathological report is essential to prove malignancy. The recent committee opinion from The American College of Obstetricians and Gynecologists endorsed TVS as a useful tool to initially evaluate women presenting with postmenopausal bleeding, with the 99% negative predictive value for endometrial cancer. Still, when histopathological evaluation was indicated and endometrial biopsy failed to obtain adequate sample, hysteroscopy, with dilatation and curettage was recommended as the next step of management.[5]

Office-based endometrial biopsy is an accessible and low-cost procedure to gain endometrial tissue. Still, there were high sample inadequacy (5.9%) and histological diagnosis inconsistency (14.3%).[6]

In the recent systematic review and meta-analysis, as compared to hysteroscopy, the weighted failure rate of endometrial biopsy was as high as 11% (range, 1% - 53%) and insufficient specimens were reported to be 31% (range, 7% - 76%). Among 7% (range, 0% - 18%) of the women with insufficient or failed samples, an endometrial cancer was registered.[2]

In a study, assessing the concordance between preoperative hysteroscopic directed biopsy and the final pathology, the overall accuracy to detect endometrial cancer was 80.2% with 79.4% concordant pathological grading.[7]

Another meta-analysis in 2015 reported that the estimated sensitivity of hysteroscopy for endometrial cancer was 82.6% (95% confidence interval [CI], 66.9% - 91.8%) and the specificity was 99.7% (95% CI, 98.1% - 99.9%).[8]

Ianieri et al[9] proposed the new scoring system for diagnosing hyperplasia and adenocarcinoma, which compiled the commonly found morphologic hysteroscopic findings, for instance, irregular aspect of the polyps, atypical vessels, and crumbling of the endometrial neoplasm. This scoring system revealed the high sensitivity and specificity of 95.4% and 98.2%, respectively, to identify endometrial cancer.

Regarding preoperative staging of endometrial cancer, hysteroscopic directed biopsy showed a higher accuracy than endometrial biopsy (92% vs 58%; $P < 0.001$) to differentiate between atypical endometrial hyperplasia and cancer, with an exception of equal accuracy to identify grade 3 tumor (93% vs 92%). Hysteroscopic directed biopsy was also more accurate to indicate cervical involvement than magnetic resonance imaging (MRI) and TVS (94% vs 84% vs 80%; $P < 0.02$).[10]

Based on these additional benefits in the detection of endometrial pathology, gynecologists should familiarize themselves with the hysteroscopic techniques to integrate this procedure in their practices.

Narrow Band Imaging Hysteroscopy

Narrow band imaging (NBI) is an endoscopic technique, using an illumination system with narrow bandwidth filters. Therefore, the emitted light is restricted to the selected wavelengths which penetrate the tissue differently, enhancing the pattern, texture and vascularity of the mucosa.[11]

Surico et al[12], reported the increased sensitivity of NBI hysteroscopy to predict endometrial cancer, comparing to conventional hysteroscopy (94.7% vs 84.2%) without the loss of specificity (97.9% vs 99.5%).

The multicenter controlled study, recruiting 801 outpatient women, was conducted by Tinelli et al[13] to confirm the improved sensitivity, in comparison with conventional hysteroscopy (93% vs 81%; $P < 0.05$). Nonetheless, there was no difference in specificity (99% vs 99%) and accuracy (99% vs 98%).

NBI utilization was expanded to flexible hysteroscopy and it retained the significantly higher sensitivity (97.2%; 95% CI, 90.3% - 99.7%) than flexible hysteroscopy with white light (82.6%; 95% CI 74.4% - 89.0%). Meanwhile, the specificity was 90.6% (95% CI, 75.0% - 98.0%) which was similar to conventional flexible hysteroscopy (85.1%; 95% CI, 76.3% - 91.6%).[14]

Peritoneal Dissemination of Malignant Cells

The use of distension media, whether it is carbon dioxide, or liquid media such as 32% dextran 70, 1.5% glycine, Ringer's or normal saline solution, is necessary to obtain optimal visualization. Since the introduction of hysteroscopy to increasingly detect endometrial cancer, there has been a raised concern on the possibility of malignant cell dissemination in to the peritoneal cavity which can possibly impair the prognosis of disease.

Polyzos et al,[15] who conducted a systemic review and meta-analysis in 2010, comparing between the patients with and without preoperative hysteroscopy, reported a statistically significant higher rate of positive peritoneal cytology in the patients undergoing preoperative hysteroscopy (Odd ratio [OR], 1.78; 95% CI, 1.13 - 2.79; $P = 0.01$). This meta-analysis included the studies dating before 2009, when the new FIGO staging, disregarding peritoneal cytology, was launched. Consequently, hysteroscopy resulted in the significantly higher disease upstaging, solely due to positive peritoneal cytology (OR, 2.61; 95% CI, 1.47 - 4.63; $P = 0.001$). A non-significant trend for higher malignant cells was noticed in the hysteroscopy group when the distension media pressure reached or exceeded 100 mmHg. Sufficiently powered trials were required to define the correlation between hysteroscopy and prognosis.

Another meta-analysis, performed in 2011, confirmed a statistically significant higher rate of positive peritoneal cytology in the patients undergoing preoperative hysteroscopy; however, the subgroup analysis showed no significant difference in the patients with early diseases (stage I and II) (OR, 2.97; 95% CI, 0.82 - 10.7; $P = 0.10$). No significant difference was observed between both groups when the inflation pressure reached or exceeded 100 mmHg (OR, 2.29; 95% CI, 0.92 - 5.68; $P = 0.08$). There was no evidence to support the distinctive disease survival rate or recurrence following hysteroscopy.[16]

The subsequent retrospective study of 227 patients, going through either hysteroscopy or dilatation and curettage (D&C), demonstrated no difference in the overall incidence of positive peritoneal cytology (13.2% in the hysteroscopy group vs 12% in the D&C group; $P = 0.80$). Regardless, a detailed analysis of the patients with stage I endometrial cancer revealed a significantly higher rate of positive cytology in the hysteroscopy group (12.8% vs 3.4%; $P = 0.04$).[17]

Considering type II endometrial carcinoma, with the conspicuous concern for worsened prognosis and peritoneal dissemination, a cohort retrospective analysis of 140 patients was accomplished in 2017. Correspondingly, 30% of the patients undergoing diagnostic hysteroscopy had positive peritoneal cytology, in comparison with 12% in the D&C group ($P = 0.002$). The median disease-specific survival was clinically different (53 months vs 63.5 months); even so, no statistical significance was proved ($P = 0.34$), including the patients in stage I and II (60 months vs 71 months; $P = 0.82$). The recurrent rate (33% vs 32%; $P = 0.92$) and locations of recurrence were indifferent.[18]

Although there are multiple studies on the peritoneal dissemination of malignancy following hysteroscopy, the results are still controversial, with the lack of randomized controlled trials or long-term monitoring on patients. Preoperative diagnostic hysteroscopy should be considered for the patients when the virtues of acquiring adequate sampling outweigh the potential risk. Owing to the insufficiency of data on appropriate hysteroscopic fluid pressure, the operator should implement the lowest pressure of distension media possible.[19] Care must be taken to avoid uterine perforation and the operator's level of expertise should be optimal.

Hysteroscopy and Sentinel Lymph Node Detection

As the gynecologic malignancy treatment is entering the era of minimally invasive and customized treatment, sentinel lymph node (SLN) biopsy is an attractive concept. Initially introduced to melanoma treatment, currently SLN is plausible for many gynecologic malignancies, especially endometrial cancer. Several ongoing trials are in progress to validate the application of SLN identification and biopsy. The debatable issues were the most suitable method for tracer administration and the variation of SLN locations in endometrial cancer, especially in the para-aortic area.

Kang et al[20] carried out the meta-analysis on SLN procedure in endometrial cancer in 2011, suggesting the detection rate and sensitivity of 78% (95% CI, 73% - 84%) and 93% (95% CI, 87% - 100%), respectively. Moreover, pericervical injection was preferred in terms of detection rate ($P = 0.03$) and the hysteroscopic injection was associated with the decreased detection rate ($P = 0.04$).

From the multicenter, prospective, cohort trial in 385 patients, SLN mapping, by cervical injection of indocyanine green (ICG), detected the isolated para-aortic SLN in 3 patients. Two of these three patients had metastatic para-aortic lymph node with negative pelvic lymph node.[21]

A systematic review and meta-analysis, by Bodurtha et al[22] in 2017, reported the detection rate of 81% (95% CI, 77% - 84%) with a 50% (95% CI, 77% - 84%) bilateral pelvic lymph node detection rate and 17% (95% CI, 11% - 23%) para-aortic detection rate. Although cervical injection maximized the bilateral pelvic SLN detection, the para-aortic detection was obviously lower, in comparison with the uterine injection (7% vs 27%; $P = 0.001$).[22]

The recent study in a single center reported 202 SLN procedures, after hysteroscopic peritumoral injection of either ICG or technetium 99m, out of which disclosed a detection rate as high as 93.2%. The sensitivity was 86.4% (95% CI, 68.4% - 100%) and the negative predictive value was 96.4% (95% CI, 86.7% - 100%). In 50.8% of the cases, SLN was identified in both pelvic and para-aortic lymph nodes. Five patients' SLN situated only in the para-aortic area. This SLN study contradicted the rest with the non-inferiority of detection rate from the hysteroscopic injection.[23]

The review and consensus recommendation from The Society of Gynecologic Oncology mentioned the hysteroscopically guided sub-endometrial tumor injections as the method with higher rate for para-aortic SLN detection; while, the cervical injection was preferable due to the highest detection rate and the simplicity of administration. As yet, the accuracy of para-aortic SLN detection was not entirely established.[24]

Hysteroscopy for Treatment

At present, the childbearing age of women has gradually delayed. An early stage endometrial cancer, stage IAG1, is generally considered as a disease with good prognosis and fertility-sparing management has progressively been accepted. Besides the hormonal therapy, hysteroscopic resection plays a part in terms of tumor removal.

There were a number of case series but one of the groundbreaking studies belonged to Mazzon et al,[25] who also introduced the three-step technique of hysteroscopic resection. Six patients were successfully treated with four subsequent pregnancies.[25]

Alonso et al[26] published a review of literature in 2015, comprising 4 studies with a total of 36 patients. All of the patients were treated with hysteroscopic resection, followed by the hormonal therapy. The complete response rate was 88.9% and 4 recurrences were documented.

De Marzi et al[27] evaluated the rate of intrauterine adhesion and responses of 23 patients with atypical complex hyperplasia or endometrial cancer grade 1, after hysteroscopic resection and hormonal therapy with megestrol acetate 160 mg daily. No intrauterine adhesion was observed in the follow-up hysteroscopy. One relapse of disease was recorded after the median follow-up time of 25 months (range, 8 - 37). Subsequently, six patients conceived with seven pregnancies.[27]

A large case series was from a single institution in Italy, with a 15-year of experience. Twenty-eight patients who wish for fertility-preservation were recruited for the hysteroscopic resection, followed by hormonal therapy with oral megestrol acetate or levonorgestrel intrauterine device. Twenty-five patients (89.3%) achieved the complete response, with the median time to complete response of 3 months (range 3-9 months) after progestin therapy. Two recurrences (7.7%) were encountered, accompanying with the synchronous ovarian cancer. Out of 57.7% of the patients who attempted to conceive, the pregnancy rate and live birth rate were 93.3% and 86.6%, respectively.[28]

There was increasing data on the hysteroscopic resection of endometrial cancer; yet, so far, the possibility of conducting a randomized controlled trial is limited by the restricted number of endometrial cancer patients managed with the fertility-sparing option. A larger trial or meta-analysis, with the data focusing on the patients' overall survival is crucial to progressively justify this conservative treatment.

Conclusions

Nowadays, hysteroscopy has an important role in the diagnosis of endometrial cancer, remarkably in the cases suspected of cancer, ensuing the inadequacy or failure of endometrial biopsy. NBI is a novel technology that tentatively refine the sensitivity of hysteroscopy. Even if there was no solid evidence to empathize the deteriorated prognosis of cancer from the cell spillage, the hysteroscopic fluid pressure should be closely monitored. SLN biopsy is inevitably the future of endometrial cancer treatment and hysteroscopic injection of tracers is the promising method to enhance para-aortic mapping. Fertility-sparing treatment, consisting of hysteroscopic resection and hormonal therapy, is an alluring alternative, awaiting more studies to verify the outcomes.

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กล้องส่องโพรงมดลูกและมะเร็งเยื่อบุโพรงมดลูก

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บทคัดย่อ

มะเร็งเยื่อบุโพรงมดลูก (Endometrial cancer) เป็นมะเร็งที่พบบ่อยในสตรี ส่วนใหญ่ผู้ป่วยมักมาพบแพทย์ตั้งแต่ระยะเริ่มแรกของโรค เนื่องจากอาการนำส่วนใหญ่คือ เลือดออกผิดปกติทางช่องคลอด นอกจากประวัติการตรวจร่างกายแล้ว การตรวจอัลตราซาวนด์ (Ultrasound) ทางช่องคลอดและการเก็บชิ้นเนื้อภายในโพรงมดลูกมีบทบาทสำคัญในการวินิจฉัยโรค แต่ในกรณีที่ได้ชิ้นเนื้อไม่เพียงพอสำหรับการวินิจฉัย การตรวจเพิ่มเติมด้วยกล้องส่องโพรงมดลูกมีบทบาทเพิ่มความไวและความแม่นยำ แต่ต้องควบคุมความดันสารน้ำที่ใช้ถ่างขยายโพรงมดลูกให้เหมาะสม เพื่อลดการกระจายของเซลล์มะเร็งเข้าสู่ช่องท้อง ซึ่งอาจมีผลต่อการพยากรณ์โรค ในการทำแผนที่ต่อมน้ำเหลืองเซนทิเนล (Sentinel lymph node mapping) การฉีดสารตรวจจับผ่านทางกล้องส่องโพรงมดลูกมีแนวโน้มช่วยเพิ่มอัตราการตรวจพบต่อมน้ำเหลืองข้างหลอดเลือดแดงเอออร์ตา (Para-aortic area) นอกจากนี้ การส่องกล้องในโพรงมดลูกและตัดเนื้องอกร่วมกับการรักษาด้วยฮอร์โมนโปรเจสติน (Progestin) ยังสามารถใช้ดูแลรักษาผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกระยะเริ่มต้น ซึ่งช่วยให้ผู้ป่วยมีโอกาสหายสูง

คำสำคัญ: มะเร็งเยื่อบุโพรงมดลูก กล้องส่องโพรงมดลูก

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