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ORIGINAL ARTICLE

# Characteristic hysteroscopy appearance considerations for detecting uterine endometrial malignancies

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**Abstract**

**Aim:** The effectiveness of hysteroscopy in diagnosing endometrial lesions has been demonstrated, showing high diagnostic accuracy for malignant endometrial lesions. Although the characteristic appearances of atypical and malignant endometria have been reported, they are not definitive and sometimes complicated. This study aimed to identify a small number of characteristic features to detect endometrial abnormalities using a simple judgment system and analyze the diagnostic characteristics and their accuracy in endometrial malignancy diagnosis.

**Methods:** We performed a retrospective analysis of hysteroscopy video data of 250 patients, of which we selected for analysis based on pathology examination 152 cases with benign changes, 16 with atypical endometrium, and 18 with carcinoma in situ or endometrial cancer. Endometrial characteristics assessed included protrusion, desquamation, extended vessel, atypical vessel, and white/yellow lesion.

**Results:** Multivariable analysis revealed that desquamation ($p = 0.001$, odds ratio [OR] 5.28), atypical vessels ($p < 0.001$, OR 8.50), and white/yellow lesions ($p = 0.011$, OR 1.37) were significant predictors for endometrial malignancy. From their contribution status, scoring points of 4, 6, and 1 were settled according to the odds ratio proportions. When scores ≥5 (at least both desquamation and white/yellow lesions or only atypical vessels) were used to define endometrial malignancy, sensitivity and specificity were 100% and 92%, respectively. When detecting cancer, atypical, and benign cases, sensitivity and specificity were 88% and 90%, respectively.

**Conclusion:** Our characteristics hysteroscopic findings showed a higher predictive ability in detecting endometrial malignancies. However, further examination with more cases would be needed to accurately diagnose endometrial malignancy by hysteroscopy.

**KEYWORDS**
diagnosis, endometrial cancer, endometrial hyperplasia, endometrial neoplasms, hysteroscopy

## INTRODUCTION

Recently, the incidence of endometrial cancer (EC) has increased in several countries, including Japan. The number of EC cases in 2018 in Japan was 17 089, and EC was the most prevalent gynecological malignancy, surpassing cervical ($n = 10\,978$) and ovarian ($n = 13\,049$) cancers.[1] Several studies have demonstrated the advantage of hysteroscopy in diagnosing endometrial malignancies, including high diagnostic accuracy for EC. Positive hysteroscopy

results are highly suggestive of EC.[2] Although the characteristic appearances of atypical and malignant endometria have been reported, they are not definitive. Scoring systems for malignant hysteroscopic findings were previously reported, based on mostly many characteristic components containing such as atypical vessels, irregular endometrial thickening, dilated glandular orifices, crumbling of endometrial neoplasm, multiple or irregular aspects of the polyp, growth of cerebroid and arborescent aspects, and abnormal endometrial color. These appearances include benign lesions, some of which are unclear.[3,4] Those scoring systems are detailed and reflect many aspects of endometrial changes, but are somehow complicated to judge or to get used to the procedure. The visual diagnosis of EC is based on a gross distortion of the endometrial cavity resulting from a nodular, polypoid, papillary, or mixed pattern of neoplastic growth. Focal necrosis, microcalcifications, friable consistency, and atypical vessels are other characteristics of EC that can be easily detected on hysteroscopic inspection.[5] We have been performing hysteroscopy for endometrial abnormalities, including both benign lesions and malignancies, focusing on the following endometrial characteristics: protrusion, desquamation, extended vessel, atypical vessel, and white/yellow lesion. Among those five characteristics, we aimed to identify any single or combination of characteristics that might contribute to endometrial malignancy detection and diagnosis accuracy.

# METHODS

## Patients

This retrospective analysis included patients who underwent hysteroscopy at the University of Tokyo Hospital Clinic between September 2017 and December 2018 with opt-out consent. Among the 250 patients who underwent hysteroscopy, we selected for analysis based on pathology findings 152 patients with benign tumors, 16 with atypical endometrium, and 18 with carcinoma in situ or EC. The ethics committee approved this study (No. 3084-(3), the University of Tokyo Hospital).

## Hysteroscopy

Hysteroscopy examinations were performed under medical insurance for patients requiring medical care for various reasons. All examinations were performed in an outpatient setting without anesthesia. We used a VISERA HYF type V (OLYMPUS, Tokyo, Japan) with a 3.8 mm flexible scope for diagnostic hysteroscopy. The saline perfusion pressure was 225 mmHg (30 kPa) except when atypical or malignant diseases were suspected before or during hysteroscopy. The pressure was reduced to 75 mmHg (10 kPa) in such cases.

For malignancy evaluation, we focused on the following five uterine endometrial features, as shown in Figure 1: protrusion, desquamation, extended vessel, atypical vessel, and white/yellow lesions. Protrusions are often present as polyps and submucosal myomas; however, they might also be present in atypical and malignant diseases such as atypical polypoid adenomyoma and some EC.[6,7] Desquamation is when a small white mass, assumed to be necrotic tissue flaking from the endometrium, floats in the uterine cavity and appears as a snowstorm. This phenomenon has been previously reported to be a characteristic observed, for example, in patients with abnormal uterine bleeding and irregular endometrium or malignant possibility.[8,9] Extended vessels are those extending to the top of the protrusion. Atypical vessels include those with meandering, expansion, inconsistent diameter, and disruption, frequently mentioned as features representing endometrial malignancy.[4,6,10] A white/yellow lesion indicates focal necrosis or microcalcifications on the endometrial surface.[5] An experienced consultant, blinded to the pathology results, retrospectively judged these five features as positive or negative using hysteroscopy videos. Pathological results of the endometrium were checked either by blind biopsy or surgery. Endometrial cancers were identified from the results of hysterectomy. As for atypical endometrial cases, they were confirmed by hysterectomy or by several times of biopsy to exclude underestimation of cancer.

## Statistical analysis

The Kruskal–Wallis test and multivariable logistic regression analysis were performed using JMP Pro, Version 15, SAS Institute Japan. Differences were considered statistically significant at $p < 0.05$.

# RESULTS

## Patient characteristics

Among 250 cases who underwent hysteroscopy, 64 were unclear for pathological examination and subtracted from analysis. Of the 16 patients in the atypical endometrium group, 15 had atypical endometrial hyperplasia, and 1 had atypical polypoid adenomyoma. Of the 18 patients with malignant tumors, 10 had complex atypical endometrial hyperplasia-to-in situ carcinoma, and 8 had grade 1 EC.

## Endometrial tissue score analysis

The multivariable analysis results presented in Table 1 show that of the five hysteroscopic features, desquamation ($p = 0.001$), atypical vessels ($p < 0.001$), and white/

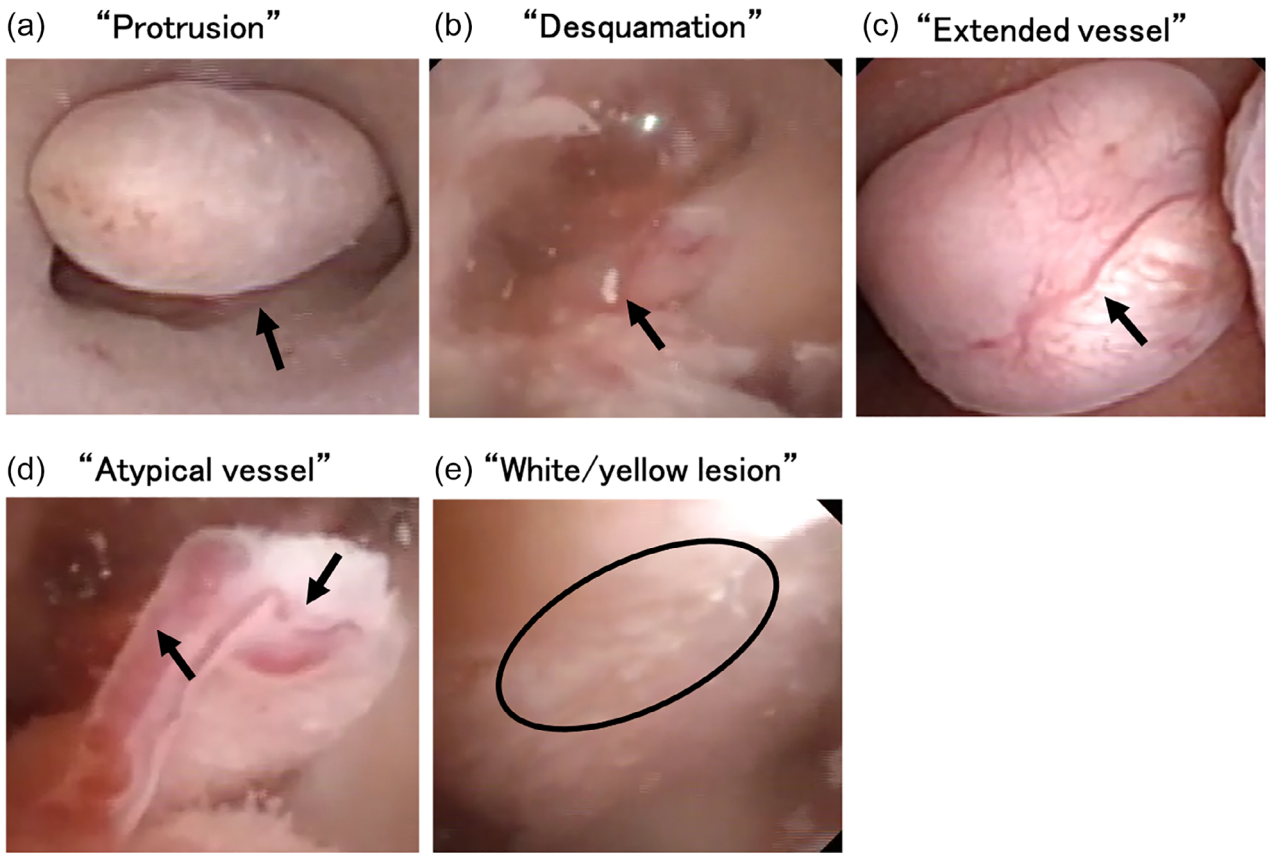


**FIGURE 1** Five major abnormal findings observed by hysteroscopy. Arrows and circles in the panels indicate typical parts. (a) Protrusion; (b) desquamation; (c) extended vessel, a vessel extended to reach the top of any protrusion; (d) atypical vessel, including meandering and expansion (left arrow) and disruption (right arrow); (e) white/yellow lesion.

**TABLE 1** Multivariable analysis of five characteristic findings in relation to endometrial malignancy.

| Characteristic findings | *p*-Value | Regression coefficient (95%CI) | Odds ratio | Likelihood ratio | Score |
|---|---|---|---|---|---|
| Protrusion | 0.0835 | −0.67 (−1.56–0.06) | | | |
| Desquamation | 0.0014 | 0.94 (0.37–1.52) | 5.28 | 10.75 | 4 |
| Extended vessel | 0.2694 | 0.44 (−0.35–1.25) | | | |
| Atypical vessel | <0.0001 | 2.32 (1.59–3.21) | 8.50 | 44.68 | 6 |
| White/yellow lesion | 0.0110 | 0.86 (0.18–1.54) | 1.37 | 5.68 | 1 |

*Note*: Characteristics with $p < 0.05$ were determined as malignancy-related findings. Contributions to malignancy diagnosis were calculated.
Abbreviation: CI, confidence interval.

yellow lesions ($p = 0.011$) were independent predictors for malignancy. The odds ratios (ORs) of these three factors were 5.28, 8.50, and 1.37, respectively. We assigned them scoring points based on their odds ratio proportions: when a score of 1 for white/yellow lesions (OR = 1.37), 4 for desquamation (from ORs ratio of desquamation to white/yellow lesions: 5.28/1.37 = 3.85), and 6 for atypical vessels (8.50/1.37 = 6.20).

The scores of the 186 patients and their pathological findings are shown in Figure 2. The median scores for benign, atypical, and malignant tumors were 0, 4.5, and 10, respectively, differing significantly among the groups ($p < 0.001$; Figure 2a). The number of cases with each score in the benign, atypical, and malignant groups is shown in Figure 2b. Hysteroscopy of malignant tumors rarely showed a score of 0, whereas pathologically benign cases rarely scored high.

The scoring system sensitivity and specificity in differentiating malignancies from benign and atypical endometria by hysteroscopy and the various cutoff values are presented in Table 2. When endometrial malignancy diagnosis was made, if the score was ≥5 points, the sensitivity and specificity in detecting endometrial malignancy were 100% and 92%, respectively. In addition, positive and negative predictive values were 58% and 100%,

respectively. Hysteroscopic findings reached a score of ≥5 if atypical vessels or desquamation and white/yellow lesions were detected.

As shown in Table 3, if any of the three characteristic findings (atypical vessels, desquamation, and white/yellow lesions) were detected, an atypical lesion or malignancy was found with a sensitivity of 88% and specificity of 90%, with positive predictive value of 67% and negative predictive value of 97%.

Many studies have reported adverse events during office hysteroscopy.[11,12] However, we observed no adverse events such as vasovagal syndrome,[11]

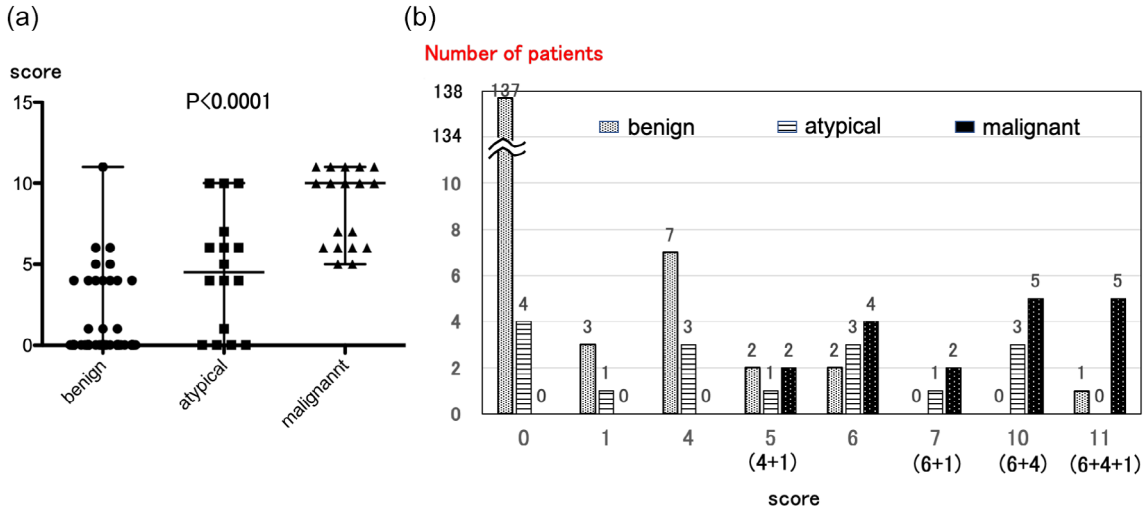


**FIGURE 2** Score distribution according to the pathological malignancy. (a) Scores and pathology results. The scores differed significantly among the three groups (non-parametric one-way analysis of variance; $p < 0.001$). (b) Number of cases in each score (0 to 11) in the benign, atypical, and malignant groups.

**TABLE 2** Cutoff values for diagnosing uterine endometrial cancer using the devised scoring system.

| Hysteroscopy score cut off ≥ | Malignant ($n = 18$) | Benign ($n = 152$) + atypical ($n = 16$), total $n = 168$ | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|
| 1 | 18 | 27 | 100 | 84 |
| 4 | 18 | 23 | 100 | 86 |
| 5 | 18 | 13 | 100 | 92 |
| 6 | 16 | 10 | 89 | 94 |
| 7 | 12 | 5 | 67 | 97 |
| 10 | 10 | 4 | 56 | 98 |
| 11 | 5 | 1 | 28 | 99 |

*Note*: The hysteroscopy score was calculated by summing the scores of desquamation (4 points if positive), atypical vessels (6 points), and white or yellow lesions (1 point).

**TABLE 3** Cutoff values for diagnosing uterine endometrial atypia and cancer using the devised scoring system.

| Hysteroscopy score cut off ≥ | Malignant ($n = 18$) + atypical ($n = 16$), total $n = 34$ | Benign ($n = 152$) | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|
| 1 | 30 | 15 | 88 | 90 |
| 4 | 29 | 12 | 85 | 92 |
| 5 | 26 | 5 | 76 | 97 |
| 6 | 23 | 3 | 68 | 98 |
| 7 | 16 | 1 | 47 | 99 |
| 10 | 13 | 1 | 38 | 99 |
| 11 | 5 | 1 | 15 | 99 |

*Note*: The hysteroscopy score was calculated by summing the scores of desquamation (4 points if positive), atypical vessels (6 points), and white or yellow lesions (1 point).

bleeding that required additional treatment, or uterine perforation.[12]

## DISCUSSION AND CONCLUSION

Office hysteroscopy has been reported as useful for diagnosing EC and sampling endometrial tissue.[13] Notable complications of diagnostic hysteroscopy for malignant lesions include the risk of dissemination. Some reports, including a meta-analysis of nine trials, showed that suspicious or positive peritoneal cytology at the time of surgery was associated with a history of hysteroscopy[14–17]; however, several reports concluded that positive cytology after hysteroscopy did not affect the clinical stage or prognosis of patients with type I EC. For those with type II EC, which is more aggressive, the presurgical examination should be restricted to biopsies or curettages.[16,18–20]

Hysteroscopy can detect malignant features such as irregular or ulcerated surfaces with areas of necrosis due to insufficient blood supply. Ulcerations, found only in malignant lesions, were considered the endpoint of irregular surfaces.[21] While ulceration is not an inevitable feature of endometrial malignancies, especially in early stages such as atypical endometrium, desquamation might serve as a proxy for initial-stage ulceration. Hysteroscopy can observe several endometrial characteristics. Judgment and diagnosis become more complicated with the increase in the number of characteristics used in a hysteroscopic scoring system, while the specificity and positive predictive value decrease. Harika et al. introduced a hysteroscopy scoring system of eight components to diagnose endometrial malignancy. They reported sensitivity, specificity, and positive and negative predictive values of 100%, 67.8%, 22.2%, and 100%, respectively, for diagnosing EC when the score was ≥9.[3,4] We selected the minimum set of components required to diagnose endometrial malignancy, focusing on those directly linked to malignancy with accuracy. On the other hand, when detecting atypical or benign cancers, a case with at least one of three characteristics could be possible. However, the sensitivity and specificity were less accurate than detecting cancer only. This indicated that our three features would be inadequate when detecting atypical endometrium.

The positive and negative predictive values were not considered in this study. We accept many patients suspected of having endometrial malignancy referred by other clinics; therefore, the endometrial malignancy rate among our patients would be higher than that of the general population undergoing hysteroscopy examination. Furthermore, samples with unclear pathological results were excluded. Therefore, our positive and negative predictive values would have been higher or lower than the expected results following hysteroscopic examinations in general clinics.

Office hysteroscopy is considered a safe procedure with a slight risk of a vasovagal reaction. Agostini et al. reported a vasovagal reaction risk of under 1% based on examining over 2000 patients. The rate when using a rigid hysteroscope was higher than when using a flexible one ($p = 0.009$) and when using $CO_2$ than when using saline ($p = 0.014$), regardless of the indication for hysteroscopy or the parity and menopausal status of the patient.[11] The complication rate during operative hysteroscopy, including vasovagal reaction, was estimated at 1.6%.[22,23]

The limitations of this study would be that case numbers were small for both endometrial malignancy and endometrial atypia, and some diagnostic training for hysteroscopy would still be required to detect malignant characteristics, although they are not so complicated. Furthermore, the study outcome is not generalizable because the population is not representative, there was a higher prevalence of disease than in day-to-day clinical practice, and only one assessor did the hysteroscopy video review.

Recently, artificial intelligence-assisted technologies have been introduced into the medical imaging field. Endometrial malignancy diagnosis using a combination of artificial intelligence and hysteroscopy is a next-generation technology.[24,25] The usefulness of technology was demonstrated in a study that showed that the diagnostic accuracy, sensitivity, and specificity were all approximately 90%.[25] Accurate sampling of suspicious lesions is indispensable for pathological diagnosis. Soon, biopsies of suspicious lesions detected by artificial intelligence based on office hysteroscopy will become available and commonly used.

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### CONFLICT OF INTEREST STATEMENT

Dr. Mayuyo Mori is an Editorial Board member of JOG Journal and a co-author of this article. To minimize bias, she was excluded from all editorial decision-making related to the acceptance of this article for publication. Besides this, the authors declare no conflict of interest for this article.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, because of the requirement by the ethics committee for opt-out consent.

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