Comparison of Two Sampling Procedures for Diagnosing Endometrial Carcinoma and Hyperplasia: Outpatient Tissue Biopsy Versus Cytologic Examination

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Abstract

Background: We compared the sensitivity of 2 diagnostic procedures—tissue biopsy and cytologic examination—for detecting endometrial carcinoma and hyperplasia in outpatients. The patients’ degree of acceptance of these methods was also evaluated.

Methods: The study included 124 women who had been diagnosed with carcinoma and hyperplasia by histological examination in private clinics or were suspected to have endometrial carcinoma and hyperplasia—for example, those presenting with uterine bleeding and/or abnormal endometrial morphology on cytologic examination—at Jikei University Hospital, University of Yamanashi Hospital and National Hospital Organization Kure Medical Center from January 28, 1999, to August 28, 2006. Both cytologic examination (using Endocyte®) and tissue biopsy (using Suresample™) of the endometrium were performed before complete curettage and/or hysterectomy. McNemar’s chi-square test was used to evaluate the statistical significance.

Results: The sensitivity of tissue biopsy for detecting endometrial carcinoma and hyperplasia was 84% and 91%, respectively, and that of cytologic examination was 78% and 55%, respectively. There was a significant difference in the sensitivity of the 2 methods for detecting hyperplasia (p = 0.045). No patients complained of severe pain, and no other complication occurred during both methods. Both methods were well tolerated by the patients.

Conclusion: Our data indicate a certain diagnostic superiority of tissue biopsy over cytologic examination.

Keywords: Endocyte®, Suresample™, Endometrial carcinoma; Hyperplasia; Diagnostic procedure

Introduction

Each year, there are about 142,000 new cases of endometrial carcinoma worldwide, and an estimated 42,000 women die because of this type of cancer [1]. The surgical stage, determined according to the criteria of the International Federation of Gynecology and Obstetrics, reflects the 5-year survival, which is around 85% for stage I, 75% for stage II, 45% for stage III, and 25% for stage IV disease [1]. Endometrial cancer is often preceded by endometrial hyperplasia, which is a spectrum of morphologic and biologic alterations of the endometrial glands and stroma and is often secondary to hyperestrogenism. It has been shown that progression to carcinoma occurs in 1% of patients with simple hyperplasia, 3% of patients with complex hyperplasia, 8% of patients with simple hyperplasia with atypia, and 29% of patients with complex hyperplasia with atypia [2].

The Japanese Ministry of Health and Welfare investigated the effectiveness of mass endometrial carcinoma screening. During the 9-year study, 126 cases were detected by mass screening and 1,069 cases were diagnosed in outpatient clinics. Early-stage cases were significantly more frequent in the screening group (p < 0.001): 88.1% of the patients in the screening group had stage I disease, as compared to 65.3% of the patients in the outpatient group. The 5-year survival rate was also significantly higher in the screening group than in the outpatient group (94.7% vs. 84.3%; p = 0.041) [3]. These statistics suggest that early detection of endometrial carcinoma and hyperplasia is necessary to improve the prognosis of these diseases.

Outpatient endometrial sampling is now replacing complete curettage as the method of choice for diagnosing endometrial disease. This procedure is easy to perform, associated with minimal patient discomfort, and reported to be highly sensitive in detecting endometrial carcinoma [4-14]. The Pipelle de Cornier® device (Laboratoire CCD, Paris, France) is an endometrial biopsy sampler that is seemingly better tolerated by patients than most other endometrial biopsy devices [15,16]. However, we cannot use this device because it is not available in Japan. Instead, we collect endometrial tissue by using the Suresample™ device (Laboratoire CCD, Paris, France) is an endometrial biopsy sampler that is seemingly better tolerated by patients than most other endometrial biopsy devices [15,16]. However, we cannot use this device because it is not available in Japan. Instead, we collect endometrial tissue by using the Suresample™ device (Laboratoire CCD, Paris, France) which is similar in design to the Pipelle® device. This endometrial sampler has an aperture not only on the side near the distal tip, similar to the Pipelle® device, but also at the distal tip and is expected to collect a larger sample. However, in Japan, cytologic examination is often used initially to detect endometrial carcinoma and its precursor stages, as stipulated by a 1987 health insurance law for the elderly. During this cytologic
examination, endometrial cells are collected using the Endocyte® sampler (Laboratoire CCD, Paris, France). The cell processing technique is similar to that used for a cervical cytology smear and is thus relatively inexpensive.

A few studies have compared the 2 above-mentioned sampling procedures. However, in these studies, the diagnostic sensitivity was not sufficiently evaluated because of the small number of carcinoma and hyperplasia cases used for the investigation [13,17]. In the present study, in order to determine the optimal technique for detection of endometrial carcinoma and hyperplasia, we compared the diagnostic sensitivity of cytologic examination using Endocyte® and tissue biopsy using Suresample®; we also estimated the degree of patient acceptance for both these procedures.

Materials and Methods

This study included 124 patients who had been diagnosed with carcinoma and hyperplasia by histological examination in private clinics or were suspected of having carcinoma and hyperplasia—for example, those presenting with uterine bleeding and/or abnormal endometrial morphology on cytologic examination—at Jikei University Hospital, University of Yamanashi Hospital and National Hospital Organization Kure Medical Center from January 28, 1999, to August 28, 2006. Patients with complications such as pregnancy, acute pelvic infection, infection of the uterine cervix, and coagulation disorder were excluded. Both cytologic examination and tissue biopsy were performed for all the patients; the former was performed before the latter. This study was approved by the hospital ethics committees, and informed consent was obtained from all the patients.

Cytologic materials were obtained using Endocyte®. The Endocyte® sampler is composed of flexible plastic, is presterilized, and measures 21 cm in length; its greatest external diameter is 2.6 mm. Along its length are graduation marks that guide the operator in introducing the device into the endometrial cavity, as described by Byrne [8]. The collected cellular components were placed on a glass slide, crushed, and smeared using the regular pull-apart method. After fixation in 95% alcohol, Papanicolaou staining was performed. The cytologic findings were divided into different classes on the basis of structural abnormalities, such as papillary clusters, type A stroma, arborescent clusters, and back-to-back structures (Table 1) [18,19]. Outpatient tissue biopsy was performed using Suresample®. Suresample® is a flexible, clear polypropylene suction curette containing an internal piston and measures 24 cm in length and 3.1 mm in external diameter. It has a round aperture with a diameter of 1.5 mm at the distal tip of its sheath and 2 oval apertures each measuring 5.9 × 1.5 mm at 3.2 mm from the distal tip. In order to obtain a specimen, the device is inserted into the uterine cavity and negative pressure is then created within the sheath by rotating the device while also being moved back and forth several times within the uterine cavity. Suresample® is then withdrawn, and the tissue sample is ejected into 10% buffered formalin by using the piston. The entire sample is histologically examined.

After collecting the sample for both procedures, the patient was asked to comment on the intensity of any pain experienced during the procedure. Pain or discomfort was subjectively graded as mild, moderate, or severe. Thereafter, in 93 patients, complete curettage and/or hysterectomy was performed. In the remaining 31 patients, these procedures were not performed because of the attending physician’s decision or the patient’s refusal. The final diagnosis was made on the basis of the histological findings of the samples obtained during complete curettage and/or hysterectomy. The diagnosis made using both outpatient procedures was then compared with the final diagnosis.

We estimated sensitivity for detecting endometrial carcinoma, sensitivity for detecting endometrial hyperplasia, and specificity of each procedure separately and reported them with 95% confidence intervals. Patients who were not diagnosed histologically were excluded from this analysis. McNemar’s chi-square test was used to compare each measure of diagnostic accuracy. All reported p values for statistical tests are two-tailed, and p < 0.05 was taken to indicate statistical significance. Data management and statistical analysis were conducted at an independent academic data center, Translational Research Center, Kyoto University Hospital, using SAS version 9.2 (SAS Institute, Cary, NC).

Results

The median age of the patients was 54 years (range: 23-85 years). Of the 124 patients, 68 (55%) were postmenopausal, and 88 (71%) showed abnormal uterine bleeding.

Of the 93 patients who underwent complete curettage and/or hysterectomy, 69 were finally diagnosed with endometrial carcinoma, 11 with endometrial hyperplasia, 6 with other tumor, and 7 with normal endometrium. Of the 69 patients with endometrial carcinoma, 50 had endometrioid adenocarcinoma; 12, adenosquamous; 2, serous papillary adenocarcinoma; 2, clear cell adenocarcinoma; 1, mucinous adenocarcinoma; and 2, mixed carcinoma. Of the 50 endometrioid adenocarcinoma tumors, 33 were well differentiated, 12 were moderately differentiated, and 5 were poorly differentiated. Of the 11 patients with endometrial hyperplasia, 5 had complex hyperplasia with atypia, 3 had complex hyperplasia without atypia, and 3 had simple hyperplasia without atypia.

Of the 69 patients with endometrial carcinoma, cytological examination using Endocyte® revealed carcinoma (class V) in 54 patients, hyperplasia (class III or IV) in 7, and a normal endometrium (class II) in 5; in 3 patients, adequate samples could not be obtained.

| Class | Findings |
|-------|----------|
| I     | No abnormal findings. |
| II    | Inflammatory findings or reactive changes because of an intrauterine device(UID). |
| IIb   | Papillary clusters with few structural abnormalities. Complex hyperplasia not fully suspected but follow-up necessary. |
| III   | Papillary clusters accompanied by structural abnormalities. Complex hyperplasia suspected. |
| IV    | Small number of arborescent clusters. Complex hyperplasia with atypia or worse suspected. |
| V     | Clear glandular cavity with back-to-back structures and arborescent clusters. Endometrial cancer diagnosed. |

*EH*: endometrial hyperplasia; *EMCA*: endometrial carcinoma

Table 1: Different classes of cytologic findings of the endometrium.

| Class (cell) | Normal endometrium | EH (Atypical) | EMCA | Other tumor | Not performed | Total |
|-------------|--------------------|---------------|------|-------------|---------------|-------|
| I           | 3                  | 0             | 0    | 0           | 6             | 9     |
| II          | 4                  | 5 (1)         | 5    | 1           | 13            | 28    |
| III         | 0                  | 5 (3)         | 6    | 1           | 4             | 16    |
| IV          | 0                  | 1 (1)         | 1    | 0           | 3             | 5     |
| V           | 0                  | 94            | 0    | 0           | 2             | 60    |
| Inadequate  | 0                  | 0             | 3    | 0           | 3             | 6     |
| Total       | 7                  | 11 (5)        | 69   | 6           | 31            | 124   |

EH: endometrial hyperplasia; EMCA: endometrial carcinoma

Table 2: Comparison between cytologic examination and the final histological study.
Suresample™ identified 58 cases of endometrial carcinoma, while 6 were misdiagnosed as endometrial hyperplasia. In 5 patients, adequate samples could not be obtained. Of the 11 patients with carcinoma, while 6 were misdiagnosed as endometrial hyperplasia. In the present study too, the sensitivity of cytologic examination for detecting carcinoma tended to be lower than that of outpatient tissue biopsy. Other reports have showed that the sensitivity of cytologic examination for diagnosing endometrial carcinoma is 74.1–100% [8-14]. One study evaluated and compared the accuracy of sampling using Endopap® and Pipelle® for diagnosing postmenopausal disease. The sensitivity of Endopap® and Pipelle® for detecting endometrial disease was 56% and 51% and the specificity was 94% and 100%, respectively. The sensitivity for endometrial carcinoma was 80% for Endopap® and 100% for Pipelle®. The authors therefore favored Pipelle® for diagnosing endometrial disease in symptomatic postmenopausal women [13].

In the present study too, the sensitivity of cytologic examination for detecting carcinoma tended to be lower than that of outpatient tissue biopsy. Furthermore, 5 patients with carcinoma were falsely diagnosed as having a normal endometrium by outpatient tissue biopsy. Other reports have showed that the sensitivity of cytologic examination for diagnosing endometrial carcinoma is 74.1–100% [8-14]. One study evaluated and compared the accuracy of sampling using Endopap® and Pipelle® for diagnosing postmenopausal disease. The sensitivity of Endopap® and Pipelle® for detecting endometrial disease was 56% and 51% and the specificity was 94% and 100%, respectively. The sensitivity for endometrial carcinoma was 80% for Endopap® and 100% for Pipelle®. The authors therefore favored Pipelle® for diagnosing endometrial disease in symptomatic postmenopausal women [13].

In the present study too, the sensitivity of cytologic examination for detecting carcinoma tended to be lower than that of outpatient tissue biopsy. Furthermore, 5 patients with carcinoma were falsely diagnosed as having a normal endometrium by cytologic examination. Such false negatives pose a grave risk for patients when screened for endometrial carcinoma.

Outpatient endometrial sampling also aims to detect endometrial hyperplasia, because of the supposed role of the latter as a precursor of endometrial carcinoma. However, detecting endometrial hyperplasia in the smear of endometrial samples is very difficult. Therefore, the diagnostic rate is not always high because of the lack of cellular atypia. In fact, it has been reported that hyperplasia can be detected in only 32.3–80.5% of cases [8-12,14]. A meta-analysis shows that the sensitivity of the Pipelle® device in detecting atypical hyperplasia is 81% [5]. In the present study, the sensitivity of cytologic examination for detecting hyperplasia was 55%, whereas that of outpatient tissue biopsy was 91%. Thus, the difference between the sensitivity of these 2 methods is significant (p =0.045).

At the time of sampling, adverse effects such as severe pain and bloody discharge decrease the patient’s acceptance of the collection method. The adverse effects of the Pipelle® device, used without anesthesia, have been evaluated by surveying 40 patients. Although 2 patients (5%) complained of severe pain, none of the biopsy attempts were prematurely terminated as a result of pain and no complications related to endometrial sampling occurred [6]. The incidence and intensity of pain during and after a cytologic procedure using Endocyt® have also been examined. The present pain intensity index developed by Melzack assesses the overall discomfort or pain experienced on a scale of 0-5. Pain was reported as 0 (no pain) by 60% patients, as 1 (mild) by 30%, and as 2 (discomfort) by 10% [17,20]. In the present study, the intensity of pain tend to be stronger during cytologic examination using Endocyt® than tissue biopsy using Suresample™, despite the larger diameter of the Suresample™ probe. As the cytologic examination performed before the tissue biopsy made the insertion of the Suresample™ probe easier, we cannot provide definitive conclusions on the superiority of Suresample™ with regard to patient acceptance. However, during both procedures, none of the patients complained of severe pain and no complications occurred. This suggests that both outpatient sampling procedures were well tolerated, which is a finding consistent with those of previous reports [6,17,20].

**Table 3: Comparison between outpatient biopsy and the final histological study.**

| Biopsy | Normal endometrium | EH (Atypical) | EMCA | Other tumor | Not performed | Total |
|--------|--------------------|--------------|------|------------|---------------|-------|
| Normal endometrium | 6 | 0 | 0 | 3 | 17 | 26 |
| EH | 1 | 10 (5) | 6 | 0 | 4 | 21 |
| EMCA | 0 | 0 | 58 | 1 | 1 | 60 |
| Other tumor | 0 | 0 | 0 | 1 | 2 | 3 |
| Inadequate | 1 | 0 | 5 | 1 | 7 | 14 |
| Total | 7 | 11 (5) | 69 | 6 | 31 | 124 |

**Table 4: Comparison of diagnostic accuracy between cytologic examination and tissue biopsy.**

| | Cytologic examination (95% Confidence interval) (%) | Tissue biopsy (95% Confidence interval) (%) | p** |
|----------------|-------------------------------------------------|------------------------------------------|-----|
| Sensitivity for detecting endometrial carcinoma | 78.3 (66.7–87.3) | 84.1 (73.3–91.8) | 0.157 |
| Sensitivity for detecting endometrial hyperplasia | 54.5 (23.4–83.3) | 90.9 (58.7–99.8) | 0.045 |
| Specificity | 100.0 (59.0–100.0) | 85.7 (42.1–99.6) | *2 |

*p McNemar’s chi-square test
*Not calculable due to specificity of 100%

Discussion

To the best of our knowledge, this is the first study to investigate the diagnostic accuracy of outpatient endometrial tissue biopsy using Suresample™. However, there are several studies on the use of the Pipelle® device, which is similar to Suresample™ [4-7,13,15,16]. A meta-analysis revealed that the Pipelle® device has a sensitivity of 99.6% and 91% in postmenopausal and premenopausal patients, respectively [5]. Another review showed that the sensitivity of the Pipelle® device varies between 86% and 100% [4]. We found the sensitivity of Suresample™ to be 84%, which is lower than that of the Pipelle® device, as mentioned above. In the present study, the inadequate sample (no specimen obtained or insufficient specimen for adequate assessment for histological or cytological diagnosis) at the outpatient examination was regarded as ‘negative’ for the calculation of the sensitivity, in contrast to some previous studies where inadequate diagnoses were excluded from the calculations [4,8,10-12]. Had we calculated sensitivity by excluding inadequate samples, the sensitivity of Suresample™ for detecting endometrial carcinoma would be 91%, which is similar to the values reported in previous studies. Moreover, no patient with carcinoma was falsely diagnosed as having a normal endometrium by outpatient tissue biopsy. Other reports have showed that the sensitivity of cytologic examination for diagnosing endometrial carcinoma is 74.1–100% [8-14]. One study evaluated and compared the accuracy of sampling using Endopap® and Pipelle® for diagnosing postmenopausal disease. The sensitivity of Endopap® and Pipelle® for detecting endometrial disease was 56% and 51% and the specificity was 94% and 100%, respectively. The sensitivity for endometrial carcinoma was 80% for Endopap® and 100% for Pipelle®. The authors therefore favored Pipelle® for diagnosing endometrial disease in symptomatic postmenopausal women [13].

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Our data indicated a certain diagnostic superiority of outpatient tissue biopsy to cytologic examination. Because of the small number of patients with a normal endometrium, we could not sufficiently evaluate the specificity for detecting endometrial disease. Furthermore, this study did not compare the two methods in terms of cost effectiveness. Therefore, cytologic examination for detecting endometrial carcinoma and hyperplasia cannot be completely disregarded. Yet, our data suggest that the use of tissue biopsy in an endometrial carcinoma screening program might improve the detection rate of endometrial carcinoma and hyperplasia. For example, in the cases of patients with normal endometrial morphology on cytologic examination, who show strongly suspicious symptoms such as abnormal endometrium thickness on the ultrasonography and/or continuous genital bleeding, reexamination using tissue biopsy should be considered. Diagnostic superiority of outpatient tissue biopsy to cytologic examination is most likely because cytologic examination cannot provide the architectural detail. Recently, liquid-based cytology and cell block preparation were reported as the methods that had more excellent architectural preservation than cytologic examination cannot provide the architectural detail. Furthermore, this study did not compare the two methods in terms of cost effectiveness.

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